# An Update on the Management of Myeloma

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# Outline

- Redefining Goal of First Line of Therapy

- Updates on Induction therapy for TE patients
  3 vs 4 drugs? Perseus, Iskia studies

- Updates on relapse/refractory myeloma
  CAR-T
  Bispecific Antibodies
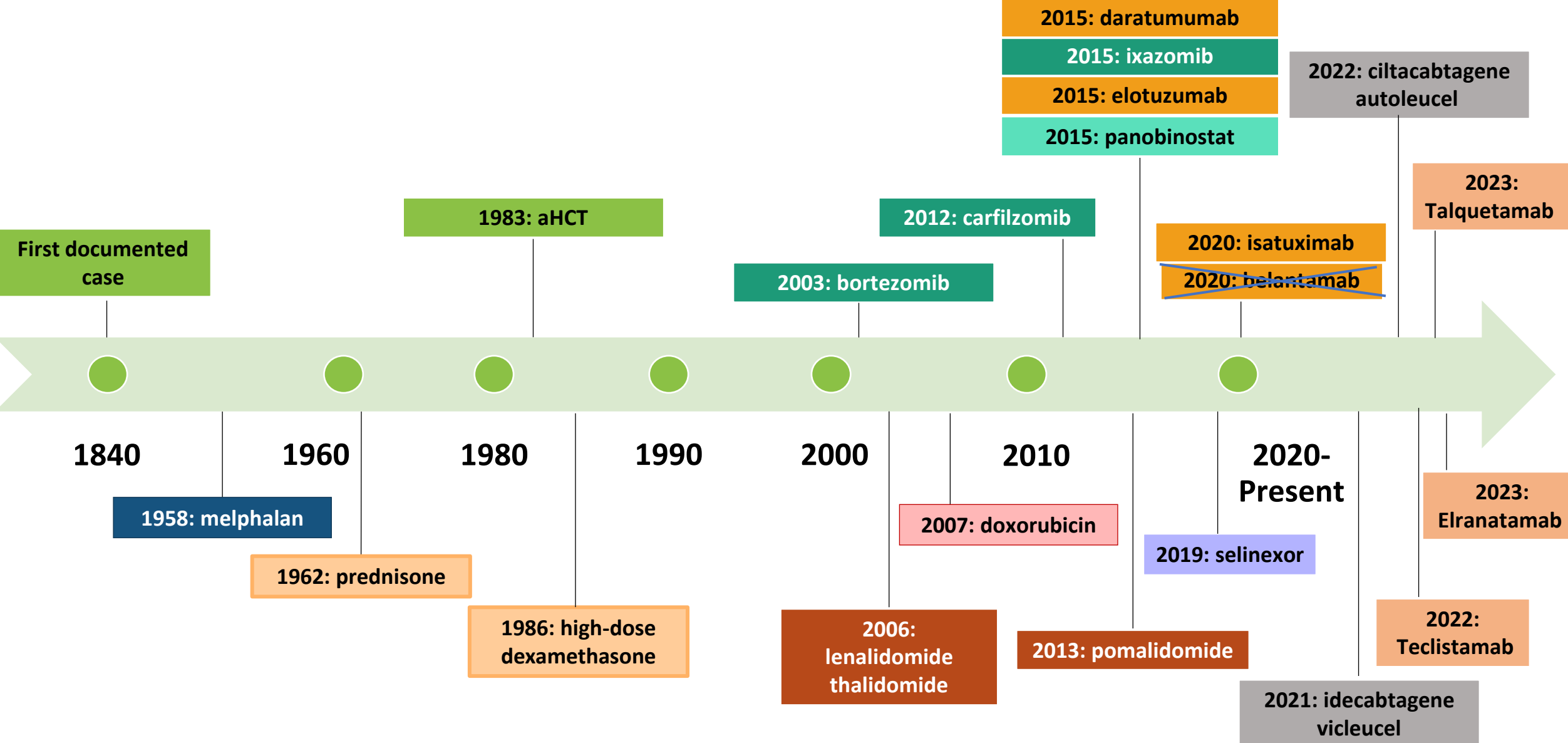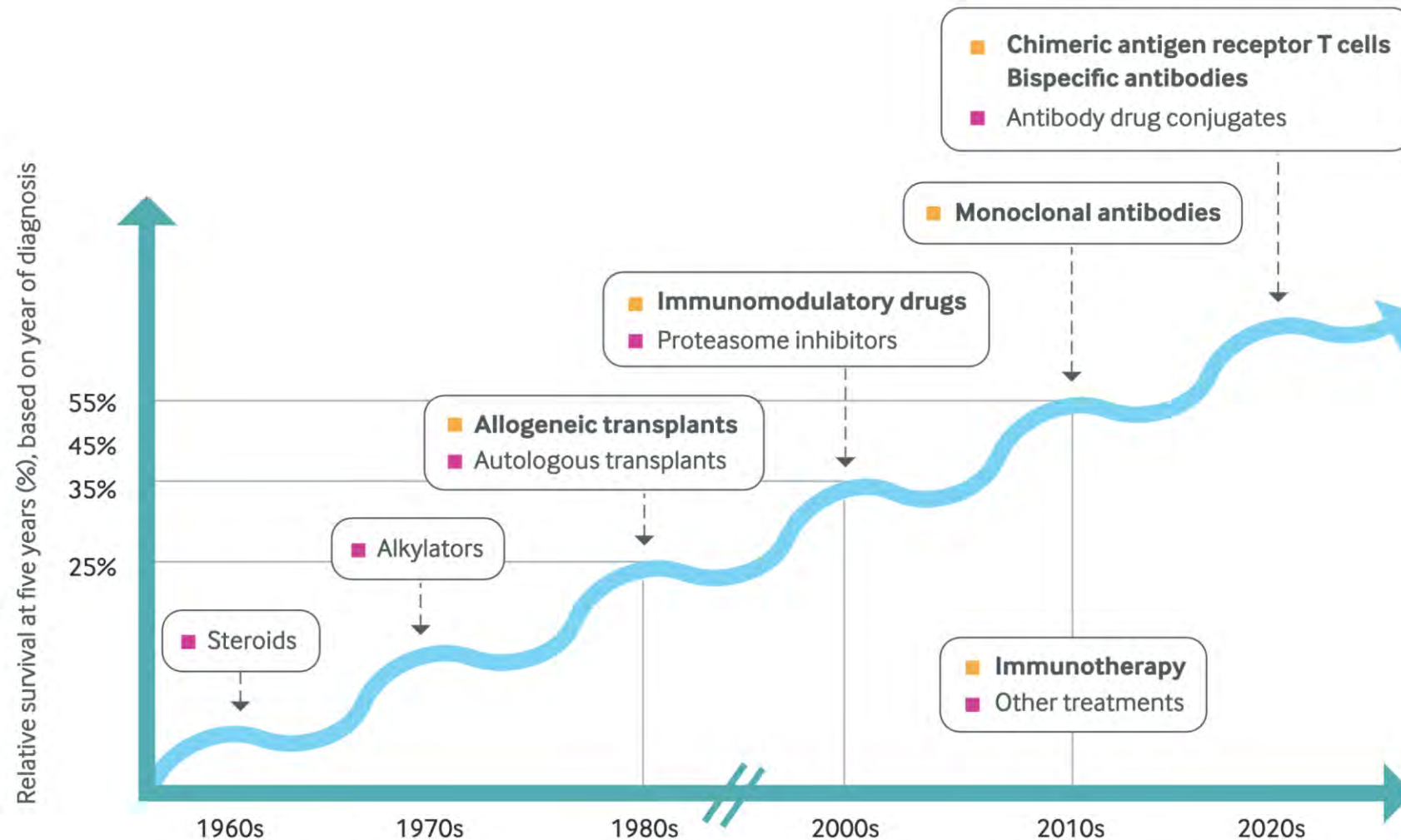
# Milestones in Multiple Myeloma Drug Approvals



2015: daratumumab
2015: ixazomib
2015: elotuzumab
2015: panobinostat
2022: ciltacabtagene autoleucel
2023: Talquetamab
1983: aHCT
2012: carfilzomib
2020: isatuximab
2020: belantamab
First documented case
2003: bortezomib
1958: melphalan
2007: doxorubicin
2019: selinexor
2023: Elranatamab
1962: prednisone
1986: high-dose dexamethasone
2006: lenalidomide thalidomide
2013: pomalidomide
2022: Teclistamab
2021: idecabtagene vicleucel

1840    1960    1980    1990    2000    2010    2020-Present

Image adapted from Kyle R, et al. *Blood*. 2008;111:2962; Raje N, et al. *N Engl J Med*. 2019;380:1726; Li W, et al. *Circulation*. 2016;133:908.

# The Good News



Shah, U.A. and S. Mailankody, BMJ, 2020

# The not so good news…



**Asymptomatic** (Monoclonal gammopathy of unknown significance or smoldering multiple myeloma)

**Symptomatic** (Multiple Myeloma)

*Malignant Progression*

**Remission duration decreases with increasing number of salvage regimens**

Tumor Burden

Active Myeloma

Relapse

Relapse

Refractory Relapse

Plateau Remission

Therapy

Time

# First Shot = Best Shot

- In non-transplant patients, attrition rates are high and remain steady through 5th LOT
- In transplant patients, attrition rates were lower, but increased with each successive LOT

**Table 4** Attrition rates by LOT

| LOT | Frequency, N | Attrition, % | Deaths, n (%) | No subsequent treatment in follow-up, n (%) |
|---|---|---|---|---|
| Non-transplant | | | | |
| 1 | 22,062 | – | 2841 (12.9) | 9716 (44.0) |
| 2 | 9505 | 56.9 | 1155 (12.2) | 3168 (33.3) |
| 3 | 5182 | 45.5 | 636 (12.3) | 1575 (30.3) |
| 4 | 2971 | 42.7 | 364 (12.3) | 901 (30.3) |
| 5 | 1706 | 42.6 | 209 (12.3) | 508 (29.8) |
| Transplant | | | | |
| 1 | 2763 | – | 36 (1.3) | 543 (19.6) |
| 2 | 2184 | 21.0 | 60 (2.7) | 613 (28.1) |
| 3 | 1511 | 30.8 | 63 (4.2) | 494 (32.7) |
| 4 | 954 | 36.9 | 60 (6.3) | 276 (28.9) |
| 5 | 618 | 35.2 | 49 (7.9) | 180 (29.1) |

*LOT* Line of therapy, *SD* Standard deviation
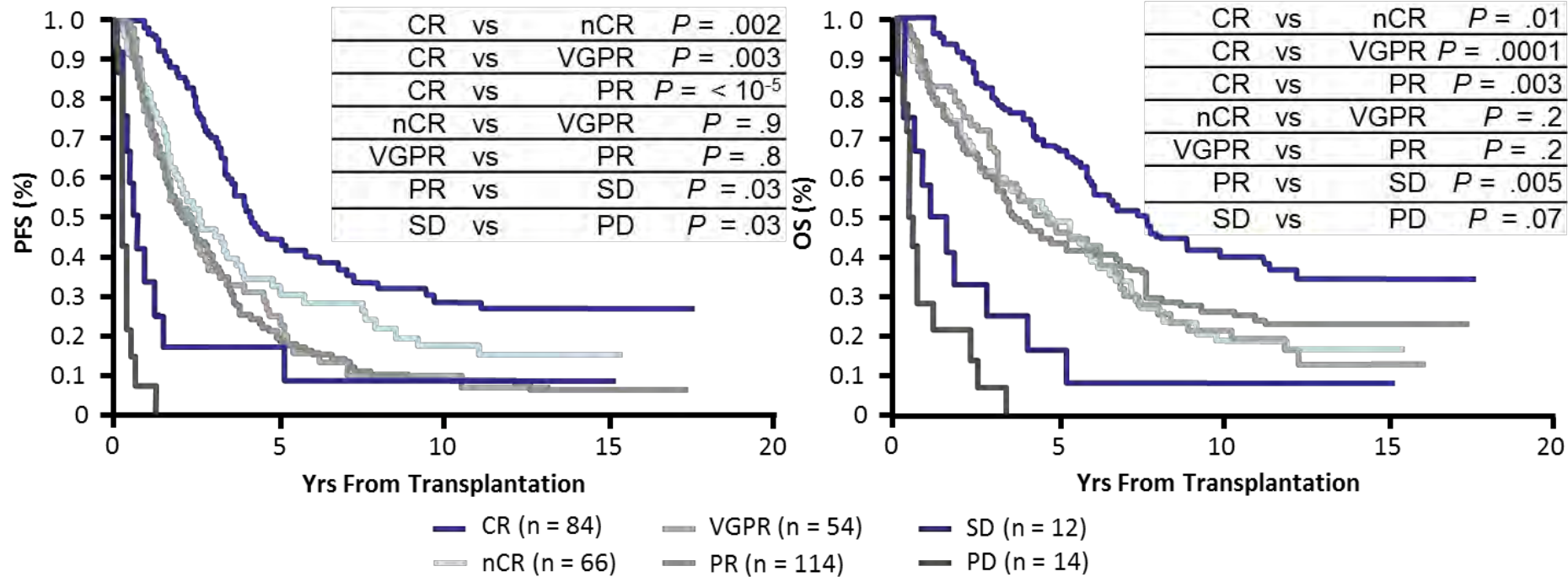


Mean Treatment Duration by LOT in Patients with NDMM
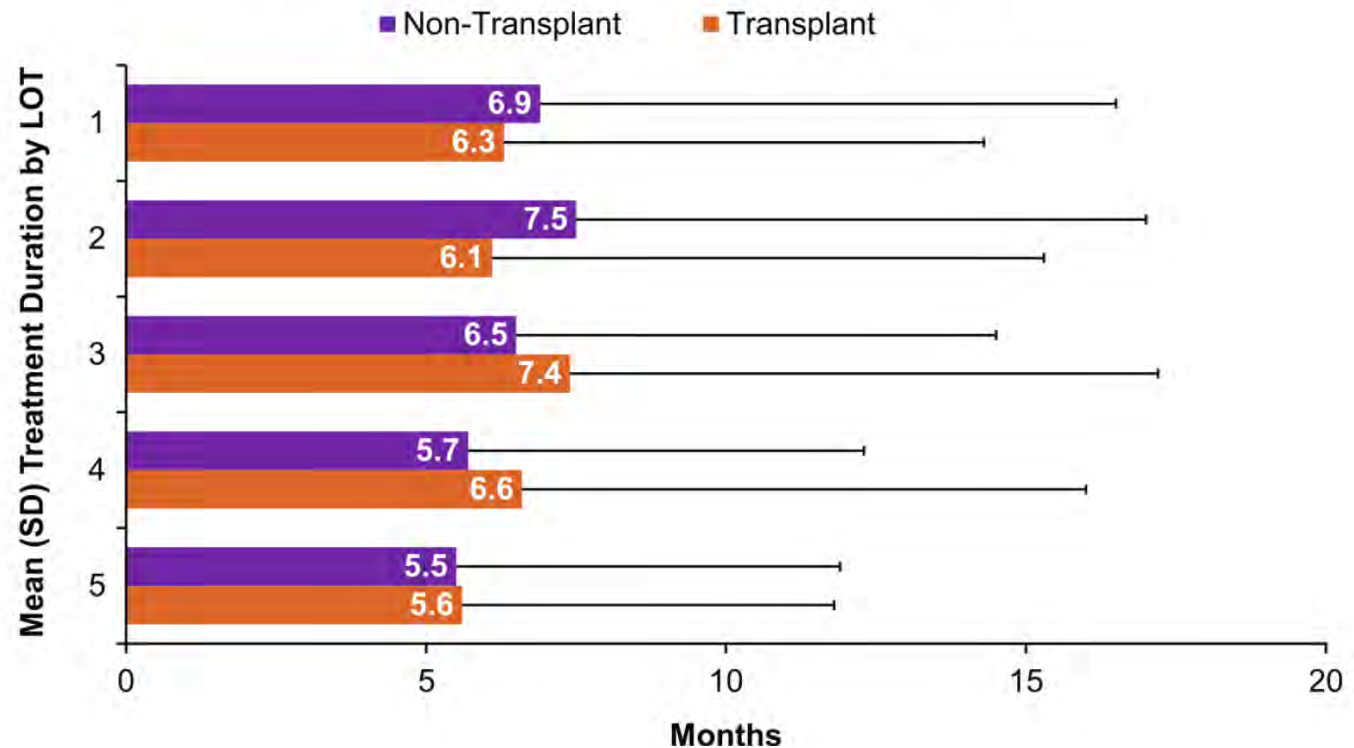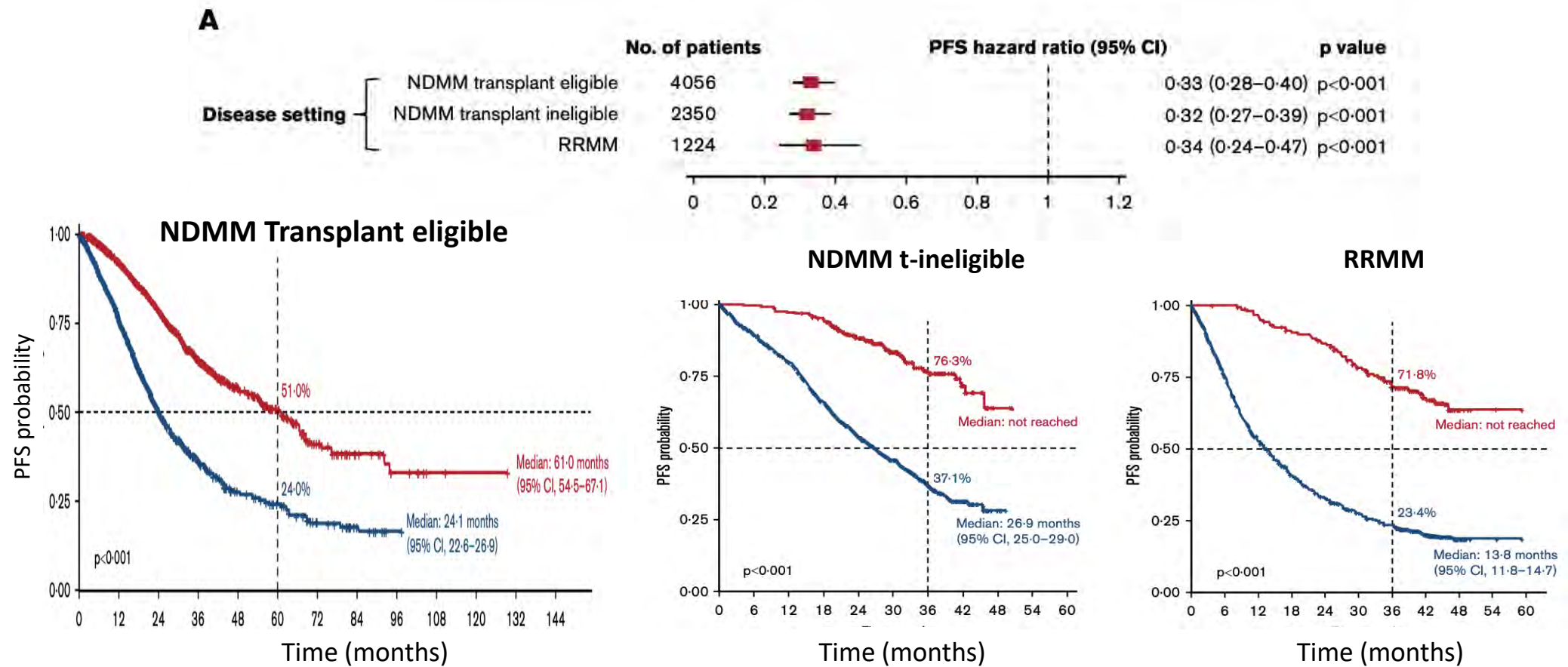
# Response status and patient outcomes.



Deeper responses = better outcomes - *Not new news-* **2011**

Prognostic influence of 6 response categories on PFS/OS

Martinez-Lopez J*, et al*. Blood. 2011;118:529-534.

# Redefining the Goal of Therapy:
# Minimal Residual Disease (MRD) status and MM outcomes.



Munshi et al Blood Adv 2020
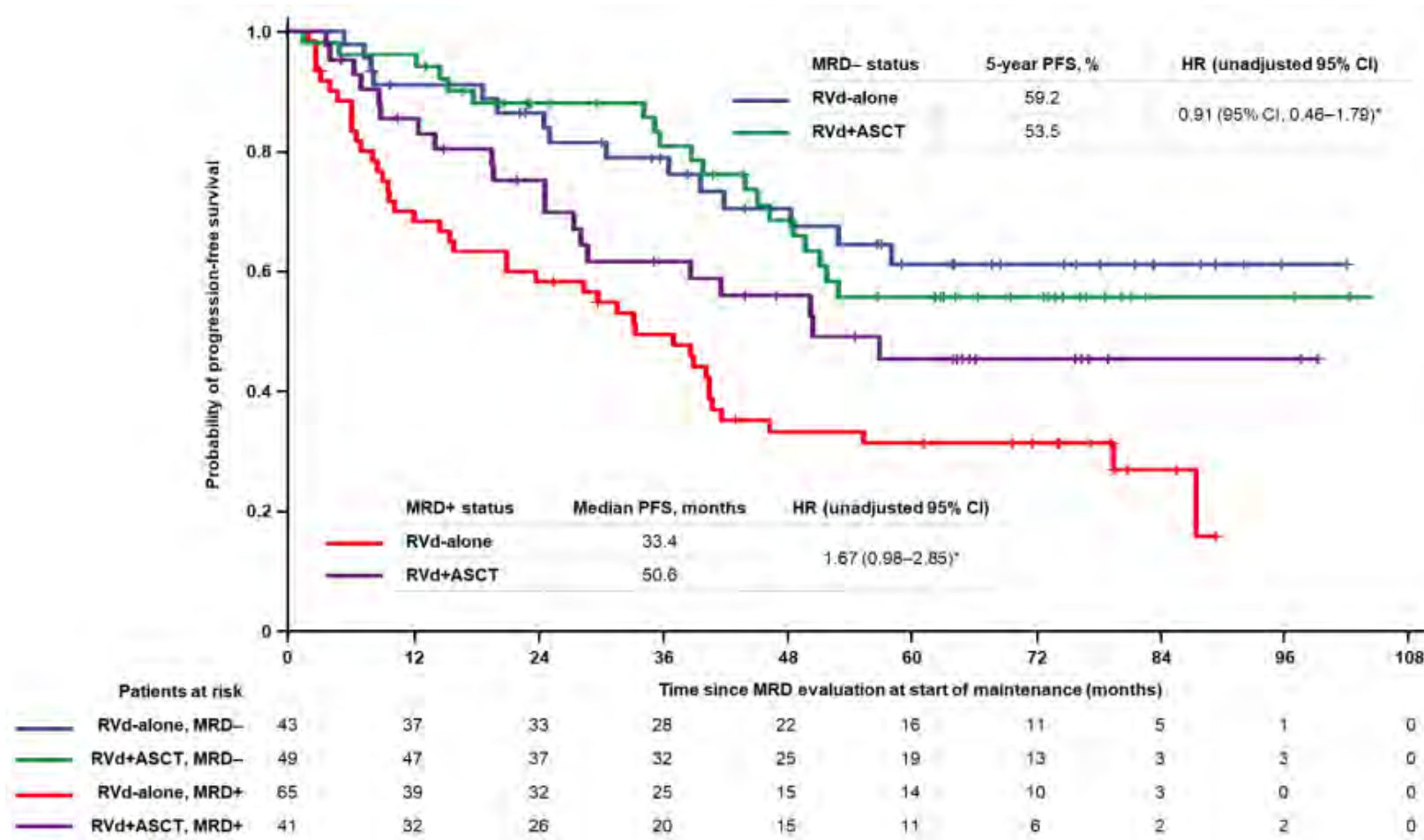
# Phase 3 DETERMINATION: MRD/PFS by MRD

**Preliminary analyses**

↓

**Pts w/ samples from start of maintenance**
108 RVD-alone, 90 RVd + ASCT

↓

**Rate of MRD-negative status (NGS $10^{-5}$)**
**40% (n=43) vs 54% (n=49)**

Odds ratio: 0.55
95% CI, 0.3-1.01

**PFS by MRD status from start of maintenance therapy**



| MRD− status | 5-year PFS, % | HR (unadjusted 95% CI) |
|---|---|---|
| RVd-alone | 59.2 | 0.91 (95% CI, 0.46–1.79)* |
| RVd+ASCT | 53.5 | |

| MRD+ status | Median PFS, months | HR (unadjusted 95% CI) |
|---|---|---|
| RVd-alone | 33.4 | 1.67 (0.98–2.85)* |
| RVd+ASCT | 50.6 | |

Patients at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| RVd-alone, MRD− | 43 | 37 | 33 | 28 | 22 | 16 | 11 | 5 | 1 | 0 |
| RVd+ASCT, MRD− | 49 | 47 | 37 | 32 | 25 | 19 | 13 | 3 | 3 | 0 |
| RVd-alone, MRD+ | 65 | 39 | 32 | 25 | 15 | 14 | 10 | 3 | 0 | 0 |
| RVd+ASCT, MRD+ | 41 | 32 | 26 | 20 | 15 | 11 | 6 | 2 | 2 | 0 |

Time since MRD evaluation at start of maintenance (months)

Richardson P, et al. ASCO 2022. Richardson P, et al. *N Engl J Med.* 2022;387:132-147.

# Why is MRD important?

Multiple studies and meta-analyses have shown the **strong association** between MRD negativity and PFS/OS
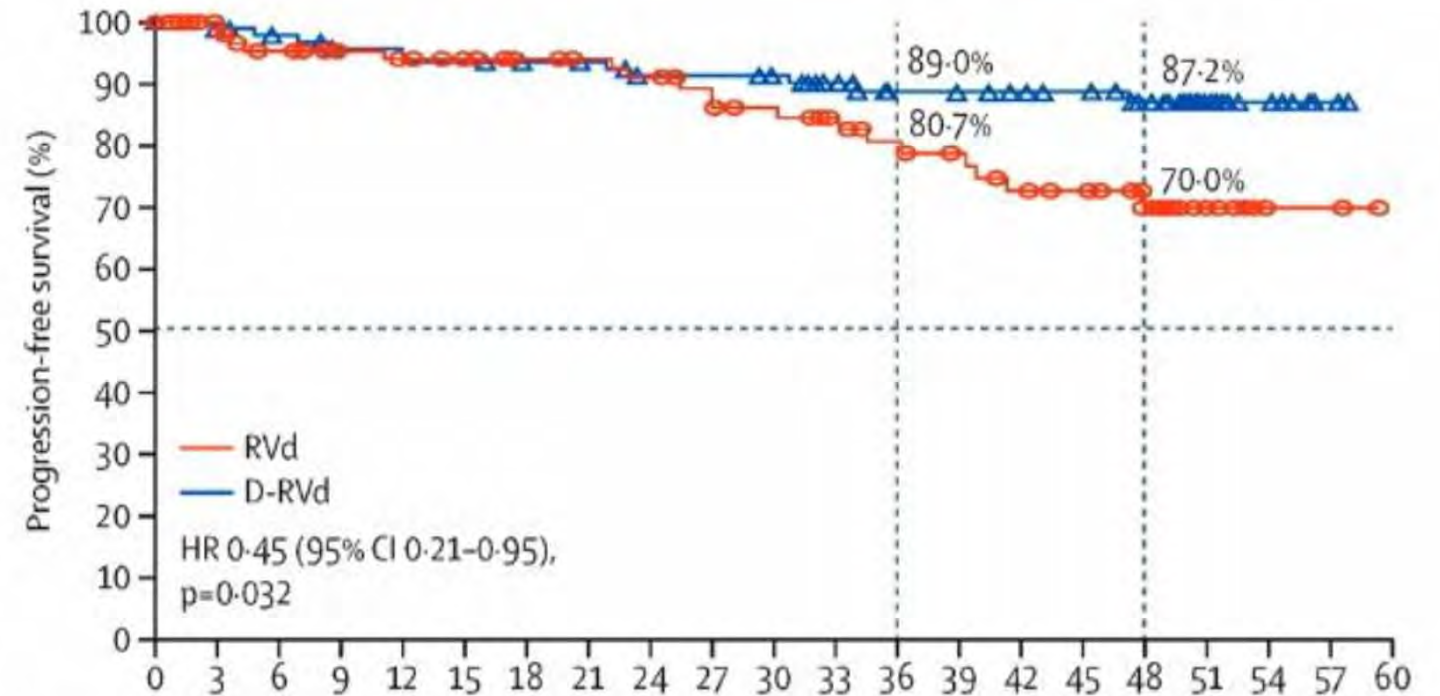
# Refining Induction Therapy
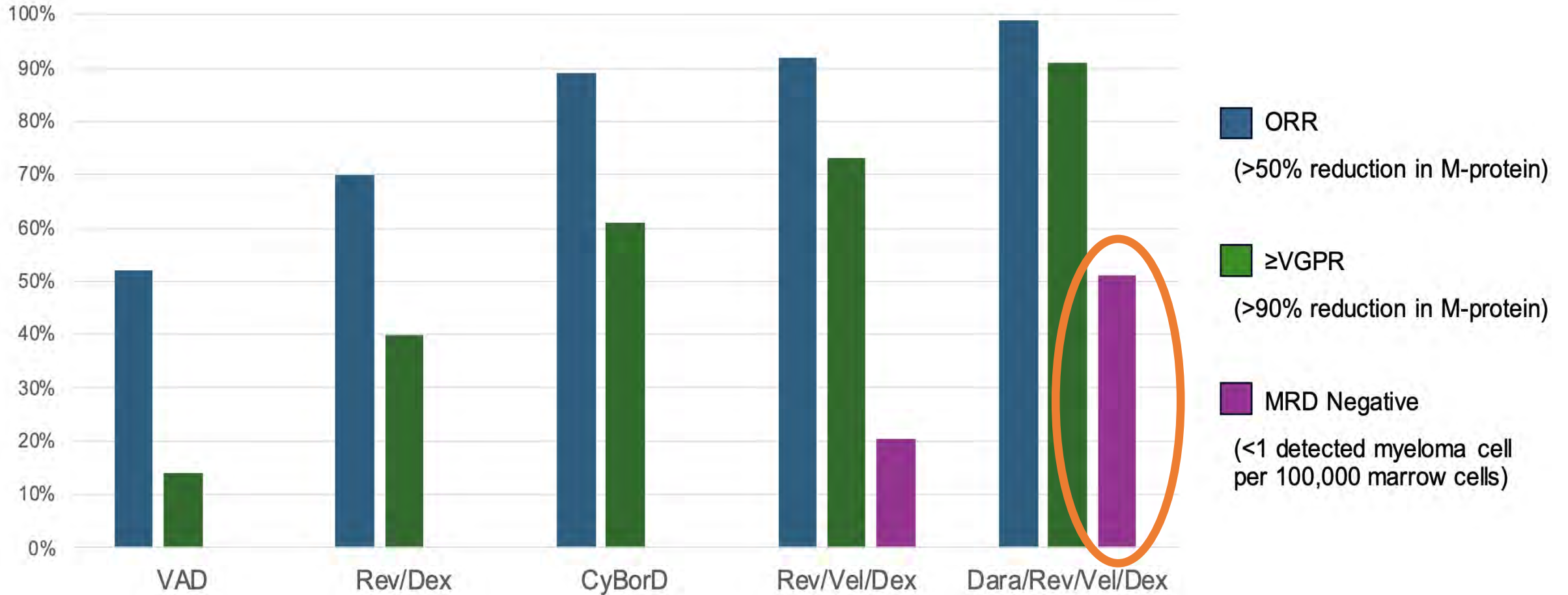
# GRIFFIN: Quad Regimen 2024 SOC for Fit Patients

Addition of daratumumab to RVd improves depth of response and progression-free survival in transplant-eligible NDMM
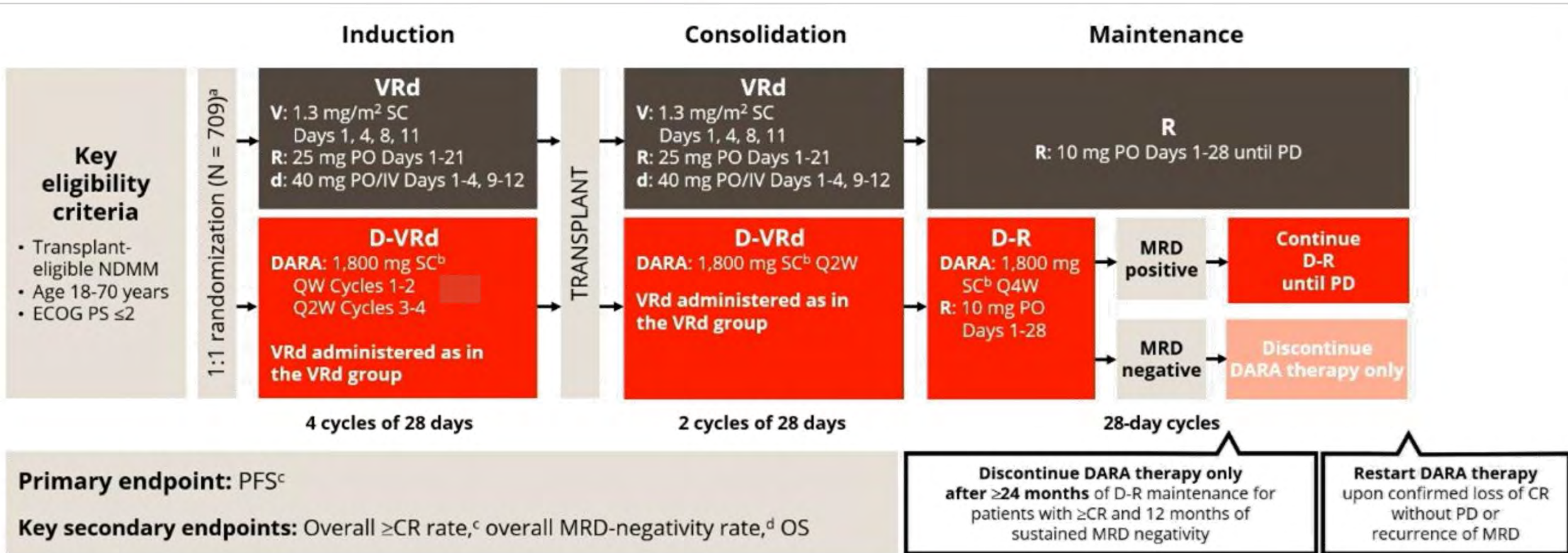
Ph 3 Quad Regimens at ASH 2023:

- **PERSEUS (D-RVd)**
- **IsKia (Isa-KRd)**



Kaplan-Meier plot of progression-free survival (%) over months. HR 0·45 (95% CI 0·21–0·95), p=0·032. RVd (red) and D-RVd (blue). D-RVd: 89·0% then 87·2%. RVd: 80·7% then 70·0%.

Number at risk (number censored)

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RVd | 103 | 93 | 77 | 72 | 70 | 68 | 63 | 61 | 59 | 53 | 51 | 46 | 42 | 39 | 35 | 33 | 25 | 12 | 3 | 3 | 0 |
| | (0) | (9) | (22) | (27) | (28) | (30) | (35) | (37) | (37) | (40) | (42) | (46) | (48) | (50) | (51) | (53) | (60) | (73) | (82) | (82) | (85) |
| D-RVd | 104 | 98 | 94 | 90 | 90 | 89 | 86 | 85 | 81 | 81 | 79 | 68 | 59 | 58 | 56 | 54 | 45 | 23 | 12 | 3 | 0 |
| | (0) | (5) | (8) | (10) | (10) | (10) | (12) | (13) | (15) | (15) | (17) | (27) | (35) | (36) | (38) | (40) | (48) | (70) | (81) | (90) | (93) |

# PERSEUS: Study Design



**Key eligibility criteria**
- Transplant-eligible NDMM
- Age 18-70 years
- ECOG PS ≤2

1:1 randomization (N = 709)[a]

**Induction**

**VRd**
V: 1.3 mg/m² SC Days 1, 4, 8, 11
R: 25 mg PO Days 1-21
d: 40 mg PO/IV Days 1-4, 9-12

**D-VRd**
DARA: 1,800 mg SC[b]
QW Cycles 1-2
Q2W Cycles 3-4

VRd administered as in the VRd group

4 cycles of 28 days

TRANSPLANT

**Consolidation**

**VRd**
V: 1.3 mg/m² SC Days 1, 4, 8, 11
R: 25 mg PO Days 1-21
d: 40 mg PO/IV Days 1-4, 9-12

**D-VRd**
DARA: 1,800 mg SC[b] Q2W

VRd administered as in the VRd group

2 cycles of 28 days

**Maintenance**

**R**
R: 10 mg PO Days 1-28 until PD

**D-R**
DARA: 1,800 mg SC[b] Q4W
R: 10 mg PO Days 1-28

MRD positive → Continue D-R until PD

MRD negative → Discontinue DARA therapy only

28-day cycles

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

**Primary endpoint:** PFS[c]

**Key secondary endpoints:** Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

# PERSEUS: Demographics and Clinical Characteristics

| | D-VRd (n = 355) | VRd (n = 354) |
|---|---|---|
| Age | | |
| Median (range), years | 61.0 (32-70) | 59.0 (31-70) |
| Category, n (%) | | |
| <50 years | 54 (15.2) | 54 (15.3) |
| ≥50 and <65 years | 207 (58.3) | 213 (60.2) |
| ≥65 years | 94 (26.5) | 87 (24.6) |
| Male, n (%) | 211 (59.4) | 205 (57.9) |
| ECOG PS,[a] n (%) | | |
| 0 | 221 (62.3) | 230 (65.0) |
| 1 | 114 (32.1) | 108 (30.5) |
| 2 | 19 (5.4) | 16 (4.5) |
| 3 | 1 (0.3) | 0 |
| MM diagnosis, n (%) | | |
| N | 354 | 352 |
| CRAB criteria only[b] | 125 (35.3) | 113 (32.1) |
| Biomarkers of malignancy only | 52 (14.7) | 65 (18.5) |
| CRAB criteria and biomarkers of malignancy | 177 (50.0) | 174 (49.4) |

| | D-VRd (n = 355) | VRd (n = 354) |
|---|---|---|
| ISS stage,[c] n (%) | | |
| N | 355 | 353 |
| I | 186 (52.4) | 178 (50.4) |
| II | 114 (32.1) | 125 (35.4) |
| III | 55 (15.5) | 50 (14.2) |
| Number of extramedullary plasmacytomas, n (%) | | |
| 0 | 340 (95.8) | 338 (95.5) |
| ≥1 | 15 (4.2) | 16 (4.5) |
| Cytogenetic profile,[d] n (%) | | |
| Standard risk | 264 (74.4) | 266 (75.1) |
| High risk | 76 (21.4) | 78 (22.0) |
| Indeterminate | 15 (4.2) | 10 (2.8) |

- **D-VRd and VRd treatment arms were well balanced**

# PERSEUS: Patient Disposition

**Median follow-up: 47.5 months**

| | D-VRd (n = 351) | VRd (n = 347) |
|---|---|---|
| Patients who discontinued study treatment, n (%) | 91 (25.9) | 188 (54.2) |
| Reason for discontinuation, n (%) | | |
| Adverse event | 32 (9.1) | 78 (22.5) |
| Progressive disease | 29 (8.3) | 72 (20.7) |
| Patient refused further study treatment | 10 (2.8) | 14 (4.0) |
| Death | 9 (2.6) | 11 (3.2) |
| Physician decision | 8 (2.3) | 9 (2.6) |
| Lost to follow-up | 3 (0.9) | 2 (0.6) |
| Non-compliance with study drug | 0 | 1 (0.3) |
| Other | 0 | 1 (0.3) |



Bar chart — % of patients:
- Completed induction + consolidation: D-VRd 89.5%, VRd 86.2%
- Received ASCT: D-VRd 89.7%, VRd 87.0%
- Entered maintenance: D-VRd 91.7%, VRd 86.5%
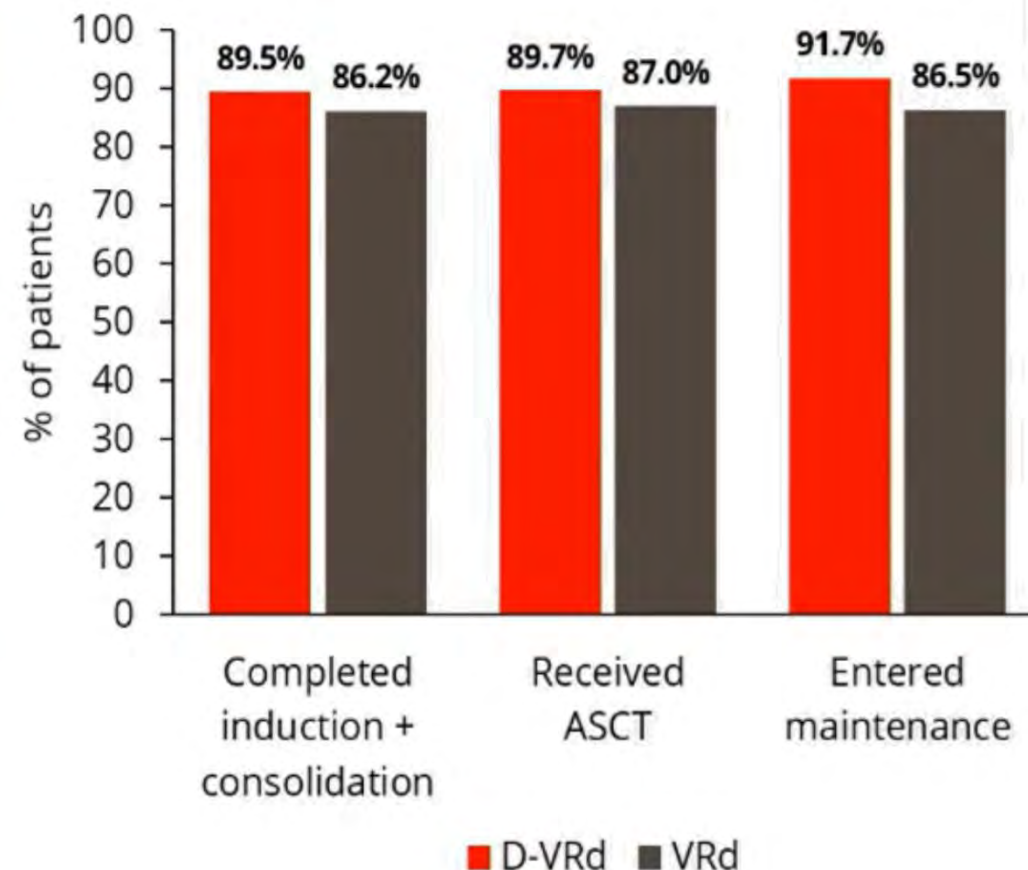
■ D-VRd  ■ VRd

- Among patients receiving maintenance (D-VRd, n = 322; VRd, n = 300), 81 (25.2%) patients in the D-VRd group and 58 (19.3%) patients in the VRd group discontinued lenalidomide during maintenance

# PERSEUS: Stem Cell Collection and Transplantation

| | D-VRd | VRd |
|---|---|---|
| Patients receiving plerixafor for mobilization, n (%)[a] | 134 (40.0) | 72 (22.7) |
| Median CD34$^+$ cells collected, $10^6$/kg[b] | 5.5 | 7.4 |
| Patients receiving transplant, n (%)[c] | 315 (89.7) | 302 (87.0) |
| Patients achieving hematopoietic reconstitution, n (%)[d] | 314 (99.7) | 300 (99.3) |
| Median time to engraftment, days[e] | 14 | 14 |

- **Stem cell mobilization and collection were feasible with D-VRd**
- **D-VRd did not impact the ability to receive transplant or engraftment**

# PERSEUS: Overall ≥CR Rates



| Subgroup | VRd | D-VRd | Odds ratio (95% CI) |
|---|---|---|---|
| | no. of patients with ≥CR/total no. (%) | | |
| **Sex** | | | |
| Male | 143/205 (69.8) | 185/211 (87.7) | 3.08 (1.86-5.12) |
| Female | 105/149 (70.5) | 127/144 (88.2) | 3.13 (1.69-5.80) |
| **Age** | | | |
| <65 y | 186/267 (69.7) | 235/261 (90.0) | 3.94 (2.43-6.37) |
| ≥65 y | 62/87 (71.3) | 77/94 (81.9) | 1.83 (0.91-3.68) |
| **Race** | | | |
| White | 226/323 (70.0) | 289/330 (87.6) | 3.03 (2.02-4.53) |
| Other | 22/31 (71.0) | 23/25 (92.0) | 4.70 (0.91-24.25) |
| **ISS stage** | | | |
| I | 129/178 (72.5) | 167/186 (89.8) | 3.34 (1.87-5.95) |
| II | 84/125 (67.2) | 101/114 (88.6) | 3.79 (1.91-7.54) |
| III | 34/50 (68.0) | 44/55 (80.0) | 1.88 (0.77-4.58) |
| **Type of MM** | | | |
| IgG | 122/185 (65.9) | 178/204 (87.3) | 3.54 (2.12-5.90) |
| Non-IgG | 73/96 (76.0) | 72/78 (92.3) | 3.78 (1.45-9.83) |
| **Cytogenetic risk** | | | |
| Standard risk | 182/266 (68.4) | 234/264 (88.6) | 3.60 (2.27-5.70) |
| High risk | 59/78 (75.6) | 63/76 (82.9) | 1.56 (0.71-3.44) |
| Indeterminate | 7/10 (70.0) | 15/15 (100) | NE (NE-NE) |
| **ECOG PS** | | | |
| 0 | 160/230 (69.6) | 195/221 (88.2) | 3.28 (2.00-5.39) |
| ≥1 | 88/124 (71.0) | 117/134 (87.3) | 2.82 (1.49-5.34) |

- **Overall ≥CR rate was significantly higher with D-VRd versus VRd**
- **≥CR rate was improved with D-VRd versus VRd across subgroups**

# PERSEUS: Overall and Sustained MRD Neg Rates

**MRD negativity ($10^{-5}$)**

$P < 0.0001$[b]
Odds ratio, 3.40
(95% CI, 2.47-4.69)

- D-VRd (n = 355): 75.2%
- VRd (n = 354): 47.5%
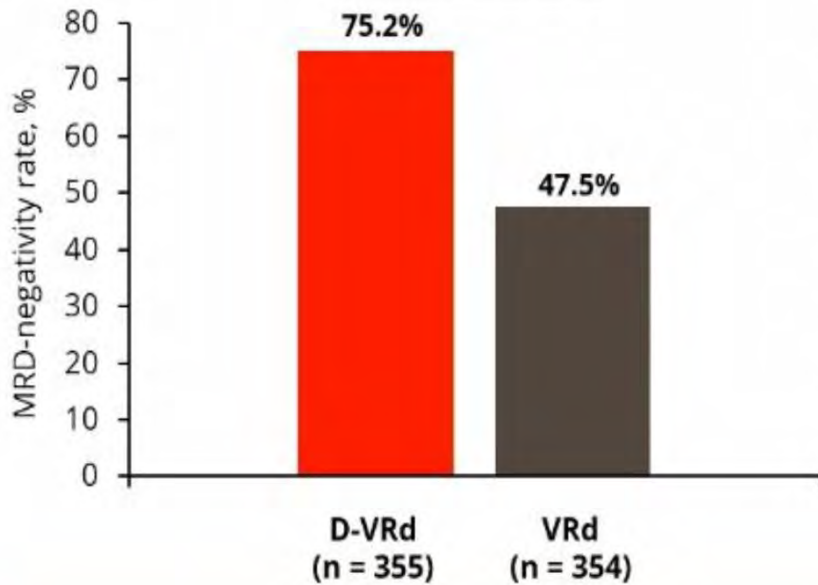
**MRD negativity ($10^{-6}$)**

$P < 0.0001$[b]
Odds ratio, 3.97
(95% CI, 2.90-5.43)

- D-VRd (n = 355): 65.1%
- VRd (n = 354): 32.2%
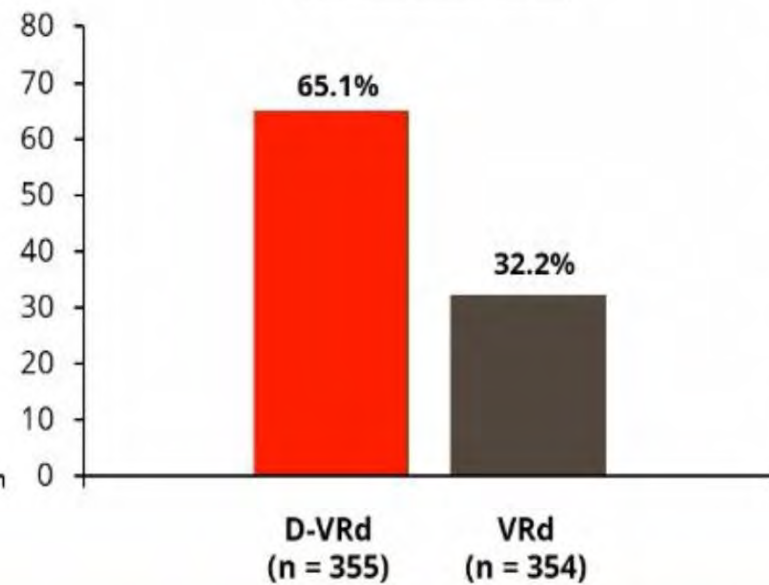
**Sustained MRD negativity ($10^{-5}$) ≥12 months**

$P < 0.0001$[c]
Odds ratio, 4.42
(95% CI, 3.22-6.08)

- D-VRd (n = 355): 64.8%
- VRd (n = 354): 29.7%

Y-axis: MRD-negativity rate, %
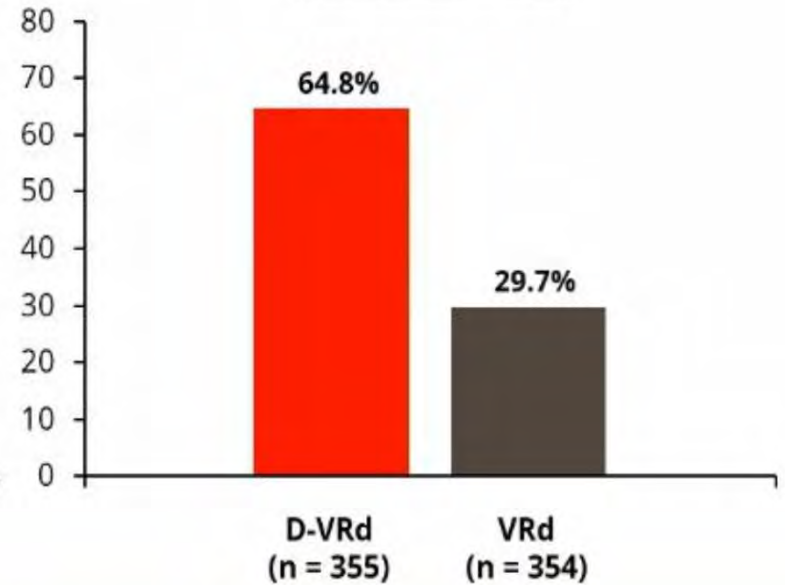
- Deep and durable MRD negativity was achieved with D-VRd
- 64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol[d]

# PERSEUS: MRD-negativity Rates Over Time



**MRD negativity ($10^{-5}$)**

MRD-negativity rate, %

Post-consolidation:
- D-VRd (n = 355): 57.5%
- VRd (n = 354): 32.5%

Overall:
- D-VRd (n = 355): 75.2%
- VRd (n = 354): 47.5%

**MRD negativity ($10^{-6}$)**

Post-consolidation:
- D-VRd (n = 355): 34.4%
- VRd (n = 354): 16.1%
- Δ18%

Overall:
- D-VRd (n = 355): 65.1%
- VRd (n = 354): 32.2%
- Δ33%
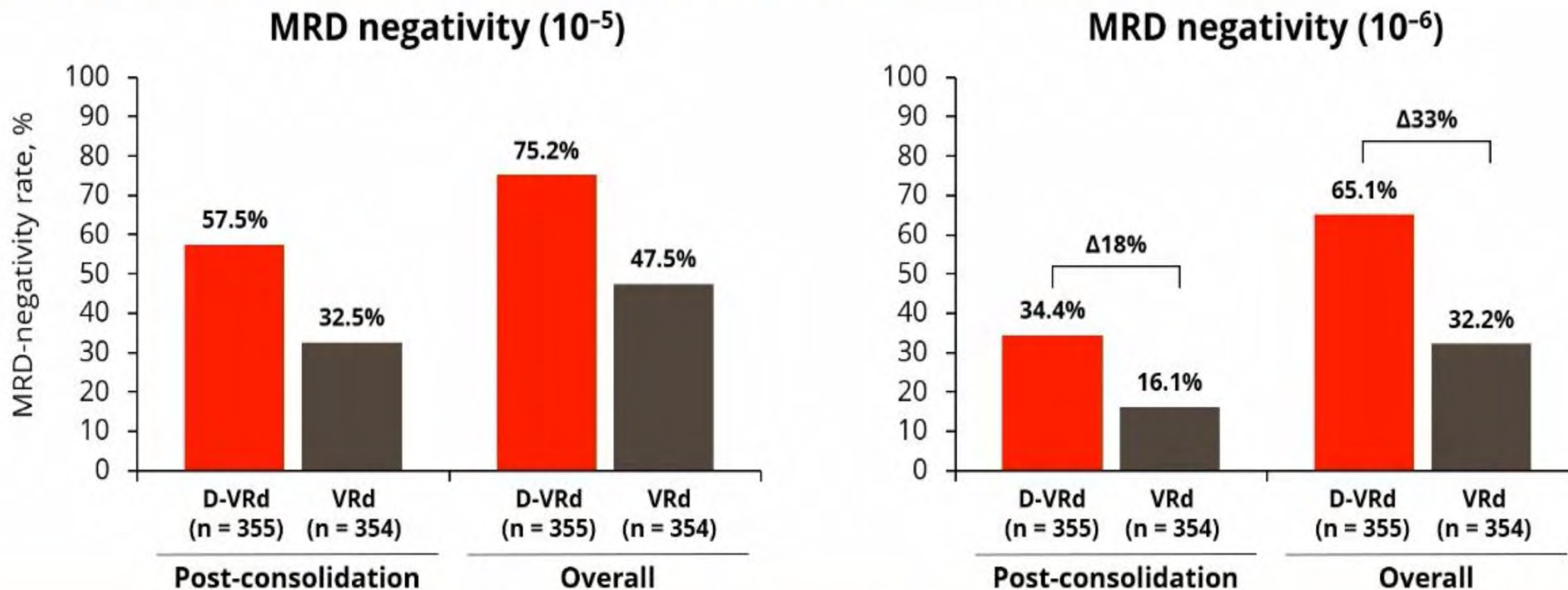
- Rates of MRD negativity improved during maintenance
- The absolute difference between D-VRd and VRd widened over time and is most evident at the deeper threshold of $10^{-6}$

# PERSEUS: Progression-Free Survival



**Median follow-up: 47.5 months**

48-month PFS

**84.3%** D-VRd

**67.7%** VRd

HR, 0.42; 95% CI, 0.30-0.59; *P* <0.0001

% surviving without progression

Months

No. at risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VRd | 354 | 335 | 321 | 311 | 304 | 297 | 291 | 283 | 278 | 270 | 258 | 247 | 238 | 228 | 219 | 175 | 67 | 13 | 0 |
| D-VRd | 355 | 345 | 335 | 329 | 327 | 322 | 318 | 316 | 313 | 309 | 305 | 302 | 299 | 295 | 286 | 226 | 90 | 11 | 0 |
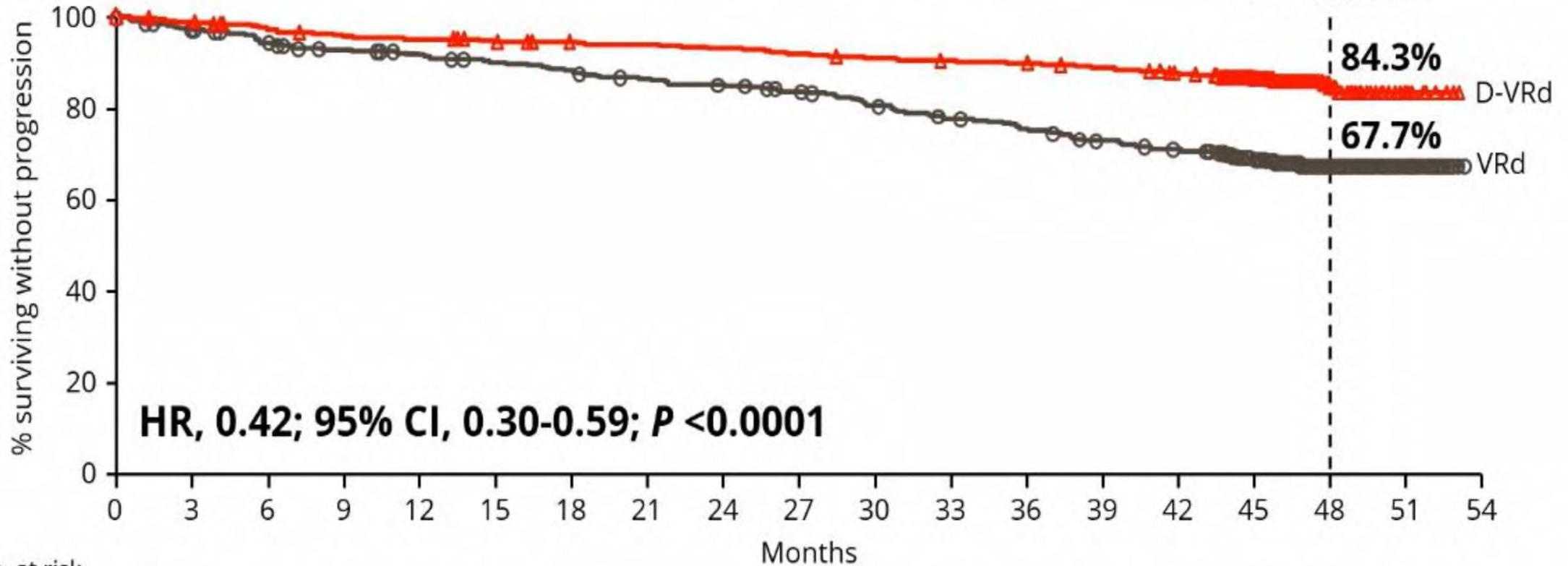
**• 58% reduction in the risk of progression or death in patients receiving D-VRd**

# PERSEUS: PFS in Prespecified Subgroups



| Subgroup | D-VRd no. of progression events or deaths/total no. | VRd | HR (95% CI) |
|---|---|---|---|
| **Sex** | | | |
| Male | 36/211 | 61/205 | 0.51 (0.34-0.77) |
| Female | 14/144 | 42/149 | 0.29 (0.16-0.53) |
| **Age** | | | |
| <65 y | 30/261 | 84/267 | 0.30 (0.20-0.46) |
| ≥65 y | 20/94 | 19/87 | 0.97 (0.52-1.81) |
| **Race** | | | |
| White | 47/330 | 95/323 | 0.42 (0.30-0.60) |
| Other | 3/25 | 8/31 | 0.40 (0.11-1.50) |
| **ISS stage** | | | |
| I | 18/186 | 35/178 | 0.46 (0.26-0.81) |
| II | 19/114 | 43/125 | 0.37 (0.22-0.64) |
| III | 13/55 | 25/50 | 0.42 (0.22-0.83) |
| **Type of MM** | | | |
| IgG | 28/204 | 58/185 | 0.36 (0.23-0.57) |
| Non-IgG | 13/78 | 31/96 | 0.46 (0.24-0.88) |
| **Cytogenetic risk** | | | |
| Standard risk | 25/264 | 62/266 | 0.35 (0.22-0.56) |
| High risk | 24/76 | 38/78 | 0.59 (0.36-0.99) |
| Indeterminate | 1/15 | 3/10 | 0.16 (0.02-1.56) |
| **ECOG PS** | | | |
| 0 | 28/221 | 60/230 | 0.42 (0.27-0.66) |
| ≥1 | 22/134 | 43/124 | 0.41 (0.25-0.69) |

Favors D-VRd    Favors VRd

- **PFS was improved with D-VRd versus VRd across clinically relevant subgroups**

# PERSEUS: Overall Survival



|  | D-VRd (n = 355) | VRd (n = 354) |
|---|---|---|
| Events, n (%) | 34 (9.6) | 44 (12.4) |

HR, 0.73

No. at risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VRd | 354 | 343 | 337 | 334 | 328 | 322 | 322 | 319 | 317 | 315 | 310 | 307 | 303 | 298 | 296 | 263 | 127 | 27 | 1 | 0 |
| D-VRd | 355 | 347 | 343 | 341 | 338 | 335 | 331 | 329 | 329 | 326 | 325 | 323 | 321 | 316 | 312 | 284 | 135 | 21 | 1 | 0 |
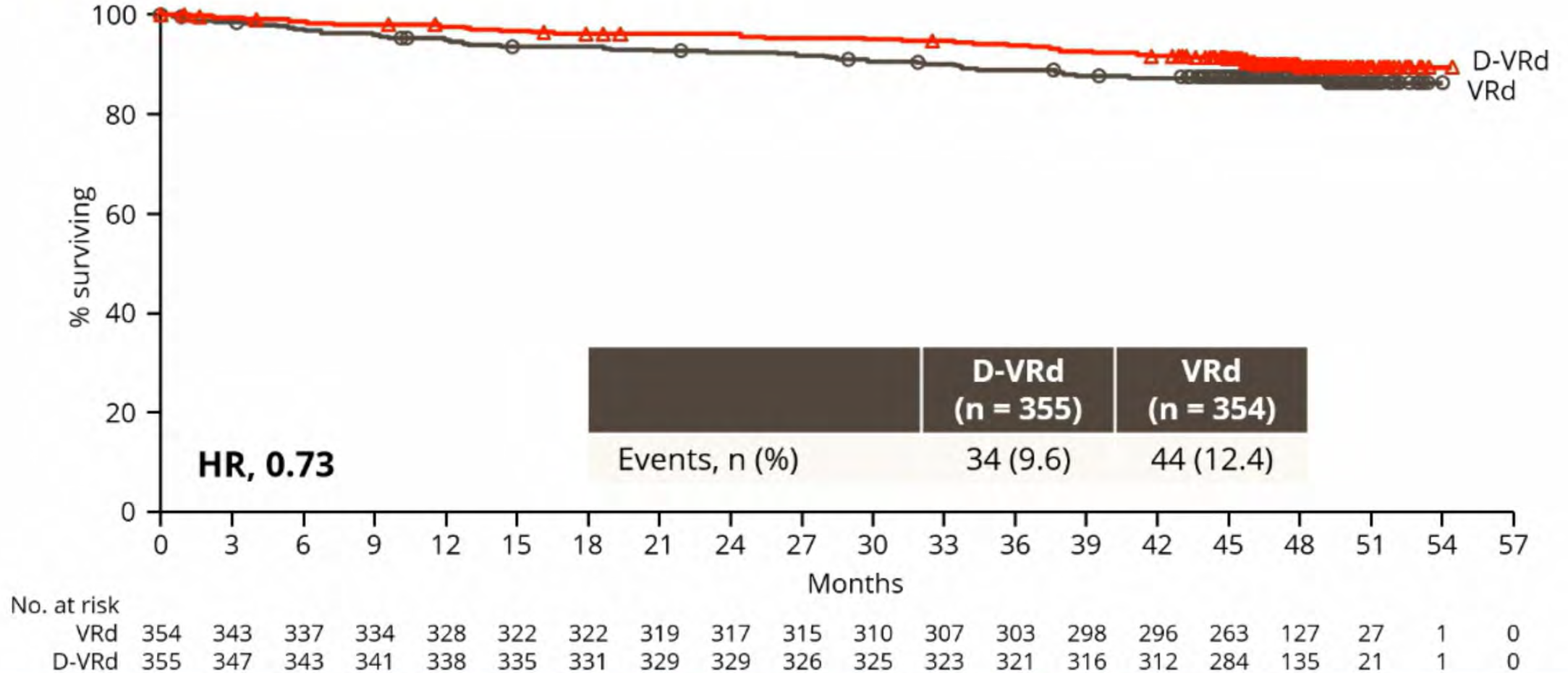
**• OS data trend favorably for D-VRd**

# PERSEUS: Safety

| Event, n (%)[a] | D-VRd (n = 351) | | VRd (n = 347) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| HEMATOLOGIC | | | | |
| **Neutropenia** | **243 (69.2)** | **218 (62.1)** | **204 (58.8)** | **177 (51.0)** |
| **Thrombocytopenia** | **170 (48.4)** | **102 (29.1)** | **119 (34.3)** | **60 (17.3)** |
| Anemia | 78 (22.2) | 21 (6.0) | 72 (20.7) | 22 (6.3) |
| Febrile neutropenia | 34 (9.7) | 33 (9.4) | 38 (11.0) | 35 (10.1) |
| NON-HEMATOLOGIC | | | | |
| Diarrhea | 214 (61.0) | 37 (10.5) | 188 (54.2) | 27 (7.8) |
| **Peripheral sensory neuropathy** | **188 (53.6)** | **15 (4.3)** | **179 (51.6)** | **14 (4.0)** |
| Constipation | 119 (33.9) | 8 (2.3) | 118 (34.0) | 6 (1.7) |
| Pyrexia | 111 (31.6) | 8 (2.3) | 109 (31.4) | 9 (2.6) |
| Insomnia | 95 (27.1) | 8 (2.3) | 61 (17.6) | 6 (1.7) |
| Asthenia | 94 (26.8) | 12 (3.4) | 89 (25.6) | 9 (2.6) |
| Cough | 85 (24.2) | 1 (0.3) | 51 (14.7) | 0 |
| Fatigue | 84 (23.9) | 10 (2.8) | 92 (26.5) | 18 (5.2) |
| Rash | 82 (23.4) | 9 (2.6) | 94 (27.1) | 17 (4.9) |
| Back pain | 80 (22.8) | 2 (0.6) | 66 (19.0) | 1 (0.3) |
| Peripheral edema | 72 (20.5) | 4 (1.1) | 74 (21.3) | 1 (0.3) |
| Nausea | 71 (20.2) | 2 (0.6) | 58 (16.7) | 2 (0.6) |
| **Infections** | **305 (86.9)** | **124 (35.3)** | **266 (76.7)** | **95 (27.4)** |
| COVID-19 | 123 (35.0) | 12 (3.4) | 83 (23.9) | 4 (1.2) |
| Upper respiratory tract infection | 111 (31.6) | 2 (0.6) | 87 (25.1) | 6 (1.7) |
| Pneumonia | 64 (18.2) | 37 (10.5) | 38 (11.0) | 21 (6.1) |

# IsKia: Study Design



42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021

**Induction**
*Four 28-day cycles*

**Post-ASCT consolidation**
*Four 28-day cycles*

**Light consolidation**
*Twelve 28-day cycles*

**Key eligibility criteria:**

TE NDMM patients aged <70 years

**Stratification:**
- Centralized FISH (standard risk/missing vs. high risk defined as del(17p) and/or t(4;14) and/or t(14;16);
- ISS (I vs. II and III)

**R**

**4× KRd**

K: 20 mg/m² IV dd 1 cc 1 only; followed by 56 mg/m² IV dd 8,15 cc 1 and dd 1,8,15 cc 2-4
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

**4× Isa-KRd**

Isa: 10 mg/kg IV dd 1,8,15,22 cc 1, followed by 10 mg/kg IV dd 1 and 15 cc 2 to 4.
K: 20 mg/m² IV dd 1 cc 1 only; followed by 56 mg/m² IV dd 8,15 cc 1 and dd 1,8,15 cc 2-4
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

**MOBILIZATION**
Cy: 2-3 g/m²
*followed by*
**G-CSF**
for stem-cell collection

*and*

**MEL200-ASCT**
MEL: 200 mg/m²
*followed by*
**ASCT**

**4× KRd**

K: 56 mg/m² IV dd 1,8,15 cc 5-8
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

**4× Isa-KRd**

Isa: 10 mg/kg IV dd 1,15 cc 5-8
K: 56 mg/m² IV dd 1,8,15 cc 5-8
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

**12× KRd**

K: 56 mg/m² IV dd 1,15
R: 10 mg PO dd 1-21
d: 20 mg PO dd 1,15

**12× Isa-KRd**

Isa: 10 mg/kg IV d 1
K: 56 mg/m² IV dd 1,15
R: 10 mg PO dd 1-21
d: 20 mg PO dd 1,15

# IsKia: Patient Characteristics

| | | isa-KRd n=151 | KRd n=151 |
|---|---|---|---|
| Age, years | Median (IQR) | 61 (55–66) | 60 (54–63) |
| Sex, n (%) | Female | 72 (48) | 67 (44) |
| | Male | 79 (52) | 84 (56) |
| Cytogenetic risk as per IMWG, n (%) *High risk: t(4;14), t(14;16), or del(17p)* | Standard risk | 115 (82) | 113 (81) |
| | High risk | 25 (18) | 26 (19) |
| | Missing | 11 | 12 |
| No. of HRCA risk: 0 vs. 1 vs. 2+ HRCA, n (%) *del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21)* | 0 HRCA | 78 (56) | 75 (54) |
| | 1 HRCA | 49 (35) | 49 (35) |
| | 2+ HRCA | 13 (9) | 15 (11) |
| | Missing | 11 | 12 |
| R-ISS, n (%) | I | 50 (35) | 48 (34) |
| | II | 82 (58) | 85 (59) |
| | III | 10 (7) | 10 (7) |
| | Missing | 9 | 8 |
| R2-ISS, n (%) | I | 34 (24) | 35 (25) |
| | II | 45 (32) | 47 (34) |
| | III | 52 (37) | 51 (37) |
| | IV | 8 (6) | 6 (4) |
| | Missing | 12 | 12 |

# IsKia: Patient Disposition

|  | Isa-KRd n=151 | KRd n=151 |
|---|---|---|
| **Patients who discontinued study treatment, n (%)** | 25 (17) | 15 (10) |
| **Reasons for discontinuation, n (%)** | | |
| Adverse event | 9 (6) | 7 (5) |
| Progressive disease | 3 (2) | 3 (2) |
| Medical decision | 4 (3) | 0 |
| Withdrawal of consent by patient | 5 (3) | 4 (3) |
| Death | 4 (3) | 1 (<1) |

- Median follow-up: 21 months

- Completed induction and consolidation:
  - Isa-KRd 83%
  - KRd 90%

Reasons for discontinuation, Adverse Events:
-IsaKRd: Dress Syndrome G4 (n=1); maculo-popular rash G3 (n=1); Infection (n=2, G1 n=1; G2, n=1); pancytopenia G4 (n=2); renal failure G4 (n=1); cardiovascular toxicity G2 (N=2)
-KRd: anaphylactic reaction G4 (n=1); vasculitis G3 (n=1); rash G2 (n=1); Infection (n=3); pancytopenia G2 (n=1); TLS G3 (n=1); cardiovascular toxicity G3 (n=2) G4 (n=1)
Deaths:
-IsaKRd : progressive disease (n=1); Infection (n=3)
-KRd: infection (n=1)

# IsKia: Post-Consolidation MRD-negativity (ITT analysis)



**NGS, $10^{-5}$**

OR 1.67, p=0.049

- Isa-KRd (N=151): 77%
- KRd (N=151): 67%

**NGS, $10^{-6}$**

OR 2.29, p<0.001

- Isa-KRd (N=151): 67%
- KRd (N=151): 48%
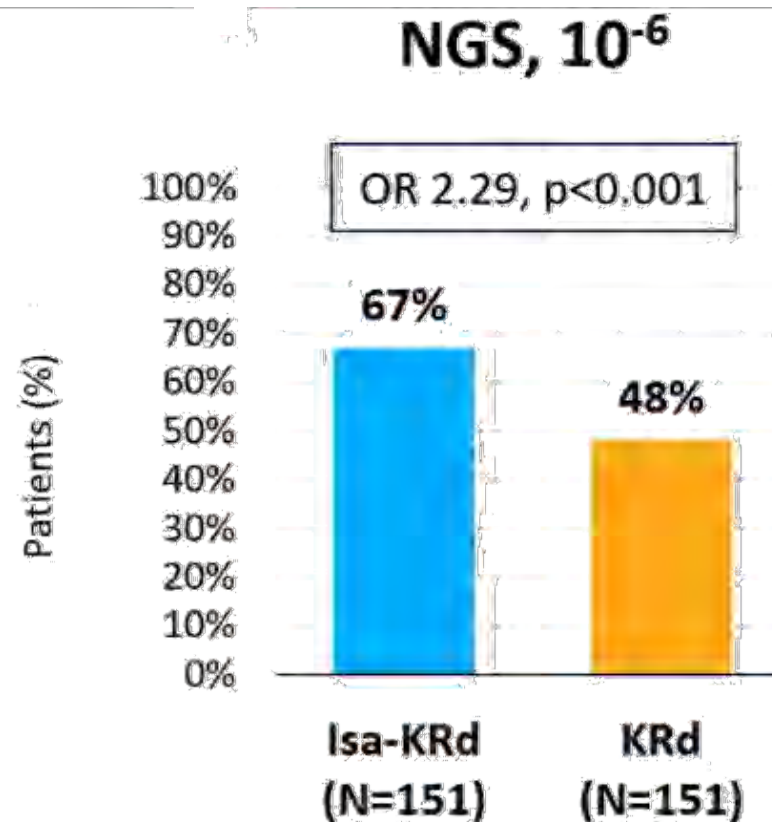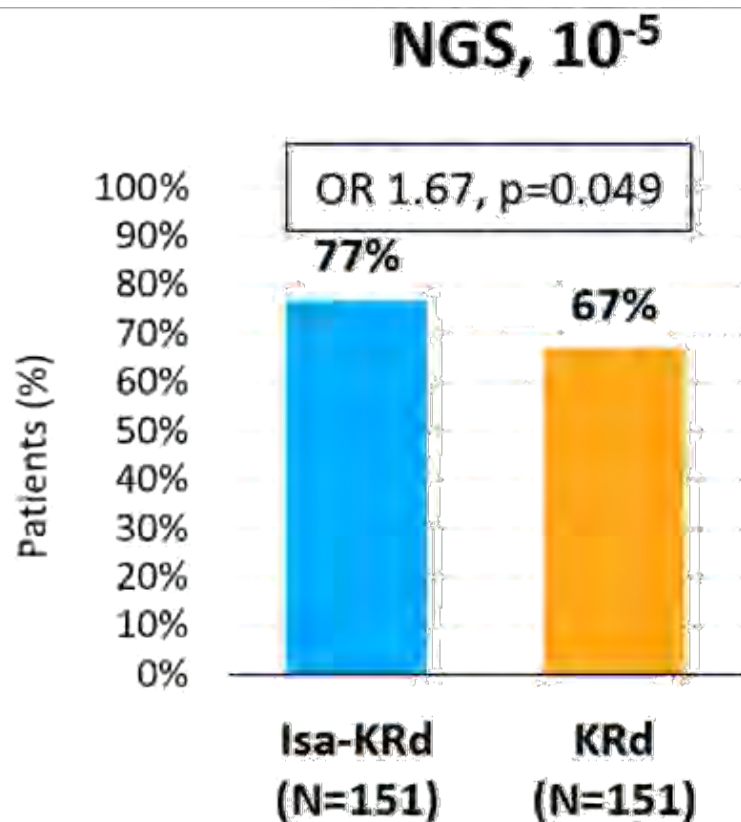
≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.

High MRD compliance and sample quality (97-100% of sample evaluable at $10^{-5}$ and $10^{-6}$ cut-offs).

Consistent MRD results were detected by next-generation flow

In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

# IsKia: MRD-negativity Rates Improved Over Time ($10^{-5}$)
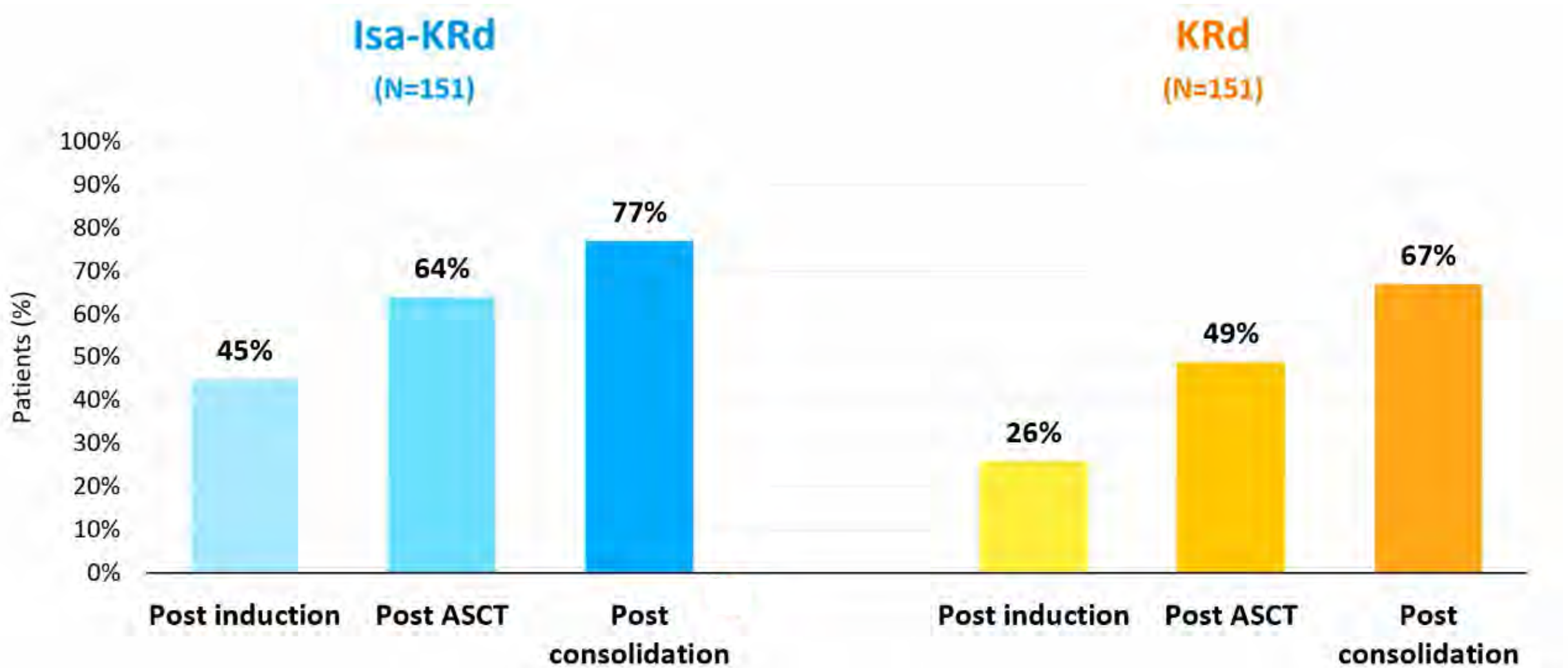
# IsKia: MRD-negativity Rates Improved Over Time ($10^{-6}$)
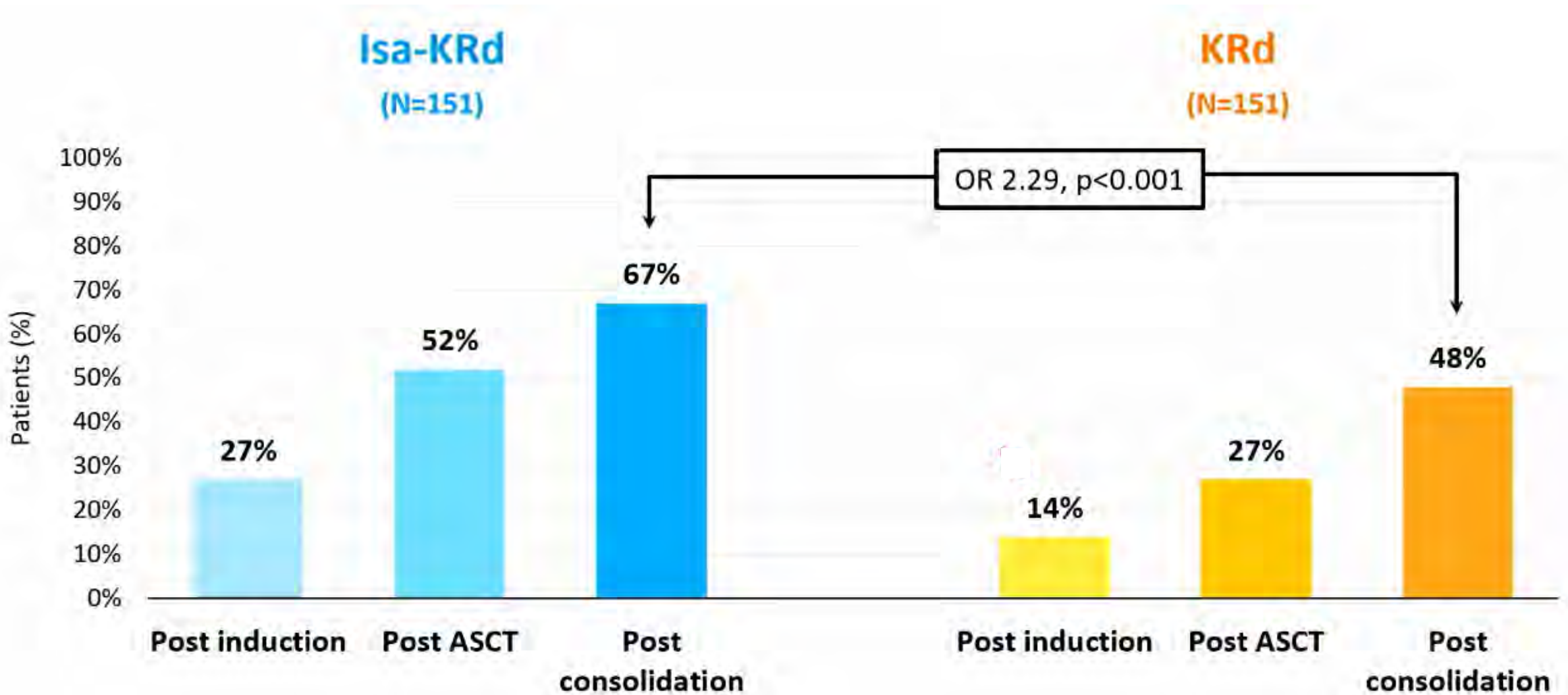
# IsKia: Post-consolidation MRD-negativity by NGS
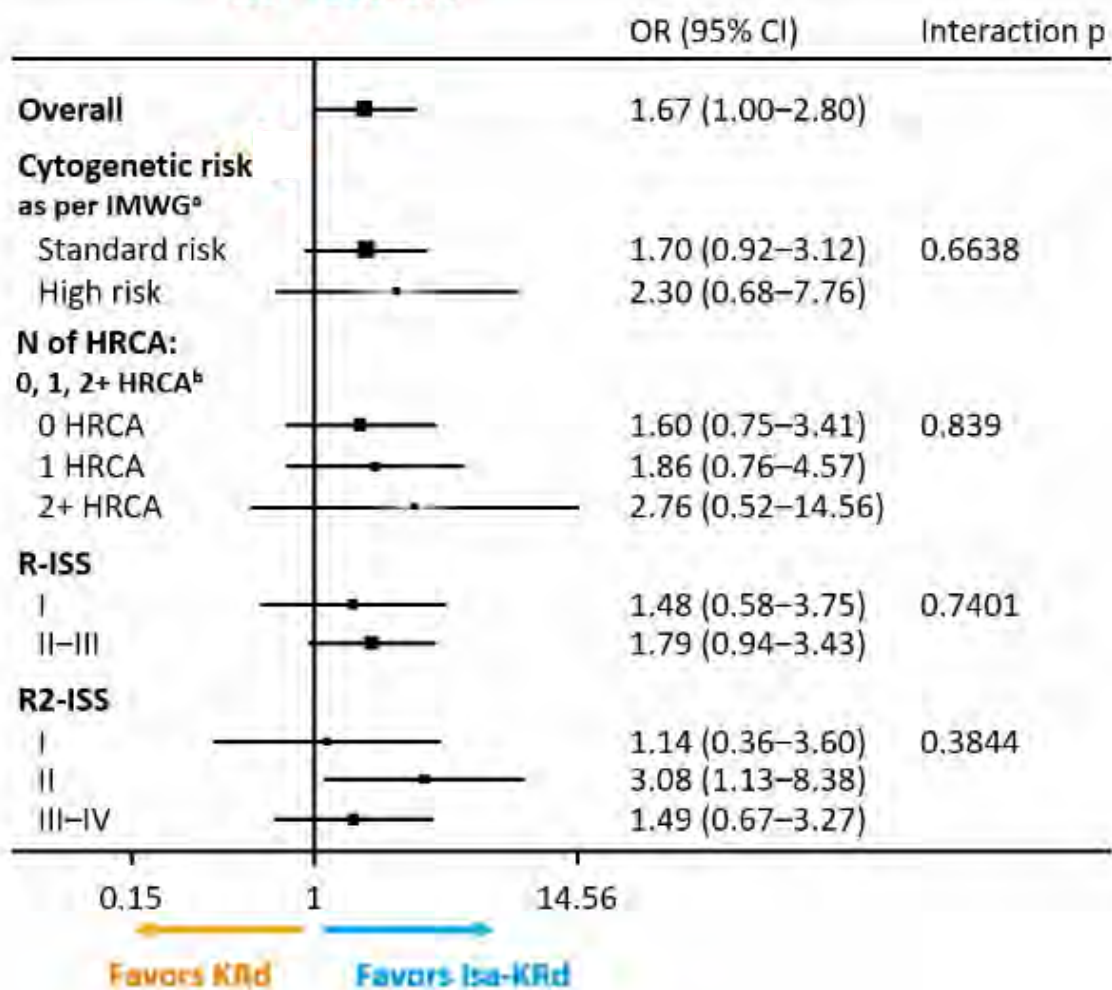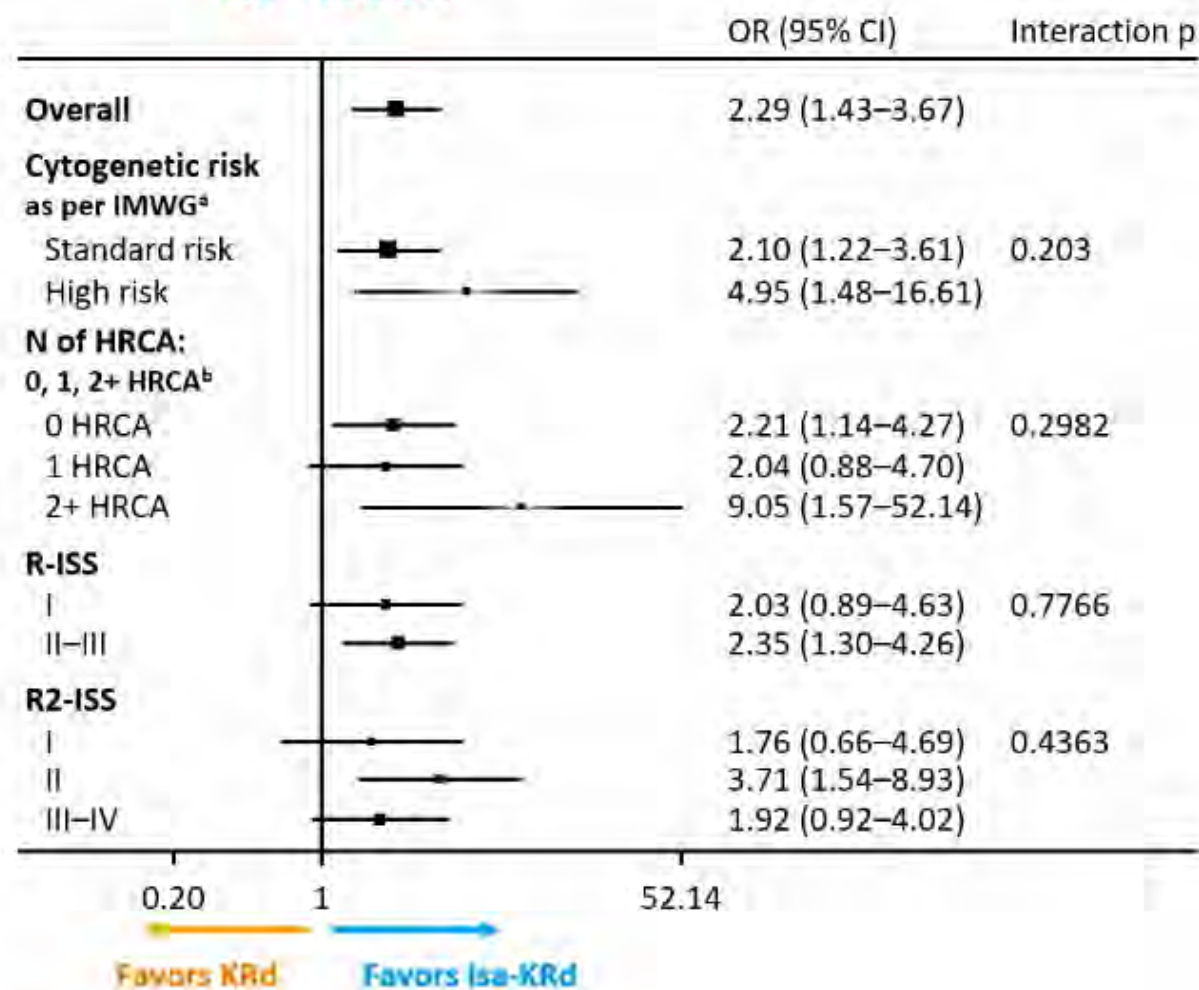
# IsKia: Safety

| | Isa-KRd (n=151) | | KRd (n=151) | |
|---|---|---|---|---|
| | Any grade, n (%) | Grade 3-4, n (%) | Any grade, n(%) | Grade 3-4, n (%) |
| **Pts with ≥1 hematologic toxicity** | 83 (55) | 61 (40) | 67 (44) | 46 (30) |
| Anemia | 32 (21) | 5 (3) | 28 (19) | 5 (3) |
| Neutropenia | 62 (41) | 55 (36)* | 39 (26) | 33 (22)* |
| Thrombocytopenia | 51 (34) | 22 (15) | 38 (25) | 25 (17) |
| **Pts with ≥1 Non-Hematologic toxicity** | 136 (90) | 61 (41) | 129 (85) | 56 (37) |
| Infections (excluding COVID19) | 55 (36) | 23 (15) | 49 (32) | 17 (11) |
| Asthenia/fatigue | 37 (25) | 5 (3) | 40 (26) | 3 (2) |
| Dyspnea | 20 (13) | 2 (1) | 9 (6) | 1 (<1) |
| Rash | 33 (22) | 5 (3) | 40 (26) | 5 (3) |
| Peripheral neuropathy | 22 (15) | 0 | 25 (17) | 0 |
| Infusion-related reactions | 30 (20) | 5 (3) | 2 (1) | 0 |
| Cardiac disorders | 11 (7) | 1 (<1) | 19 (13) | 5 (3) |
| Vascular disorders | 29 (19) | 7 (5) | 33 (22) | 15 (10) |
| *Hypertension* | 5 (3) | 2 (1) | 6 (4) | 3 (2) |
| *Thromboembolism* | 12 (8) | 4 (3) | 16 (11) | 9 (6) |
| Gastrointestinal disorders | 79 (52) | 10 (7) | 73 (48) | 8 (5) |
| *Nausea* | 36 (24) | 4 (3) | 31 (21) | 2 (1) |
| *Vomiting* | 18 (12) | 2 (1) | 12 (8) | 1 (<1) |
| *Diarrhea* | 41 (27) | 6 (4) | 37 (25) | 5 (3) |

**SARS-CoV-2 infection**

| Isa-KRd (n=151) | | KRd (n=151) | |
|---|---|---|---|
| Any grade, n (%) | Grade ≥3, n (%) | Any grade, n (%) | Grade ≥3, n (%) |
| 39 (26) | 3 (2) | 28 (19) | 2 (1) |

*p-value =0.008

# Conclusion

**D-VRd produced deep and durable responses in ASCT-eligible, NDMM patients versus VRd.**

- 48-month PFS: 84.3% vs 67.7%, **p<0.0001**

- ≥CR: 87.9% vs 70.1%, **p<0.0001**

- Overall MRD-negativity: 75.2% vs 47.5%, **p<0.0001**

Rates of MRD-negativity improved during maintenance, and 64% of patients were able to discontinue daratumumab after achieving MRD-negativity with at least two years of maintenance.

**In the primary analysis of the IsKia trial, Isa-KRd improved post-consolidation MRD negativity vs KRd.**

- Post-Consolidation MRD-negativity:
    - MRD-negativity, $10^{-5}$: 77% vs 67%, **p=0.049**
    - MRD-negativity, $10^{-6}$: 67% vs 48%, **p<0.001**

1-year sustained MRD negativity data is expected later this year.

# Application to current practice

For transplant eligible

- Use quadruplet for induction (eg RVD dara)

- Consider consolidation if MRD positive post BMT

- Consider doublet for maintenance if MRD positive or high risk disease after consolidation

For transplant ineligible

- Use CD 38/ len containing triplet as induction for STD risk(DRd)

- Use quadruplet for high risk (DRVd lite)

- Consider doublet for maintenance in MRD positive after 8-12 months of induction therapy

# Novel Therapies in Relapsed/Refractory Myeloma

**Chimeric Antigen Receptor T-Cells**



MM cell death

scFv

signaling domain

Cytotoxic cytokines
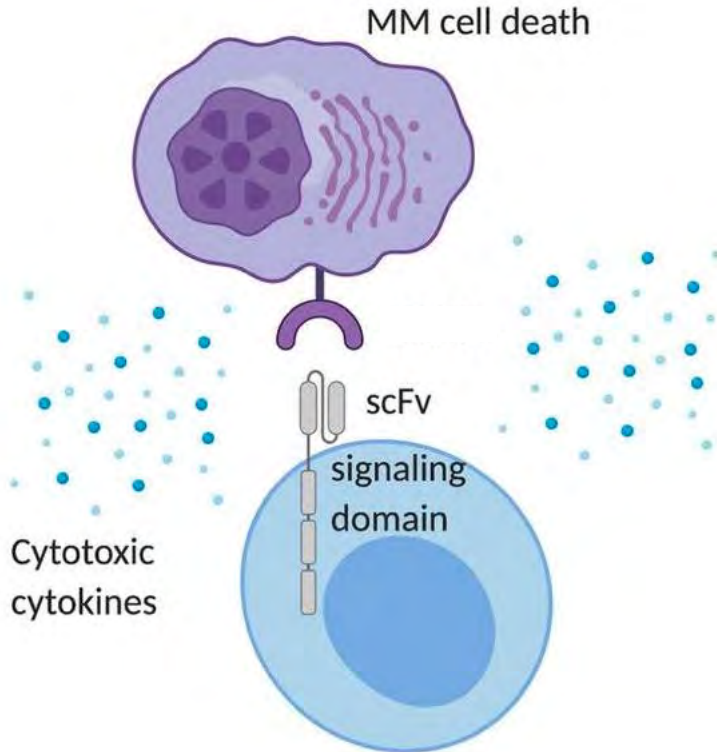
BCMA-Targeting CAR-T
- **Ide-cel**: Approved Mar 2021
- **Cilta-cel**: Approved Feb 2022

**Bispecific T-Cell Engagers**



CD3

MM cell death

Cytotoxic cytokines
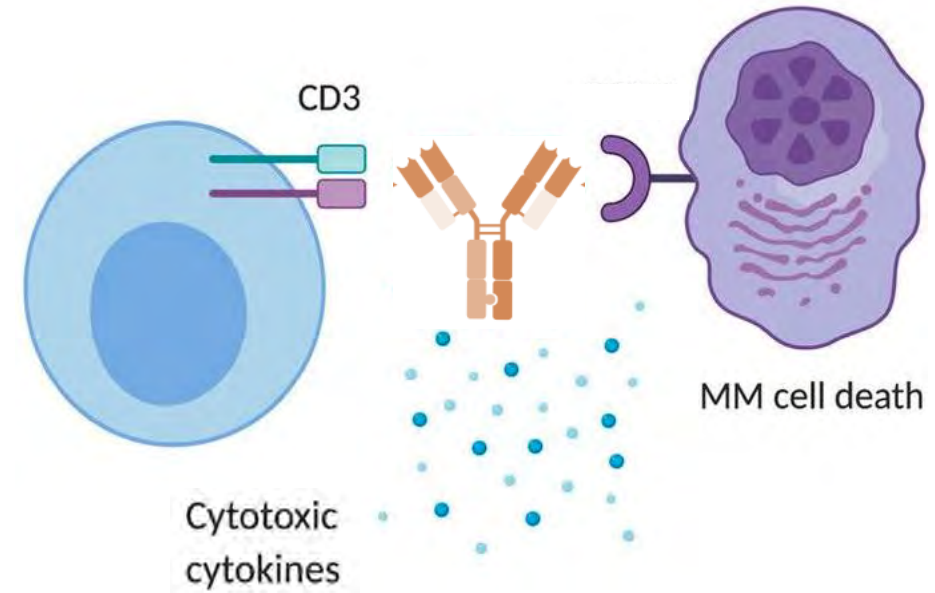
BCMA-Targeting Bispecifics
- **Teclistamab**: Approved Oct 2022
- **Elranatamab**: Approved Aug 2023

GPRC5D-Targeting Bispecific
- **Talquetamab**: Approved Aug 2023

Image Adapted from: Yu B, et al. *J Hematol Oncol.* 2020;13(1):125.

# Current indications for both CAR-T and Bispecifics in RRMM

Triple class exposed: PI, IMID & anti-CD38+ monoclonal antibody

Progressing/Relapsed disease

≥4 prior lines of therapy

# KARMMA-3 and CARTITUDE-4, CAR-T outperforms SOC - ?could lead to earlier indication

P Rodriguez-Otero et al. N Engl J Med 2023;388:1002-1014.
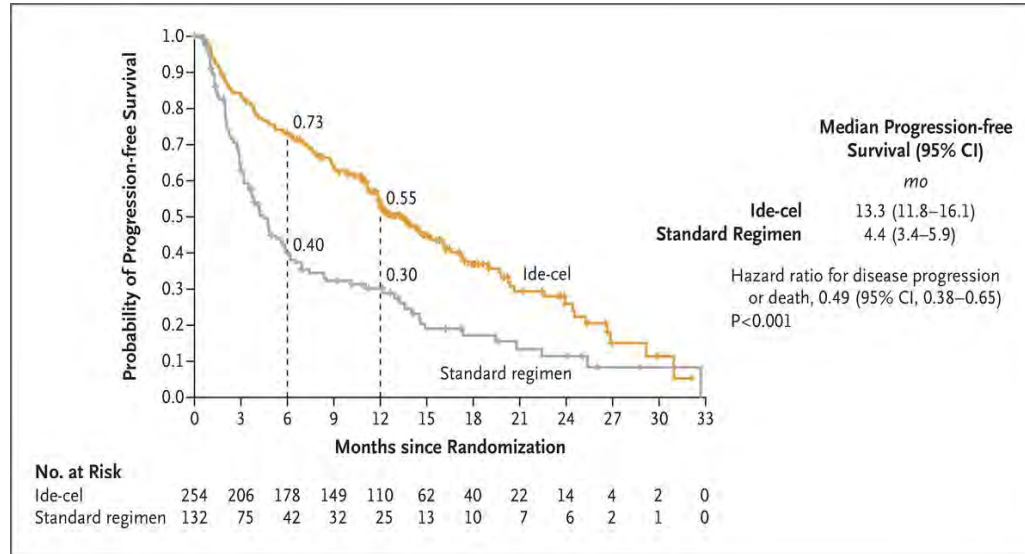
J San-Miguel et al. N Engl J Med 2023;389:335-347.
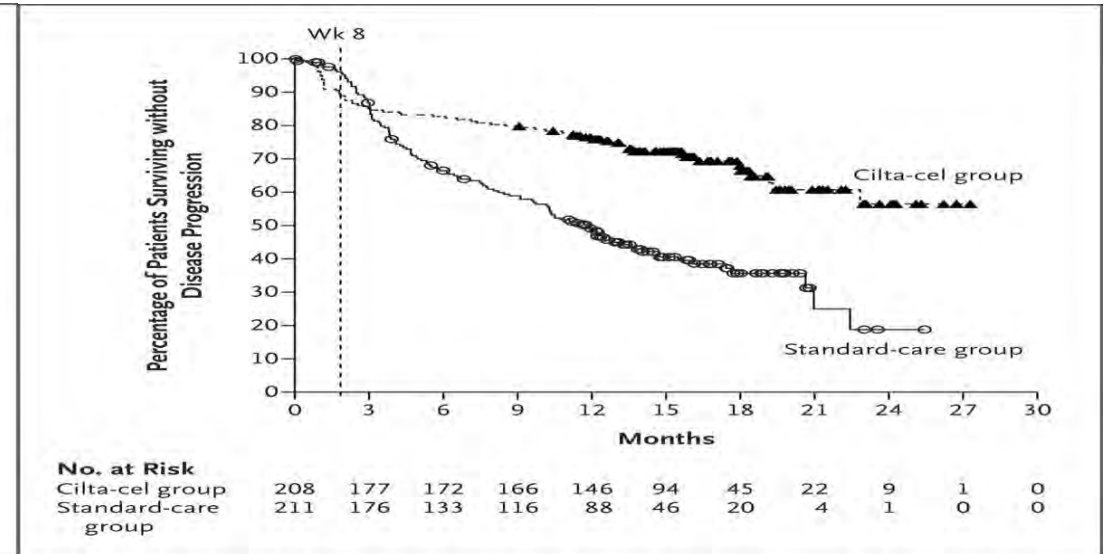


| Parameter | KarMMa-3 | | CARTITUDE-4 | |
|---|---|---|---|---|
| | Ide-Cel | SOC | Cilta-Cel | SOC |
| Inclusion criteria | 2-4 prior lines including PI + IMiD + Dara | | 1-3 prior lines, Len-refractory | |
| Prior lines of therapy, n, median (range) | 3 (2-4) | 3 (2-4) | 2 (1-3) | 2 (1-3) |
| Refractory to anti-CD38 antibodies, n (%) | 242 (95) | 123 (93) | 50 (24) | 46 (22) |
| Triple-class refractory, n (%) | 164 (65) | 89 (67) | 30 (14) | 33 (16) |
| ORR, n (%) | 181 (71) | 55 (42) | 176 (85) | 142 (67) |
| ::: CR, n (%) | 98 (39) | 7 (5) | 152 (73) | 46 (22) |
| ::: VGPR, n (%) | 153 (60) | 20 (16) | 169 (81) | 96 (46) |
| MRD-negative $10^{-5}$, n (%) | 51/254 (20) | 1 (1) | 126/144 (88) | 33/101 (33) |
| DOR, mo, median | 14.8 | 9.7 | Not reached; 85% at 12 mo | Not reached; 63% at 12 mo |
| PFS, mo, median | 13.3 | 4.4 | Not reached; 76% at 12 mo | 11.8 49% at 12 mo |

# Future of CAR-T in MM

- Newly diagnosed transplant eligible
- Newly diagnosed transplant ineligible
- Novel CAR-T (**GPRC5D CAR/Dual BCMA-GPRC5D CAR-T, ddBCMA CAR**)
- Consolidation post Auto in suboptimal response and >=1 prior lines

# KarMMa-2 cohort 2c: efficacy and safety of idecabtagene vicleucel in patients with clinical high-risk multiple myeloma due to inadequate response to frontline autologous stem cell transplantation
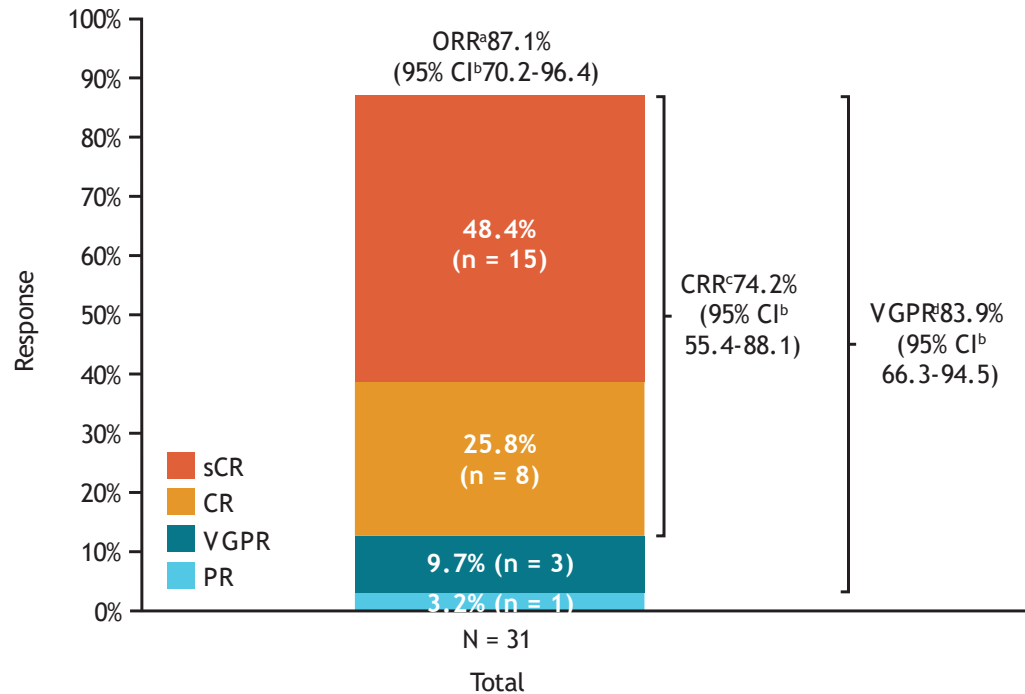


**MRD negativity in all patients and those in ≥ CR**

In patients who achieved ≥ CR, sustained MRD negativity at $10^{-5}$ was observed in 69.6% (16 of 23, 95% CI 49.1–84.4) at 12 months; of these 16 patients, 11 sustained MRD negativity at 24 months (2 patients had no MRD data available, and 3 were indeterminate)

In all evaluable patients, sustained MRD negativity at $10^{-5}$ was observed in 60.7% (17 of 28; 95% CI 42.4–76.4) at 12 months

## 24 months PFS of 83.1%

Madhav Dhodapkar, Melissa Alsina, ASH 2023

# Bispecific T-Cell Engagers
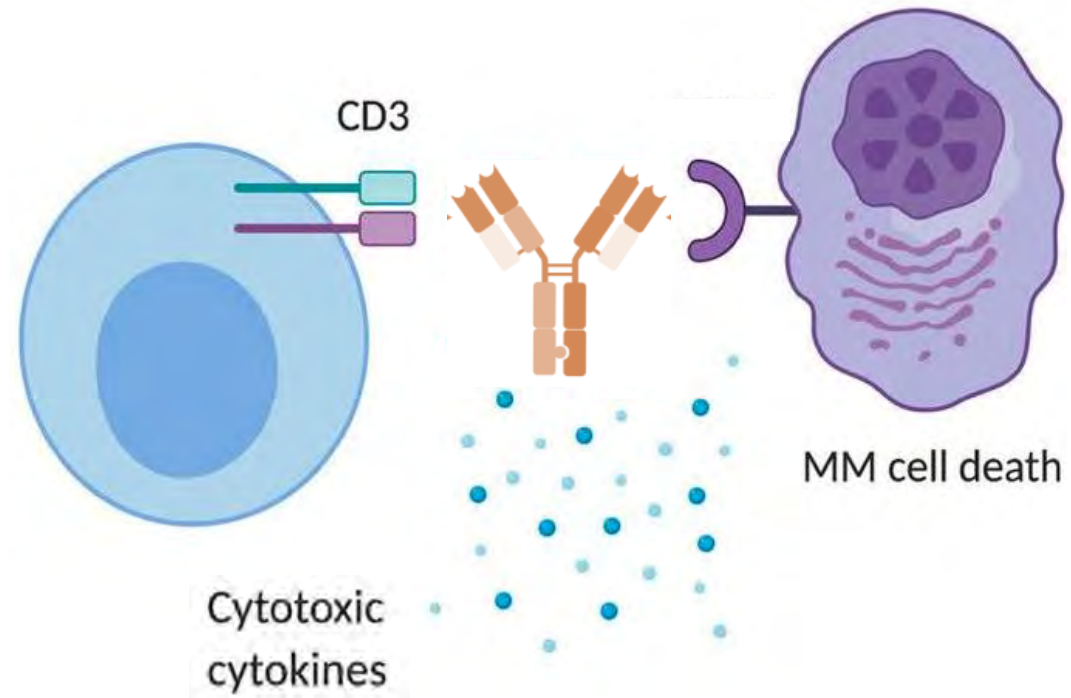
# Overview of Teclistamab

Teclistamab is a BCMA-directed CD3 T-cell engager approved in October 2022 for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including:

- Proteasome inhibitor

- Immunomodulatory agent

- Anti-CD38 monoclonal antibody

# MajesTEC-1: Trial Design and ORR
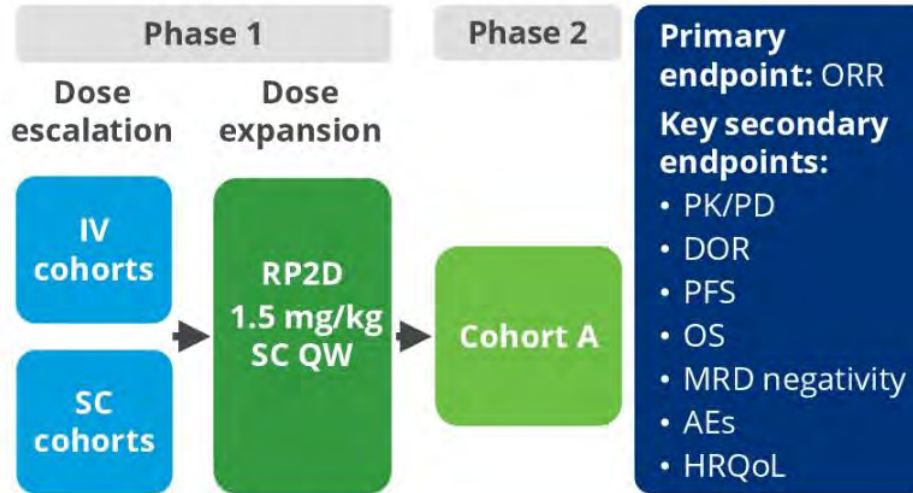


| Treatment history | N = 165 |
|---|---|
| ≤3 prior lines of treatment | 74.4 (32/43) |
| >3 prior lines of treatment | 59.0 (72/122) |
| High-risk cytogenetics and/or EMD | 53.3 (32/60) |

ORR: 63.0% (104/165)

≥ CR: 45.5%

≥ VGPR: 59.4%

sCR 37.6
CR 7.9
VGPR 13.9
PR 3.6

Usmani et al., ASCO 2023
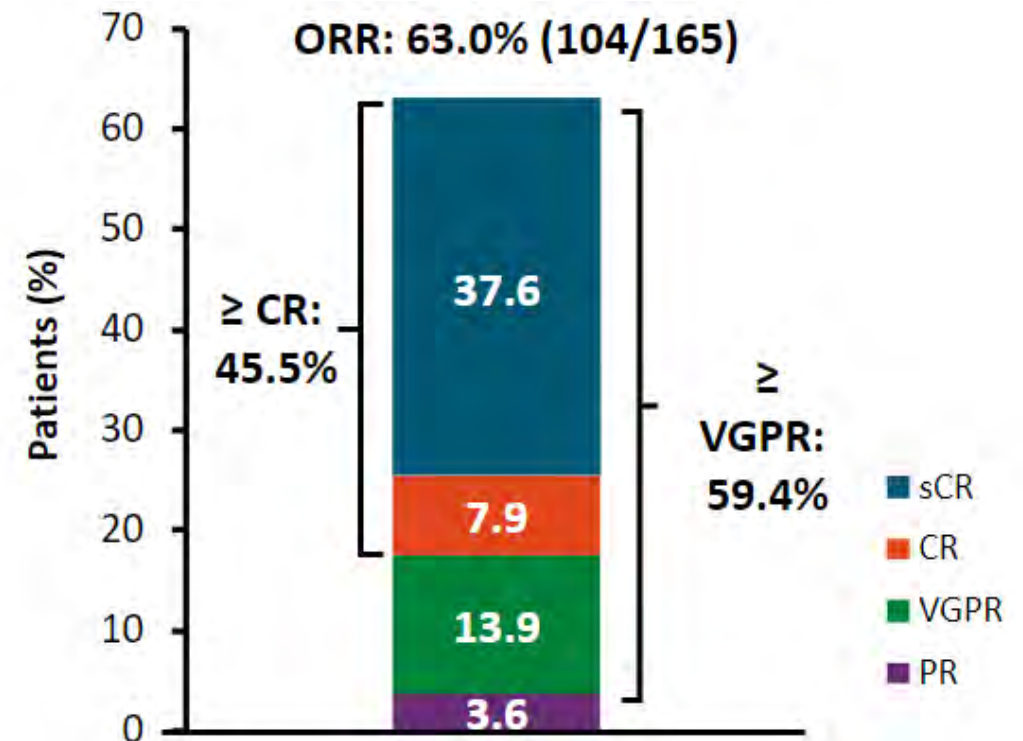
# MajesTEC-1: Duration of Response
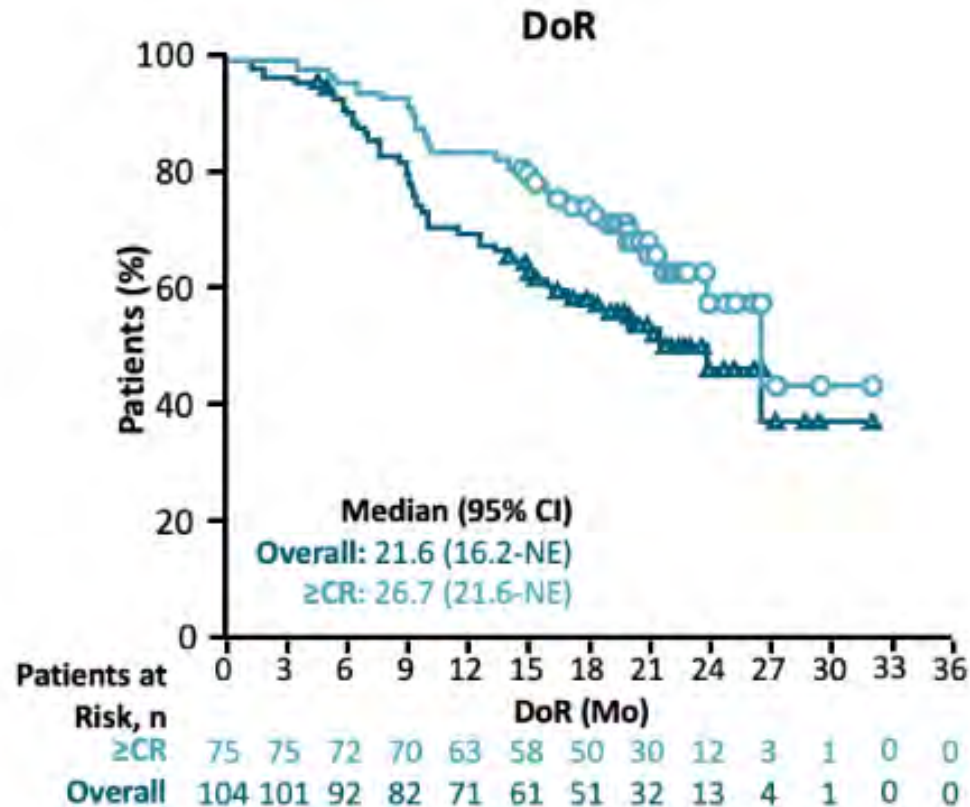


| Parameter, mo (95% CI) | All patients (n=165) | ≥ CR (n=75) |
|---|---|---|
| Median PFS | 11 (9-16) | 27 (23-NE) |
| Median OS | 22 (15-NE) | NR (NE-NE) |

**Median time to ≥CR**: 4.6 mo (range 1.6-18.5)

42 patients evaluable for MRD at Day 100
- **Rate of uMRD ($10^{-5}$)**: 81%

54 patients evaluable at any point
- **Rate of uMRD ($10^{-5}$)**: 81.5%

Usmani et al., ASCO 2023

# MajesTEC-1: Deep Responses with Q2W or Q4W Dosing



SUD 1: 0.06 mg/kg → SUD 2: 0.3 mg/kg → Treatment dose 1: 1.5 mg/kg → Subsequent treatment doses: 1.5 mg/kg QW

Option to switch to Q2W (Q4Wᵃ) dosing if:
- ≥PR after ≥4 cycles (Phase 1)
- ≥CR for ≥6 months (Phase 2)
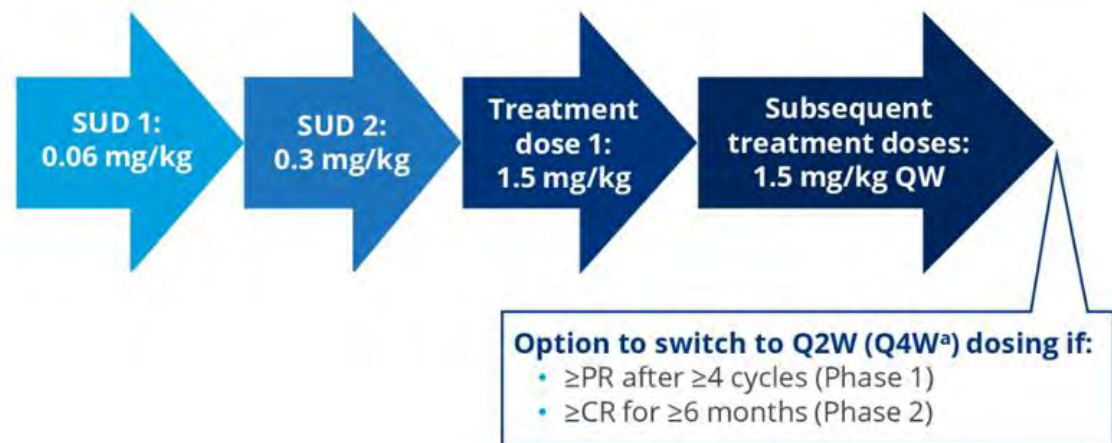
104/165 pts responded to RP2D of Teclistamab
- **63 pts switched to Q2W dosing**
- **9 pts switched to Q4W dosing**

After switching, mDOR not yet reached
- 68.7% (95% CI: 53.6-79.7%) remained in response for 2+ years from time of first response
- **42/63 responders maintained a response after switching to less frequent dosing**

Schedule change:
- Weekly  - Biweekly  - Monthly

Months
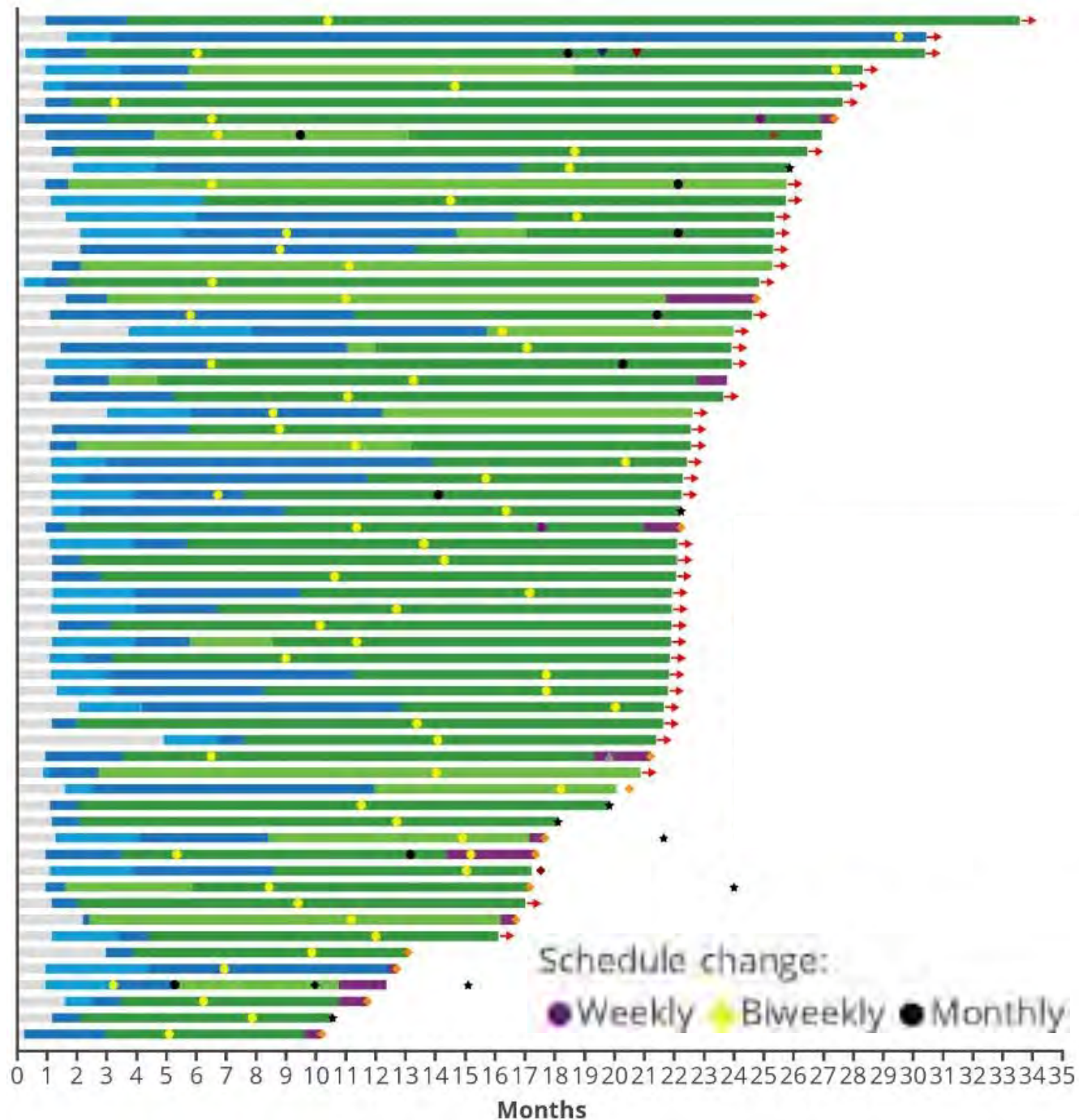
# MajesTEC-1: Safety

**Median treatment duration: 8.5 mo (range: 0.2-24.4)**

- 1 AE led to dose reduction
- 8 AEs led to discontinuation(5 due to infection)
- 7 treatment-related deaths (4 due to COVID-19)
- All cases of ICANS resolved

## CRS

- Any Grade: 72.1%
- Grade 3 or 4: 0.6%

## ICANS

- Any Grade: 3%
- No grade 3 or 4 ICANS events

| AEs ≥20%, n (%) | Any Grade | Grade 3/4 |
|---|---|---|
| **Hematologic** | | |
| Neutropenia | 118 (71.5) | 108 (65.5) |
| Anemia | 90 (54.5) | 62 (37.6) |
| Thrombocytopenia | 70 (42.4) | 37 (22.4) |
| Lymphopenia | 33 (20.0) | 15 (9.1) |
| **Non-Hematologic** | | |
| Infection | 132 (80.0) | 91 (55.2) |
| CRS | 119 (72.1) | 1 (0.6) |
| ICANS | 5 (3.0) | 0 |
| Diarrhea | 56 (33.9) | 6 (3.6) |
| Pyrexia | 52 (31.5) | 1 (0.6) |
| Fatigue | 48 (29.1) | 4 (2.4) |
| Nausea | 45 (27.3) | 1 (0.6) |
| Injection site erythema | 43 (26.1) | 0 |
| Headache | 40 (24.2) | 1 (0.6) |
| Arthralgia | 42 (25.5) | 1 (0.6) |
| Constipation | 36 (21.8) | 0 |
| Cough | 44 (26.7) | 0 |

Usmani et al., ASCO 2023

# MajesTEC-1: Reduction in Grade ≥3 Infection
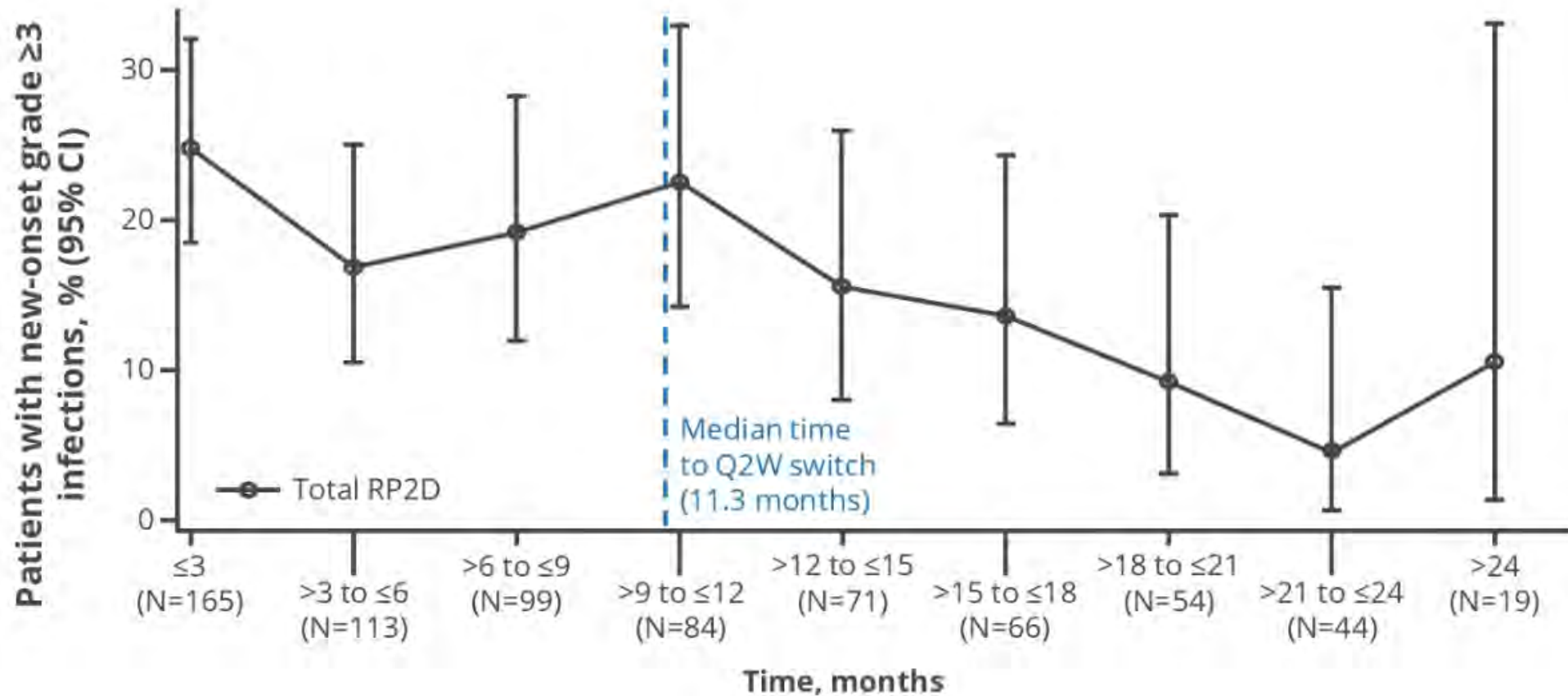


Pts who switched to Q2W by 1 year had fewer grade ≥3 treatment-emergent infections compared to those who remained on QW (15.6% vs 33.3%)

Usmani et al., ASCO 2023
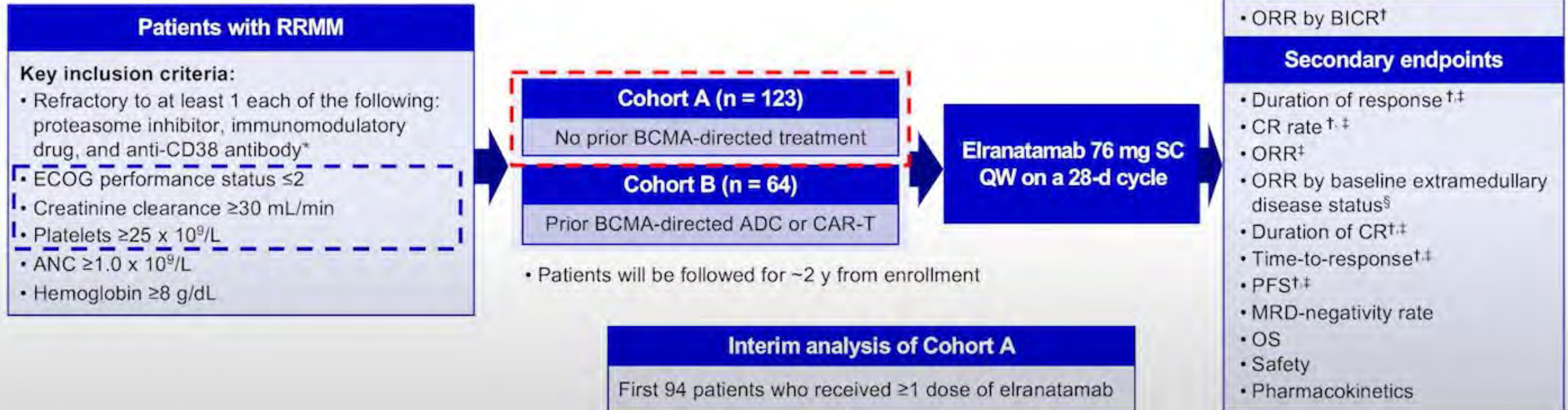
# Overview of Elranatamab

Elranatamab is another bispecific BCMA-directed CD3 T-cell engager

On **August 14, 2023**, Elranatamab received FDA approval for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy
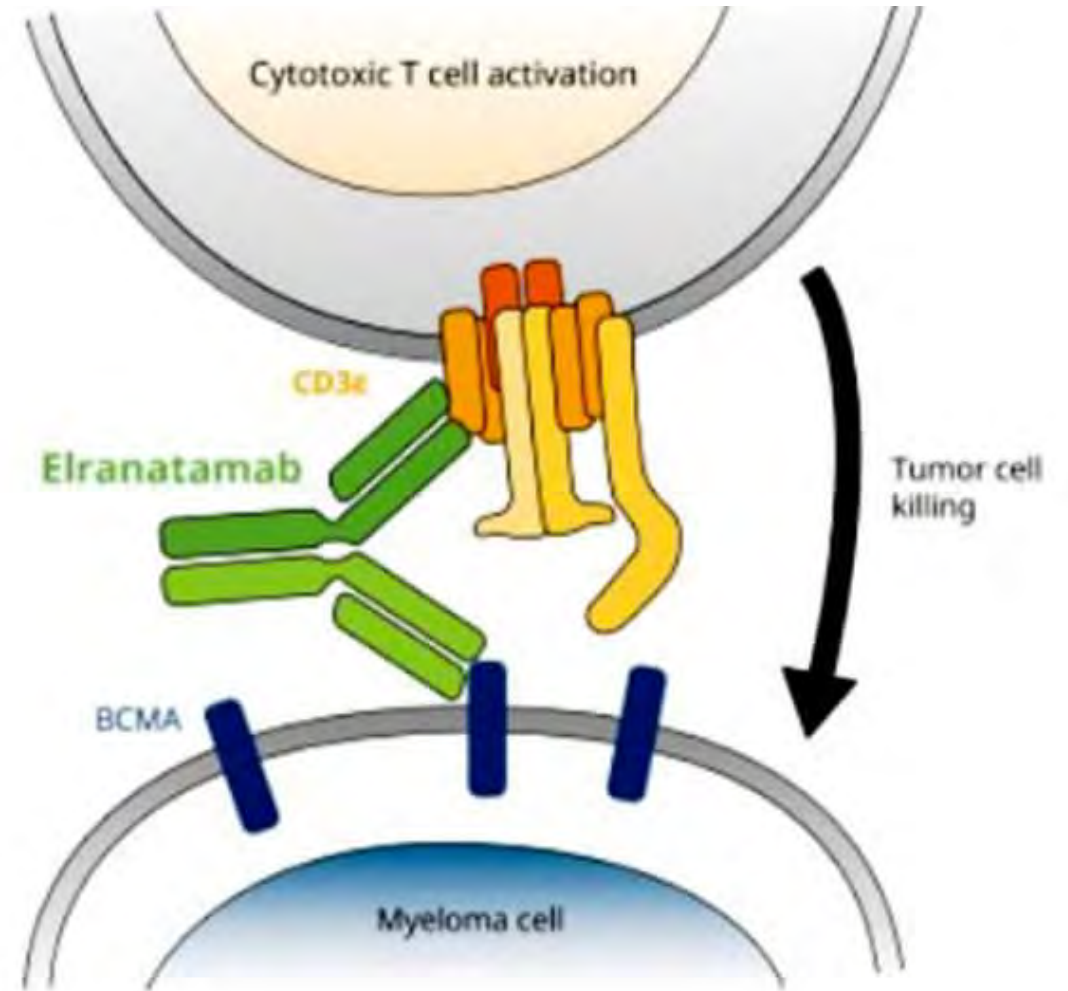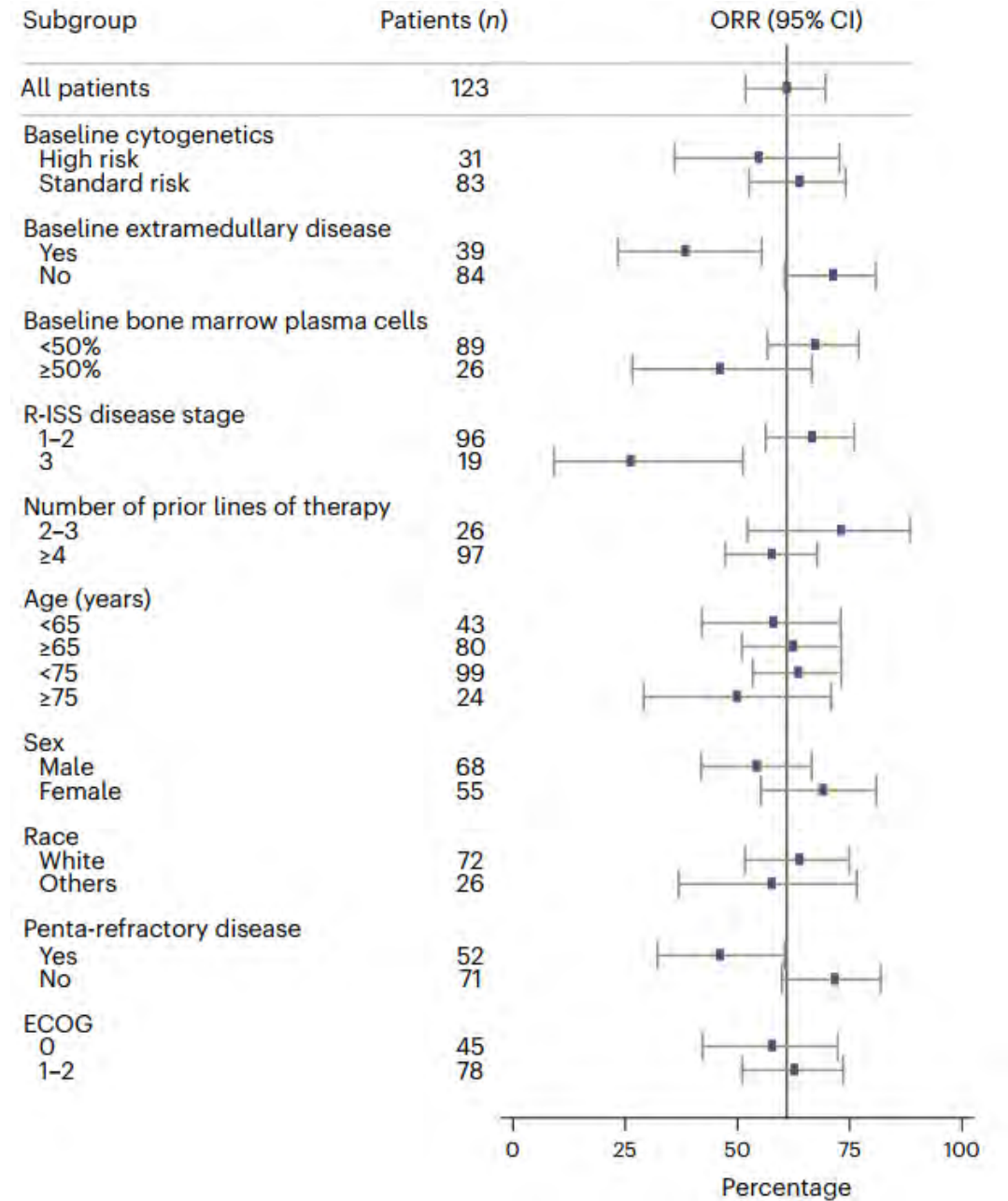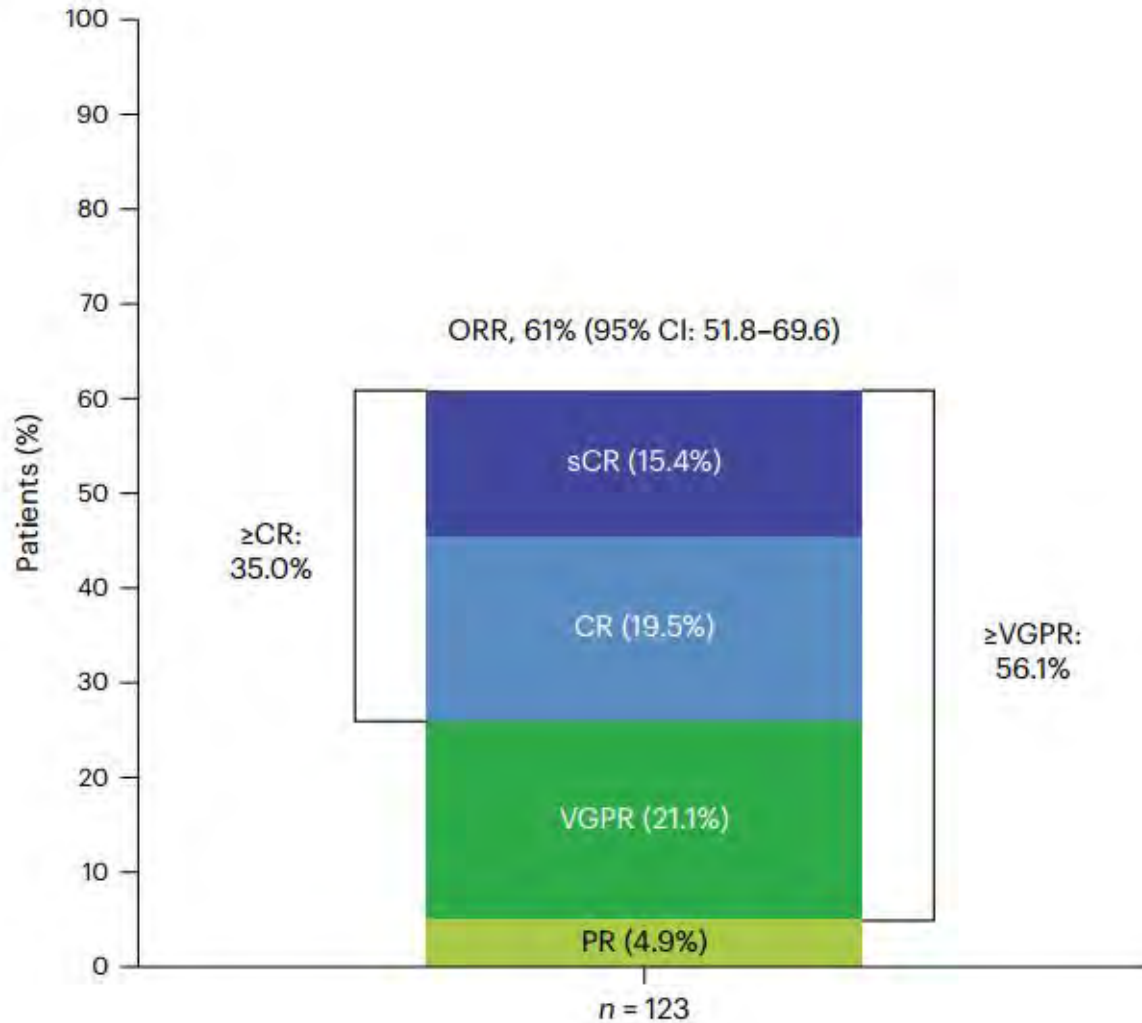
# MagnetisMM-3: Trial Design

- MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study
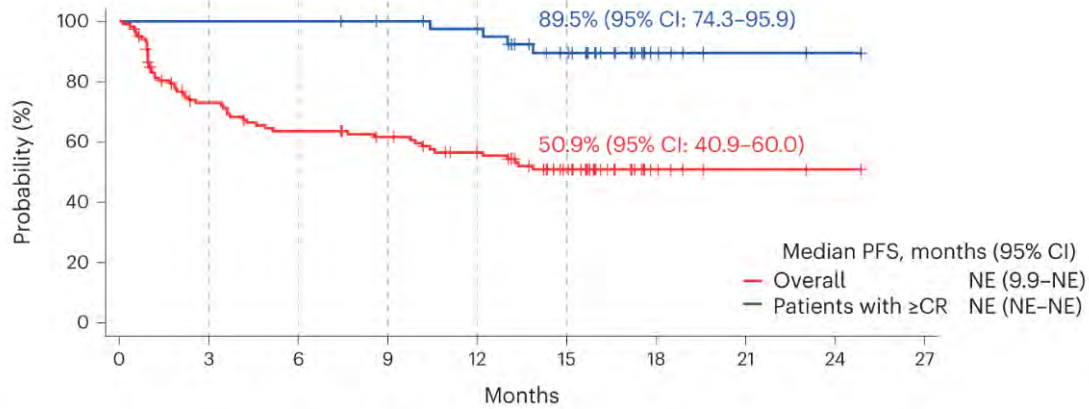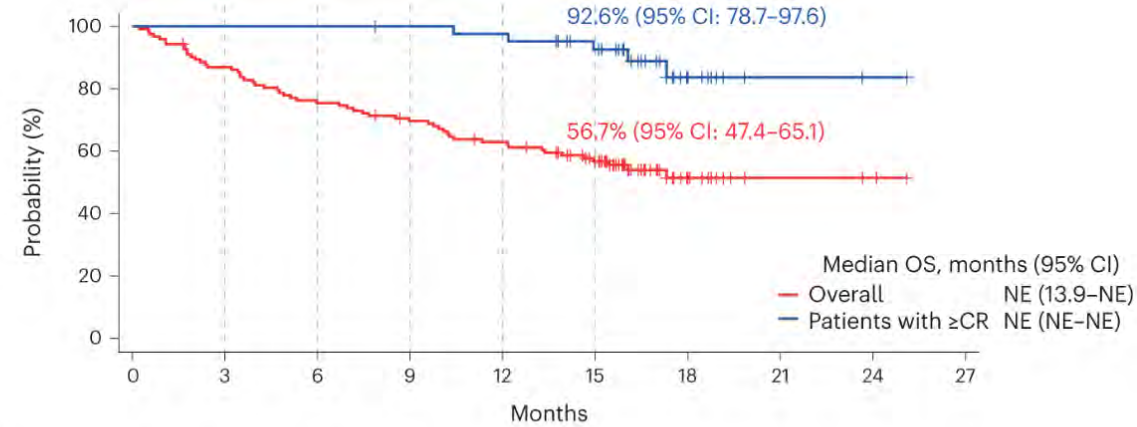  - Interim analysis data-cut off: March 23, 2022



**Patients with RRMM**

Key inclusion criteria:
- Refractory to at least 1 each of the following: proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody*
- ECOG performance status ≤2
- Creatinine clearance ≥30 mL/min
- Platelets ≥25 x 10⁹/L
- ANC ≥1.0 x 10⁹/L
- Hemoglobin ≥8 g/dL

**Cohort A (n = 123)**
No prior BCMA-directed treatment

**Cohort B (n = 64)**
Prior BCMA-directed ADC or CAR-T

- Patients will be followed for ~2 y from enrollment

**Elranatamab 76 mg SC QW on a 28-d cycle**

**Primary endpoint**
- ORR by BICR†

**Secondary endpoints**
- Duration of response†,‡
- CR rate†,‡
- ORR‡
- ORR by baseline extramedullary disease status§
- Duration of CR†,‡
- Time-to-response†,‡
- PFS†,‡
- MRD-negativity rate
- OS
- Safety
- Pharmacokinetics

**Interim analysis of Cohort A**
First 94 patients who received ≥1 dose of elranatamab

Lesokin et al., Nat Med 2023

# MagnetisMM-3: Response



Lesokin et al., Nat Med 2023

# MagnetisMM-3: PFS and OS



| | Overall Population mo (95% CI) | | Pts with ≥CR mo (95% CI) | |
|---|---|---|---|---|
| Median Duration of Response | NE (12.0 – NE) | | | |
| Median PFS | NE (9.9 – NE) | | NE (NE – NE) | |
| Median OS | NE (13.9 – NE) | | NE (NE – NE) | |

Lesokin et al., Nat Med 2023

# MagnetisMM-3: Safety

Grade 3 or 4 treatment-emergent AEs were reported in 87 patients (70.7%).

**Dose Interruption or Reduction**

Dose interruption: 77.2%
- Infection: 50.4%
- Hematologic: 40.7%
- Neutropenia: 35%

Dose reduction: 28.5%

| Treatment-Emergent Adverse Effect, n (%) | Any grade | Grade 3/4 |
|---|---|---|
| Any TEAE | 123 (100%) | 87 (70.7%) |
| **Hematologic** | | |
| Anemia | 60 (48.8%) | 46 (37.4%) |
| Neutropenia | 60 (48.8%) | 60 (48.8%) |
| Thrombocytopenia | 38 (30.9%) | 29 (23.6%) |
| Lymphopenia | 33 (26.8%) | 31 (25.2%) |
| **Non-Hematologic** | | |
| Cytokine release syndrome | 71 (57.7%) | 0 |
| Diarrhea | 52 (42.3%) | 2 (1.6%) |
| Fatigue | 45 (36.6%) | 4 (3.3%) |
| Decreased appetite | 41 (33.3%) | 1 (0.8%) |
| Pyrexia | 37 (30.1%) | 5 (4.1%) |
| COVID-19 related | 36 (29.3%) | 19 (15.4%) |
| Injection site reaction | 33 (26.8%) | 0 |
| Nausea | 33 (26.8%) | 0 |
| Hypokalemia | 32 (26.0%) | 13 (10.6%) |
| Cough | 31 (25.2%) | 0 |
| Headache | 29 (23.6%) | 0 |

Lesokin et al., Nat Med 2023

# Dosing Schedules

## Elranatamab FDA Label

| Dosing Schedule | ELREXFIO Dosing Schedule (2.2) | | |
|---|---|---|---|
| | Day | ELREXFIO Dose | |
| Step-up Dosing Schedule | Day 1 | Step-up dose 1 | 12 mg |
| | Day 4 | Step-up dose 2 | 32 mg |
| | Day 8 | First treatment dose | 76 mg |
| Weekly Dosing Schedule | One week after first treatment dose and weekly thereafter through week 24 | Subsequent treatment doses | 76 mg |
| Biweekly (Every 2 Weeks) Dosing Schedule* | Week 25 and every 2 weeks thereafter | Subsequent treatment doses | 76 mg |

*Responders only week 25 onward.

## Teclistamab FDA Label

| Dosing Schedule | TECVAYLI Recommended Dosing Schedule (2.1) | | |
|---|---|---|---|
| | Day | Dose | |
| Step-up Dosing Schedule | Day 1 | Step-up dose 1 | 0.06 mg/kg |
| | Day 4 | Step-up dose 2 | 0.3 mg/kg |
| | Day 7 | First treatment dose | 1.5 mg/kg |
| Weekly Dosing Schedule | One week after first treatment dose and weekly thereafter | Subsequent treatment doses | 1.5 mg/kg once weekly |

### Q2W and Q4W Explored in MajesTEC-1

SUD 1: 0.06 mg/kg → SUD 2: 0.3 mg/kg → Treatment dose 1: 1.5 mg/kg → Subsequent treatment doses: 1.5 mg/kg QW

**Option to switch to Q2W (Q4W[a]) dosing if:**
- ≥PR after ≥4 cycles (Phase 1)
- ≥CR for ≥6 months (Phase 2)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761345s000lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761291s000lbl.pdf
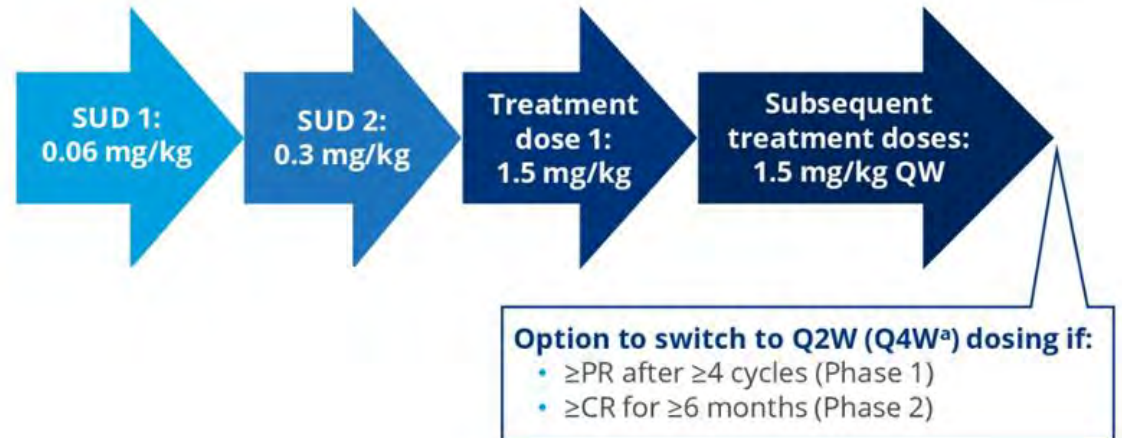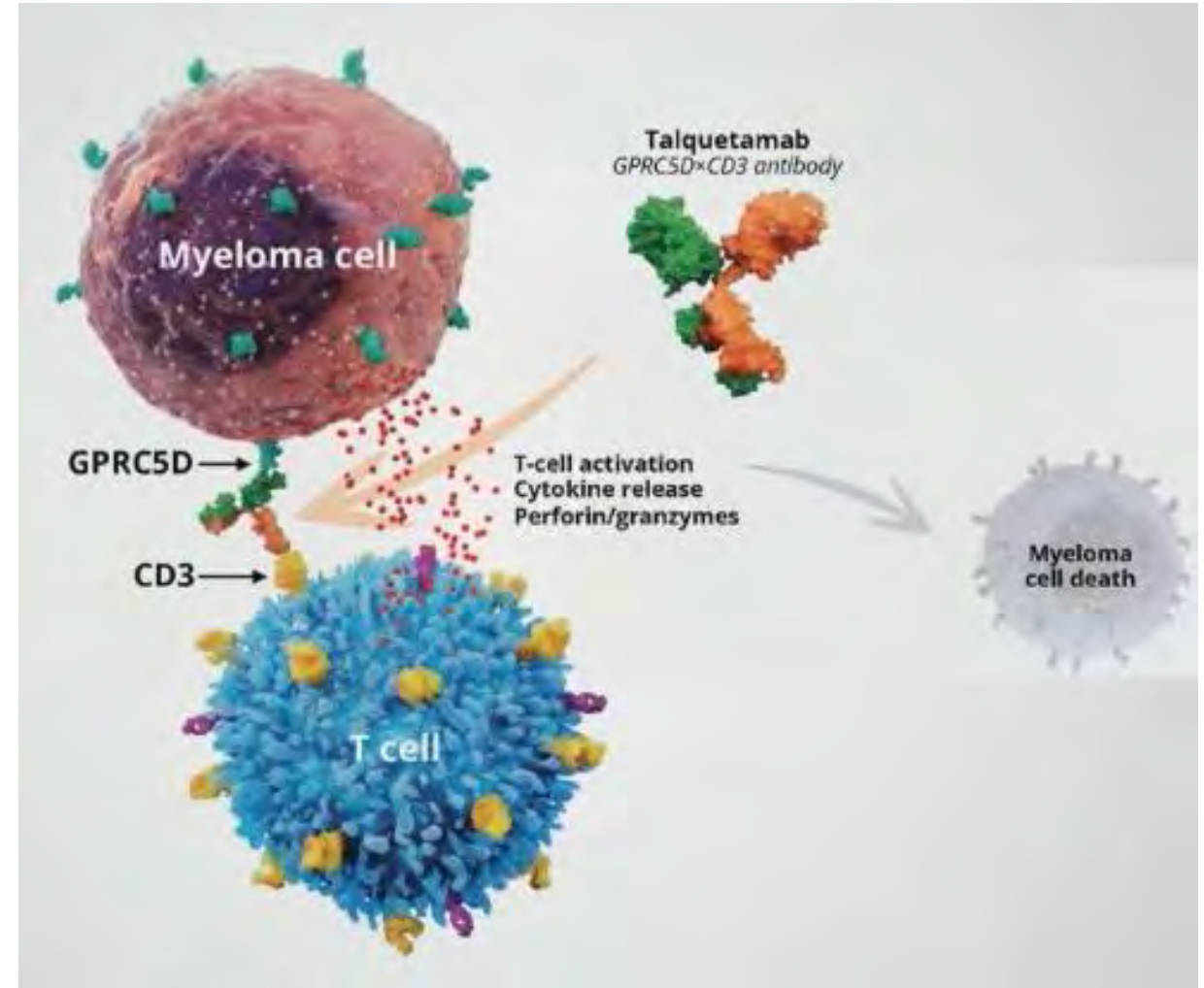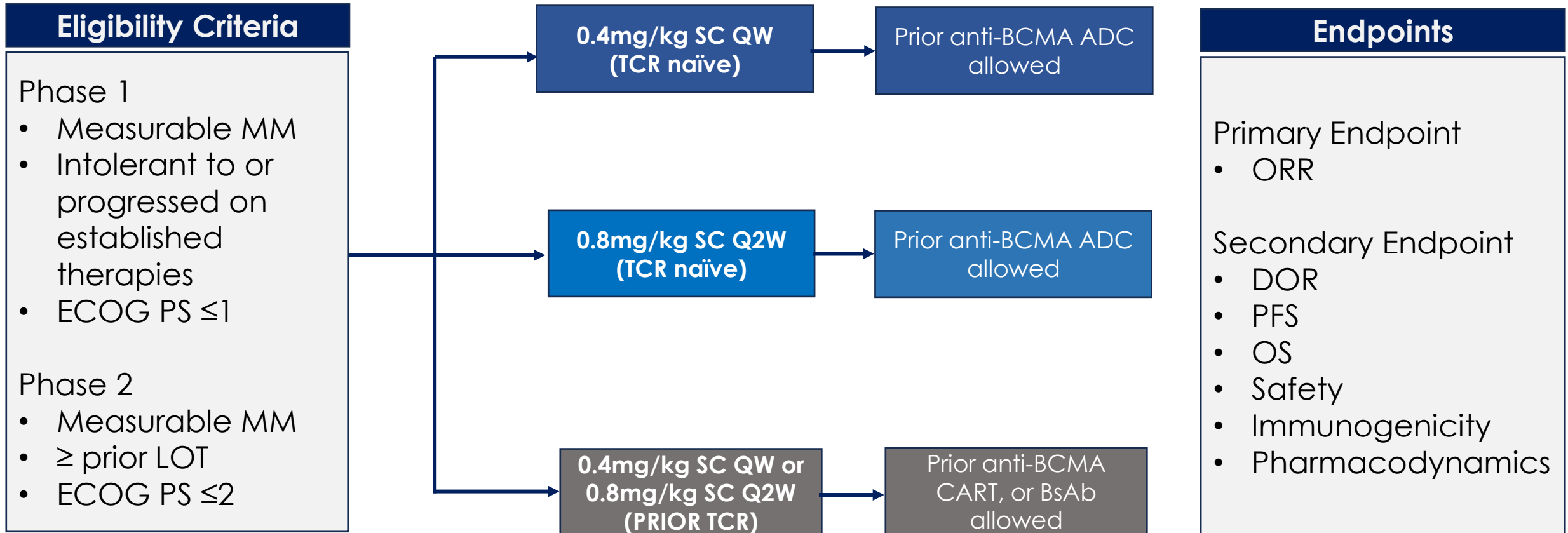
# Overview of Talquetamab

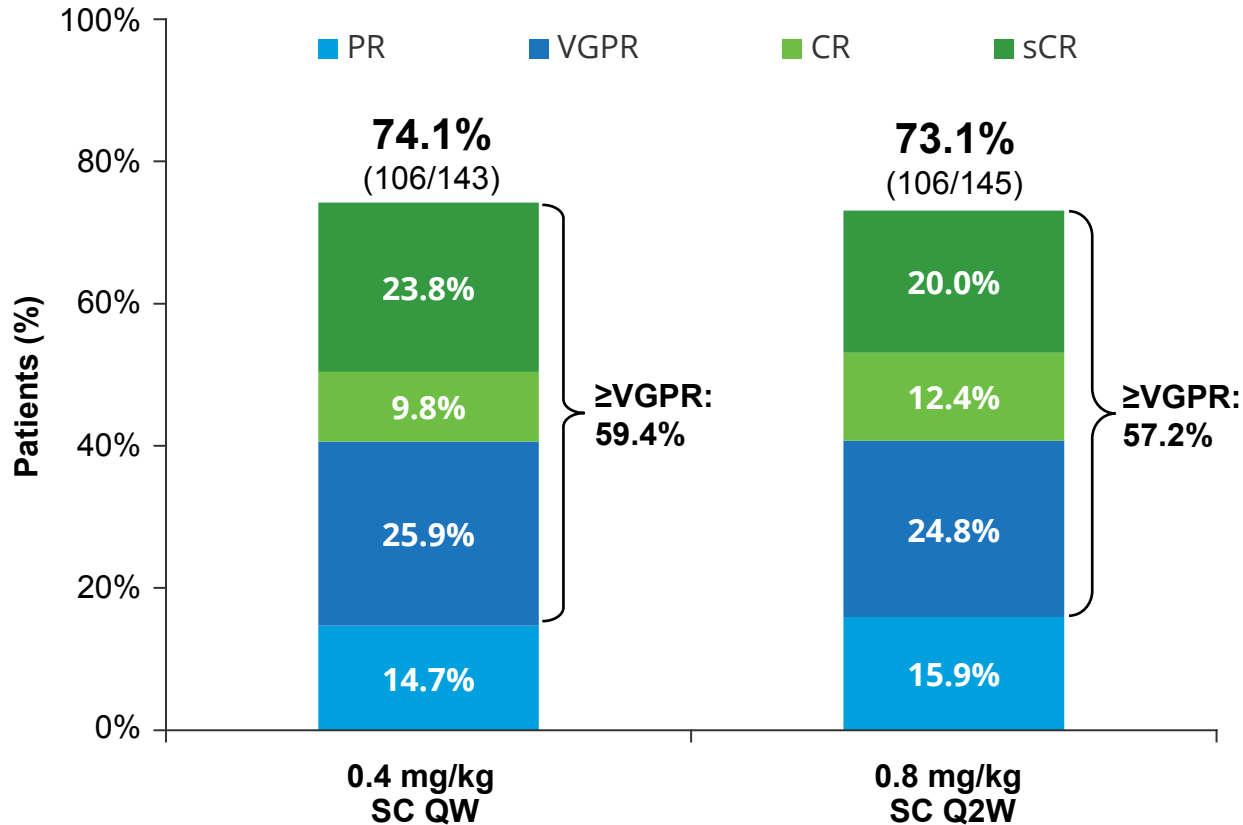Talquetamab is a novel bispecific GPRC5D-directed CD3 T-cell engager

On **August 9, 2023**, Talquetamab received FDA approval for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy

# MonumenTAL-1: Study Design

## Eligibility Criteria

**Phase 1**
- Measurable MM
- Intolerant to or progressed on established therapies
- ECOG PS ≤1

**Phase 2**
- Measurable MM
- ≥ prior LOT
- ECOG PS ≤2

**0.4mg/kg SC QW (TCR naïve)** → Prior anti-BCMA ADC allowed

**0.8mg/kg SC Q2W (TCR naïve)** → Prior anti-BCMA ADC allowed

**0.4mg/kg SC QW or 0.8mg/kg SC Q2W (PRIOR TCR)** → Prior anti-BCMA CART, or BsAb allowed

## Endpoints

Primary Endpoint
- ORR

Secondary Endpoint
- DOR
- PFS
- OS
- Safety
- Immunogenicity
- Pharmacodynamics

Adapted from Schinke et al., ASCO 2023

# MonumenTAL-1: Objective Response Rate

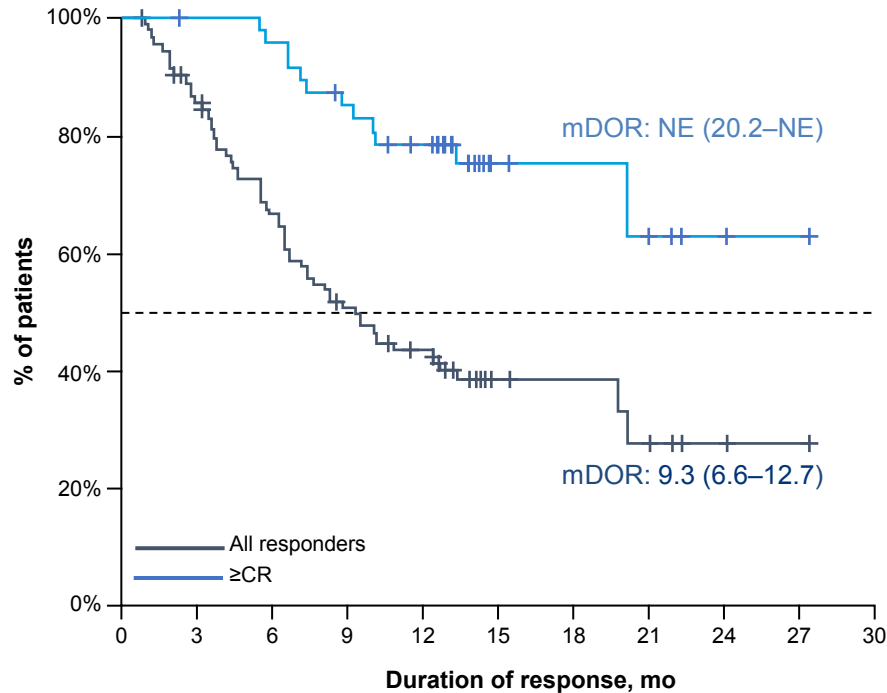**Triple-class refractory**: 72.6% (95% CI, 63.1–80.9) and 71.0% (95% CI, 61.1–79.6)

**Penta-drug refractory**: 71.4% (95% CI, 55.4–84.3) and 70.6% (95% CI, 52.5–84.9)

**ORR was consistent across subgroups** including baseline ISS stage III disease, baseline cytogenetic risk, number of prior therapies, refractoriness to prior therapy, and belantamab exposure, except among patients with baseline plasmacytomas

**Chart legend:** PR, VGPR, CR, sCR

**0.4 mg/kg SC QW:**
74.1% (106/143)
- sCR: 23.8%
- CR: 9.8%
- VGPR: 25.9%
- PR: 14.7%
- ≥VGPR: 59.4%

**0.8 mg/kg SC Q2W:**
73.1% (106/145)
- sCR: 20.0%
- CR: 12.4%
- VGPR: 24.8%
- PR: 15.9%
- ≥VGPR: 57.2%

Y-axis: Patients (%), 0%–100%

| Timing, months | 0.4 mg/kg SC QW n=143 | 0.8 mg/kg SC Q2W n=145 |
|---|---|---|
| Median (range) follow-up, efficacy | 14.9 (0.5[b]–29.0) | 8.6 (0.2[b]–22.5) |
| Median (range) time to first response[c] | 1.2 (0.2–10.9) | 1.3 (0.2–9.2) |
| Median (range) time to best response[c] | 2.2 (0.8–12.7) | 2.7 (0.3–12.5) |

Chari et al., ASH 2022

# MonumenTAL-1: Duration of Response

### DOR, 0.4 mg/kg SC QW[a]



mDOR: NE (20.2–NE)

mDOR: 9.3 (6.6–12.7)

- All responders
- ≥CR

| Patients at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 106 | 87 | 67 | 50 | 39 | 8 | 7 | 5 | 2 | 1 | 0 |
| 48 | 47 | 45 | 39 | 34 | 7 | 6 | 5 | 2 | 1 | 0 |

**mPFS**: 7.5 months (95% CI: 5.7–9.4; 33% censored)

### DOR, 0.8 mg/kg SC Q2W[b]



mDOR: NE (10.6–NE)

mDOR: 13.0 (10.6–NE)

- All responders
- ≥CR
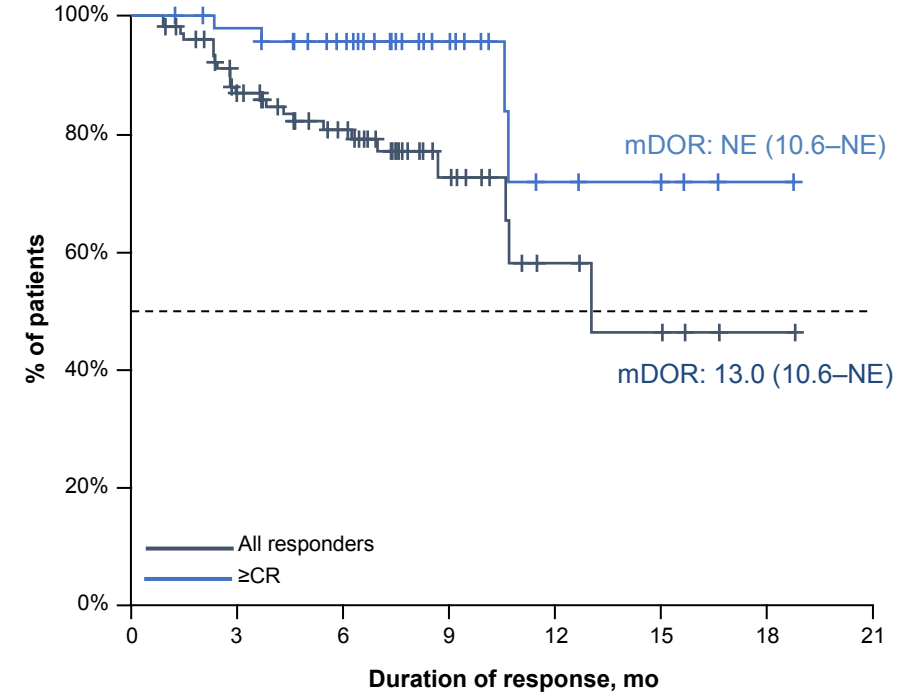
| Patients at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| 106 | 82 | 51 | 16 | 6 | 4 | 1 | 0 |
| 47 | 44 | 32 | 14 | 5 | 4 | 1 | 0 |

**mPFS**: 11.9 months (95% CI: 8.4–NE; 61% censored)

Chari et al., ASH 2022

# MonumenTAL-1: Adverse Effects

Most high-grade AEs were cytopenias

## Infections

### 0.4 mg/kg QW

- Any Grade: 57.3%
- Grade 3/4: 16.8%
- Opportunistic Infection: 3.5%
- COVID-19: 9.1%
  - Grade 3/4: 0.7%

### 0.8 mg/kg Q2W

- Any Grade: 50.3%
- Grade 3/4: 11.7%
- Opportunistic Infection: 2.8%
- COVID-19: 11.0%
  - Grade 3/4: 2.1%

| AEs (≥20% of any RP2D cohort) | 0.4 mg/kg SC QW (n=143) Median Follow-up, 11.0 months | | 0.8 mg/kg SC Q2W (n=145) Median Follow-up, 5.1 months | |
|---|---|---|---|---|
| | Any Grade n (%) | Grade 3/4 (%) | Any Grade (%) | Grade 3/4 (%) |
| CRS | 113 (79.0) | 3 (2.1) | 105 (72.4) | 1 (0.7) |
| Anemia | 64 (44.8) | 45 (31.5) | 57 (39.3) | 36 (24.8) |
| Neutropenia | 49 (34.3) | 44 (30.8) | 41 (28.3) | 32 (22.1) |
| Lymphopenia | 40 (28.0) | 37 (25.9) | 38 (26.2) | 37 (25.5) |
| Thrombocytopenia | 39 (27.3) | 29 (20.3) | 39 (26.9) | 24 (16.6) |
| **Skin-related AEs[d]** | 80 (55.9) | 0 | 98 (67.6) | 1 (0.7) |
| **Nail-related AEs[e]** | 74 (51.7) | 0 | 63 (43.4) | 0 |
| **Dysgeusia[f]** | 69 (48.3) | NA | 67 (46.2) | NA |
| **Rash-related AEs[g]** | 56 (39.2) | 2 (1.4) | 39 (26.9) | 8 (5.5) |
| Weight decreased | 57 (39.9) | 3 (2.1) | 47 (32.4) | 2 (1.4) |
| Pyrexia | 53 (37.1) | 4 (2.8) | 35 (24.1) | 1 (0.7) |
| Asthenia | 37 (25.9) | 3 (2.1) | 13 (9.0) | 2 (1.4) |
| Dry mouth | 36 (25.2) | 0 | 53 (36.6) | 0 |
| Diarrhea | 34 (23.8) | 3 (2.1) | 32 (22.1) | 0 |
| Dysphagia | 34 (23.8) | 0 | 33 (22.8) | 3 (2.1) |
| Fatigue | 32 (22.4) | 5 (3.5) | 29 (20.0) | 1 (0.7) |
| Decreased appetite | 25 (17.5) | 2 (1.4) | 29 (20.0) | 2 (1.4) |

Chari et al., ASH 2022

# MonumenTAL-1: Prospective Dose Reduction Maintains Response

- Patients with prospective dose reduction were required to be in response (n=19)

- Dose reduction occurred at a median of 3.1 mo (range, 2.3 – 4.2) relative to treatment start
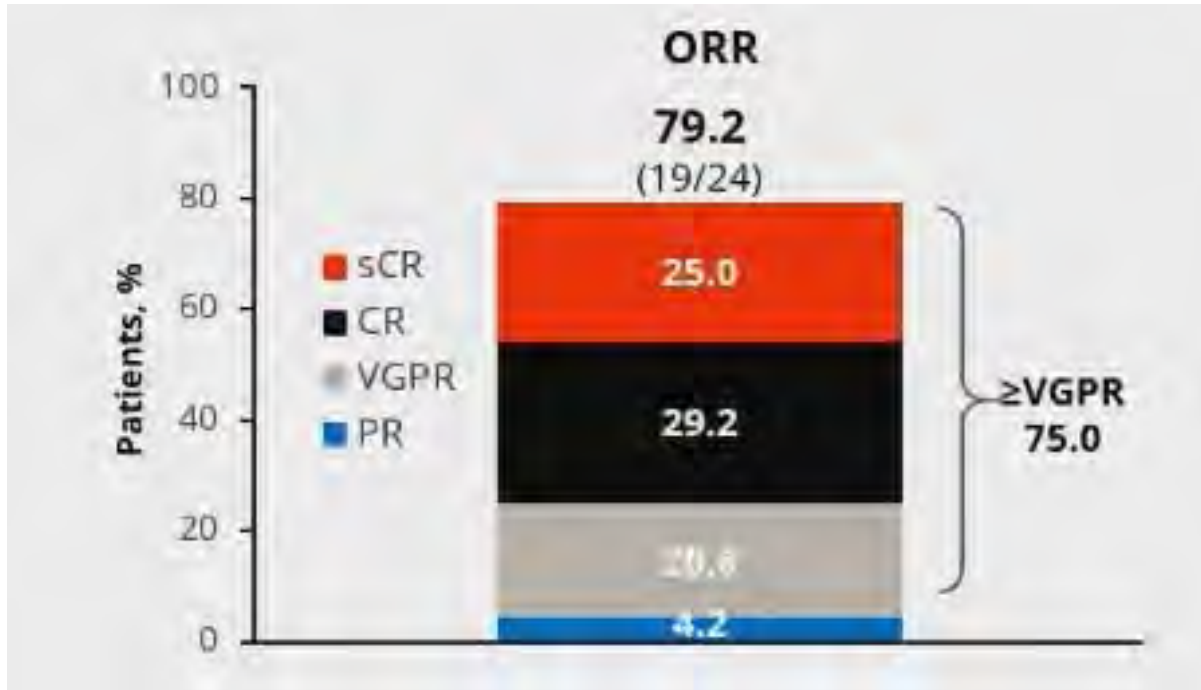
| | Prospective Dose Reduction Cohort (n=19) | 0.8 mg/kg Q2W Registrational Cohort (n=145) |
|---|---|---|
| **Median PFS, mo (95% CI)** | 13.2 (8.8 – NE) | 14.2 (9.6 – NE) |
| **12-mo PFS rate, %** | 50.1% | 54.4% |
| **Median DOR, mo (95% CI)** | NE (8.3 – NE) | NE (13.0 – NE) |





Chari et al. ASH 2023.
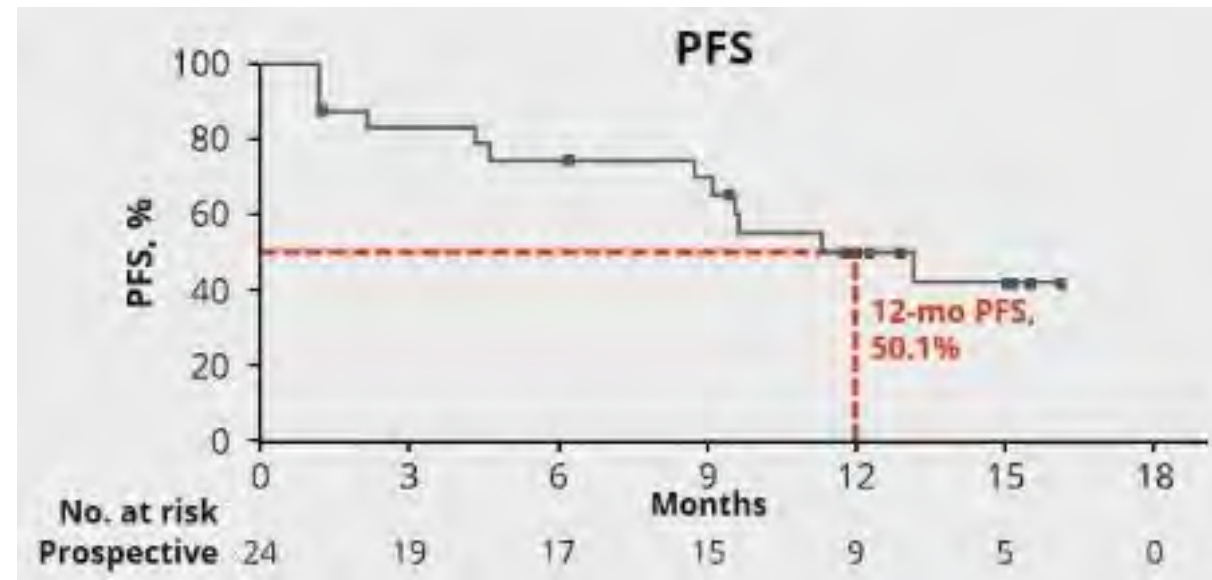
# Conclusion

- CAR-T and bispecific antibodies are excellent targeted therapy options for RRMM patients who have failed at least four prior lines of therapy.

- There are now two FDA-approved, BCMA-directed BsAbs. Teclistamab and elranatamab have similar efficacy and safety profiles and are both excellent, off-the-shelf options.

- Talquetamab is the first FDA-approved GPRC5D-targeting agent in RRMM and is effective in patients who have developed resistance to BCMA-directed therapies.

- Infections, CRS, and ICANS are seen with all three agents.

- Talquetamab is associated with lower rate of infections, but patients experience unique skin, nail, and taste-related toxicities. Dose reduction appears to be an effective strategy to manage GPRC5D-related toxicity.

# and more to come….



| Proteasome Inhibitors | Immunomodulatory Agents | Monoclonal Antibodies | BCMA-Specific Targets | Small-Molecule Inhibitors | CELMoDs | Novel Bispecifics |
|---|---|---|---|---|---|---|
| Bortezomib | Lenalidomide | Daratumumab | Teclistamab | Selinexor | Iberdomide | Talquetamab (GPRC5D/CD3) |
| Carfilzomib | Pomalidomide | Isatuximab | Idecabtagene vicleucel | Venetoclax [if t(11;14)] | Mezigdomide | Cevostamab (FcRH5/CD3) |
| Ixazomib | Thalidomide | Elotuzumab | Ciltacabtagene autoleucel | Panobinostat | | |
| | | Felzartamab | JCARH125 | | | |
| | | TAK 079 | REGN-5458 | | | |
| | | SAR 442085 | Elranatamab | | | |
| | | | AMG701 | | | |

Rajkumar SV, et al. *Am J Hematol.* 2020;95:548; Su C, et al. *J Hematol Onco.* 2021;14:115.

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# Questions?

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