7th Annual

LEAD2025

Enriching Experiences for Women in Hematology & Oncology

Updates in Multiple Myeloma

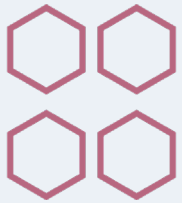
Shivani Kapur
Assistant Professor of Medicine
Hematology/Oncology
University of Pennsylvania

LEGES SINE MORIBUS VANAE

Bio Ascend™
A Vaniam Group Company

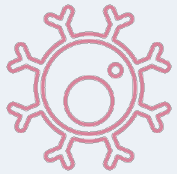
University of Nebraska Medical Center
Nebraska Medicine

Outline



Era of Quadruplet therapy

MRD testing to guide therapy

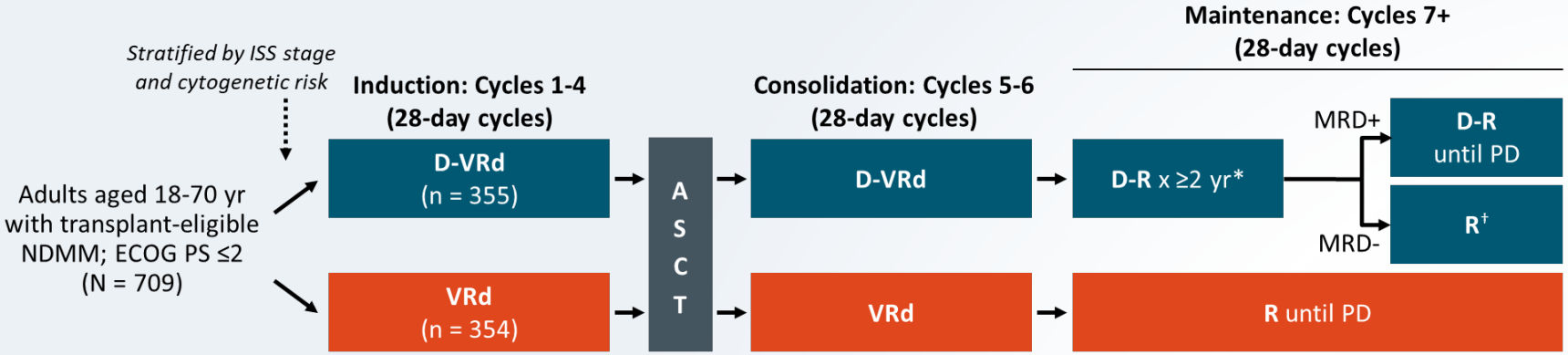


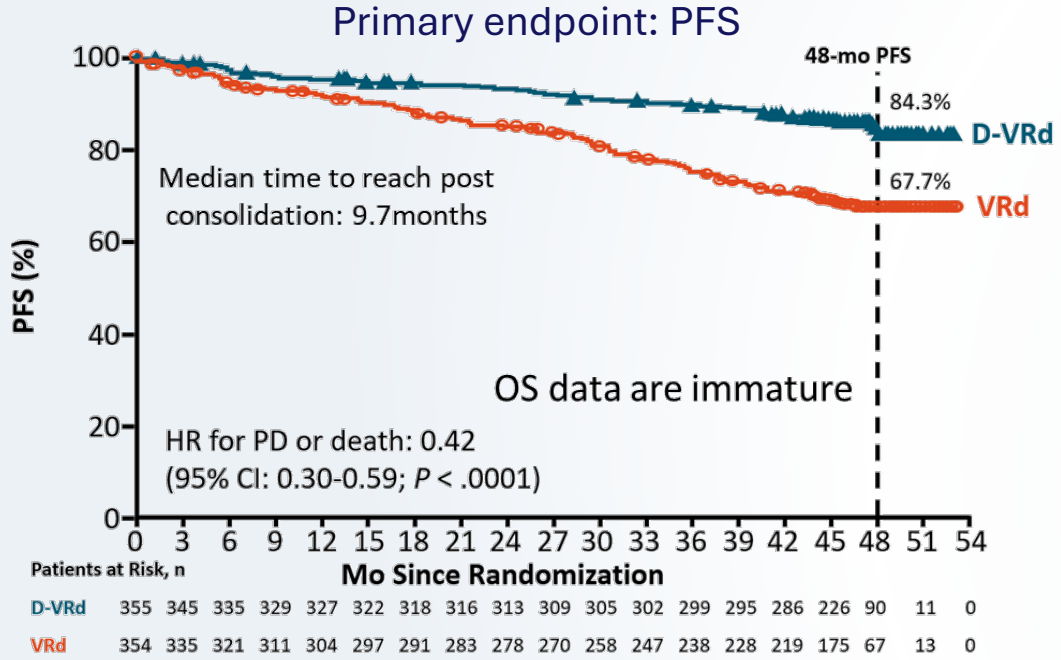
Cellular therapy – from RRMM to earlier LOT

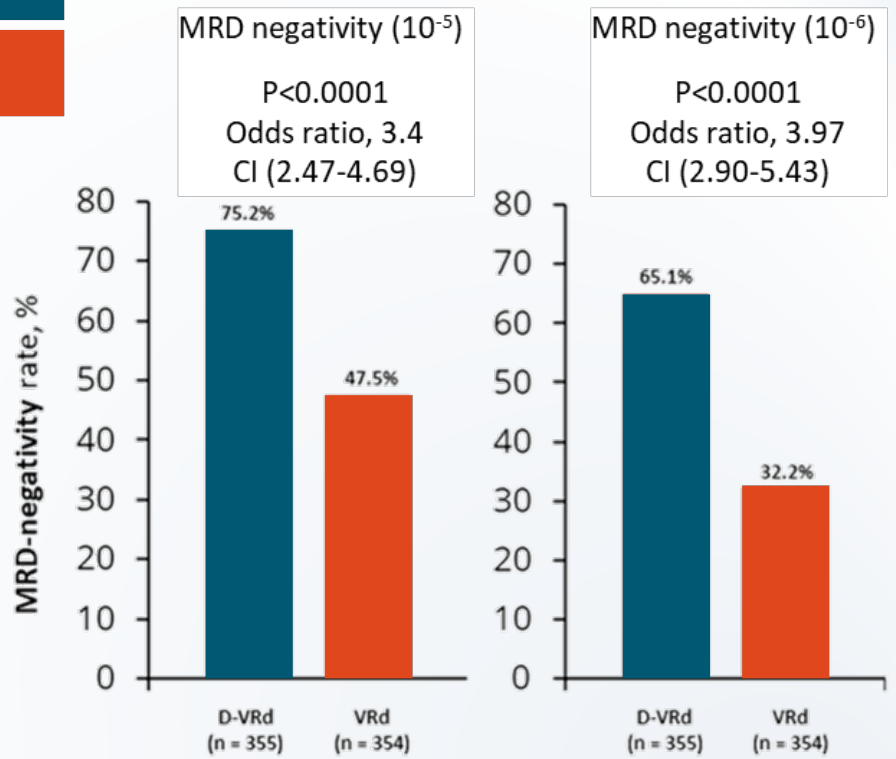
Novel agents

Quadruplet therapy: sustained MRD negativity rates

- PERSESUS (DVRd vs VRd TE-NDMM) 2 year sustained MRD negativity 56% vs 23%



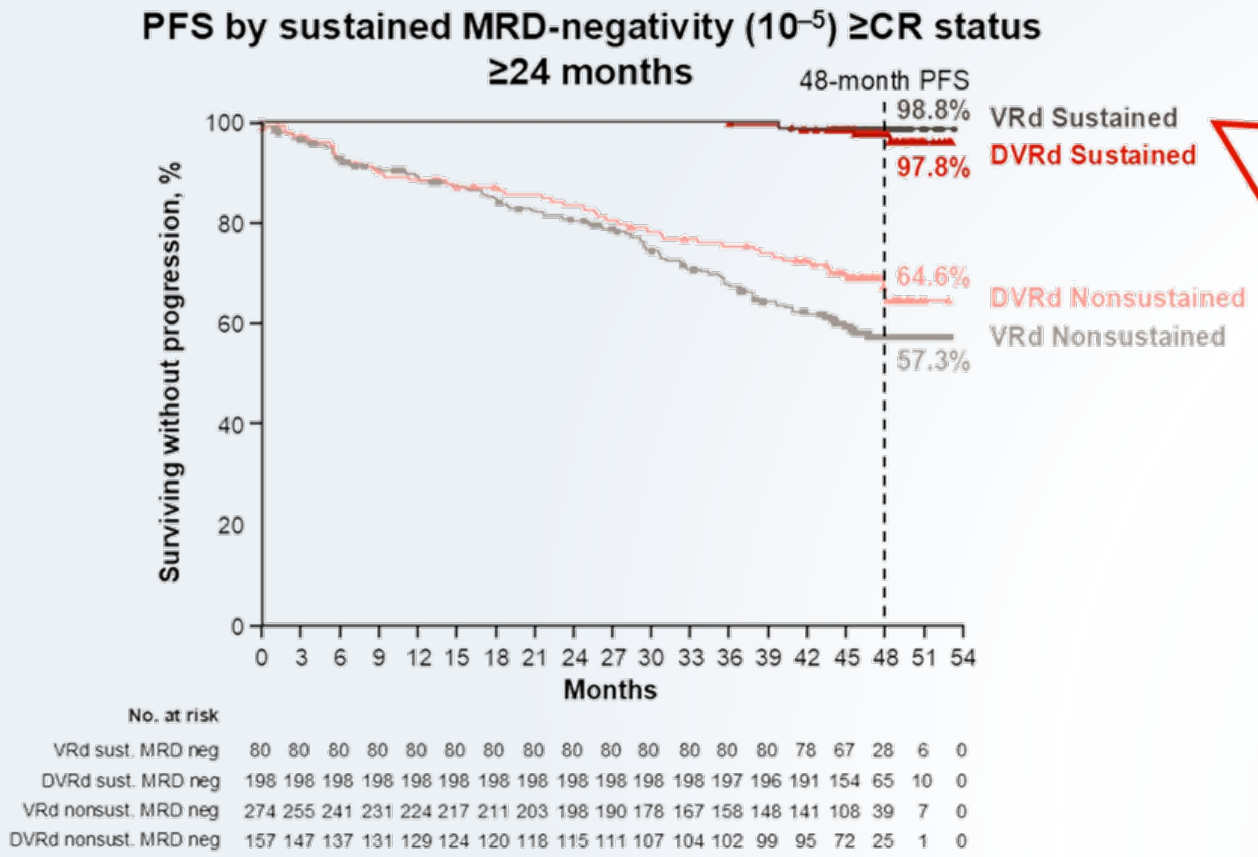


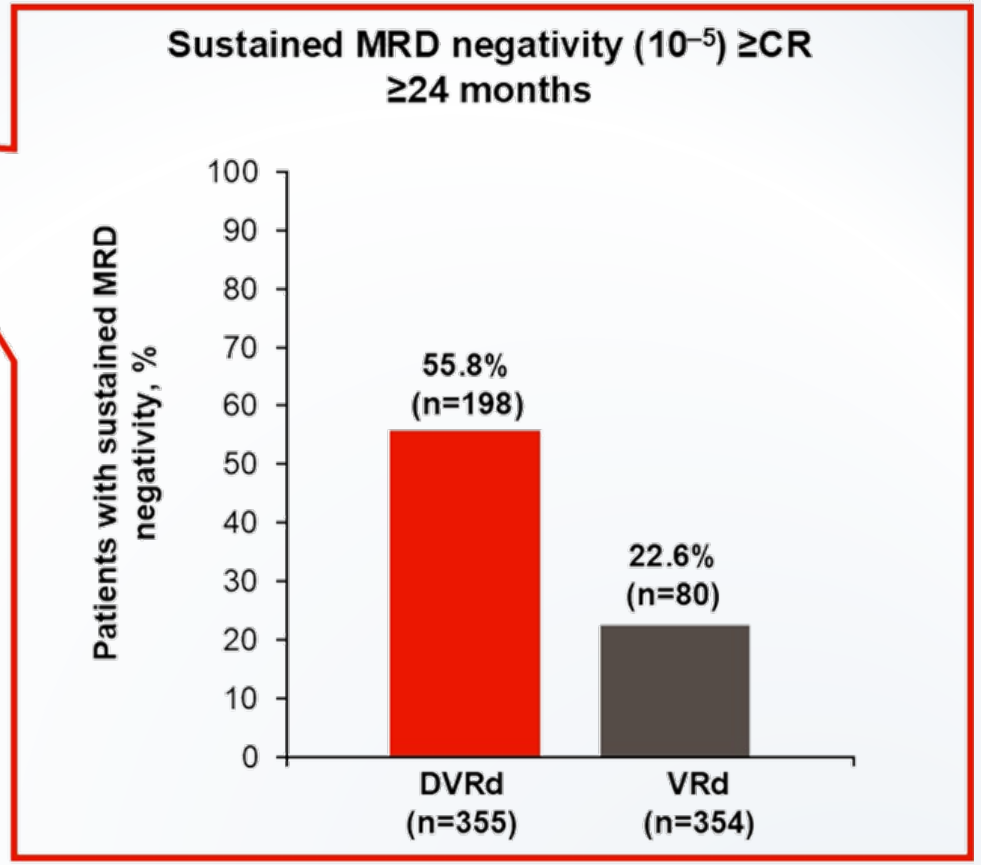


Sonneveld. NEJM. 2023, Rodriguez-Otero. ASCO 2024. Abstr 7502. NCT03710603.

Quadruplet therapy

- PERSESUS (DVRd vs VRd TE-NDMM) 2-year 56% vs 23%



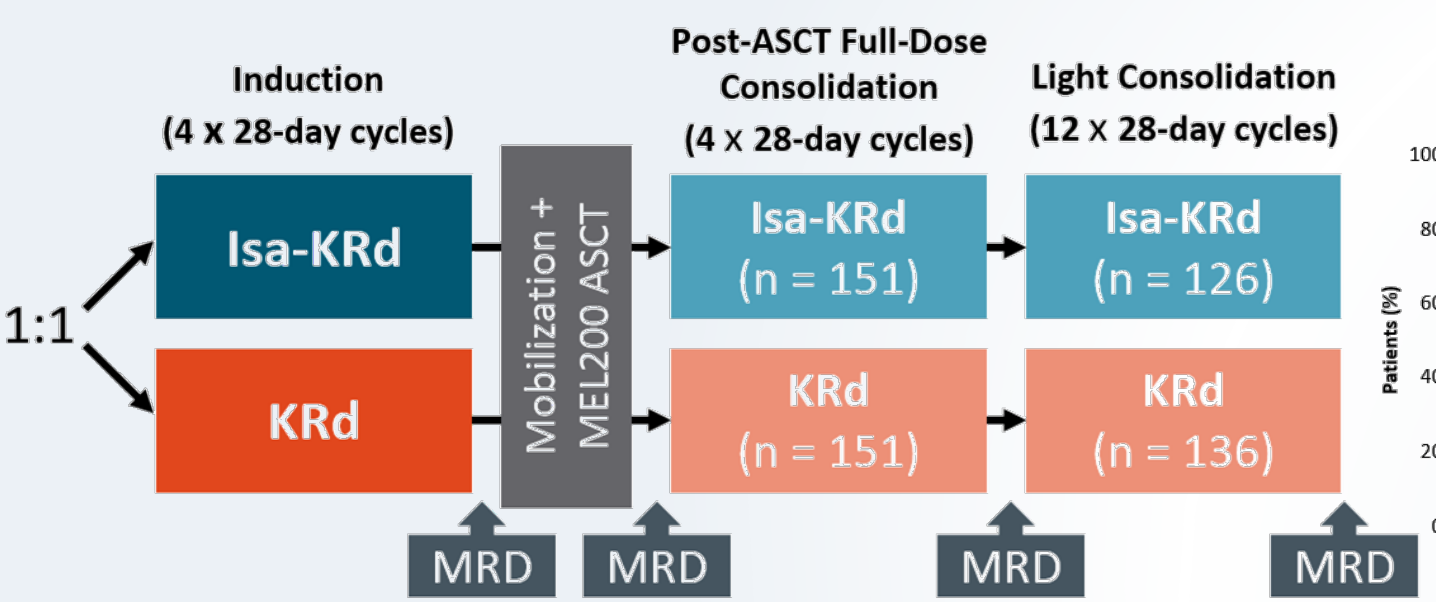


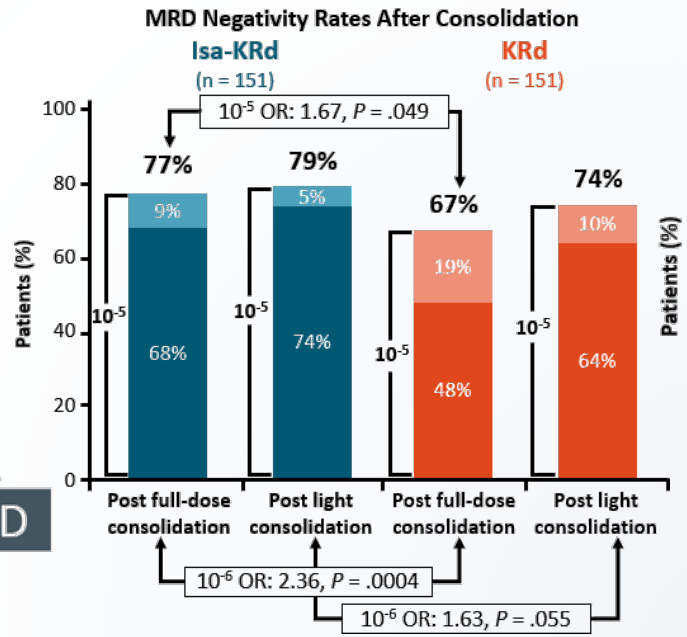
- Sustained MRD-negativity (10⁻⁵) ≥CR rates for ≥24 months were more than twice as high with DVRd vs VRd
- Among these patients, 48-month PFS rates exceeded 95% in both arms

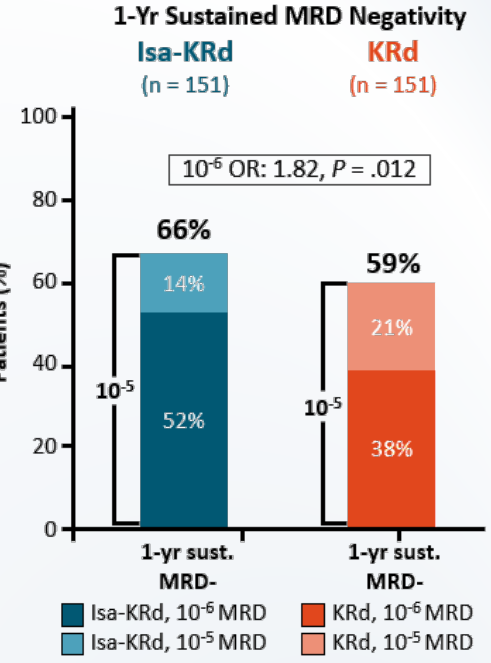
Sonneveld. NEJM. 2023, Rodriguez-Otero. ASCO 2024. Abstr 7502. NCT03710603.

Quadruplet therapy: sustained MRD negativity rates

- PERSESUS (DVRd vs VRd TE-NDMM) 2-year 56% vs 23%
- IsKia (IsaKRd vs KRd) MRD negativity 1-year 66% vs 59%



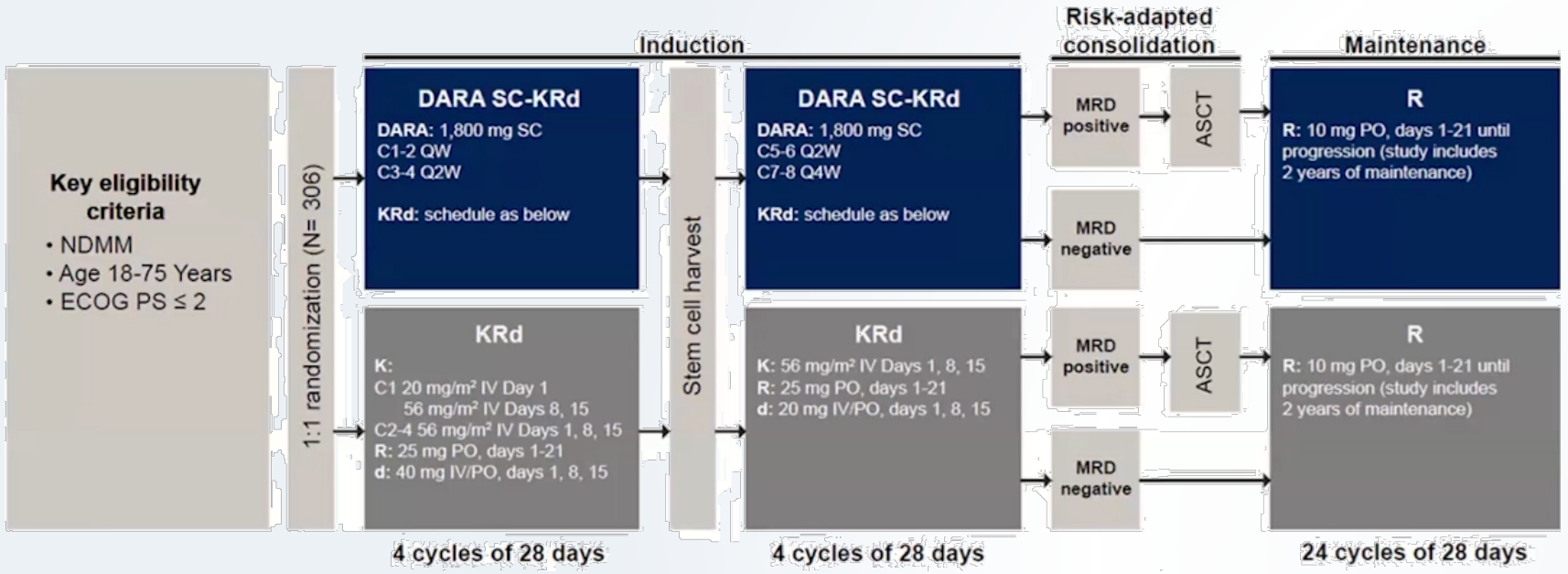


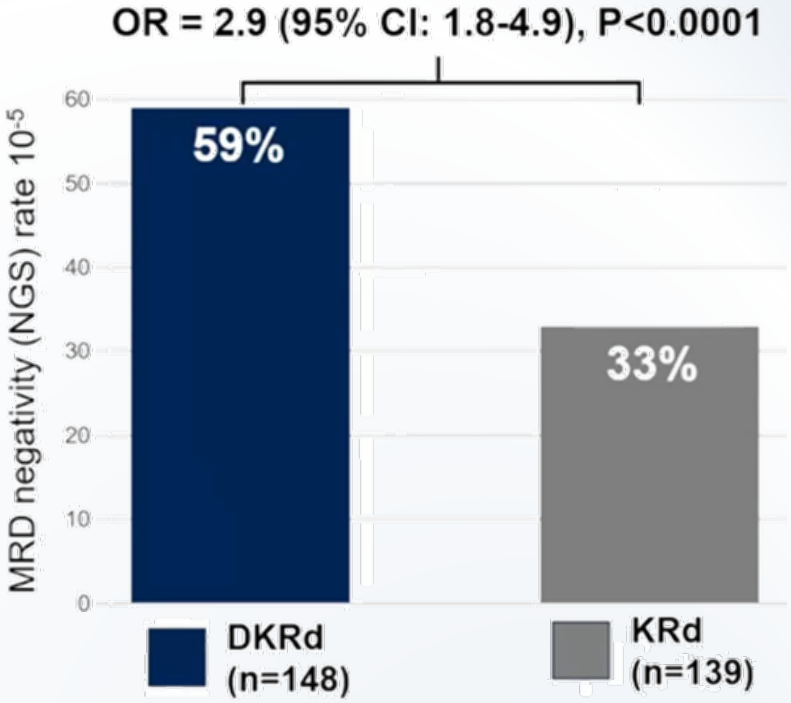


Gay. ASCO 2025. Abstr 7502. Gay. EHA 2025. Abstr S208.

Quadruplet therapy

- PERSESUS (DVRd vs VRd TE-NDMM) 2-year 56% vs 23%
- IsKia (IsaKRd vs KRd) MRD negativity 1-year 66% vs 59%
- ADVANCE study (DKRd vs KRd) MRD negativity 59% vs 33%



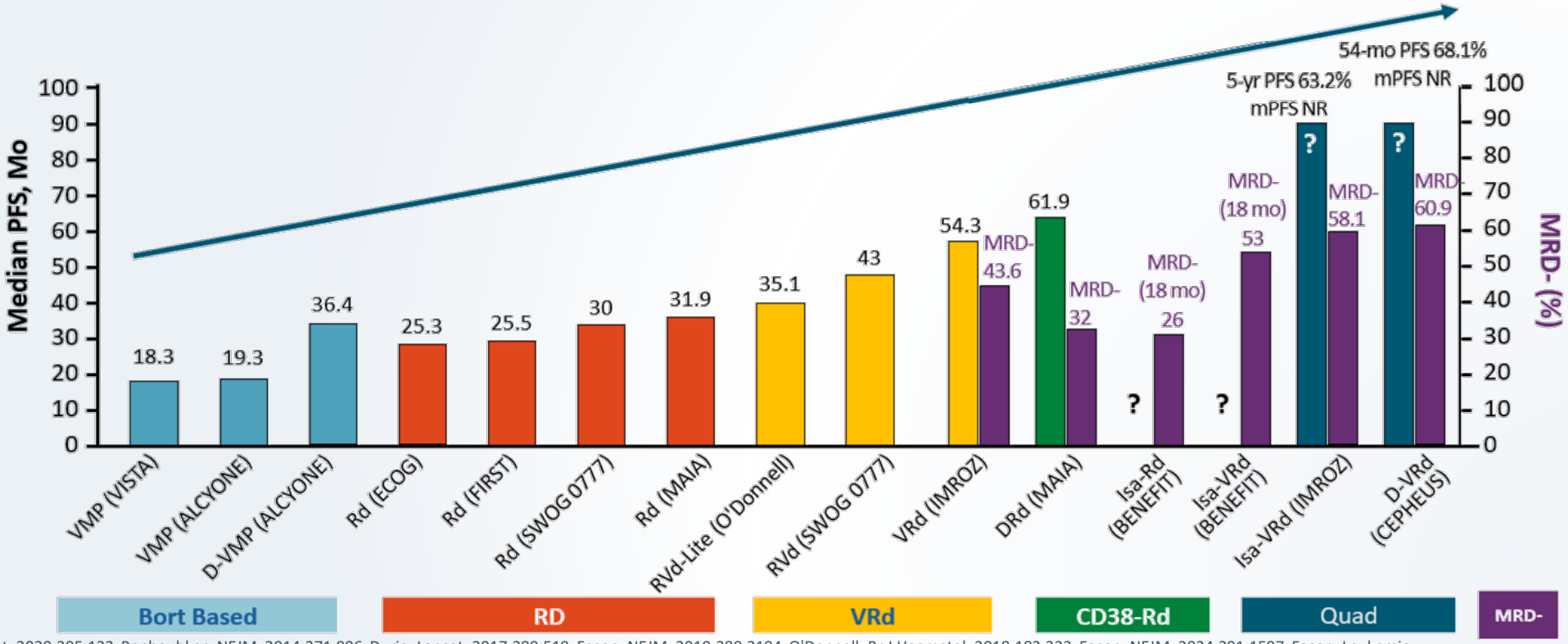


Primary endpoint: MRD neg x 10^{-5} after 8 cycles of induction

Landgren CO JCO 43, 7503-7503(2025).

Quadruplet therapy

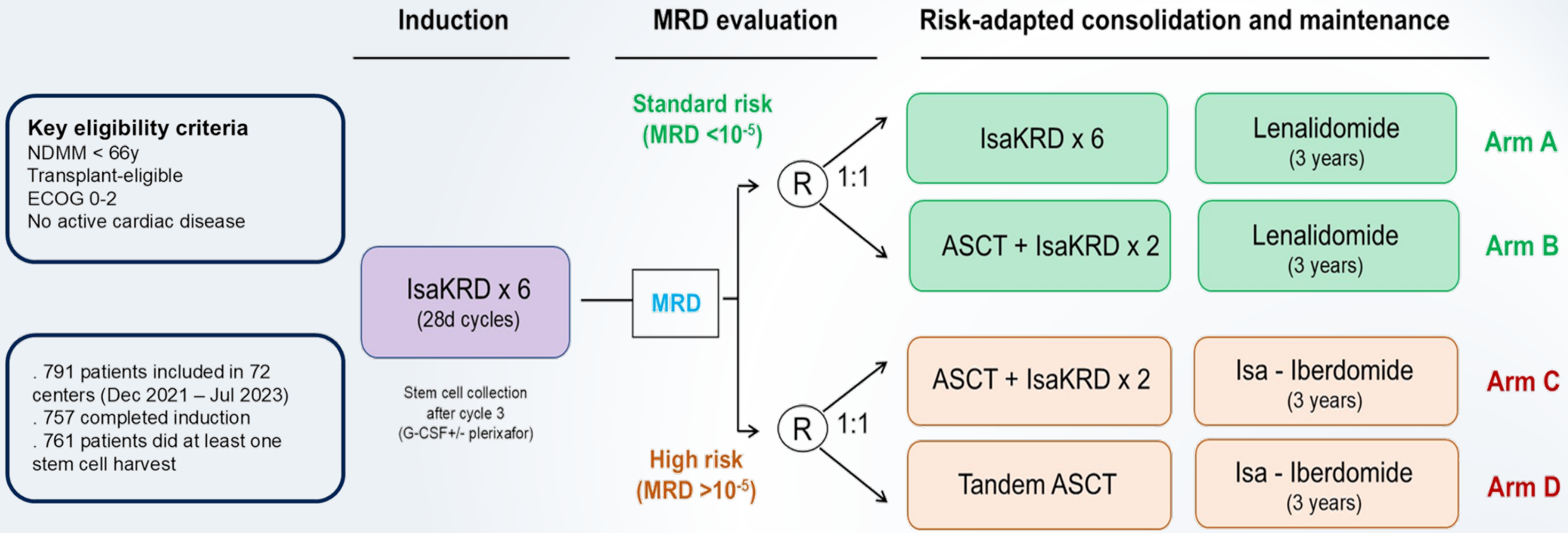
- PERSESUS (DVRd vs VRd TE-NDMM) 2-year 56% vs 23%
- IsKia (IsaKRd vs KRd) MRD negativity 1-year 66% vs 59%
- ADVANCE study (DKRd vs KRd) MRD negativity 59% vs 33%
- CEPHEUS, IMROZ ad BENEFIT confirm quad use in NDMM irrespective of transplant eligibility



Bortezomib PI. Mateos. Lancet. 2020;395:132. Benboubker. NEJM. 2014;371:906. Durie. Lancet. 2017;389:519. Facon. NEJM. 2019;380:2104. O'Donnell. Br J Haematol. 2018;182:222. Facon. NEJM. 2024;391:1597. Facon. Leukemia. 2025;39:942. Leleu. Nature Medicine. 2024;30:2235. Usmani. IMW 2024. Abstr OA–63.

MIDAS: MRD-driven Rx after Isa-KRD (TE-NDMM)

Multicenter (France and Belgium), open-label, randomized, phase III trial



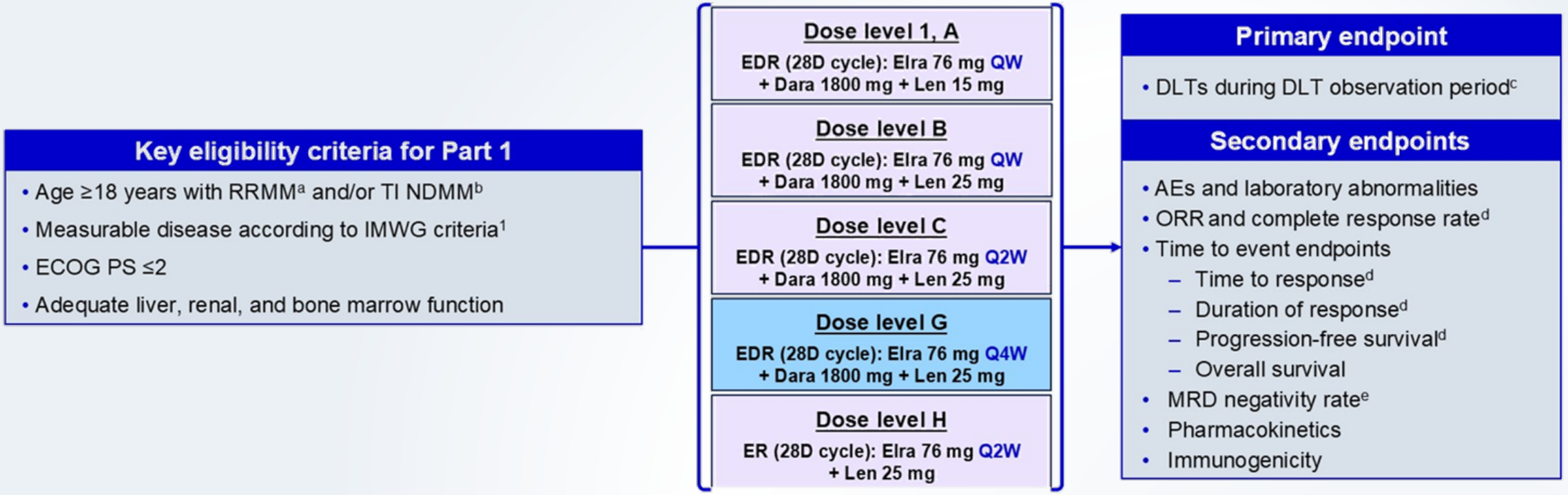
Primary endpoint: MRD negativity at 10^{-6} prior to maintenance therapy

Perrot ASCO 2025

✓ Key Takeaway Points

- ✓ Not primetime in absence of key efficacy outcomes
  - ✓ Sustained MRD negativity ideally at 24 months
  - ✓ PFS/OS especially in high risk population
- ✓ May help guide early vs delayed ASCT discussion
  - ✓ In a highly responsive subset, 1st-line ASCT may be deferred
- ✓ Tandem ASCT not necessary after effective induction

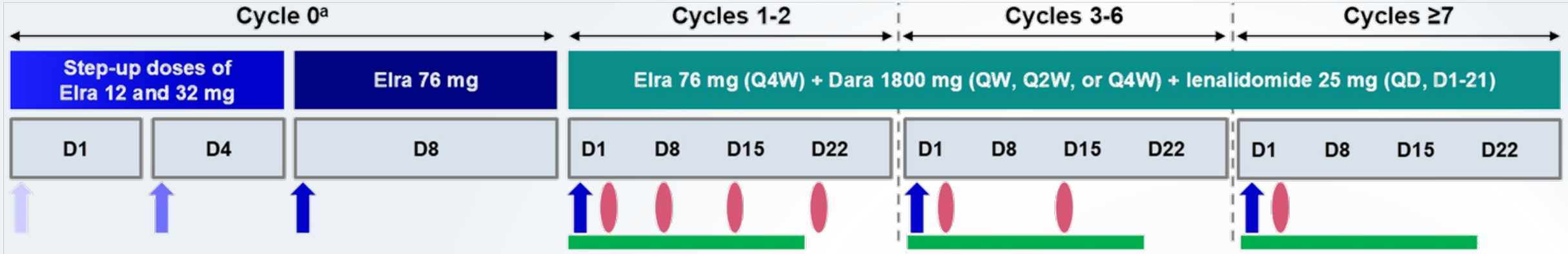
MagnetisMM-6: Elranatamab +DR in NDMM (nTE)



MagnetisMM-6 Part 1 **dose level G** is evaluating the combination of **elranatamab 76 mg SC Q4W**, **daratumumab 1800 mg SC**, and **lenalidomide 25 mg PO** in patients with transplant-ineligible **NDMM** (Data cutoff: April 1, 2025)

Quach ASCO 2025

Dose level G dosing schedule



Elranatamab 12 mg SC

Elranatamab 32 mg SC

Elranatamab 76 mg SC

Daratumumab 1800 mg SC

Lenalidomide 25 mg PO

Elranatamab premedication
- Diphenhydramine 25 mg (or equivalent) PO or IV
- Acetaminophen 650 mg (or paracetamol 500 mg) PO
- Dexamethasone 20 mg (or equivalent) PO or IV

Daratumumab premedication
- Diphenhydramine 25-50 mg (or equivalent) PO or IV
- Acetaminophen 650-1000 mg (or paracetamol 500) PO
- Dexamethasone 20 mg (or equivalent) PO or IV

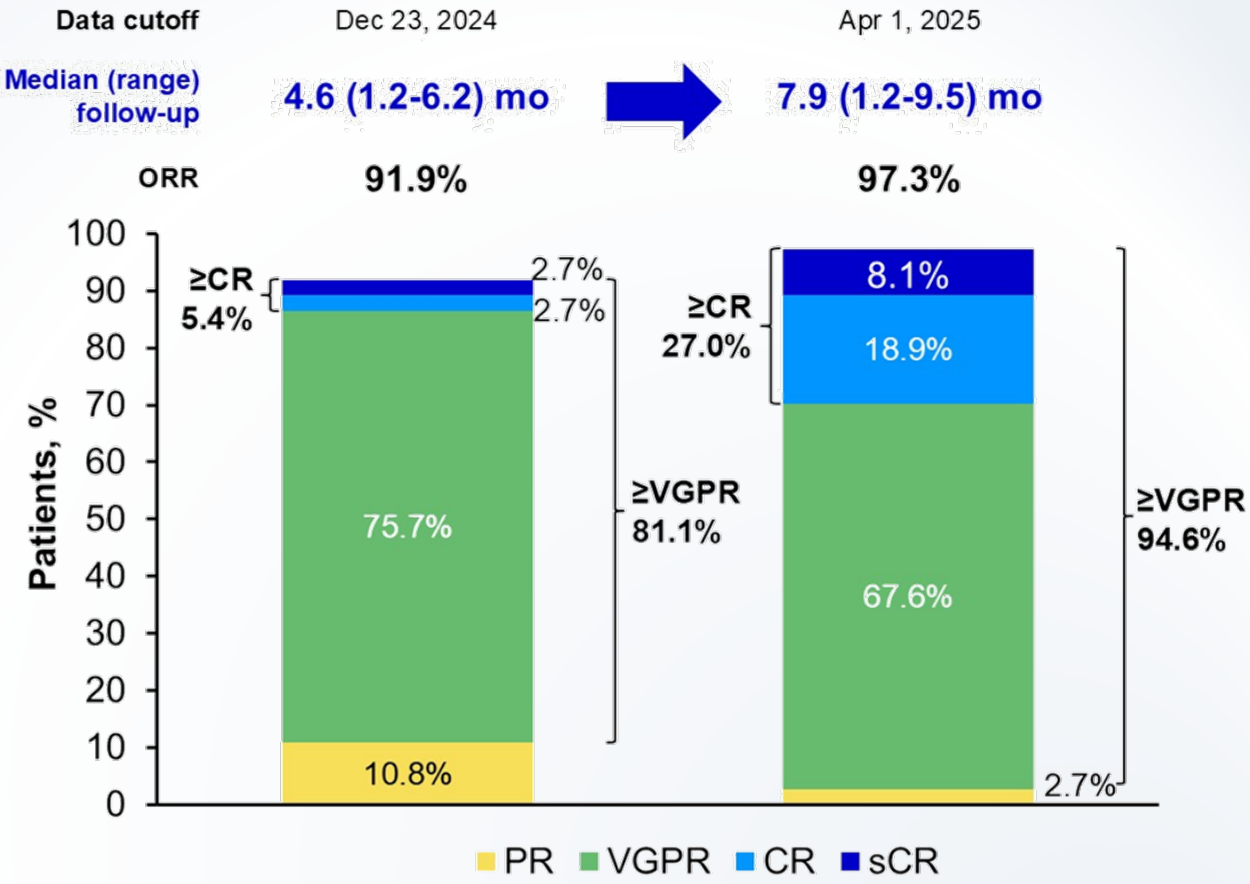
[a] **Protocol-required hospitalization for elranatamab**
- Dose 1: 48 hours
- Dose 2: 24 hours

Cycle length
- Cycle 0: 14 days
- Cyle ≥1: 28 days

Quach ASCO 2025

Early emerging response data

- Confirmed ORR 97.3% (85.8-99.9)
- 94.6% had VGPR or better
- 27% had CR or better
- Responses occurred early
  - median time to response 1.5 (0.3-4.2) mth



Quach ASCO 2025

✓ Key Takeaway Points

- ✓ Elranatamab + DR effective in transplant-ineligible NDMM
- ✓ Safety profile consistent with known toxicities
  - ✓ Most frequent TEAE were hematologic, infectious and CRS
  - ✓ All CRS and ICANS were grade ≤2
- ✓ Phase 3 MagnetisMM-6 part 2 to evaluate EDR vs DRd in transplant ineligible and transplant-deferred NDMM

Quach ASCO 2025

CARTITUDE-1: Long term (≥5 yr) outcomes in RRMM

Phase 1b/2 trial. Current analysis median f/u: 61.3 months

Eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior LOT or double refractory to a PI and an IMiD
- Prior PI, IMiD, and anti-CD38 mAb exposure

Screening

CARTITUDE-1

Apheresis → Bridging therapy (As needed) → Lymphodepletion → **Cilta-cel infusion** (*Target dose: 0.75×10^6 CAR+ viable T cells/kg (day 1)*) → Posttreatment follow-up

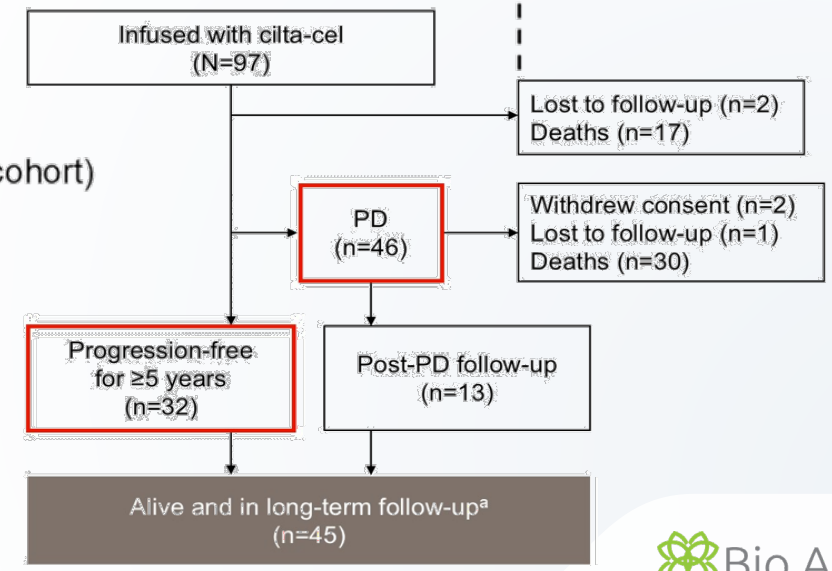
CARTinue

15-year postinfusion follow-up study

Patient evaluations per local SOC (reported annually at minimum)

Analyses (N=97)

- Phase 1b (n=29) and phase 2 (n=68)
- Efficacy and safety
- Postinfusion assessments[a] (day 1–100)
- Posttreatment assessments[a] (day 101–end of cohort)
- Biomarker correlative analyses[b]

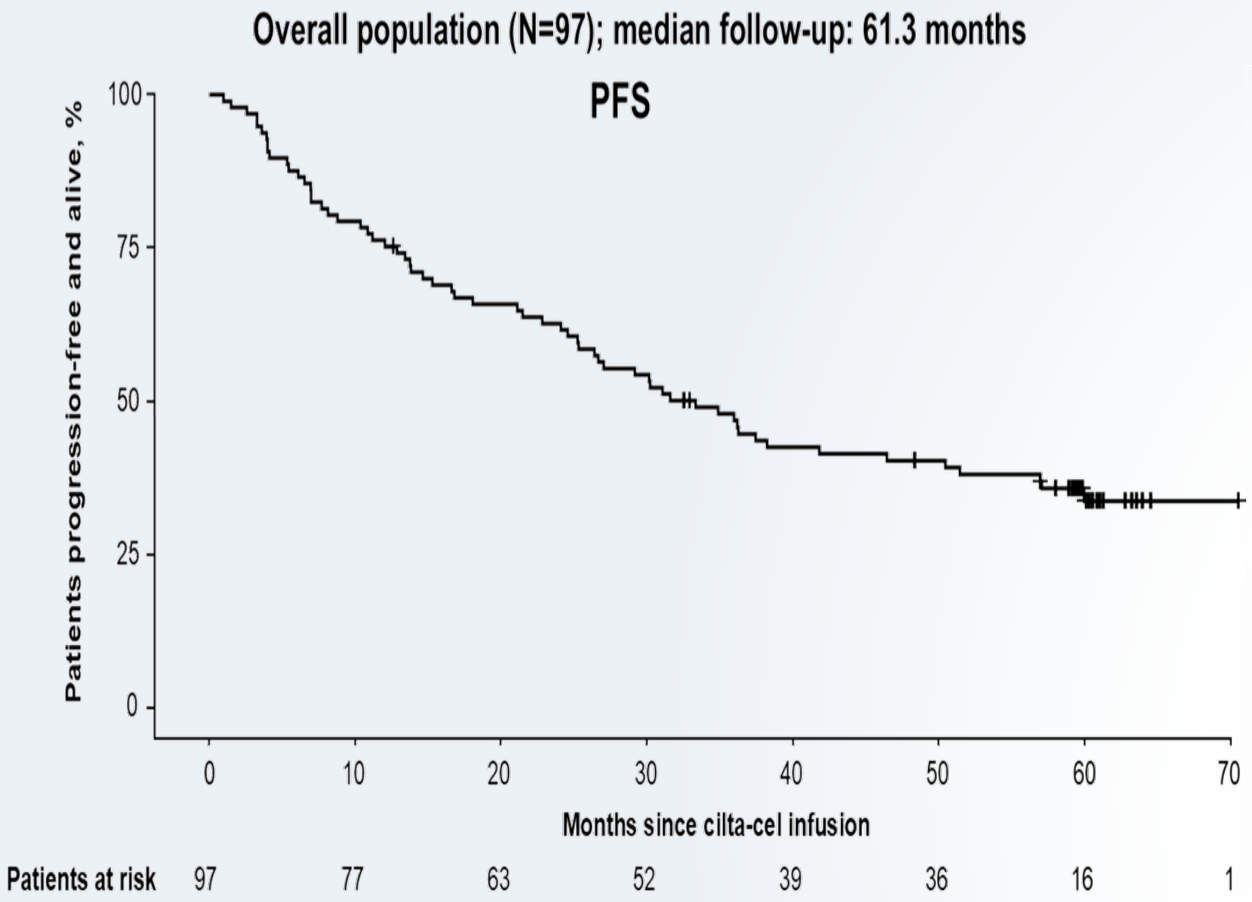


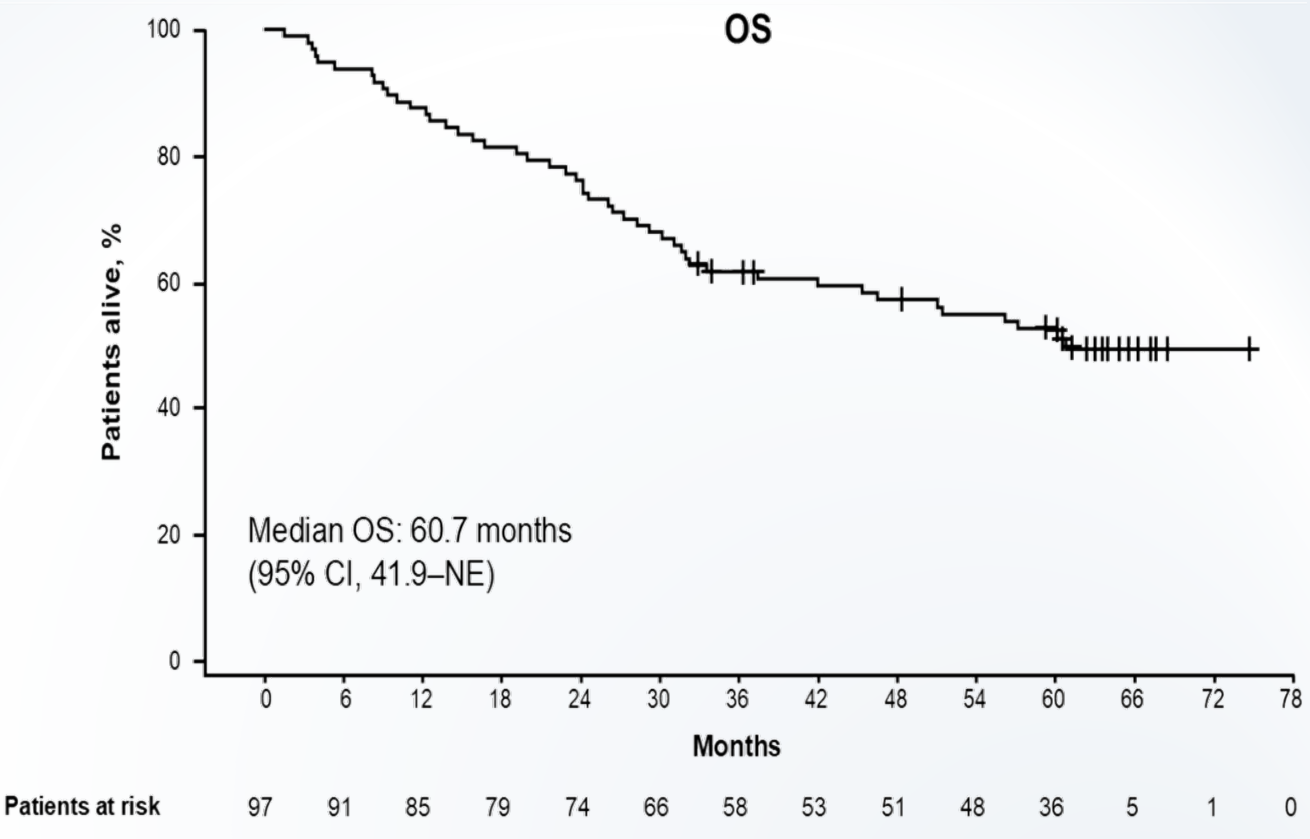
At 33.4m median followup –
Median PFS after Cilta-cel was 34.9months
Median OS was not reached.

Voorhees ASCO 2025

Progression-Free ≥5 yr: 33%

Median OS: 5 yr

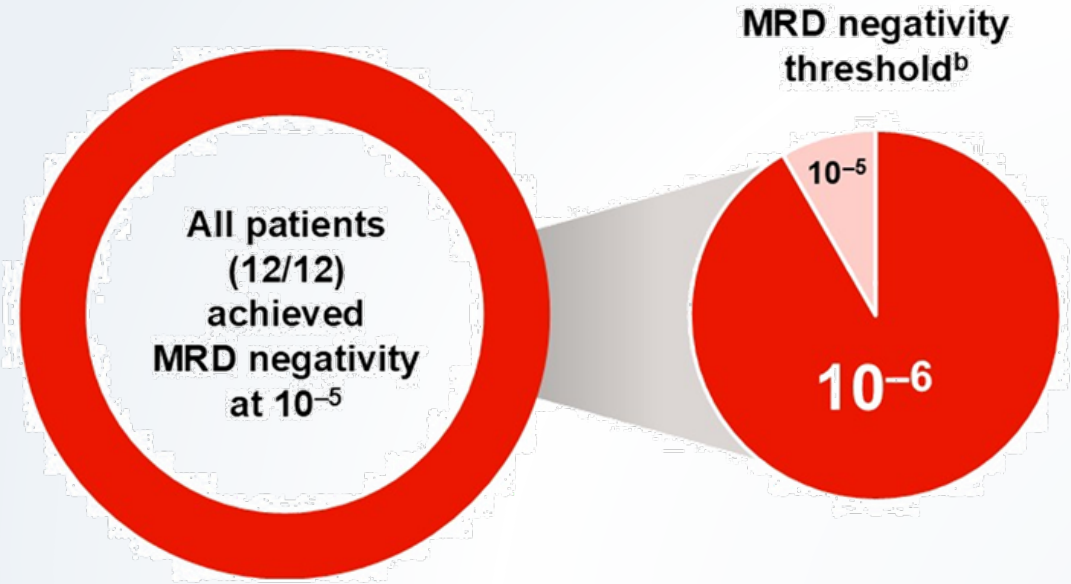




Voorhees ASCO 2025

Sustained MRD Negativity in a subset of pts with sCR

- Of the patients who were progression-free, 12 patients in sCR from a single center underwent serial MRD and PET/CT assessments[a]



All patients (12/12) were MRD-negative[b] and imaging-negative at year 5 or later following cilta-cel infusion

[a]Of the remaining 20 patients (from the 32 who were progression-free at ≥5 years), during the course of CARTITUDE-1, 12 patients were MRD-negative at 10^{-6}, 1 was MRD-positive, and the rest were unevaluable (5 had no clone identified, 1 failed QC, and 1 was indeterminate). [b]The 1 patient who was MRD-negative at 10^{-5} was determined by flow cytometry.
cilta-cel, ciltacabtagene autoleucel; MRD, minimal residual disease; PET/CT, positron emission tomography/computed tomography; QC, quality control; sCR, stringent complete response.

Comparable +PD vs -PD

	≥5 years progression-free (n=32)		PD within 5 years (n=46)
Age, years, median (range)	60.0 (43–78)		61.5 (47–77)
High-risk cytogenetics,[a] n/N (%)	**7/30 (23.3)[b]**	≈	**12/45 (26.7)**
Extramedullary plasmacytomas, n (%)	**4 (12.5)[c]**		**6 (13.0)**
Time to progression on last prior LOT, months, median (range)	3.98 (0.7–48.6)[d]		3.89 (0.7–21.5)[e]
Prior LOT, median (range)	6.5 (3–14)		5.0 (3–18)
Triple-class[f] refractory, n (%)	29 (90.6)		39 (84.8)
Penta-drug[g] refractory, n (%)	15 (46.9)		15 (32.6)
Bone marrow plasma cells, %, median (range)	**5.0 (0.8–80.0)**		**24.0 (0.0–95.0)**
Soluble BCMA, µg/L, median (range)	**36.0 (3.7–864.6)**		**58.5 (3.8–1342.9)**
High baseline tumor burden,[h] n (%)	2 (6.3)		8 (17.4)

Patients with high-risk cytogenetics and extramedullary plasmacytomas were equally likely to be progression-free. Of note, the percentage of patients with high tumor burden was numerically lower among patients who were progression-free

[a]Either del17p, t(14;16), or t(4;14). [b]4 patients had del17p, 2 had t(14;16), and the remaining 1 patient had a double hit of del17p and t(14;16). [c]Extramedullary disease denotes soft tissue plasmacytoma that was not contiguous with bone. [d]n=29. [e]n=42. [f]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [g]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody. [h]Low tumor burden defined as meeting all following parameters (as applicable): bone marrow % plasma cell <50%, serum M protein <3 g/dL, serum FLC <3000 mg/L. High tumor burden defined as meeting any of the following parameters: bone marrow % plasma cell ≥80%, serum M protein ≥5 g/dL, serum FLC ≥5000 mg/L. Intermediate tumor burden did not fit either criteria of high or low tumor burden. BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucel; FLC, free light chain; IMiD, immunomodulatory drug; LOT, line of therapy; PD, progressive disease; PI, proteasome inhibitor.

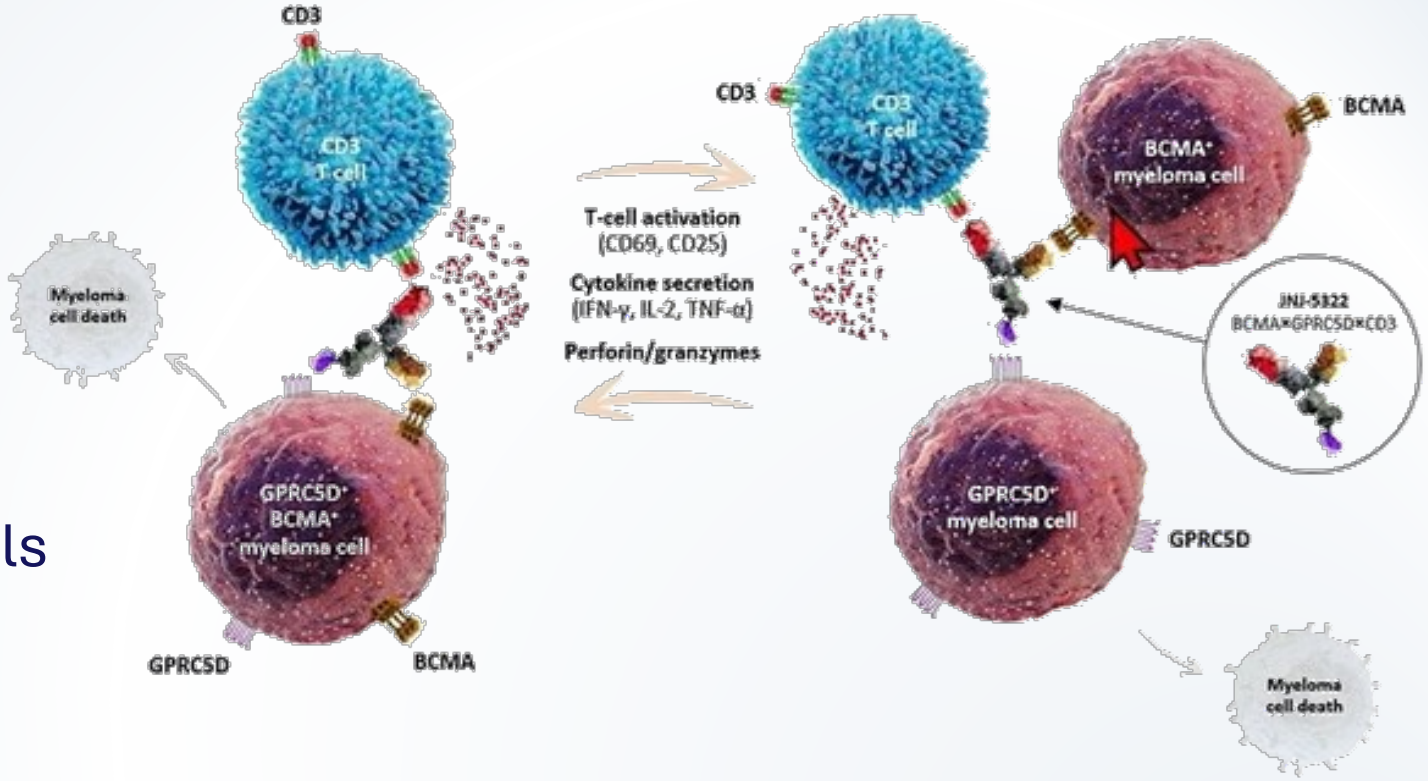
Voorhees ASCO 2025

✓ Key Takeaway Points

- ✓ Excellent long-term efficacy - 5yr PFS- 33%, 5 yr OS- 50%
- ✓ Baseline indicators for long term benefit
  - ✓ Lower tumor burden, favorable immune profile, better hematologic parameter BUT… What about those who relapse early after Cilta-cel ?
- ✓ Role in early line of therapy needs careful evaluation
  - ✓ Longer follow-up for late onset motor and neuro-cognitive toxicity

JNJ-5322 Trispecific Ab: CD3, BCMA and GPRC5D

- Dual Antigen may enhance tumor response by circumventing tumor heterogeneity and antigen loss and improve potency due to antigen binding avidity
- JNJ-5322 is an IgG1 trispecific antibody that binds to CD3 on T cells and BCMA/GPRC5D on MM cells



Trispecific Ab (JNJ-5322): Phase 1 (RRMM)

Key eligibility criteria

- Triple-class exposed RRMM[a]

Key objectives

- Identify RP2D
- Safety, including DLTs
- Preliminary efficacy assessment

N=147 all doses investigated (all SC)

Dose Escalation

- 5 mg → 40–120 mg Q4W
- 3.6/5.0 mg → 10–30 mg Q2W
- MABEL 0.4 –10 mg Q2W

Dose Optimization

- 5 mg → 50 mg Q4W
- 5 mg → 100 mg Q4W
- 5 mg → 100 mg → 300 mg Q4W

Loading Dose/Schedule Optimization

- 5 mg → 200 mg Q4W[b] → 100 mg Q4W
- 5 mg → 100 mg Q8W
- 5 mg → 200 mg Q8W[c] → 100 mg Q8W

Optimization for Outpatient Dosing

- Lower (2.5 mg) vs higher (10 mg) SUD
- 2–4 vs 6–8 days between step-up and full dose
- Prophylactic tocilizumab

RP2D identification

- 5 mg SC → 100 mg Q4W SC

The RP2D with 1 SUD was determined based on safety-, PK-, and efficacy-guided endpoints; the MTD was not reached

NWCJ van de Donk ASCO 2025

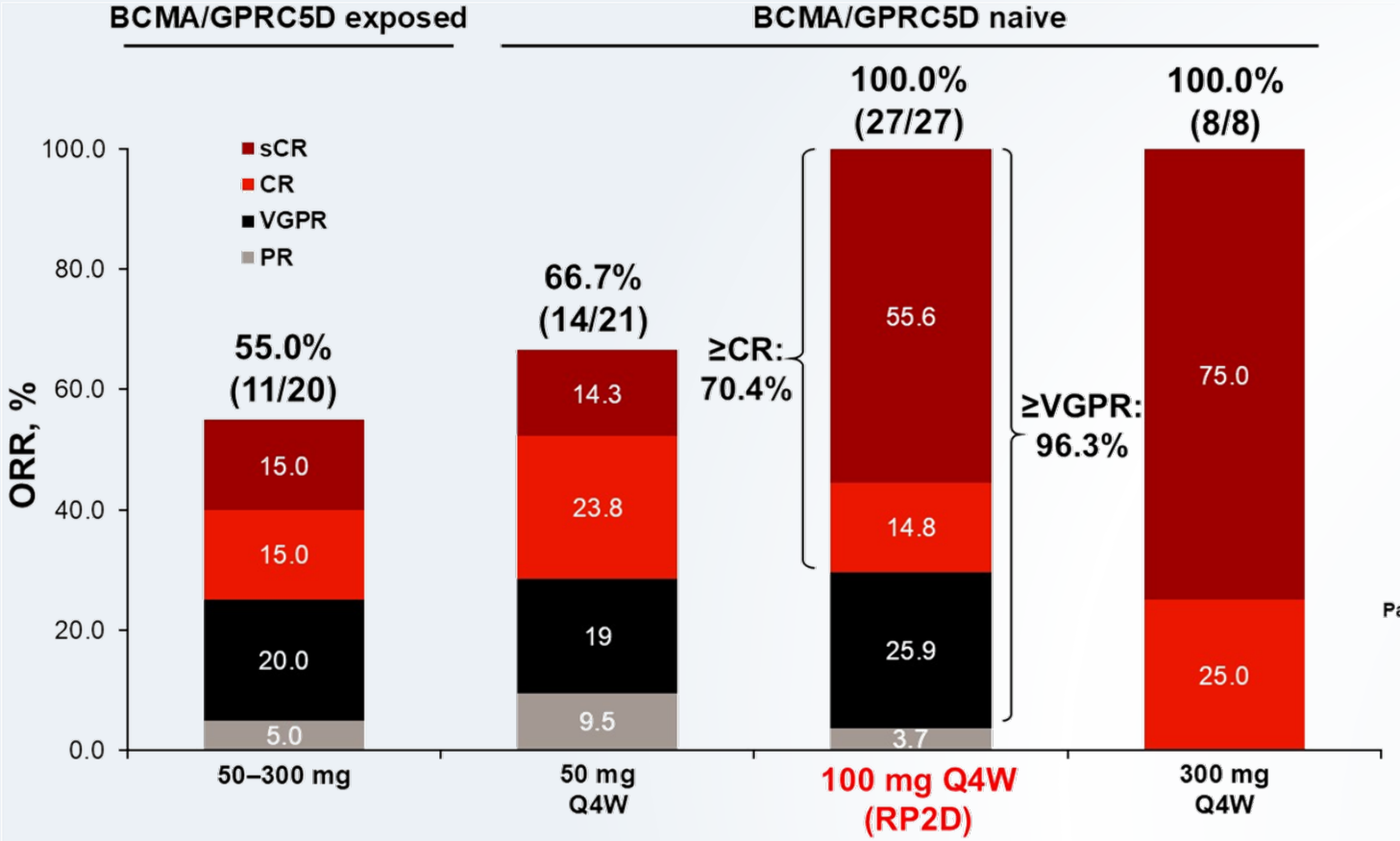
Baseline characteristics

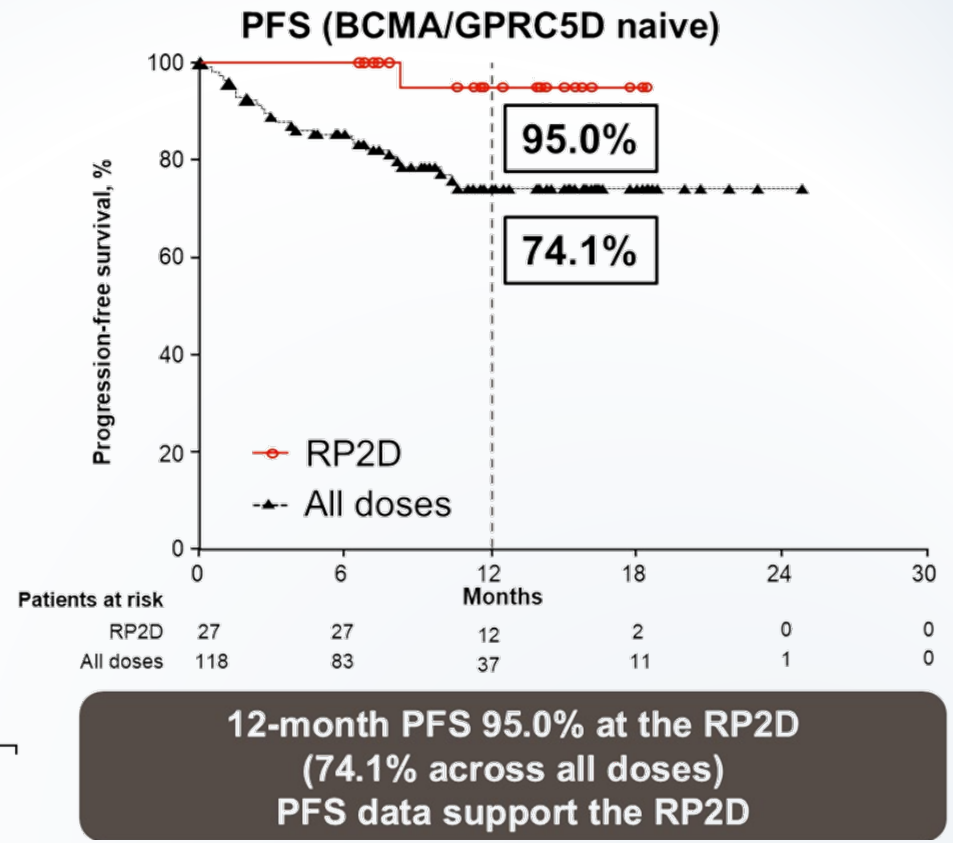
Characteristic	RP2D (n=36)	All doses (N=147)
Median follow-up, months (range)	11.6 (0.4–18.6)	9.3 (0.3–25.8)
Median age, years (range)	67.5 (43–87)	64.0 (39–87)
Male, n (%)	22 (61.1)	87 (59.2)
Race, n (%)		
White	28 (77.8)	110 (74.8)
Black/African American	1 (2.8)	13 (8.8)
Asian	1 (2.8)	7 (4.8)
Multiple	2 (5.6)	2 (1.4)
Unknown/not reported	4 (11.1)	15 (10.2)
Extramedullary plasmacytomas ≥1,[a] n (%)	3 (8.3)	16 (10.9)
High-risk cytogenetics,[b] n (%)	9 (27.3)	39 (31.2)
ISS stage,[c] n (%)		
I	19 (52.8)	77 (53.1)
II	12 (33.3)	50 (34.5)
III	5 (13.9)	18 (12.4)
Years since diagnosis,[d] median (range)	7.0 (0.9–18.7)	6.9 (0.7–31.9)

Characteristic	RP2D (n=36)	All doses (N=147)
Median prior LOT, n (range)	4.0 (2–11)	4.0 (1–11)
Exposure status, n (%)		
Triple-class[e]	36 (100.0)	147 (100.0)
Penta-drug[f]	15 (41.7)	72 (49.0)
BCMA/GPRC5D exposed	9 (25.0)	29 (19.7)
Prior BCMA	8 (22.2)	26 (17.7)
Prior GPRC5D	1 (2.8)	5 (3.4)
BCMA/GPRC5D naive	27 (75.0)	118 (80.3)
Antibody-drug conjugate	2 (5.6)	7 (4.8)
CAR-T therapy	4 (11.1)	12 (8.2)
Bispecific antibody	6 (16.7)	16 (10.9)
Refractory status, n (%)		
PI	19 (52.8)	86 (58.5)
IMiD	36 (100.0)	136 (92.5)
Anti-CD38	36 (100.0)	138 (93.9)
Triple-class[e]	19 (52.8)	79 (53.7)
Penta-drug[f]	2 (5.6)	10 (6.8)
To last LOT	34 (94.4)	132 (89.8)

Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with one 5 mg SUD.
[a]≥1 nonradiated, bone-independent lesion ≥2 cm. Patients with paraskeletal plasmacytomas were permitted but not counted as EMD. [b]FISH or karyotype testing in n=33 (RP2D) and n=125 (total). Defined as del(17p), t(4;14), or t(14;16). [c]n n=145 (total). [d]n n=35 (RP2D) and n=144 (total). [e]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [f]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb.

ORR – 86% at RP2D , 73% overall





12-month PFS 95.0% at the RP2D (74.1% across all doses) PFS data support the RP2D

Median follow up 12.2 months

Median time to first response 1.2 months

Median time to best response 5.9 months

NWCJ van de Donk ASCO 2025

Key Takeaway Points

- ✓ Convenient dosing
- ✓ Effective: BCMA/GPRC5D naïve ORR 100% !! (≥ CR, 70%)
- ✓ Safety profile comparative to Bispecifics
  - ✓ better oral TEAE profile, ↓wt loss
  - ✓ Grade 3/4 infection rates similar (28%) – IVIg is must
  - ✓ CRS events were low grade – prophylactic Tocilizumab

Thank you

✉ Shivani.kapur@pennmedicine.upenn.edu