Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

Moderator

Neil Love, MD

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Faculty

Jesús G Berdeja, MD
Director of Multiple Myeloma Research
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Rafael Fonseca, MD
Chief Innovation Officer
Getz Family Professor of Cancer
Distinguished Mayo Investigator
Mayo Clinic in Arizona
Phoenix, Arizona

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Anne and Bernard Gray Family
Chair in Cancer
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Robert Z Orlowski, MD, PhD
Florence Maude Thomas
Cancer Research Professor
Department of Lymphoma and Myeloma
Professor, Department of Experimental Therapeutics
Director, Myeloma Section
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Moderator
Neil Love, MD
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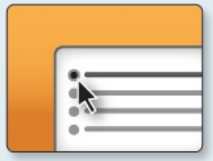
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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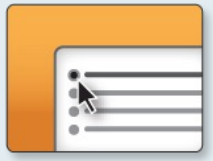
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Spencer Henick Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Bhavana (Tina) Bhatnagar, DO
West Virginia University
Cancer Institute
Wheeling, West Virginia

Kimberly Ku, MD
Bloomington, Illinois

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Hans Lee, MD
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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Henna Malik, MD
Texas Oncology
North Houston, Willowbrook/Cypress
Houston, Texas

Erik Rupard, MD
Drexel University College of Medicine
West Reading, Pennsylvania

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Syed Farhan Zafar, MD
Florida Cancer Specialists
Fort Myers, Florida

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Commercial Support

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Contracted Research	bluebird bio
Steering Committee	Amgen Inc, Roche Laboratories Inc

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Moderator

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Agenda

Module 1: Front-Line Treatment of Multiple Myeloma (MM) — Dr Orlowski

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Fonseca

Module 3: Current Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Berdeja

Module 5: Other Investigational Novel Agents for MM — Dr Lonial

Agenda

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▸ *Real World Cases and Questions*

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Module 1: Front-Line Treatment of Multiple Myeloma (MM) — Dr Orlowski

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Case Presentation: 50-year-old woman with NDMM and 1q gain who presents with a pathologic fracture and receives daratumumab/RVd

Dr Tina Bhatnagar (Wheeling, West Virginia)

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Dr Erik Rupard
(West Reading, Pennsylvania)

Case Presentation: Otherwise healthy 89-year-old man with NDMM who is disinclined to undergo aggressive therapy

Dr Hans Lee
(Houston, Texas)

Case Presentation: 79-year-old transplant-ineligible woman with NDMM

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Induction Therapy for Newly Diagnosed Multiple Myeloma

Robert Z. Orlowski, M.D., Ph.D.

Director, Myeloma Section, & Deputy Chair, Department of Lymphoma/Myeloma

Florence Maude Thomas Cancer Research Professor

Principal Investigator, MD Anderson SCOR in High Risk Plasma Cell Dyscrasias

Chair, SWOG Myeloma Committee

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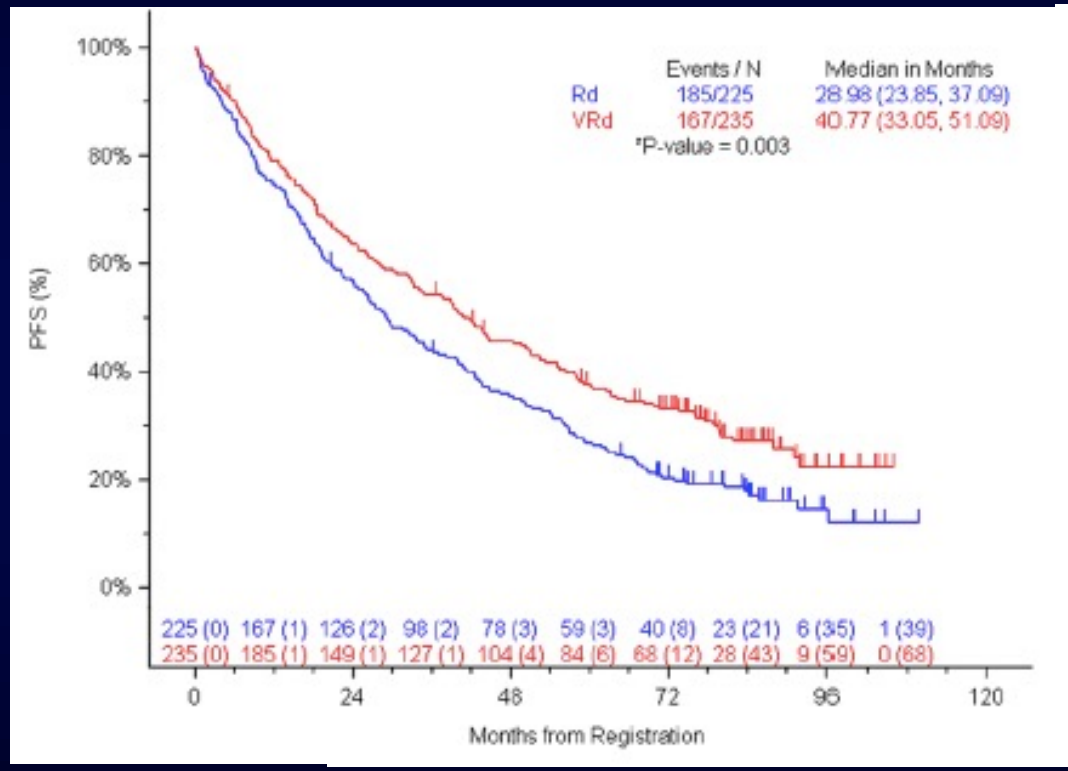
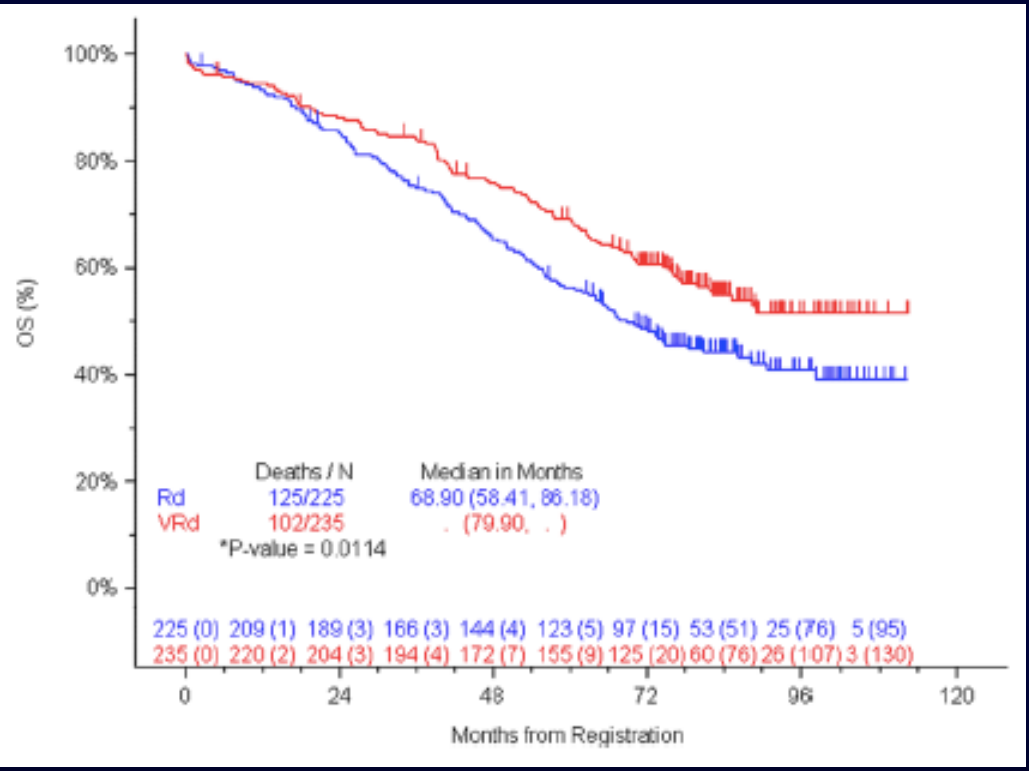
NCCN Guidelines (V2.2023)

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES[a-d]
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/lenalidomide/dexamethasone
Other Recommended Regimens • Daratumumab/lenalidomide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/thalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[f] • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab/bortezomib/thalidomide/dexamethasone • Daratumumab/carfilzomib/lenalidomide/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[g] (VTD-PACE) • Ixazomib/cyclophosphamide/dexamethasone[f] • Ixazomib/lenalidomide/dexamethasone (category 2B)

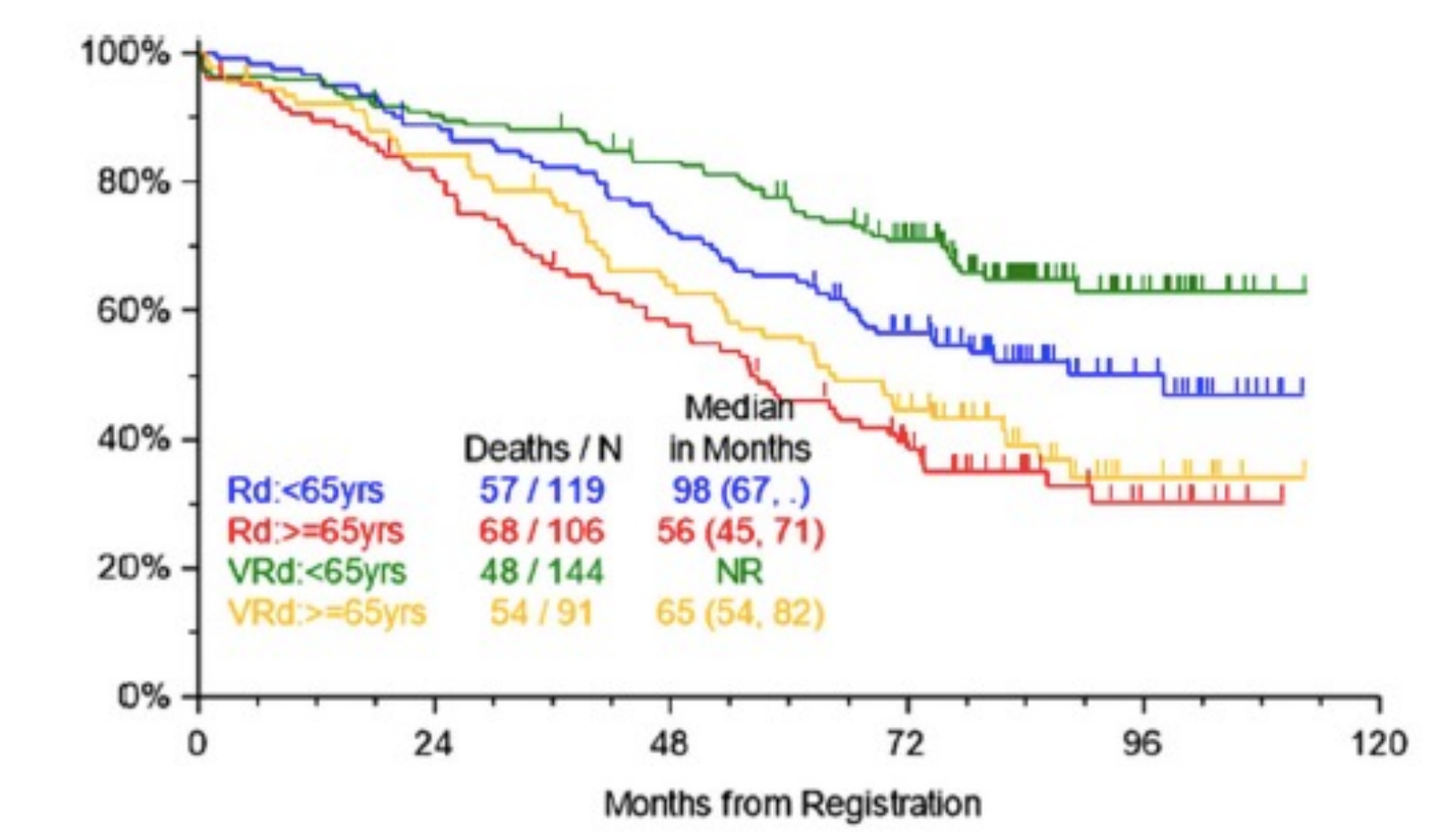
https://www.nccn.org/guidelines

VRd : SWOG S0777





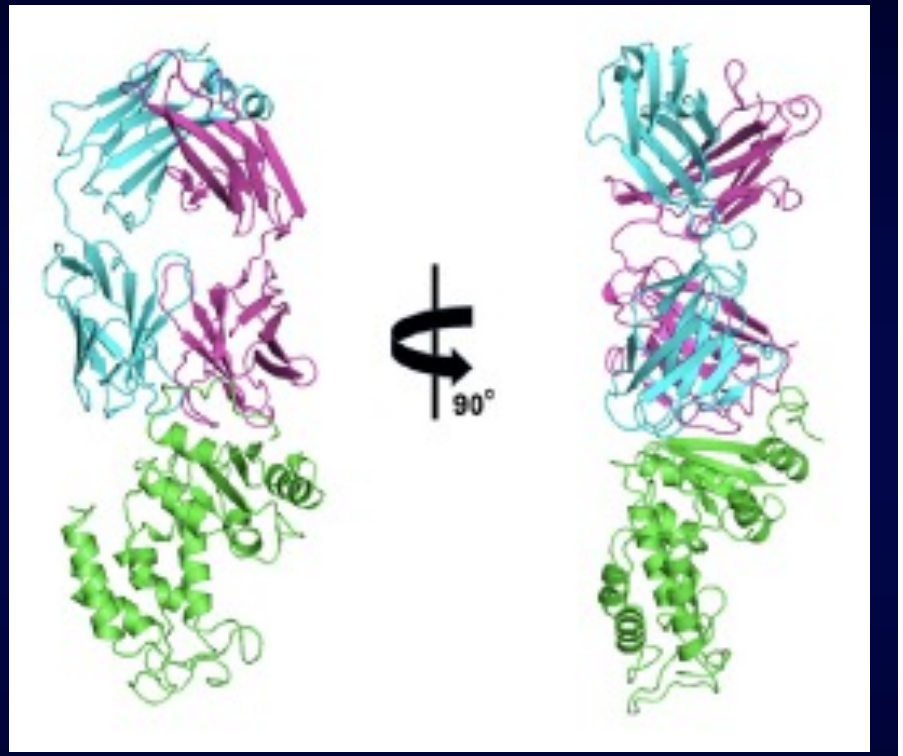
OS by Age



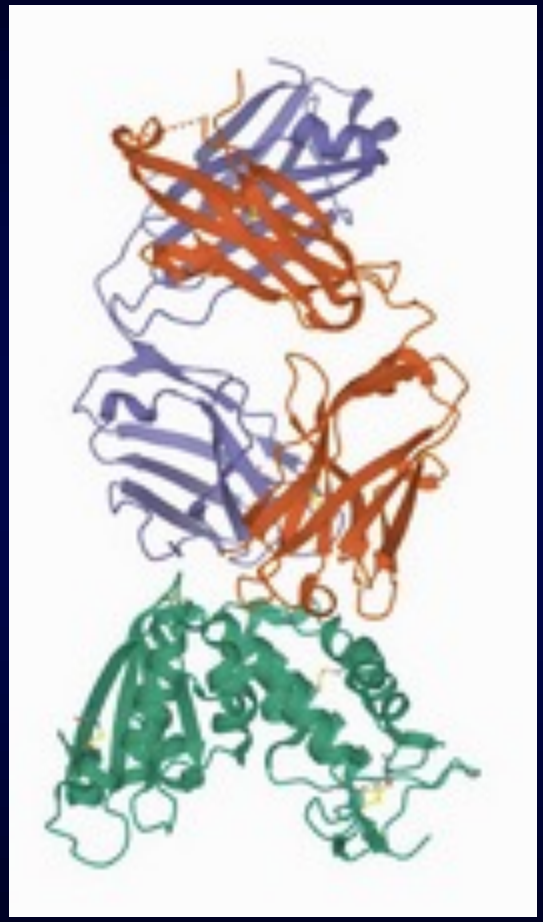
Age < 65 years: HR= 0.640 (0.421,0.973);
stratified, two-sided p= 0.028

Age ≥ 65 years: HR= 0.769 (0.520,1.138);
stratified, two-sided p= 0.168

Daratumumab & Isatuximab



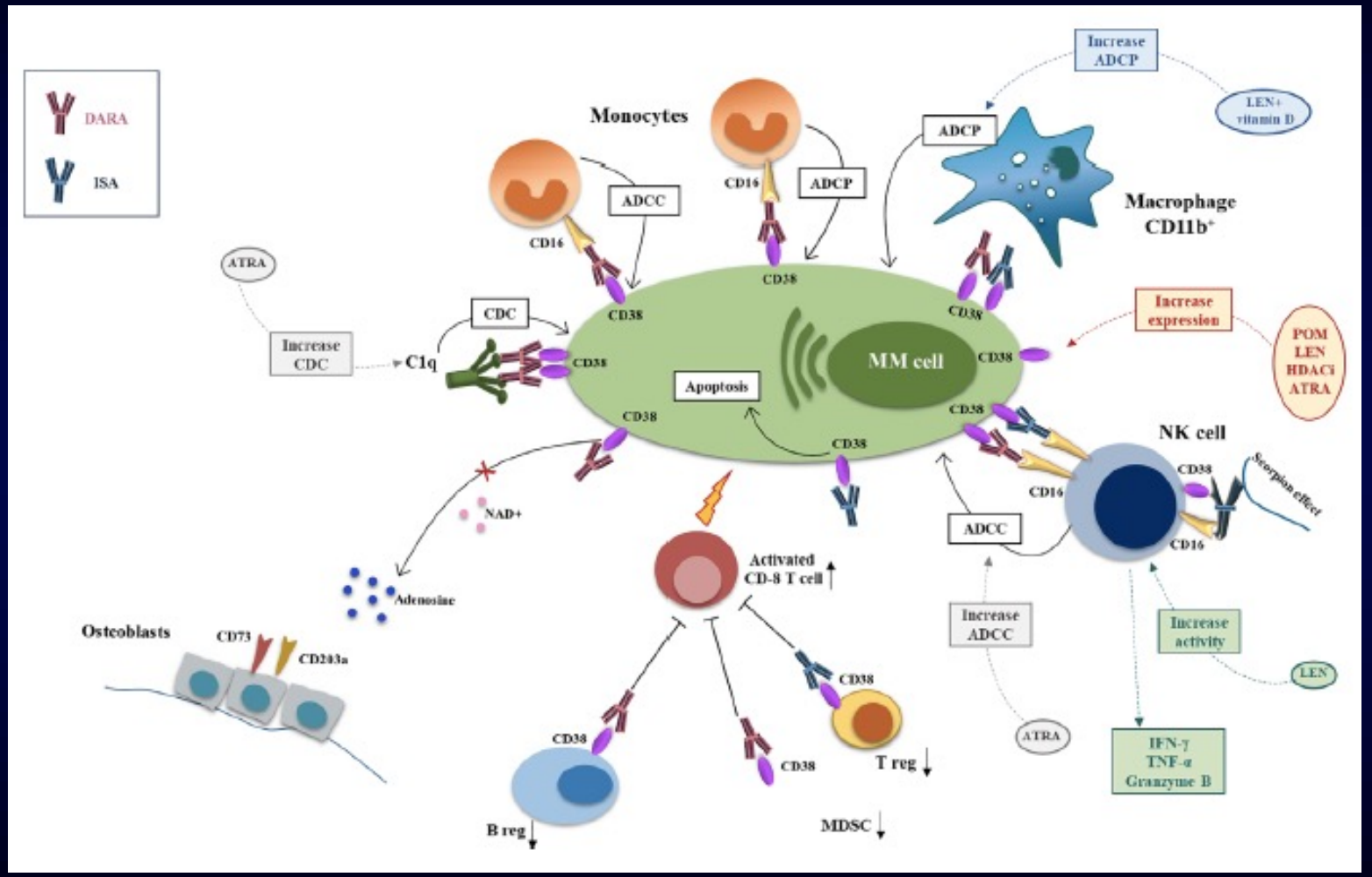
- CD38 bound to Fab of Dara



- CD38 bound to Fab of Isa

Lee, HT et al. Biochem Biophys Res Commun. 536: 26, 2021.
Deckert, J et al. Clin Cancer Res. 20: 4574, 2014.

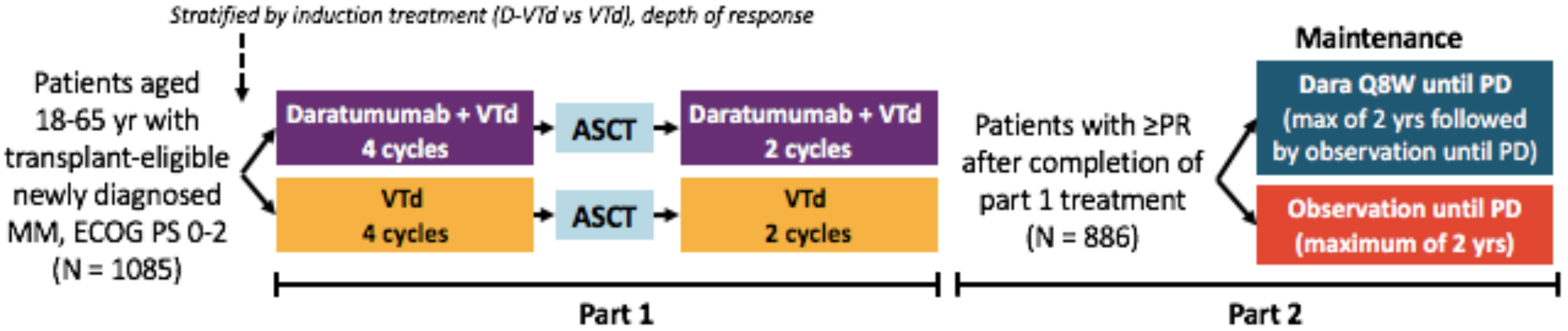
Multiple Mechanisms of Action



Romano, A et al. Front Oncol. 2021 Jul 8;11:684561. doi: 10.3389/fonc.2021.684561.

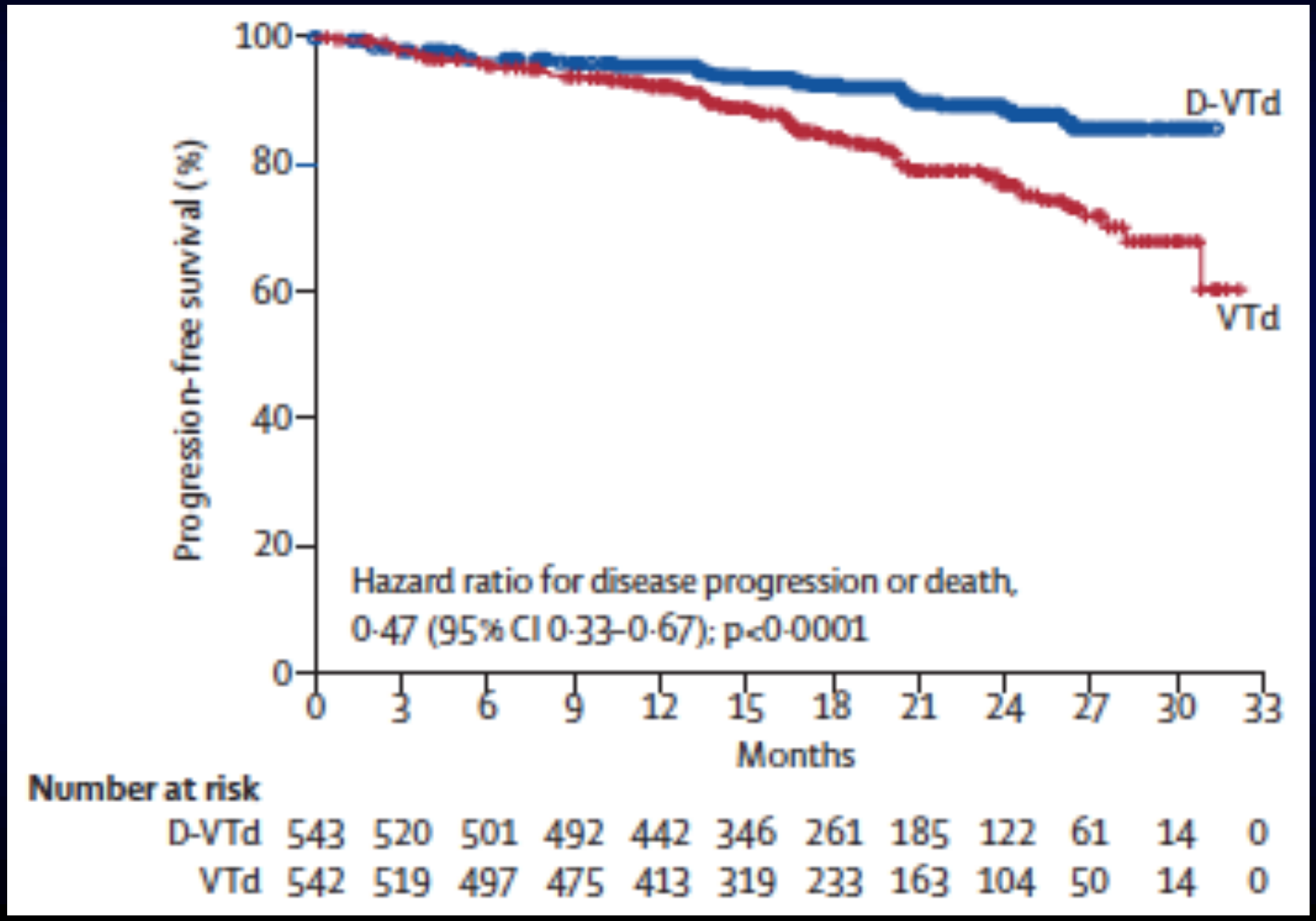
CASSIOPEIA : D-VTd vs. VTd

Bortezomib, thalidomide, and dexamethasone with or without **daratumumab** before and after autologous stem-cell transplantation for newly diagnosed

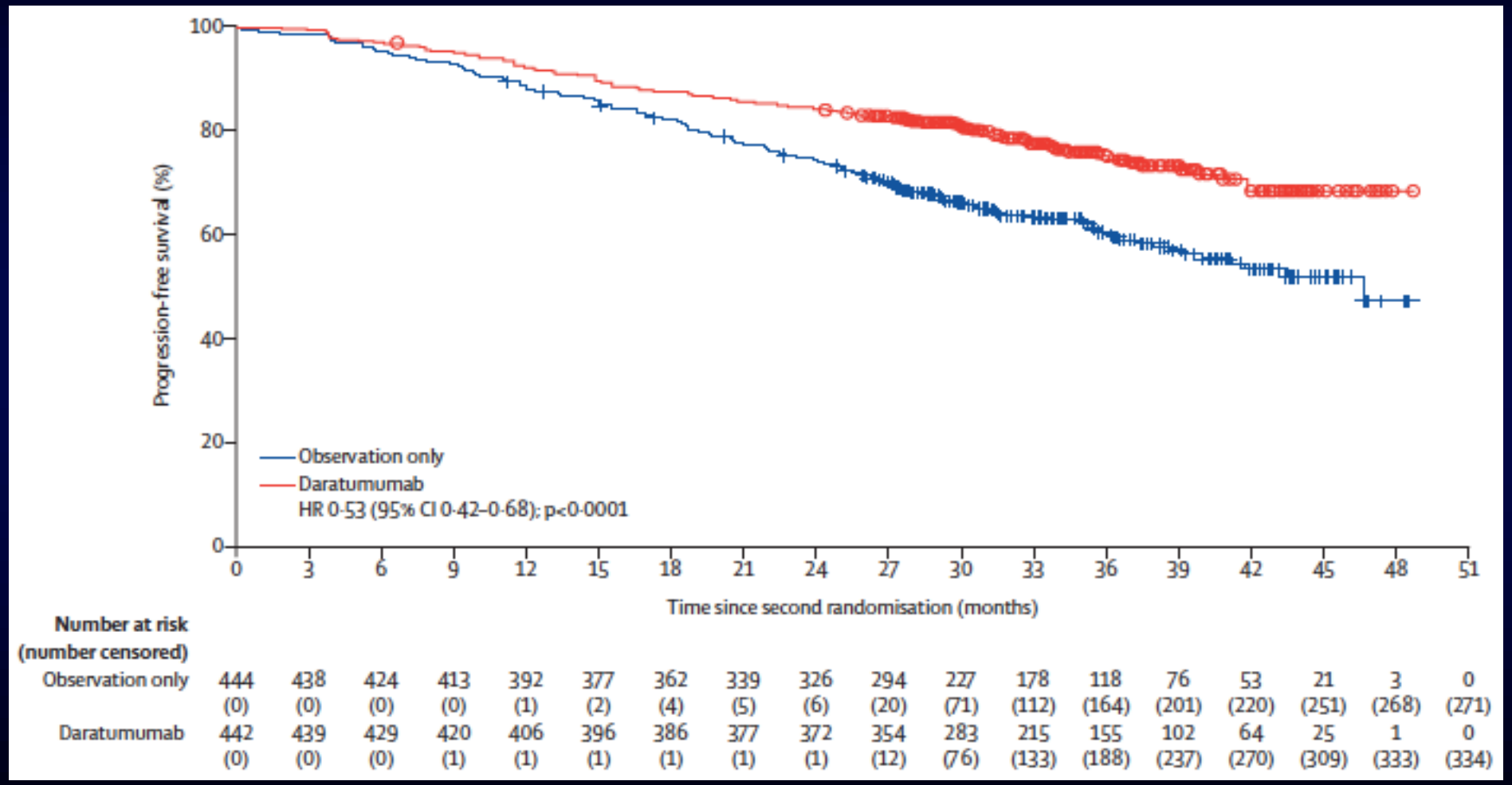


PMID: 31171419 Clinical Trial.

First Randomization Data

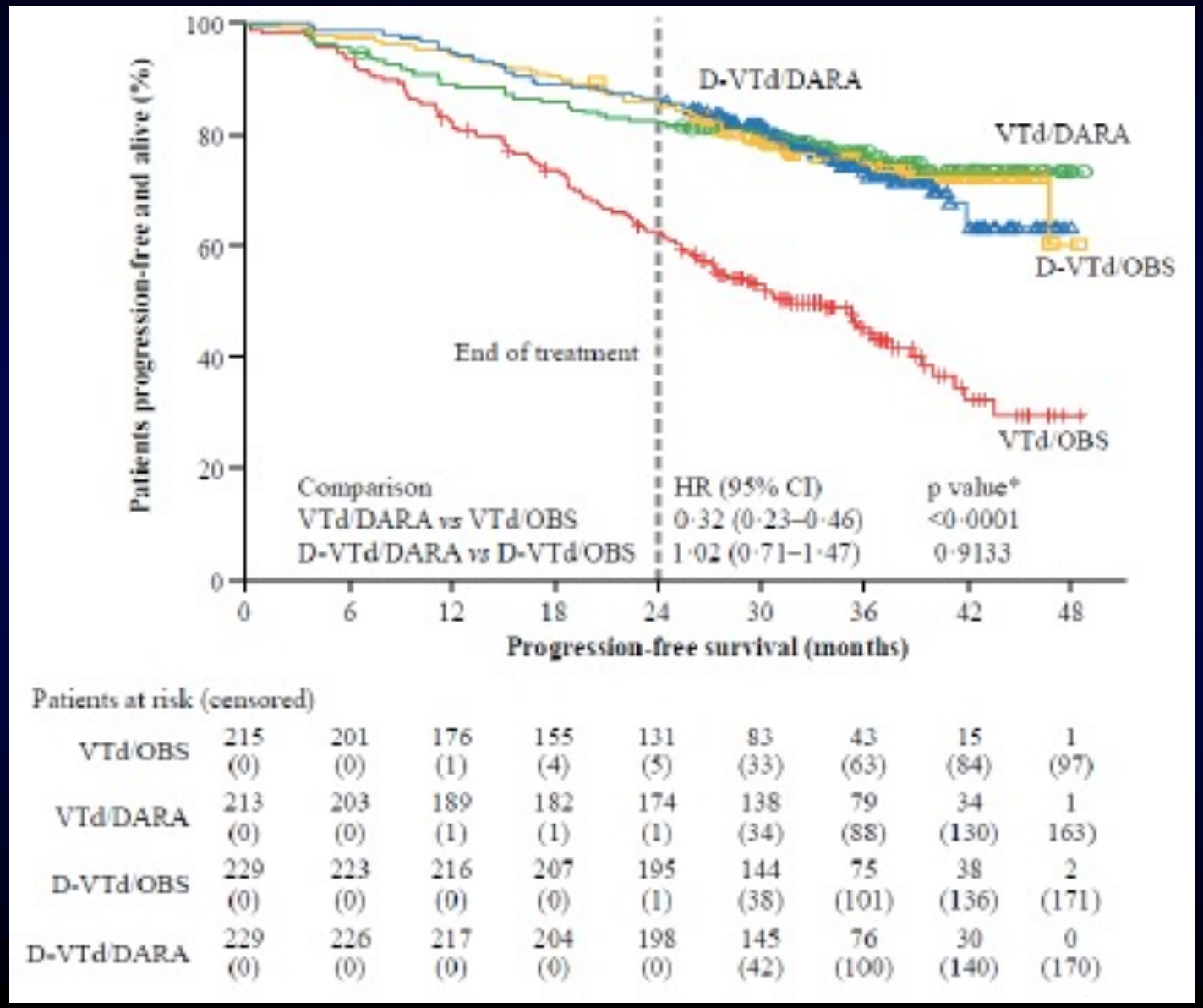


Second Randomization Data



Number at risk (number censored)																	
Observation only	444 (0)	438 (0)	424 (0)	413 (0)	392 (1)	377 (2)	362 (4)	339 (5)	326 (6)	294 (20)	227 (71)	178 (112)	118 (164)	76 (201)	53 (220)	21 (251)	3 (268)	0 (271)
Daratumumab	442 (0)	439 (0)	429 (0)	420 (1)	406 (1)	396 (1)	386 (1)	377 (1)	372 (1)	354 (12)	283 (76)	215 (133)	155 (188)	102 (237)	64 (270)	25 (309)	1 (333)	0 (334)

Intriguing Question

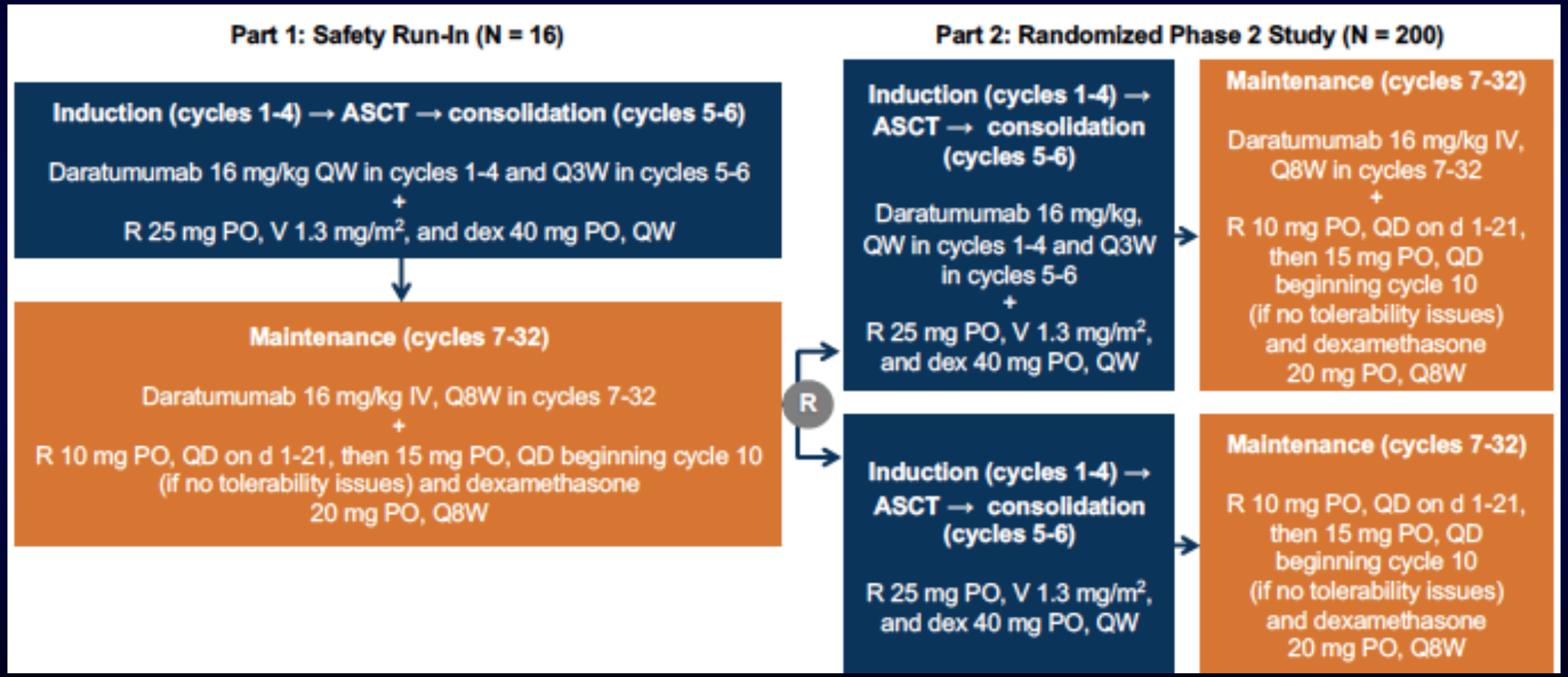


Patients at risk (censored)

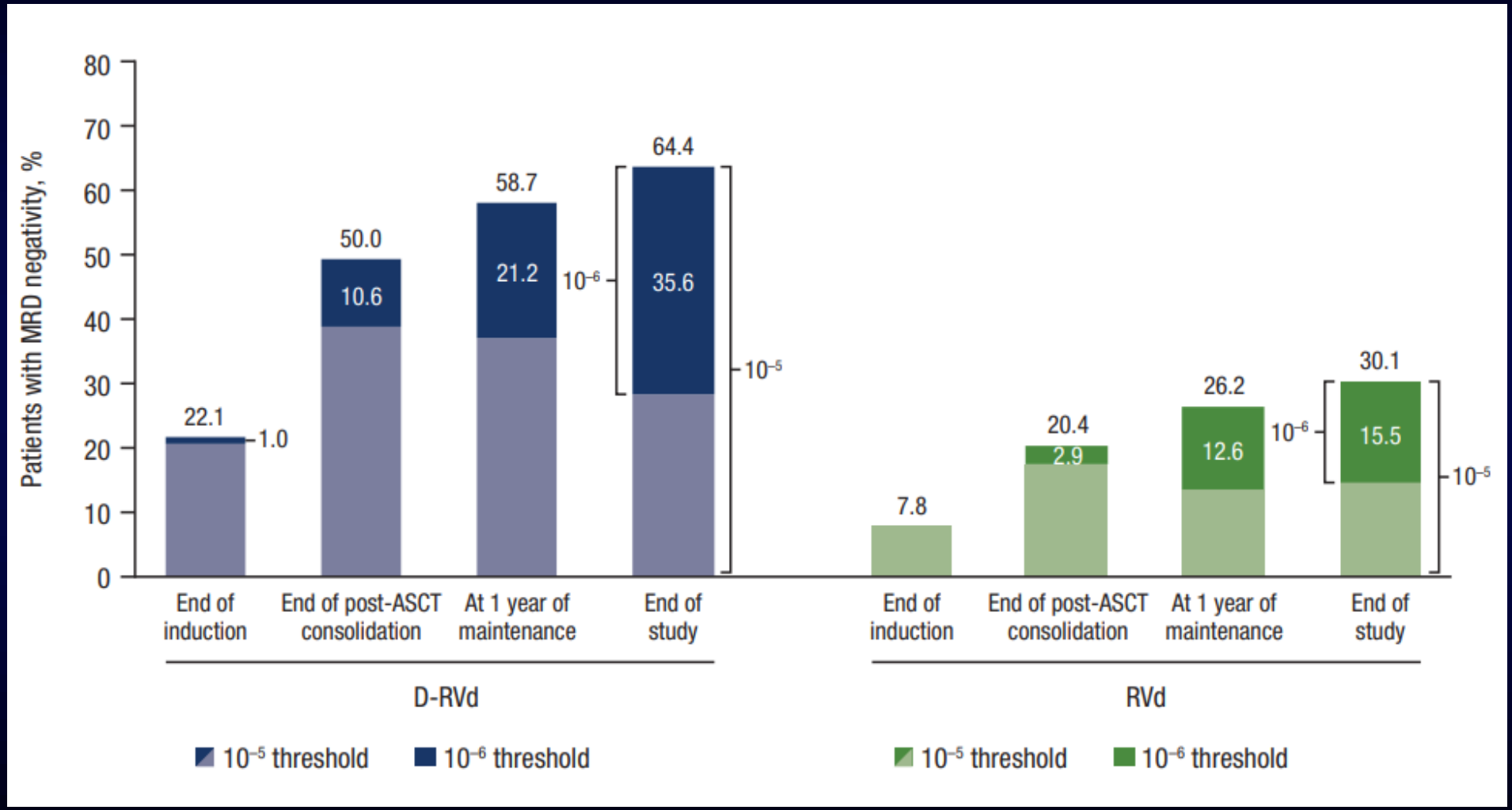
VTd/OBS	215 (0)	201 (0)	176 (1)	155 (4)	131 (5)	83 (33)	43 (63)	15 (84)	1 (97)
VTd/DARA	213 (0)	203 (0)	189 (1)	182 (1)	174 (1)	138 (34)	79 (88)	34 (130)	1 163)
D-VTd/OBS	229 (0)	223 (0)	216 (0)	207 (0)	195 (1)	144 (38)	75 (101)	38 (136)	2 (171)
D-VTd/DARA	229 (0)	226 (0)	217 (0)	204 (0)	198 (0)	145 (42)	76 (100)	30 (140)	0 (170)

- Is Dara needed in both induction & maint., or is one or the other sufficient?

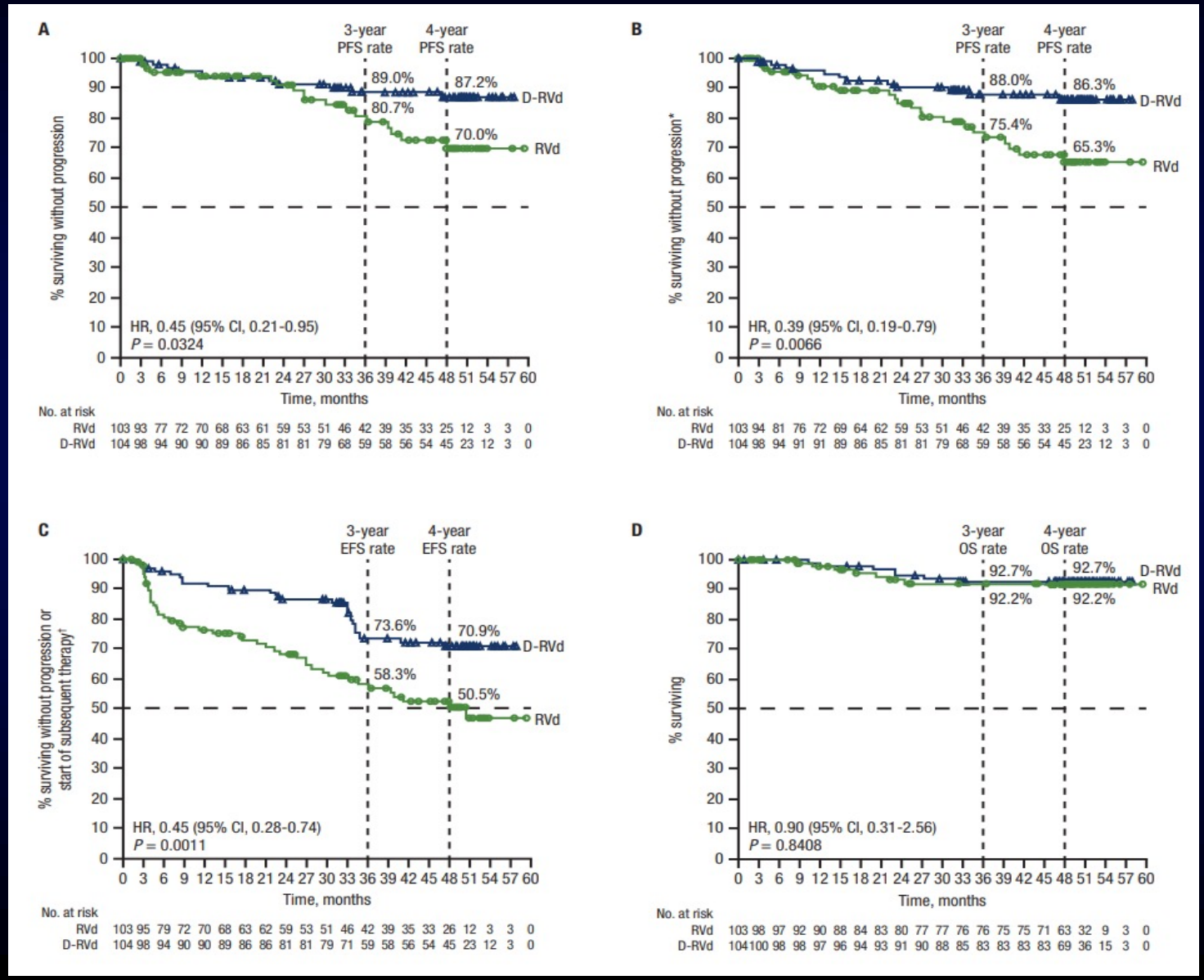
Final Analysis of GRIFFIN



Outcomes Data

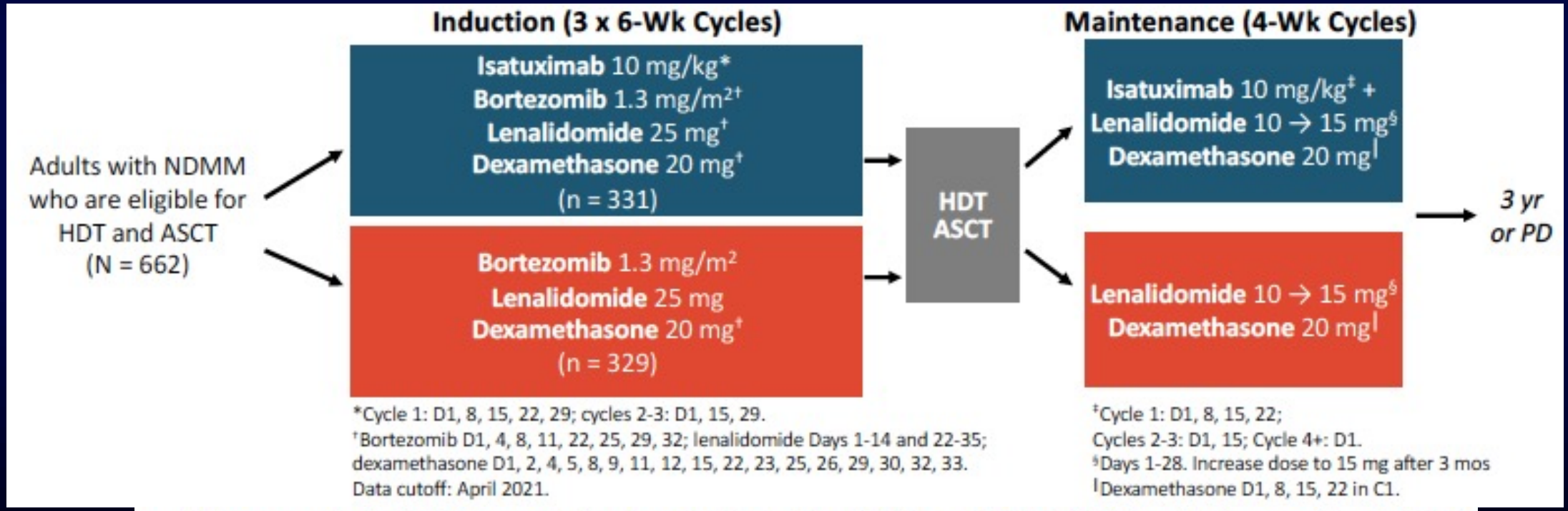


Long Term Outcomes



GMMG-HD7 Trial : Isatuximab

- Addition of Isa to VRd for transplant-eligible myeloma patients



- Primary endpoint: MRD negativity at end of induction (NGF, sensitivity 10^{-5}) stratified according to R-ISS
- Secondary endpoints: CR after induction, safety
- MRD negativity assessed after cycle 3, HDT, 12 mos, and 24 mos as well as at end of study

	Isatuximab group (negative/n)	Control group (negative/n)	Odds ratio (95% CI)	p value homogeneity test
Age (years)				0·27
26–60	103/198	59/175	2·13 (1·41–3·25)	
>60	63/133	58/154	1·49 (0·93–2·39)	
Sex				0·90
Male	99/204	71/206	1·79 (1·21–2·67)	
Female	67/127	46/123	1·87 (1·13–3·11)	
WHO score				1·00
Grade 0/1	148/295	106/298	1·82 (1·31–2·54)	
Grade >1	18/35	11/30	1·83 (0·68–5·05)	
Renal impairment				0·81
Yes	8/19	7/22	1·56 (0·43–5·75)	
No	158/312	110/307	1·84 (1·33–2·54)	
International Staging System				0·93
Stage III	37/78	21/66	1·93 (0·98–3·87)	
Stage II	63/129	37/114	1·99 (1·18–3·37)	
Stage I	66/124	59/149	1·74 (1·07–2·82)	
High-risk cytogenetics				0·93
No	123/254	78/234	1·88 (1·30–2·72)	
Yes	34/58	29/66	1·81 (0·89–3·72)	
Elevated lactate dehydrogenase				0·43
No	135/268	105/286	1·75 (1·25–2·46)	
Yes	31/63	12/43	2·50 (1·11–5·89)	
Revised International Staging System				0·47
Stage III	13/27	12/26	1·08 (0·37–3·22)	
Stage II	112/219	61/185	2·13 (1·42–3·20)	
Stage I	37/77	35/98	1·66 (0·91–3·07)	
Overall	**166/331**	**117/329**	**1·82 (1·33–2·48)**	

Proportion of patients (%)

100 90 80 70 60 50 40 30 20 10 0

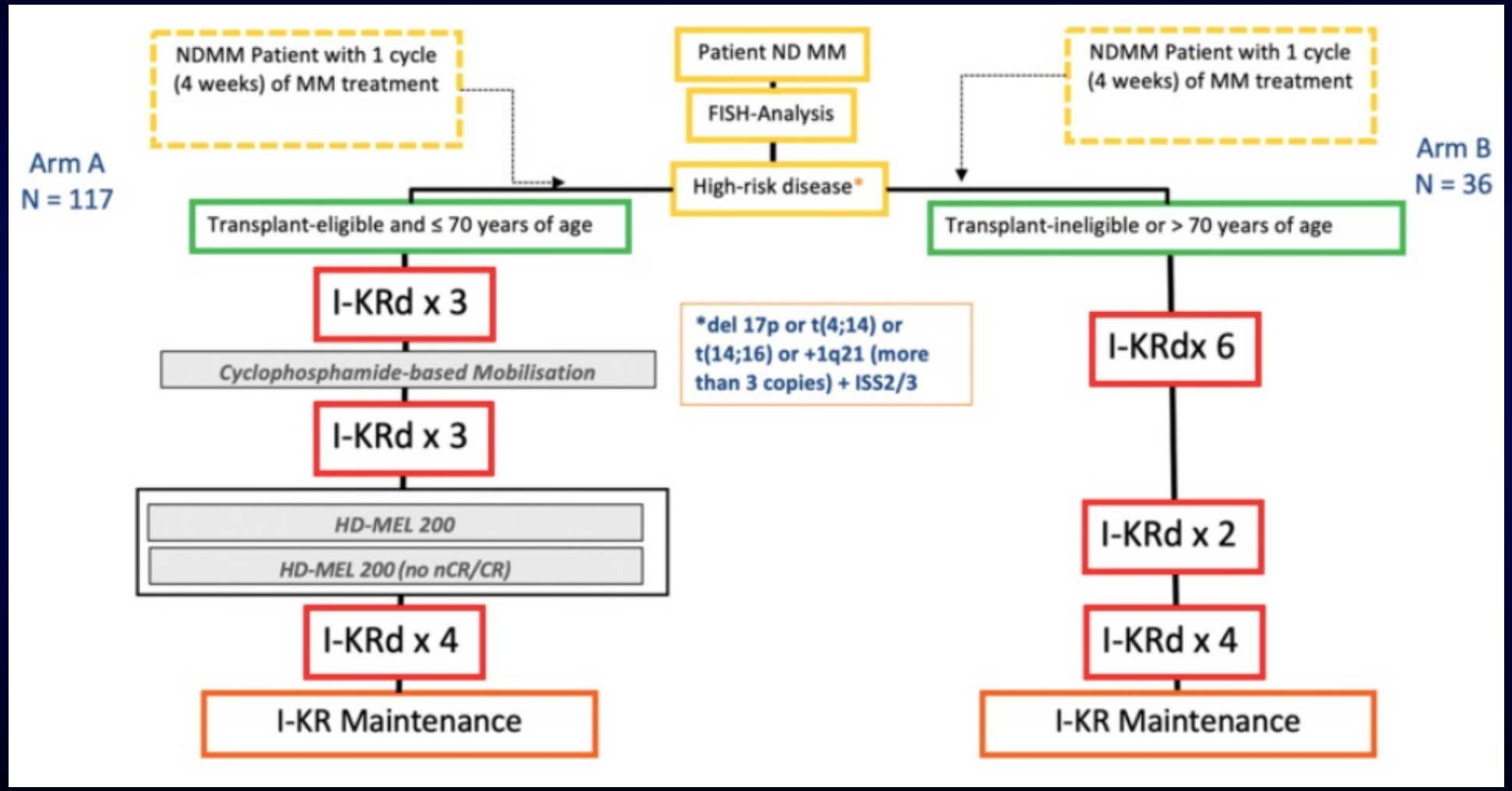
0·4 0·5 0·6 0·7 0·9 1·0 1·1 1·3 1·6 2·0 2·4 3·0 3·6 4·4 5·4

Favours lenalidomide, bortezomib, and dexamethasone

Favours isatuximab plus lenalidomide, bortezomib, and dexamethasone

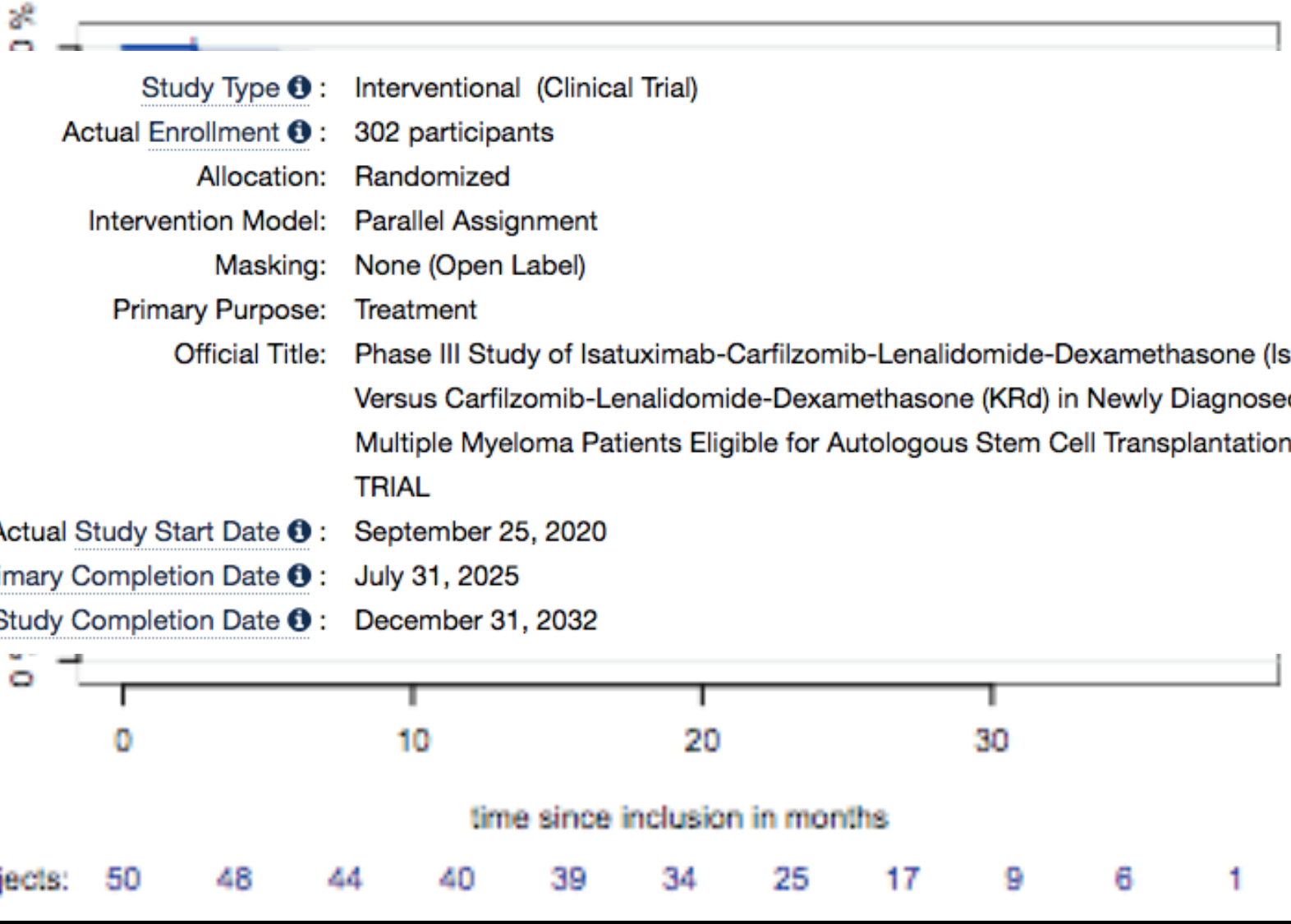
...tus
...response
...plete response
...d partial response
...sponse
...response
...ease
...ve disease
...sable but no
...ve disease
...able

GMMG-CONCEPT Trial : Isa + KRd



Interim Analysis

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	302 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Phase III Study of Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone (Isa-KRd) Versus Carfilzomib-Lenalidomide-Dexamethasone (KRd) in Newly Diagnosed Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation (IsKia TRIAL
Actual Study Start Date :	September 25, 2020
Estimated Primary Completion Date :	July 31, 2025
Estimated Study Completion Date :	December 31, 2032



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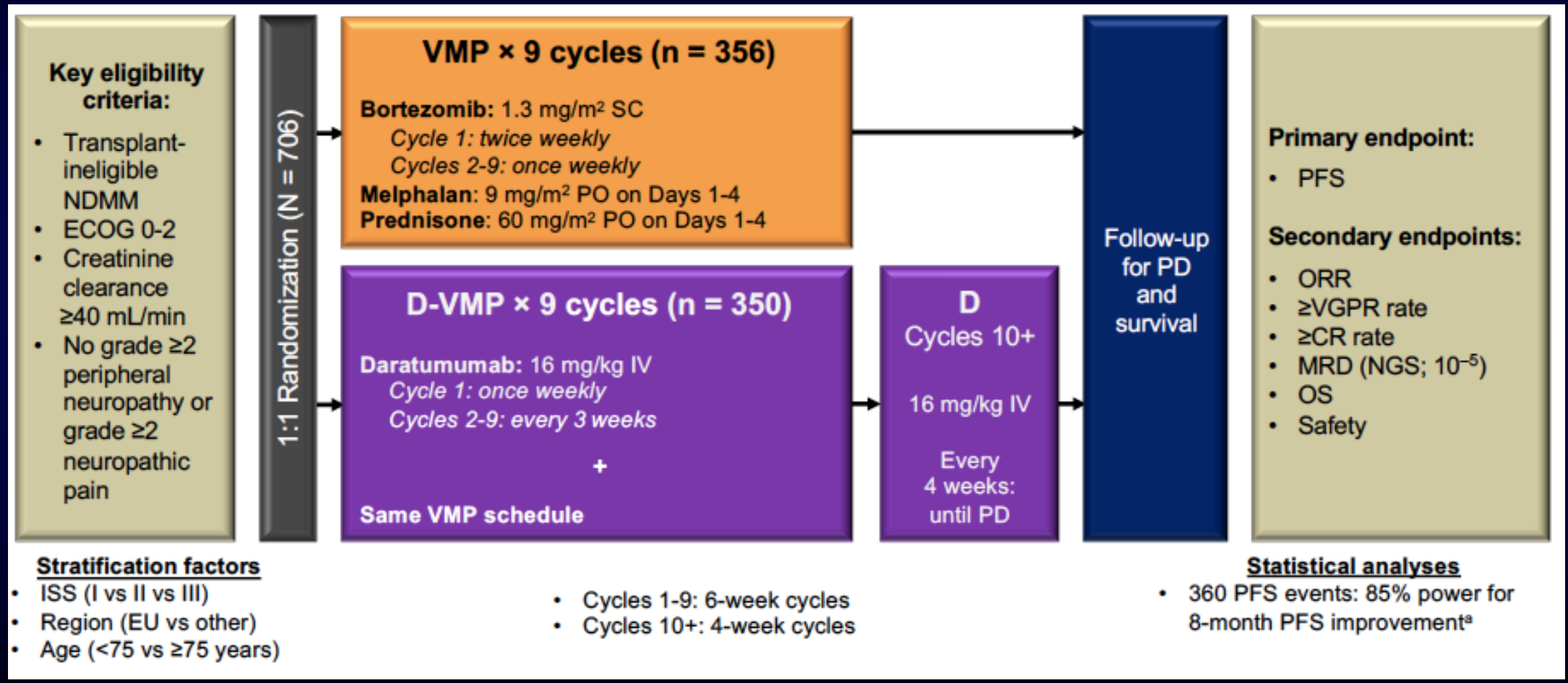
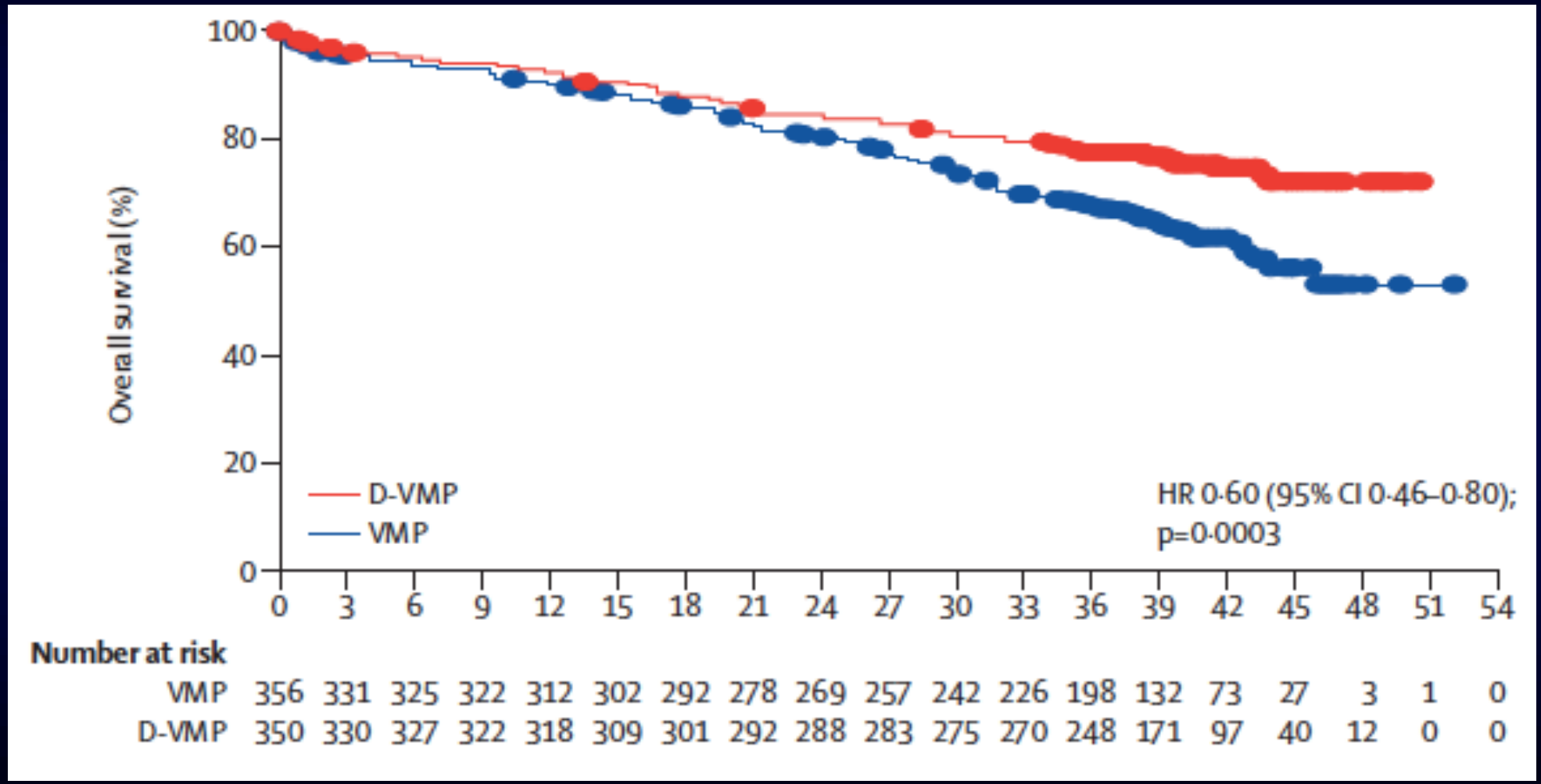
• Daratumumab/bortezomib/melphalan/prednisone (category 1) • Carfilzomib/lenalidomide/dexamethasone	• Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone
Useful In Certain Circumstances	
• Lenalidomide/low-dose dexamethasone (category 1)[k] • Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone[e]	• Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients • Carfilzomib/cyclophosphamide/dexamethasone[f] • Cyclophosphamide/lenalidomide/dexamethasone

https://www.nccn.org/guidelines

ALCYONE Trial



PFS1, 2, and OS


Overall survival (%)
100
80
60
40
20
0
D-VMP
VMP
HR 0·60 (95% CI 0·46–0·80);
p=0·0003
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54
Number at risk
VMP 356 331 325 322 312 302 292 278 269 257 242 226 198 132 73 27 3 1 0
D-VMP 350 330 327 322 318 309 301 292 288 283 275 270 248 171 97 40 12 0 0

MAIA Study

- Randomized phase III trial

Stratified by ISS (I vs II vs III), region (N America vs other), age (< 75 vs ≥ 75 yrs)

Patients with ASCT-ineligible NDMM, ECOG PS 0-2, CrCl ≥ 30 mL/min (N = 737)

Daratumumab 16 mg/kg IV (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7+) + **Lenalidomide** 25 mg/day PO on Days 1-21 + **Dexamethasone** 40 mg/wk* PO or IV (n = 368)

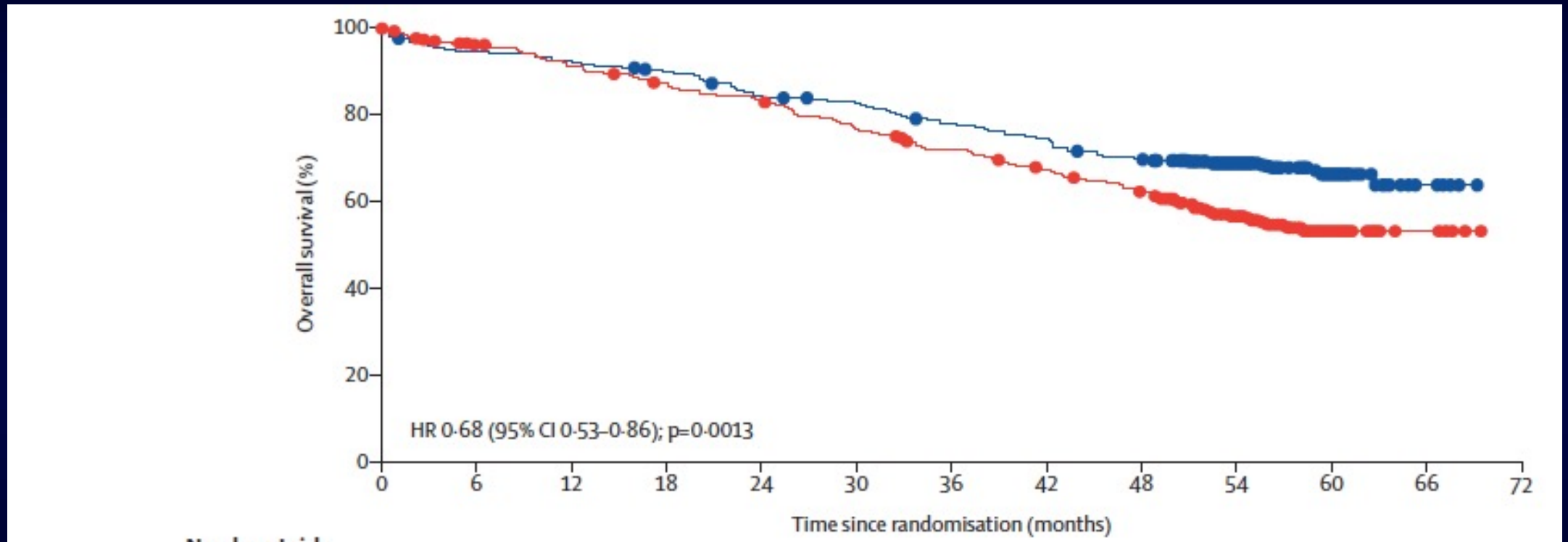
Lenalidomide 25 mg/day PO on Days 1-21 + **Dexamethasone** 40 mg/wk* PO or IV (n = 369)

28-day cycles until progression

*Reduced to 20 mg/wk if > 75 yrs of age or BMI < 18.5.

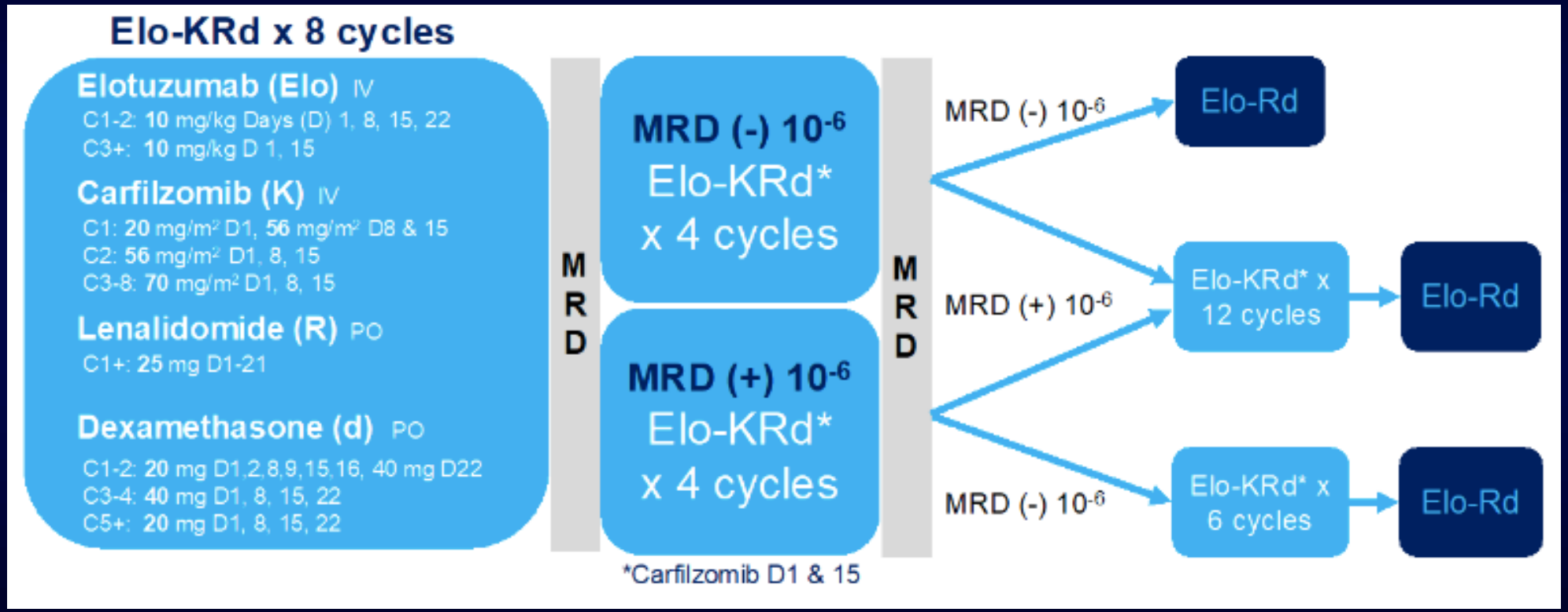
- Primary endpoint: PFS
- Secondary endpoints : ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, safety

PFS & OS Updates

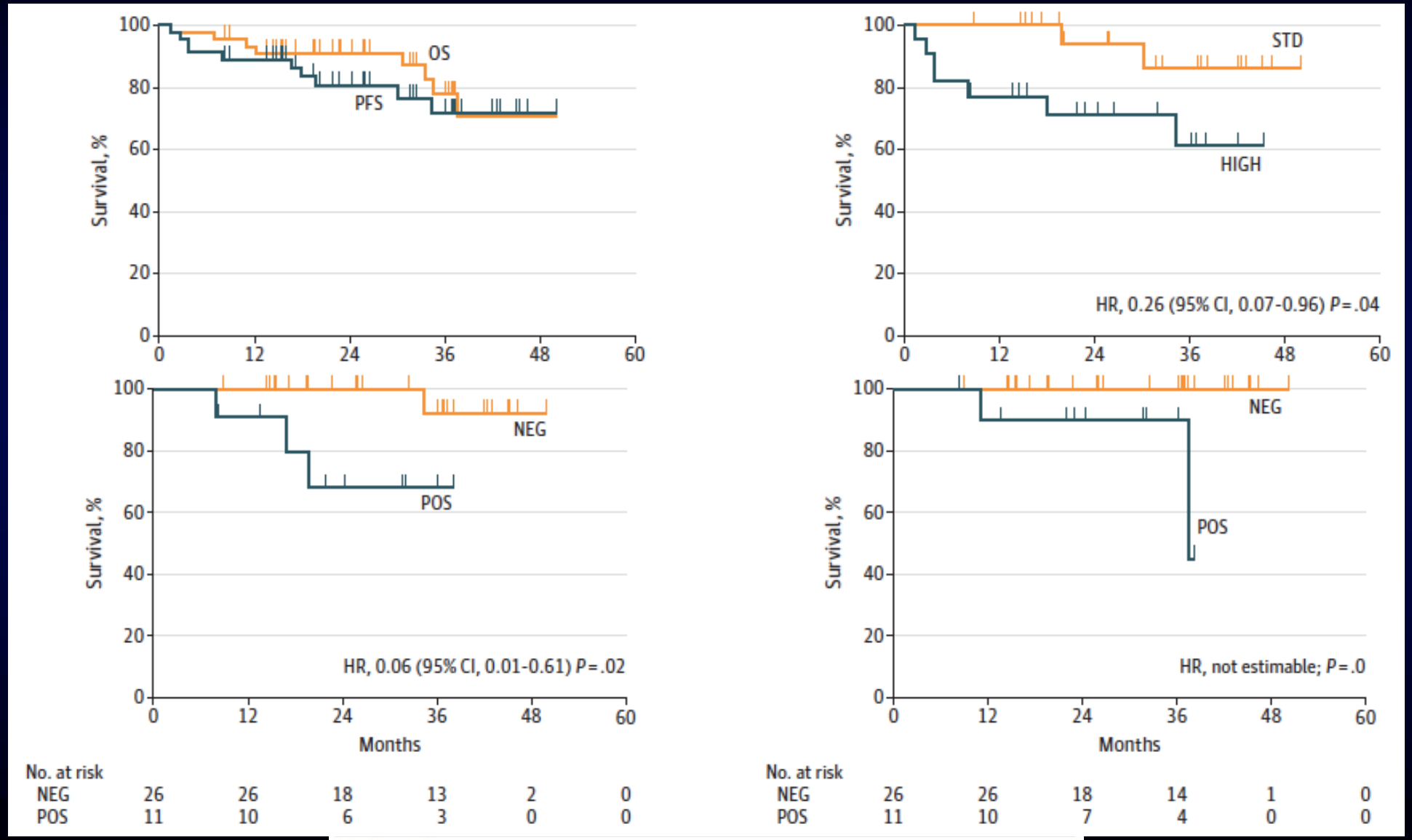


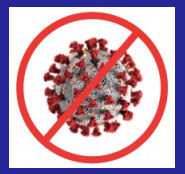
Number at risk (number censored)													
Lenalidomide and dexamethasone	369 (0)	343 (13)	324 (14)	308 (16)	294 (16)	270 (17)	251 (20)	232 (22)	213 (24)	134 (85)	42 (171)	5 (208)	0 (213)
Daratumumab plus lenalidomide and dexamethasone	368 (0)	346 (3)	338 (3)	328 (5)	305 (6)	297 (8)	280 (9)	266 (9)	249 (10)	170 (86)	63 (189)	6 (245)	0 (251)

Using MRD to Guide Therapy



Outcomes


Survival, %
OS
PFS
HR, 0.06 (95% CI, 0.01-0.61) P=.02
NEG
POS
Months
No. at risk
NEG 26 26 18 13 2 0
POS 11 10 6 3 0 0
STD
HIGH
HR, 0.26 (95% CI, 0.07-0.96) P=.04
HR, not estimable; P=.0
NEG 26 26 18 14 1 0
POS 11 10 7 4 0 0



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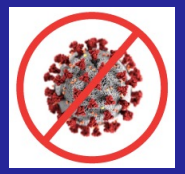
Conclusions

- For transplant-eligible patients
  - VRd remains a standard of care
  - Emerging quadruplets with α-CD38 mAbs
  - PERSEUS (Dara) & GMMG-HD7 (Isa)
- For transplant-ineligible patients
  - VRd-lite or DaraRd
  - CEPHEUS (Dara) & IMROZ (Isa)
  - S2209: VRd-lite-R vs. DRd-R vs. DRd-DR



Remaining Questions

- Possibility for molecularly-, risk-, or response-adapted therapy?
- Modifications of current regimen to achieve CR and MRD-negativity in closer to 100%?
- Transition to fixed duration of treatment versus treat to progression to preserve options at time of relapse?

Discussion Question

From a clinical perspective, daratumumab and isatuximab seem very similar/the same.

- Agree
- Disagree, daratumumab seems to have a better profile
- Disagree, isatuximab seems to have a better profile
- I'm not sure

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Fonseca

RTP
RESEARCH
TO PRACTICE

Dr Neil Morganstein
(Summit, New Jersey)

Case Presentation: 69-year-old transplant-eligible man with well-controlled HIV-1 and standard-risk NDMM

Dr Syed Zafar
(Fort Myers, Florida)

Case Presentation: 69-year-old man with high-risk, t(4;14) multiregimen-refractory MM with travel limitations who receives belantamab mafodotin

RTP
RESEARCH
TO PRACTICE

Dr Henna Malik
(Houston, Texas)

Case Presentation: 72-year-old woman who receives daratumumab, bortezomib and dexamethasone for relapsed MM 6 years after RVd → ASCT → maintenance bortezomib

Dr Erik Rupard
(West Reading, Pennsylvania)

Case Presentation: 56-year-old man with NDMM who received RVd → maintenance lenalidomide, which was discontinued by the patient after 1 year

RTP
RESEARCH
TO PRACTICE

MAYO CLINIC

Rafael Fonseca, M.D.
Chief Innovation Officer

Mayo Clinic in Arizona
Multiple Myeloma

Phoenix, Arizona

Rochester, Minnesota

Jacksonville, Florida

MAYO CLINIC

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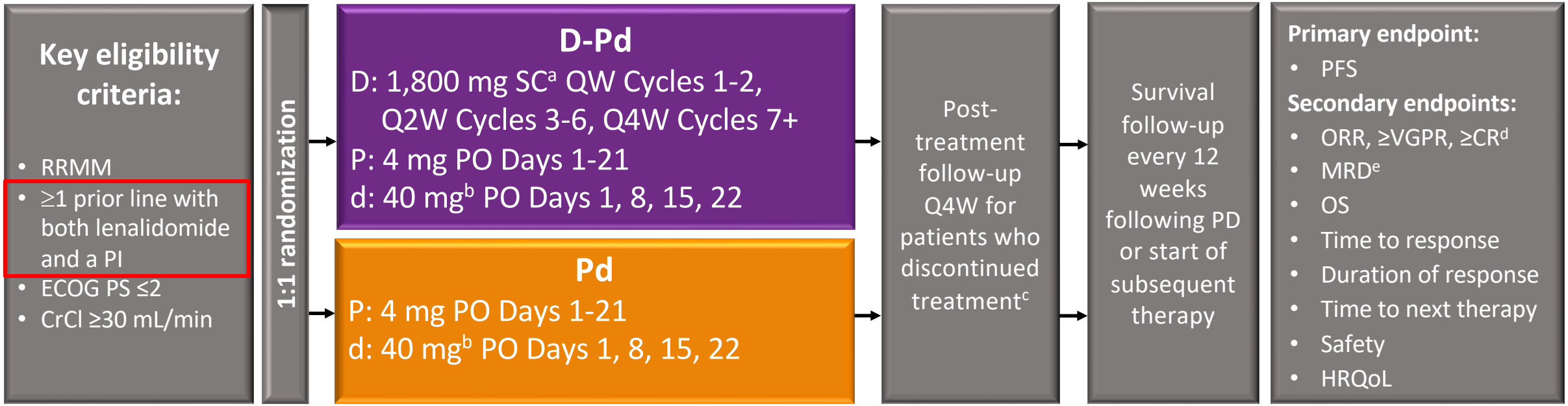
APOLLO Dara-Pd



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

@rfonsi1, fonseca.rafael@mayo.edu

Dimopoulos et al ASH 2020

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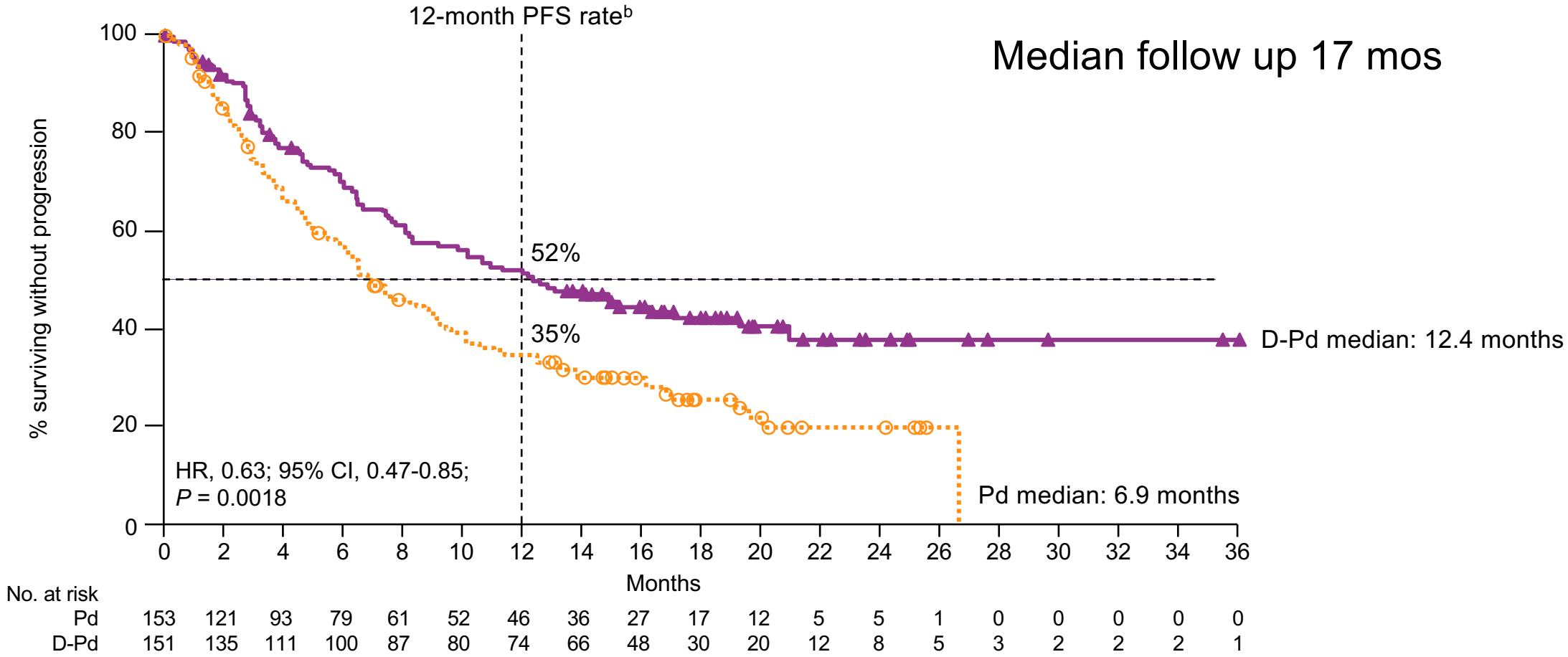
APOLLO Dara-Pd



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

@rfonsi1, fonseca.rafael@mayo.edu

Dimopoulos et al ASH 2020

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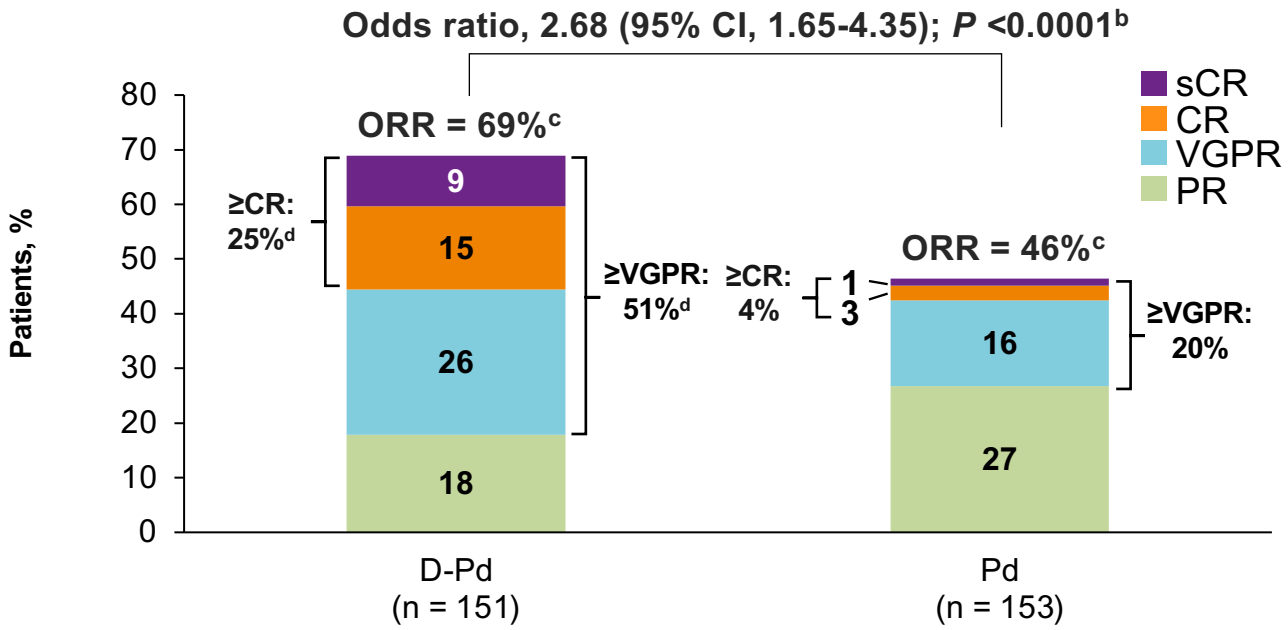
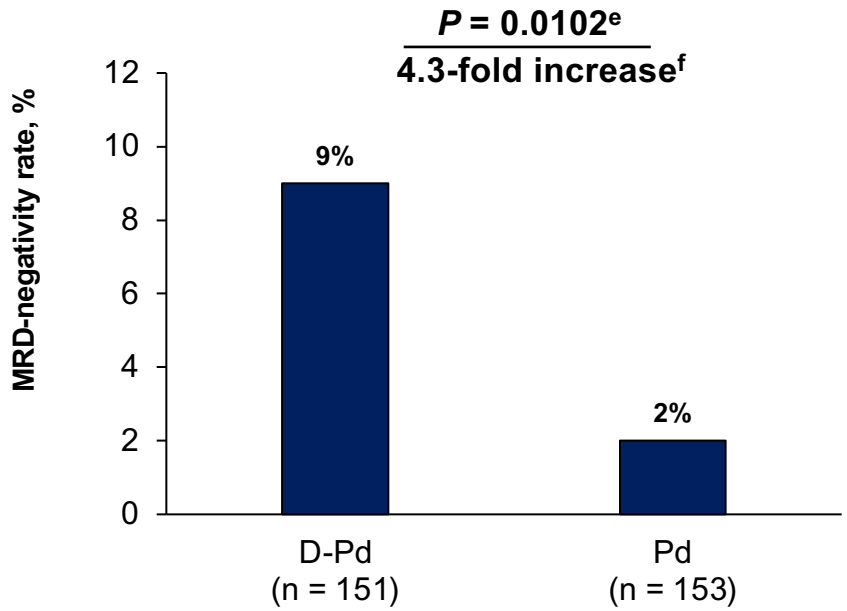
APOLLO Dara-Pd

Hematologic response



MRD negativity



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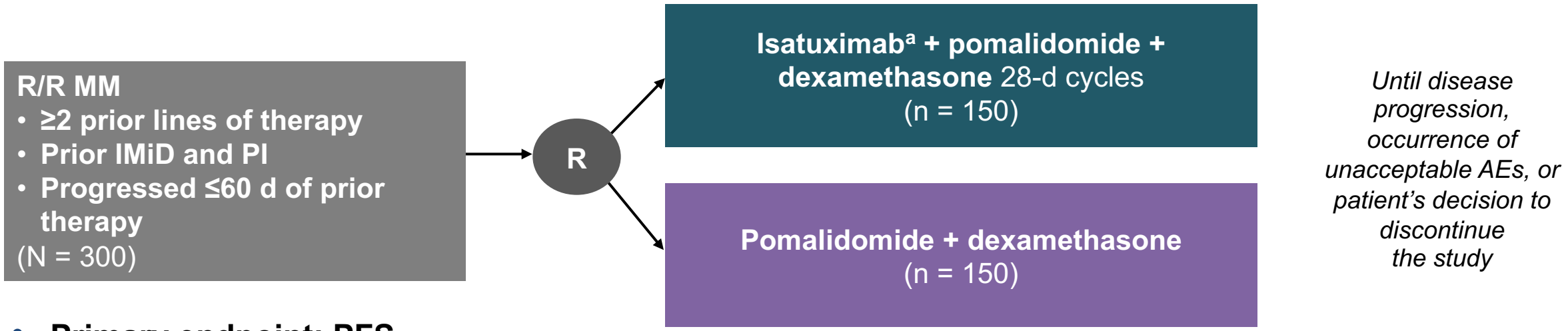
Dimopoulos et al ASH 2020

MAYO CLINIC

ICARIA: Isatuximab + Pd



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

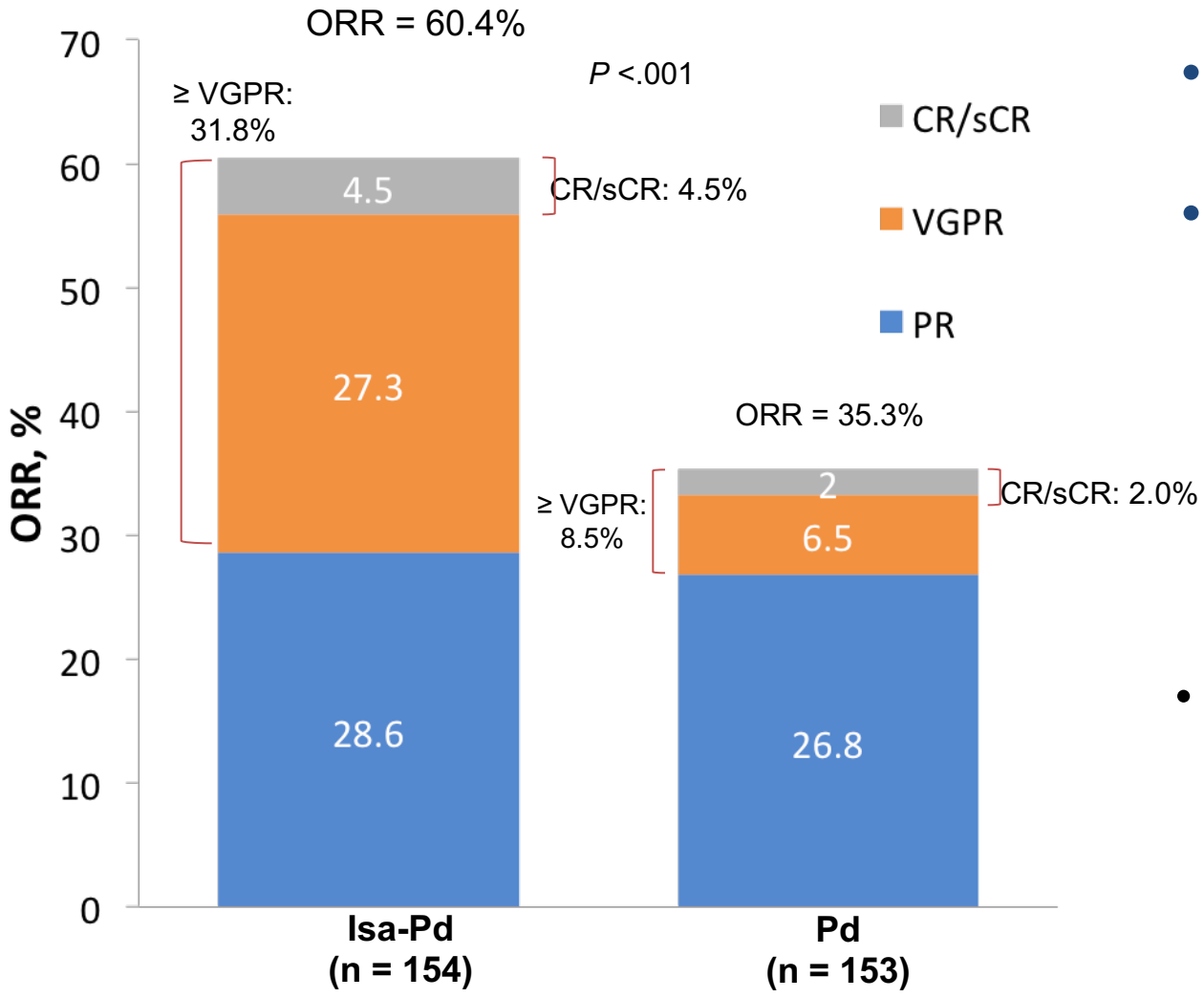
[a]Isatuximab 10 mg/kg IV on d 1, 8, 15, and 22 in the first cycle; d 1 and 15 in subsequent cycles. Pomalidomide 4 mg on d 1-21. Dexamethasone 40 mg for patients aged <75 y and 20 mg for patients aged ≥75 y on d 1, 8, 15, and 22.

1. Richardson PG, et al. ASCO 2019. Abstract 8004; 2. https://clinicaltrials.gov/ct2/show/NCT02990338. Accessed September 6, 2019.

@rfonsi1, fonseca.rafael@mayo.edu

MAYO CLINIC

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

@rfonsi1, fonseca.rafael@mayo.edu

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

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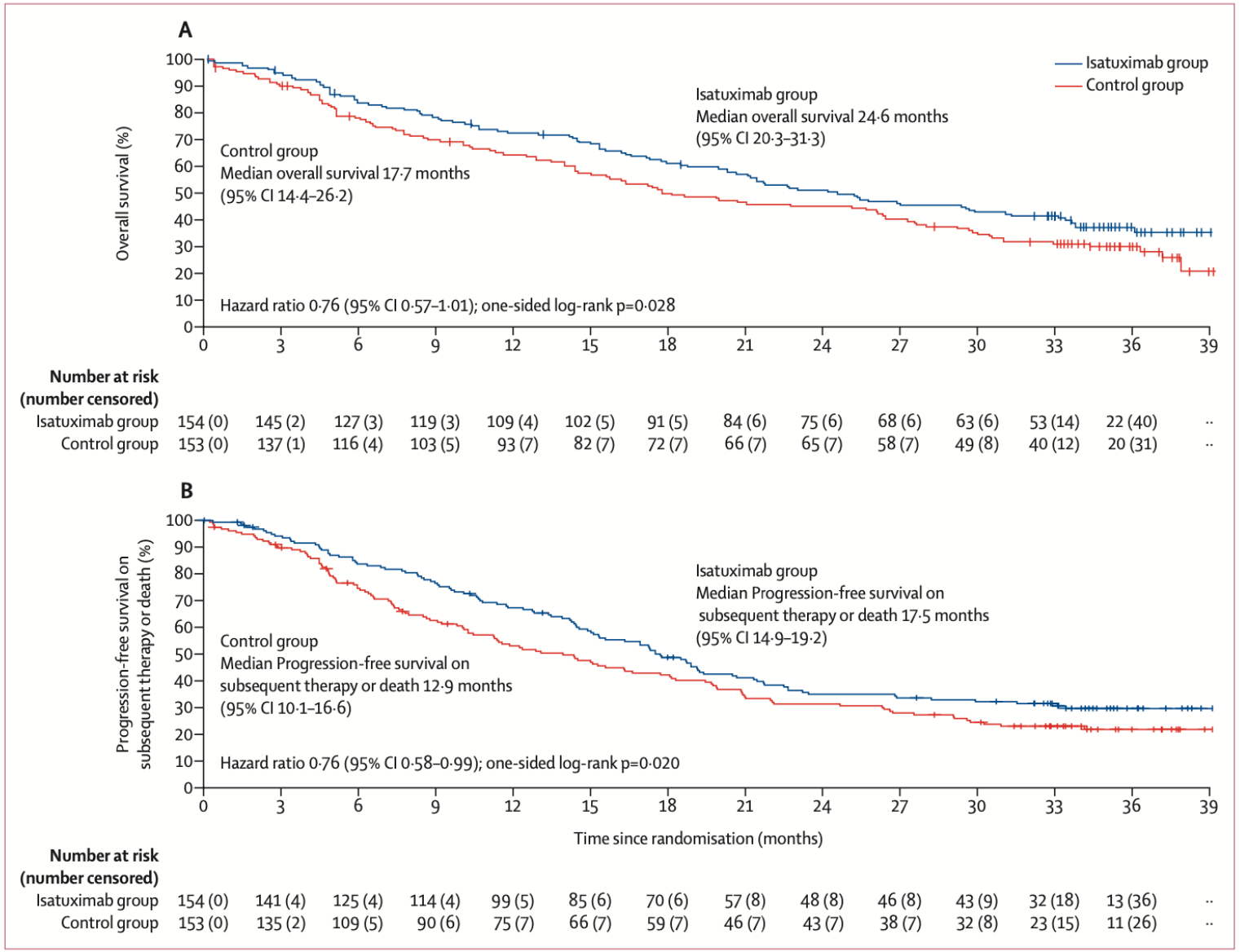
ICARIA-MM: OS

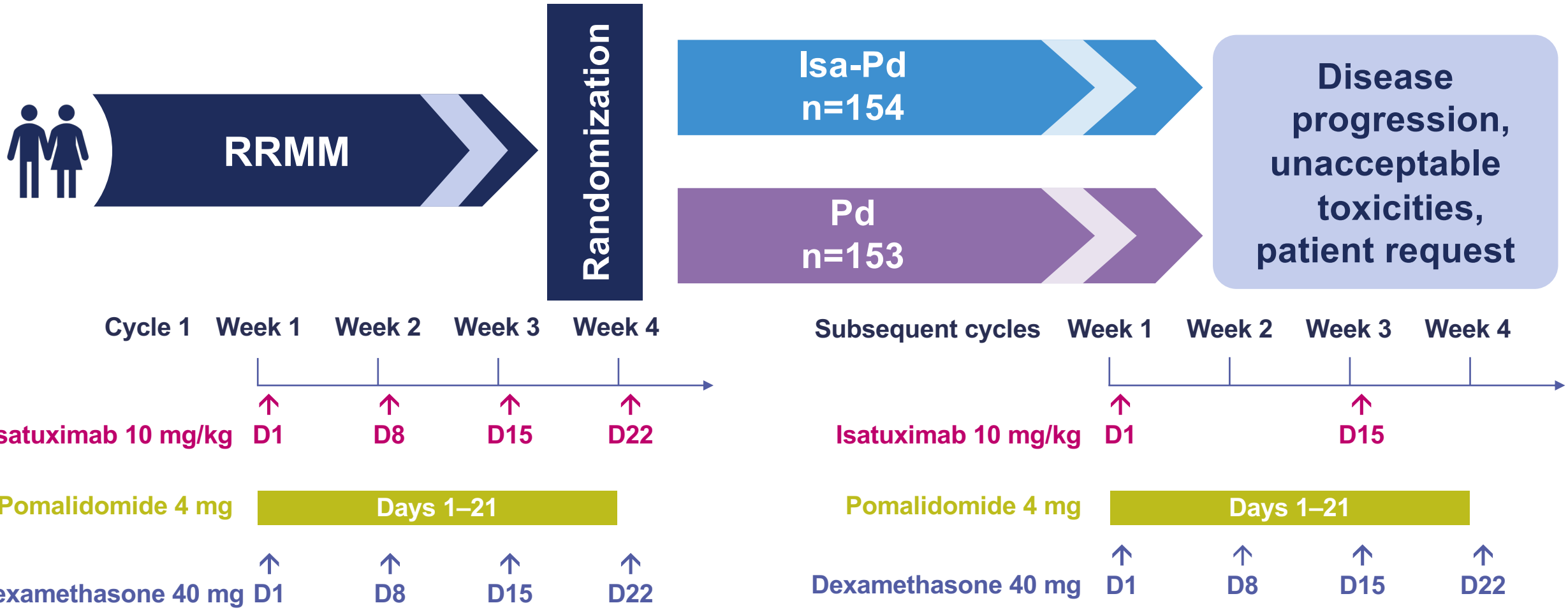


@rfonsi1, fonseca.rafael@mayo.edu

Richardson PG, et al. Lancet Oncology Feb 2022.

MAYO CLINIC

ICARIA-MM Study design



@rfonsi1, fonseca.rafael@mayo.edu

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ICARIA-MM Background and objectives

- **A prespecified updated overall analysis at 24 months after the primary analysis demonstrated:[1]**
  - **Median OS of 24.6 months (95% CI: 20.3–31.3) with Isa-Pd and 17.7 months (95% CI: 14.4–26.2) with Pd (HR 0.76; 95% CI: 0.57–1.01)**
- **This final OS analysis of ICARIA-MM was planned when 220 death events occurred. Efficacy was assessed in randomized patients. Safety was assessed in patients receiving ≥1 study dose**

@rfonsi1, fonseca.rafael@mayo.edu

Richardson PG, et al. Lancet Oncol. 2022;23:416–427.

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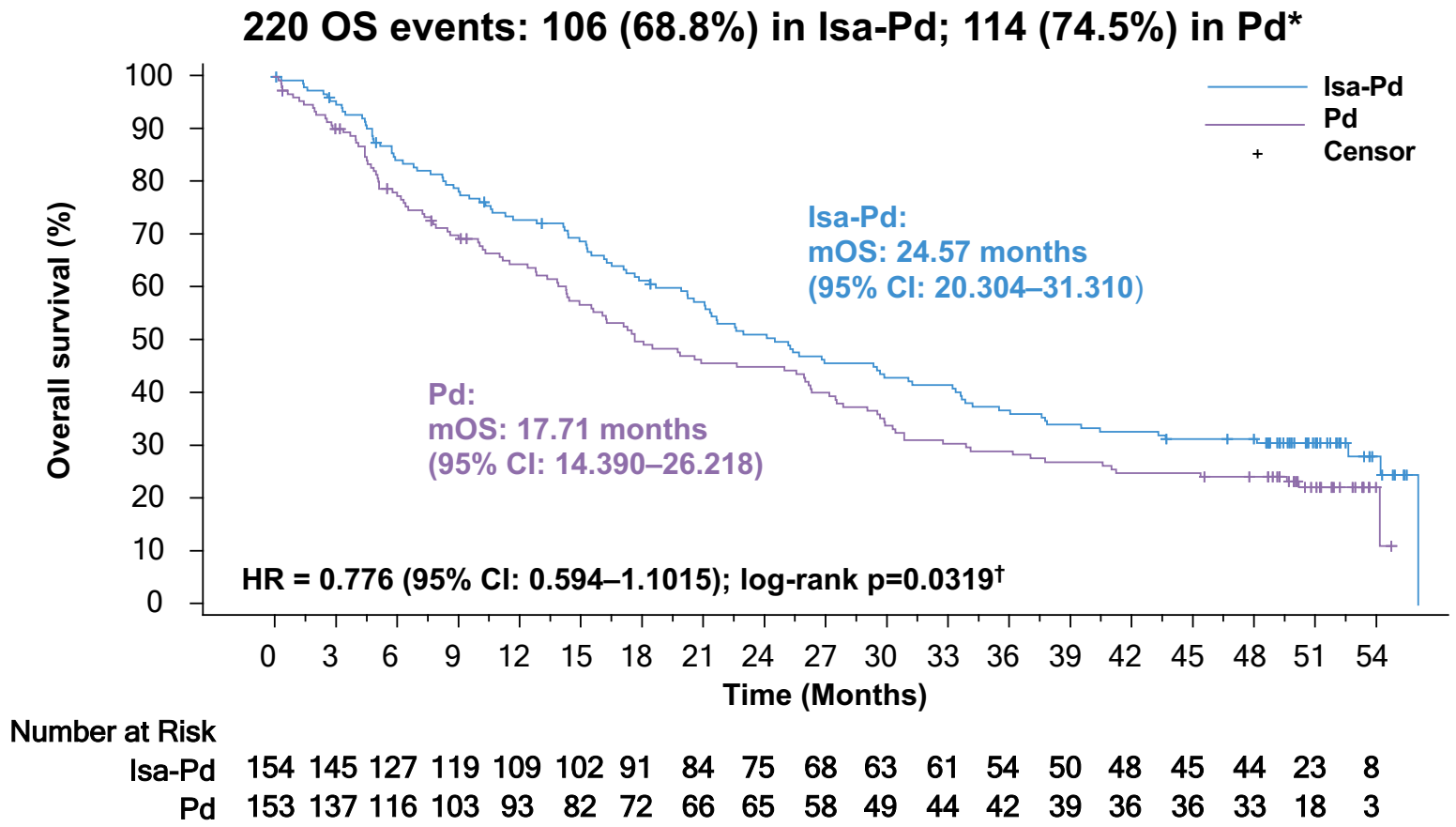
ICARIA-MM Final OS analysis



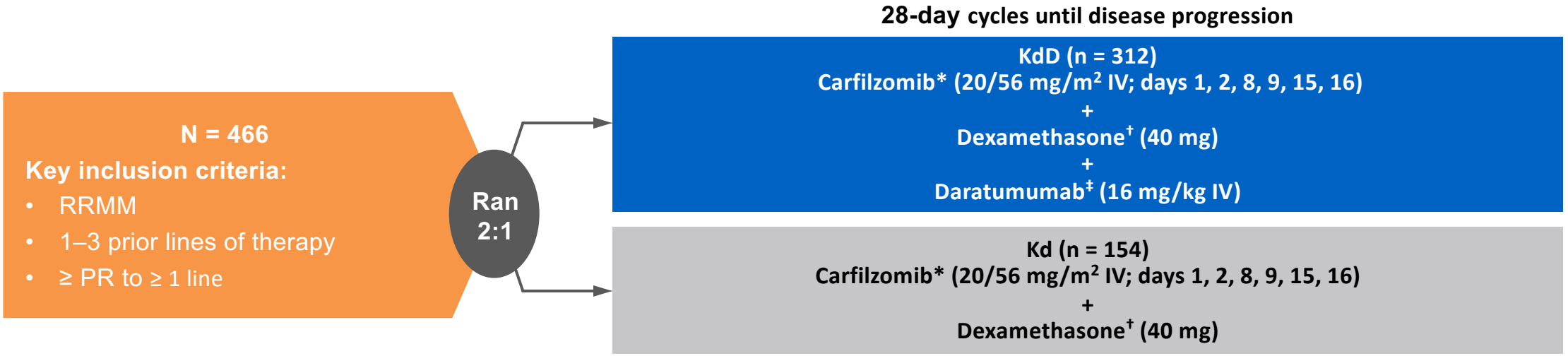
*Cutoff date: January 27, 2022.
†One-sided p-value, significance level is set to 0.02.
CI, confidence interval; HR, hazard ratio; Isa-Pd, isatuximab plus pomalidomide and dexamethasone; mOS, median overall survival; OS, overall survival; Pd, pomalidomide and dexamethasone.

@rfonsi1, fonseca.rafael@mayo.edu

MAYO CLINIC

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.

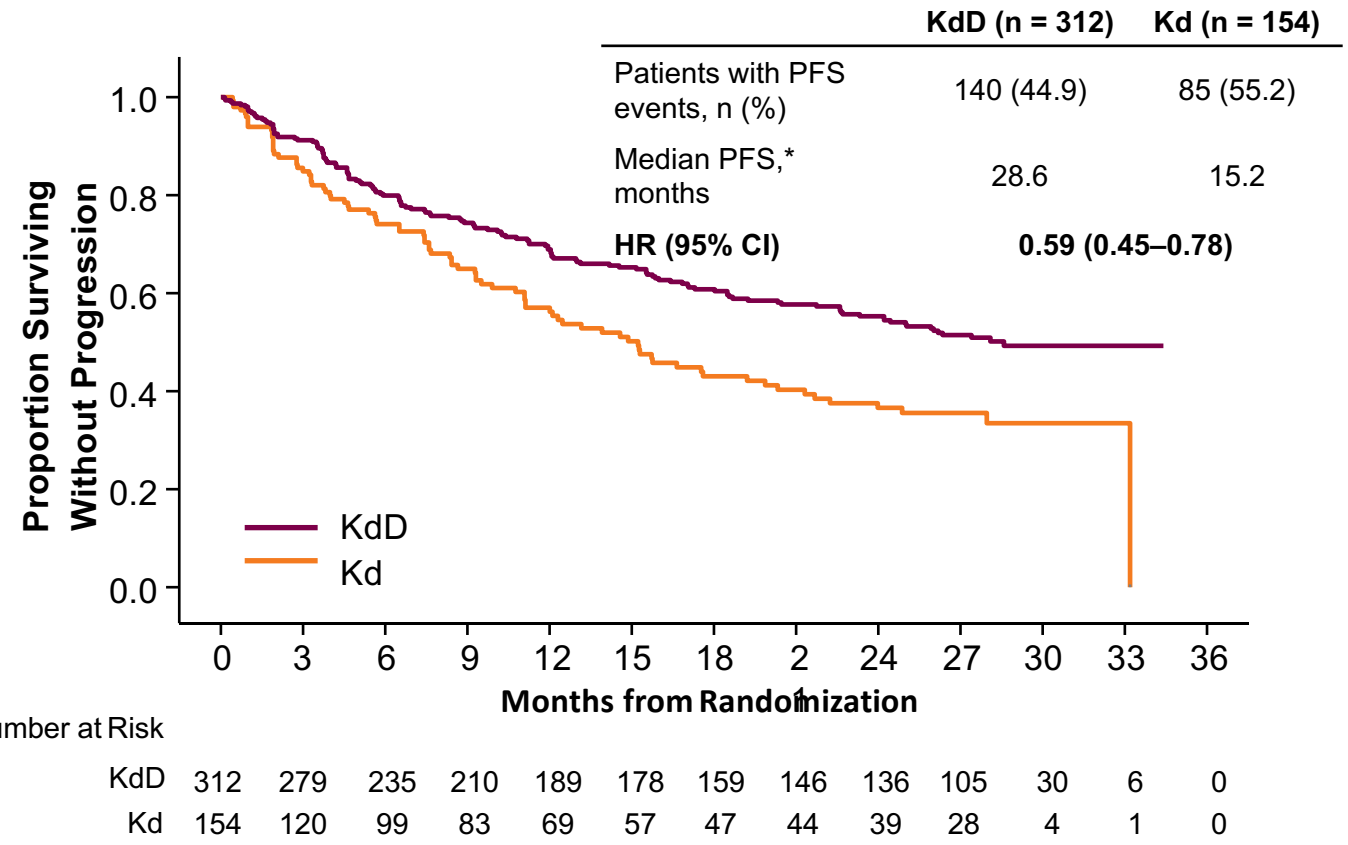
1. Dimopoulos M, et al. *Lancet*. 2020;396:186-97. 2. Dimopoulos M, et al. Presented at 62nd ASH Annual Meeting and Exposition; Dec 5–8, 2020; Virtual. Abstract 2325.

@rfonsi1, fonseca.rafael@mayo.edu

Lancet Oncology. 23(1):65-76, 2022 01

MAYO CLINIC

CANDOR (KdD vs Kd in RRMM)



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 M, et al. Presented at 62nd ASH Annual Meeting and Exposition; Dec 5–8, 2020; Virtual. Abstract 2325.

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Lancet Oncology. 23(1):65-76, 2022 01

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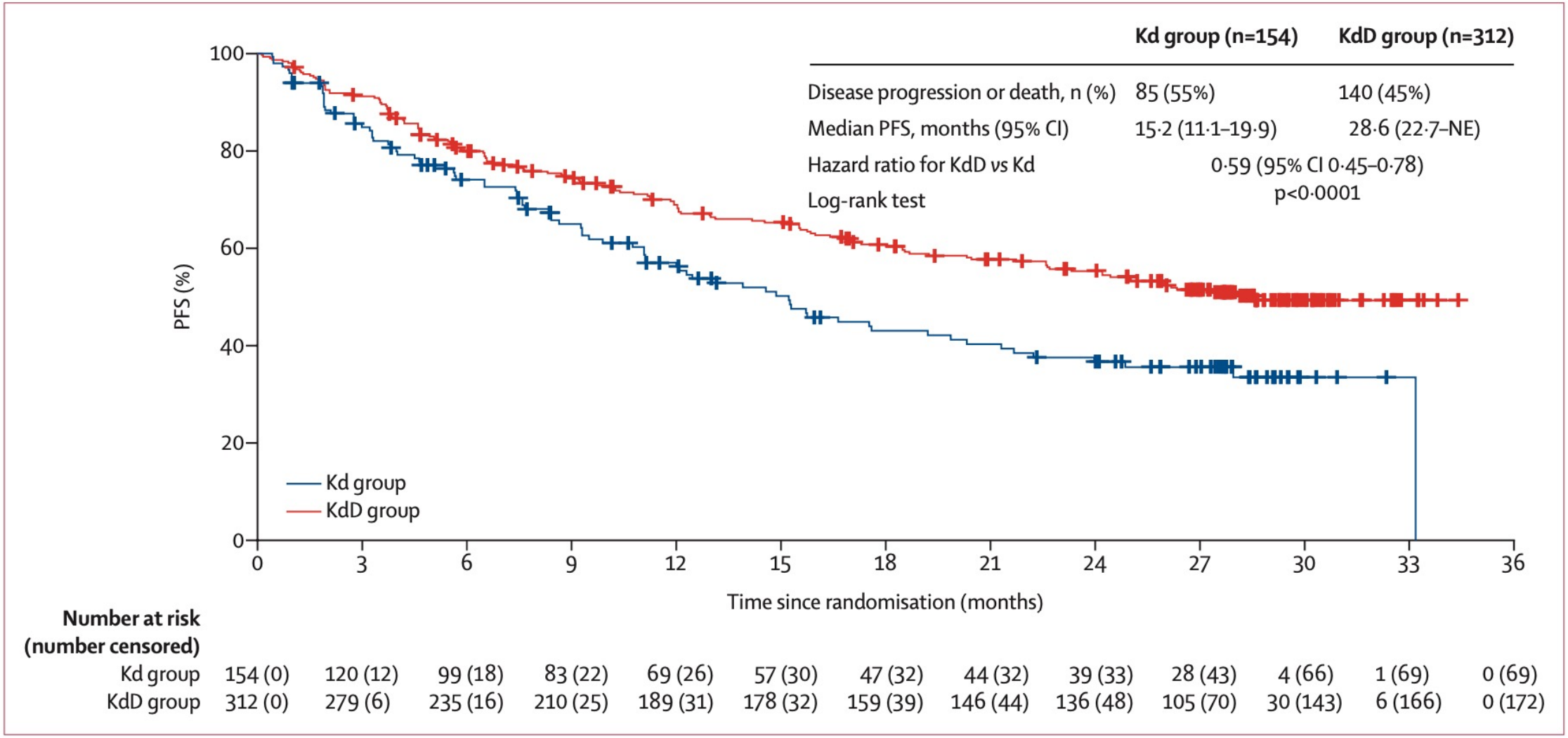
CANDOR (KdD vs Kd in RRMM)



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Lancet Oncology. 23(1):65-76, 2022 01

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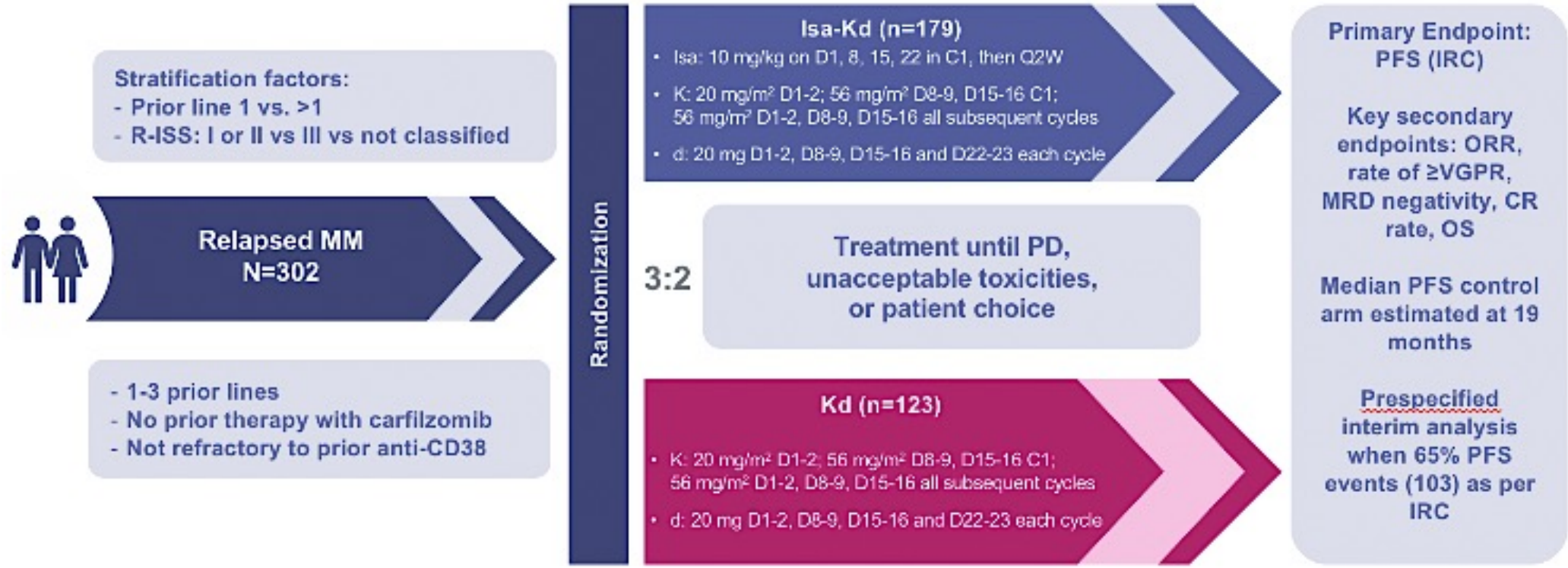
IKEMA



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 (%)

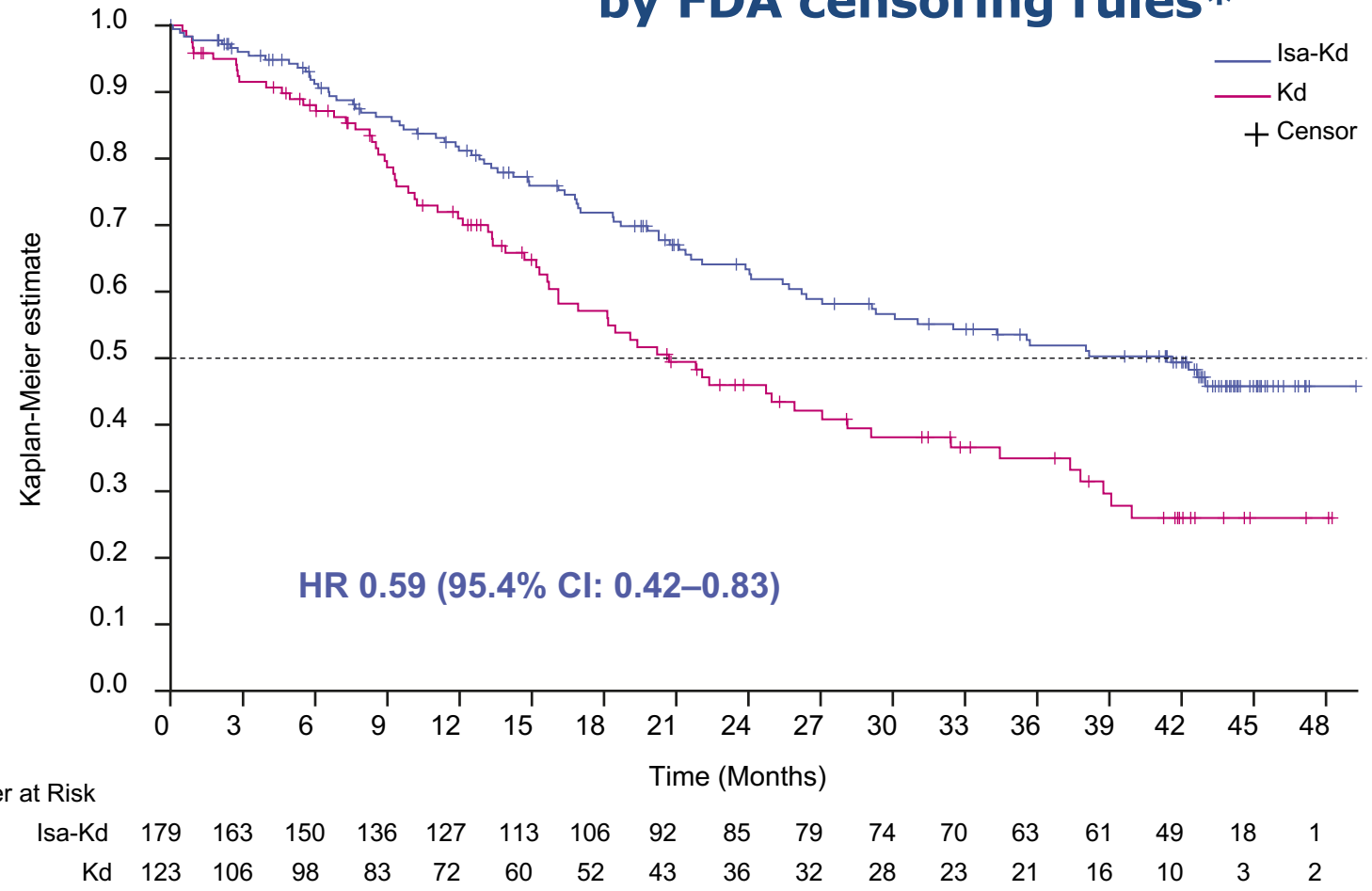
IMiD	78 (43.6)	58 (47.2)
Lenalidomide	57 (31.8)	42 (34.1)
PI	56 (31.3)	44 (35.8)

@rfonsi1, fonseca.rafael@mayo.edu

Moreau et al Lancet 2021 https://doi.org/10.1016/S0140-6736(21)00592-41

MAYO CLINIC

IKEMA Updated PFS – IRC assessment
by FDA censoring rules*



Isa-Kd
mPFS: 41.7 months
(95% CI: 27.1–NC)

Kd
mPFS: 20.8 months
(95% CI: 16.2–28.2)

PFS analysis by IRC using FDA censoring rules showed consistent results with the interim analysis

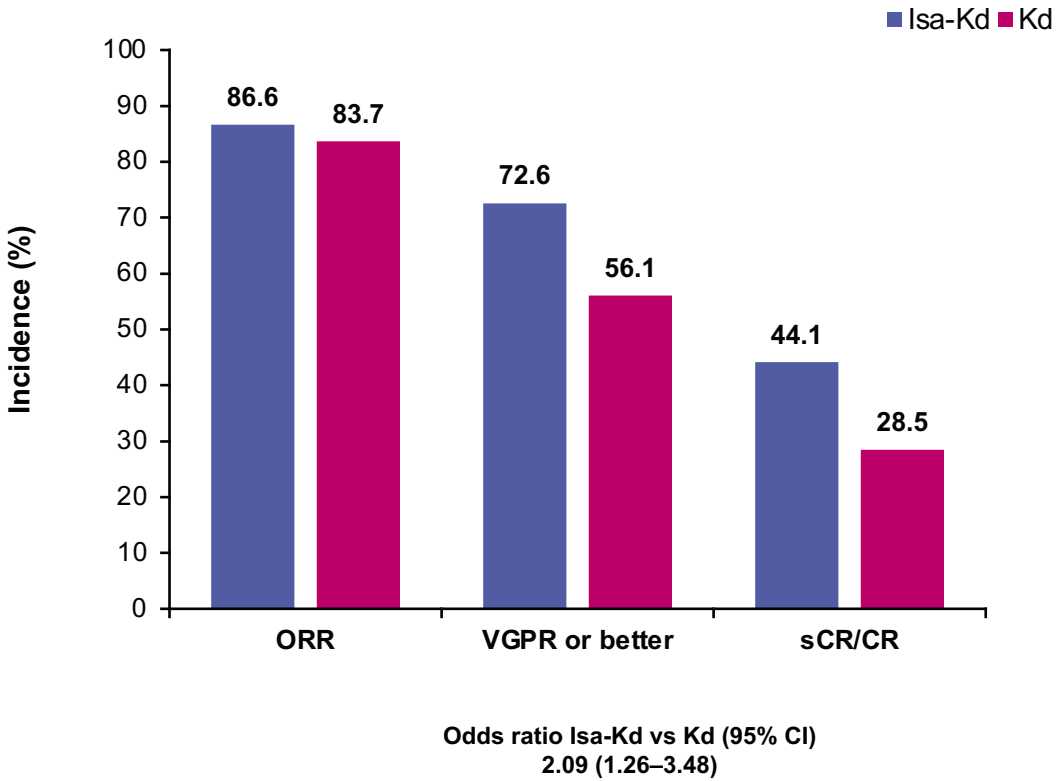
1. Moreau P, et al. COMy 2022

@rfonsi1, fonseca.rafael@mayo.edu

MAYO CLINIC

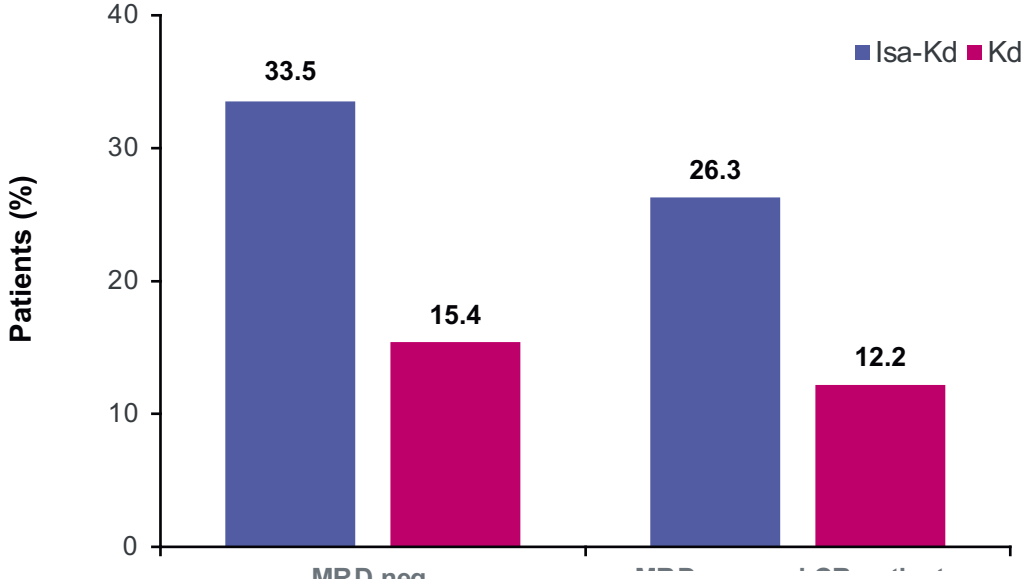
IKEMA Depth of response

Best overall response



Odds ratio Isa-Kd vs Kd (95% CI)
2.09 (1.26–3.48)

MRD neg rate (NGS 10^{-5})



Odds ratio Isa-Kd vs Kd (95% CI)
2.78 (1.55–4.99)

Odds ratio Isa-Kd vs Kd (95% CI)
2.57 (1.35–4.88)

MRD negativity rate with Isa-Kd in the ITT population was 33.5% (29.6% at IA)
MRD negativity and CR rate with Isa-Kd in the ITT population was 26.3% (20.1% at IA)

1. Moreau P, et al. COMy 2022

@rfonsi1, fonseca.rafael@mayo.edu

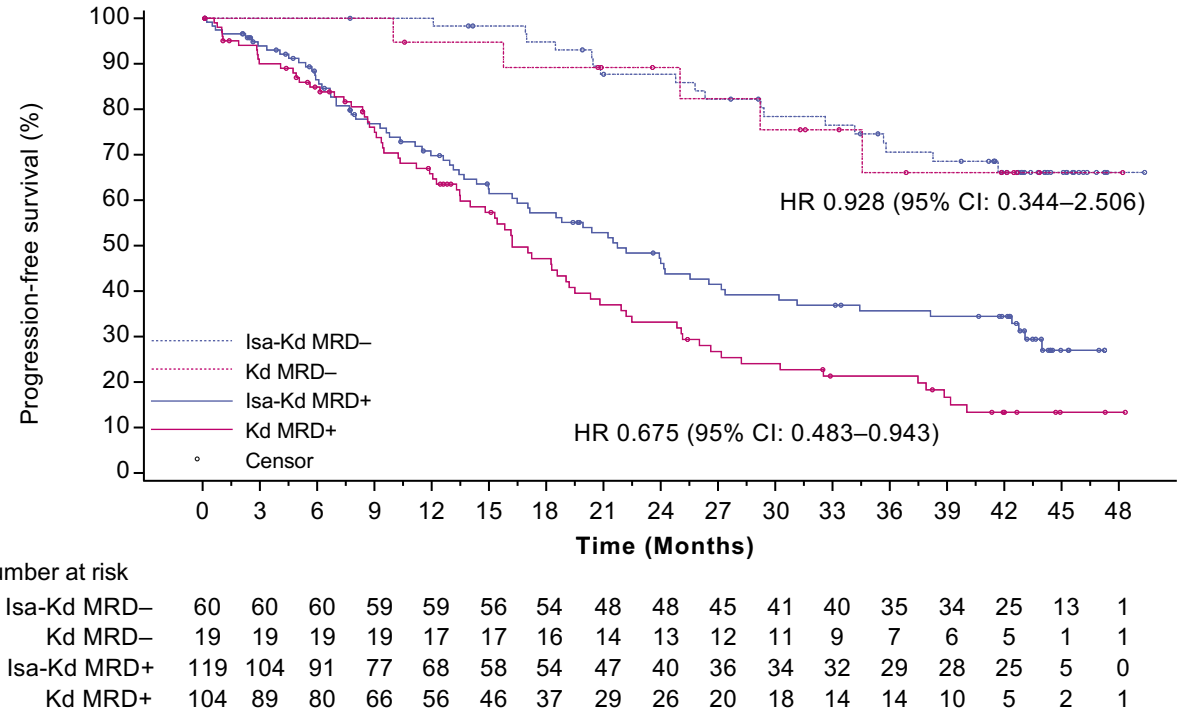
MAYO CLINIC

Patient disposition and progression-free survival by MRD status

Patient disposition by MRD status

ITT population, n (%)	MRD– (n=79)		MRD+ (n=223)	
	Isa-Kd (n=60)	Kd (n=19)	Isa-Kd (n=119)	Kd (n=104)
Randomized and treated	60 (100)	19 (100)	117 (98.3)	103 (99.0)
Patients still on treatment	29 (48.3)	6 (31.6)	20 (16.8)	5 (4.8)
Patients with definitive treatment discontinuation	31 (51.7)	13 (68.4)	97 (81.5)	98 (94.2)

PFS by MRD status*



Number at risk

Isa-Kd MRD–	60	60	60	59	59	56	54	48	48	45	41	40	35	34	25	13	1
Kd MRD–	19	19	19	19	17	17	16	14	13	12	11	9	7	6	5	1	1
Isa-Kd MRD+	119	104	91	77	68	58	54	47	40	36	34	32	29	28	25	5	0
Kd MRD+	104	89	80	66	56	46	37	29	26	20	18	14	14	10	5	2	1

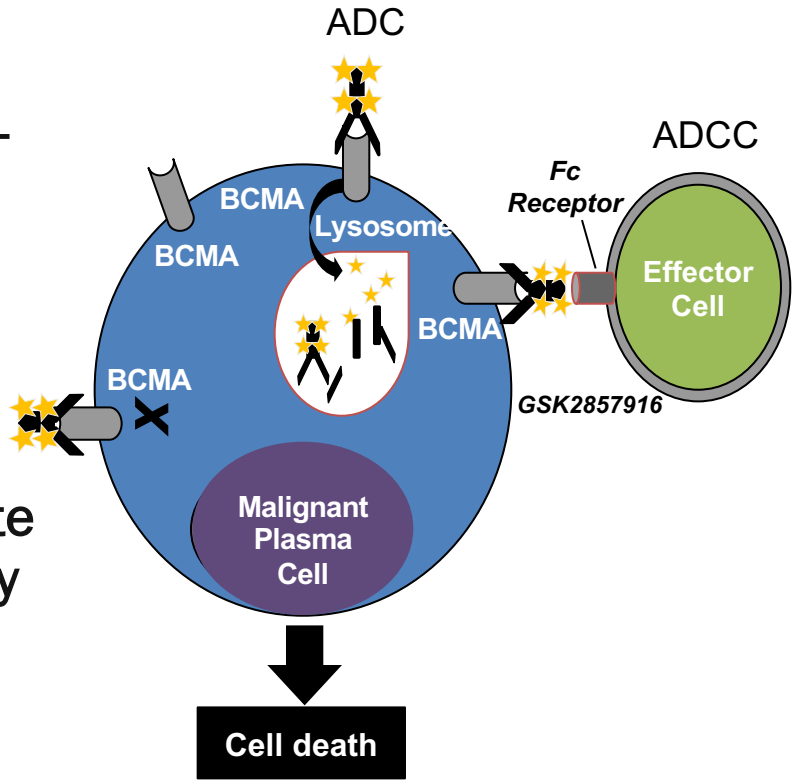
More patients in the Isa-Kd arm achieved MRD–. In both arms, more patients achieving MRD– remained on treatment.

@rfonsi1, fonseca.rafael@mayo.edu

MAYO CLINIC

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

@rfonsi1, fonseca.rafael@mayo.edu

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

Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study

Sagar Lonial, MD [1]; Hans C. Lee, MD[2]; Ashraf Badros, MD [3]; Suzanne Trudel, MD[4]; Ajay K. Nooka, MD [1]; Ajai Chari, MD [5]; Al-Ola Abdallah, MD[6]; Natalie Callander, MD[7]; Douglas Sborov, MD[8]; Attaya Suvannasankha, MD[9]; Katja Weisel, MD[10]; Peter M. Voorhees, MD[11]; Lynsey Womersley, MSc[12]; January Baron, MS[13]; Trisha Piontek, BSN[13]; Eric Lewis, MD[14]; Joanna Opalinska, MD[13]; Ira Gupta, MD[13]; and Adam D. Cohen, MD[15]

Cancer 2021;127(22):4198-212.

DREAMM-2: Single-Agent Belantamab Mafodotin Efficacy Outcomes

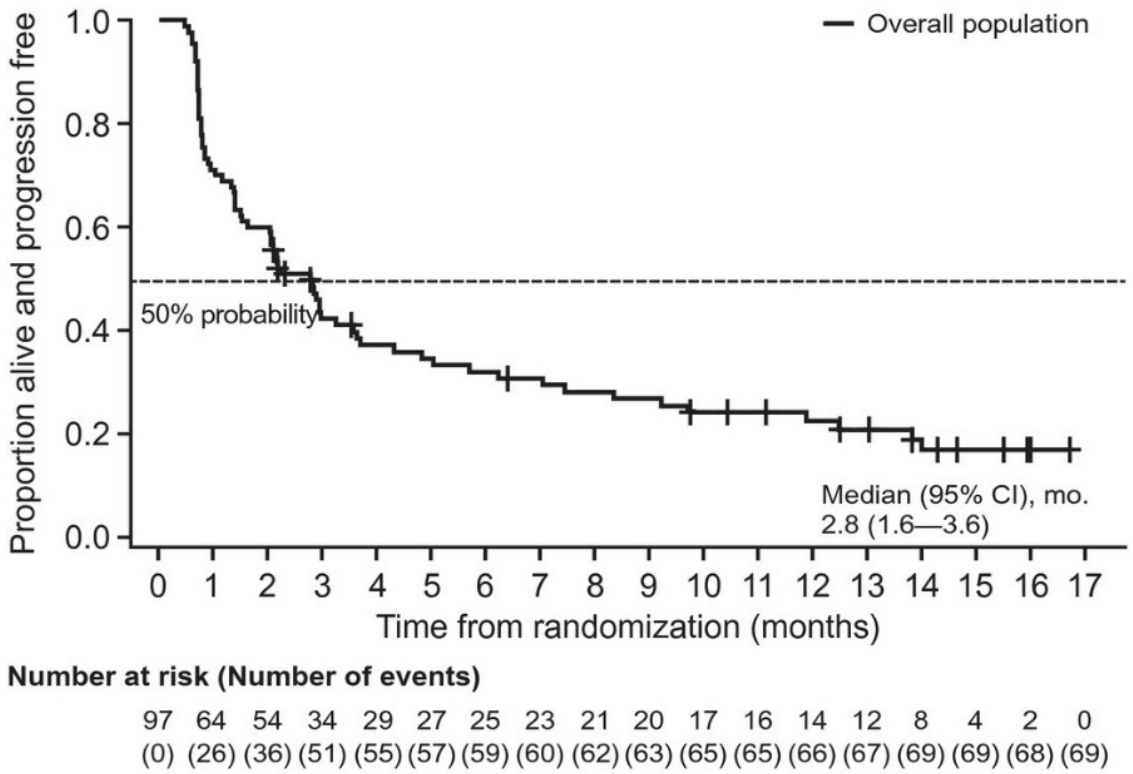
	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	32 (21.7-43.6)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.8 (1.6-3.6)	2.2 (1.2-3.6)
Probability of PFS at 6 months, % (95% CI estimates)	35 (20-50)	30 (17-43)

ORR = overall response rate; CI = confidence interval; DoR = duration of response; NR = not reached; PFS = progression-free survival

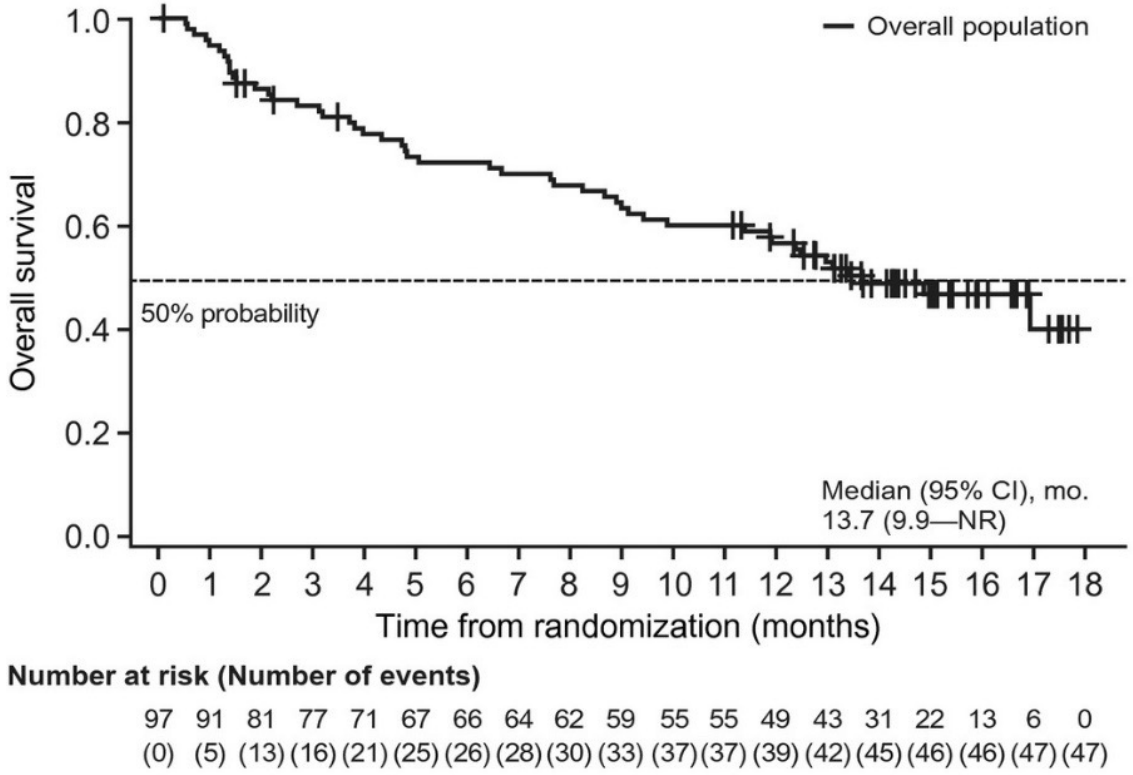
Lonial S et al. *Cancer* 2021;127(22):4198-212; ASH 2020;Abstract 1417.

DREAMM-2: Longitudinal Outcomes

Progression-Free Survival



Overall Survival (OS)

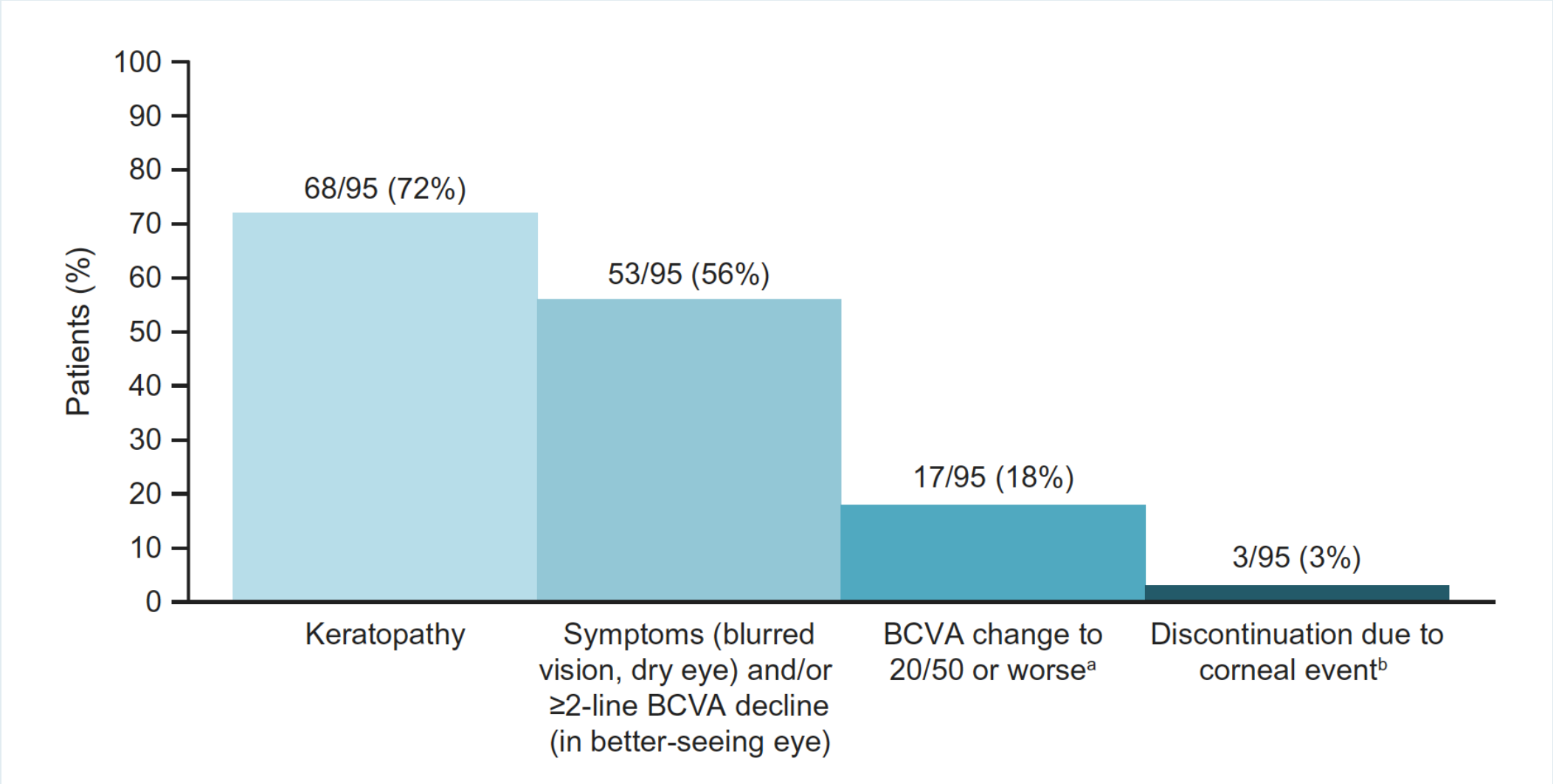


Expected median OS in triple-class refractory myeloma: 8.6 months

Lonial S et al. *Cancer* 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

DREAMM-2: Frequency of Corneal and Vision-Related Events



BCVA = best corrected visual acuity

Lonial S et al. *Cancer* 2021;127(22):4198-212.

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Update on Belantamab Mafodotin-blmf US Marketing Authorization

Press Release: November 22, 2022

"[The manufacturer] today announced it has initiated the process for withdrawal of the US marketing authorisation for belantamab mafodotin-blmf following the request of the US Food and Drug Administration (FDA). This request was based on the previously announced outcome of the DREAMM-3 phase III confirmatory trial, which did not meet the requirements of the FDA Accelerated Approval regulations. Belantamab mafodotin is a monotherapy treatment for adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

[The] Chief Medical Officer said, 'We respect the Agency's approach to the accelerated approval regulations and associated process. Multiple myeloma is a challenging disease, with poor outcomes for patients whose disease has become resistant to standard-of-care treatments. We will continue the DREAMM clinical trial programme and work with the US FDA on a path forward for this important treatment option for patients with multiple myeloma.'"

www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-blenrep-us-marketing-authorisation/

Summary of Select Clinical Trials of Belantamab Mafodotin (Belamaf) Combination Approaches for R/R Multiple Myeloma

Trial	Characteristics	ORR	Safety
DREAMM-6 (NCT03544281)	• Phase I/II • Arm A: belamaf + len/dex (n = 45) • Arm B: belamaf +bor/dex (n = 18)	• Arm A: highest ORR of 75% in the 1.9 mg/kg Q4W dose • Arm B: 78%	Arm A Grade ≥3 AEs: • Thrombocytopenia – 3 (7%) • Keratopathy – 15 (33%) Arm B Grade ≥3 AEs: • Thrombocytopenia – 12 (67%) • Keratopathy – 11 (61%)
DREAMM-4 (NCT03848845)	▪ Phase I/II (N = 34) ▪ Belamaf + pembrolizumab ▪ Dose escalation belamaf 2.5 mg/kg and 3.4 mg/kg	• 47% at RP2D of 2.5 mg/kg	All grades: • Thrombocytopenia – 12 (35%) • Keratopathy – 26 (76%)
ALGONQUIN (NCT03715478)	▪ Phase I/II (N = 56) ▪ Belamaf + pom/dex	• ≥PR/VGPR 89%/72% across all dosing cohorts	Grade ≥3 TEAEs: • Thrombocytopenia – 19 (34%) • Keratopathy – 39 (70%)

ORR = overall response rate; AEs = adverse events; PR = partial response; VGPR = very good partial response; TEAEs = treatment-emergent AEs

Popat R et al. ASH 2020;Abstract 1419; Quach H et al. ASCO 2022;Abstract 8017; Suvannasankha A et al. EHA 2022;Abstract P940; Trudel S et al. ASH 2021;Abstract 2736.

Ongoing Phase III Trials of Belantamab Mafodotin

Study	N	Setting	Treatment arms	Estimated primary completion
DREAMM-3 (NCT04162210)	380	• Relapsed/refractory multiple myeloma (RRMM) • ≥2 prior lines of treatment, including ≥2 consecutive cycles of both lenalidomide and a proteasome inhibitor (separately or in combination)	• Belantamab mafodotin • Pomalidomide/low-dose dexamethasone	June 2022
DREAMM-8 (NCT04484623)	450	• RRMM • ≥1 prior line of treatment, including a lenalidomide-containing regimen	• Belantamab mafodotin + Pomalidomide/dexamethasone • Bortezomib + Pomalidomide/dexamethasone	March 2023
DREAMM-7 (NCT04246047)	575	• RRMM • ≥1 prior line of treatment	• Belantamab mafodotin + Bortezomib/dexamethasone • Daratumumab + Bortezomib/dexamethasone	April 2023

www.clinicaltrials.gov. Accessed August 2022.

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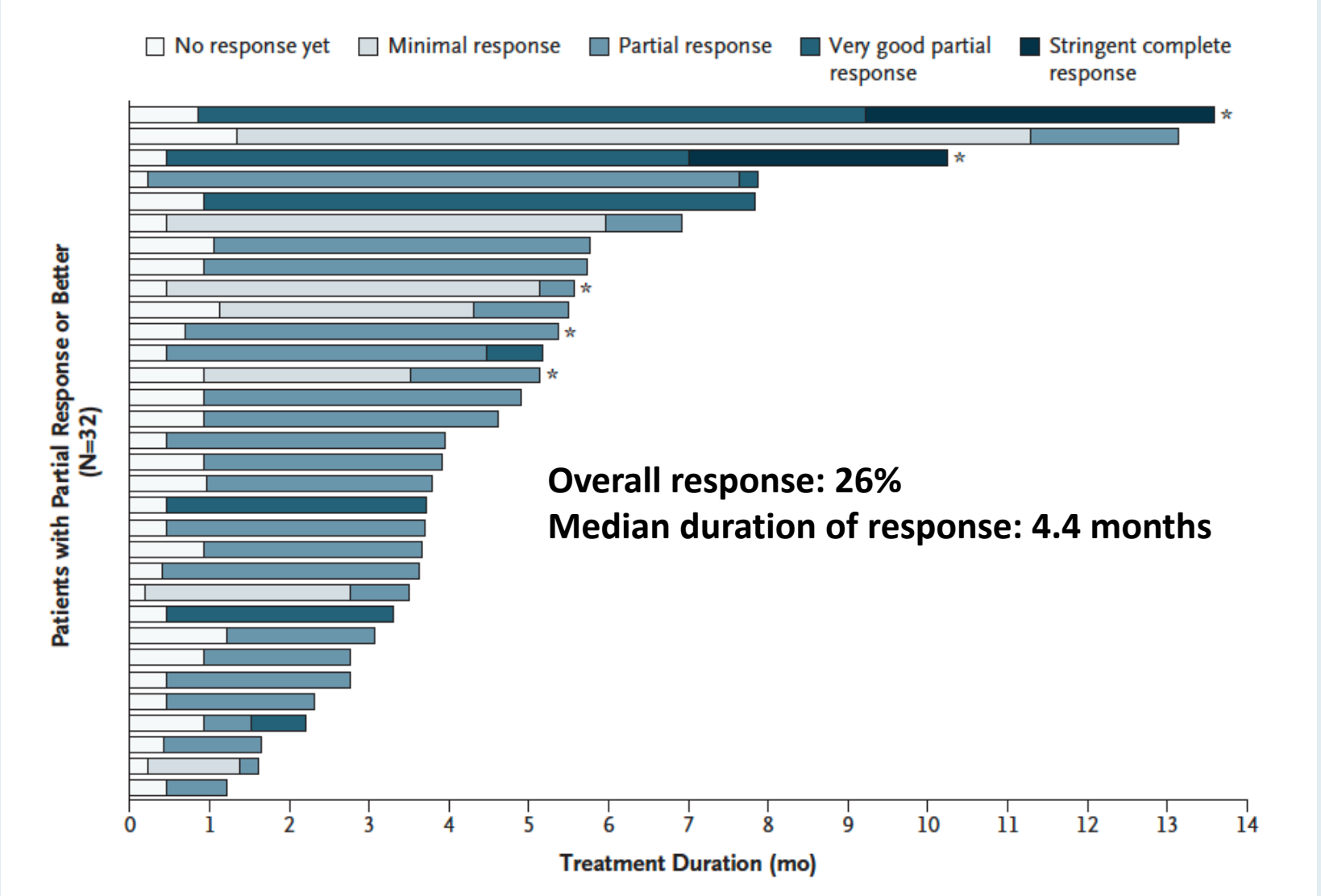
STORM: Overall Response and Duration of Response



Chari A et al. *N Engl J Med* 2019;381:727-38.

MAYO CLINIC

BOSTON Trial: Phase 3 – Vd vs SVd

Randomization 1:1

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

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

@rfonsi1, fonseca.rafael@mayo.edu

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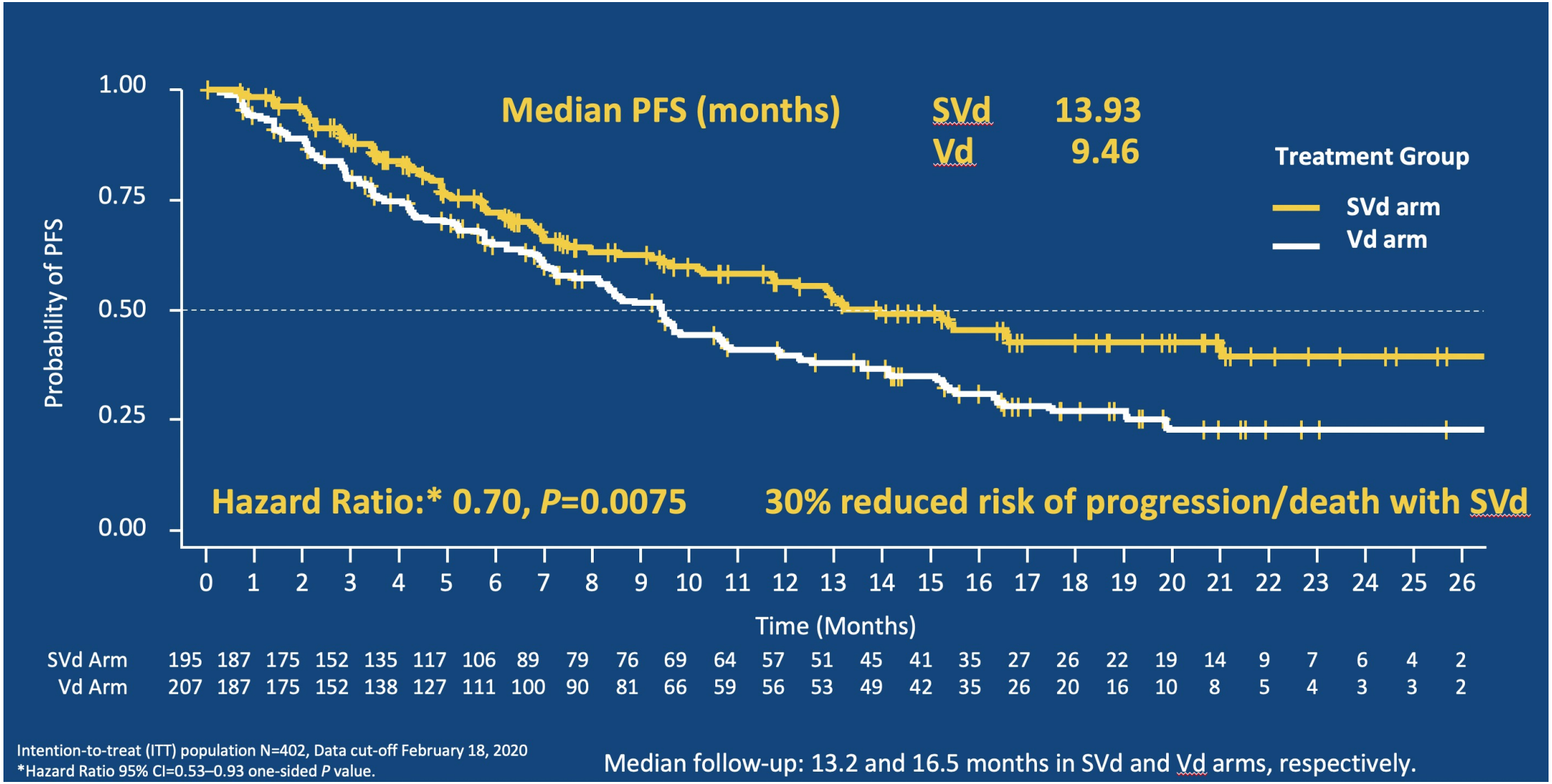
BOSTON Trial: PFS



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.

@rfonsi1, fonseca.rafael@mayo.edu

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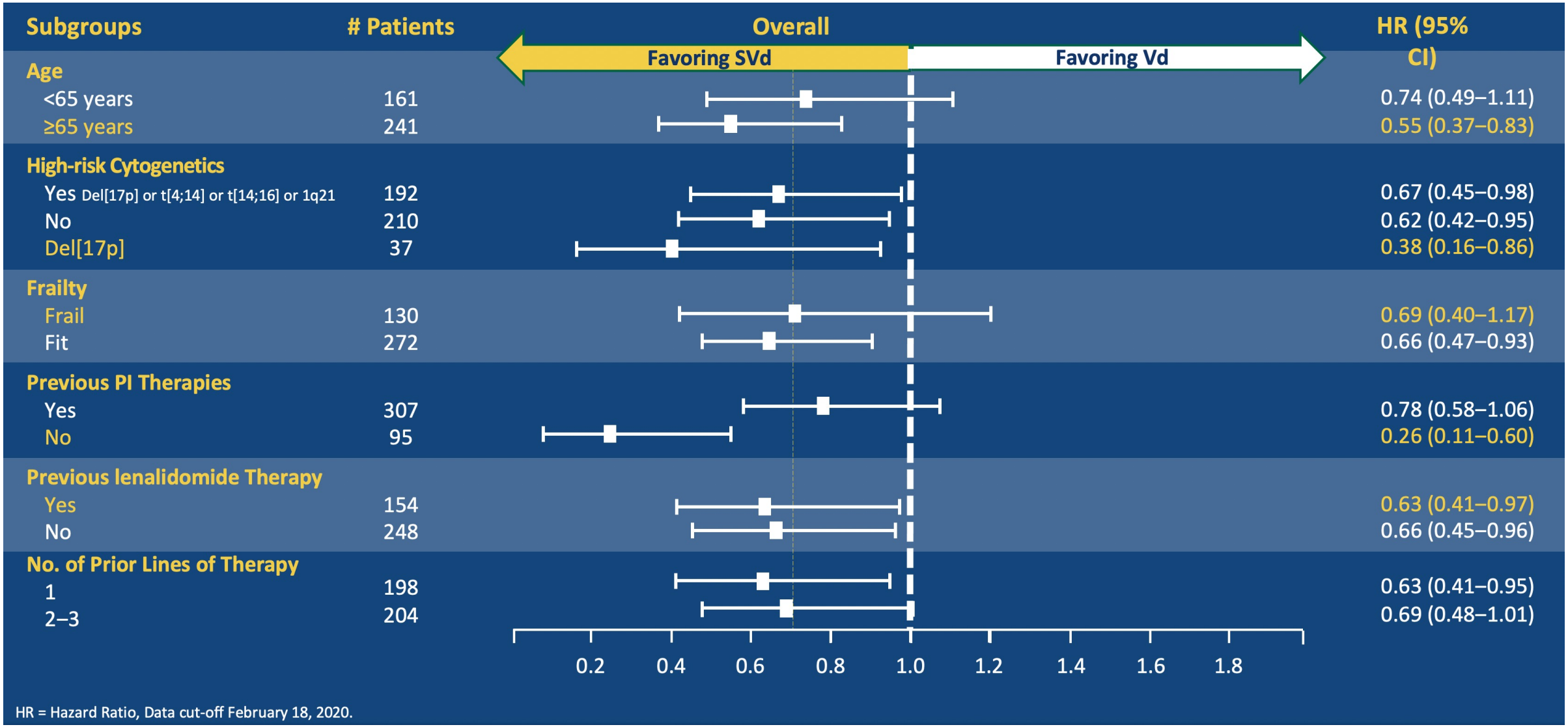
BOSTON Trial: Forest Plot



HR = Hazard Ratio, Data cut-off February 18, 2020.

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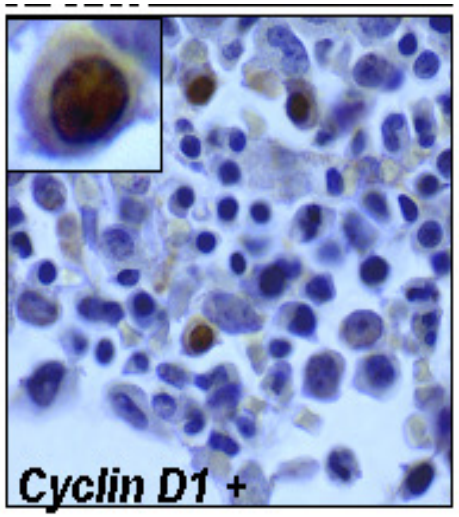
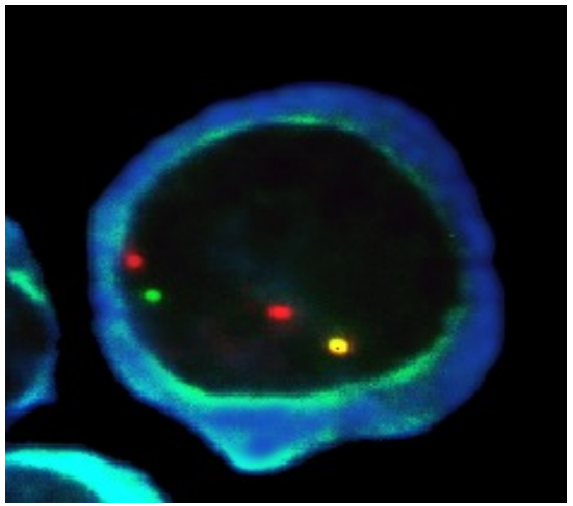
Meletios A. Dimopoulos ASCO 2020

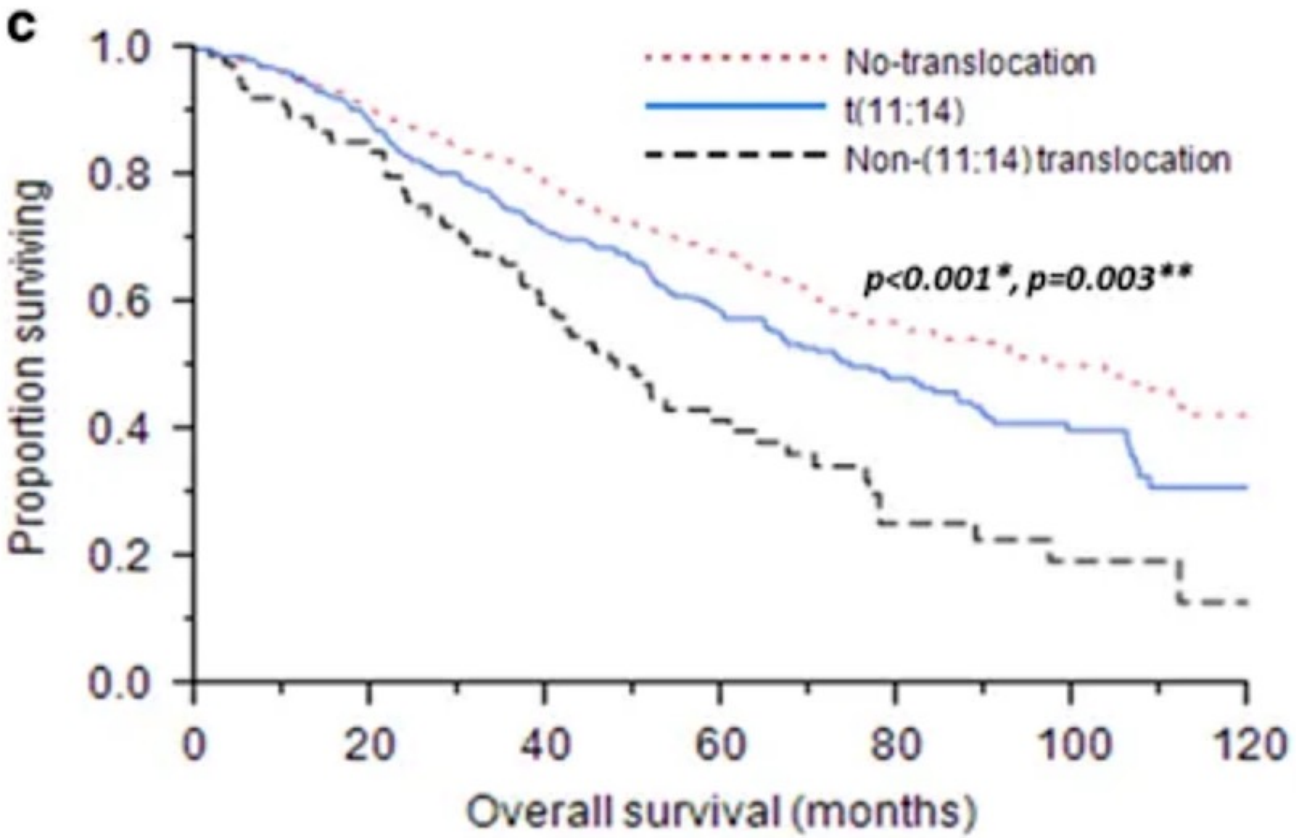
MAYO CLINIC

t(11;14) Myeloma is not a risk category





- 15% of all MM
- 50% pPCL
- 50% light chain amyloidosis
- Common in IgM MM
- Diploid



Fonseca et al Blood 2002
Lakshaman et al Leukemia 32,131 (2018)
Hayman at al Blood 20011
Tiedeman et al Leukemia 2008

@rfonsi1, fonseca.rafael@mayo.edu

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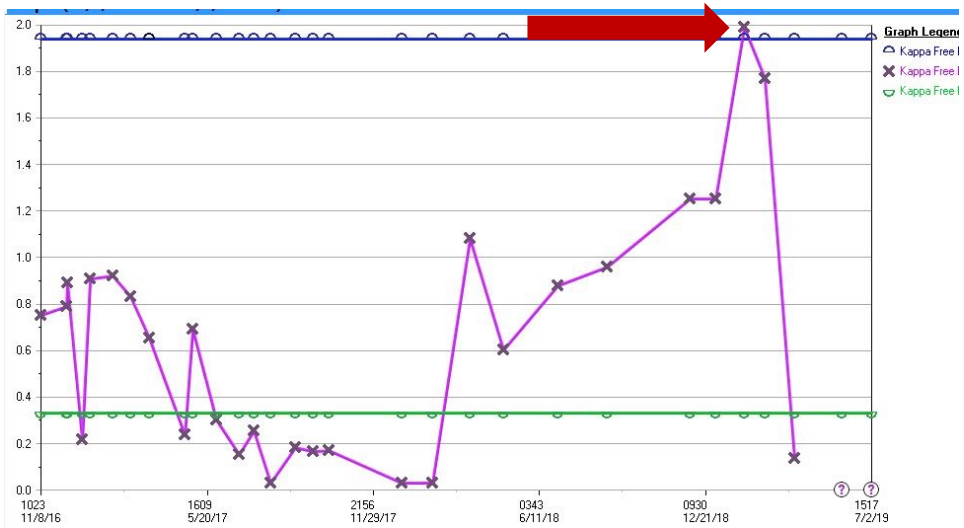
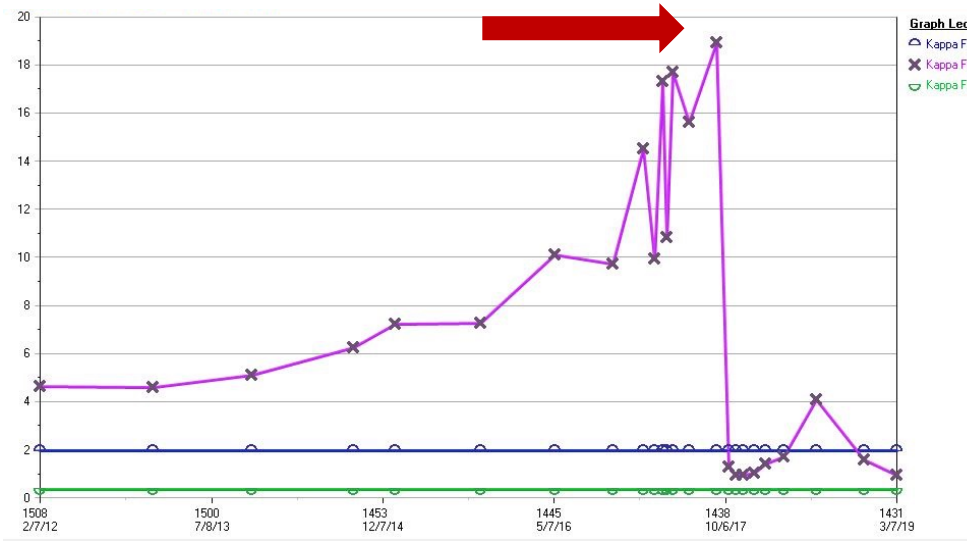
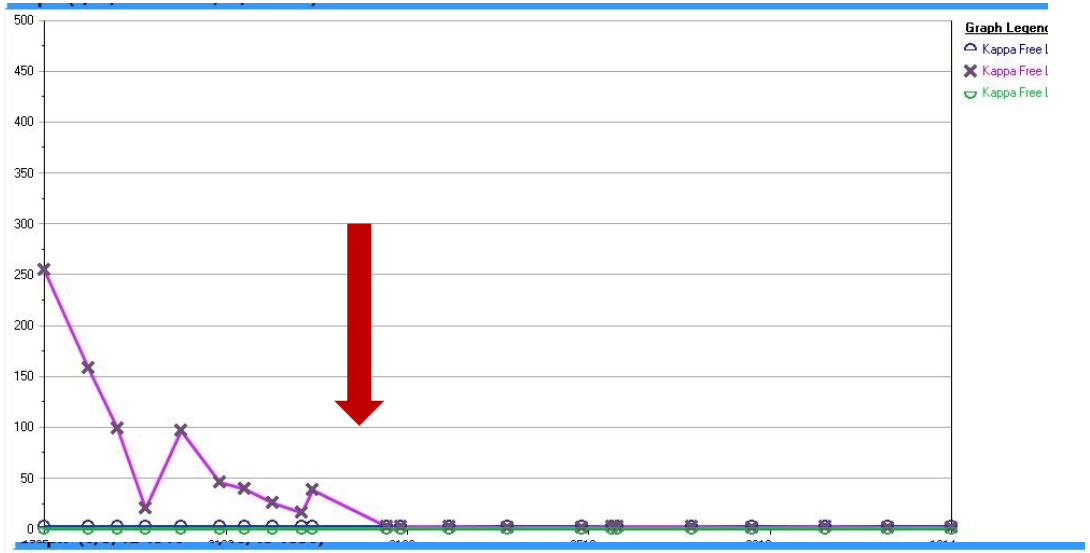
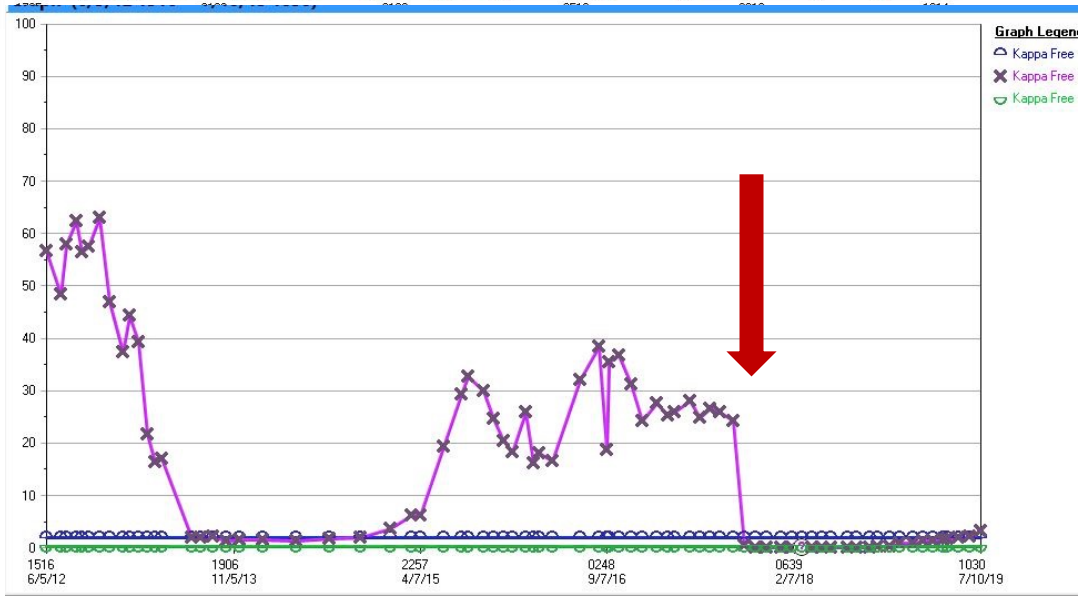
Venetoclax









@rfonsi1, fonseca.rafael@mayo.edu

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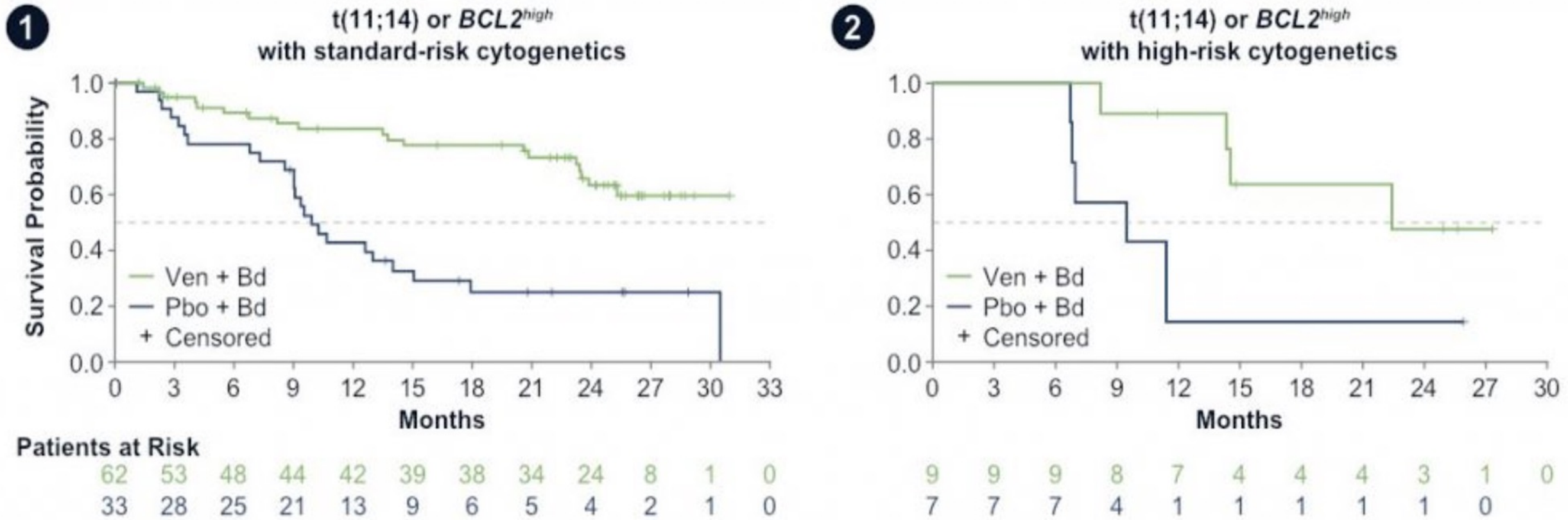
Venetoclax-Bd highly active in t(11;14) or high BCL-2

Figure 4. Investigator-Assessed PFS by *BCL2* Gene Expression and Cytogenetic Risk Status



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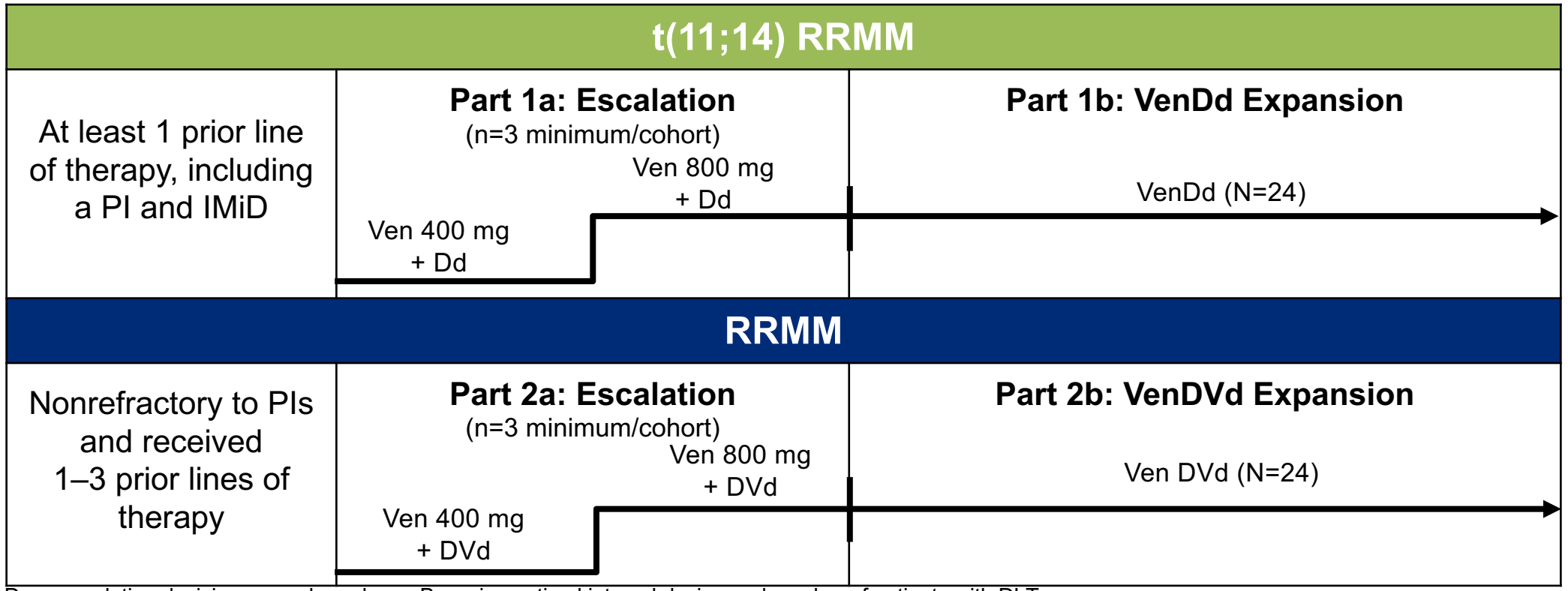
Study Design and Objectives



Dose escalation decisions were based on a Bayesian optimal interval design and number of patients with DLT.

Primary objectives

- Safety, tolerability, and preliminary efficacy (ORR) of VenDd and VenDVd regimens

Secondary objectives

- Safety profiles of VenDd and VenDVd in the expansion phases
- PFS, DOR, TTP, and MRD

@rfonsi1, fonseca.rafael@mayo.edu

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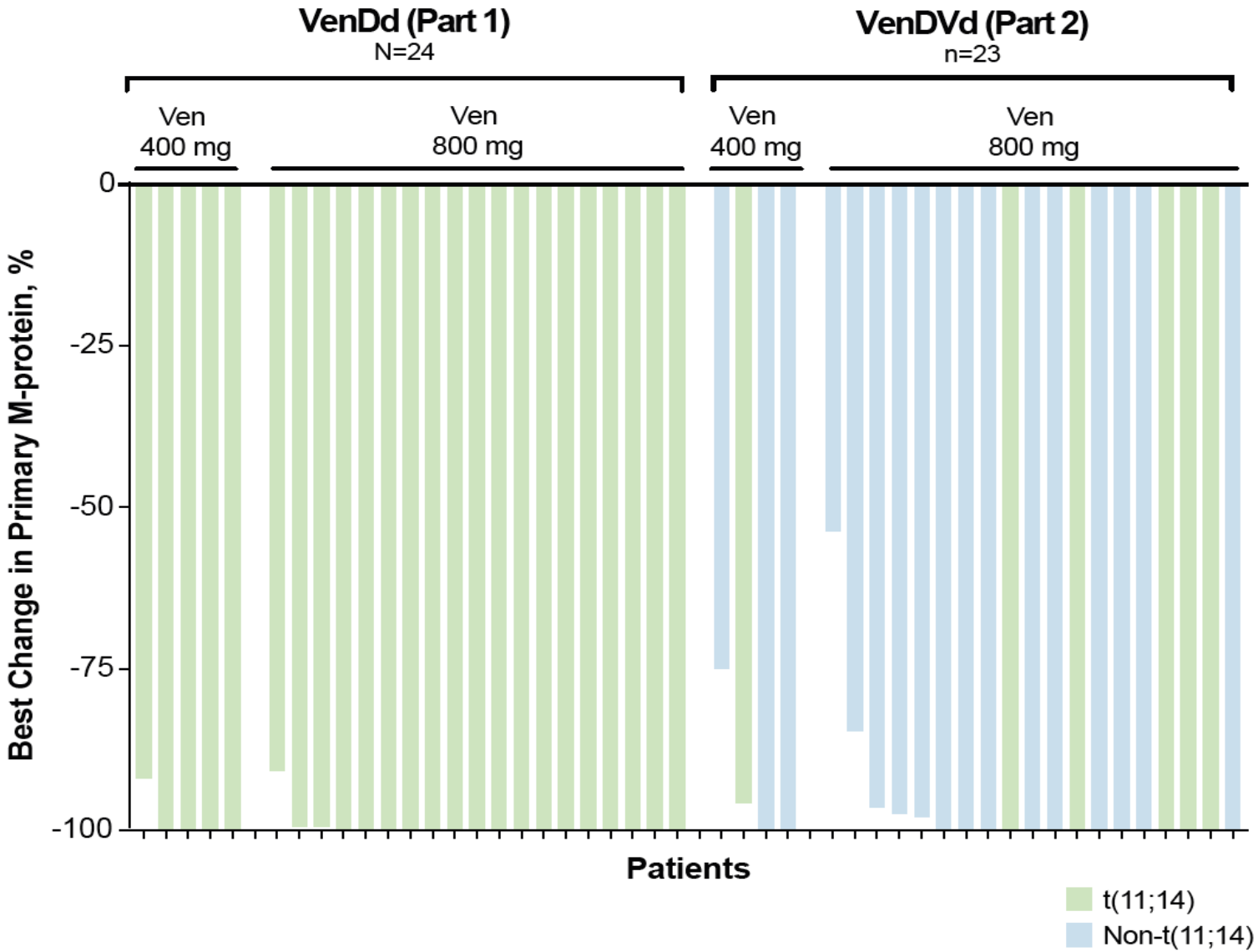
Best M-Protein Response



@rfonsi1, fonseca.rafael@mayo.edu

Discussion Question

Most myeloma investigators utilize selinexor for relapsed/ refractory MM and most often use the "BOSTON" approach of weekly selinexor and bortezomib when giving this agent.

- Agree
- Disagree
- I'm not sure

RTP RESEARCH TO PRACTICE

Module 3: Current Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Case Presentation: 71-year-old man with NDMM who receives induction daratumumab/RVd

Dr Spencer Bachow (Boca Raton, Florida)

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Dr Tina Bhatnagar
(Wheeling, West Virginia)

Case Presentation: 63-year-old woman with relapsed MM and pathologic fractures, s/p induction daratumumab/Rd and palliative RT for bone disease

Dr Kimberly Ku
(Bloomington, Illinois)

Case Presentation: 76-year-old woman with refractory MM 6 months after induction daratumumab/RVd lite

Date	Time point	Total Protein	B2M	M-spike	IgG	FLC ratio	Ca	SCr	Hgb	Plt	WBC
12/30/2021	Diagnosis/pre-treatment	8.2	3.31	1.6	2462	24.5	10.4	0.9	11.9	292	7
3/14/2021	Post cycle 1 DRd	6.8	4.91	0.9 and 0.1	1323	35.9	9.4	0.8	10.3	234	3.3
6/7/2021	Post cycle 4 DRd	6.9	3.98	0.8	1318	34.5	9.9	0.76	12.1	353	4.3
7/15/2022	Post cycle 5 DRd	5.8	--	0.7	1268	22.02	8.5	0.58	10.6	221	3.5
8/12/2022	Mid cycle 6 DRd	5.9	--	0.7	1313	20.51	8.6	0.61	11.3	208	3.3
10/6/2022	Post cycle 8 DRd	5.5	--	1.3	1347	45.37	8.3	0.74	9.1	206	2.9
11/3/2022	Post cycle 9	6.5	--	1.5	1534	55.53	8.9	0.76	10.5	254	4.3

Current Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM

Noopur Raje, MD

Center for Multiple Myeloma
MGH Cancer Center

Professor of Medicine
Harvard Medical School

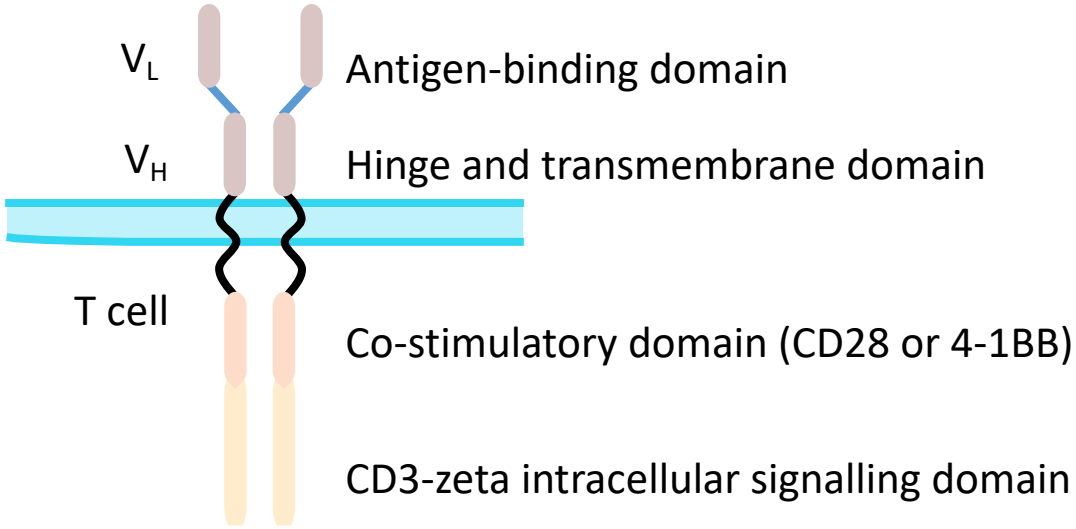
MASSACHUSETTS GENERAL HOSPITAL

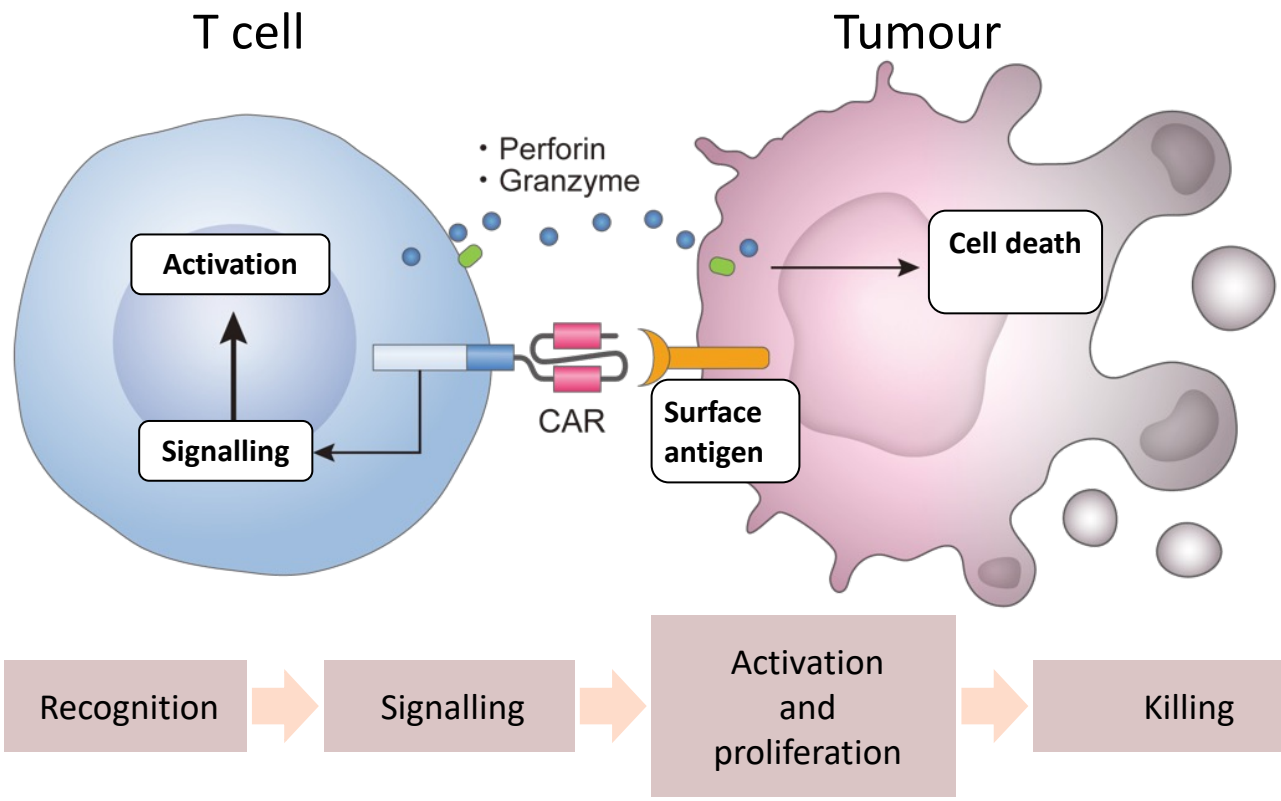
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Current Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Structural makeup and manufacturing of available BCMA-directed CAR T-cell platforms
Results from the Phase II KarMMa trial evaluating idecabtagene vicleucel (ide-cel) for R/R MM
Key data from the CARTITUDE-1 trial of ciltacabtagene autoleucel (cilta-cel) for pretreated MM
Available and emerging data with ide-cel and cilta-cel in earlier lines of treatment
Spectrum, incidence and severity of toxicities with BCMA-targeted CAR T-cell therapies
Early data with non-BCMA CAR T-cell platforms (eg, BMS-986393)

CAR T cell therapy: mechanism of action



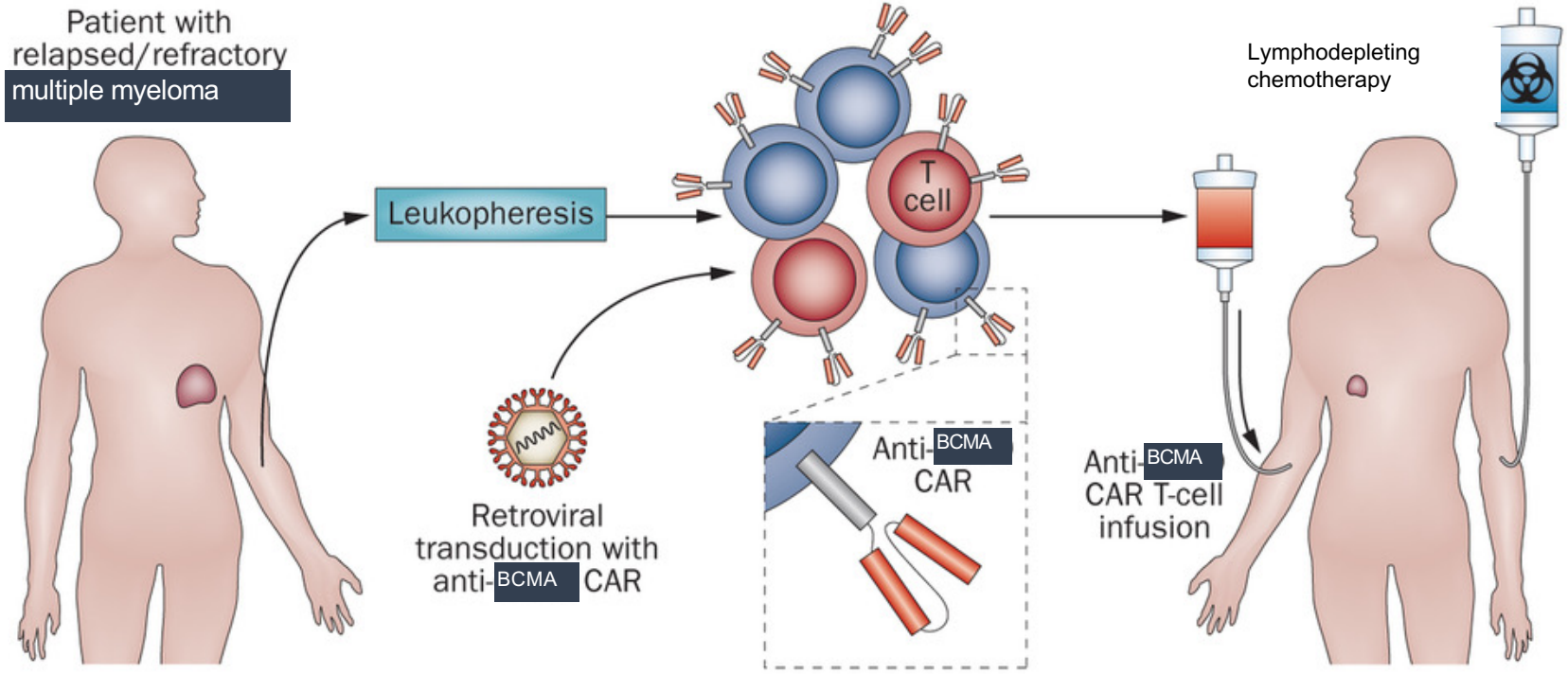


- Confer the high-affinity antigen specificity of an antibody to an autologous cytotoxic T cell
- Living drug, single infusion
- No need for immune suppression
- No risk of graft-versus-host disease

CAR, chimeric antigen receptor; V_H, variable heavy chain; V_L, variable light chain.

Abramson JS. Transfus Med Rev. 2020;34:29-33.
Images adapted from Shinshu University. Available from: www.shinshu-u.ac.jp/english/topics/research/shinshu_university_a_1.html.

CAR T-cell Therapy



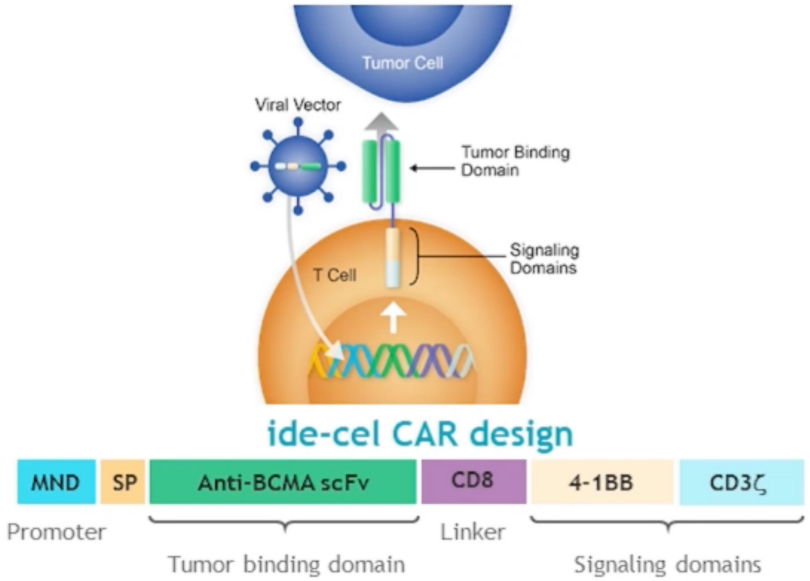
Klebanoff et al., *Nature Rev. Clin. Oncol* 2014

In ALL and lymphoma, patient's T-cells are collected and engineered to target CD19

In myeloma, CAR T-cells target myeloma-specific antigens, e.g. BCMA

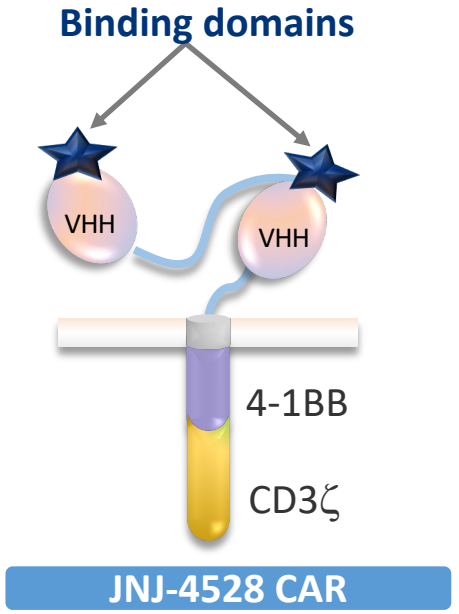
Idecabtagene-Vicleucel (ide-cel): Approved March 2021

- Autologous CAR T-cell
- Anti-BCMA scFv
- 4-1BB costimulatory domain
- CD3z intracellular signaling domain



Ciltacabtagene Autoleucel (JNJ-4528): Approved Feb 2022

- Autologous CAR T-cell
- **Two BCMA-targeting sites (increased avidity)**
- 4-1BB signaling domain
- CD3z intracellular signaling domain



****FDA Label:**

- **Four Prior Lines of Therapy**
- **Previously treated with IMID, PI and anti-CD38 monoclonal antibody**

Ide-cel vs. Cilta-cel

	Cilta-Cel	Ide-Cel
	SAFETY	
CRS (all; grade 3 or 4)	95% (5%)	84% (5%)
Median Onset CRS	**7 days**	**1 day**
ICANS (all, gr 3 or 4)	17% (2%)	18% (3%)
Infections (all, gr 3 or 4)	58% (20%)	69% (22%)
Grade 3 or 4 neutropenia > 1 mo	10%	41%
Grade 3 or 4 thrombocytopenia > 1 mo	25%	48%
Delayed neurotoxicity (all, gr 3 or 4)	**12% (9%)**	None
	EFFICACY	
ORR: CR rate	**98%; 82.5%**	**73%; 33%**
MRD negativity	92% (evaluable)	26%
PFS	NR; 24 mo 60.5%	Median 8.8 months
OS	NR; 24 mo: 74%	Median 19 mo

Administration kinetics and manufacturing failure

FDA Approved CAR-T cell product	Reference Publication	Number enrolled	Median interval between apheresis and CAR-T infusion	Manufacturing failure rate	Feasibility (% of enrolled patients receiving CAR-T product)
Ide-cel (MM)	Munshi NEJM 2021	N= 140	15 days	1%	92%
Cilta-cel (MM)	Berdeja Lancet 2021	N=113	29 days	0%	86%

Dhakal B B J Haem 2021

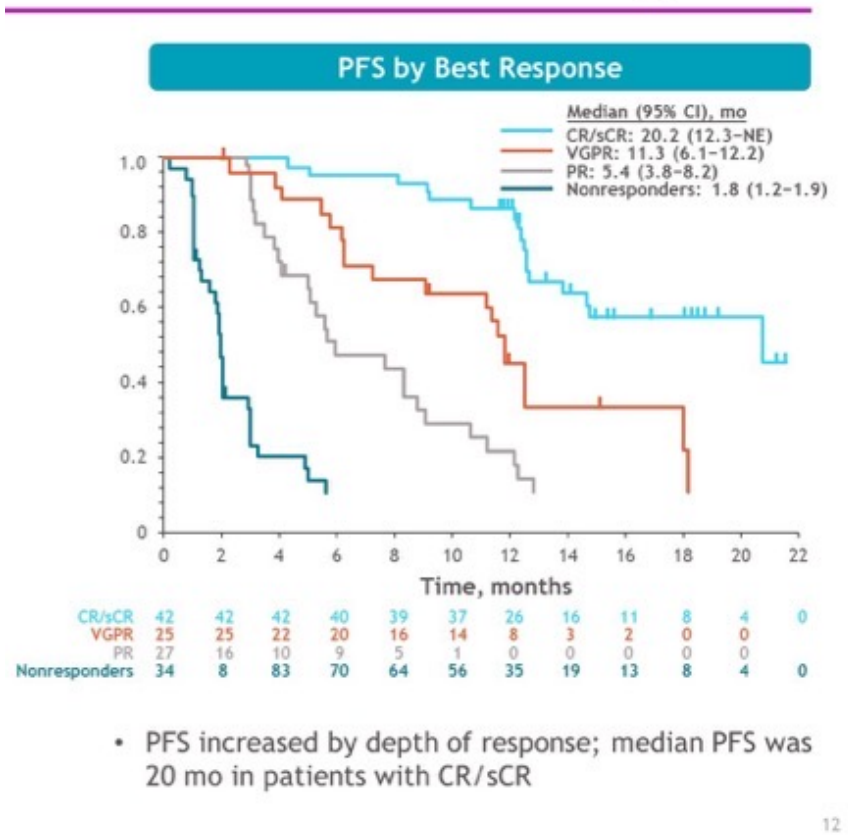
Practical Real-World Considerations

- Most commonly used first line regimen **RVD** +/- **ASCT**, with increasing use of quadruplets with the addition of **daratumumab**
- Patients frequently on **multiagent maintenance therapy** with lenalidomide +/- a proteasome inhibitor +/- daratumumab depending on risk of disease
- Increasing numbers of patients are **refractory to CD38 monoclonal antibodies** earlier in the disease course
- Thus, a patient may become **triple class refractory** as early as second line and frequently in 3rd line
- This would be ideal time for referral so subsequent **salvage therapy** can be planned in anticipation of CAR T-cell therapy
- Supply constraints with CAR T-cell therapy ongoing and demand is likely to exceed supply for the foreseeable future
- Other BCMA-directed therapy with bispecific antibodies and antibody-drug conjugates and optimal sequence remains an open question

PFS of CAR T-cells in multiple myeloma compared with diffuse large B-cell lymphoma

Idecabtagene vicleucel (KarMMa)

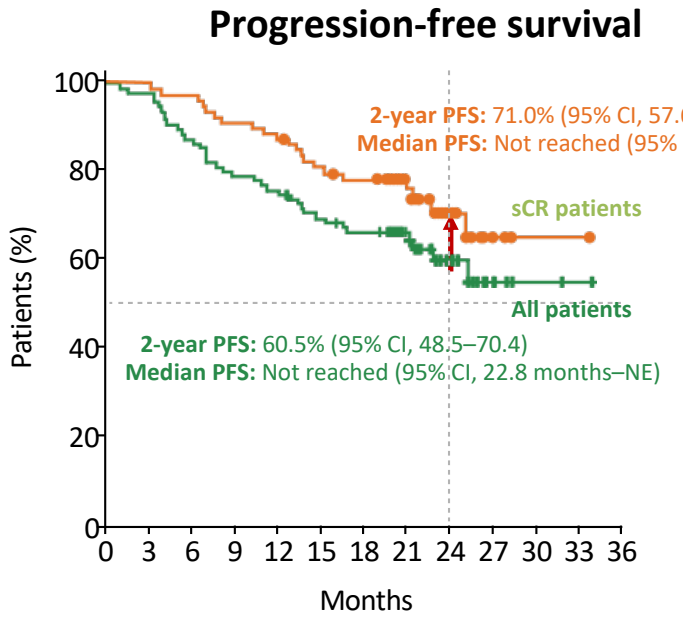
KarMMa™



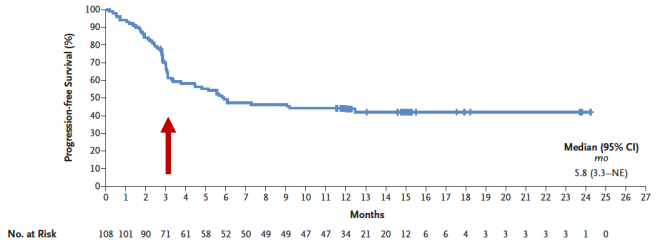
- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

12

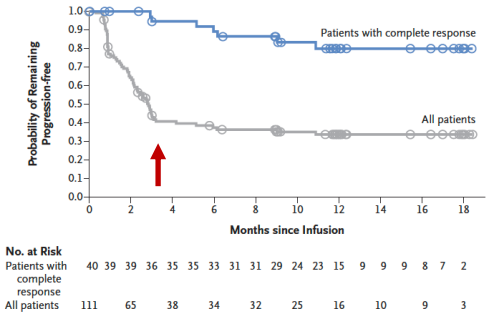
Cilta-cel (CARTITUDE)



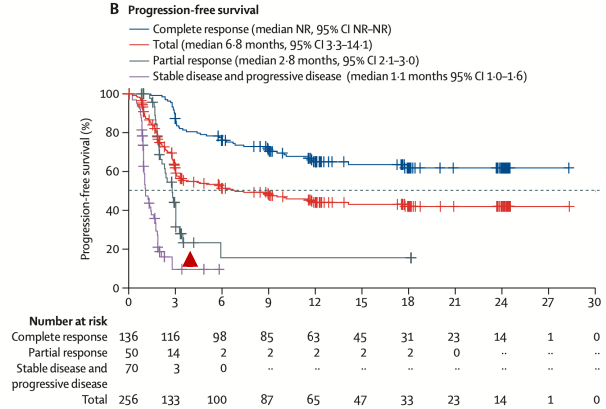
Axicabtagene ciloleucel (ZUMA-1)



Tisagenlecleucel (JULIET)



Lisocabtagene maraleucel (TRANSCEND NHL 001)



Room for improvement with CAR T….
Different biology of myeloma v. lymphoma….

Early Phase Trials:

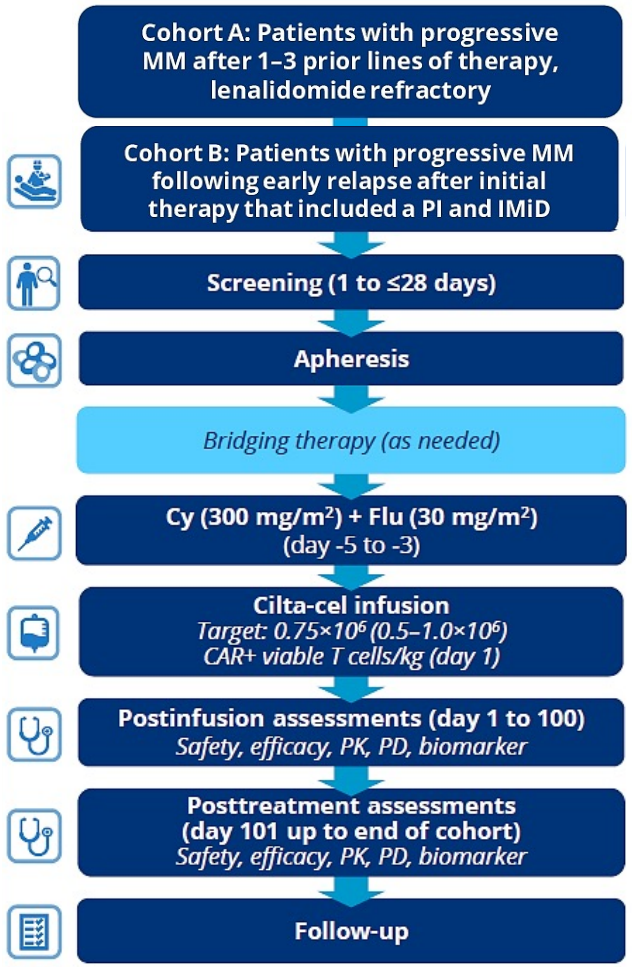
- KarMMa 3: 2-4 lines of treatment
- KarMMa 2: early relapse
- KarMMa 4: High risk

- CARTITUDE 2: early relapse
- CARTITUDE 4: 1-3 lines of treatment
- CARTITUDE 5: Upfront NT patients
- CARTITUDE 6: Upfront TE

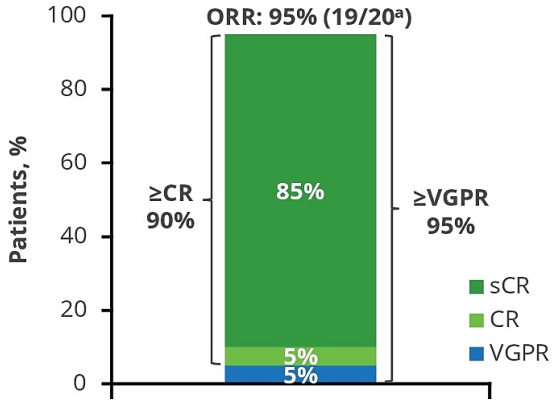
Combination Trials:

- KarMMa 7

Using CAR T-cell therapy at earlier lines of therapy: CARTITUDE-2

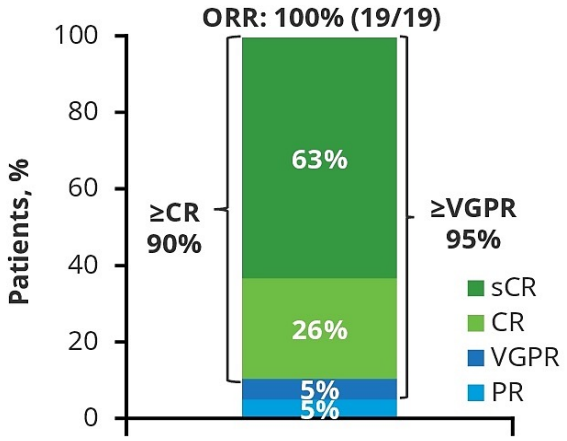


Cohort A



[a]One patient demonstrated a minimal response.
sCR, stringent CR

Cohort B



AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

[a]One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

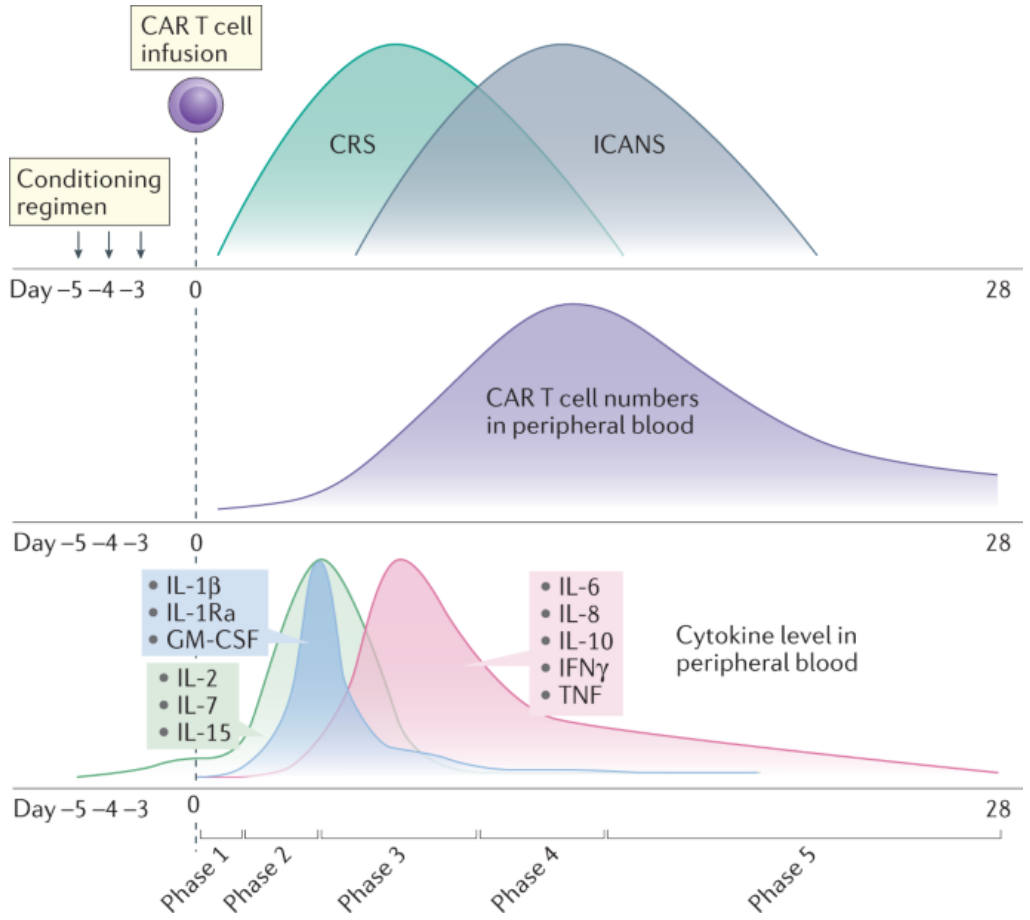
AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	6 (32)	6 (32)
Leukopenia	5 (26)	5 (26)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

CR, complete response; CRS, cytokine release syndrome; Cy, cytarabine; Flu, fludarabine; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; sCR, stringent CR; VGPR, very good partial response

Hillengass J et al. EHA 2022;abstract P959 (poster presentation)
Agha M et al. EHA 2022;abstract S185 (oral presentation)

Cytokine Release Syndrome

- Triggered by: Activation of T-cells → release cytokines/ chemokines (esp. IL-6, IFN-gamma)
- Onset: typically within first week
- Risk factors: Bulky disease, comorbidities, sepsis
- Suspect if: 1+ of the following
  - **Fever**
  - **Hypotension < 90 mm Hg**
  - **Hypoxia < 90%**
  - **Evidence of organ toxicity**



Neelapu et al. *Nat Rev Clin Oncol* 2018
Morris et al. *Nat Rev Immunology* 2021

CRS Grading and Management

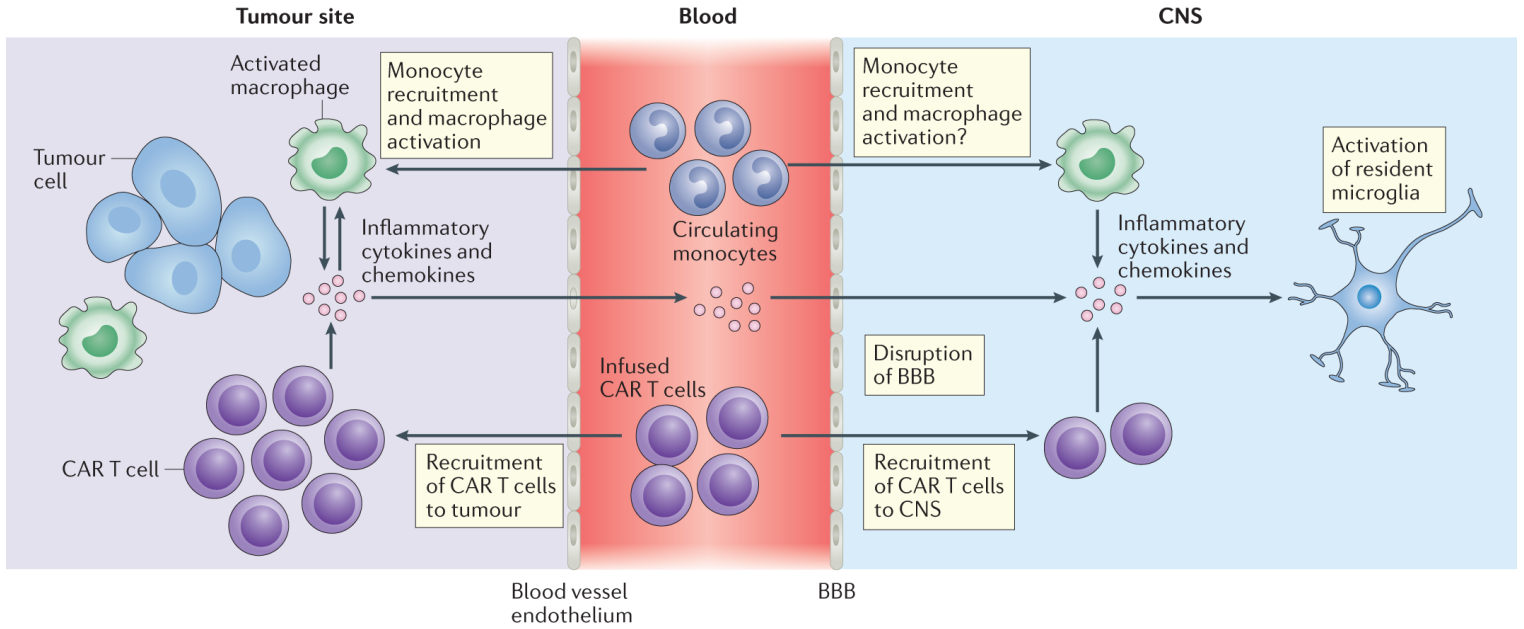
	CRS Grade 1	CRS Grade 2	CRS Grade 3	CRS Grade 4
Fever	Temperature ≥38°C			
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor (w/ or w/o vasopressin)	Requiring multiple vasopressors (excluding vasopressin)
and/or:				
Hypoxia	None	O2 NC (≤6 L/min) or blow-by	High-flow NC (>6 L/min), facemask, non-rebreather, or venturi mask	CPAP, BiPAP, intubation
MANAGEMENT				
	- Antipyretics - Infectious w/u - Antibiotics *<24 hrs: Consider tocilizumab if not responsive to antipyretics	- IV Fluids - Tocilizumab q8hr up to 2-3 doses - If early onset or no response to toci: Dexamethasone 10 mg IV	- ICU monitoring - Tocilizumab - Dexamethasone 10 mg q8-12 hrs until ≤ grade 1	- ICU management - Tocilizumab - Dexamethasone 20 mg IV q6 hrs - If no improvement after 24 hours: Methylpred 1g/d and/or anakinra

UChicago Medicine

Lee et al., BBMT 2019

Immune effector cell-associated neurotoxicity syndrome: ICANS

- Triggered by: Passive diffusion of cytokines into the brain, trafficking of CAR T-cells into CNS, monocyte recruitment and macrophage activation
- Onset: Biphasic (early or after CRS resolved)
- Suspect if:
  - **Diminished attention**
  - **Language disturbance**
  - **Impaired handwriting**
  - **Confusion, disorientation**
  - **Agitation**
  - **Aphasia, somnolence**
  - **Tremors, seizures**
  - **Motor weakness, incontinence**



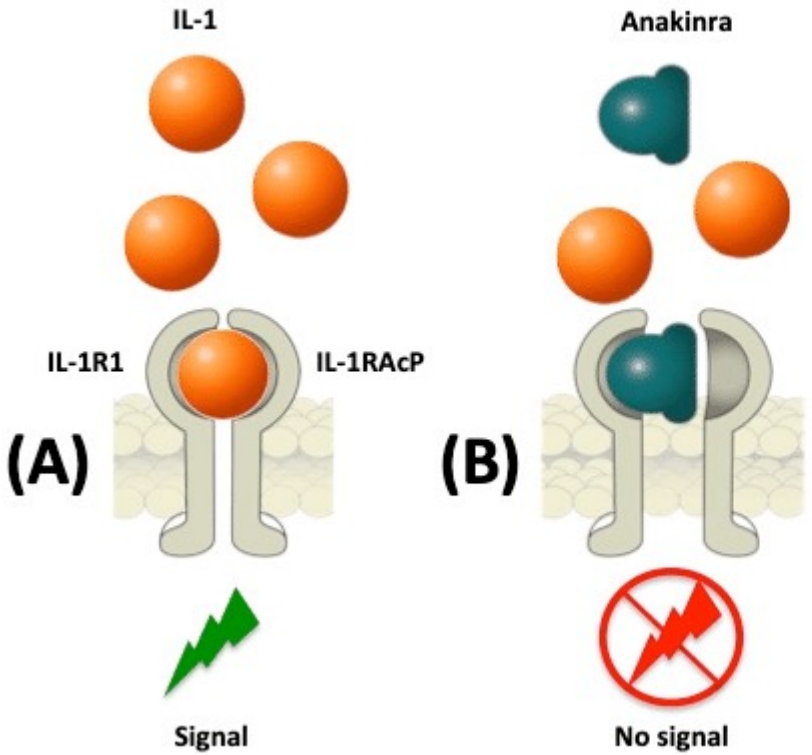
Neelapu et al. *Nat Rev Clin Oncol* 2018
Morris et al. *Nat Rev Immunology* 2021

ICANS Grading and Management

Lee et al., BBMT 2019	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unarousable or unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A		Prolonged seizure / status epilepticus
Motor findings	N/A	N/A		Paralysis
Raised ICP/ cerebral edema	N/A	N/A	Focal/local edema on imaging	Diffuse edema on imaging; posturing; CN6 palsy; papilledema; Cushing's triad
MANAGEMENT	- Head CT - MRI? LP? EEG? - Dex if high-risk	G1 + - Dex 10 mg q8-12 hours until grade $\leq$ 1, then taper	G2 + - Dex 10-20 mg IV q6-12 hrs until grade $\leq$ 1 - Cerebral edema management - Antiepileptics	G3 + - Dex 20 mg q6hrs until grade $\leq$1 - Methlpred 1g/d if no improvement - Anakinra? Siltuximab? IT chemo?

Other CAR-T toxicities

- Cytopenias
  - Supportive care
- Macrophage activation-like syndrome
  - Measure ferritin, IL-2R, NK cell activation, coags
  - Anakinra
- Immunosuppression
  - IVIg
  - Antimicrobial prophylaxis



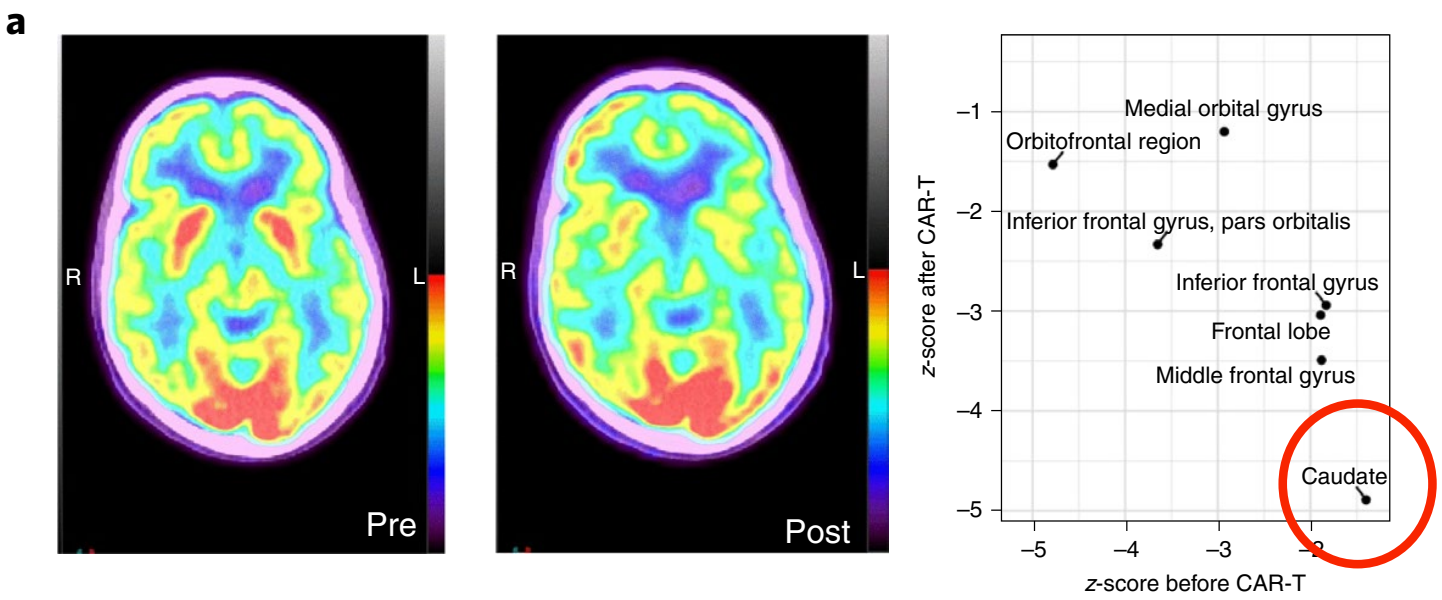
nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-021-01564-7

Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy

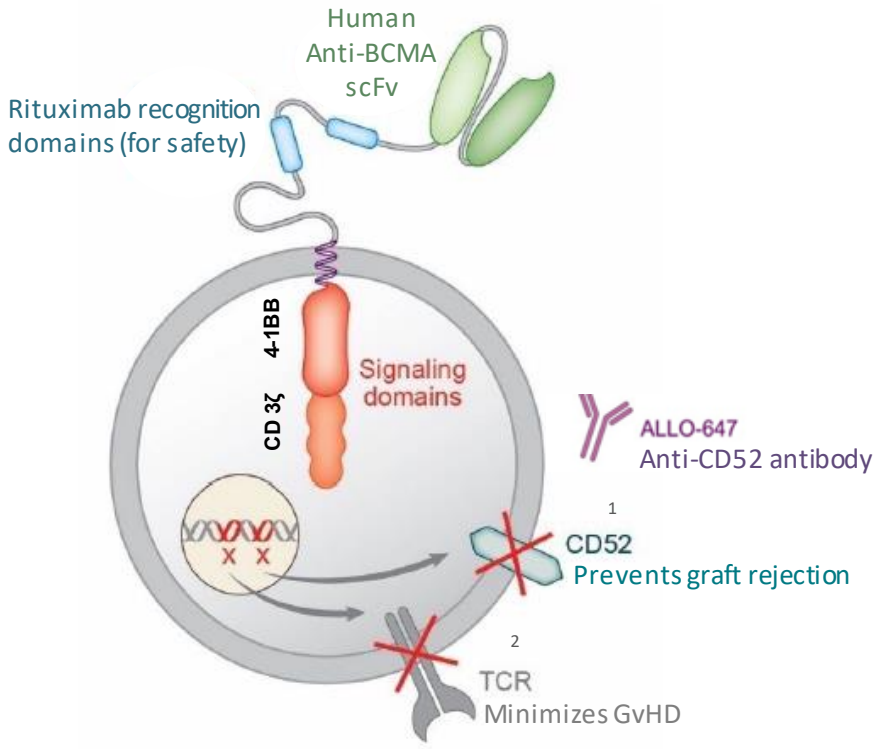
Oliver Van Oekelen[1,2,17], Adolfo Aleman[1,2,17], Bhaskar Upadhyaya[2,3,4], Sandra Schnakenberg[5,6], Deepu Madduri[2,3], Somali Gavane[7], Julie Teruya-Feldstein[5], John F. Crary[5,6,8,9,10,11], Mary E. Fowkes[5,6,18], Charles B. Stacy[12], Seunghee Kim-Schulze[3,4,13,14], Adeeb Rahman[3,4,13,14,15], Alessandro Laganà[3,13,16], Joshua D. Brody[2,3,13,14], Miriam Merad[3,4,13,14], Sundar Jagannath[2,3] and Samir Parekh[2,3,13,14] ✉



What's next?

The First Allogeneic anti-BCMA CAR T Study for R/R Multiple Myeloma

- BCMA cell therapy has demonstrated unprecedented efficacy, but is not readily available to all patients
- Allogeneic chimeric antigen receptor (CAR) T cell therapy has the potential for all eligible patients to receive therapy on demand and supports re-dosing
- ALLO-715 (anti-BCMA) is an allogeneic CAR T cell product utilizing TALEN® gene editing specifically designed to
  - Disrupt TCRα constant gene – to reduce the risk graft-versus-host disease (GvHD)
  - Edit CD52 gene – permits use of ALLO-647 (a humanized anti-CD5 mAb) to selectively deplete host T cells while protecting donor cell



1. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647
2. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD

Abstract #3832

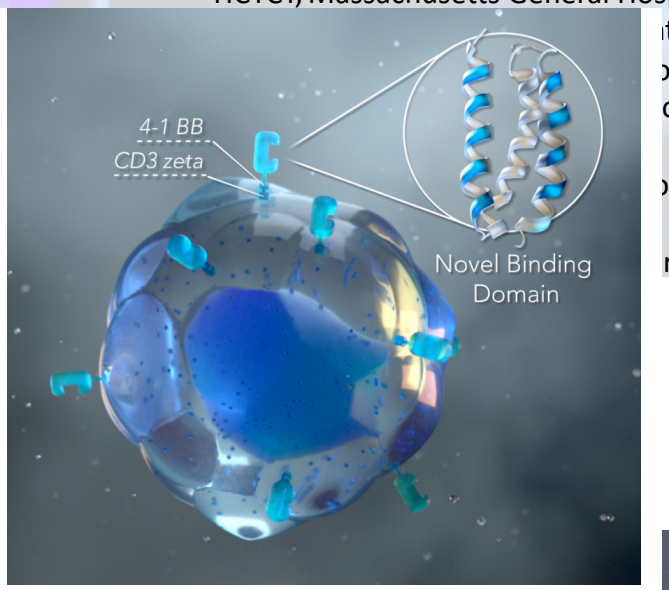
Phase I study of CART-ddBCMA: a CART-Therapy Utilizing a Novel Synthetic Binding Domain for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma

Matthew J. Frigault, MD[1], Jacalyn Rosenblatt, MD[2], Noopur S. Raje, MD[3], Gabriel Depinho, B.S.[4], Daniella Cook, BS[5], Emma K. Logan[2], Christopher R. Heery, MD[6], Christine Cornwell[6], Melissa Sheppard[7], Marcela V. Maus, MD, PhD[1], David Avigan, MD[2], Andrzej Jakubowiak[8], and Michael R. Bishop, MD[9]

[1]HCTCT, Massachusetts General Hospital Cancer Center, Boston, MA;
ter, Boston, MA;
gy, Mass General Hospital Cancer Center, Boston, MA;
oston, MA; [5]Cancer Center, Massachusetts General Hospital, Boston, MA;

f Hematology and Oncology, University of Chicago Medical Center, Chicago, IL;

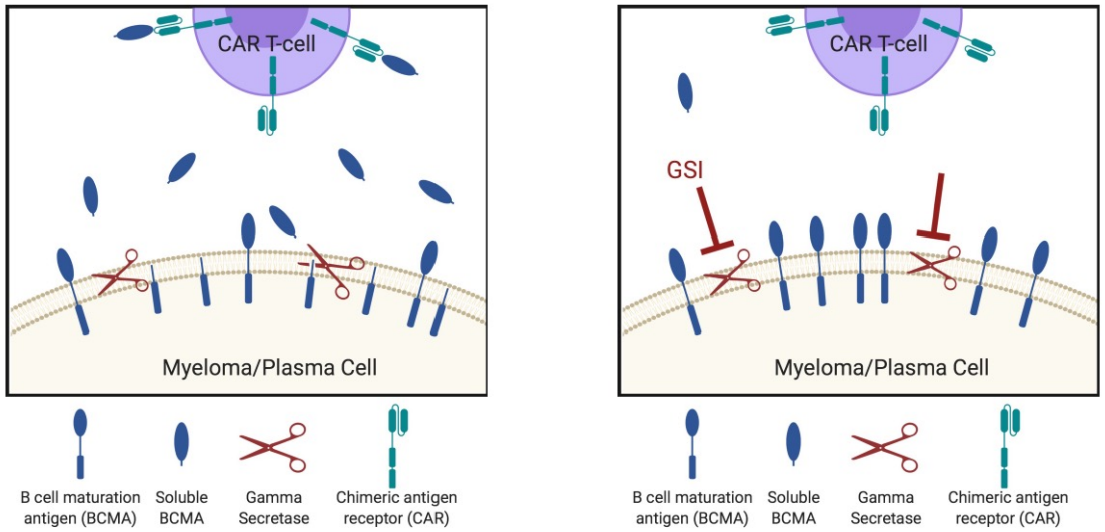
r Cellular Therapy, University of Chicago, Chicago, IL

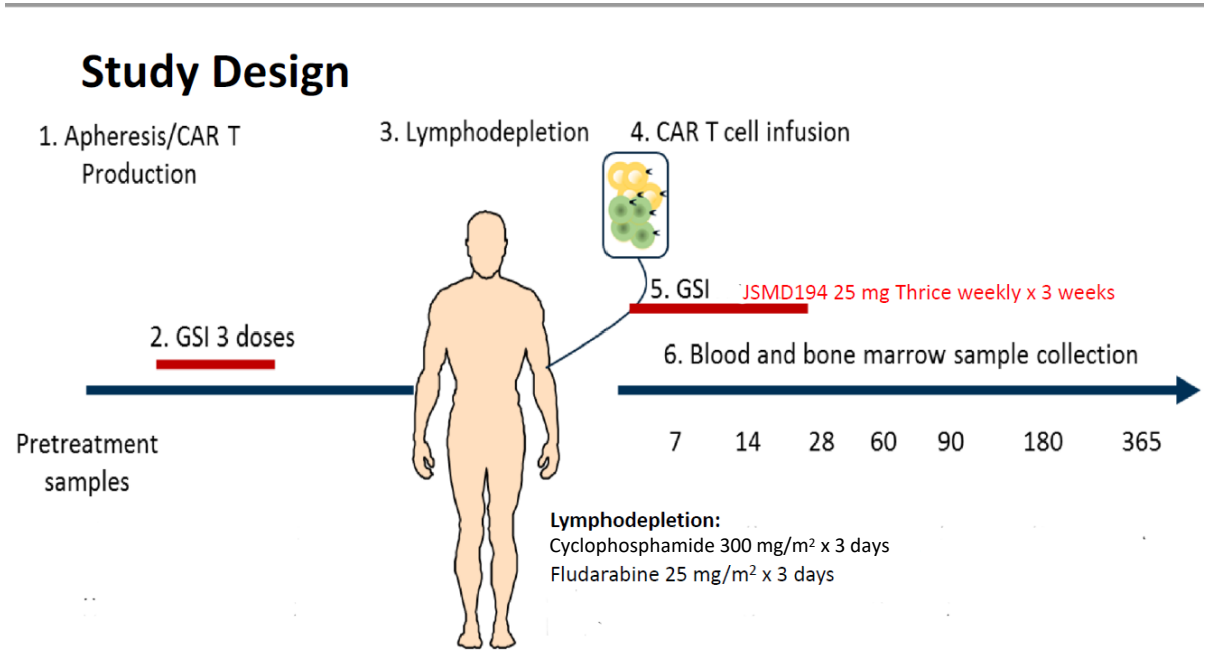


CAR-T containing a novel computationally designed synthetic protein binding domain (non-scFv) engineered to increase stability and decrease immunogenicity

Fully Human BCMA CAR T cells in Combination with a Gamma Secretase Inhibitor to Increase BCMA Expression in R/R Multiple Myeloma

Gamma Secretase Cleaves BCMA from Plasma Cells

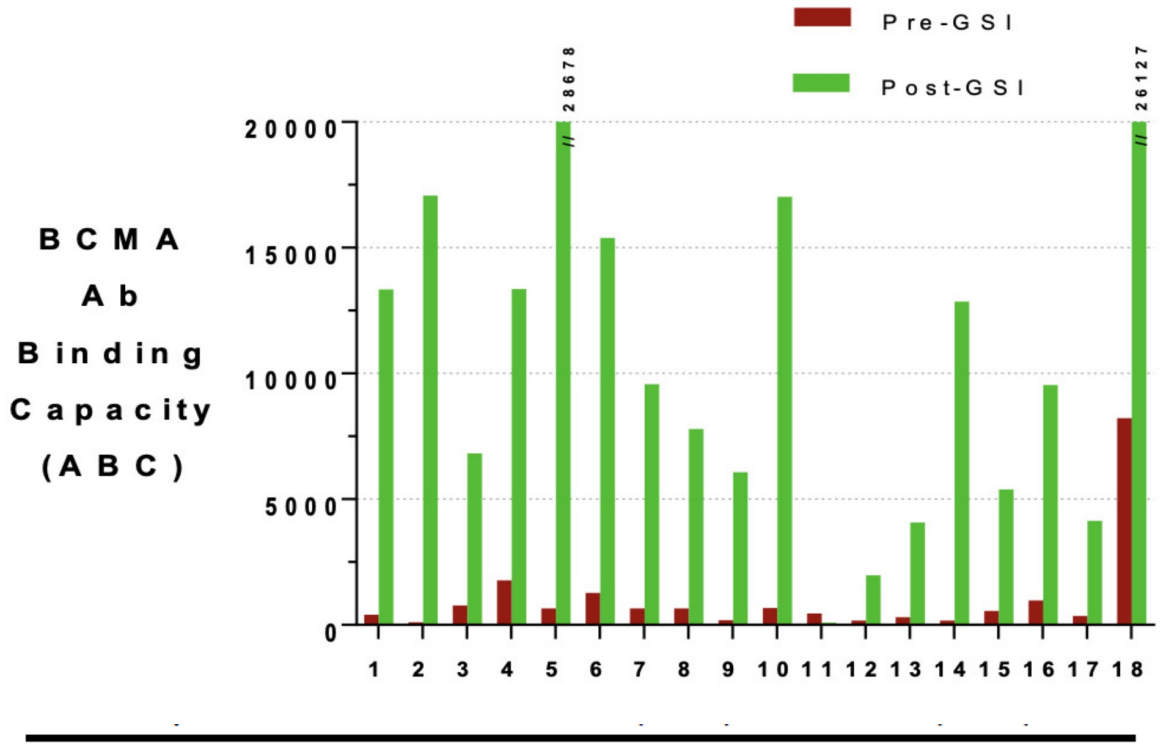




Cowan et al, ASH 2021

GSI in BCMA CAR T cells

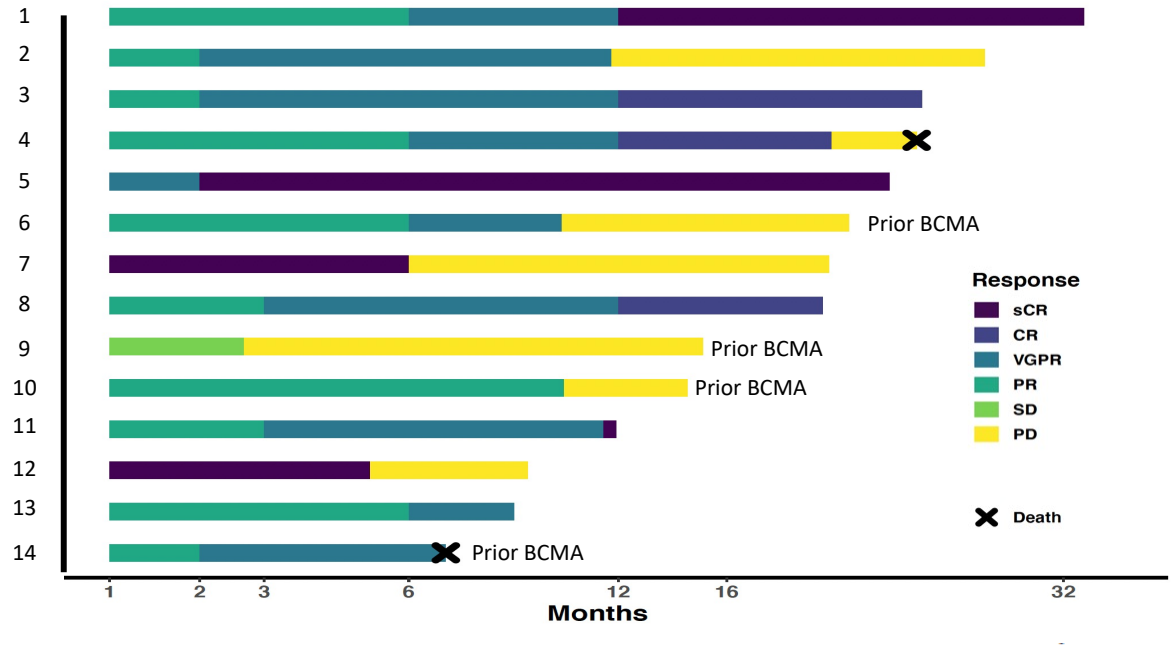
Gamma Secretase Inhibition Increases BCMA Surface Density



CRS (any grade)	17 (94%)
Neurologic Δ from baseline*	12 (66%)

Cowan et al, ASH 2021

Depth and Duration of Response

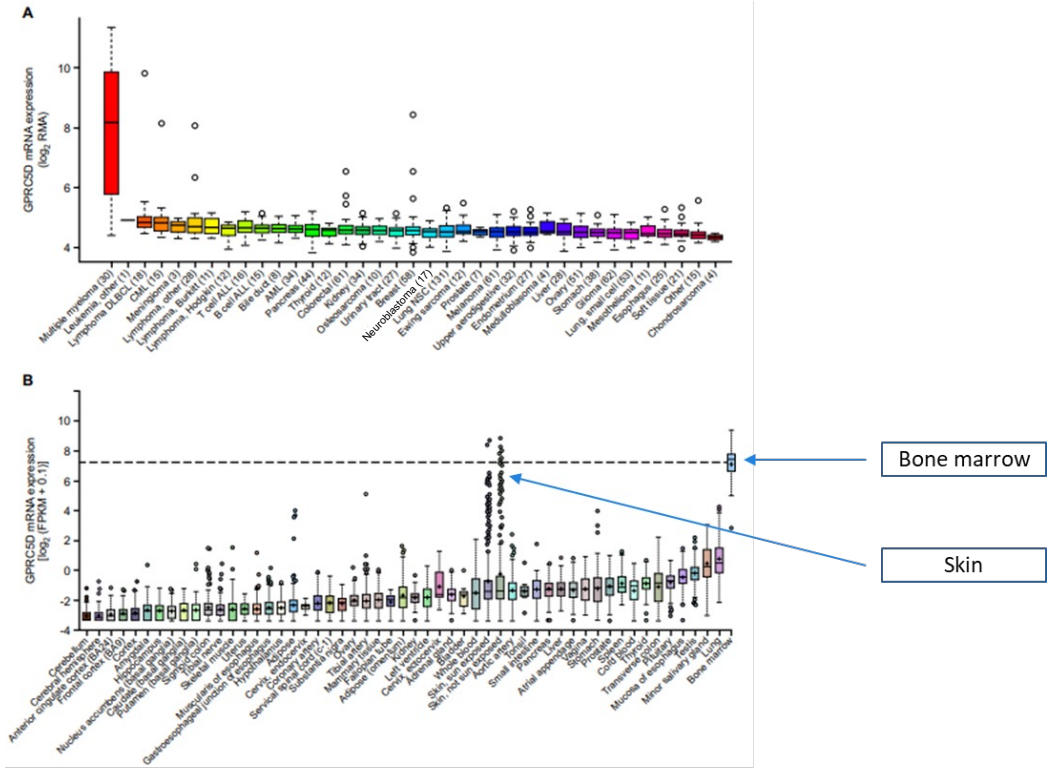


Cytokine Release Syndrome (ASTCT Grading)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
9 (50%)	6 (33%)	4 (22%)	1 (6%)	0 (0%)

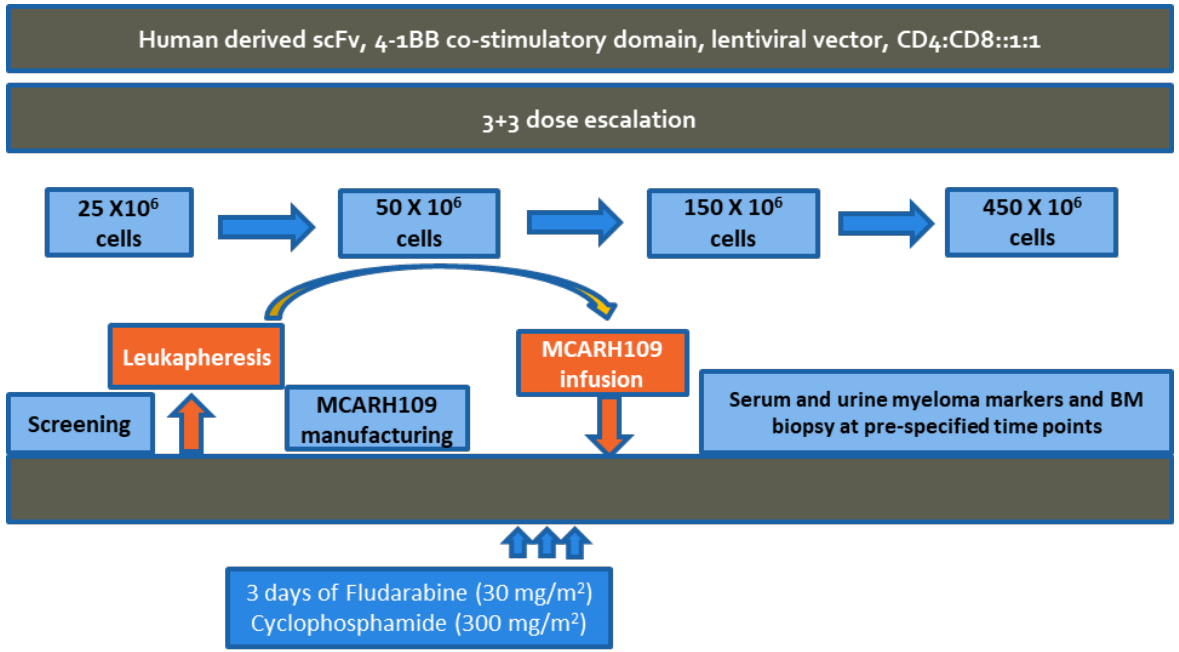
- Needs to be studied in prior BCMA therapy
- Concern for increased neurotoxicity

Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Relapsed or Refractory Multiple Myeloma



Smith EL. et al. Science Translational Medicine 2019

Study Design



Key eligibility criteria:

- 3 or more lines of therapy; Prior PI, IMiD, CD38 antibody-based therapy
- Prior BCMA and CART allowed; Non-secretory myeloma allowed

GPRC5D Targeted CAR T Cell Therapy in RR Multiple Myeloma Clinical Response (N=16)

Response	25 X10^6 CAR+ T cells (n=3)	50 X10^6 CAR+ T cells (n=3)	150 X10^6 CAR+ T cells (n=5)	450 X10^6 CAR+ T cells (n=5)	Total (N=16)
PR or better, n (%)	1 (33)	3 (100)	2 (40)	5 (100)	11 (69)
VGPR or better, n (%)	1 (33)	2 (67)	0 (0)	4 (80)	7 (44)
CR or better (%)	0 (0)	1 (33)	0 (0)	3 (60)	4 (25)
MRD negativity, n (%)	2 (67)	2 (67)	2 (40)	2 (50)	8 (50)

Response	Prior BCMA therapy (n=10)	Prior CAR T therapy (n=8)
Partial Response or better, n (%)	8 (80)	6 (75)
Complete Response or better	3 (30)	3 (38)
BM MRD negativity*, n (%)	5 (50)	2 (25)

Opportunities for combination treatment: biological rationale

IMiD effect on T cells

⬆ T cell proliferation
IL2 production
Th1-type cytokines (IFN-γ)
Costimulation (CD28)

⬇ Th2-type cytokines (IL4)
Immunosuppressive cytokines (IL10)
FOXP3 expression

- Lenalidomide enhances CAR T Cell function in MM preclinical models

Anti-CD38 mAbs:
- Induction of T cell expansion
- Depletion of CD38+ T regulatory cells
- Depletion of CD38+ MDSCs
- Depletion of CD38+ B regulatory cells

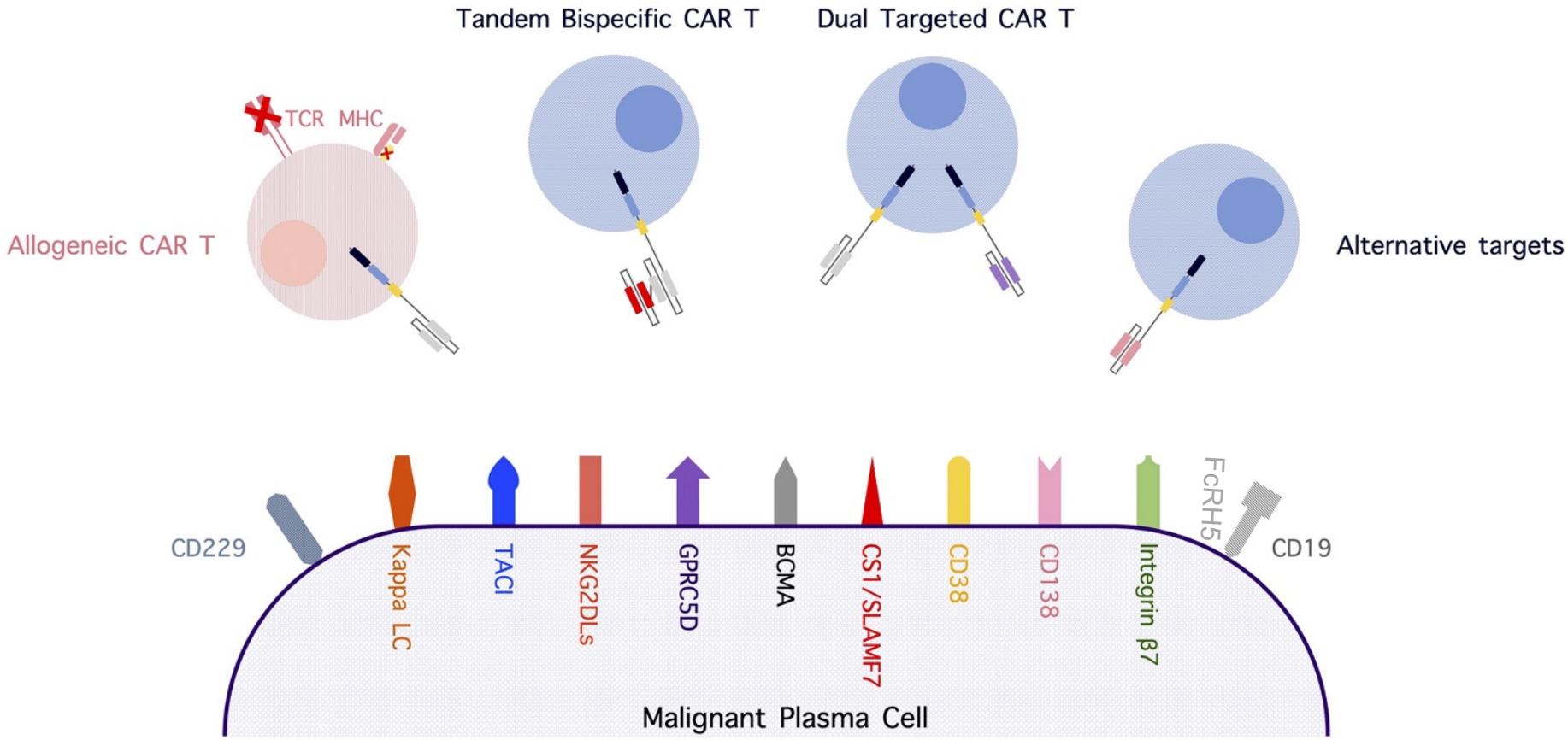
Anti-SLAMF7 mAbs:
- CD8+ T cells express SLAMF7
- Synergize with anti-PD1 mAbs in activating T cells

Checkpoint Axis:

- PD1 engagement on activated T cells induces a functionally exhausted state

- Anti-PD-1 mAbs augment CAR T cell activity in preclinical models

Future of CAR T cells and/or BiTES in Multiple Myeloma



Kitsada Wudhikarn,Sham Mailankody,Eric L. Smith, Future of CAR T cells in multiple myeloma, Hematology Am Soc Hematol Educ Program, 2020, Figure 1.

Current Understanding and Future Directions

- CAR T cells are an effective strategy in RR MM
- BCMA is a validated target
- Future will be to define how to combine/sequence with other immunotherapies
- Bring upfront
- Next generation approaches will focus on improving efficacy and DOR

Module 4: Bispecific Antibodies in the Treatment of MM — Dr Berdeja

RTP
RESEARCH
TO PRACTICE

Case Presentation: 70-year-old man with t(4;14) NDMM who initiates RVd, which is put on hold to treat severe depression

Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 76-year-old woman with multiregimen-refractory del(17p) MM who is considered for BCMA-directed therapy

Dr Spencer Bachow (Boca Raton, Florida)

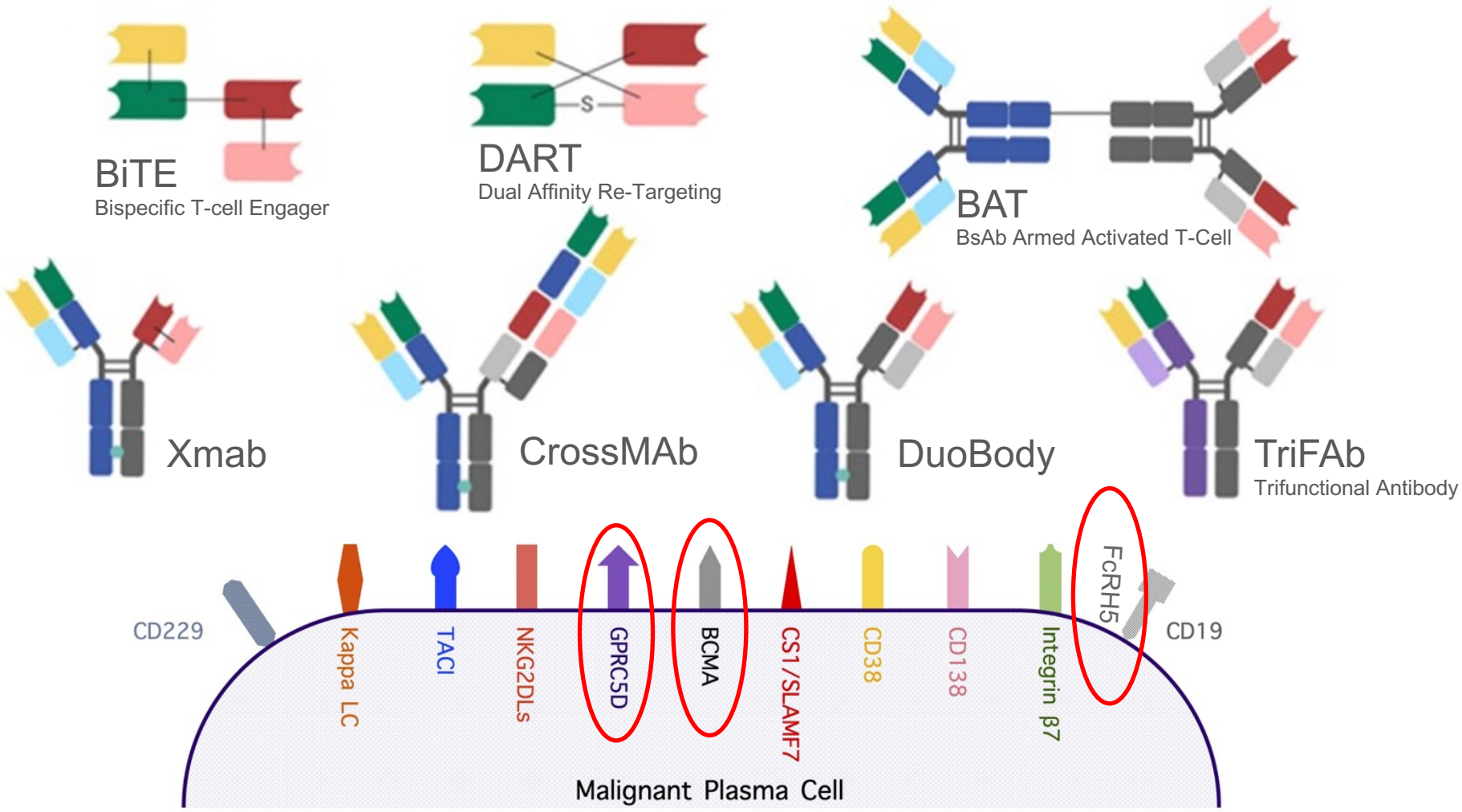
RTP
RESEARCH
TO PRACTICE

Bispecific Antibodies in the Treatment of Multiple Myeloma

Jesús G. Berdeja, M.D.
Director of Myeloma Research
Sarah Cannon Research Institute
Nashville, TN, USA

SARAH CANNON
Research Institute

Bispecific antibodies: Many platforms, many targets



Adapted from:
Lejeune. Front. Immunol. 11:762, 2020. Wudhikarn. Hematology Am Soc Hematol Educ Program. 2020;2020:272.

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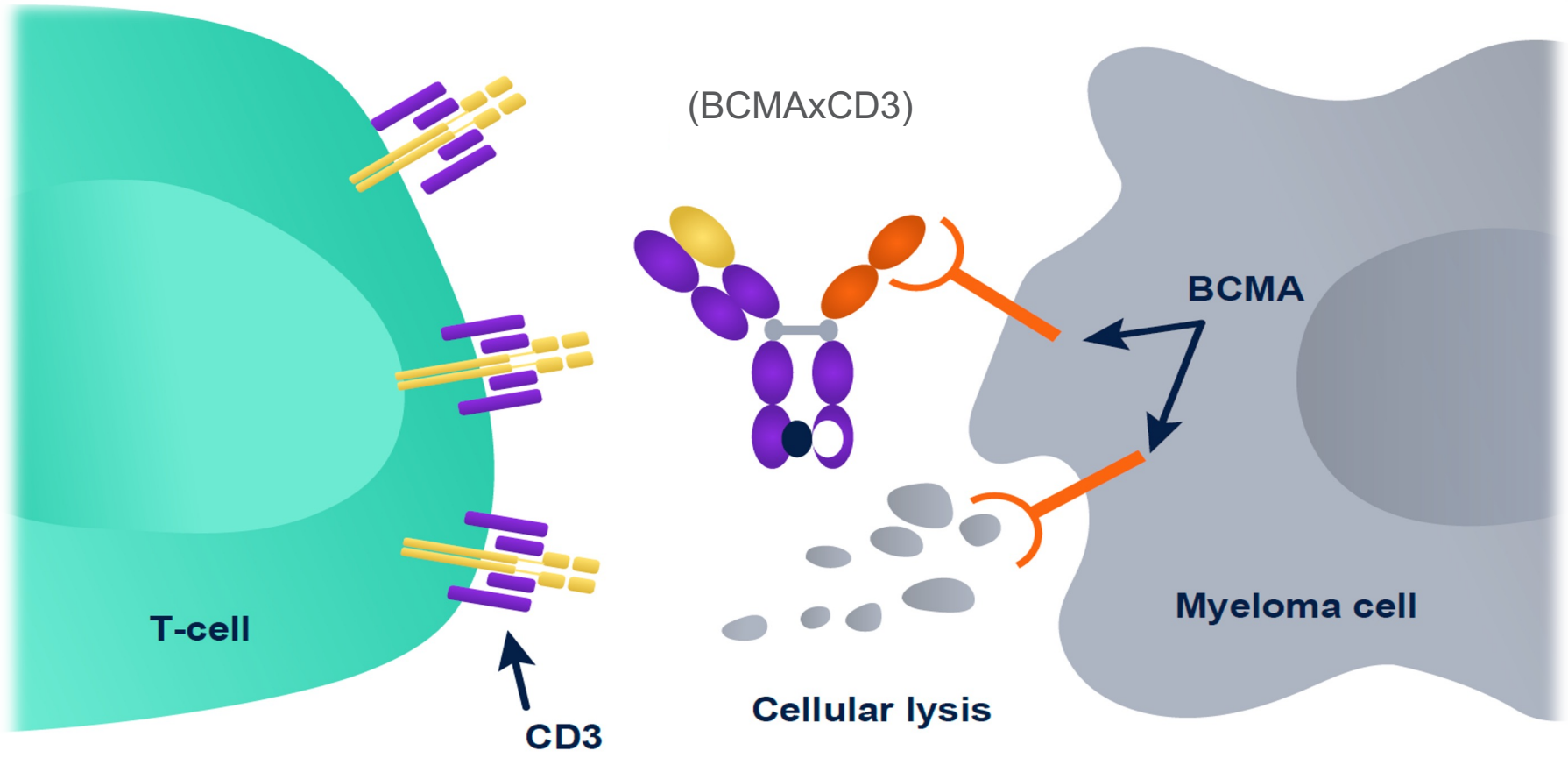
T cell redirecting bispecific antibodies



Shah N, et al. Leukemia. 2020;34:985-1005

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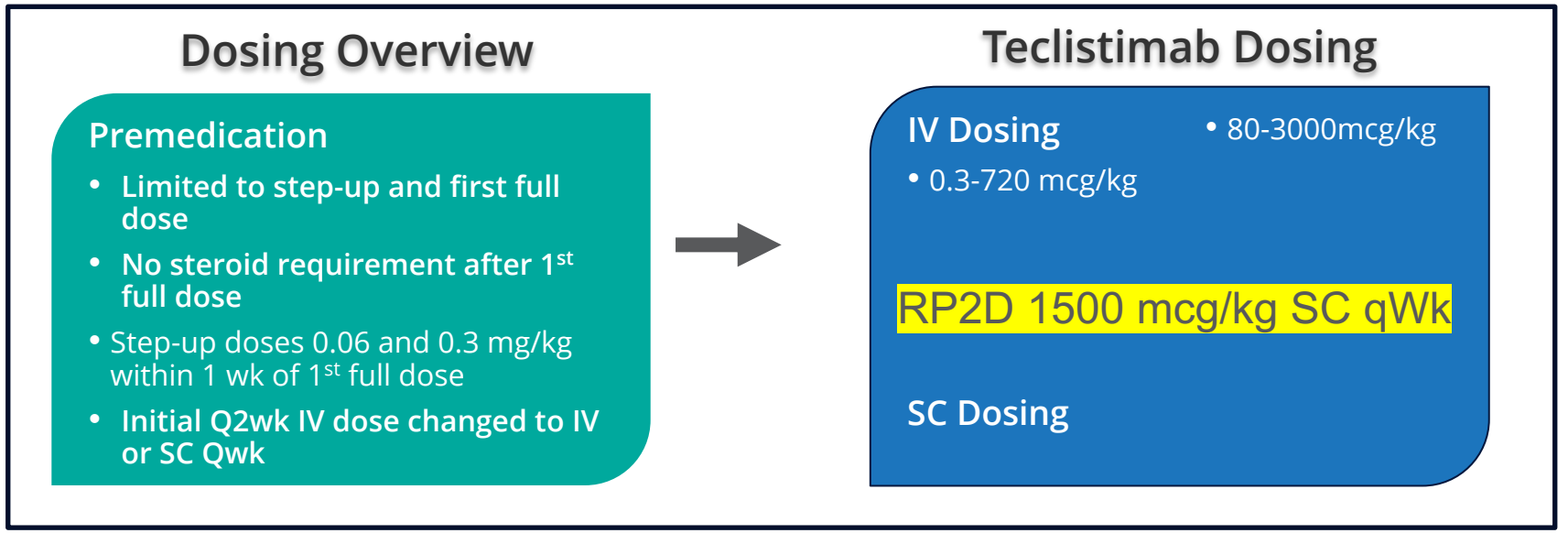
Teclistamab
MajesTEC-1: Study Design

- Phase 1/2, dose escalation study to evaluate teclistamab in patients with RRMM
- ≥3 prior lines of therapy
- No prior BCMA-targeted therapy



Primary endpoints: Phase 1 - safety and determine RP2D. Phase 2 - ORR

Key secondary endpoints: DOR, ≥VGPR, ≥ CR, sCR, TTR, MRD status, PFS, OS, safety, pharmacokinetics, immunogenicity, PRO

Moreau et al. NEJM 2022, 387(6):495-505.

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MajesTEC-1: Patient Baseline Characteristics

Characteristic	Safety Analysis N=165
Age (years), median (range)	64.0 (33–84)
Age ≥75 years, n (%)	24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%)	
White	134 (81.2)
African-American/Black	21 (12.7)
Other[a]	10 (6.1)
Bone marrow plasma cells ≥60%[b], n (%)	18 (11.3)
Extramedullary plasmacytomas ≥1[c], n (%)	28 (17.0)
High-risk cytogenetics[d], n (%)	38 (25.)
ISS stage[e], n (%)	
I	85 (52.5)
II	57 (35.2)
III	20 (12.3)

Characteristic	Safety Analysis N=165
Baseline renal function, n (%)	
<60 mL/min/1.73m^2	44 (26.7)
≥60 mL/min/1.73m^2	121 (73.3)
Time since diagnosis (years), median (range)	6.0 (0.8–22.7)
Prior lines of therapy, median (range)	5.0 (2–14)
Prior stem cell transplantation, n (%)	135 (81.8)
Exposure status, n (%)	
Triple-class exposed[f]	165 (100)
Penta-drug exposed[g]	116 (70.3)
Selinexor	6 (3.6)
Refractory status, n (%)	
Triple-class refractory[f]	128 (77.6)
Penta-drug refractory[g]	50 (30.3)
Refractory to last line of therapy	148 (89.7)

Moreau et al. NEJM 2022, 387(6):495-505.

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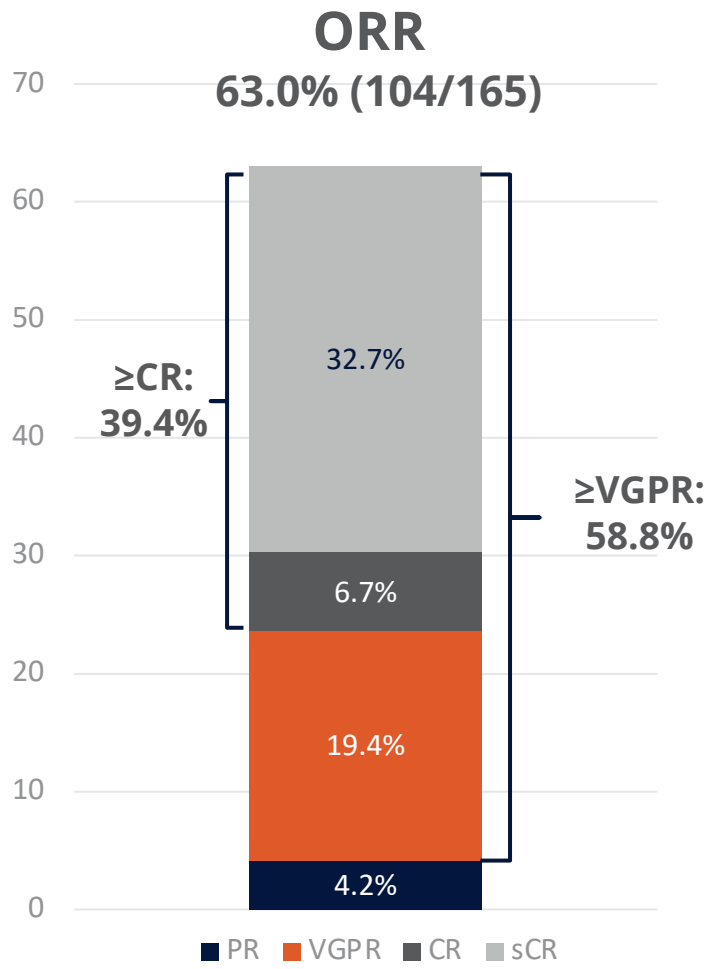
MajesTEC-1: Response



- At a median follow-up of 14.1 months:
  - ORR was 63.0% (95% CI: 55.2–70.4)
  - ≥ VGPR 58.8%
- Median time to first response: 1.2 months
- MRD negativity rate[b]
  - 26.7% at a threshold of 10^{-5}
  - 46% for patients who achieved ≥CR

Moreau et al. NEJM 2022, 387(6):495-505.

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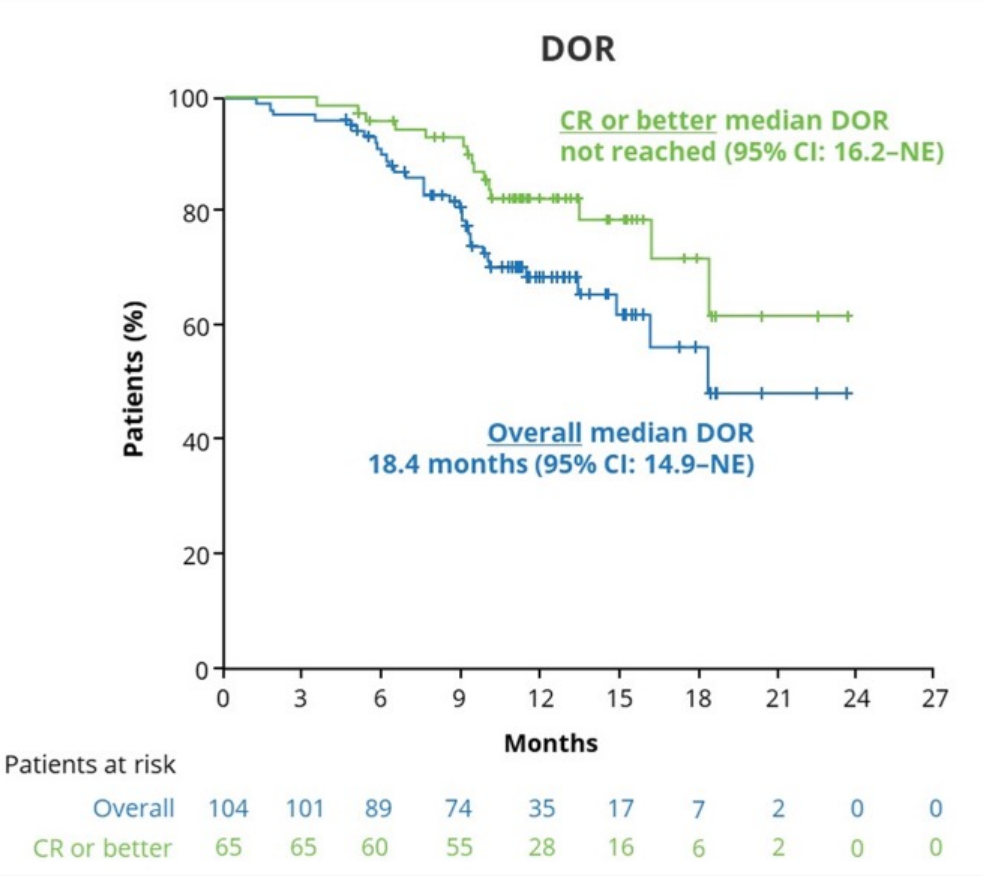
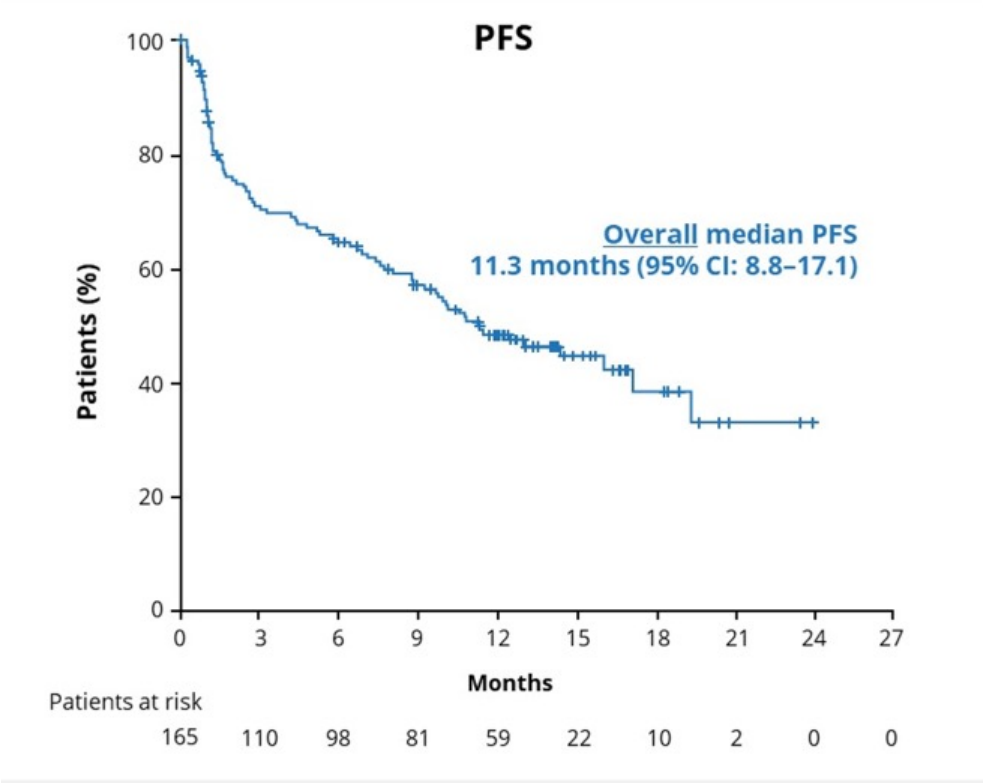
MajesTEC-1: Durability of Response





Median DOR 18.4 mos – Median PFS 11.3 mos – Median OS 18.3 mos

Moreau et al. NEJM 2022, 387(6):495-505.

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MajesTEC-1: Overall Safety Profile

Safety Analysis Set N=165		
AEs ≥20%, n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	117 (71)	106 (64)
Anemia	86 (52)	51 (37)
Thrombocytopenia	66 (40)	35 (21)
Lymphopenia	57 (35)	54 (33)
Nonhematologic		
CRS	119 (72)	1 (0.6)
Diarrhea	47 (29)	6 (4)
Fatigue	46 (28)	4 (2)
Nausea	45 (27)	1 (0.6)
Injection site erythema	43 (26)	0 (0)
Headache	39 (24)	1 (0.6)

- 2 patients discontinued due to AEs (G3 adenoviral pneumonia and G4 PML)
- Infections occurred in 126 (76%) (grade 3/4: 45%)
- 19 deaths due to AEs (5 felt to be related to teclistimab)
  - COVID-19(2); Pneumonia (1), Hepatic failure (1); PML (1)
- CRS occurred in 72%
  - All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that fully resolved
  - Median time to onset of CRS 2 days
  - 97% of events were confined to step-up and cycle 1
- Neurotoxicity was seen in 14%
  - Most were headaches 8.5%
  - ICANS was seen in 3.0%

Moreau et al. NEJM 2022, 387(6):495-505.

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First FDA-Approved BCMA-Targeted Bispecific Ab

	Indication
Teclistamab	▪ **Adults with R/R multiple myeloma after ≥4 prior lines of therapy**, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab

Teclistamab PI.

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BCMA:CD3 BISPECIFICS IN MULTIPLE MYELOMA

	Teclistamab[1,2,3]	Linvoseltamab[4]	ABBV-383[5]	elranatamab[6]	Alnuctamab[8]
Construct Study	DuoBody MajesTEC-1	Veloci-Bi Fc Phase 1	Triple chain: 2 BCMA Phase 1	DuoBody Magnetissm-3	2+1 CrossMab Phase I
Dose/Sched	IV/SC q1-2wk (Step up) RP2D 1500mcg/kg SC qwk	3-800mg IV (split W1,2) qwk, q2 wks wk16+	0.25-120-mg (no step up) IV Q3wks RP2D 40mg & 60mg IV q3wks	76mg SC QWk (2 step up 12mg and 32mg)	0.005-10mg IV qwk (Step up) 10mg-60mg SC Q1wk C1-3, Q2wx C4-6,Q4wk C6+
Population	165 (Ph1 40, Ph2 125) Median 5 LOT 78% triple refractory	167 Median 6 LOT 90% triple refractory	66* Median 5 LOT 82% triple refractory	123 Median 5 LOT 97% triple refractory 32% EMD	47* Median 4 LOT 62% triple refractory
Safety All Grade (Gr 3+)	CRS 72%(0.6%) Neurotox 14% ICANS 3%(0) Infections 76%(45%)	CRS 48%(0.6%) ICANS 4%(0) Infections ?	CRS 72%(2%) ICANS <1% Infections 43%(22%)	CRS 56%(0) ICANS 3%(0) Infections 62%(32%) PN 17%	CRS 53%(0) ICANS 1 pt, gr 1 Infections ?
Response ORR(VGPR+)	63% (59%)	75% @200-800mg	63%(47%) @40-60mg	61%	51% [77% @ ≥30mg dose]
Durability	DOR 18.4 mos PFS 11.3 mos OS 18.3 mos				
Misc	Cohort A results Excluded prior BCMA Cohort C Prior BCMA[3] ORR(VGPR+) 52.5%(47.5%)	Formerly REGN5458 RP2D 200mg	Formerly TNB-383B *Dose levels 40/60 only	- [7]Magnetissm-1 K-M estimate DOR 17.1m	*SC only - Dose expansion 10mg & 30mg SC

[1]Moreau et al. NEJM 2022, 387(6):495-505. [2]Nooka et al. ASCO 2022, Abs 8007. [3]Touzeau et al. ASCO 2022, Abs 8013.
[4]Bumma et al. ASH 2022, Abs 4555. [5]Voorhees et al. ASH 2022, Abs 1919. [6]Bahlis et al. ASH 2022, Abs 159.
[7]Raje et al. ASH 2022, Abs 158. [8]Wong et al. ASH 2022, Abs 162.

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BCMA Bispecific Ab after prior BCMA Treatments

Teclistamab

- MajesTEC-1: 40 pts enrolled in cohort C, all prior BCMA
  - 29(72.5%) prior ADC
  - 15(37.5%) prior BCMA CART
- ORR(>VGPR)
  - All – 52.5%(47.5%)
  - ADC-exposed 55.2%(48.3%)
  - CART 53.3%(46.7%)
- Med DOR NR
- Safety profile no different than entire population

Touzeau et al. ASCO 2022, Abs 8013

Elranatamab

- MagnetisMM-1: 55 total pts enrolled
  - 13(24%) prior BCMA
    - 8 prior BCMA-ADC
    - 9 prior CAR-T
- ORR(>VGPR)
  - All – 64%(58.2%)
  - Prior BCMA - 54%(46%)
  - Not broken down by type of prior BCMA

Jakubowiak et al. ASCO 2022, Abs 8014

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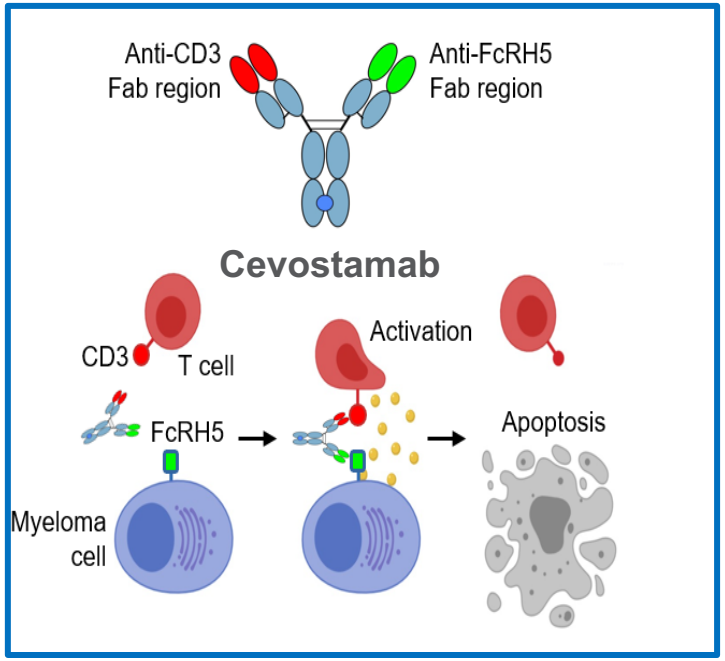
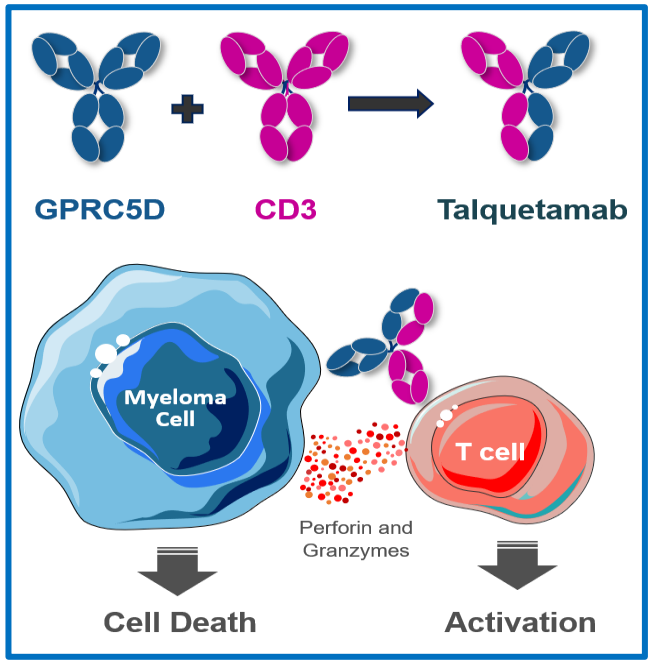
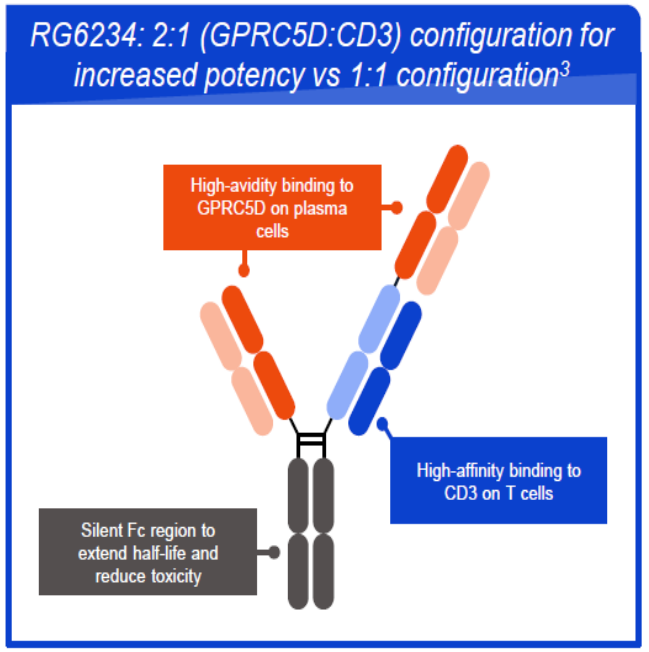
Non-BCMA Targets







FcRH5 – Fc Receptor-homolog 5

- **Expressed exclusively in B cell lineage**
- **Near ubiquitous expression on MM cells**

GPRC5D: G Protein-Coupled Receptor Class C Group 5 Member D

- **Orphan G protein-coupled receptor of unknown function**
- **Limited expression, primarily in plasma cells, skin and salivary glands**
- **Highly expressed in MM cells**

Li et al. Cancer Cell 2017;31:383–95. Sumiyoshi et al. EHA 2021. Smith Sci Transl Med 2019;11(485). Pillarisetti Blood 135(15):1232. Atamaniuk Eur J Clin Invest 42(9):953. Bacac Clin Cancer Res 2018;24:4785-97.

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Non-BCMA Bispecifics in Multiple Myeloma

	Cevostamab[1]	Talquetamab[2]	RG6234[3]
Target Study	FcRH5:CD3	GPRC5D:CD3 MonumenTAL-1	GPRC5D:CD3
Dose/Sched	0.15-198mg (Step up) IV q3wk x 17cycles	405mcg/kg SC qwk (step up)* 800mcg/kg SC q2wkw (step up)	6-10000 mcg IV q2w (Step up) 30-7200mcg SC q2wks
Population	161 (*60) Med LOT 6 85% triple refractory 33.5% prior BCMA	288 (143 + 145) Med LOT 5 74% triple refractory 27% and 16% prior BCMA	51 IV, 54 SC Med LOT 5,4 63%, 73% triple refractory 20%, 21% prior BCMA
Safety All grade (Grade 3+)	CRS 81% (1%) ICANS 14%(1%) Infections 45%(~20%)	CRS 79%(2%), 72%(1%) ICANS NR Infections 57%(19%), 50%(13%)	CRS 82%(2%), 79%(2%) ICANS 9%(2%) Infections 57% (20%), 37%(24%)
Response ORR (VGPR+)	57% (33%) @ 132-198mg* 63% prior BCMA	73%(58%)* Prior BCMA NR	71%(57%), 60%(40%) 56% prior BCMA
Misc	Treatment stops after 1 yr • Lesokhin. Poster 1924, Saturday • Trudel. Oral Abs 567 preemptive tocilizumab	*Response for 400 q wk dosing, 800 q 2wks at ASH - On target toxicity: Dysgeusia 48%, 46% Skin-related 56%,58% Nails 52%/43%	On target toxicity: GI/tongue 71%,74% Skin 72%, 81% Nails 17%, 22%

[1]Trudel et al. ASH 2021, Abs 157. [2]Chari et al. ASH 2022, Abs 157. [3]Carlo-Stella et al. ASH 2022, Abs 161.

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Bispecifics combinations

	MajesTEC-2[1]	MagnetisMM-5[2]	TRIMM-2[3]
Bispecific	teclistamab	elranatamab	talquetamab
Treatment	Tec 0.72 or 1.5mg/kg qwk + Dara + Len 25mg	Elra qwk x 6 cycles then q 2 wks + Dara	Talc 405 SC q1wk and 800 SC q2wk + Dara
Eligibility	1-3 LOT, inc PI/IMiD	≥ 3 LOT, inc PI/IMiD	≥ 3 LOT or double refractory PI/IMiD; prior anti-CD38 allowed
Population	32	28	29
# Prior Tx	2 (31% prior anti-CD38)	5 (18% triple refractory)	6 (79% prior anti-CD38)
ORR	90% (29 evaluable pts)	Will be presented	80%
≥VGPR	immature	Will be presented	67%
CRS All Grades (Grade 3/4)	81%(0) -med TT onset 2 days	50%(0) -med TT onset 2 days	55%(0%) -med TT onset 12-24h
Other Tox	ICANS 0 Neutropenia 75%(69%) Infections* 75%(28%)	ICANS 0 Neutropenia 29% (28%)	Neutropenia 41%(31%) Dysgeusia 48%
Notes	*URI, pneumonia, COVID Phase 3 MajesTEC-7 planned	Part 2: Ph3 randomized - elra mono, elra+dara or elra+dara+pom	-55% prior BCMA Rx

[1]Searle et al. ASH 2022, Abs 160. [2]Grosicki et al. ASH 2022, Abs 1921. [3]Chari et al. ASH 2021, Abs 161.

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Sampling of Future Directions – TIP @ ASH 2022

- Teclistamab
  - MajesTEC-4 (Zamagni. Poster 3242, Sun Dec 11)
    - Phase 3 Tec/Len v Len as maintenance post ASCT
  - MajesTEC-7: (Krishnan. Poster 4558, Mon Dec 12)
    - Phase 3 Tec/Dara/Len vs DRd in NDTIE pts
- Elranatamab
  - MagnetisMM-4: (Landgren. Poster 4567, Mon Dec 12)
    - Phase 1b multicohort study, currently 2 cohorts
    - Cohorts: Elranatamab +nirogacestat or Elranatamab+Len/dex
- Abbv-383
  - Combination (Rodriguez. Poster 3257. Sun, Dec 11)
    - Phase Ib multicohort study, currently 4 planned
    - Cohorts: Abbv-383 + pom/dex or len/dex or dara/dex or nirogacestat
- Linvoseltamab (REGN5458)
  - Phase Ib multcohort study, currently 4 planned (Rodriguez Otero. Poster 1936. Sat, Dec 10)
    - Cohorts: Linvo+Dara; Linvo+Carfilz; Linvo+Len; Linvo+Btz
  - Phase II study of linvoseltamab monotherapy or as induction/consolidation with ASCT (Ferreri. Poster 4551. Mon, Dec 12)
    - Patient population: NDMM both transplant eligible and ineligible
- Talquetamab
  - MonumenTAL-3 (Cohen. Poster 1925, Sat, Dec 10)
    - Phase 3, 3 arm study of Talq+Dara vs talq+Dara+Pom vs DaraPomDex
    - Patient Population: RRMM ≥1 prior LOT, including PI and IMiD

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Take Home Message

- Several BCMA:CD3 bispecifics showing impressive, durable responses
  - Teclistamab is the first to be FDA-approved
- New targets beyond BCMA
  - GPRC5D and FcRH5
- Safety profile appears similar across all studies
  - Nearly all CRS events were grade 1–2 and generally confined to first step-up and full doses
  - Infections are a concern and need to be monitored closely, consider prophylaxis
- Combination studies ongoing
- Unlike autologous CAR T, these are off-the-shelf

Module 5: Other Investigational Novel Agents for MM — Dr Lonial

RTP
RESEARCH
TO PRACTICE

Case Presentation: 84-year-old woman with CHF and t(4;14), t(11;14); t(14;16) MM who receives dose-reduced RVd and develops chalazion eye toxicity

Dr Jennifer Dallas (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

EMORY WINSHIP CANCER INSTITUTE

A Cancer Center Designated by the National Cancer Institute

EMORY UNIVERSITY SCHOOL OF MEDICINE

Other investigational Agents

Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

t(11;14) Myeloma

Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients

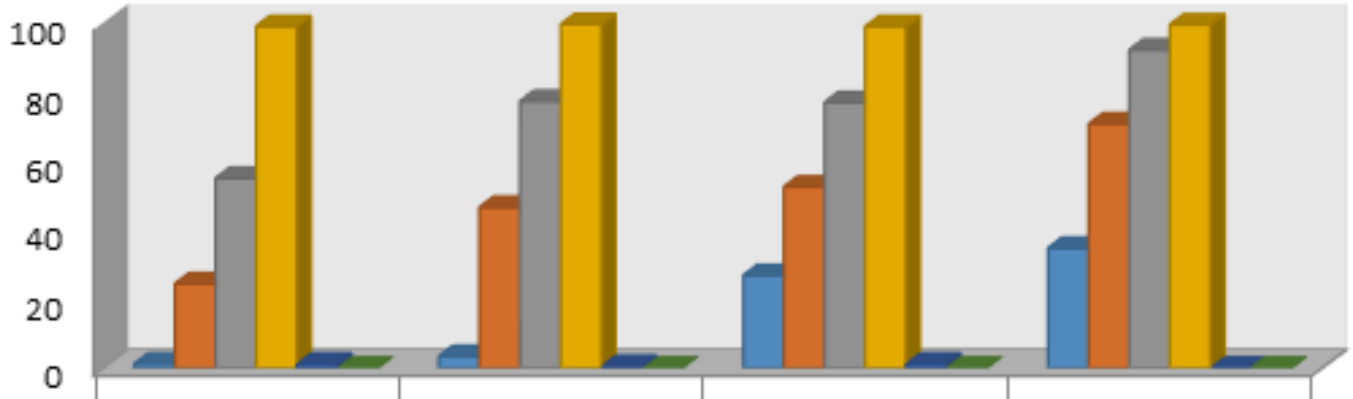
Rafael Fonseca, Emily A. Blood, Martin M. Oken, Robert A. Kyle, Gordon W. Dewald, Richard J. Bailey, Scott A. Van Wier, Kimberly J. Henderson, James D. Hoyer, David Harrington, Neil E. Kay, Brian Van Ness, and Philip R. Greipp

BLOOD, 15 MAY 2002 • VOLUME 99, NUMBER 10

TRANSLOCATION (11;14) MYELOMA

- Approximately 15% of myeloma
- Characteristic lymphoplasmacytoid morphology
- Most common abnormality in primary plasma cell leukemia
- Prevalent in AL amyloidosis
- More likely light chain myeloma
- More common in rare variants: IgM; IgD; non secretory
- Expression of CD20 more common

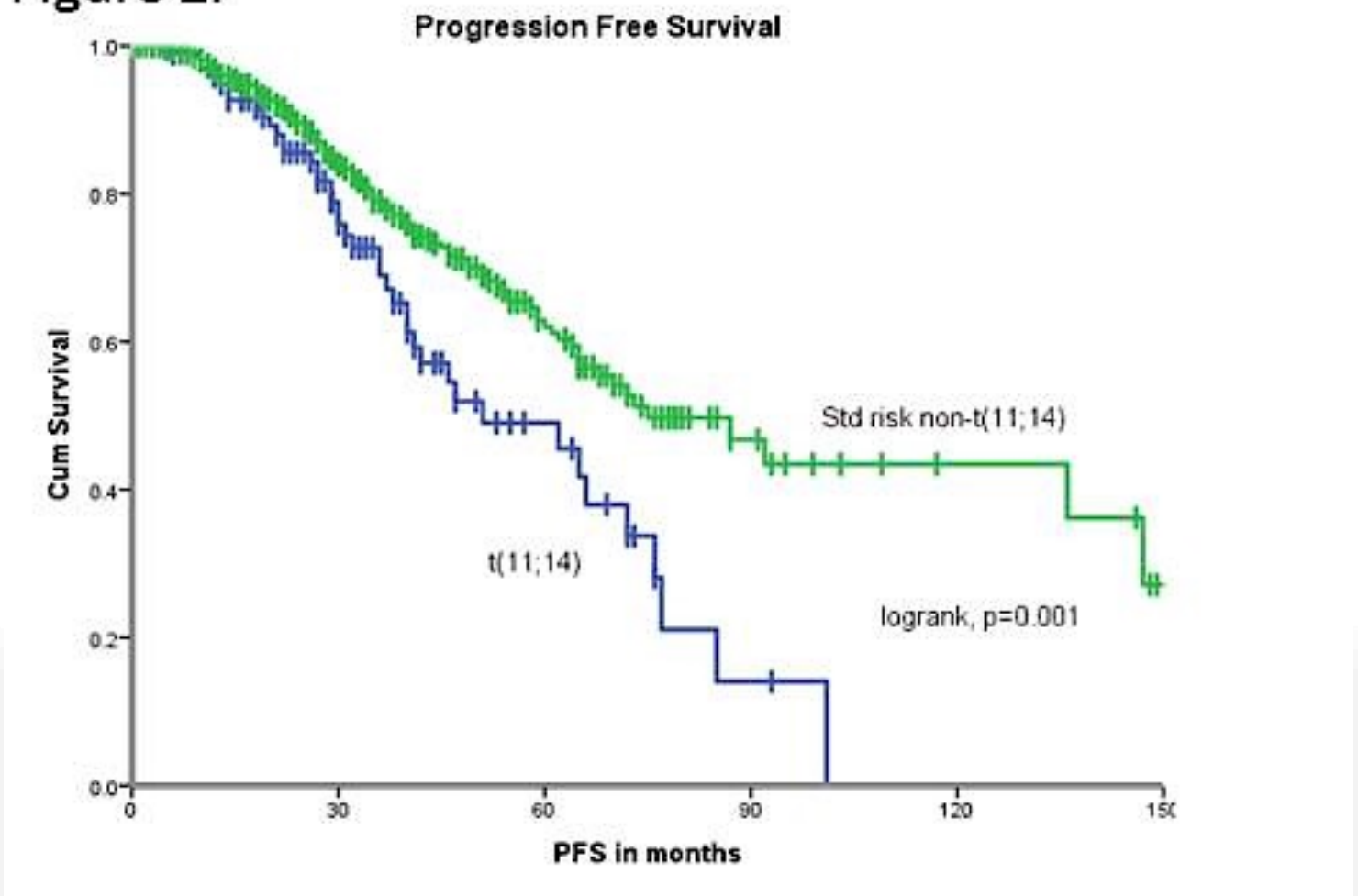
Emory experience in pts with t(11;14)



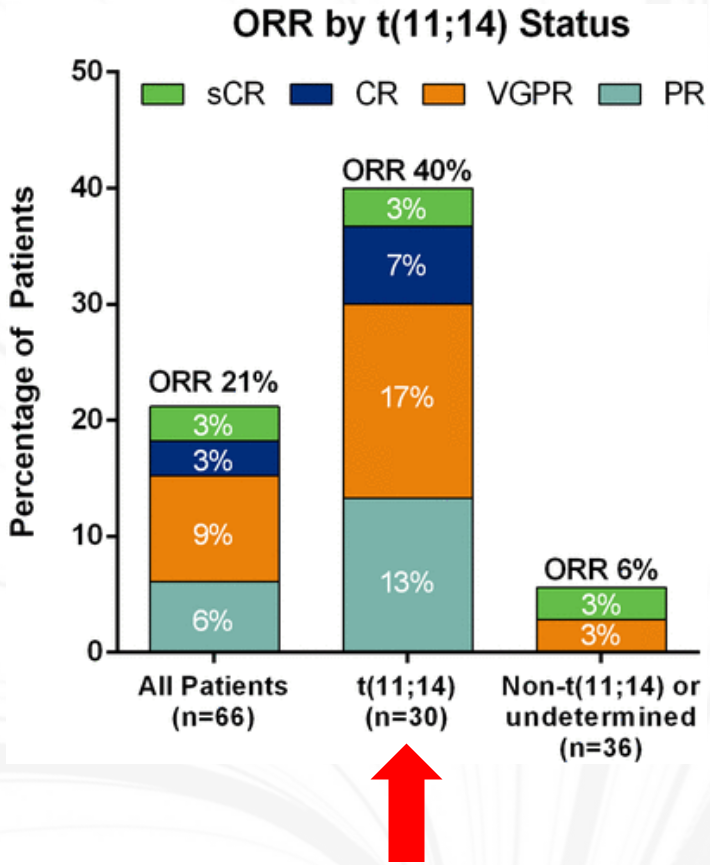
	Post-induction response t(11;14) (N=82)	Post-induction response non-t(11;14) (N=378)	Best response t(11;14) (N=82)	Best response non-t(11;14) (N=375)
sCR %	1.2	3.4	26.8	34.7
sCR + CR %	24.4	46.5	52.4	70.6
≥VGPR %	54.9	77.2	76.8	92
ORR %	98.8	99.4	98.8	99.3
SD %	1.2	0.5	1.2	0
PD %	0	0	0	0

Outcomes of t(11;14) myeloma patients treated with modern therapy are decreased compared to standard risk patients

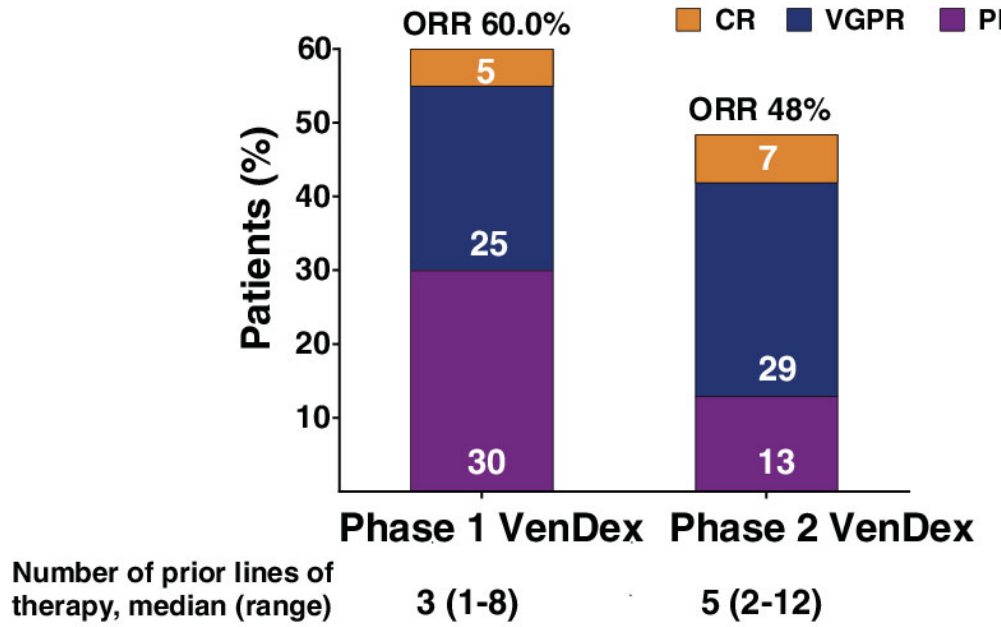
Figure 2.



TARGETING BCL2 IS EFFECTIVE IN PATIENTS WITH t(11;14) MYELOMA



Kumar *et al., Blood* , 2018

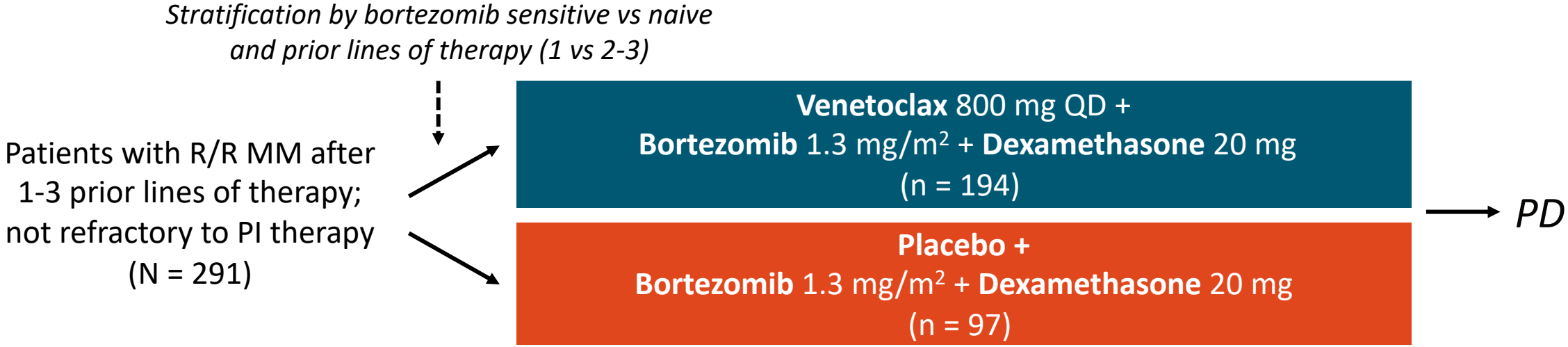


Kaufman *et al., Am. J. Hematol.*, 2021

Jonathan Kaufman
Shaji Kumar

BELLINI Final Survival Analysis: Study Design

- Double-blind, randomized 2:1, placebo-controlled phase III trial



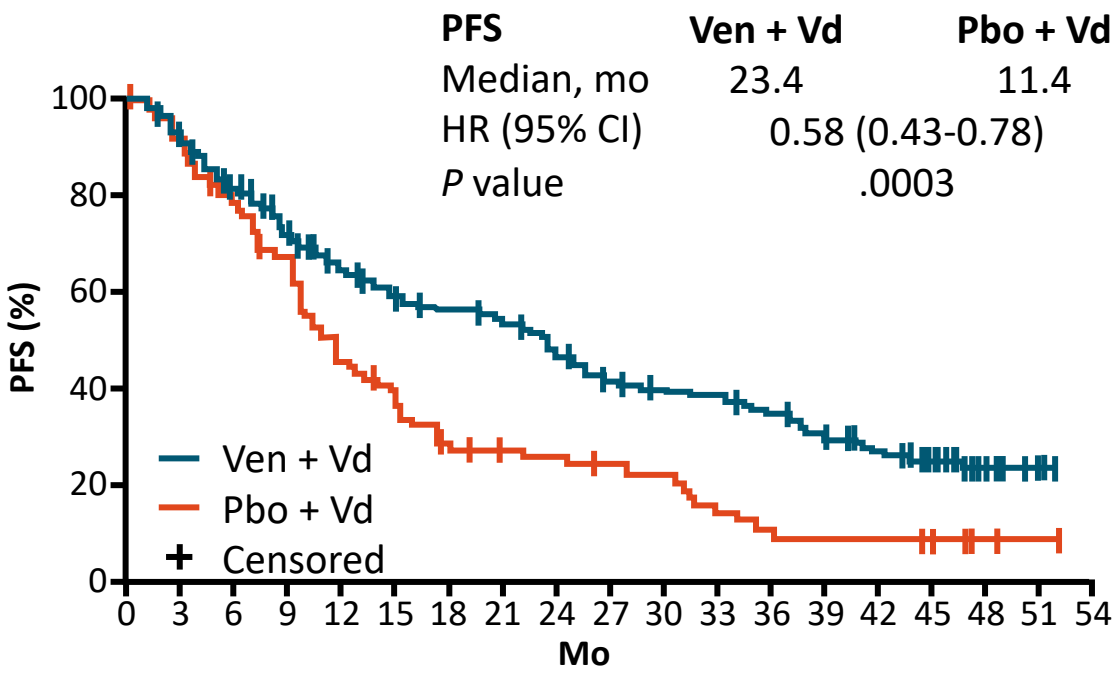
Cycles 1-8: 21-day cycles with bortezomib on Days 1, 4, 8, 11 and dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, 12; cycles 9+: 35-day cycles, bortezomib on Days 1, 8, 15, 22 and dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, 23

- **Primary endpoint:** PFS (per IRC)
- **Key secondary endpoints:** ORR, ≥VGPR, OS, QoL/PRO parameters (PFS was investigator-assessed in final OS analysis)

Kumar. ASH 2021. Abstr 84.

BELLINI Final Survival Analysis: PFS, OS in All Patients

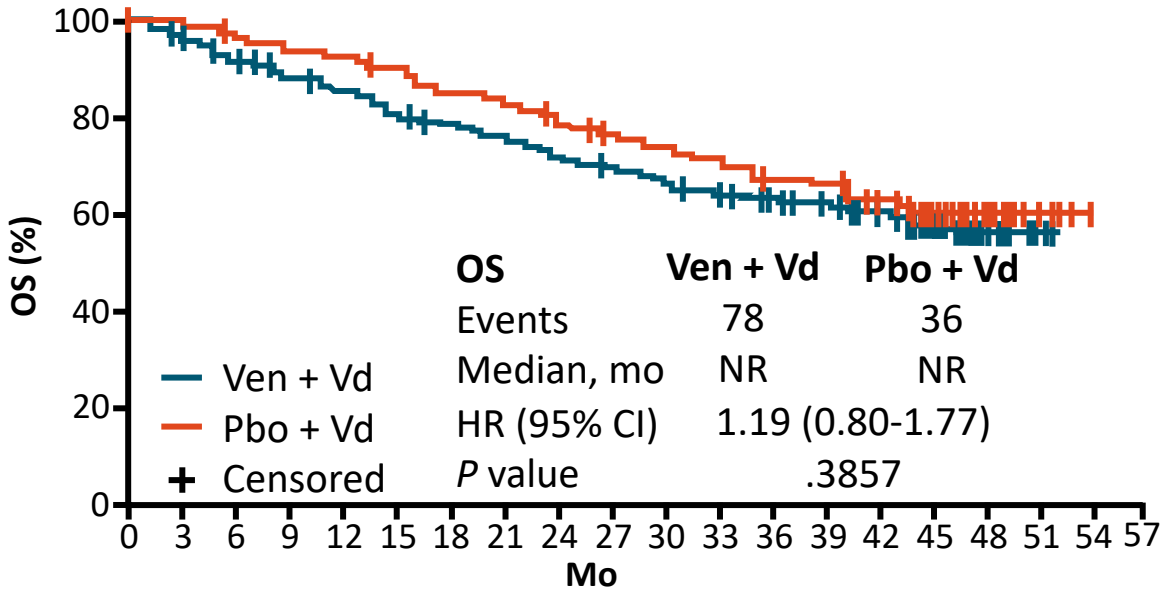
Investigator-Assessed PFS in All Patients



Patients at Risk, n

194	163	140	118	101	89	84	79	68	59	55	53	47	39	32	21	8	2	0
97	83	69	57	39	30	22	20	19	17	15	10	6	7	7	4	2	1	0

OS in All Patients



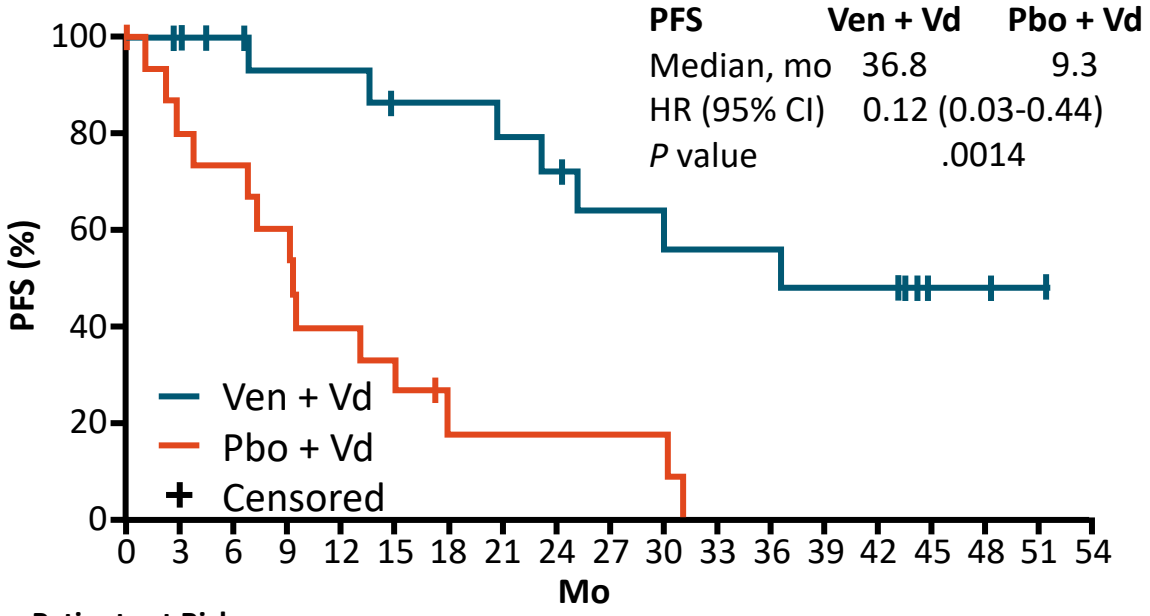
Patients at Risk, n

194	186	173	164	158	149	143	139	131	121	118	113	107	104	89	68	30	6	0	
97	95	91	88	87	84	79	78	73	67	65	63	58	57	50	37	20	6	1	0

Kumar. ASH 2021. Abstr 84. Reproduced with permission.

BELLINI Final Survival Analysis: PFS, OS in t(11;14) Subgroup

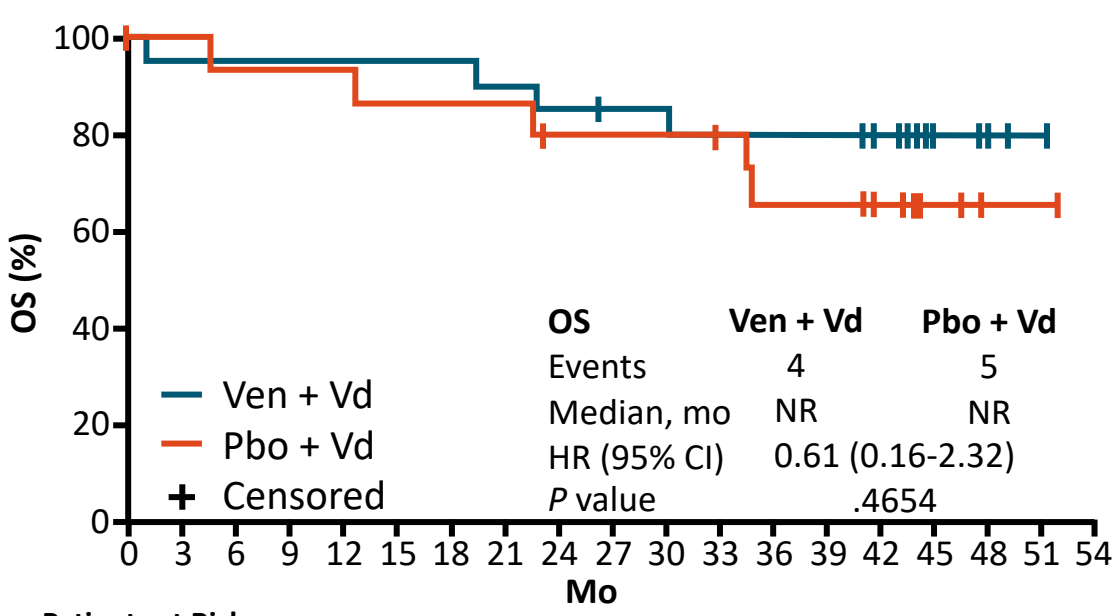
Investigator-Assessed PFS in Patients With t(11;14)



Patients at Risk, n

20	18	16	14	14	12	12	11	10	8	8	7	7	6	6	2	2	1	0
15	12	11	9	6	5	2	2	2	2	2	0							

OS in Patients With t(11;14)



Patients at Risk, n

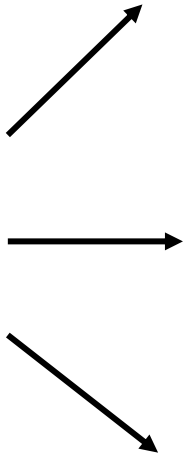
20	19	19	19	19	19	19	18	17	15	15	14	13	13	12	7	4	1	0
15	15	14	14	14	13	13	13	11	11	11	11	9	9	8	3	2	1	0

Kumar. ASH 2021. Abstr 84. Reproduced with permission.

Venetoclax/Dara/Dex vs Bortezomib/Dara/Dex in t(11;14) R/R MM: Part 3 Study Design

- Open-label, randomized phase I/II study (trial not fully accrued)

Patients with t(11;14) R/R MM after ≥1 prior therapy including IMiD; not refractory to PIs or CD38 antibodies; ECOG PS ≤2, no PN grade ≥3 or ≥2 with pain within 2 wk of first dose (N = 41)



Venetoclax 400 mg QD + **Daratumumab** 1800 mg SC + **Dexamethasone** 40 mg QW PO or IV (n = 15)

Venetoclax 800 mg QD + **Daratumumab** 1800 mg SC + **Dexamethasone** 40 mg QW PO or IV (n = 7)

Bortezomib 1.3 mg/m² SC or IV **Daratumumab** 1800 mg SC + **Dexamethasone** 20 mg PO or IV (n = 19)

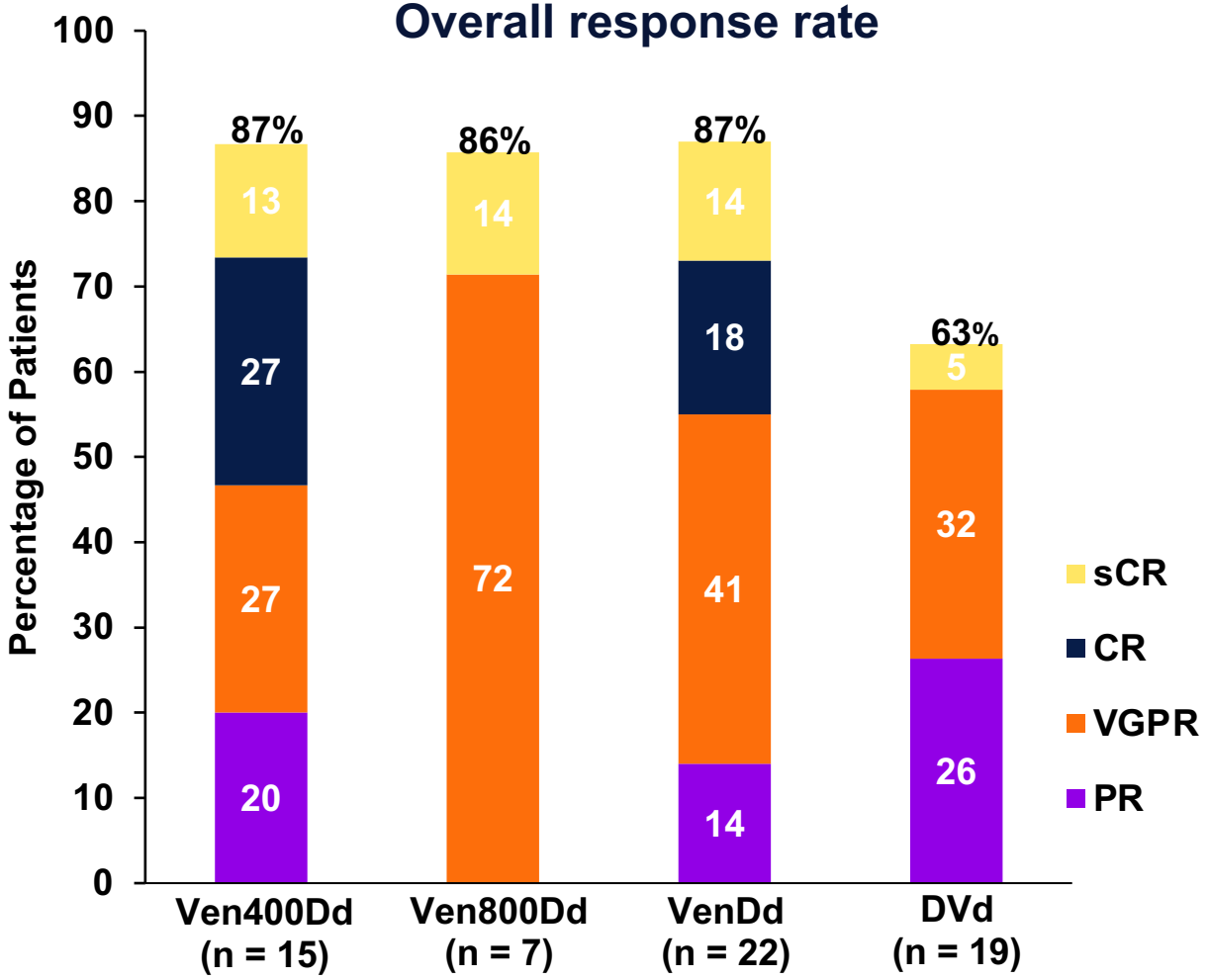
Cycle	Venetoclax	Dara	Dex
1-2 (28 days)	Once daily	D1, 8, 15, 22	Weekly
3-6 (28 days)	Once daily	D1, 15	Weekly
7+ (28 days)	Once daily	D1	Weekly
Cycle	**Bortez**	**Dara**	**Dex**
1-3 (21 days)	D1, 4, 8, 11	D1, 8, 15	D1, 2, 4, 5, 8, 9, 11, 12, 15
4-8 (21 days)	D1, 4, 8, 11	D1	D1, 2, 4, 5, 8, 9, 11, 12
9+ (28 days)	--	D1	D1

- Primary objective: safety and preliminary efficacy

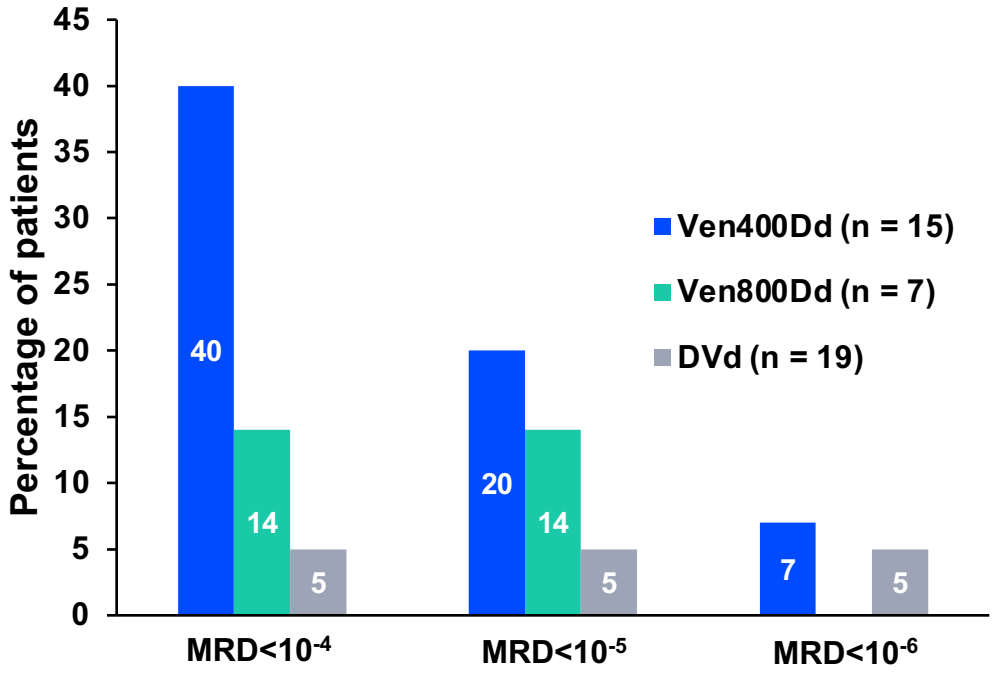
Kaufman. ASH 2021. Abstr 817.

VenDd arms achieved deep responses including MRD negativity

Overall response rate

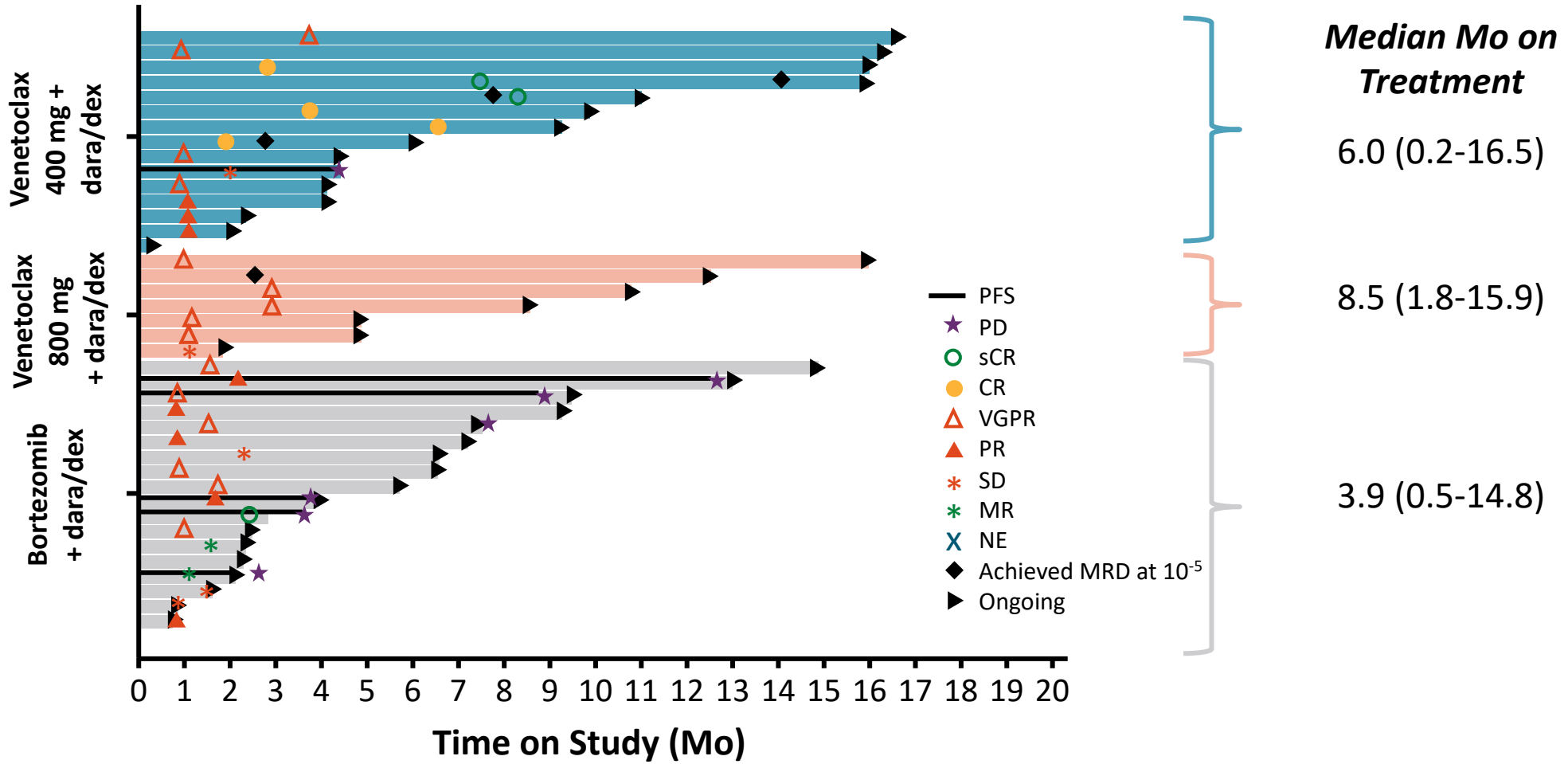


Minimal residual disease



sCR, stringent complete response, CR, complete response; ORR, overall response rate; VGPR, very good partial response; PR, partial response, MRD, minimal residual disease; Ven, venetoclax; Ven400, venetoclax 400 mg; Ven800, venetoclax 800 mg; D, daratumumab; d, dexamethasone; V, bortezomib

Venetoclax/Dara/Dex vs Bortezomib/Dara/Dex in t(11;14) R/R MM: Duration of Response

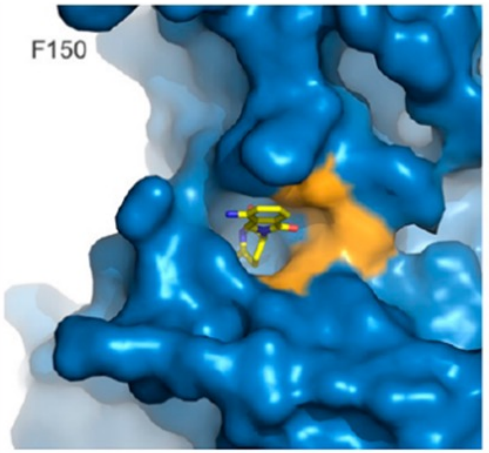


Kaufman. ASH 2021. Abstr 817. Reproduced with permission.

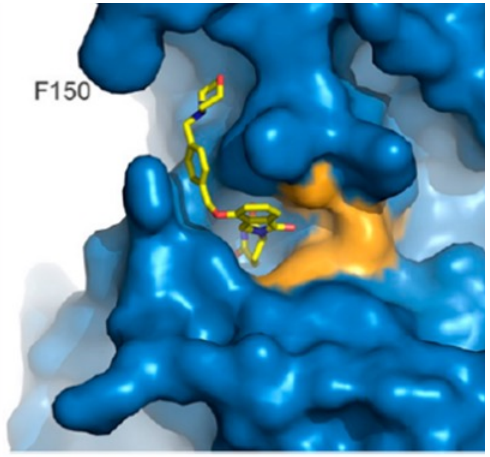
Iberdomide

- IBER binds to CRBN with higher affinity and degrades the target proteins Ikaros and Aiolos more potently compared with LEN and POM[1]

LEN[2]

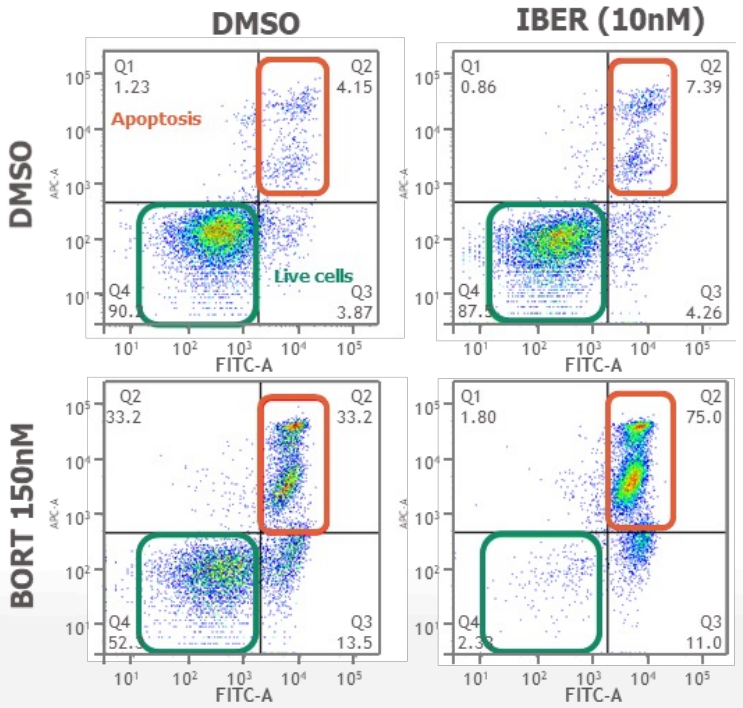


IBER[2]



EC_{50}, nM^2	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

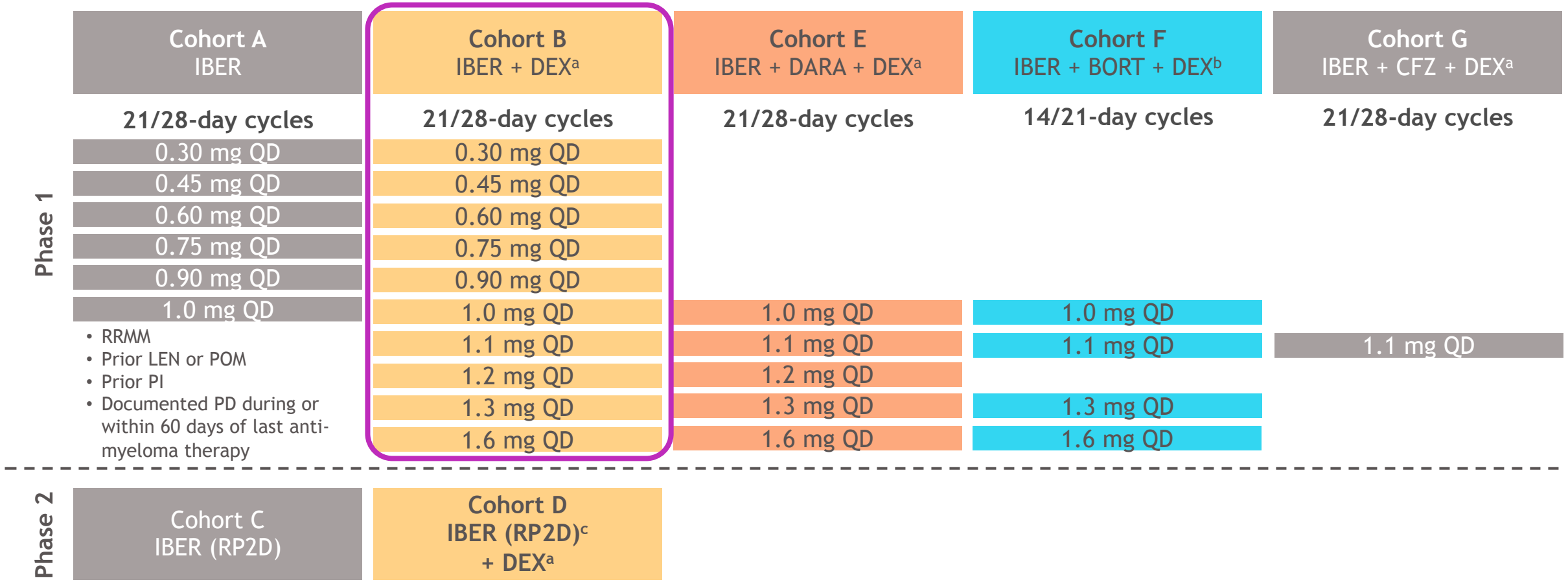
- IBER has marked synergistic tumoricidal and immune-stimulatory effects in combination with BORT or DARA in preclinical MM models[3-6]



- BORT, bortezomib; DARA, daratumumab; DSMO, dimethyl sulfoxide; EC50, half-maximal effective concentration; FITC, fluorescein isothiocyanate.
- 1. Bjorklund CC, et al. *Leukemia* 2020:34:1197–1201. 2. Adapted with permission from Matyskiela ME, et al. *J Med Chem* 2018;61:535-542 © 2018 American Chemical Society. 3. Amatangelo M, et al. *Blood* 2018; 132:1935; 4. Lonial S, et al. *Blood* 2019;134:3119. 5. Amatangelo M, et al. Presented at ASH 2020; December 5-8. Abstract 1358. 6. Amatangelo M, et al. Presented at ASH 2020; December 5-8. Abstract 1359.

van de Donk NWCJ, et al. ASH 2020. Abstract 724.

CC-220-MM-001: phase1/2 study design



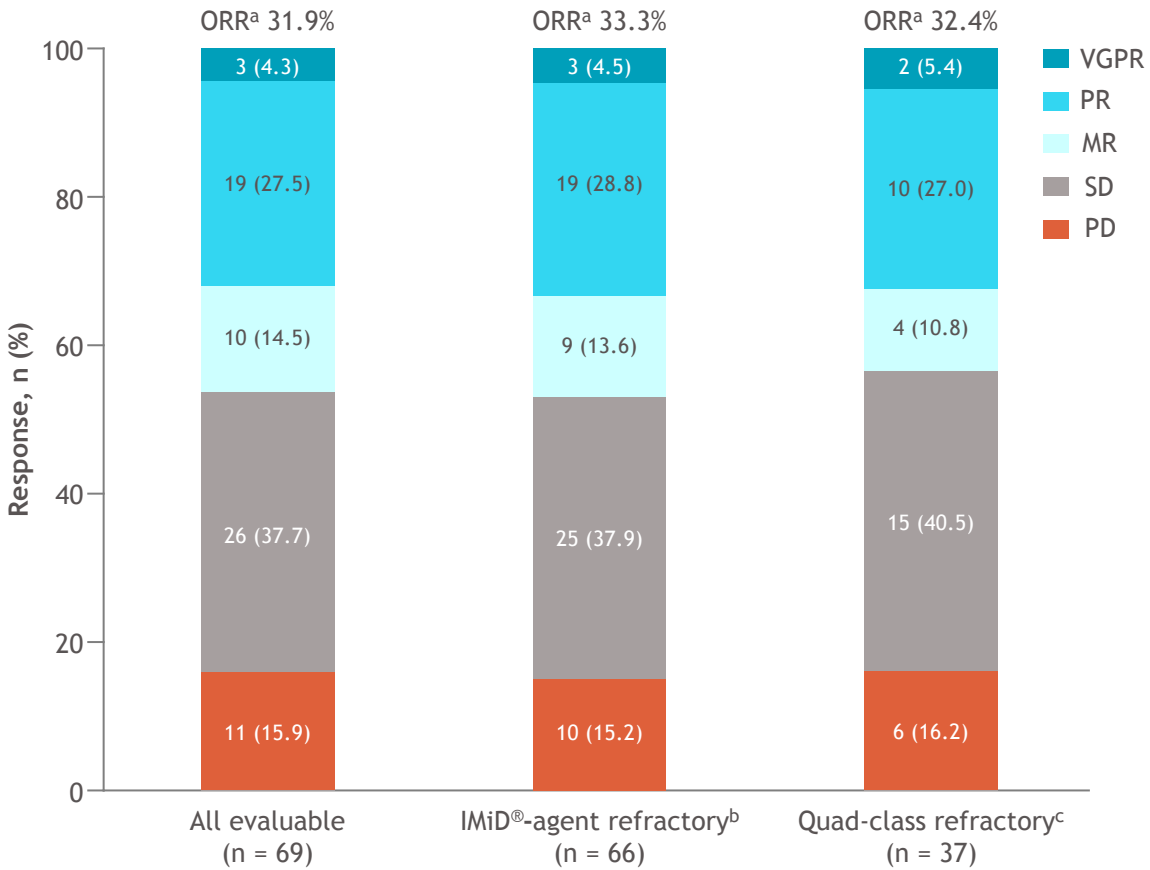
Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

[a] DEX given at a dose of 40 mg (20 mg in patients ≥ 75 years of age) on D1, 8, 15, and 22 of each 28-day cycle; [b] DEX given at a dose of 40 mg (20 mg in patients ≥ 75 years of age) on D1, 8, and 15 of each 21-day cycle. CFZ dosed once weekly (cohort G1) or twice weekly (cohort G2); [c] 1.6 mg QD.

PD, progressive disease; QD, once daily; RP2D, recommended phase 2 dose.

van de Donk NWCJ, et al. Oral presentation at ASH 2020; abstract 724.

CC-220-MM-001: response rates and safety



Common (> 20% all grade) TEAEs and events of interest, n (%)	Cohort B (IBER + DEX) (N = 75)		
	All grade	Grade 3	Grade 4
Anaemia	32 (42.7)	20 (26.7)	1 (1.3)
Neutropenia	30 (40.0)	13 (17.3)	12 (16.0)
Febrile neutropenia	4 (5.3)	4 (5.3)	0
Thrombocytopenia	13 (17.3)	3 (4.0)	5 (6.7)
Infection	38 (50.7)	16 (21.3)	1 (1.3)
Fatigue	26 (34.7)	0	1 (1.3)
Insomnia	23 (30.7)	0	0
Back pain	16 (21.3)	6 (8.0)	0
Muscle spasms	15 (20.0)	0	0
Diarrhoea	15 (20.0)	0	0
Constipation	11 (14.7)	1 (1.3)	0
Peripheral sensory neuropathy	4 (5.3)	1 (1.3)	0
Deep vein thrombosis	1 (1.3)	0	0
Pulmonary embolism	1 (1.3)	1 (1.3)	0

Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

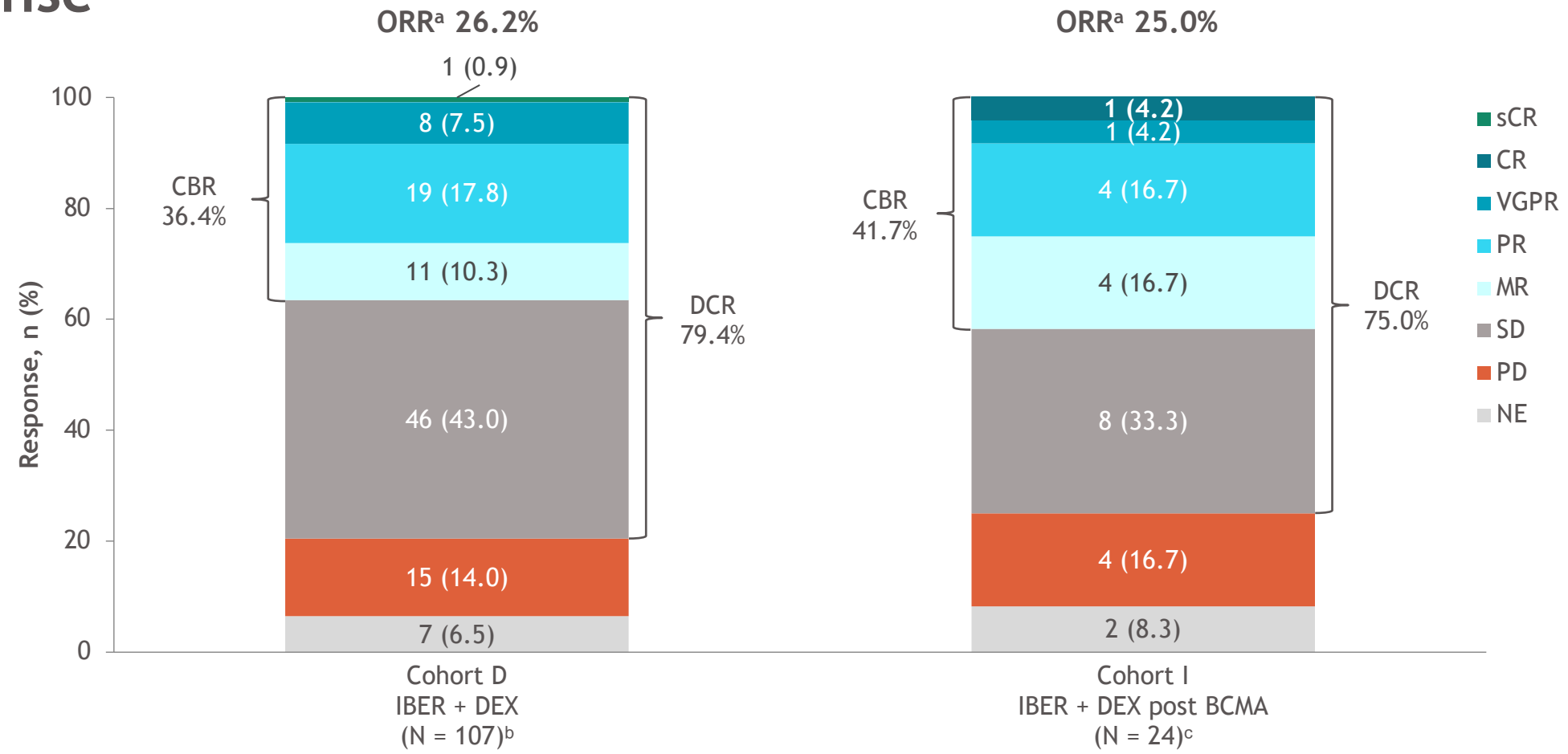
[a] PR or better. Evaluable patients include patients who have received ≥ 1 dose of IBER, had measurable disease at baseline, and ≥ 1 post-baseline response assessment; [b] Refractory to LEN or POM; [c] Refractory to ≥ 1 IMiD® agent, 1 PI, 1 anti-CD38 mAb, and 1 steroid.

mAb, monoclonal antibody; MR, minimal response; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

Lonial S, et al. Oral presentation at ASCO 2019; abstract 8006. Lonial S, et al. *Blood* 2019;134:abstract 3119.

CC-220-MM-001: cohort D and I (dose-expansion phase)

Response



Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

Numbers have been rounded-off to nearest integer.

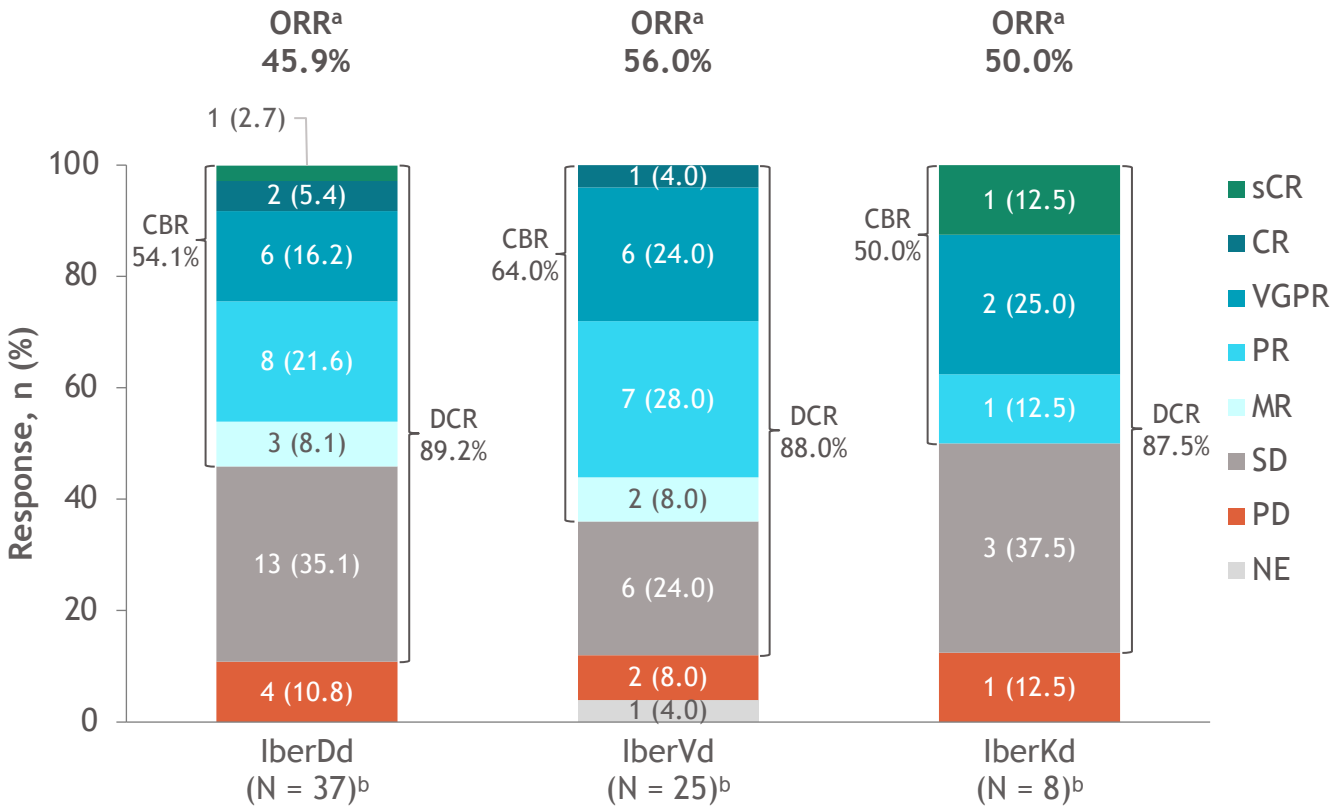
[a] PR or better; [b] 2 patients in SD and MR discontinued treatment because of death due to COVID-19; [c] Includes all treated patients who have post-baseline efficacy assessment or have discontinued treatment before any post-baseline efficacy assessment (2 patients were in C1 with no post-baseline efficacy assessments so were excluded from analysis).

CBR, clinical benefit rate; COVID, coronavirus disease; CR, complete response; DCR, disease control rate; NE, not evaluable; sCR, stringent complete response.

Lonial S, et al. Oral presentation at ASH 2021; abstract 162.

CC-220-MM-001: iberdomide in combination with DEX and DARA, BORT, or CFZ (Cohorts E, F and G) in patients with RRMM

- IBER + DEX in combination with DARA or BORT or CFZ showed a favourable safety profile in patients with heavily pretreated RRMM; TEAEs were mainly haematologic and well manageable
- The RP2D was determined at 1.6 mg in the IberDd cohort, while dose evaluation continues in the IberVd and IberKd cohorts
- Efficacy was observed even among patients refractory to IMiD® agents, DARA, and PIs



Iberdomide (IBER; CC-220) is an investigational product, currently not approved by any regulatory agency.

Numbers have been rounded-off to nearest integer.

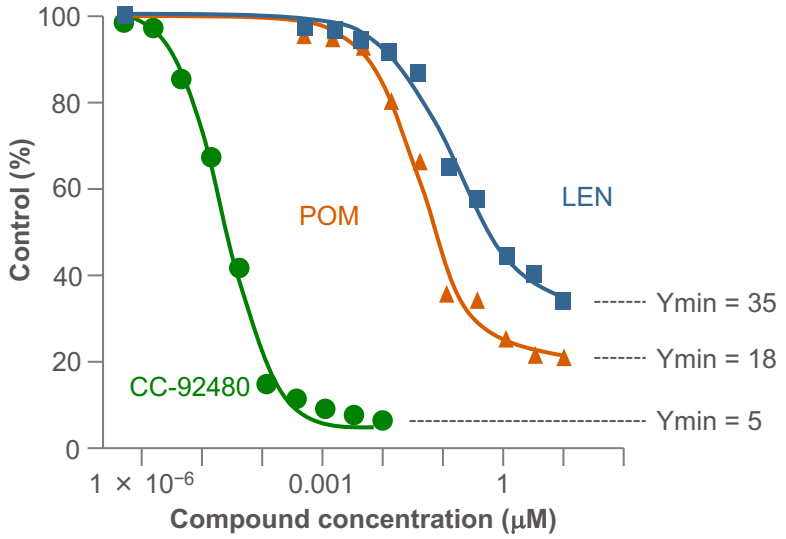
[a] PR or better; [b] Excludes treated patients who did not reach any post-baseline efficacy assessment and were still on treatment at time of data cut-off.

Lonial S, et al. Oral presentation at EHA 2021; abstract S187.

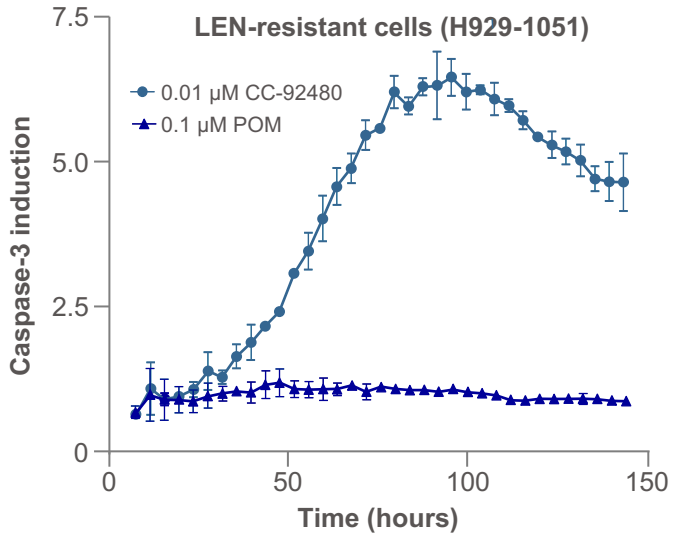
Mezigdomide (CC-92480) is a Novel CELMoD® Agent[1,2]

Efficient substrate degradation leading to apoptosis and potent antiproliferative activity in LEN and POM resistance[3]

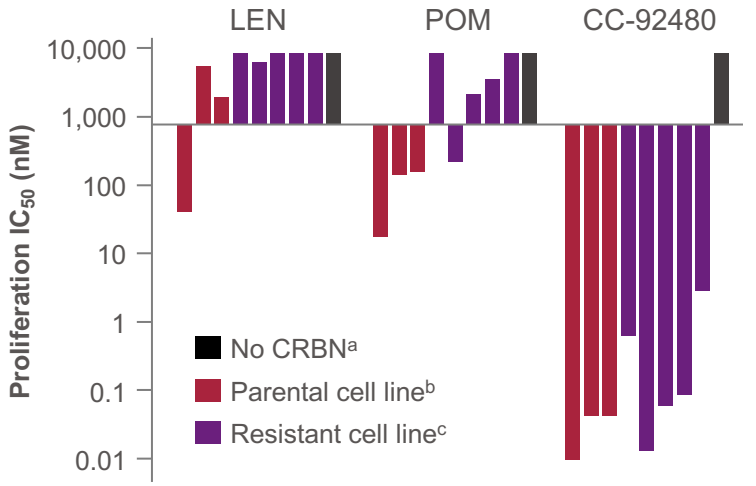
Aiolos degradation efficiency[1]

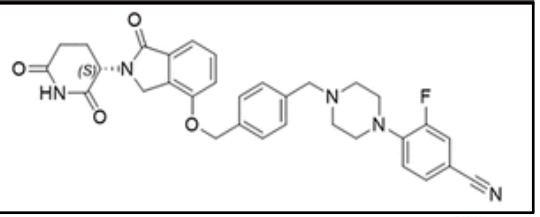
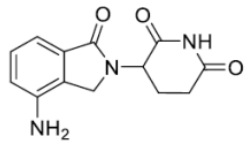
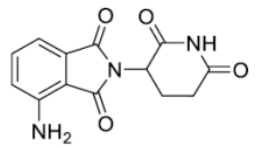


Apoptosis induction kinetics



Antiproliferative activity in LEN/POM resistance



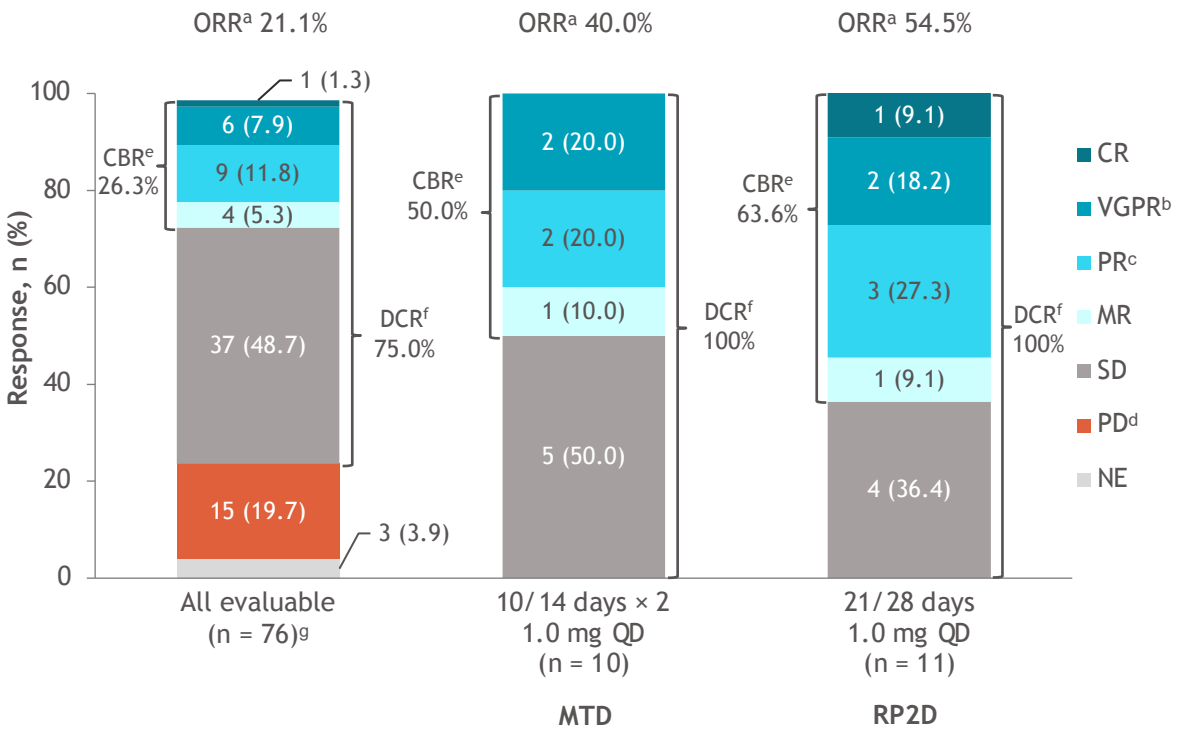
CC-92480, a potent CELMoD® agent[1]	LEN[1]	POM[1]
		

CC-92480 is an investigational product, currently not approved by any regulatory agency.

[a] DF15R; [b] DF15, H929, and OPM-2; [c] H929R1, H929R2, OPM-2R1, OPM-2R2, and OPM-2R3. IC_{50}, 50% inhibitory concentration; Ymin, maximum degradation point.

1. Hansen JD, et al. *J Med Chem* 2020;63:6648–6676; 2. Wong L, et al. *Blood* 2019;134(suppl 1). Abstract 1815; 3. Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

CC-92480-MM-001: efficacy and safety in patients with heavily pretreated RRMM



Common (> 20% all grade) TEAEs and events of interest, n (%)	All doses (N = 76)	
	Grade 3	Grade 4
Neutropenia	23 (30.3)	26 (34.2)
Febrile neutropenia	4 (5.3)	1 (1.3)
Anaemia	24 (31.6)	-
Thrombocytopenia	5 (6.6)	7 (9.2)
Fatigue	7 (9.2)	-
Pyrexia	3 (3.9)	-
Peripheral sensory neuropathy	-	-
Diarrhoea	1 (1.3)	-
Nausea	1 (1.3)	-
Deep vein thrombosis	-	-
Infections	25 (32.9)	2 (2.6)
Pneumonia[h]	11 (14.5)	-

- Prophylactic G-CSF was not permitted during C1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reduction of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

Mezigdomide (CC-92480) is an investigational product, currently not approved by any regulatory agency.

Numbers have been rounded-off to nearest integer.

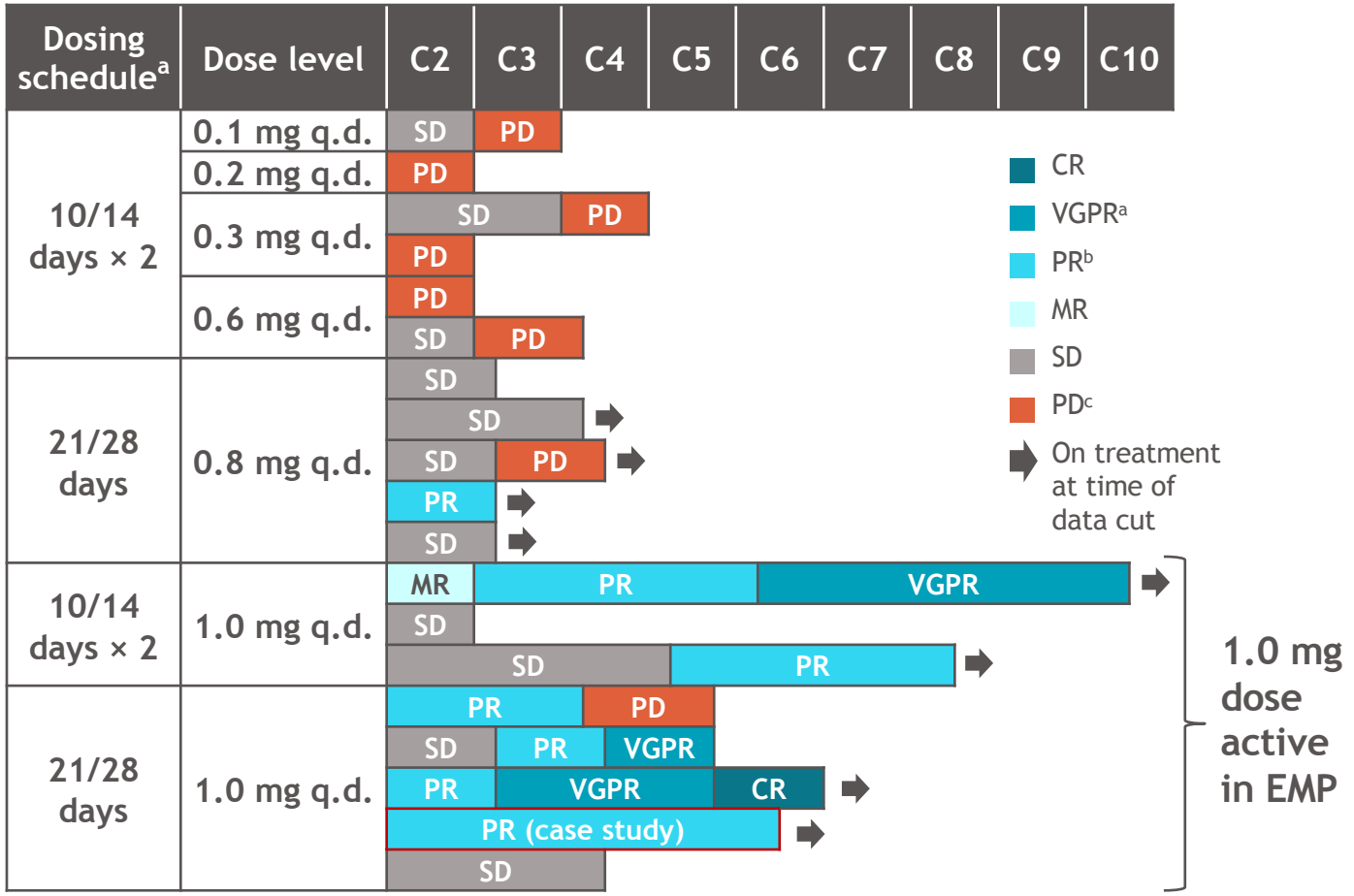
[a] PR or better; [b] 1 patient in the 21/28-day 1.0-mg QD cohort had an unconfirmed VGPR at time of data cut-off; [c] 2 patients in the 21/28-day 0.8-mg QD cohort had an unconfirmed PR at time of data cut-off; [d] 1 patient in the 21/28-day 0.8-mg QD cohort had an unconfirmed PD at time of data cut-off; [e] CBR defined as MR; [f] DCR defined as SD; [g] 1 patient had a pending response assessment at time of data cut-off; [h] 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.

Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

Responses in patients with EMP

- Only patients on continuous schedules are shown

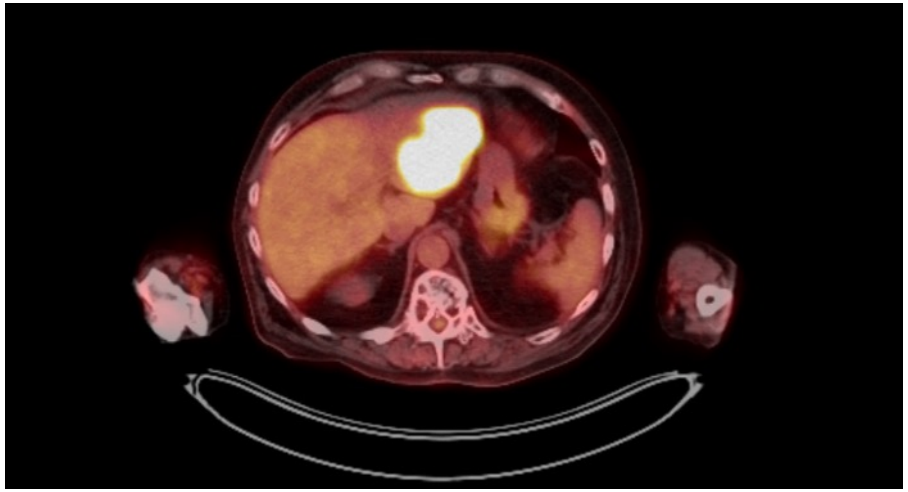


CC-92480 is an investigational product, currently not approved by any regulatory agency.

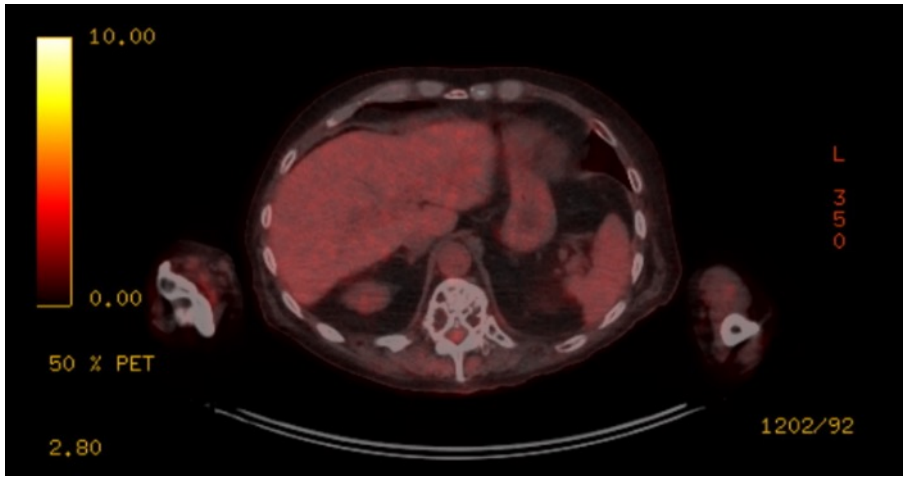
[a] 1 patient in the 21/28-day 1.0 mg q.d. cohort had an unconfirmed VGPR as of the data cut-off date. [b] 1 patient in the 21/28-day 0.8 mg q.d. cohort had an unconfirmed PR as of the data cut-off date. [c] 1 patient in the 21/28-day 0.8 mg q.d. cohort had an unconfirmed PD as of the data cut-off date. EMP, extramedullary plasmacytoma; PET, positron emission tomography.

Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

PET scan pretreatment



PET scan post CC-92480 C3D1



CFT 7455

CFT7455: A novel small molecule protein degrader, mechanism of action and pharmacologic characteristics

- Novel small molecule binds to Cereblon E3 ligase (CRBN)
- Creates a new surface on CRBN for interaction with the transcription factors IKZF1/3
- As a result, IKZF1/3 are ubiquitinated by the CRBN E3 ligase and degraded by the proteasome (Figure 2.)
- The high CRBN binding affinity (IC50=0.9nM) of CFT7455 enables rapid, deep, and durable degradation of IKZF1/3 resulting in apoptosis and potent activity in MM cell lines and multiple types of NHL cell lines in vitro
- In vivo, oral administration of CFT7455 in mice led to regression of MM and lymphoma in xenograft models
- CFT7455 promotes T-Cell activation[1,5]

Figure 1.

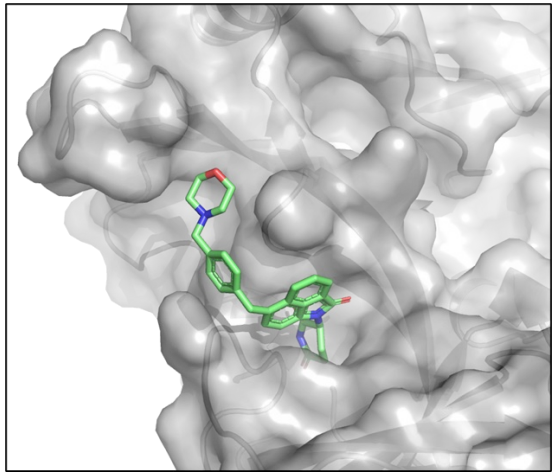


Figure 2: Mechanism of Action for CFT7455

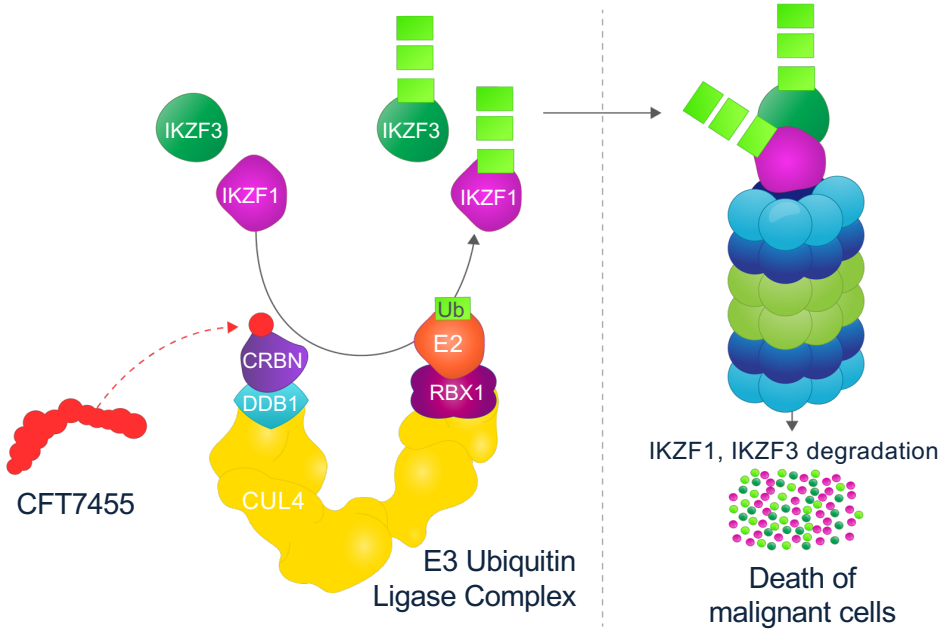
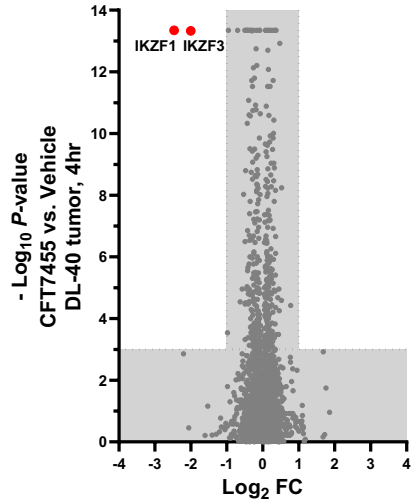


Figure 3: *In Vivo* Global Proteomics



Across ~8,000 proteins assessed in DL-40 xenograft, *in vivo*, the only proteins observed to be downregulated by CFT7455 are the intended targets IKZF1 and IKZF3

Other Precision Medicine options

- My DRUG trial presented by Kumar et al at ASCO demonstrated that mutation driven care could offer benefit in the right subsets
  - BRAF mutated
  - IDH mutated

Likely that Combination therapy will be needed for durable responses due to clonal escape

Conclusions

- Precision medicine is here, particularly for t(11;14) myeloma
- Venetoclax doesn’t need ramp up or caution used in CLL
- Combination therapy is often the way to go
- CELMoDs are here and not only have more potency, may have better AE profile
- Combinations here are the way as well
- Mutations may be important with the right agents and at the right time

Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
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