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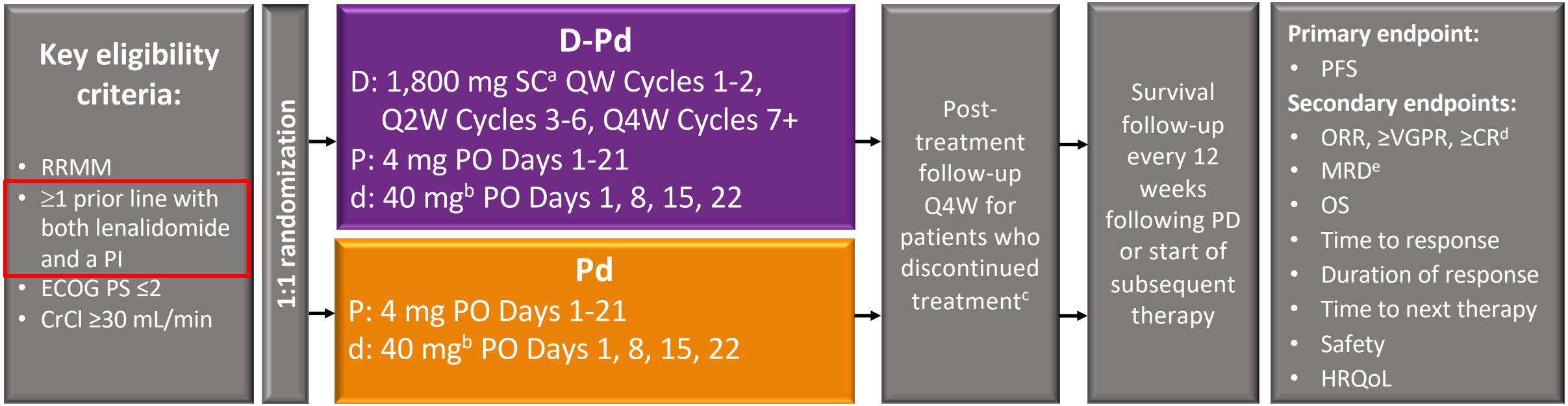
APOLLO Dara-Pd



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

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Dimopoulos et al ASH 2020

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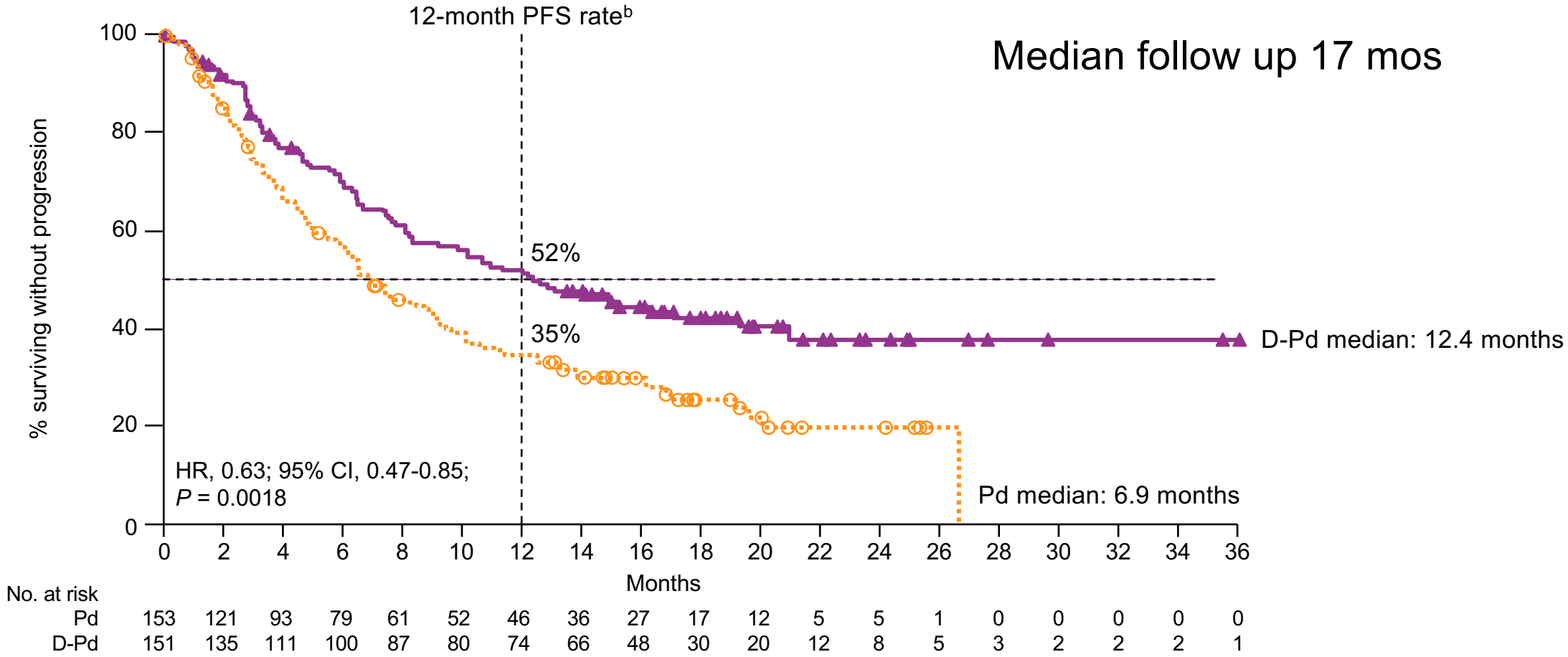

- Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

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Dimopoulos et al ASH 2020

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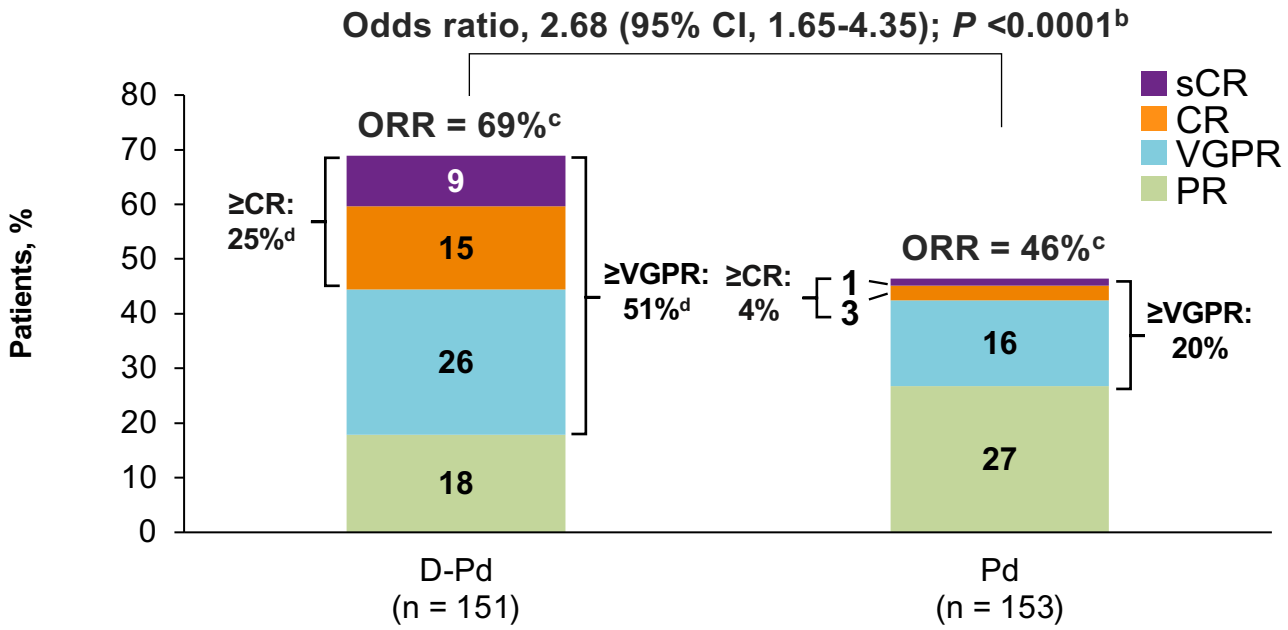
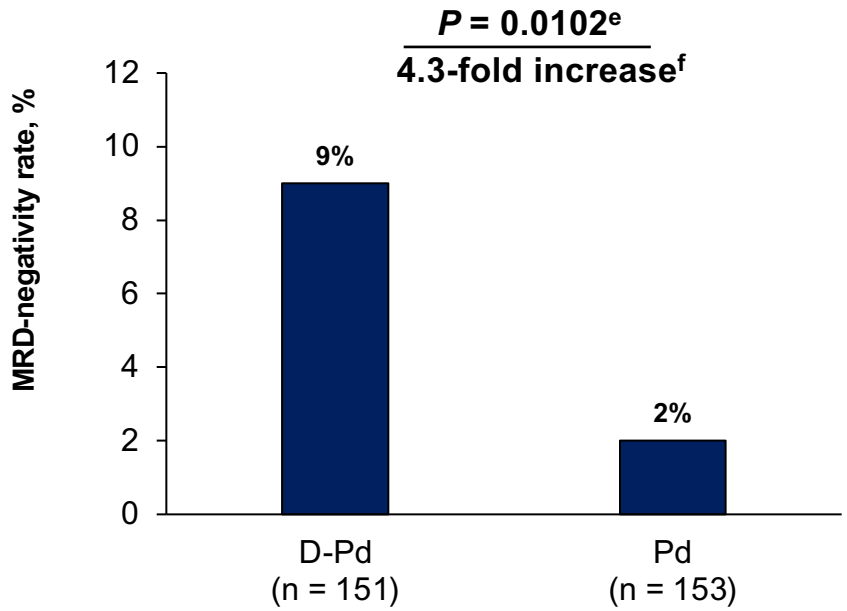
APOLLO Dara-Pd

Hematologic response



MRD negativity



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Dimopoulos et al ASH 2020

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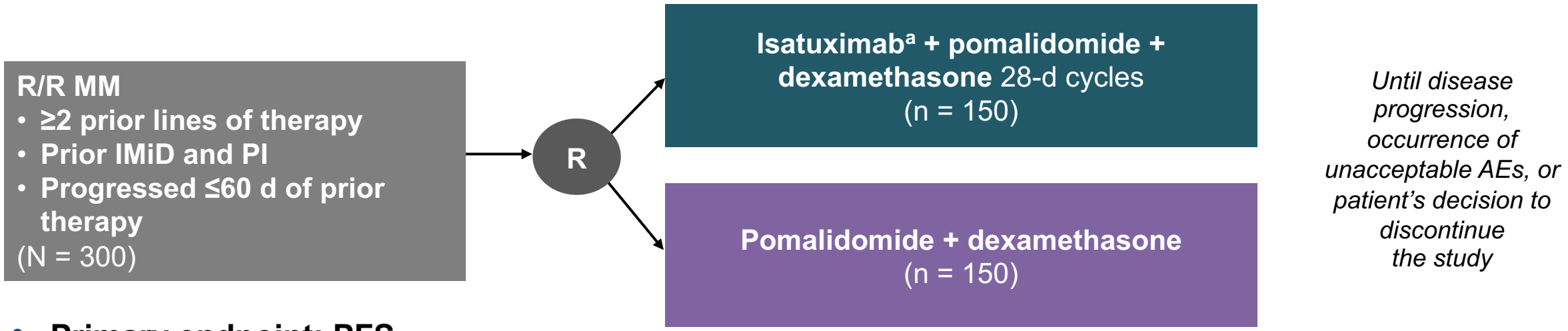
ICARIA: Isatuximab + Pd



- **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.

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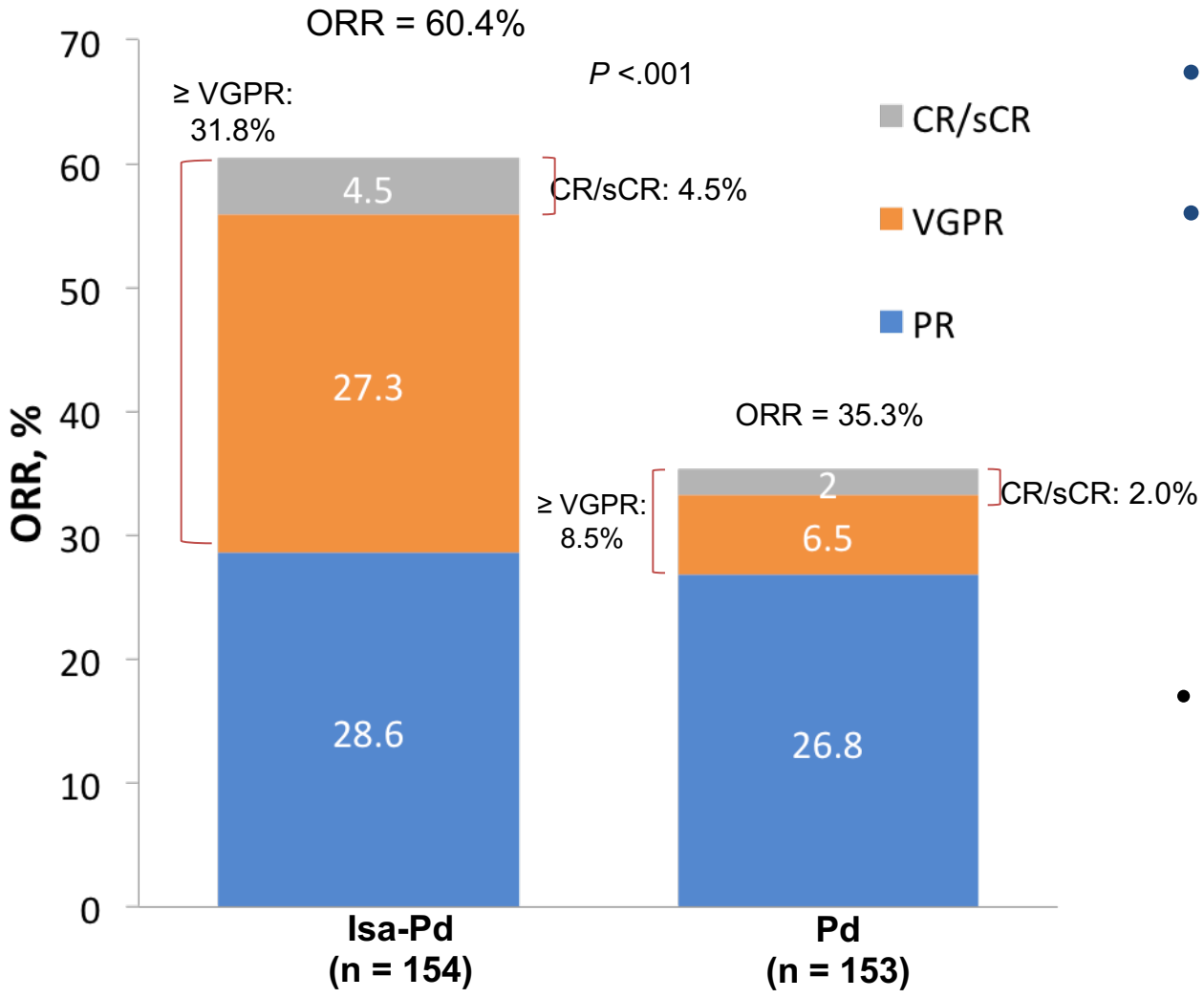
ICARIA-MM: Response



- **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

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

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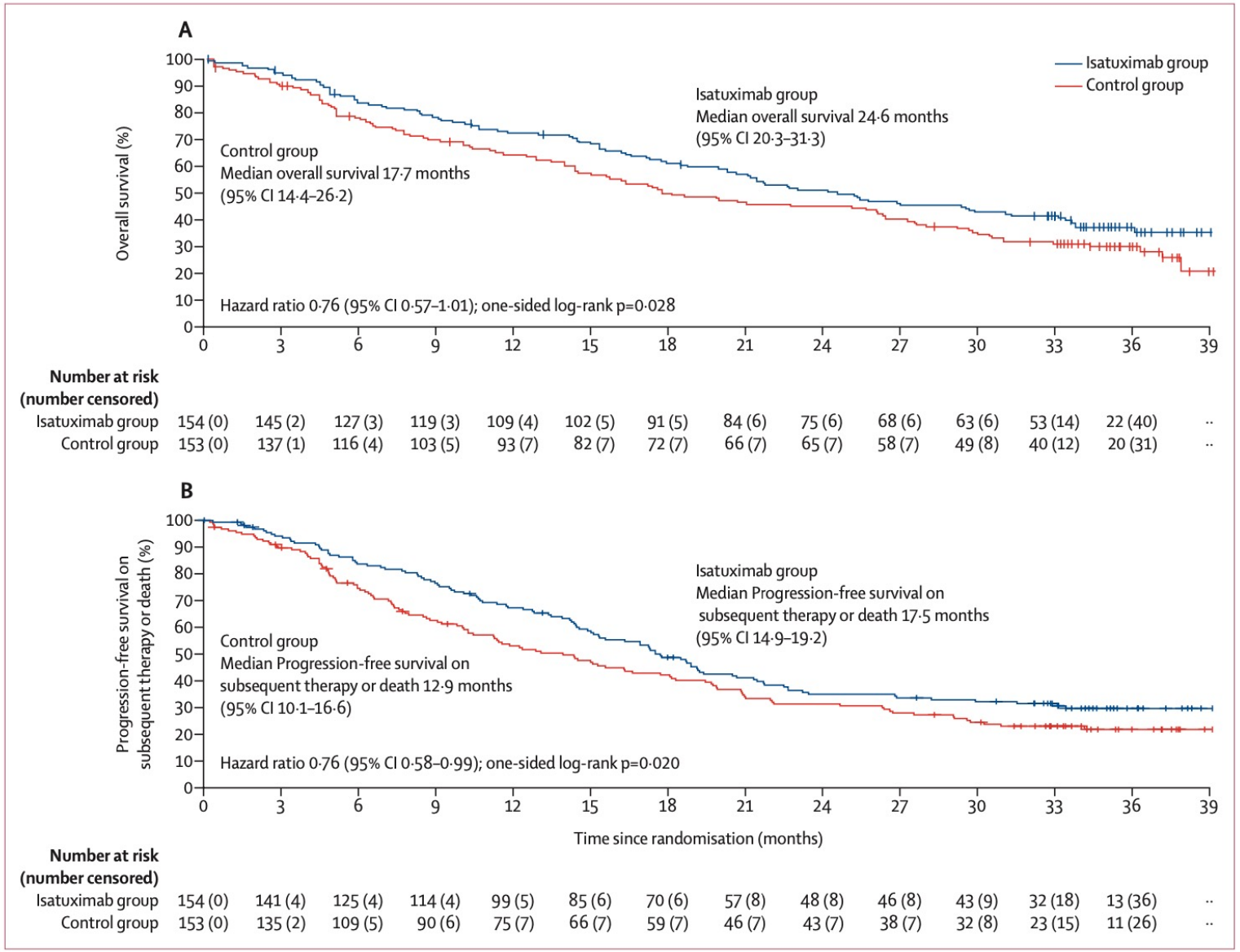
ICARIA-MM: OS



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Richardson PG, et al. Lancet Oncology Feb 2022.

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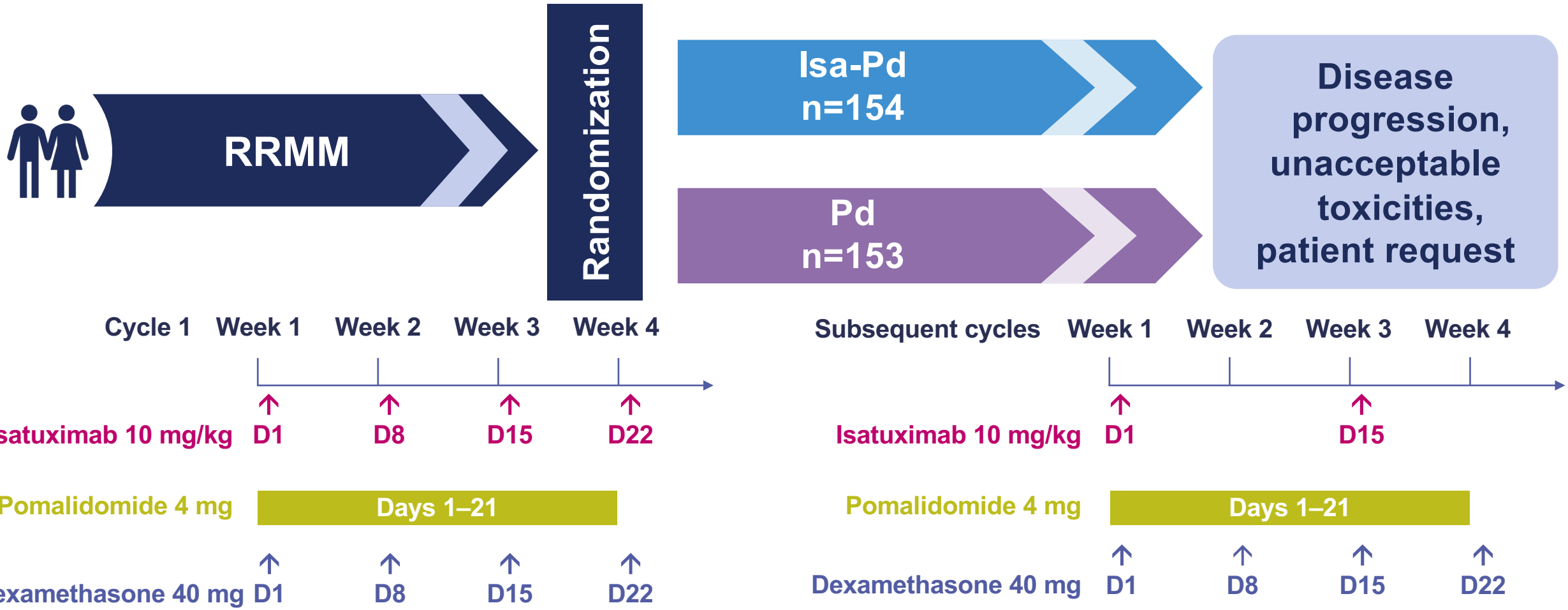
ICARIA-MM Study design



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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**

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

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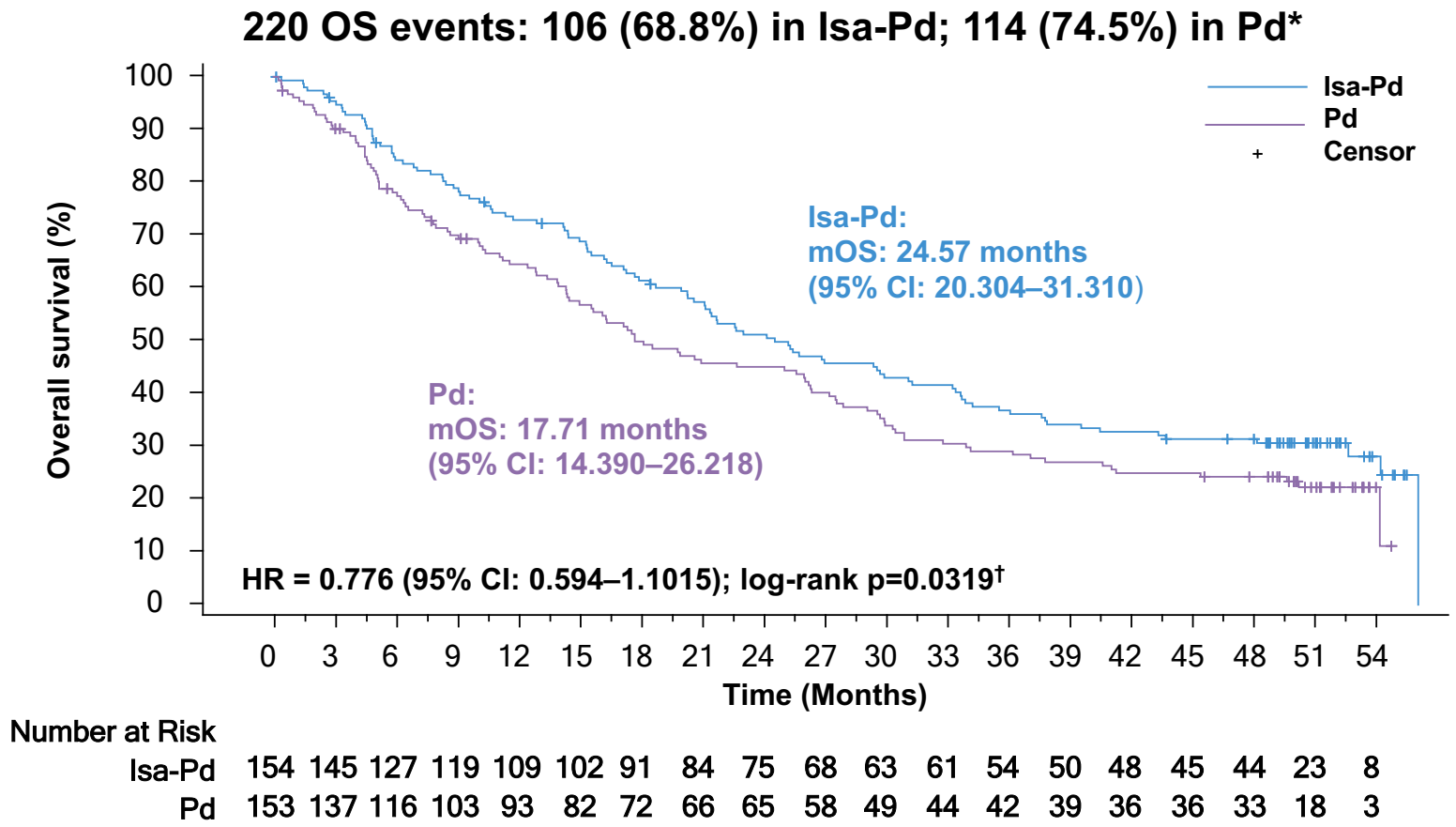
ICARIA-MM Final OS analysis



*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.

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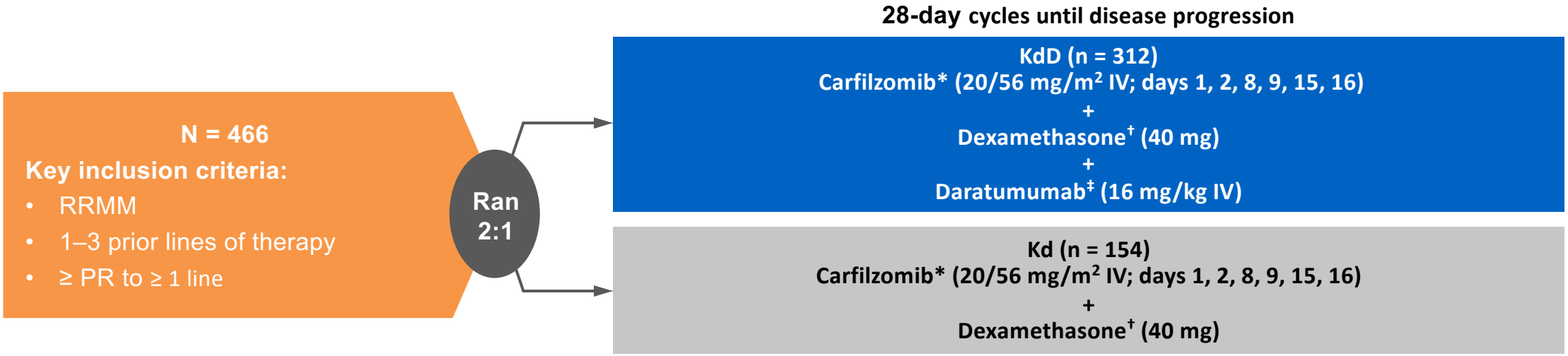
CANDOR (KdD vs Kd in RRMM)

- 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.

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

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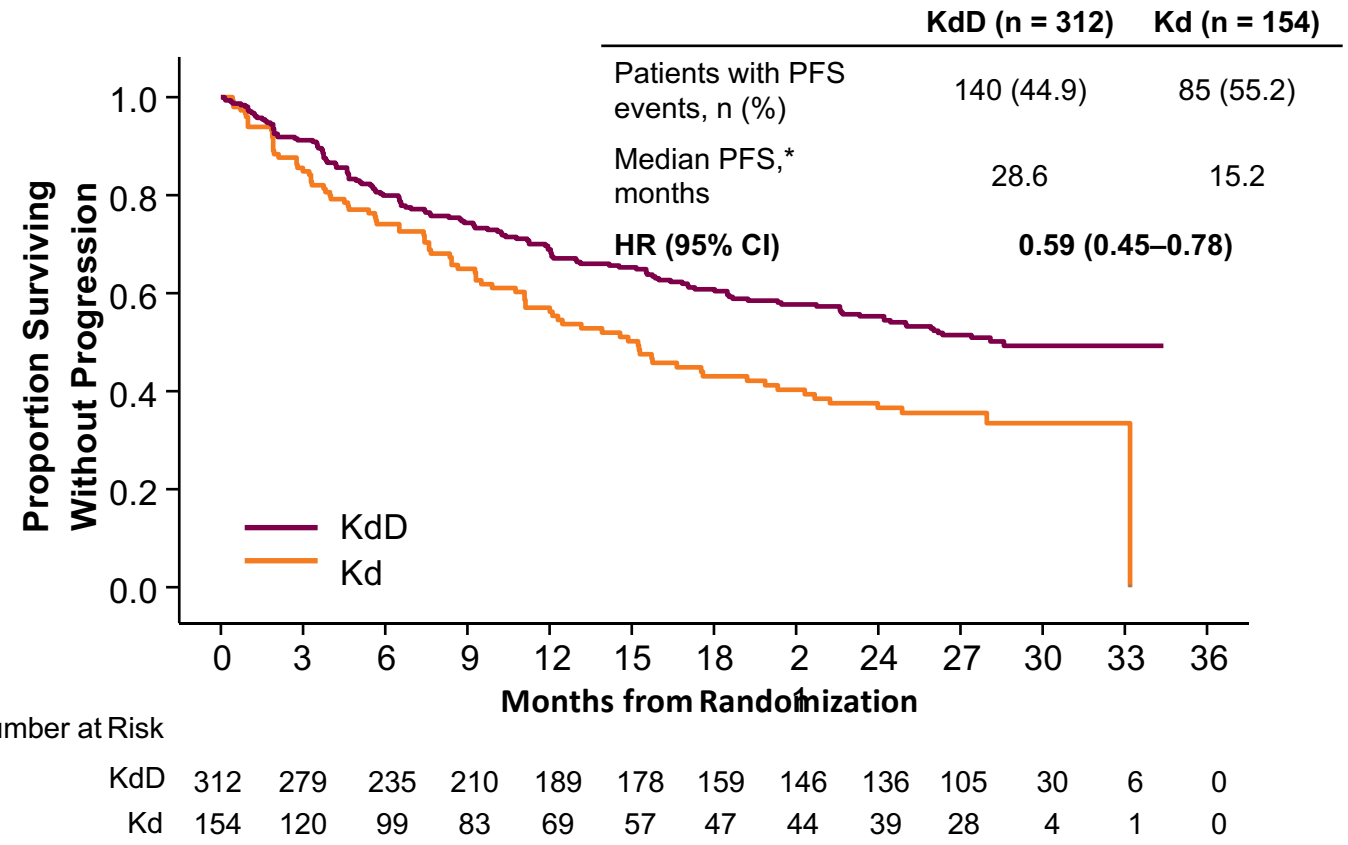
CANDOR (KdD vs Kd in RRMM)



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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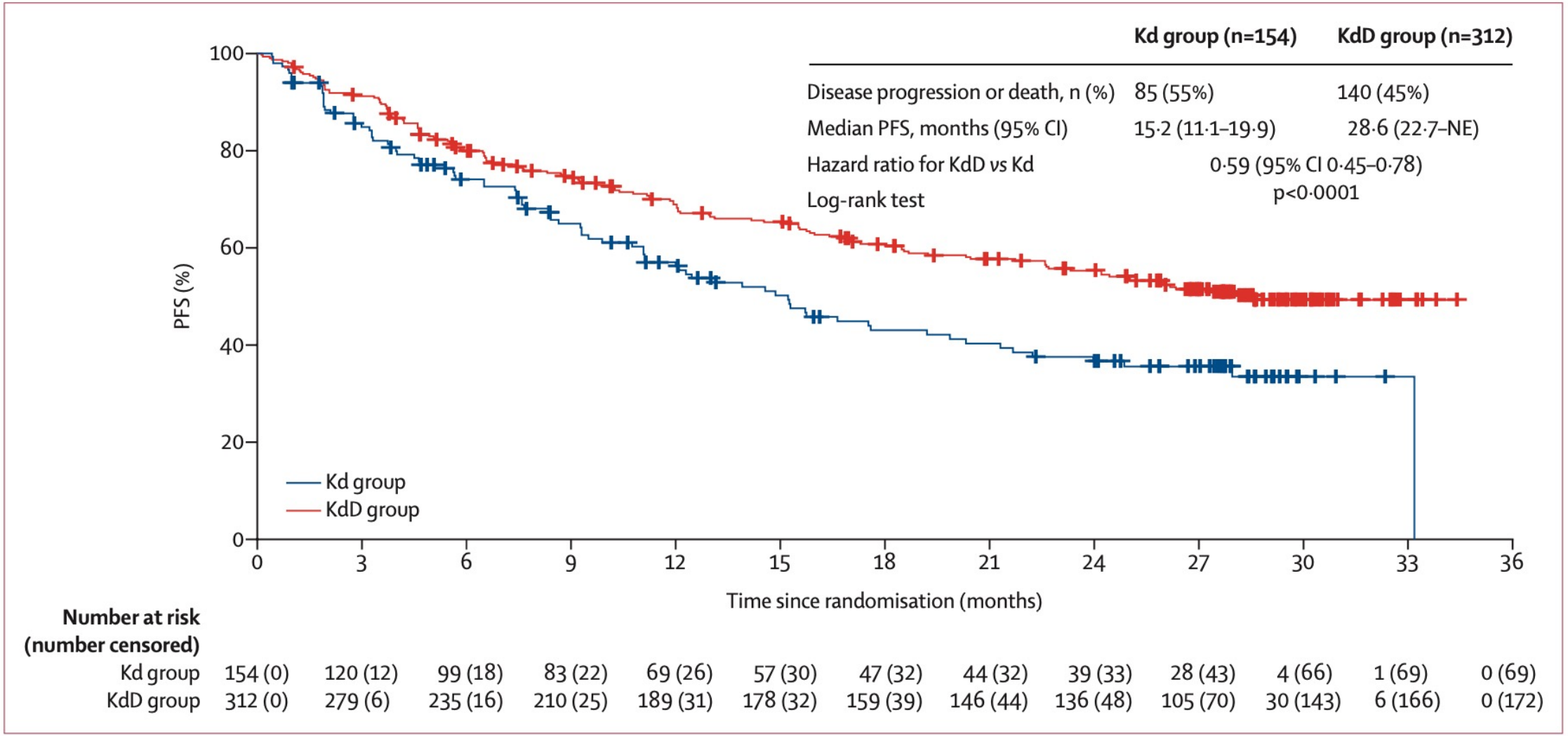
CANDOR (KdD vs Kd in RRMM)



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

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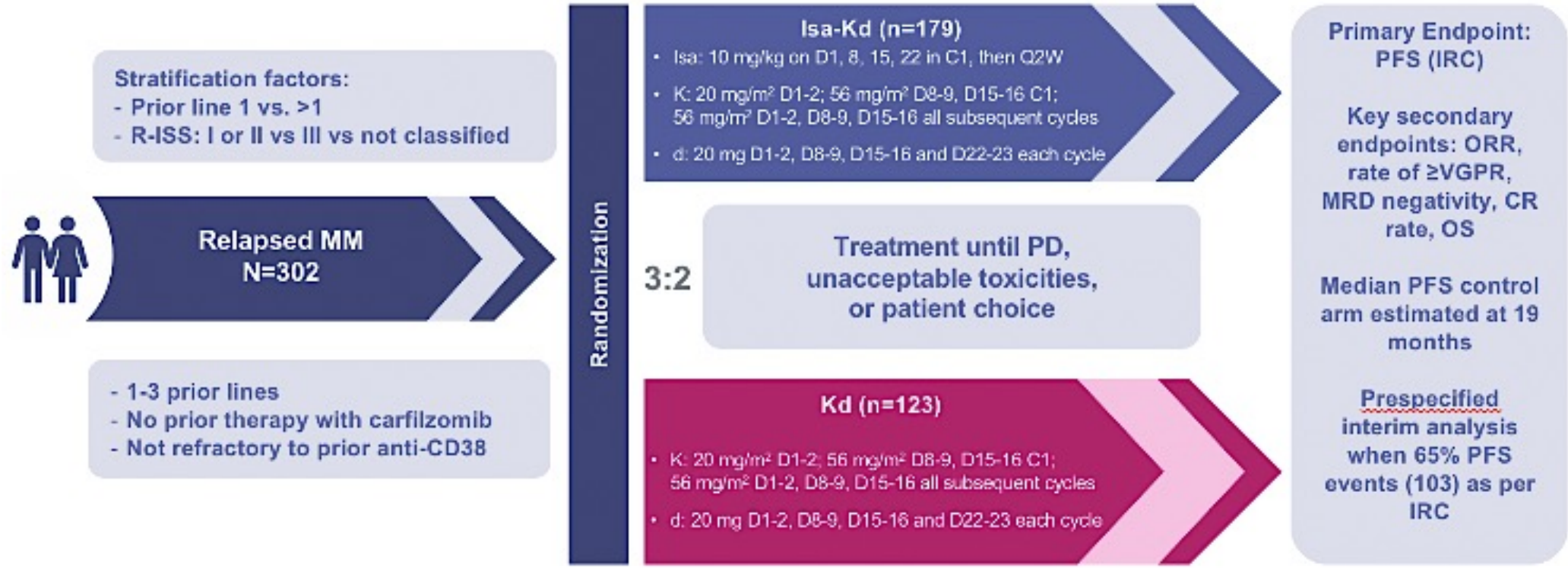
IKEMA



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)

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

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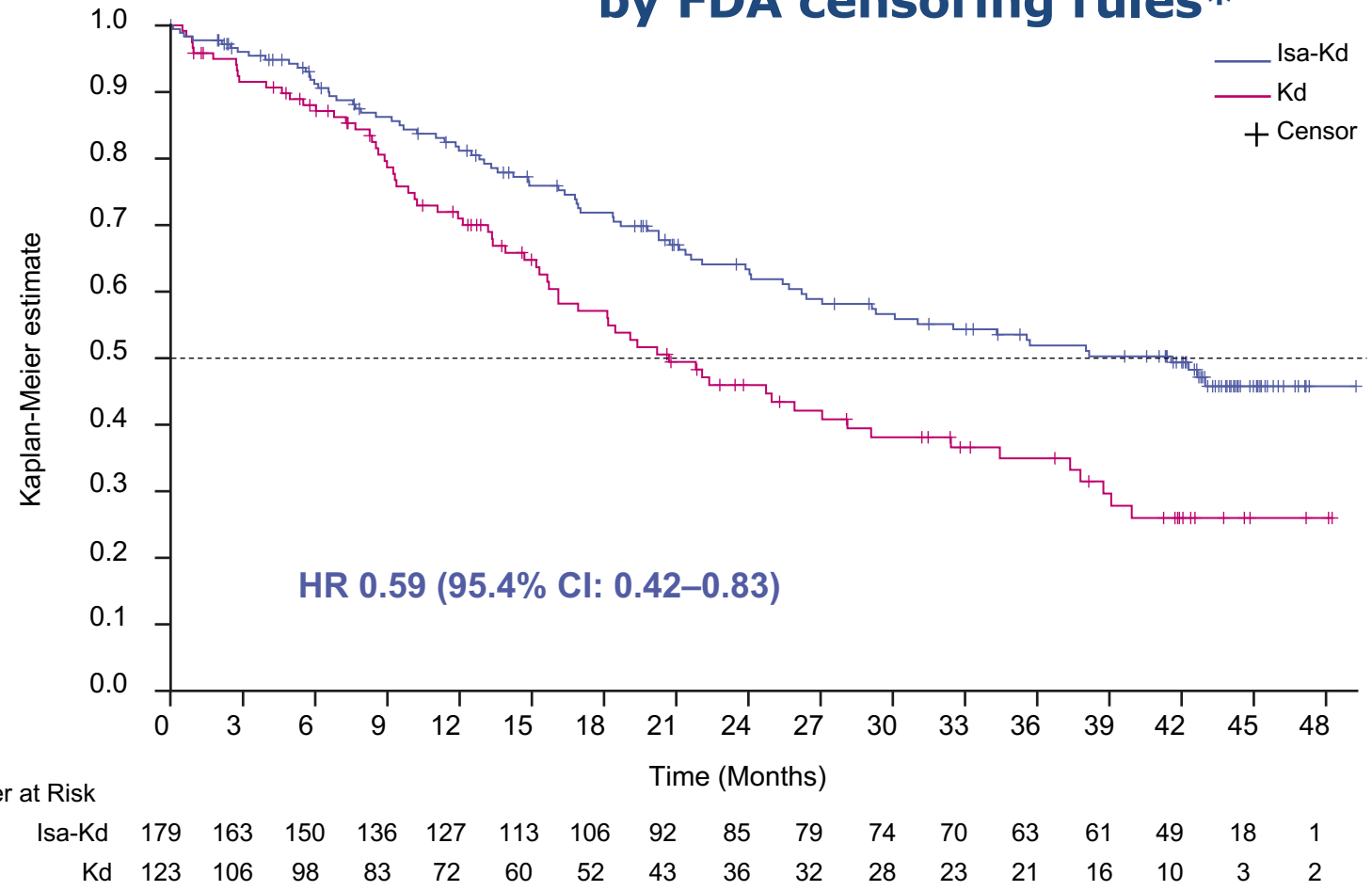
IKEMA Updated PFS – IRC assessment
by FDA censoring rules*



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

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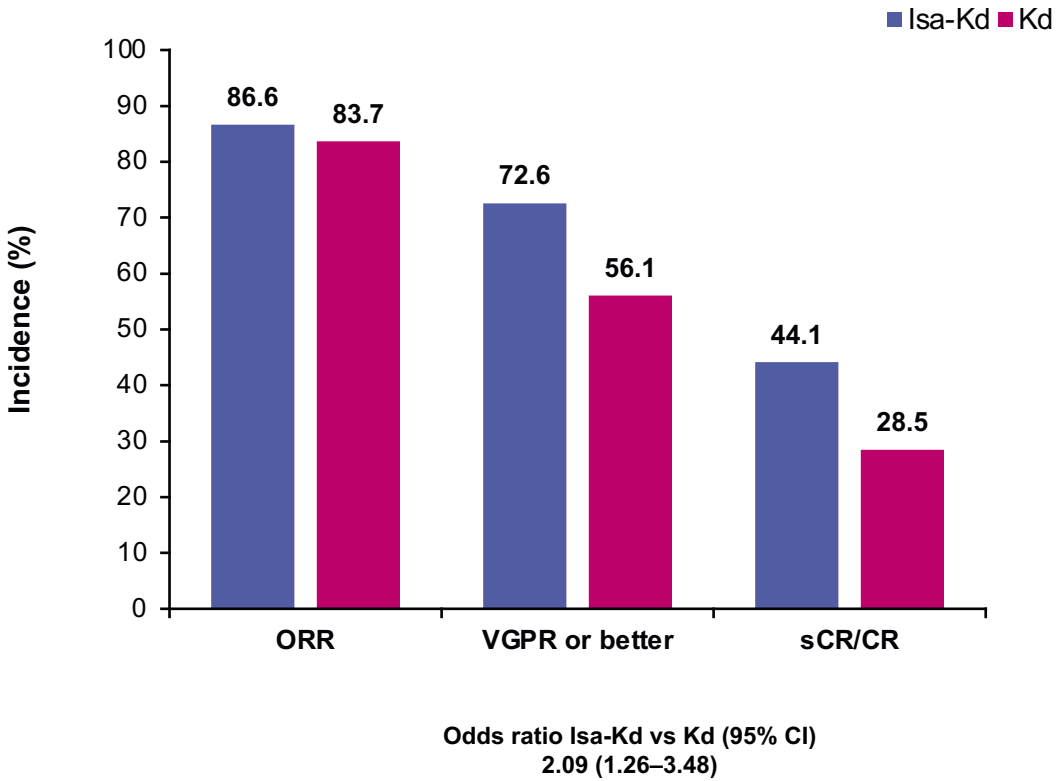
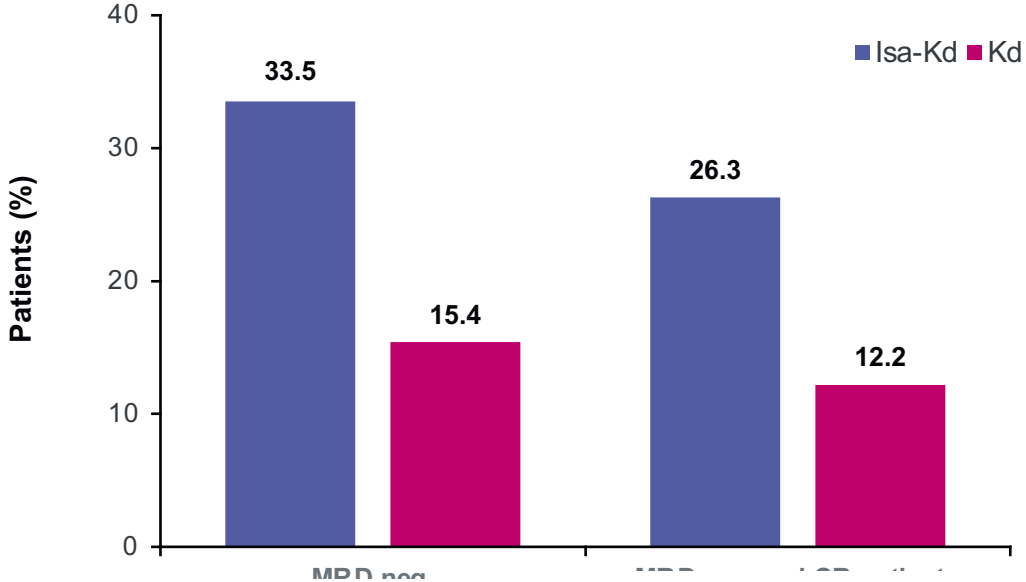
IKEMA Depth of response

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

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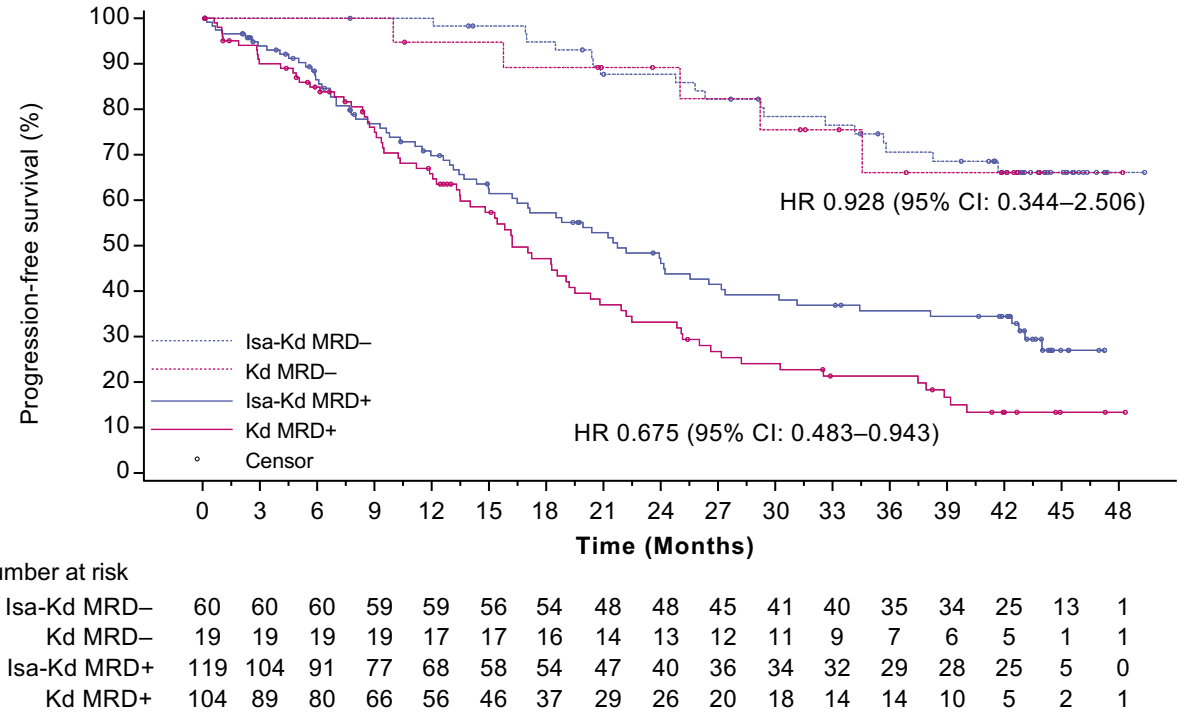
Patient disposition and progression-free survival by MRD status

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.

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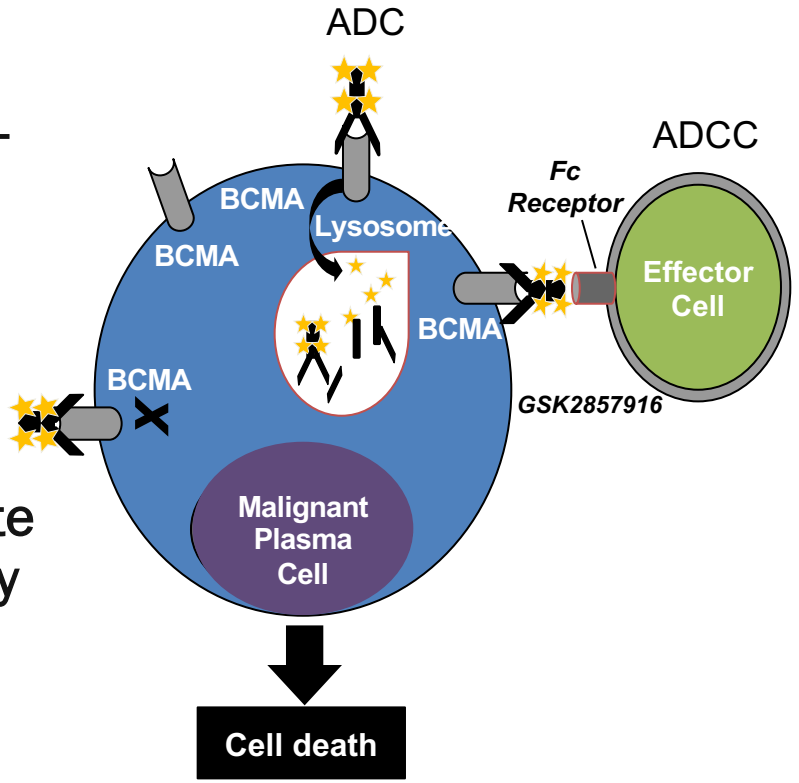
Belantamab Mafodotin: BCMA-Targeted ADC

- 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

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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

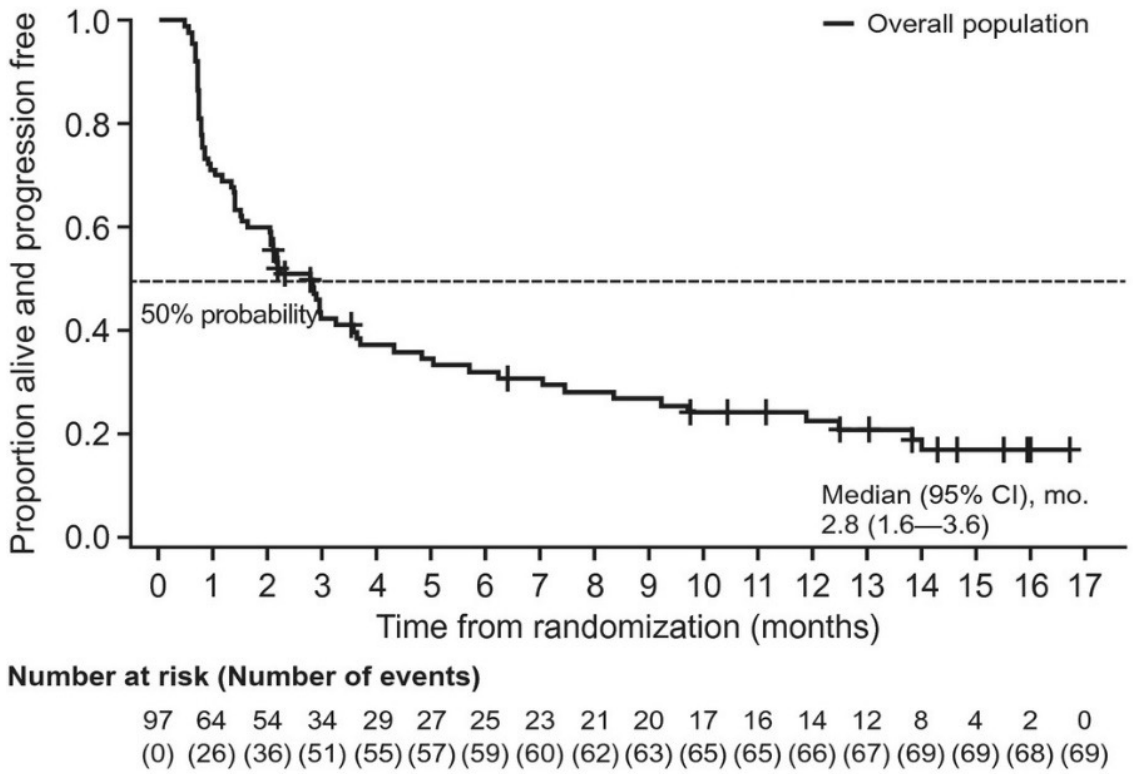
	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	32 (21.7-43.6)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates),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

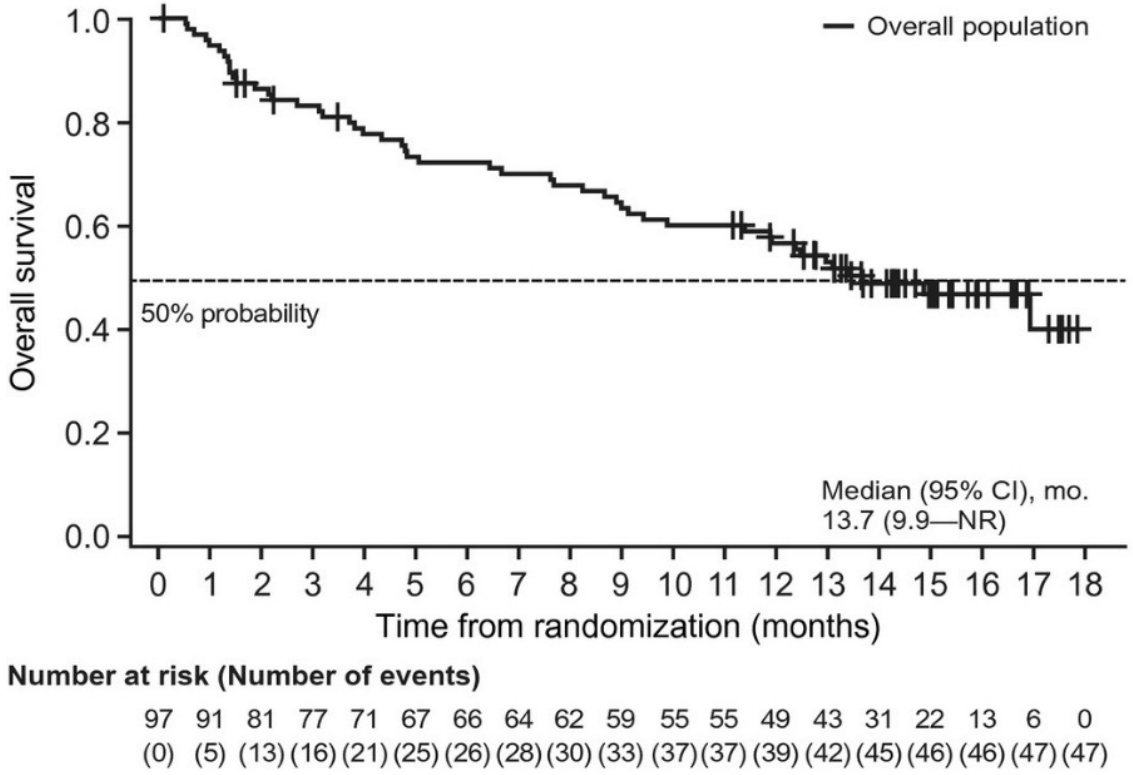
Lonial S et al. *Cancer* 2021;127(22):4198-212; ASH 2020;Abstract 1417.

DREAMM-2: Longitudinal Outcomes

Progression-Free Survival



Overall Survival (OS)

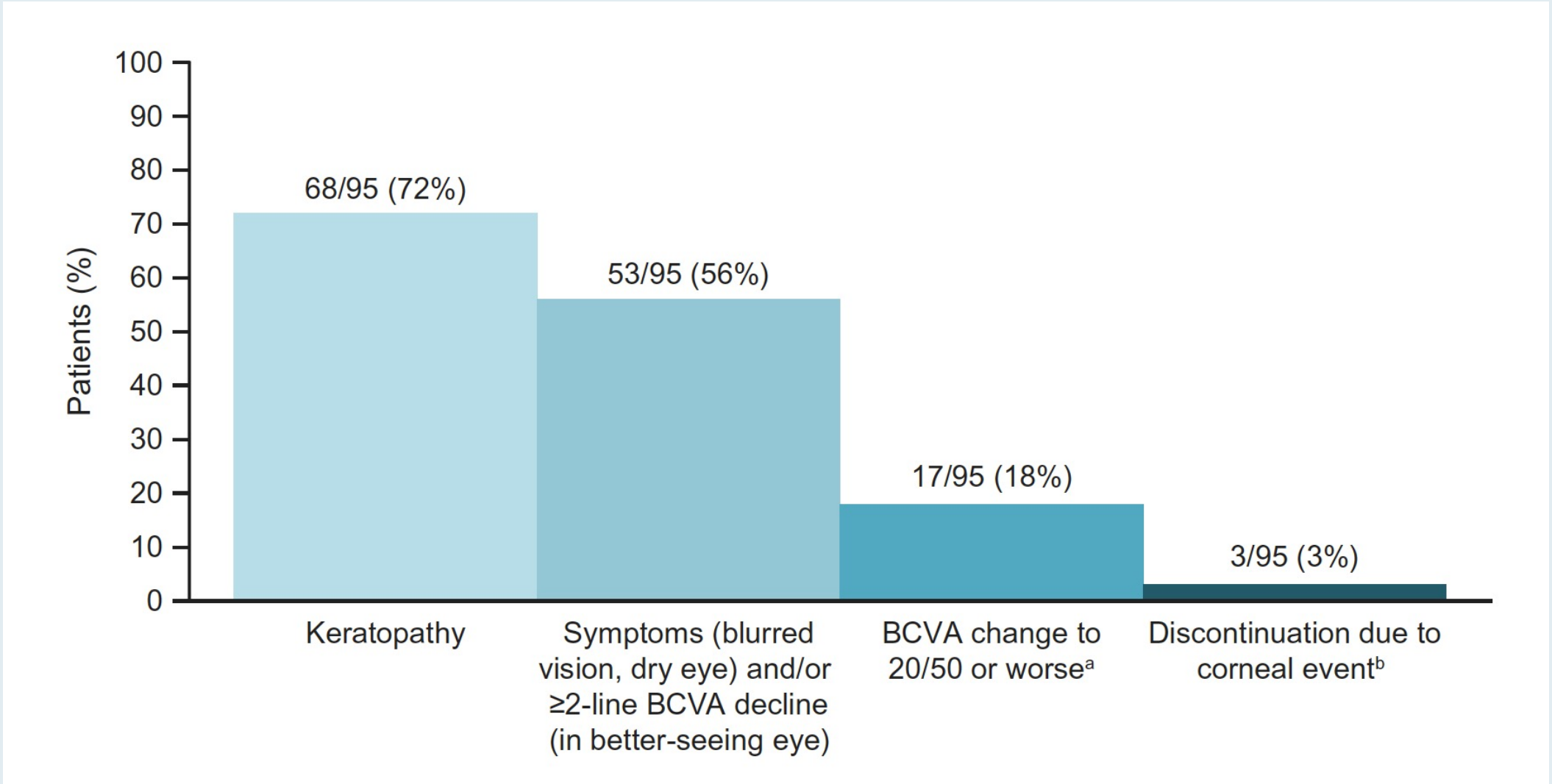


Expected median OS in triple-class refractory myeloma: 8.6 months

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.

RTP RESEARCH TO PRACTICE

Update on Belantamab Mafodotin-blmf US Marketing Authorisation

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.

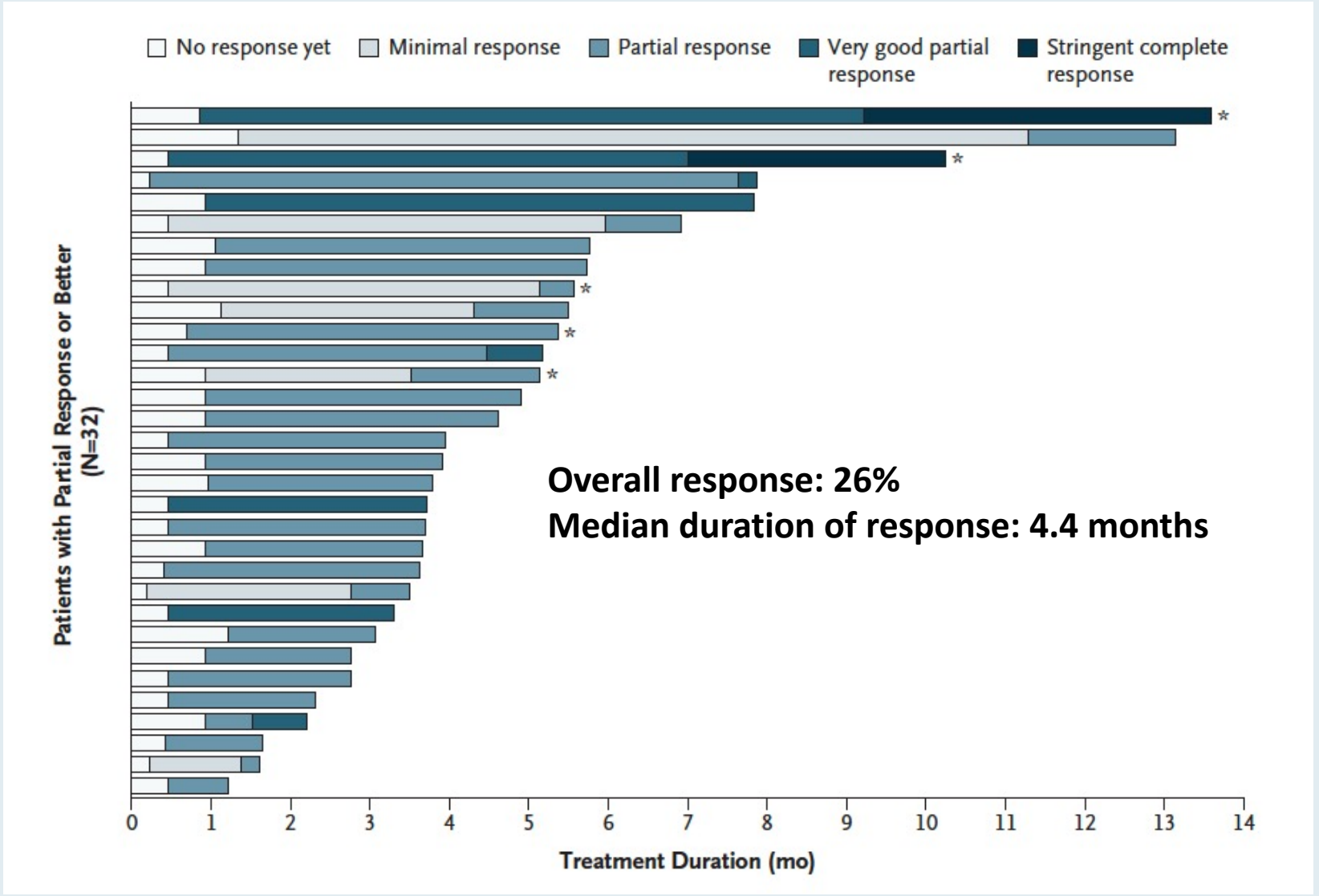
Ongoing Phase III Trials of Belantamab Mafodotin

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.

RTP RESEARCH TO PRACTICE

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

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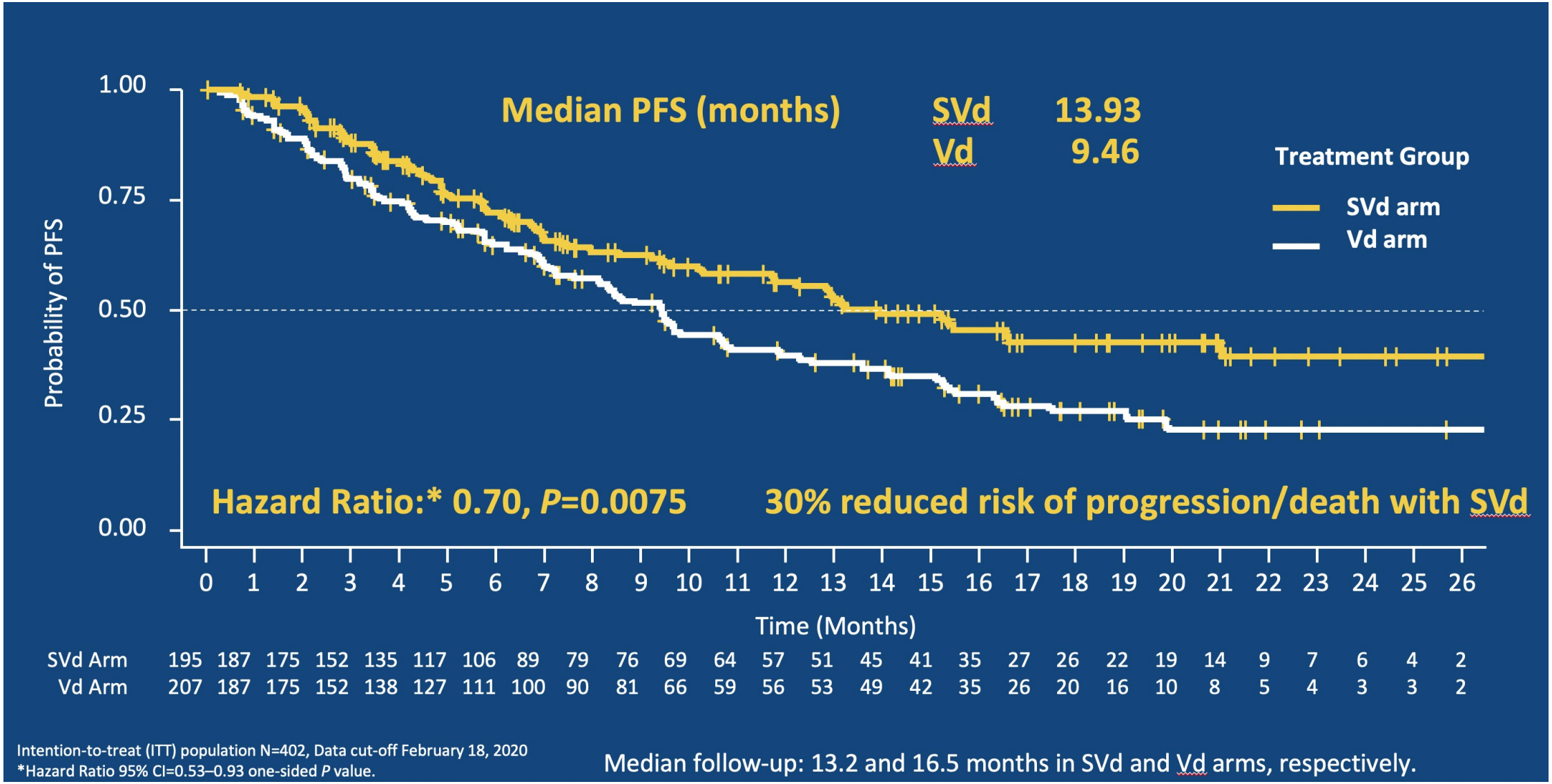
BOSTON Trial: PFS



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.

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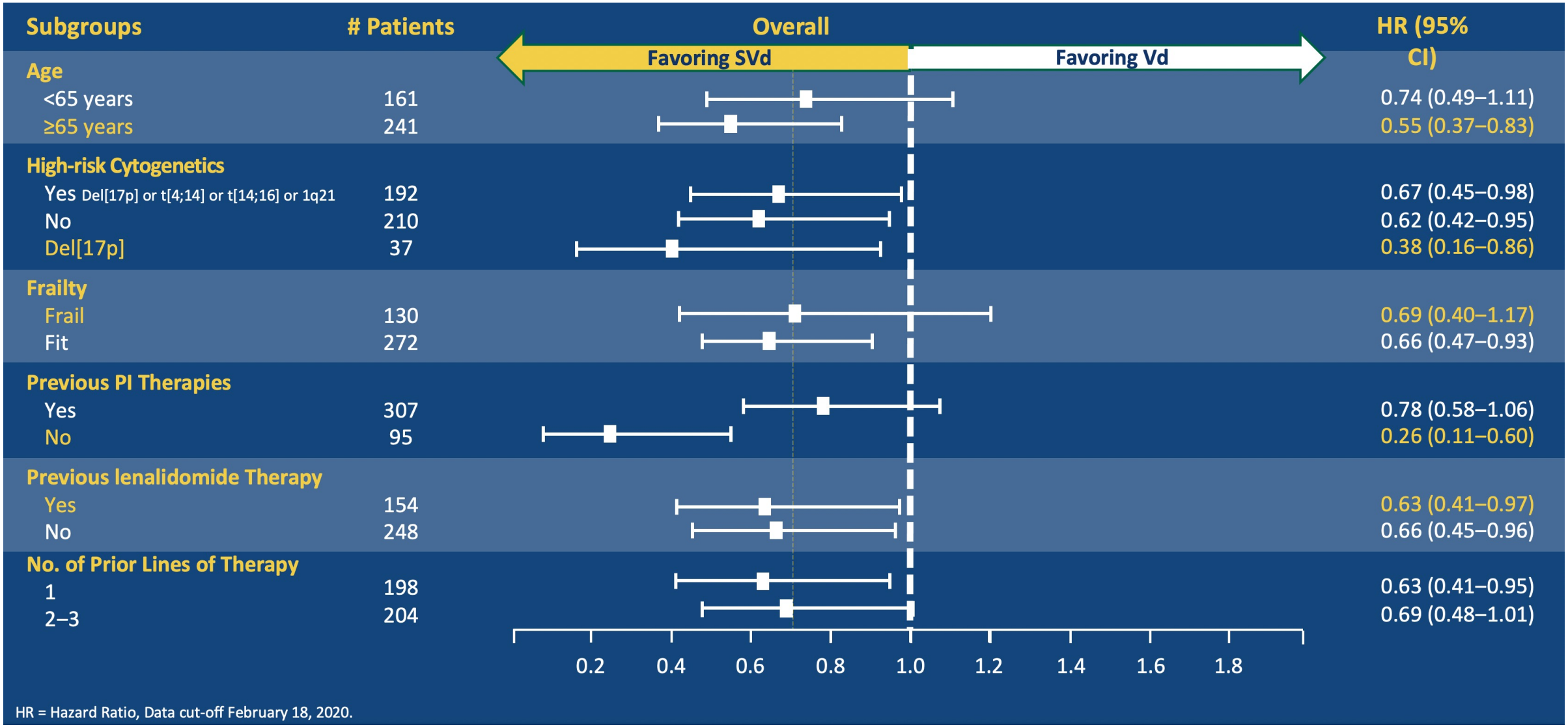
BOSTON Trial: Forest Plot



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

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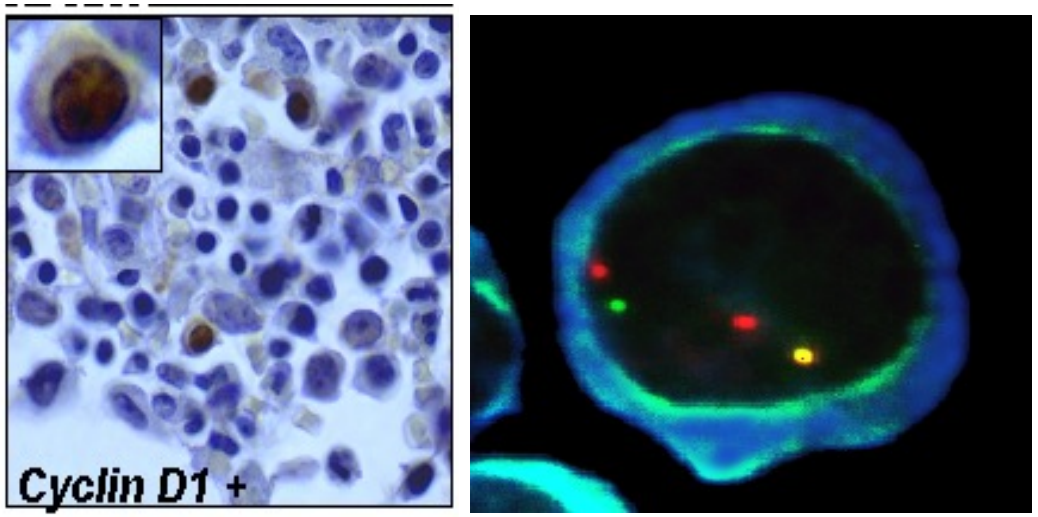
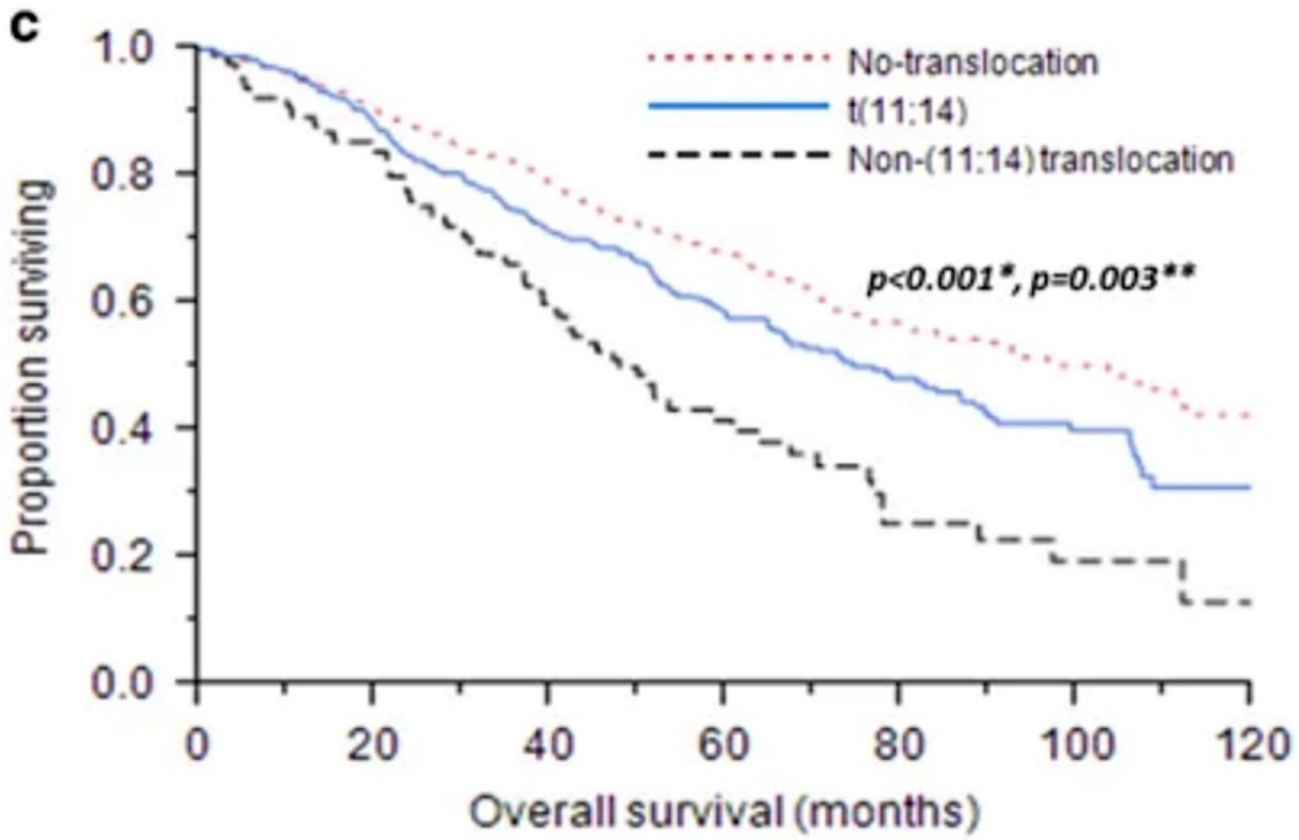
t(11;14) Myeloma is not a risk category



- 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

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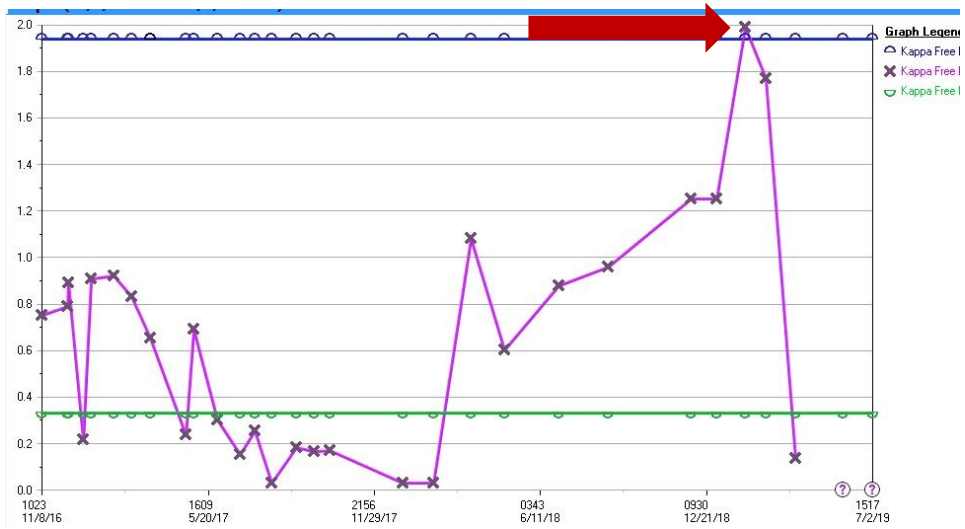
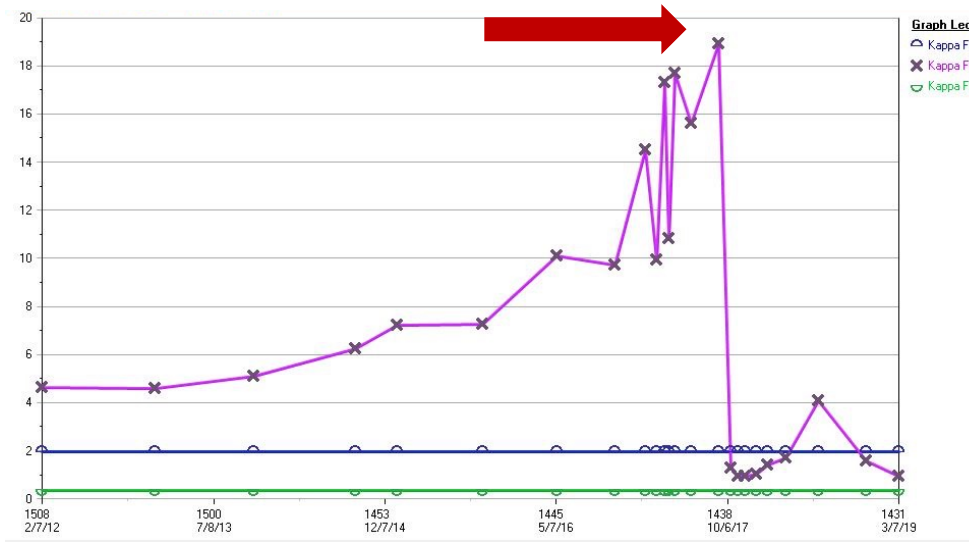
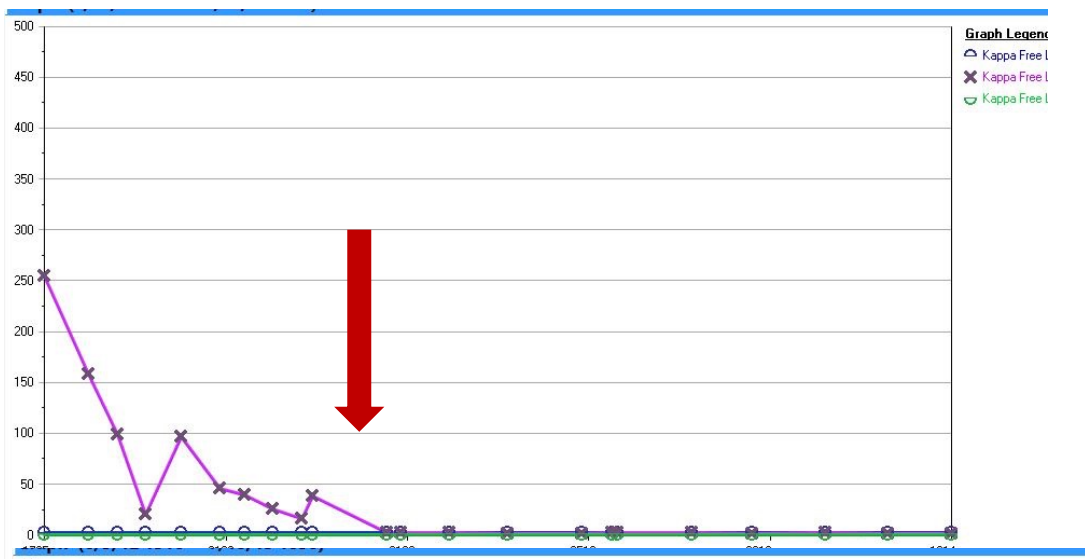
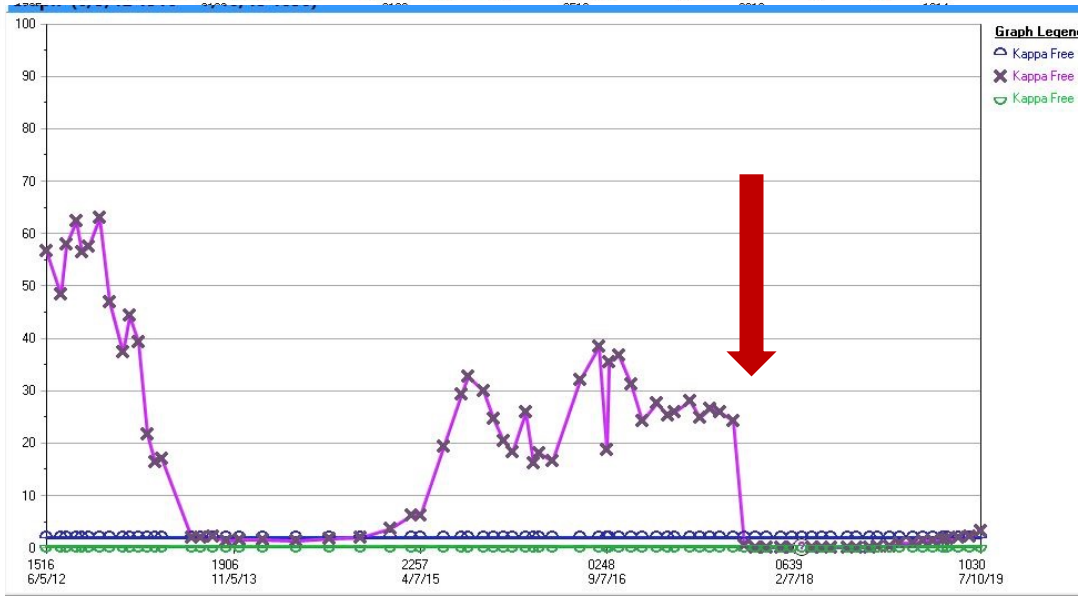
Venetoclax









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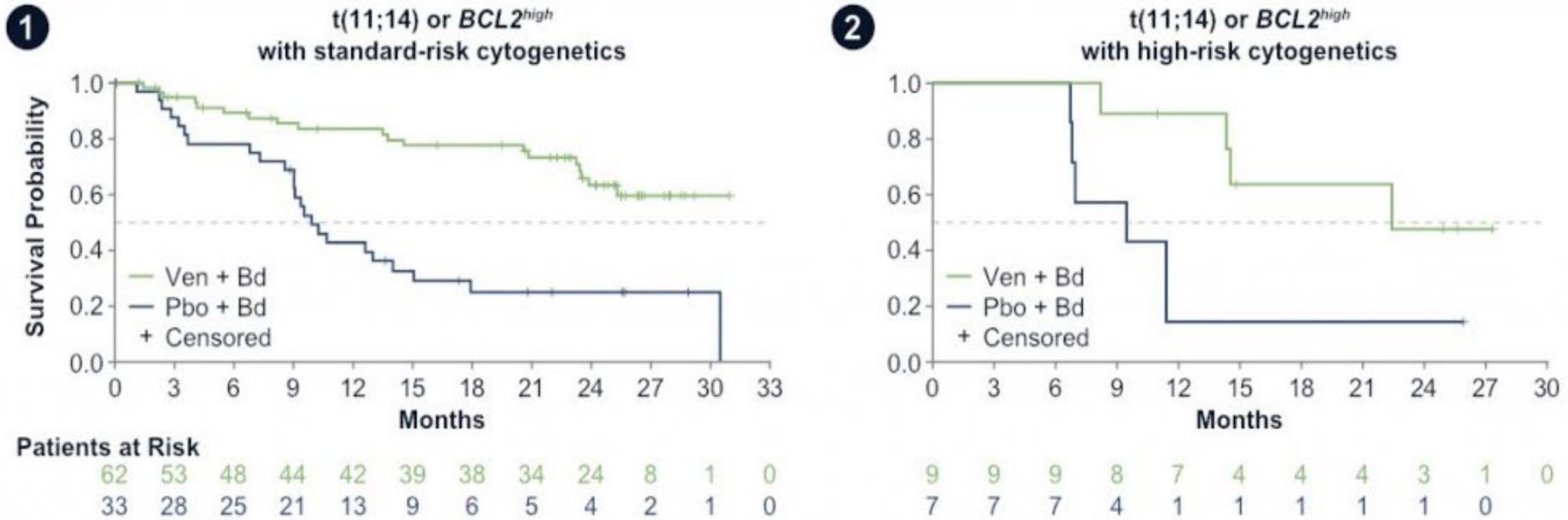
Venetoclax-Bd highly active in t(11;14) or high BCL-2

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



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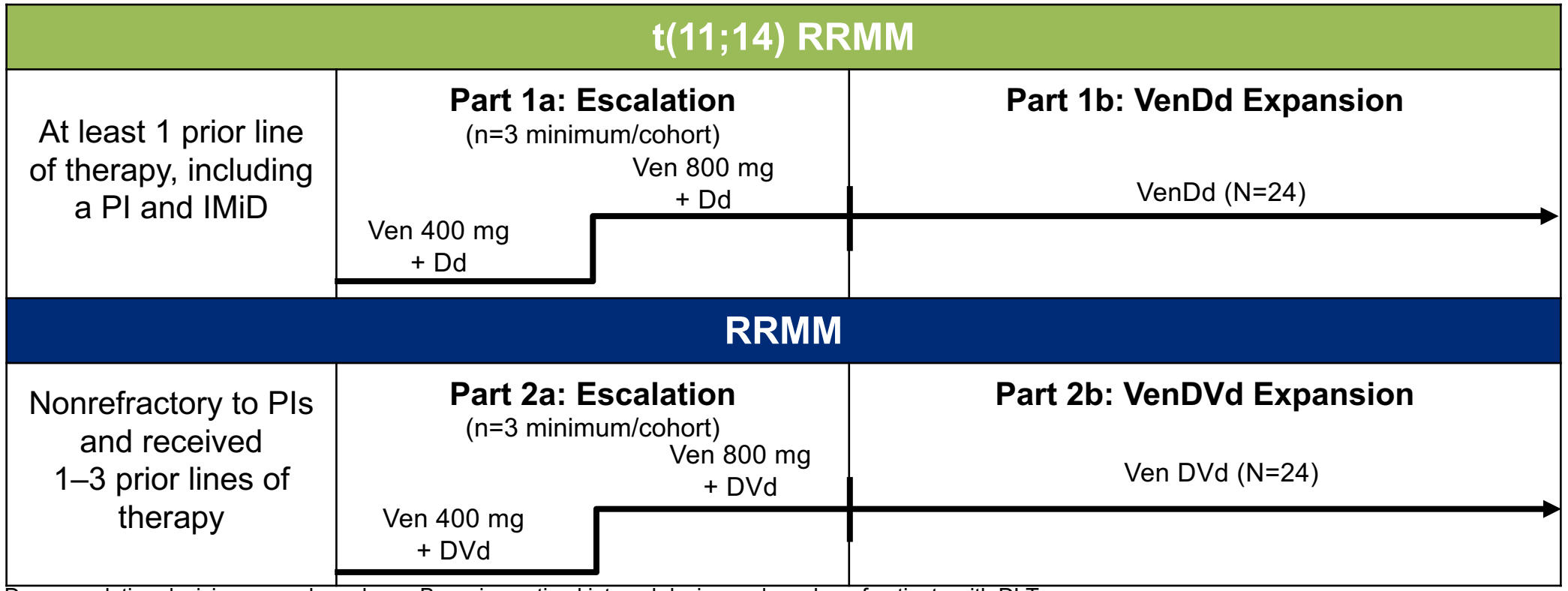
Study Design and Objectives



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

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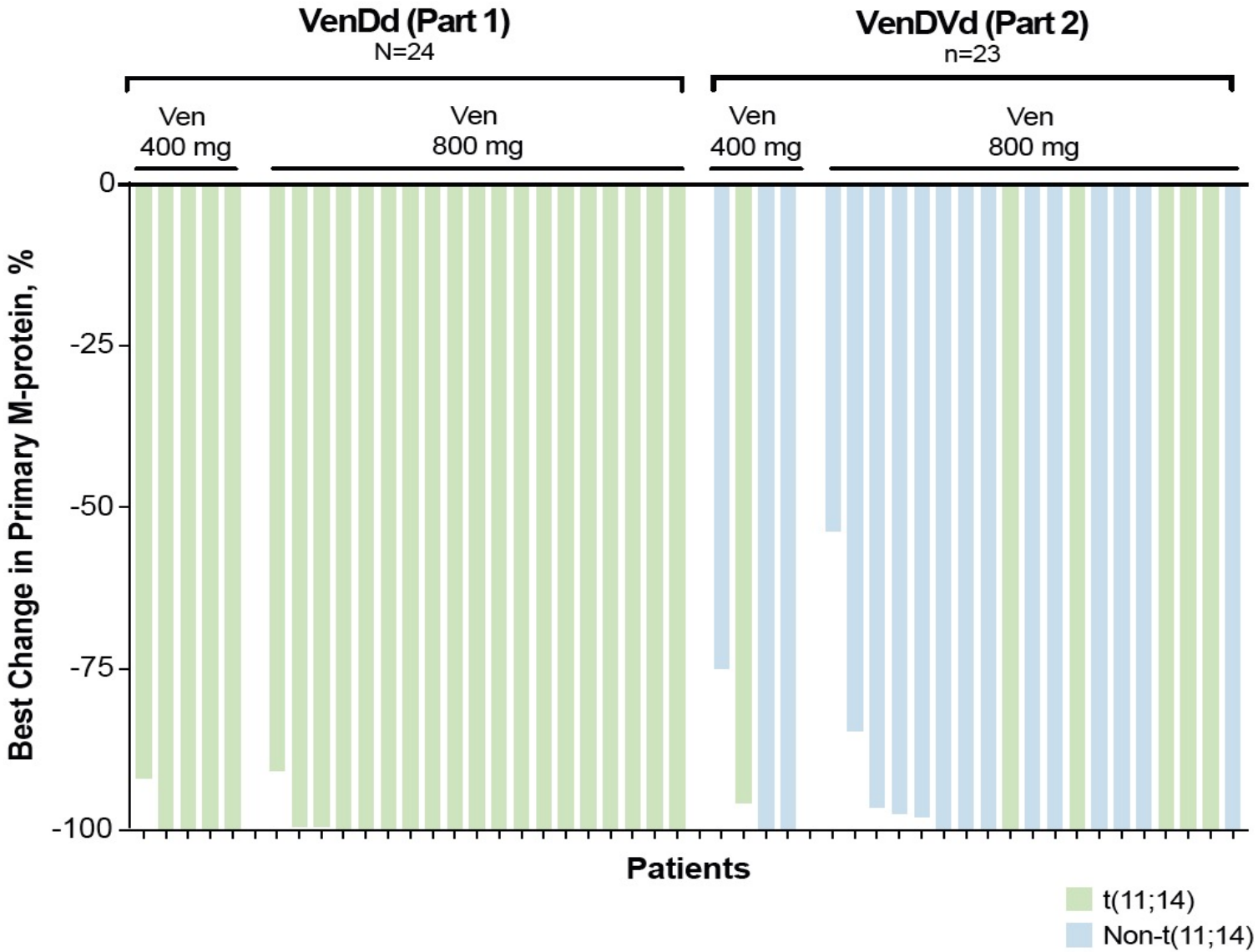
Best M-Protein Response



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EDITORIAL Review

- Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM — Dr Fonseca

- Long-term results from Phase III studies (eg, ICARIA-MM, IKEMA) supporting the use of isatuximab-based combination therapy in R/R MM
  - Slides 6-11 (ICARIA-MM, Lancet Oncol 2022)
  - Slides 15-18 (IKEMA, COMy2022)
- Key findings from the Phase III BOSTON trial of selinexor with bortezomib/dexamethasone for R/R MM
  - Slide 21-23 (ASCO 2020)
- Early results with other selinexor-containing combinations in R/R MM
  - No other datasets shown
  - Recommend adding: STORM: Selinexor/dexamethasone for triple-class refractory avaialable (NEJM 2019)
  - Other, small earlier published studies of combinations are available
- Available and emerging findings with belantamab mafodotin monotherapy for R/R MM
  - Recommend adding press release re update on US marketing authorization – How much discussion of older data and ongoing trials in light of current status?
  - Slides 19-20 (MOA, DREAMM-2, Lancet Oncol 2019); Recommend replacing with longer-term follow-up data available (Cancer 2021)
  - Recommend adding table of ongoing DREAMM-07 and DREAMM-08 studies
- Early data with belantamab mafodotin combined with other systemic therapies and/or in earlier lines of treatment
  - Not sure whether you want to add early-phase data (DREAMM-06, DREAMM-04, ALGONQUIN) available with combinations
- NOTE: APOLLO: Dara/PD in RRMM (slides 3-5) and CANDOR: KdD vs Kd in RRMM (slides 12-14)
- NOTE: Venetoclax data (slides 24-28) covered by Lonial; recommend cut

RTP RESEARCH TO PRACTICE

All Recommended Changes Agreed Upon from Dr Fonseca and Executed in the Current Deck

RTP
RESEARCH
TO PRACTICE