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First line in multiple myeloma: Is 4 better than 3?

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Disclosures

- Consultancy: Amgen, Janssen, GSK, BMS, Abbvie, Astrazeneca, Pfizer, K-36 Therapeutics, Genentech
- Research Funding: 2Seventy bio, Pfizer
- Membership on an entity's Board of Directors or advisory committees: Immuneel, Caribou biosciences

- Improve symptoms
- Obtain a deep response: attain **MRD negative disease**
- Use your best drugs rather than reserve for later
- Consider clinical trials

Treatment Attrition in Multiple Myeloma

- Real-world assessment of lines of therapy and outcomes based on 3 US insurance claims databases

| Line of Therapy | Sample Size, N | Attrition (%) | Deaths (%) | No subsequent Treatment in Follow-Up (%) | Subsequent Treatment (%) |
|--------------------------------|----------------|---------------|------------|--|--------------------------|
| Non-Transplant Patients | | | | | |
| 1 | 22,062 | -- | 12.9% | 44.0% | 43.1% |
| 2 | 9505 | 56.9% | 12.2% | 33.3% | 54.5% |
| Transplant Patients | | | | | |
| 1 | 2763 | -- | 1.3% | 19.6% | 79.0% |
| 2 | 2184 | 21.0% | 2.7% | 28.1% | 69.2% |

Put your best foot forward

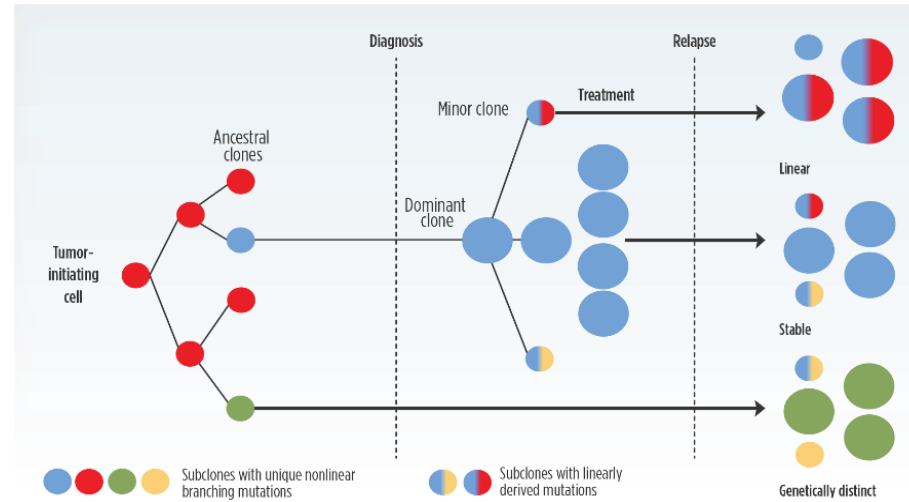
Why MRD?

Why should we get MRD negativity?

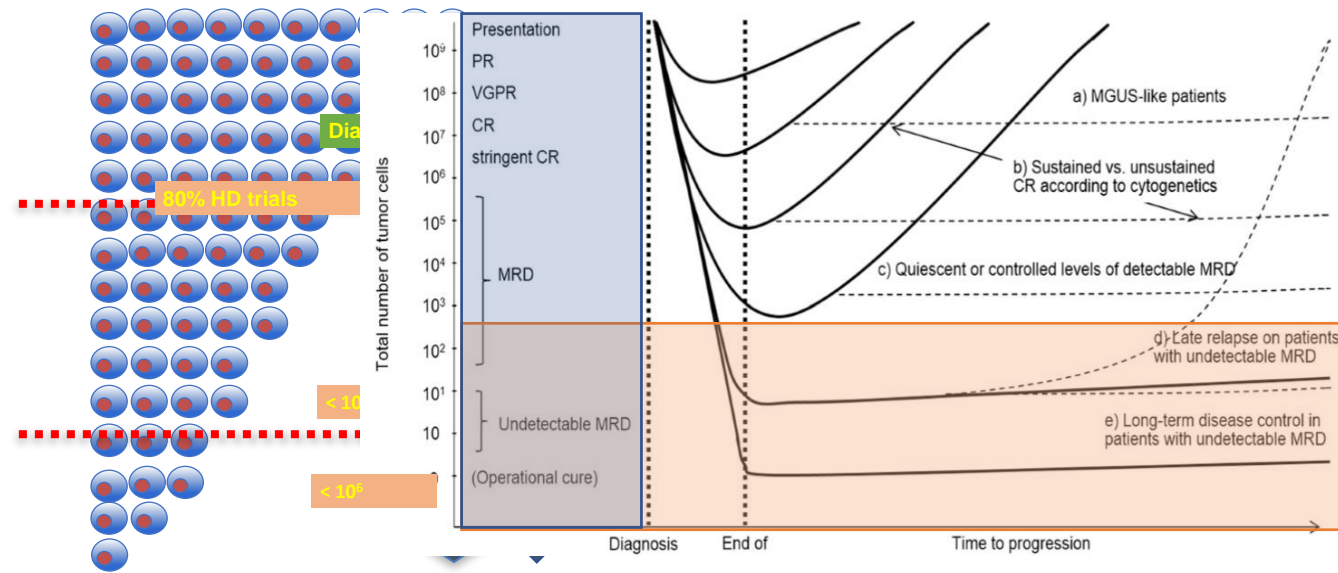
- Depth of response matters:
 - Biological Implications
 - Clinical Implications
- Current Treatments :
 - High response rates
 - Need for more sensitive methods

Evolution of Clonal Variants in MM

- **Genomic changes are present at diagnosis and increase throughout the disease course¹⁻⁴**
- **Evolve over time due to selective pressures from treatment and factors in the microenvironment^{1,4}**
- **Probability of acquisition of mutation may directly relate to number of cells.**



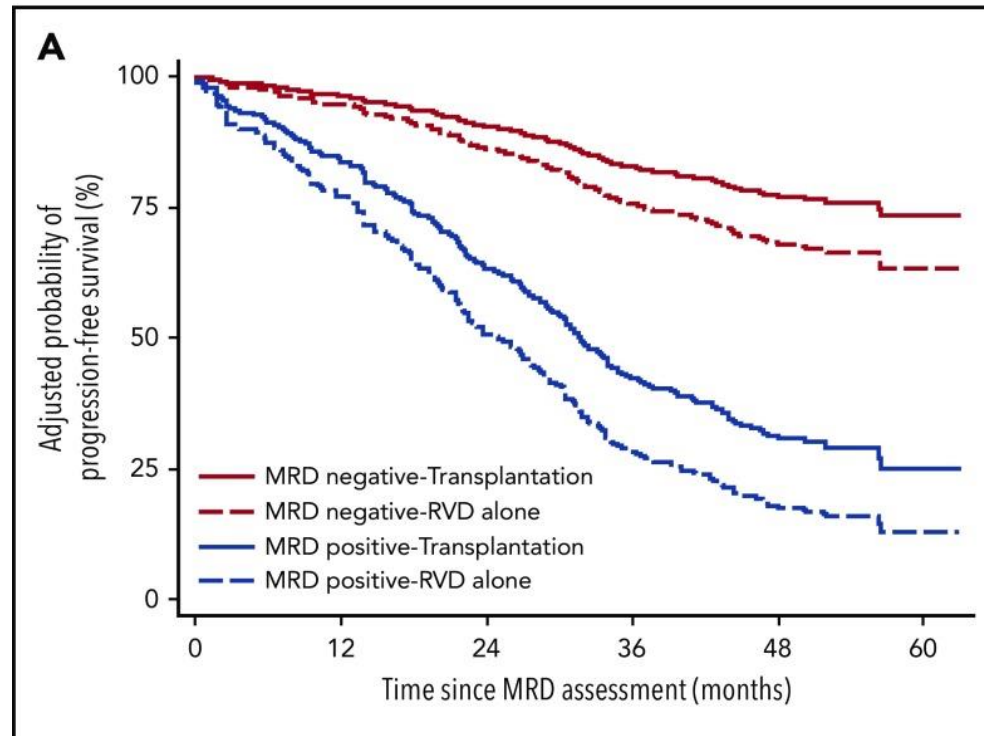
Does depth of response matter??



MRD is the new CR

Paiva *et al.*, Blood, 2015

MRD Negative Patients Have Improved Outcome Irrespective of Therapy Used



Perrot A et al Blood, 2018

Treatment landscape in NDMM is evolving – from doublets/triplets to triplets/quadruplets

IMiDs

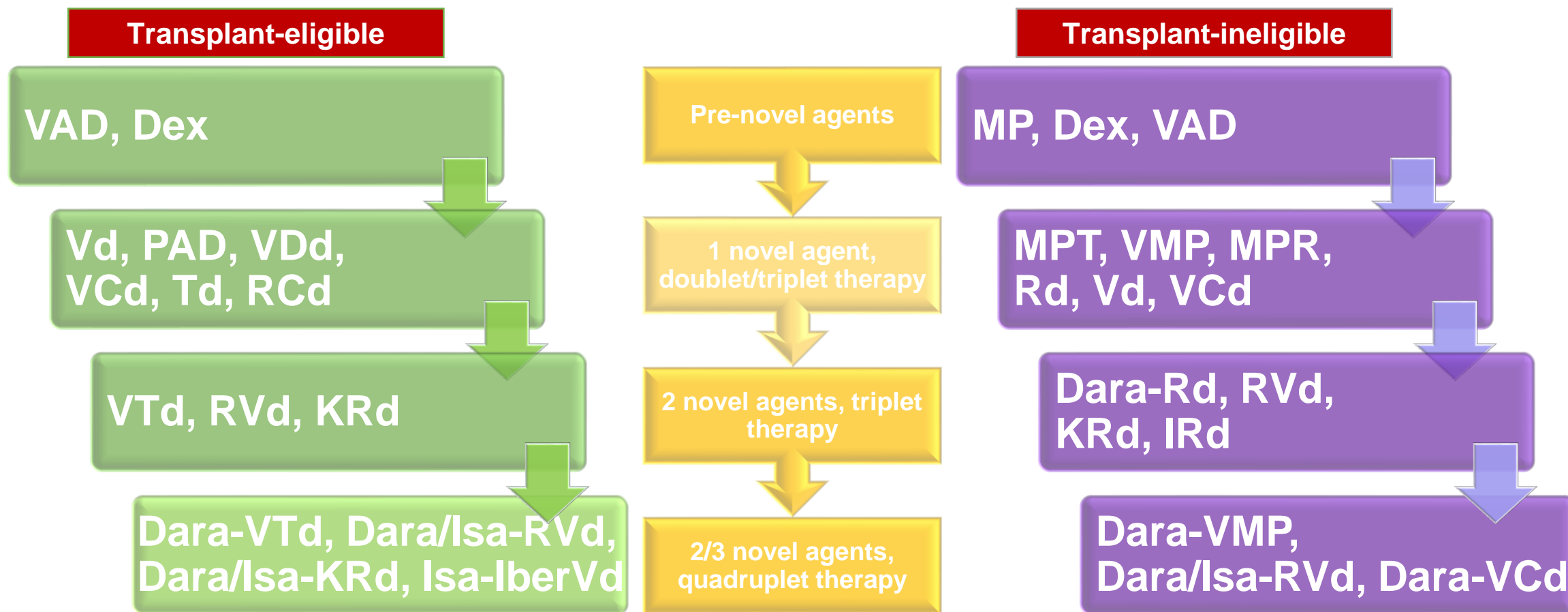
- Thalidomide
- Lenalidomide
- Pomalidomide

PIs

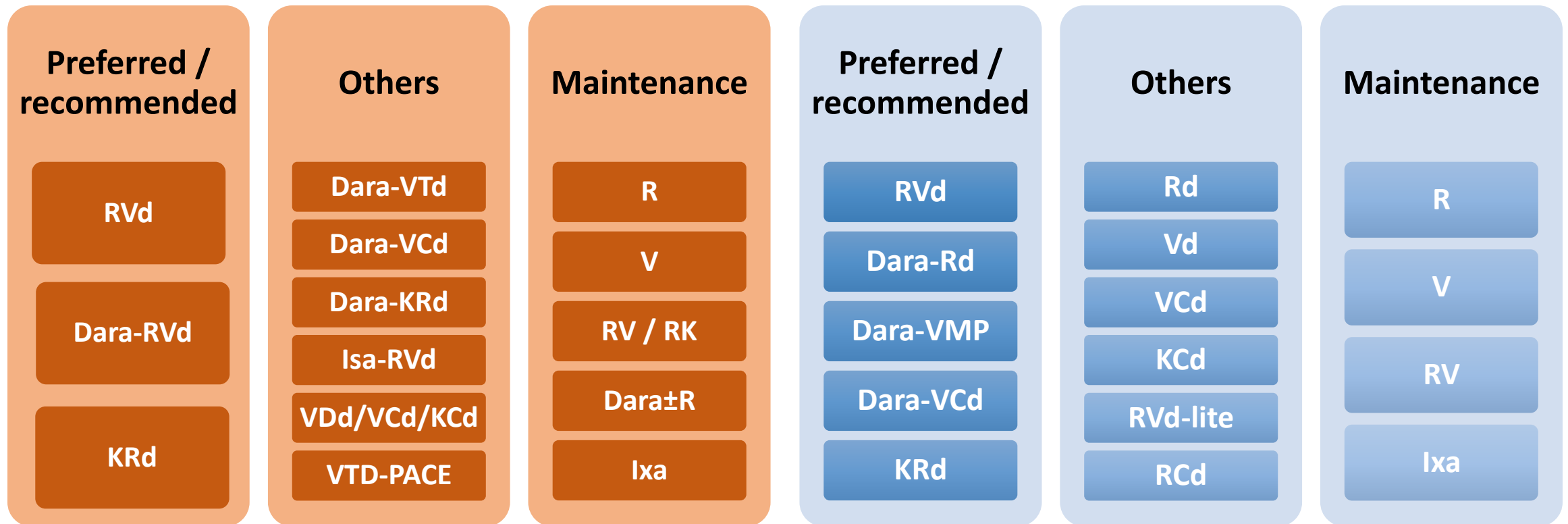
- Bortezomib
- Carfilzomib
- Ixazomib

Anti-CD38 mAbs

- Daratumumab
- Isatuximab



Anti-CD38 mAb-based quadruplets: emerging SOC's building on existing triplet backbones

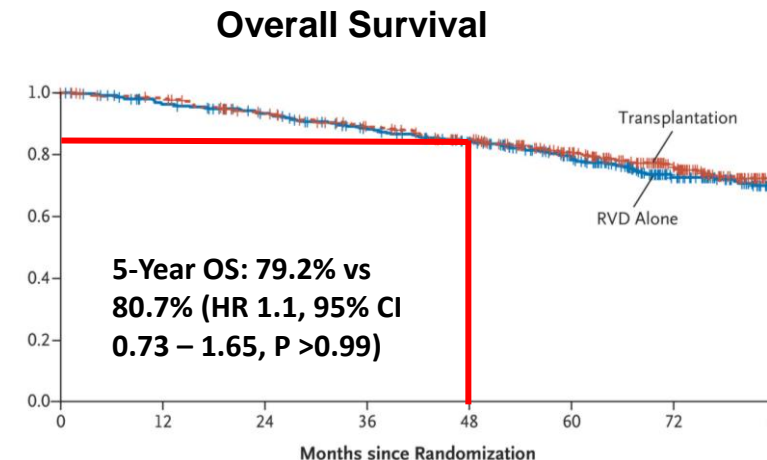
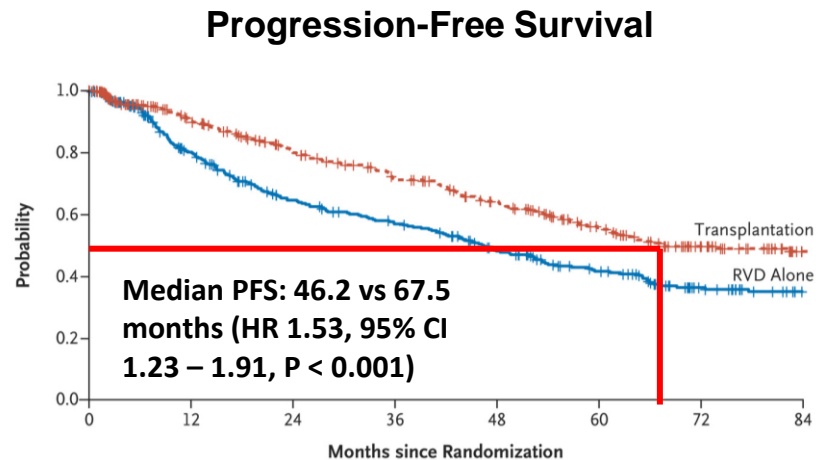


+ Isa-RVd, Dara-KRd, Isa-KRd... under ongoing investigation in NDMM

DETERMINATION: Phase III Study of Upfront vs Deferred ASCT in Newly-Diagnosed Multiple Myeloma

- 3 cycles of RVD induction → ASCT → 2 cycles of RVD consolidation → len maintenance VS 8 cycles of RVD induction → len maintenance

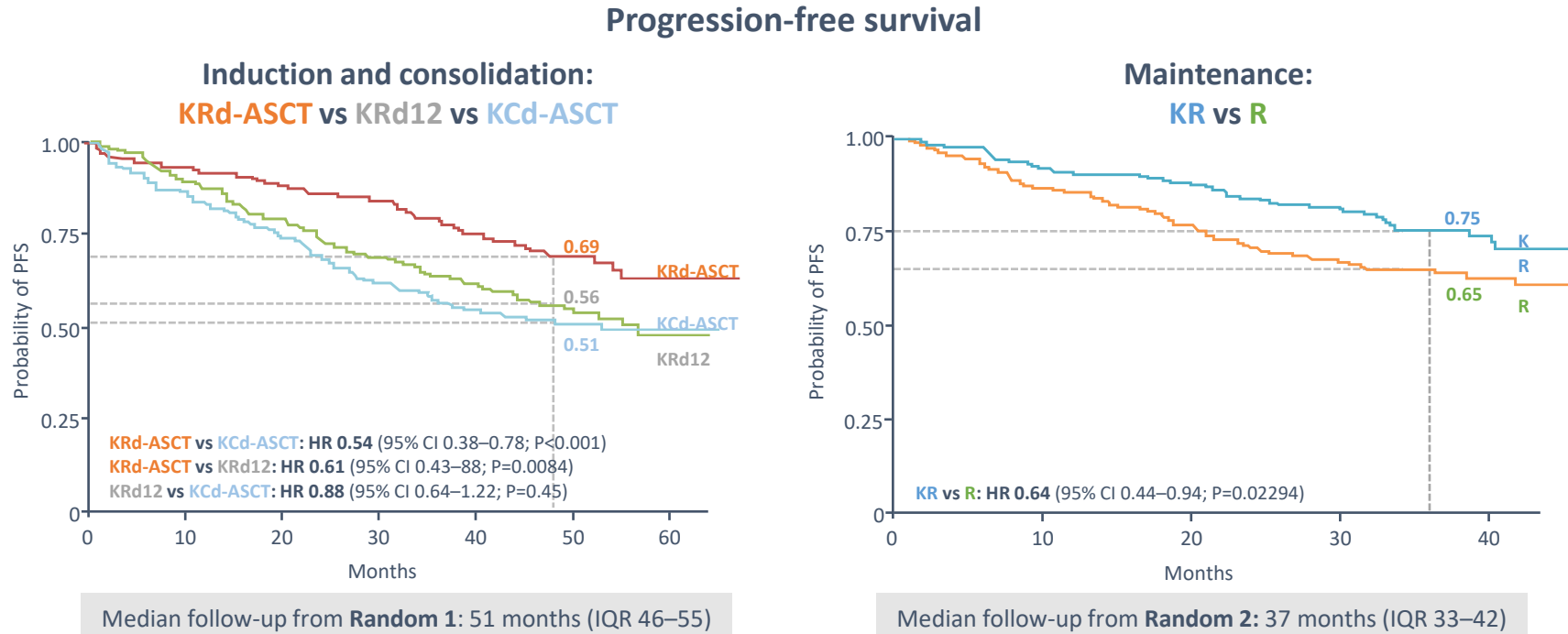
Median Follow-Up: 76 months



| No. at Risk | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|-----------------|-----|-----|-----|-----|-----|-----|----|----|
| Transplantation | 365 | 276 | 226 | 191 | 160 | 118 | 77 | 42 |
| RVD Alone | 357 | 250 | 187 | 160 | 126 | 96 | 60 | 40 |

| | | | | | | | | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Transplantation | 365 | 353 | 324 | 300 | 275 | 228 | 165 | 100 |
| RVD Alone | 357 | 332 | 313 | 285 | 258 | 214 | 143 | 100 |

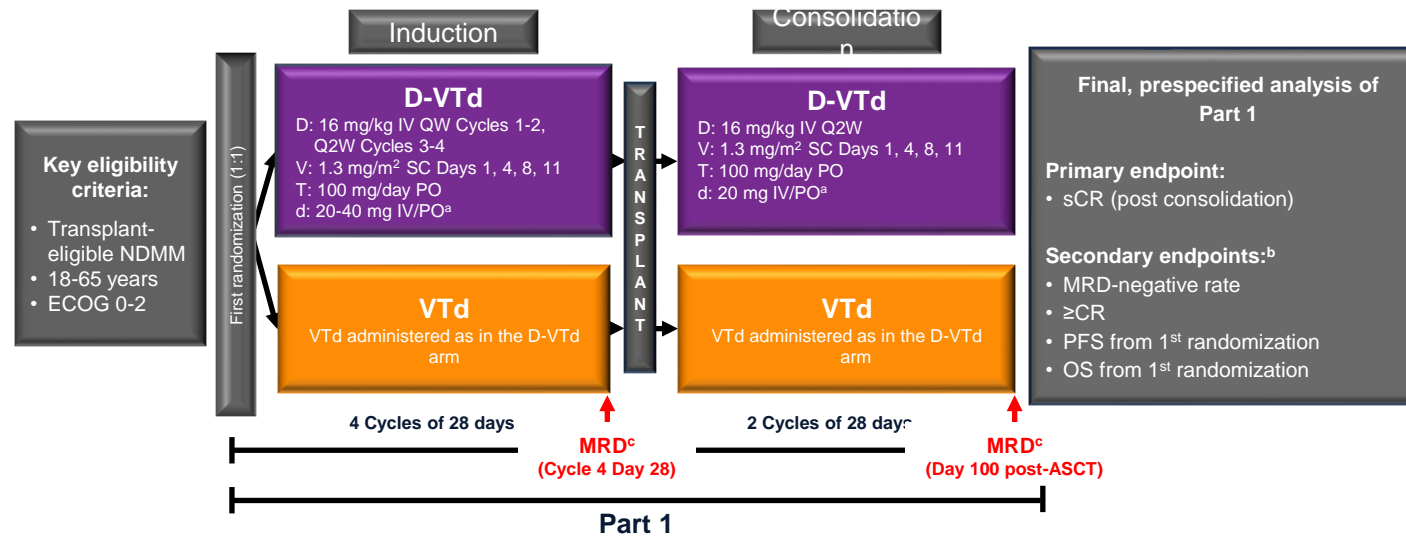
Carfilzomib-based Induction/Consolidation With or Without ASCT Followed by Lenalidomide or Carfilzomib-lenalidomide Maintenance for High-risk Patients



QUADRUPLETS in NDMM

CASSIOPEIA Study Design

- Phase 3 study of D-VT_d versus VT_d in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017

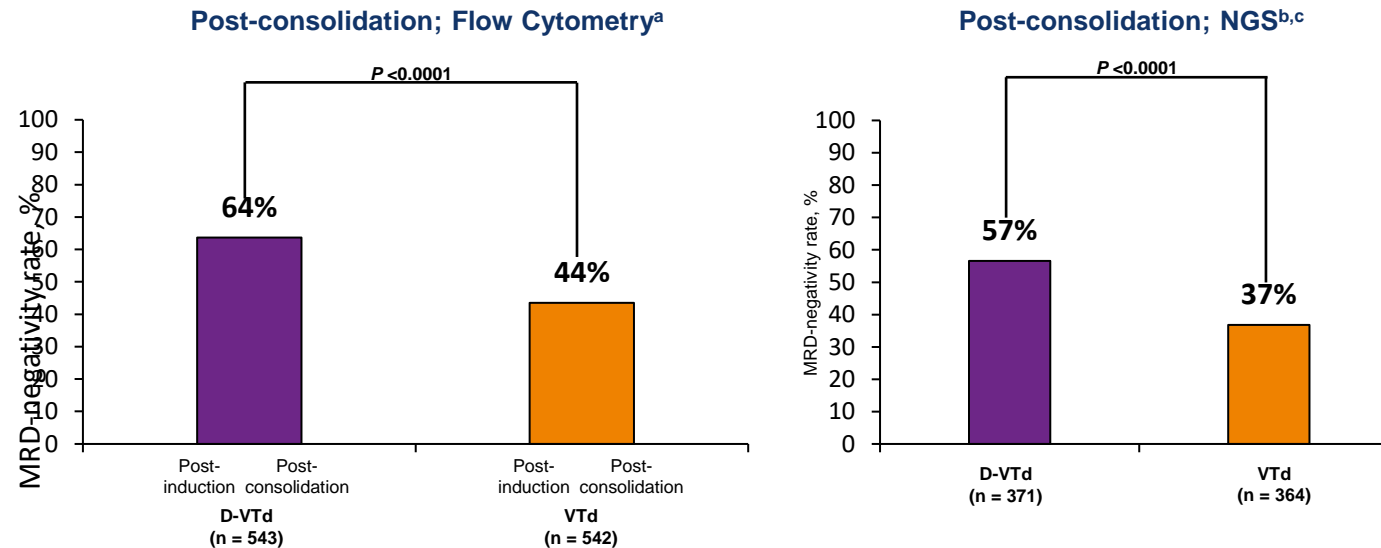


D-VT_d, daratumumab/bortezomib/thalidomide/dexamethasone; VT_d, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; sCR, stringent complete response; MRD, minimal residual disease; CR, complete response; PFS, progression-free survival; OS, overall survival.

^aDexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

^bSequentially tested in the order shown. ^cMRD analyses were performed for all patients, regardless of response.

MRD-Negativity Rates

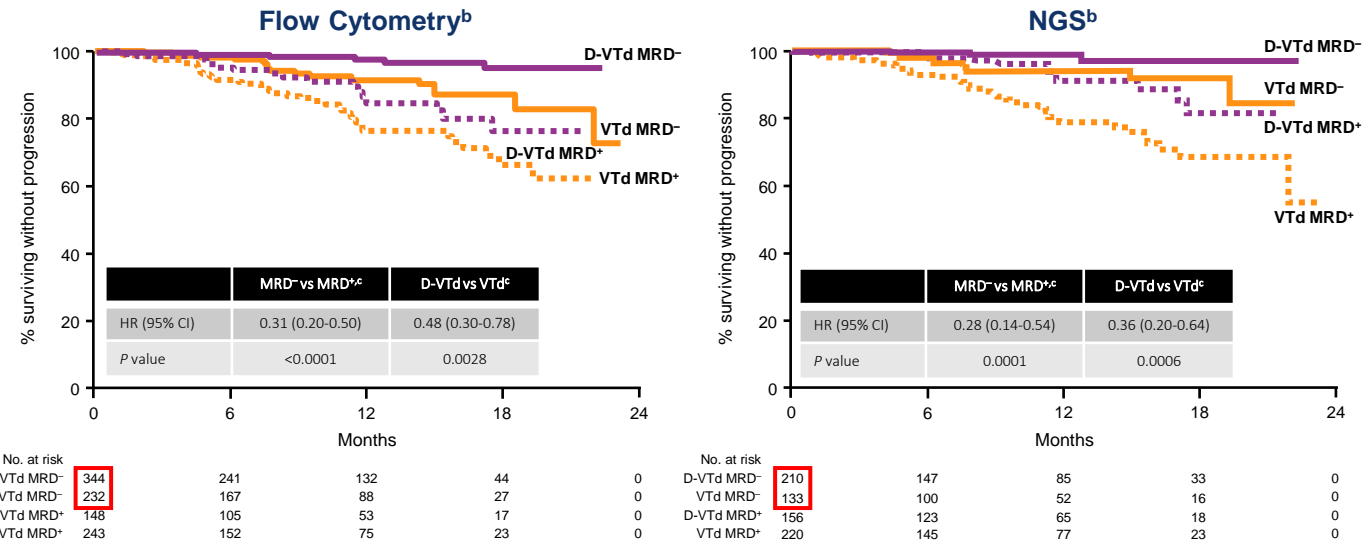


- Early (post-induction) significant difference in MRD-negativity rates for D-VTd versus VTd
- Post-consolidation MRD-negativity rates were significantly higher for D-VTd versus VTd, confirming post-induction MRD-negativity rates

^aITT population; 10⁻⁵ sensitivity threshold. ^bNGS-evaluable population; 10⁻⁵ sensitivity threshold.

^cPost-consolidation MRD-negative rates by NGS at the 10⁻⁶ sensitivity threshold (NGS-evaluable population): D-VTd, 39% versus VTd, 23%; *P* < 0.0001.

Post-consolidation PFS^a by MRD Status^b



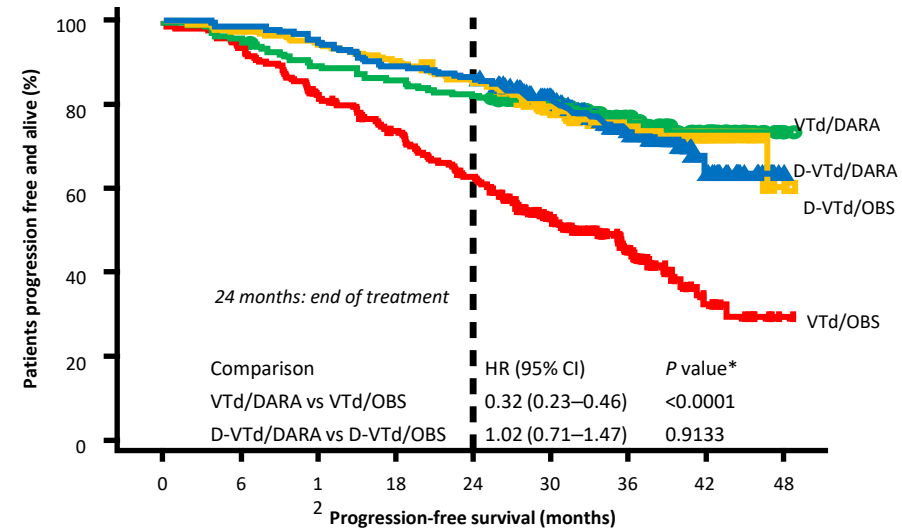
- PFS benefit in patients achieving MRD negativity
- D-VTd showed additional PFS benefit versus VTd

HR, hazard ratio.

^aLandmark analysis from post-ASCT Day 100 onward, regardless of second randomization. Patients who had a PFS event or were censored before 9 months (median time to Day 100) were excluded. ^b10⁻⁵ sensitivity threshold. ^cMultivariate analysis accounting for treatment arm and MRD negativity.

CASSIOPEIA: Daratumumab Maintenance Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

- A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy
- A PFS benefit was observed for VTd/DARA vs VTd/OBS
- PFS was not different for D-VTd/DARA vs D-VTd/OBS

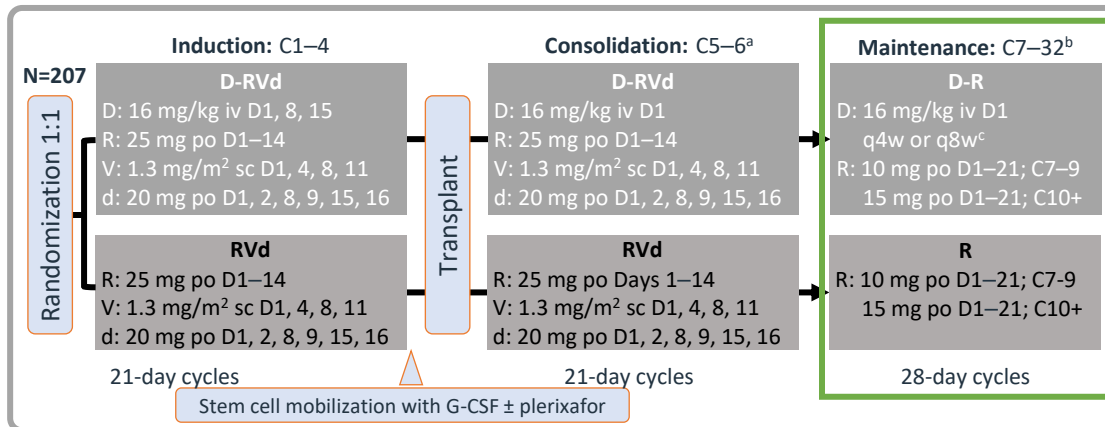


| Patients at risk | | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|------------------|------------|-----|-----|-----|-----|-----|-----|----|----|----|
| ■ | VTd/OBS | 215 | 201 | 176 | 155 | 131 | 83 | 43 | 15 | 1 |
| ■ | VTd/DARA | 213 | 203 | 189 | 182 | 174 | 138 | 79 | 34 | 1 |
| ■ | D-VTd/OBS | 229 | 223 | 216 | 207 | 195 | 144 | 75 | 38 | 2 |
| ■ | D-VTd/DARA | 229 | 226 | 217 | 204 | 198 | 145 | 76 | 30 | 0 |

GRIFFIN: Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Eligible NDMM – 24 Months of Maintenance

Study design

Key eligibility criteria: TE NDMM; 18–70 years; ECOG PS 0–2; CrCl \geq 30 mL/min²



- **Primary endpoint:** sCR by end of consolidation
- **Secondary endpoints:** MRD negativity (NGS 10⁻⁵), ORR, \geq VGPR, CR, PFS, OS

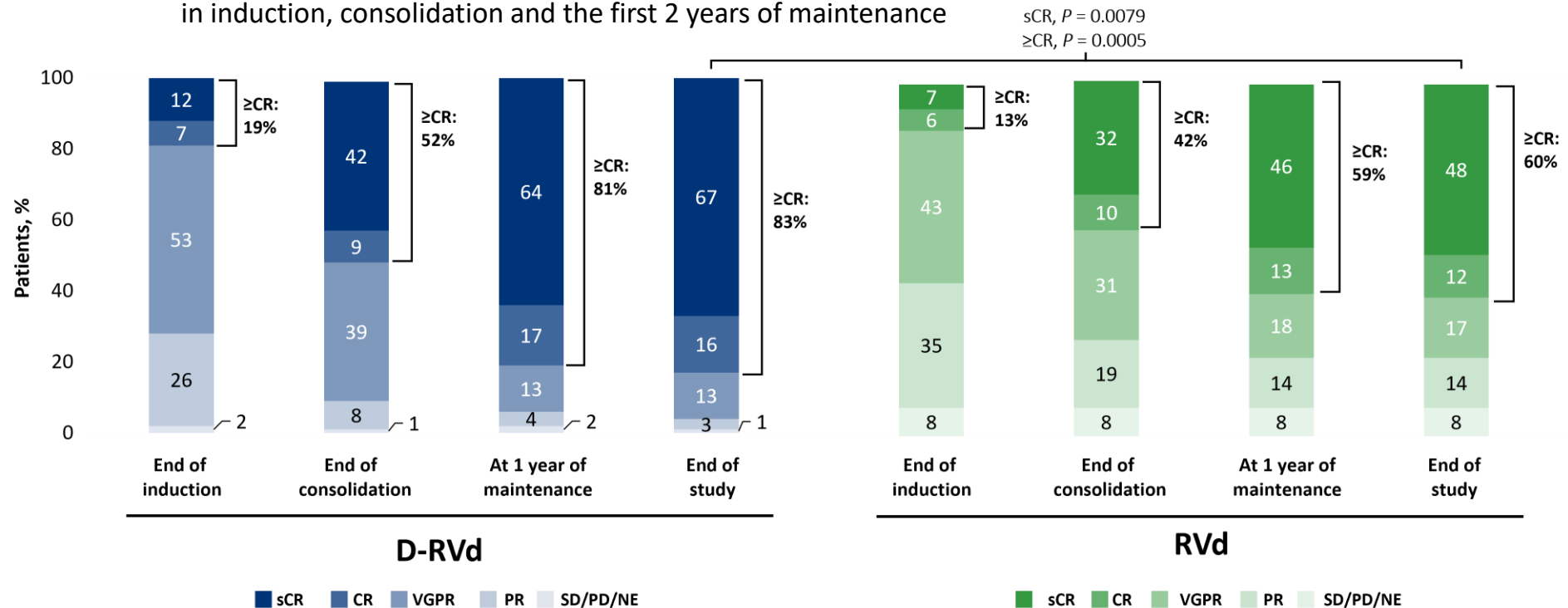
Patient disposition

| n (%) | D-RVd (n=104) | RVd (n=103) |
|---|---------------|-------------|
| Treated with maintenance therapy | 90 (87) | 70 (68) |
| Completed maintenance therapy | 67 (64) | 44 (43) |
| Discontinued treatment during maintenance therapy | 21 (20) | 21 (20) |
| Adverse event | 8 (8) | 7 (7) |
| Progressive disease | 3 (3) | 7 (7) |
| Patient withdrawal | 2 (2) | 4 (4) |
| Lost to follow-up | 2 (2) | 0 |
| Death | 1 (1) | 1 (1) |
| Other | 5 (5) | 2 (2) |

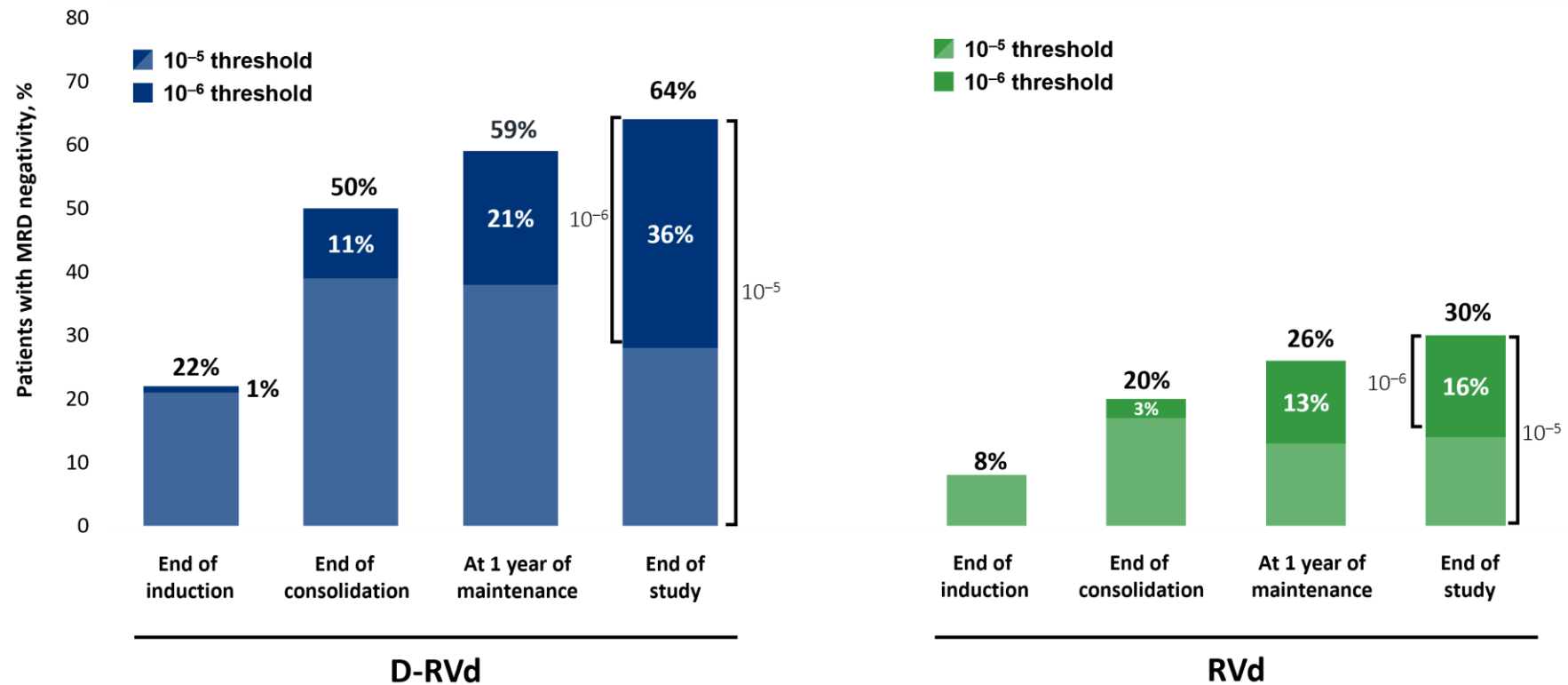
^aConsolidation initiated 60–100 days post transplant; ^bPatients who complete maintenance cycles 7–32 may continue single-agent lenalidomide thereafter; ^cProtocol amendment allowed q4w dosing option. Phase 2 trial – patient enrollment between December 2016 and April 2018

GRIFFIN: Randomized Phase II Study of Frontline Dara-RVd → ASCT → Len Maintenance ± Daratumumab

- 4 cycles of RVd induction → ASCT → 2 cycles of RVd consolidation → len maintenance ± daratumumab in induction, consolidation and the first 2 years of maintenance

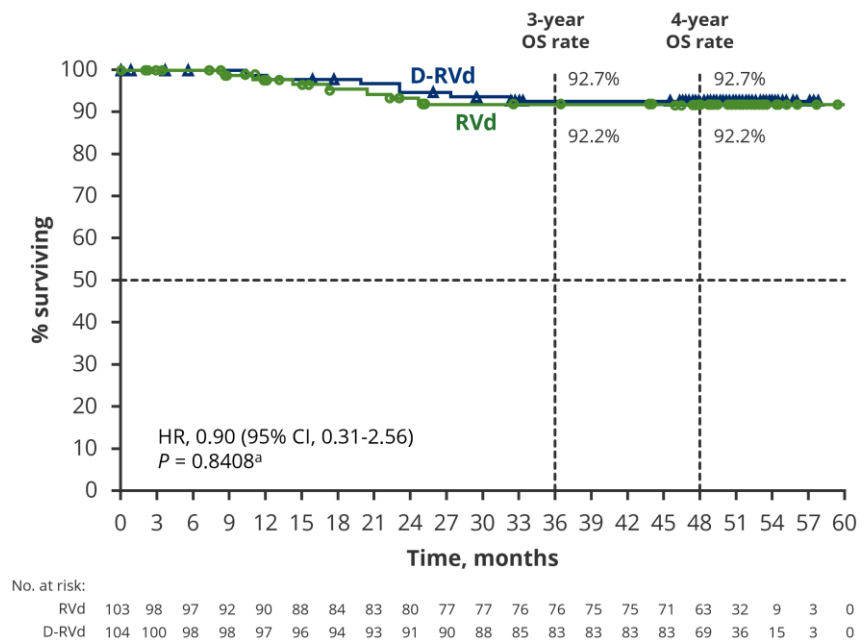
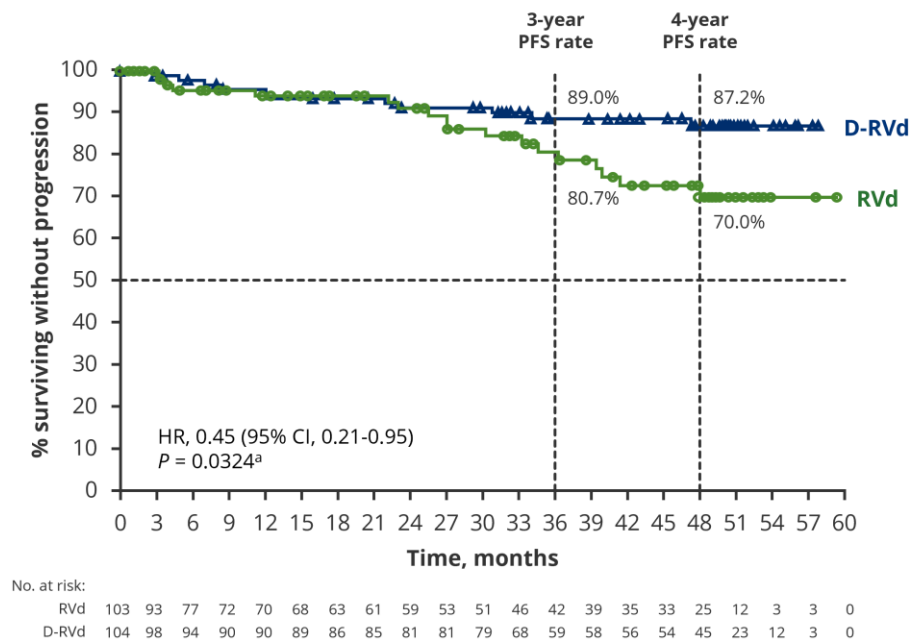


GRIFFIN: MRD



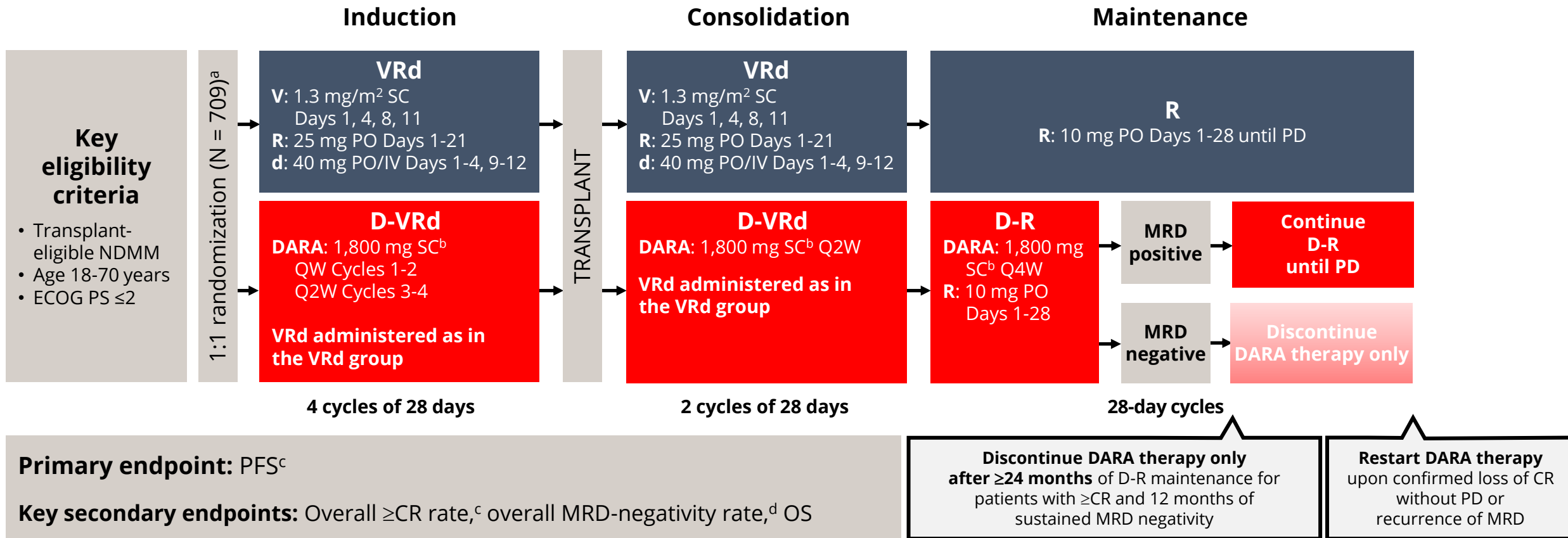
Sborov D, et al. IMS 2022.

GRIFFIN: Longitudinal Outcomes



Sborov D, et al. IMS 2022.

PERSEUS: Study Design

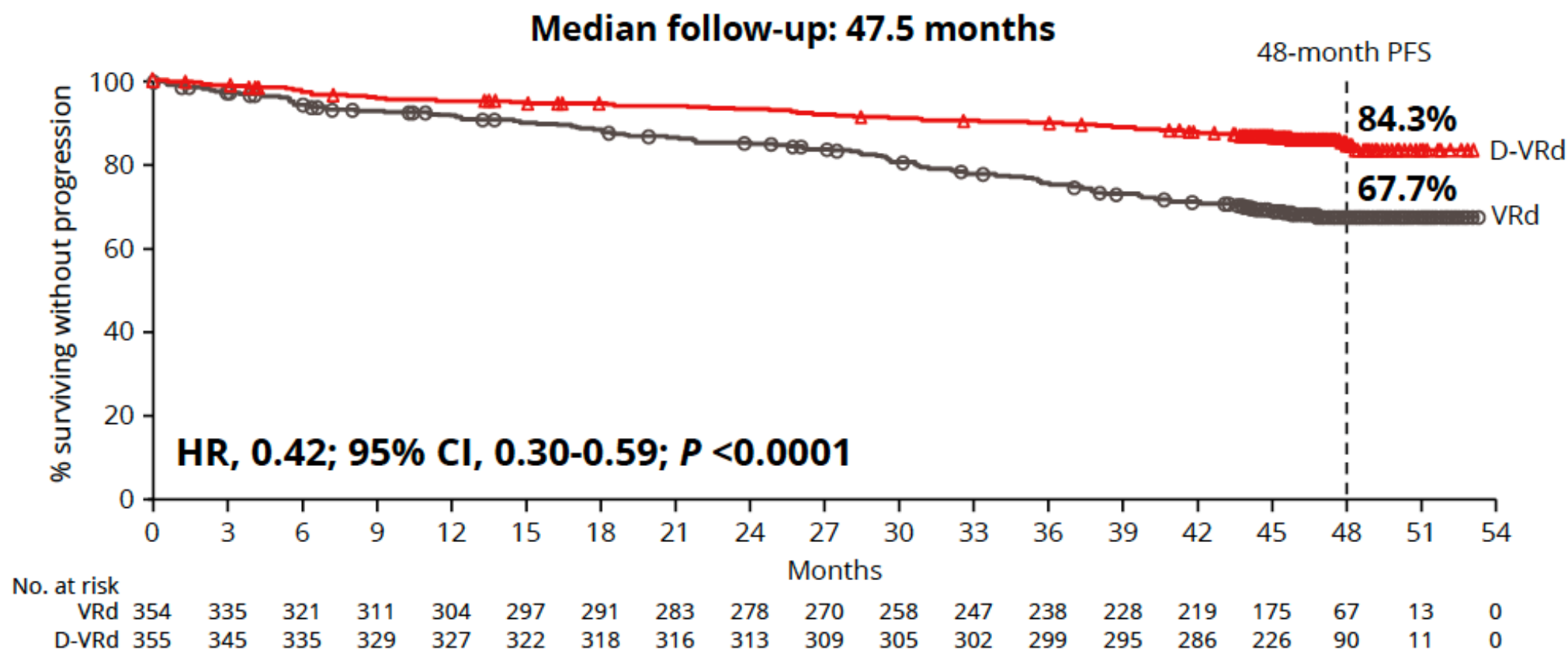


ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group;

VGPR, very good partial response. ^aStratified by ISS stage and cytogenetic risk. ^bDARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE[®] drug delivery technology, Halozyme, Inc., San Diego, CA, USA).

^cResponse and disease progression were assessed using a computerized algorithm based on IMWG response criteria. ^dMRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with \geq VGPR post-consolidation and at the time of suspected \geq CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and \geq CR at any time.

PERSEUS: Progression-free Survival

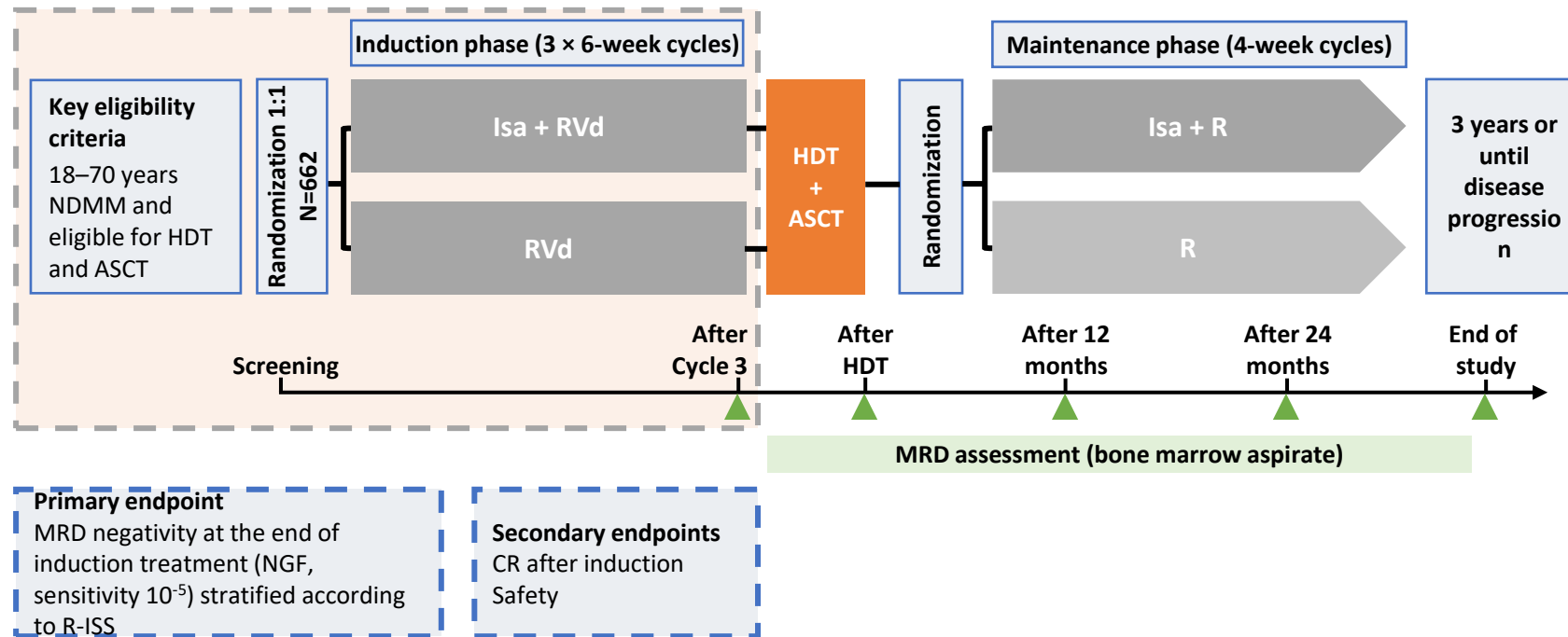


- 58% reduction in the risk of progression or death in patients receiving D-VRd



GMMG-HD7: Phase 3 Trial of Isatuximab Plus Lenalidomide, Bortezomib and Dexamethasone as Induction Therapy for Transplant-Eligible NDMM Patients

Study design



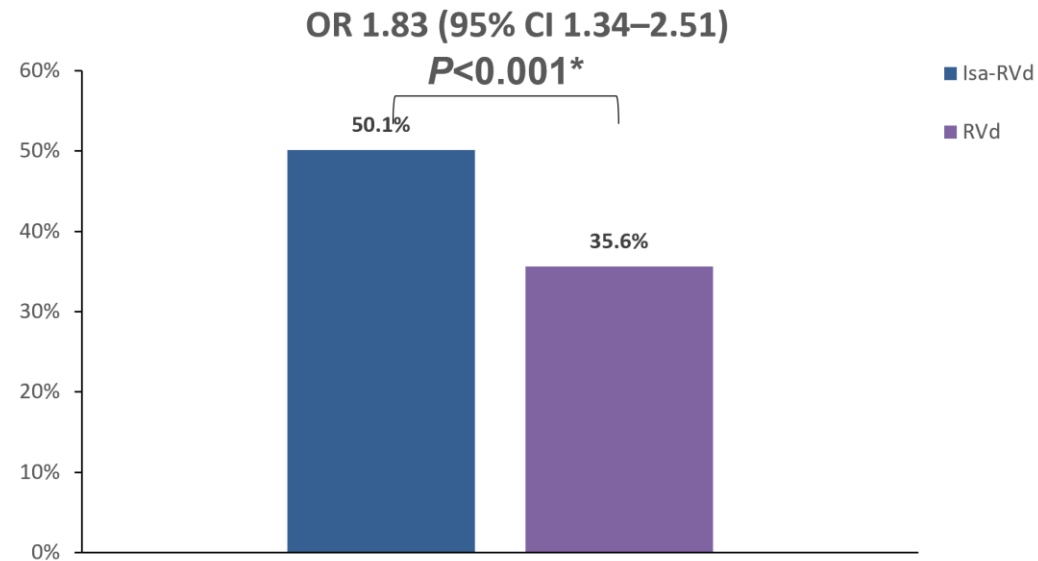
Data cutoff, April 2021; HDT, high-dose therapy; NGF, next-generation flow

Goldschmidt H, et al. ASH 2021, Virtual Meeting. Abstract 463

GMMG-HD7: MRD after Induction

- Randomization #1: RVD ± Isatuximab x 6 cycles → ASCT. Primary Endpoint: MRD negativity.
- Randomization #2: Lenalidomide maintenance ± Isatuximab. Primary Endpoint: PFS.

Patients with MRD negativity at the end of induction therapy

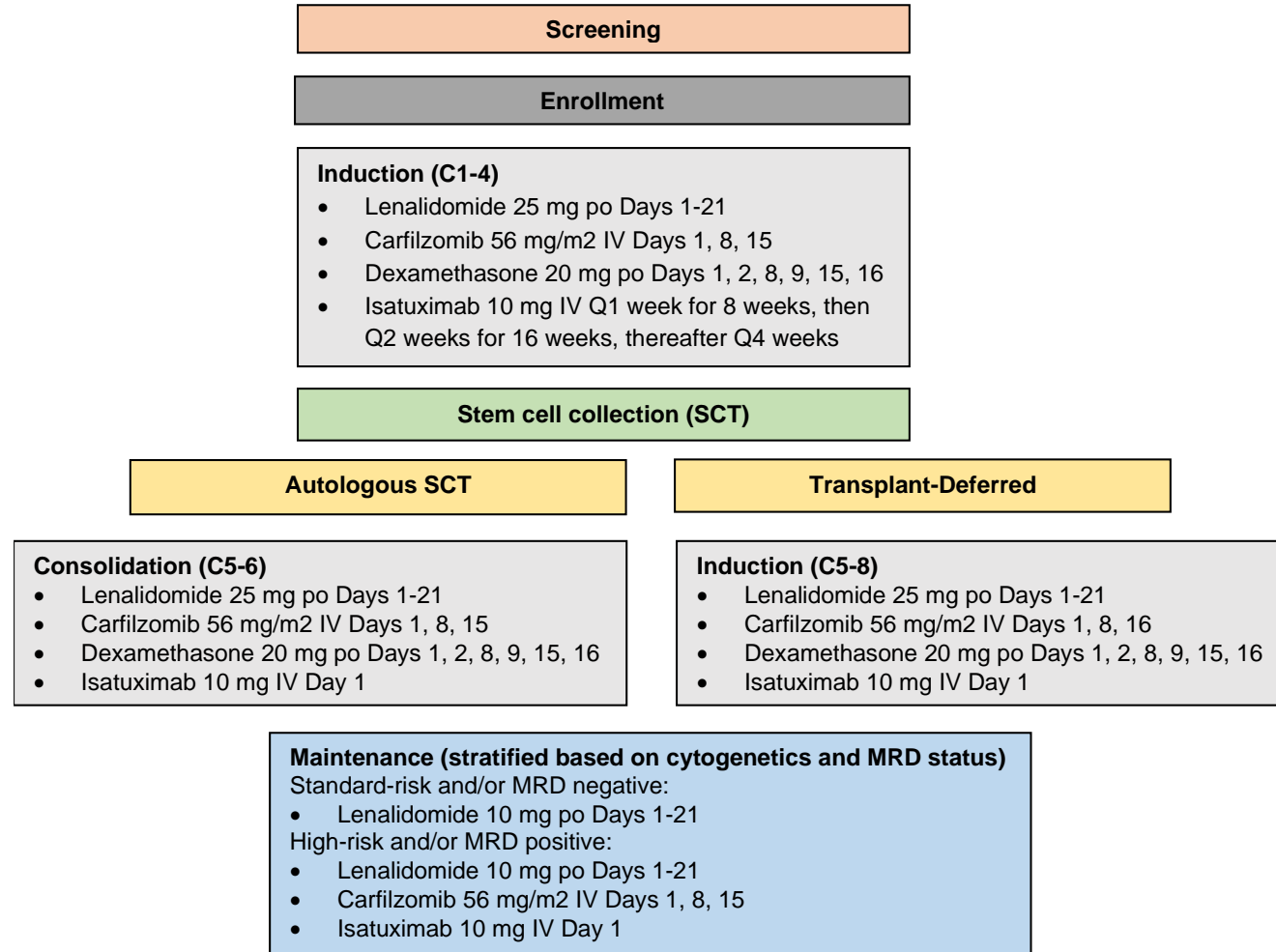


Low number of not assessable/missing[†] MRD status: Isa-RVd (10.6%) and RVd (15.2%)

Goldschmidt, H, et al. ASH 2021.

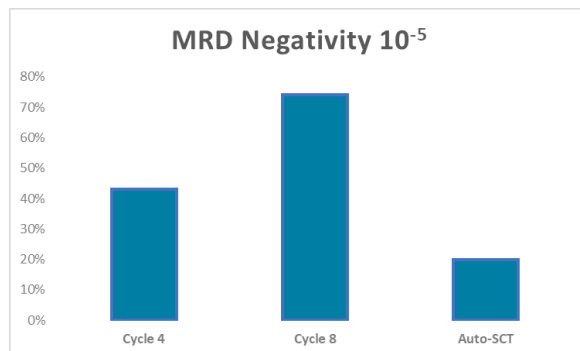
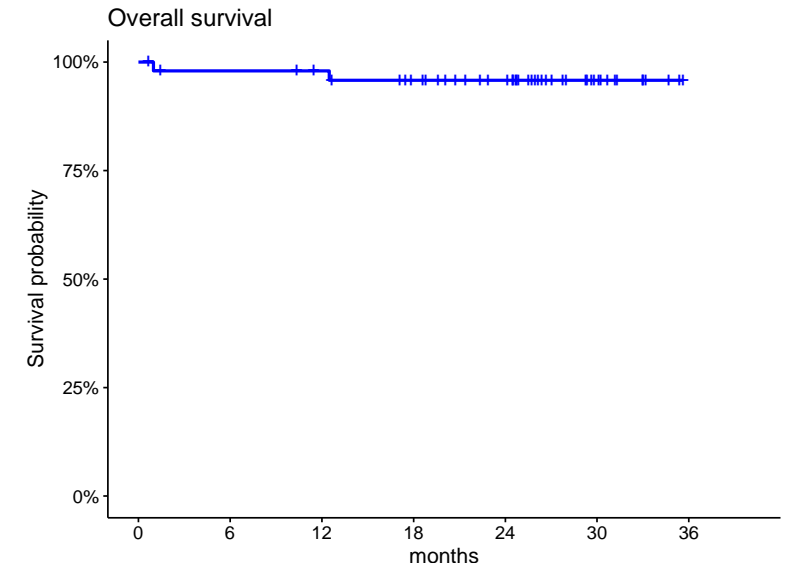
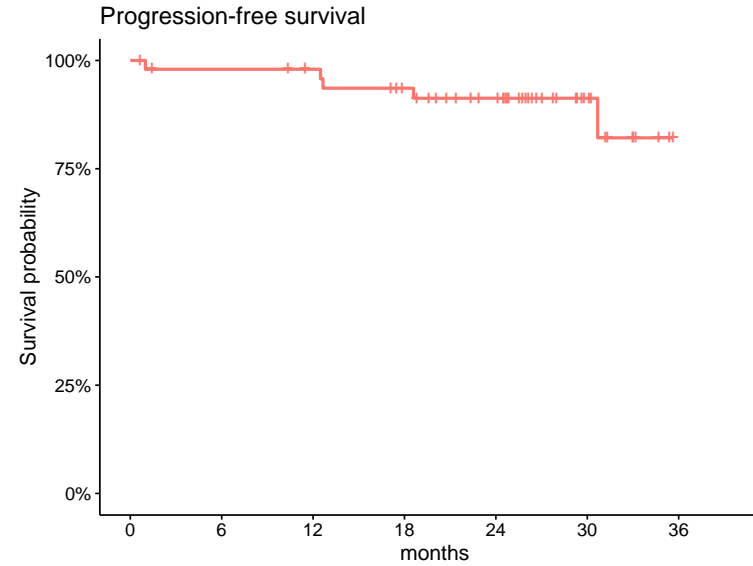
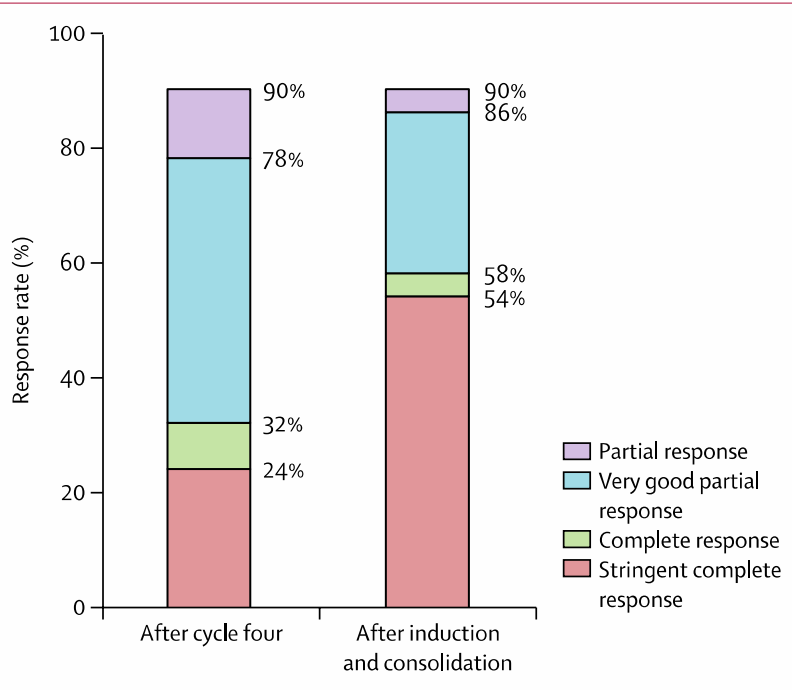
The SKylaRk Trial:

Isatuximab, Once Weekly Carfilzomib, Lenalidomide, and Dexamethasone in TE NDMM

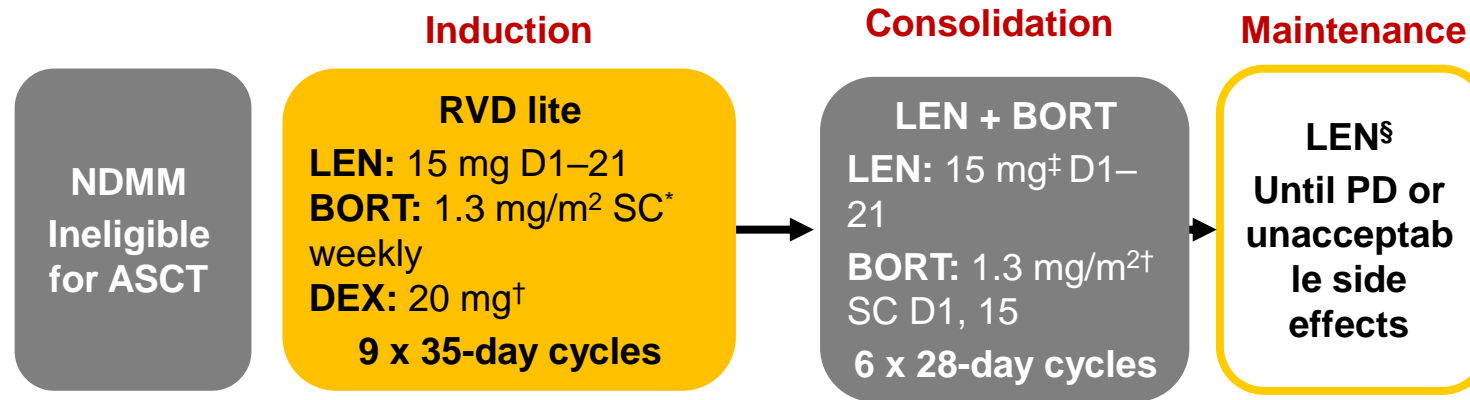


The SKylaRk Trial: Isatuximab, Once Weekly Carfilzomib, Lenalidomide, and Dexamethasone in TE NDMM

Response to Therapy



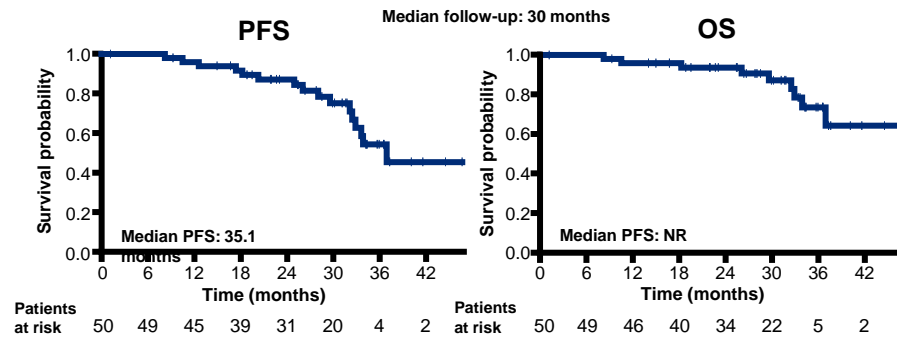
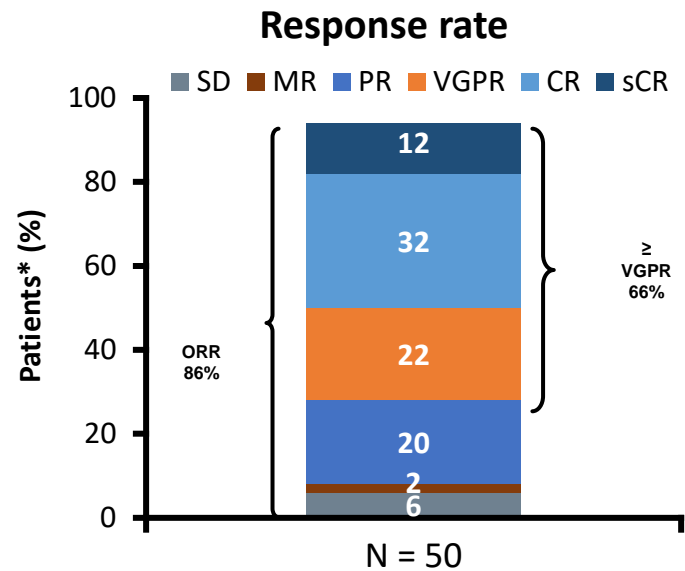
Modified RVD (RVD lite) in transplant-ineligible MM



Patient population: NDMM \geq 65 years and/or ineligible for ASCT

| Baseline characteristics, % | N = 50 |
|-------------------------------|------------|
| Median age, years (range) | 73 (65–91) |
| ISS stage at diagnosis | |
| I | 38 |
| II | 34 |
| III | 28 |
| ECOG PS | |
| 0 | 50 |
| 1 | 36 |
| 2 | 14 |

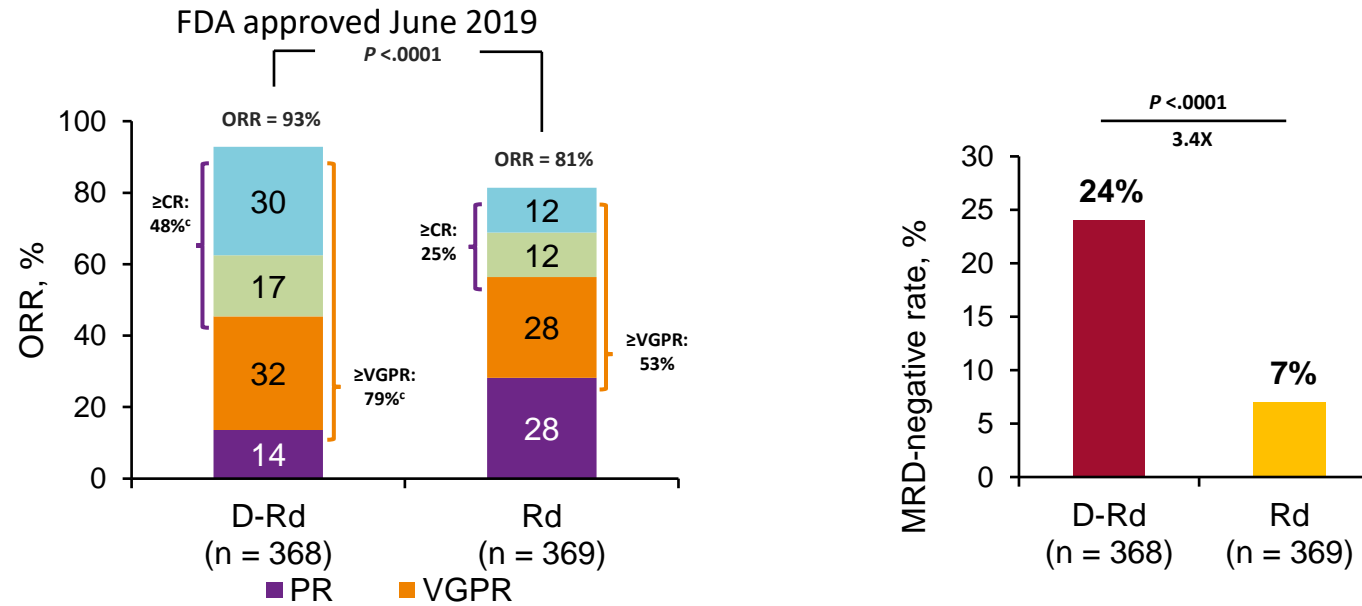
* The first 10 patients received BORT IV for Cycle 1 only followed by SC administration. Subsequent patients received bortezomib SC; † D1, 2, 8, 9, 15, 16, 22, 23 for patients \leq 75 years; D1, 8, 15, 22 for patients $>$ 75 years; ‡ Or last tolerated dose as of Cycle 9; § Optional. ASCT, autologous stem cell transplant; BORT, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; IV, intravenous; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PS, performance status; RVD, lenalidomide + bortezomib + dexamethasone; SC, subcutaneous.



- ≥ CR was 44% (ITT population, N = 50)
- ORR was 86%, ≥ VGPR was 66% for patients evaluable for response* after 4 cycles (n = 46)
- Median TTR was 1.1 months

* Six percent of patients received < 4 cycles of therapy and were therefore not evaluable. CR, complete response; ITT, intention to treat; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RVD, lenalidomide + bortezomib + dexamethasone; sCR stringent complete response; SD, stable disease; TTR, time to response; VGPR, very good partial response.

Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) vs Rd in Newly Diagnosed Multiple Myeloma Ineligible for Transplant (MAIA)



Significantly higher ORR, ≥CR rate, ≥VGPR rate, and >3-fold higher MRD-negative rate with D-Rd

Lower risk of progression or death with MRD negativity

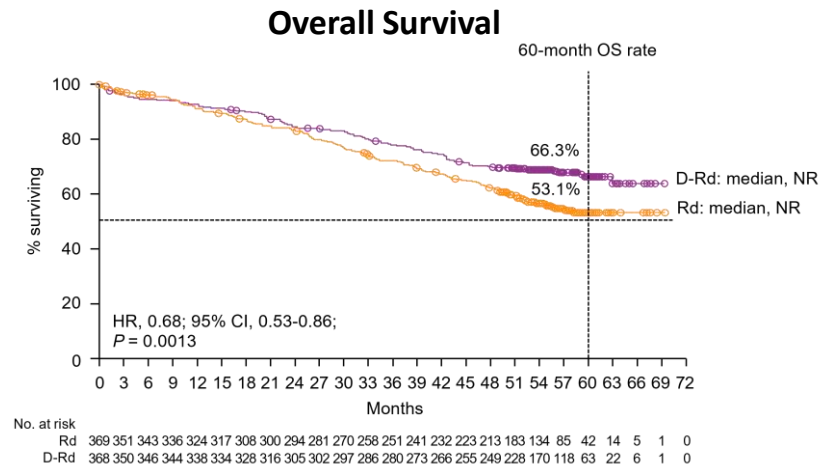
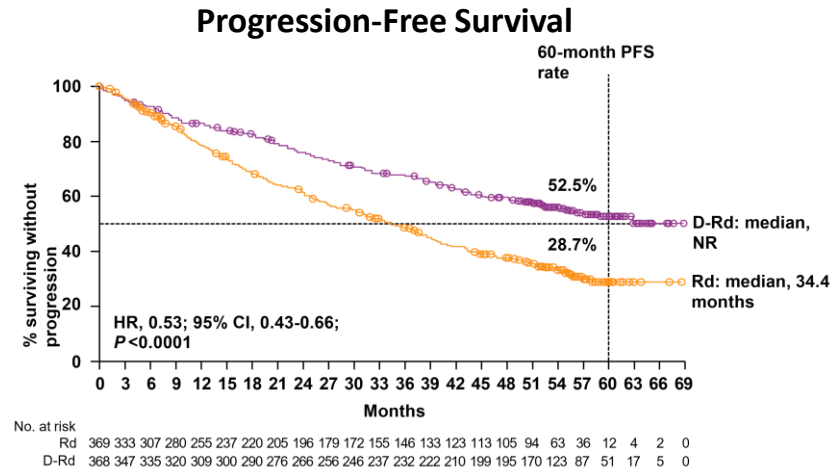
MAIA: Updated Efficacy Results

- Phase III Study of Lenalidomide and Dex ± Daratumumab
- Median Duration of Follow-Up: 56.2 mos

| Response | DRd | Rd |
|--------------------|-------|-------|
| ORR | 92.9% | 81.3% |
| PR | 13.6% | 28.2% |
| VGPR | 31.8% | 28.2% |
| CR | 17.1% | 12.5% |
| sCR | 30.4% | 12.5% |
| ≥VGPR | 79.3% | 53.1% |
| MRD- (10^{-5}) | 31% | 10% |

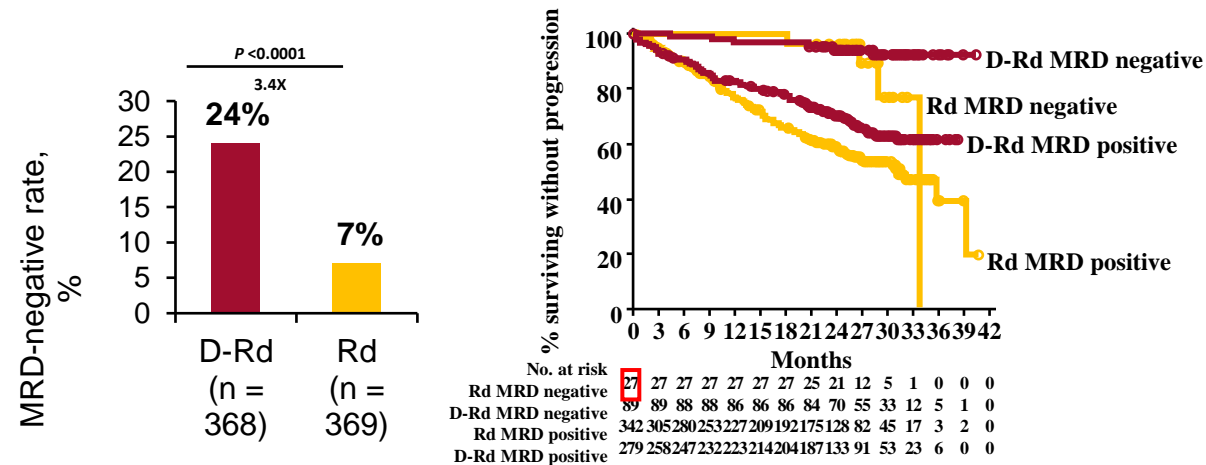
Facon, T, et al. Lancet Oncol 2021;22:1582-96.

Facon, T, et al. NEJM 2019;380:2104-15.



Transplant-ineligible Newly-diagnosed Myeloma MAIA Study Design

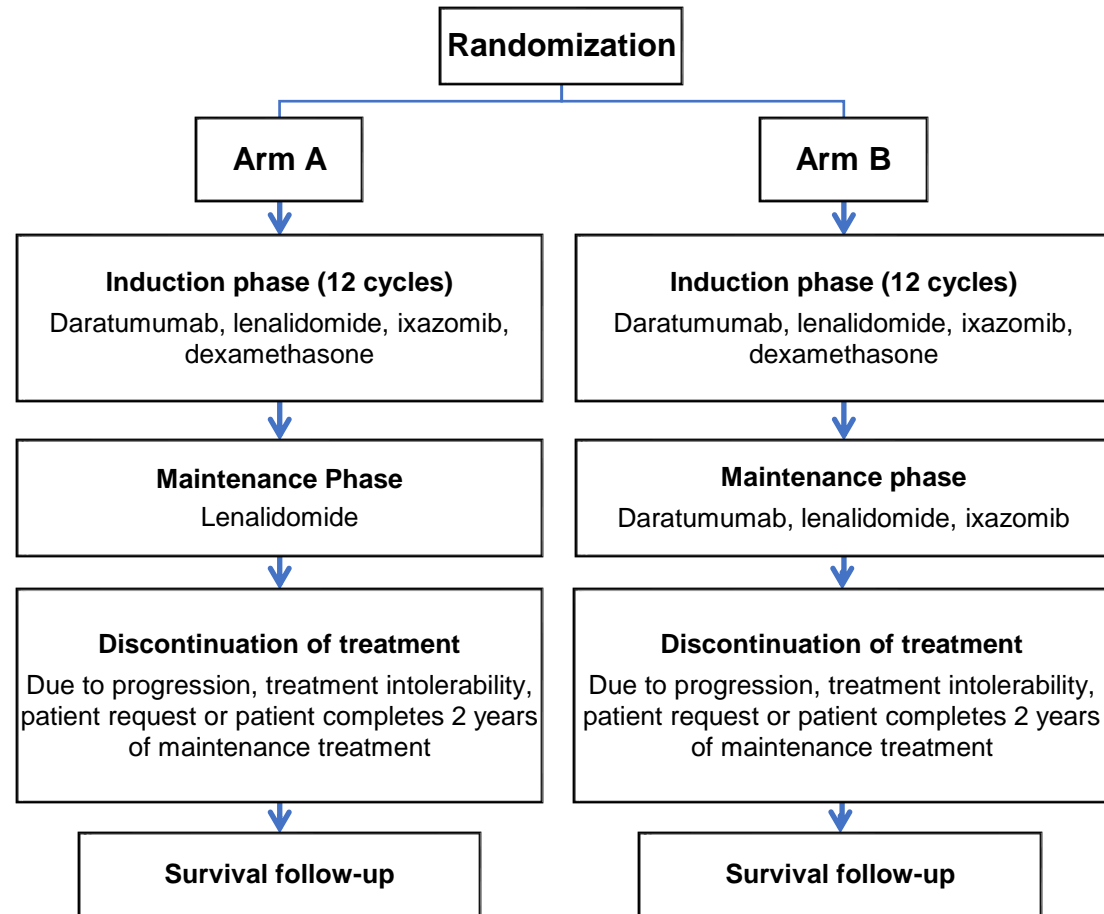
Efficacy: ORR^a and MRD^b (NGS; 10⁻⁵ Sensitivity Threshold)



Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd

PR, partial response; sCR, stringent complete response.
^aITT population. ^bAssessed at time of suspected CR/sCR, and if confirmed, at 12, 18, 24, and 30 months after first dose. ^c*P* < 0.0001;
P values were calculated using the Cochran-Mantel-Haenszel chi-square test.

Dara-IRd in Transplant ineligible patients

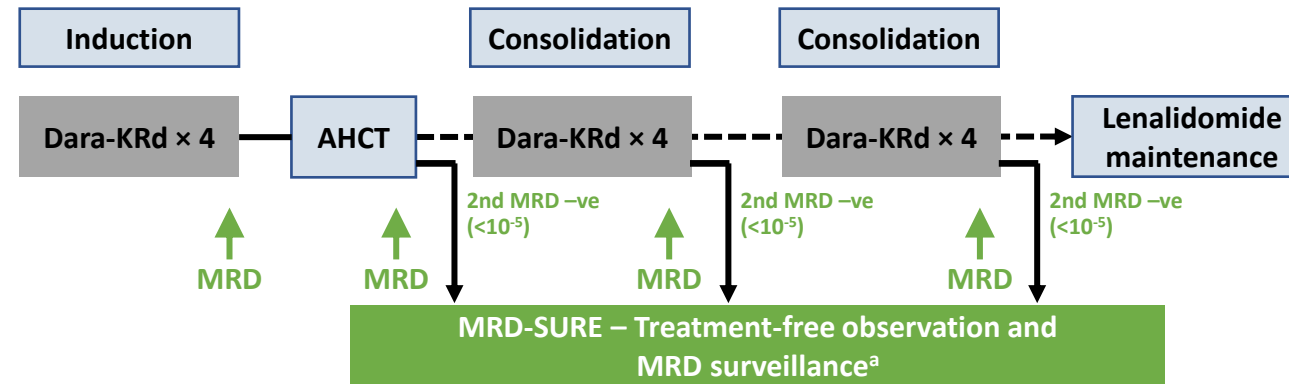


Can we use MRD to tailor therapy?

- No data to support stopping therapy for those who are MRD negative or giving additional treatments to those who are MRD positive
- Prospective trials specifically designed to ask:
 - How long do we continue treatment?
 - Do we change treatment?
 - Do we add agents?
 - Do we stop treatment?

MASTER: Daratumumab, Carfilzomib, Lenalidomide and Dex, Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation – Final Primary Endpoint Analysis

Study design



Dara-KRd

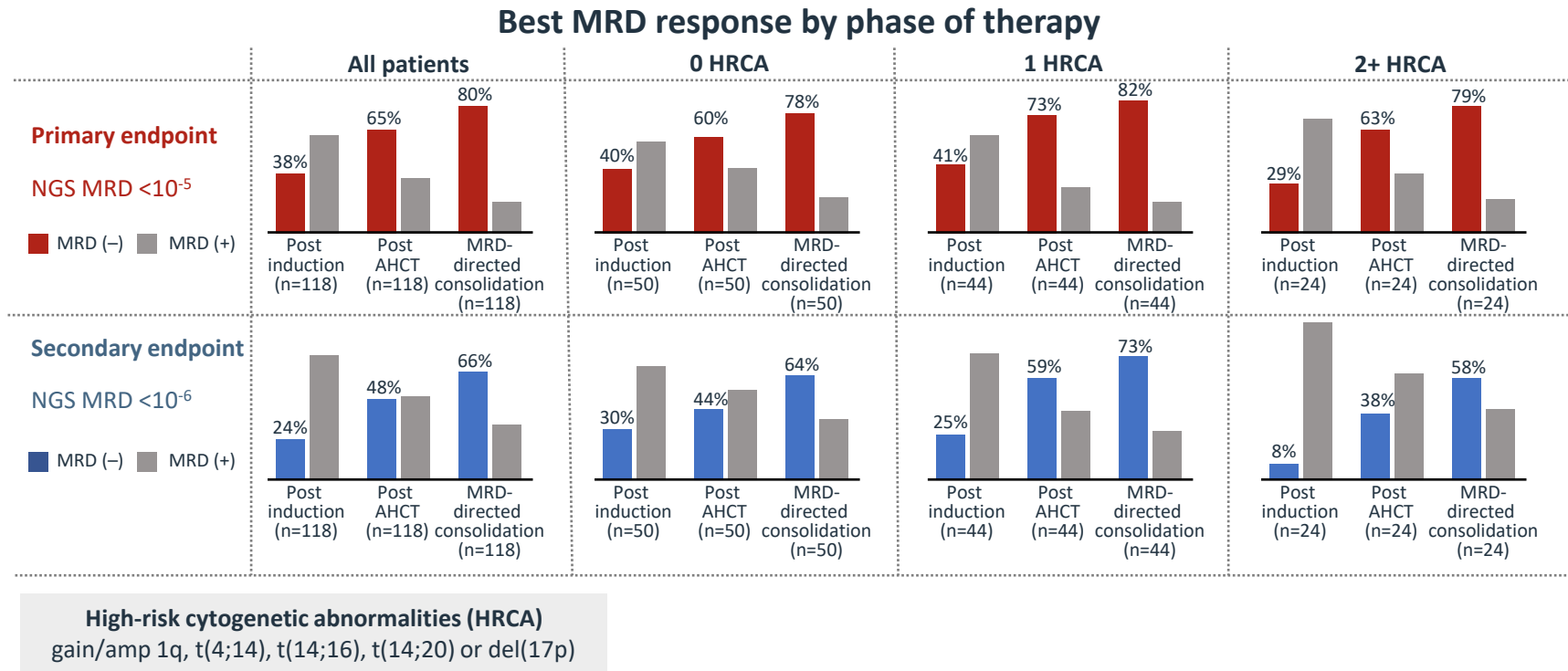
- Dara 16 mg/m² Days 1, 8, 15, 22 (Days 1, 15: C 3–6; Day 1: C >6)
- Carfilzomib (20) 56 mg/m² Days 1, 8, 15
- Lenalidomide 25 mg Days 1–21
- Dex 40 mg PO Days 1, 8, 15, 22

AHCT, allogeneic hematopoietic stem cell. MRD assessment by NGS

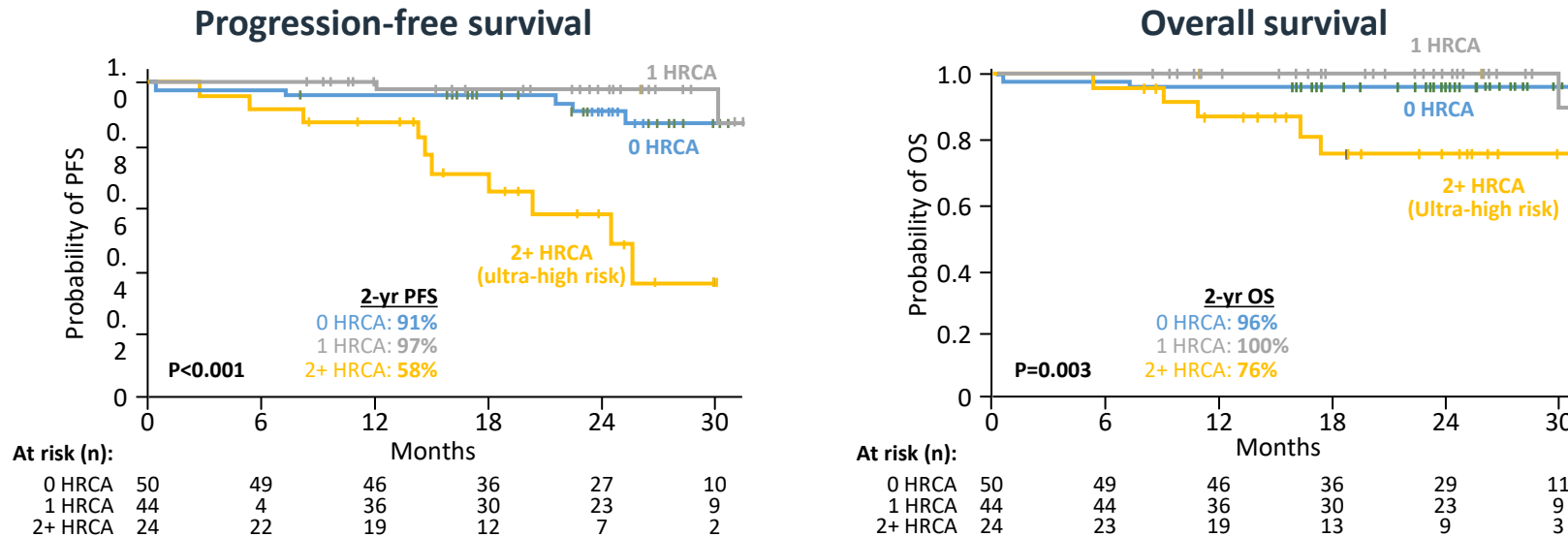
^a24 and 72 weeks after completion of therapy

Costa L, et al. ASH 2021, Virtual Meeting. Abstract 481

MASTER: Daratumumab, Carfilzomib, Lenalidomide and Dex, Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation – Final Primary Endpoint Analysis



MASTER: Daratumumab, Carfilzomib, Lenalidomide and Dex, Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation – Final Primary Endpoint Analysis



High-risk cytogenetic abnormalities (HRCA)
 gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Results and Conclusions

- Triplets and Quads are standard
- Deep and durable responses achieved
- Transplant remains an important treatment in NDMM
- High risk disease remains unmet medical need

Future for MM

- Novel agents early on
- Concept of fixed duration using MRD
- The power of immune strategies remains to be harnessed: sequencing CARs/Bites/ Dual targeting strategies in the upfront setting

Trials of Interest

- **Transplant Eligible**

- GMMG-HD7: Phase III Study
 - Randomization #1: RVd ± Isatuximab x 6 cycles + ASCT. Primary Endpoint: MRD negativity.
 - Randomization #2: Lenalidomide maintenance ± Isatuximab. Primary Endpoint: PFS.

- **Transplant Ineligible**

- CEPHEUS: Phase III study of VRd induction → Rd maintenance ± daratumumab
- IMROZ: Phase III study of VRd induction → Rd maintenance ± isatuximab
- SWOG S2209: Phase III study of VRd induction x 9 cycles → R maintenance vs DRd induction x 9 cycles → R maintenance vs DRd x 9 cycles → DR continuation therapy.

Acknowledgements



Our Patients

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@NoopurRajeMD





Thank you!

Noopur Raje

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