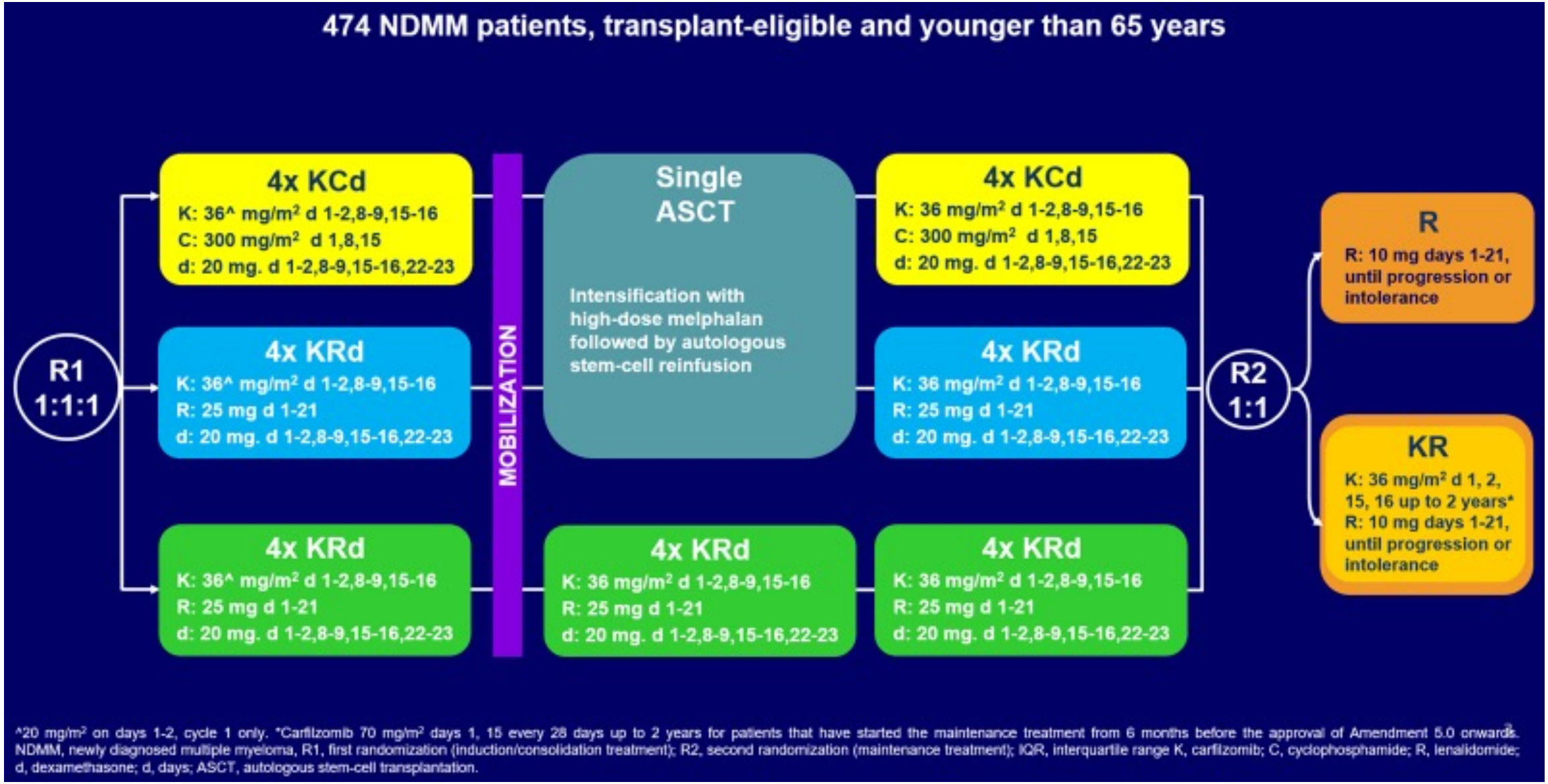
Contemporary Treatment Planning for Patients with Newly Diagnosed Multiple Myeloma (MM)

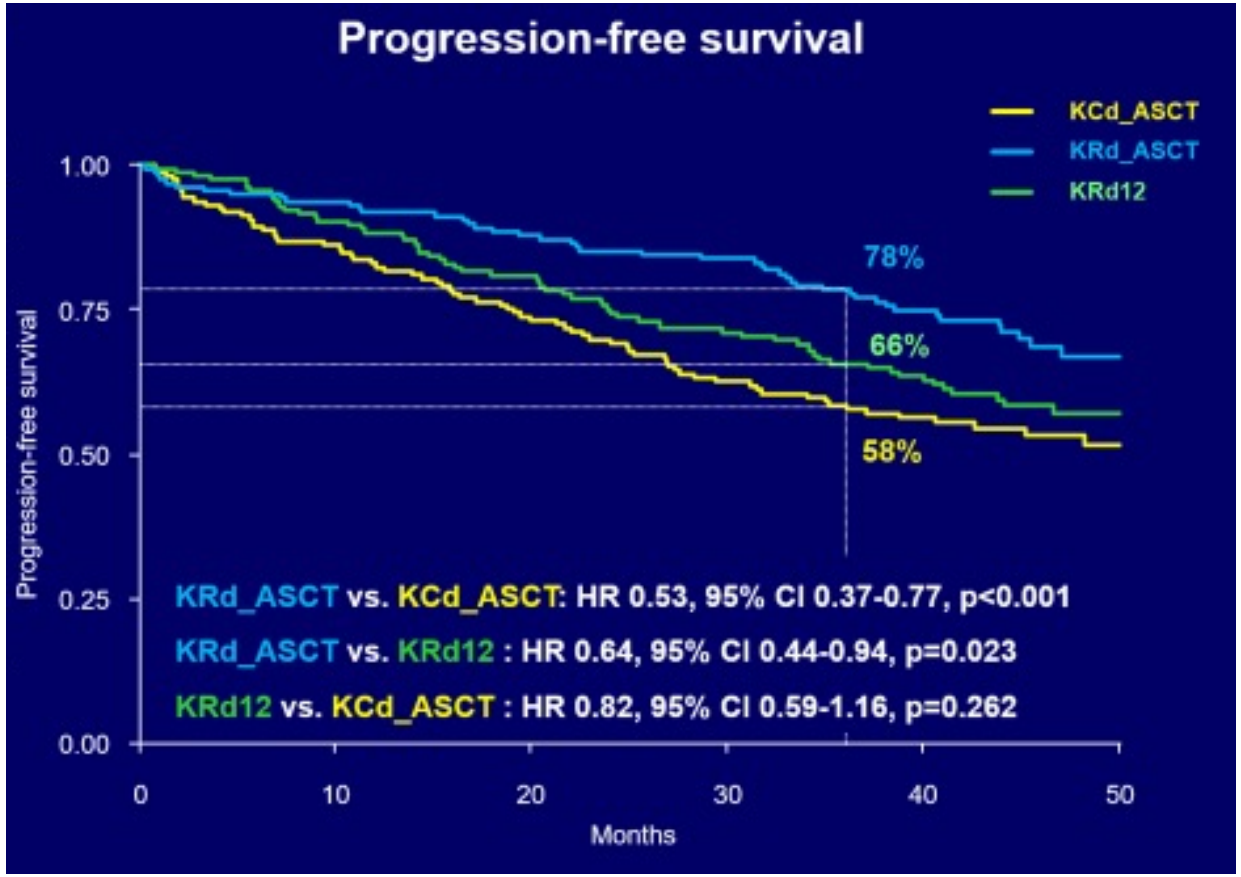
Morie A Gertz, MD, MACP

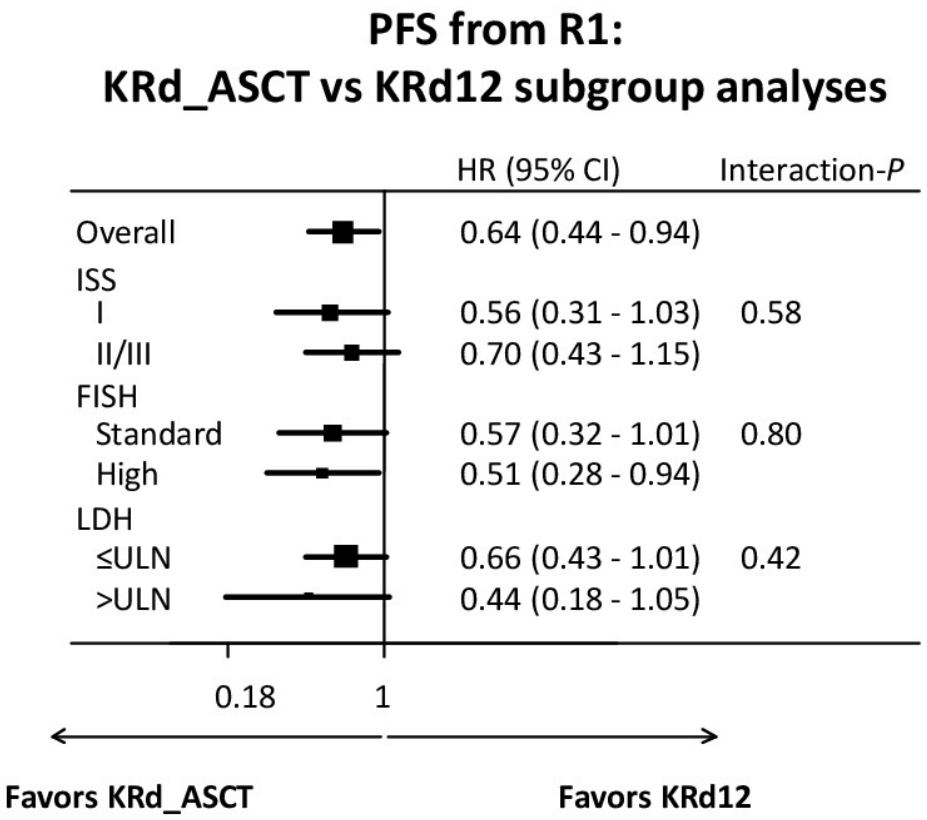
FORTE: KRd-ASCT-KRd vs KRd vs KCd-ASCT-KCd



^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards. NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

FORTE: Results from first randomization



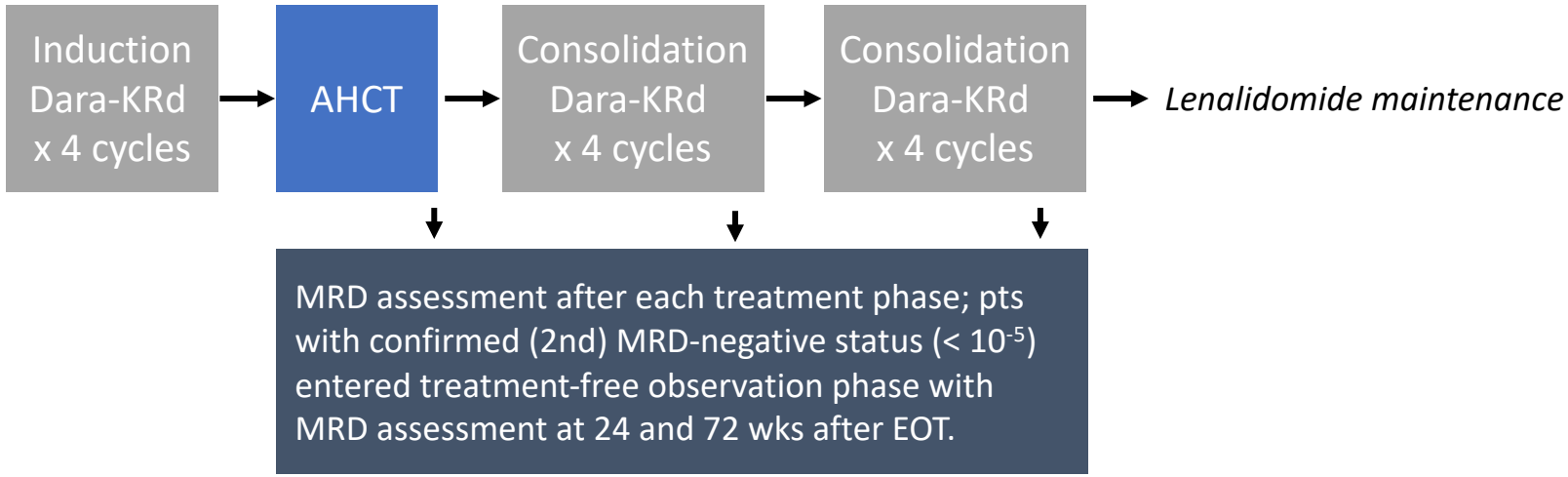


Gay F, et al. ASH 2020. Abstract 141.

MASTER: Study Design

- Multicenter, single-arm phase II trial

Untreated* patients with NDMM and measurable disease, ECOG PS 0-2, CrCl ≥ 40 mL/min, without significant cardiopulmonary disease or current/prior malignancy (N = 81)†



Dara-KRd dosing: daratumumab 16 mg/m^2 on Days 1,8,15,22 (Days 1,15 of Cycles 3-6; Day 1 Cycle > 6); carfilzomib 56 mg/m^2 Days 1,8,15; lenalidomide 25 mg Days 1-21; dexamethasone 40 mg PO Days 1,8,15,22. *1 VCD cycle permitted. †Planned recruitment N = 123.

Primary endpoint: MRD-negative remission (< 10^{-5}) on NGS assay in pts receiving induction, AHCT, and response-adapted consolidation

Secondary endpoints: safety, imaging frequency plus remission, MRD status post-AHCT, IMWG response, loss of MRD negativity in pts with no maintenance therapy

Exploratory endpoint: MRD-negative rates on NGS assay (threshold < 10^{-6})

Costa. ASH 2019. Abstr 860.

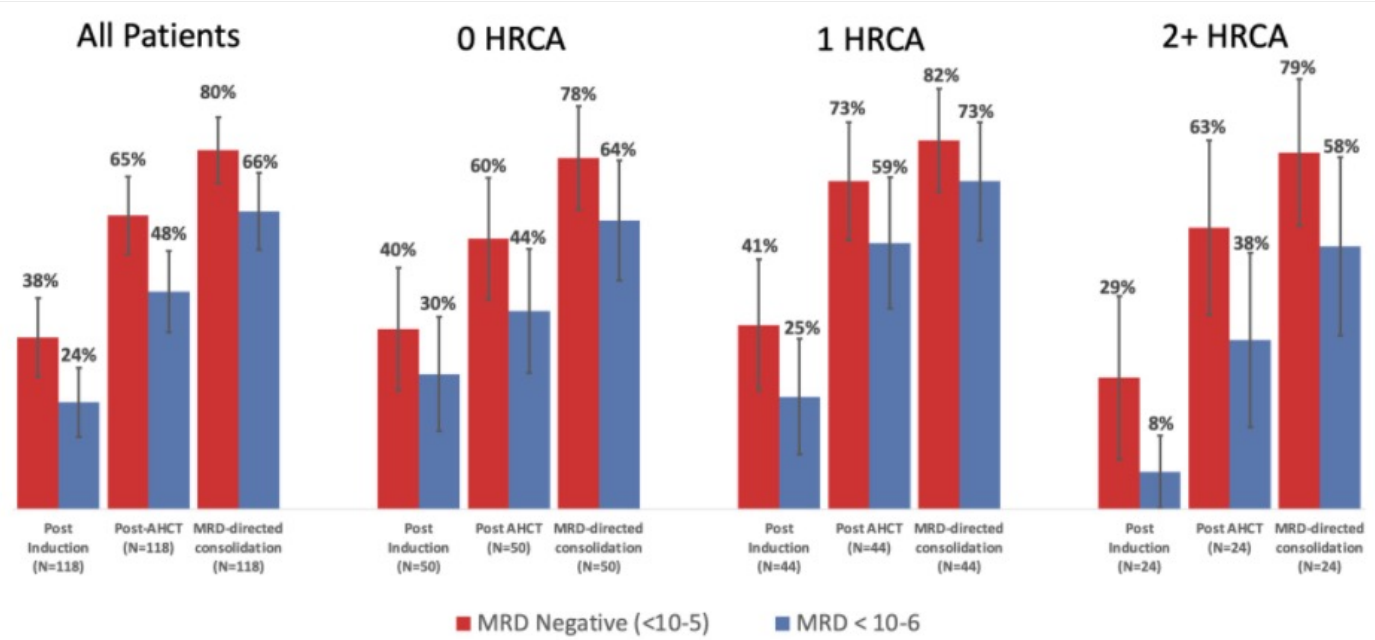


Figure 1 - Achievement of MRD negativity by intent-to-treat according to phase of therapy and number of high-risk cytogenetic abnormalities

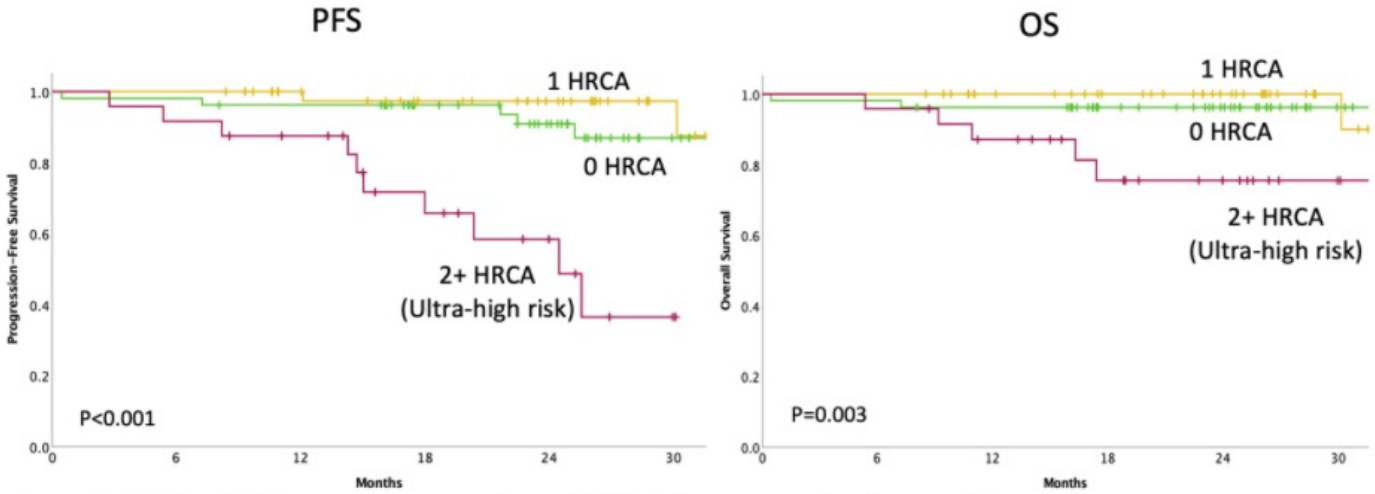
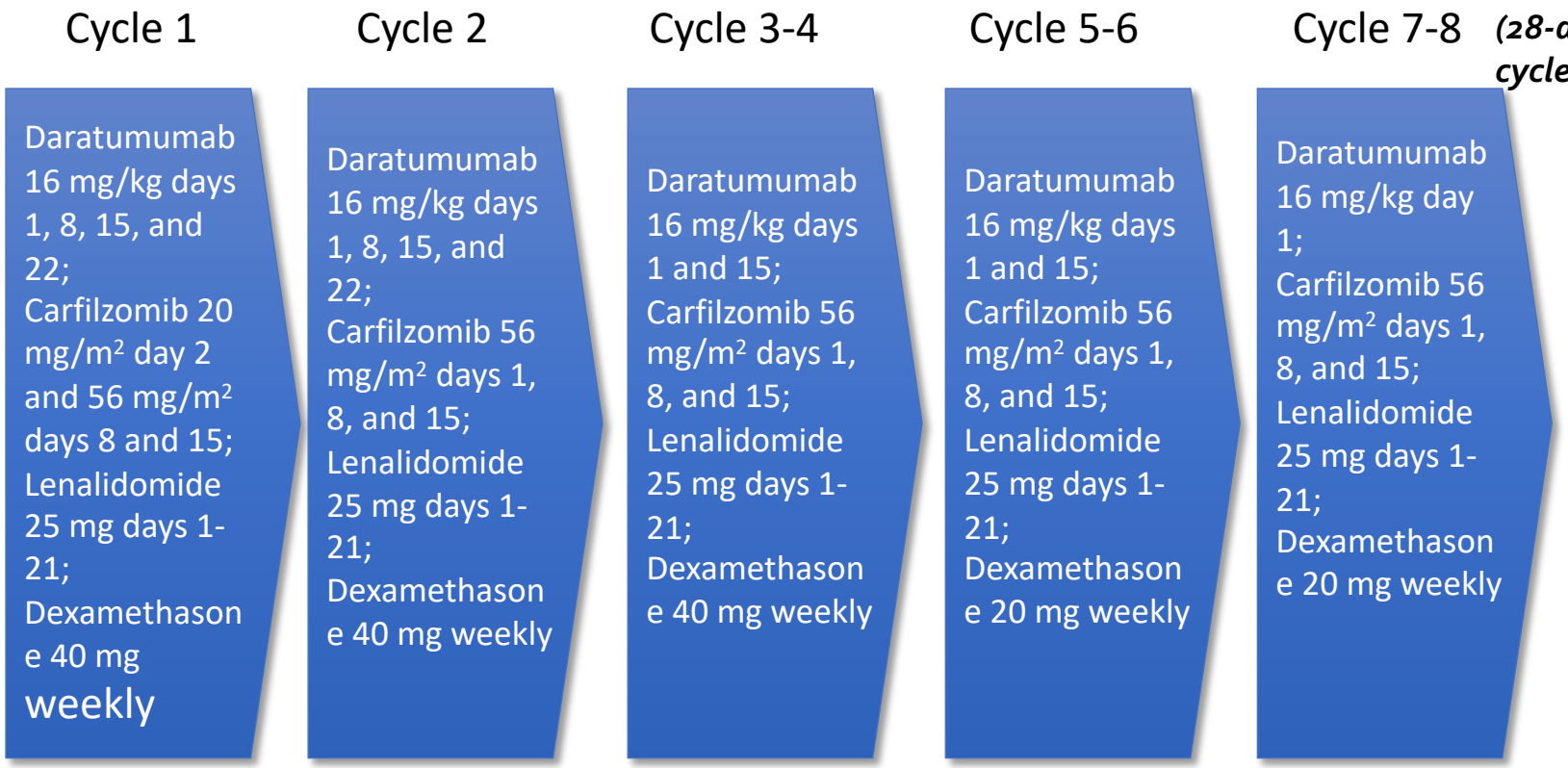


Figure 2 - PFS and OS according to number of high-risk cytogenetic abnormalities

HRCA = High-risk cytogenetic abnormalities [gain1q, t(4;14), t(14;16), t(14;20), del(17p)]

481 Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation. Final Primary Endpoint Analysis of the Master Trial

Weekly KRd-daratumumab (all pts received 8 cycles)

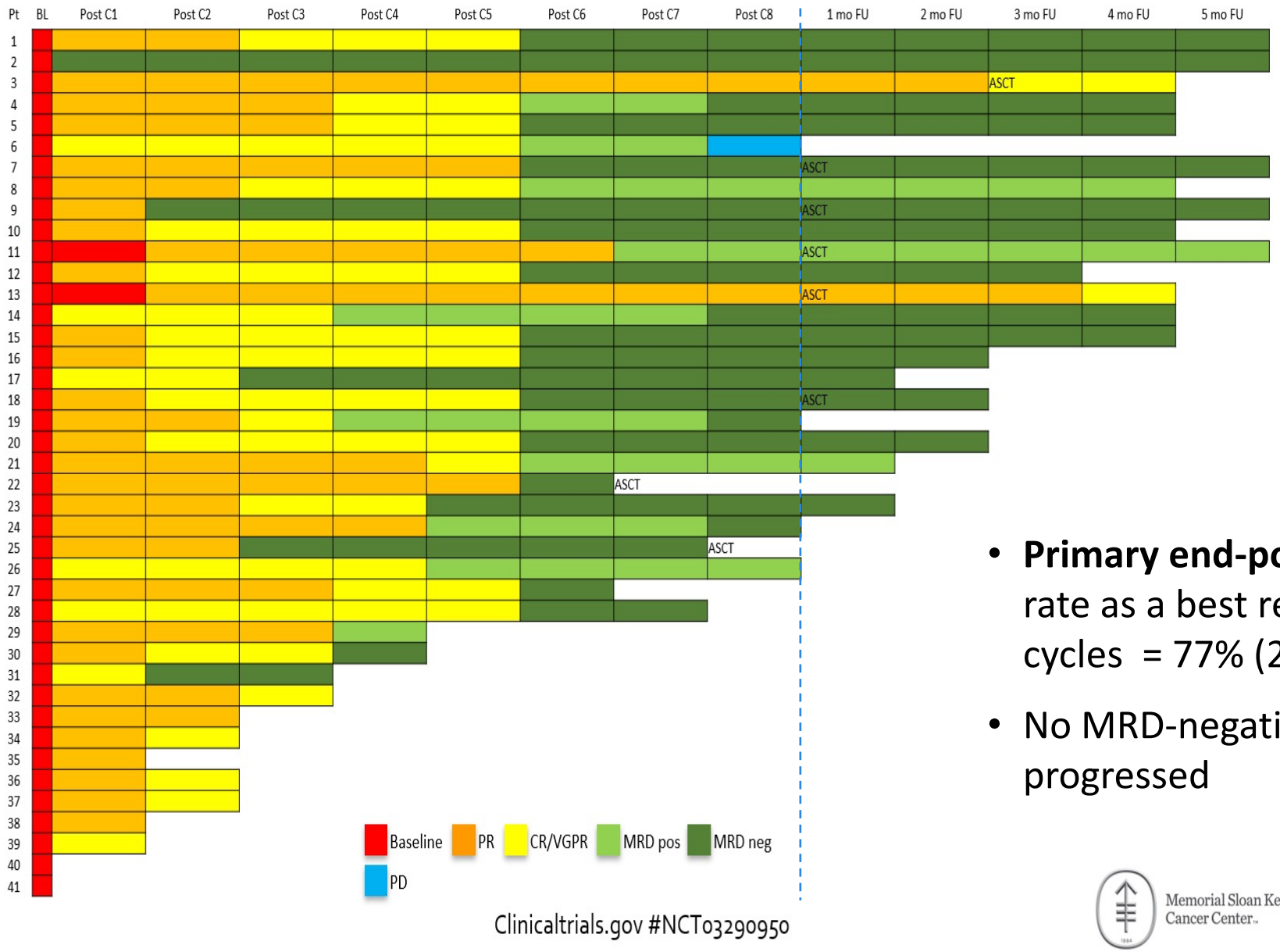


For fit patients, stem cell collection recommended after 4 to 6 cycles; therapy resumed after collection to a total of 8 cycles

- **Bi-weekly and weekly arms had comparable efficacy and safety with a substantial reduction of the number of infusion days (total of 51 *vs.* 27) favoring weekly arm**
- **We closed the bi-weekly arm after fully enrolling the first stage**

Clinicaltrials.gov #NCT03290950; MSKCC

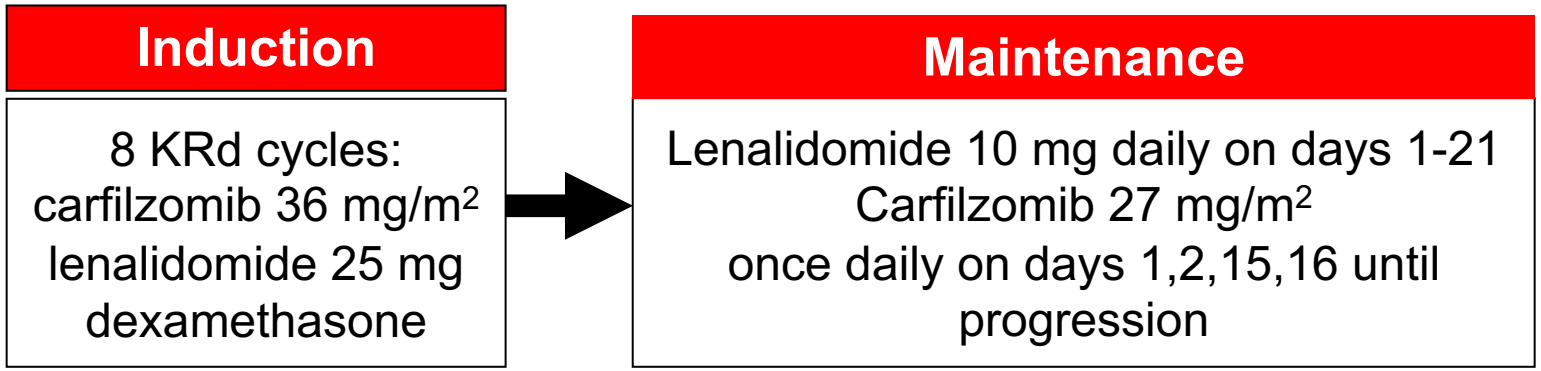
Results: response to therapy, by number of cycles



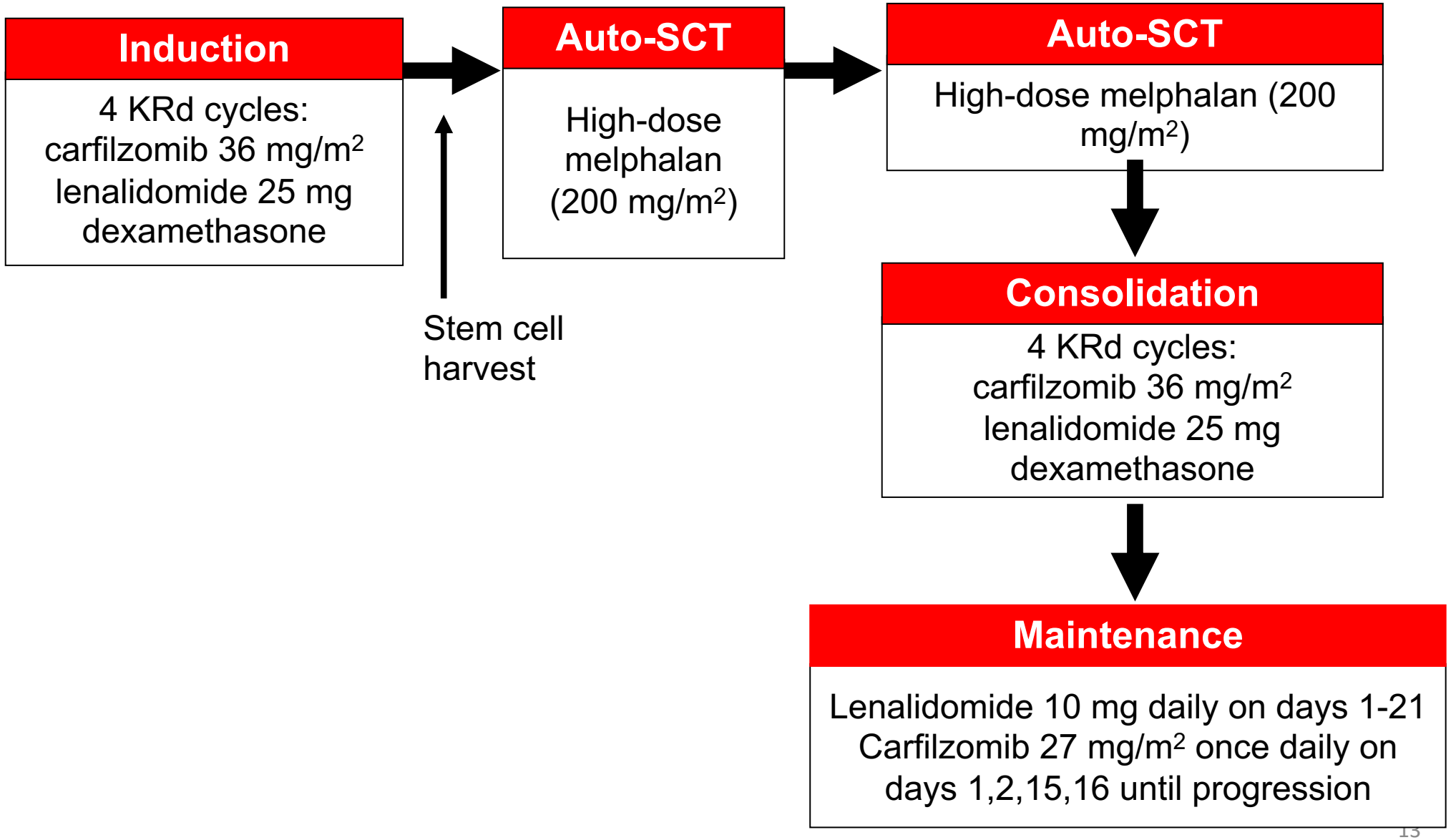
- **Primary end-point:** MRD-negativity rate as a best response after ≤8 cycles = 77% (23/30)
- No MRD-negative patients have progressed

Memorial Sloan Kettering Cancer Center

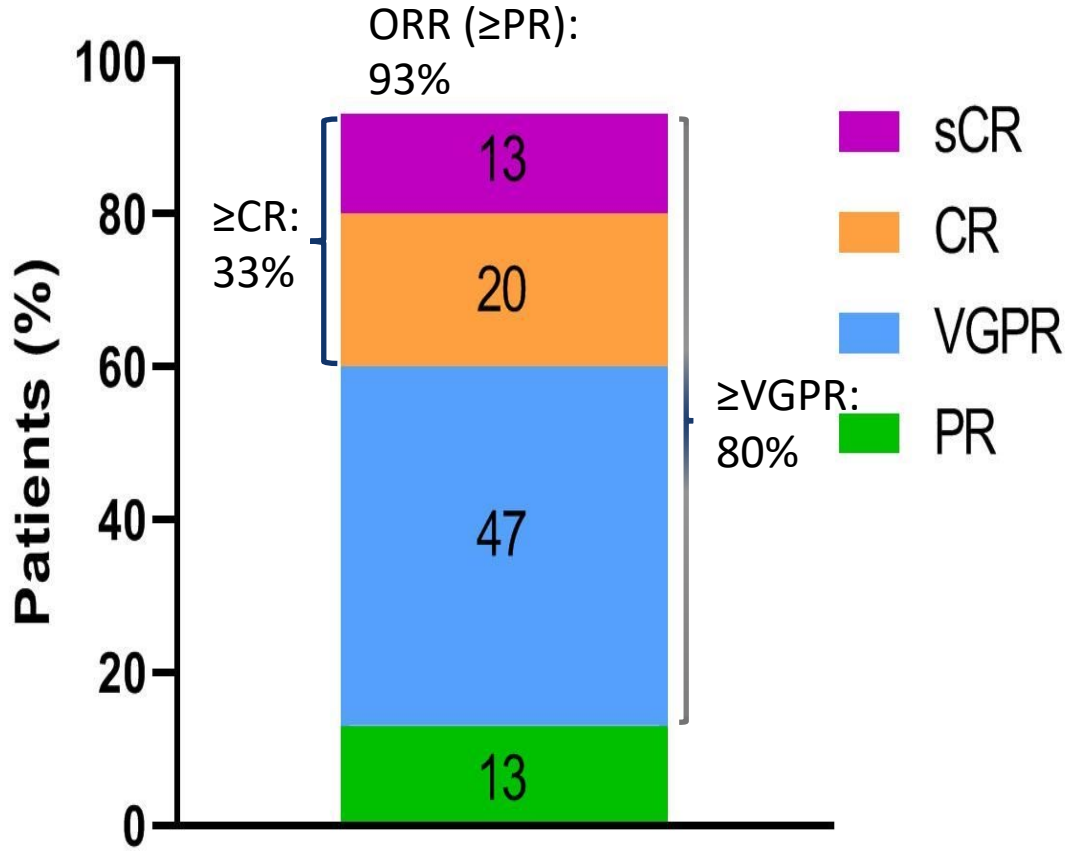
EMN12: Elderly patients: ≥66 years



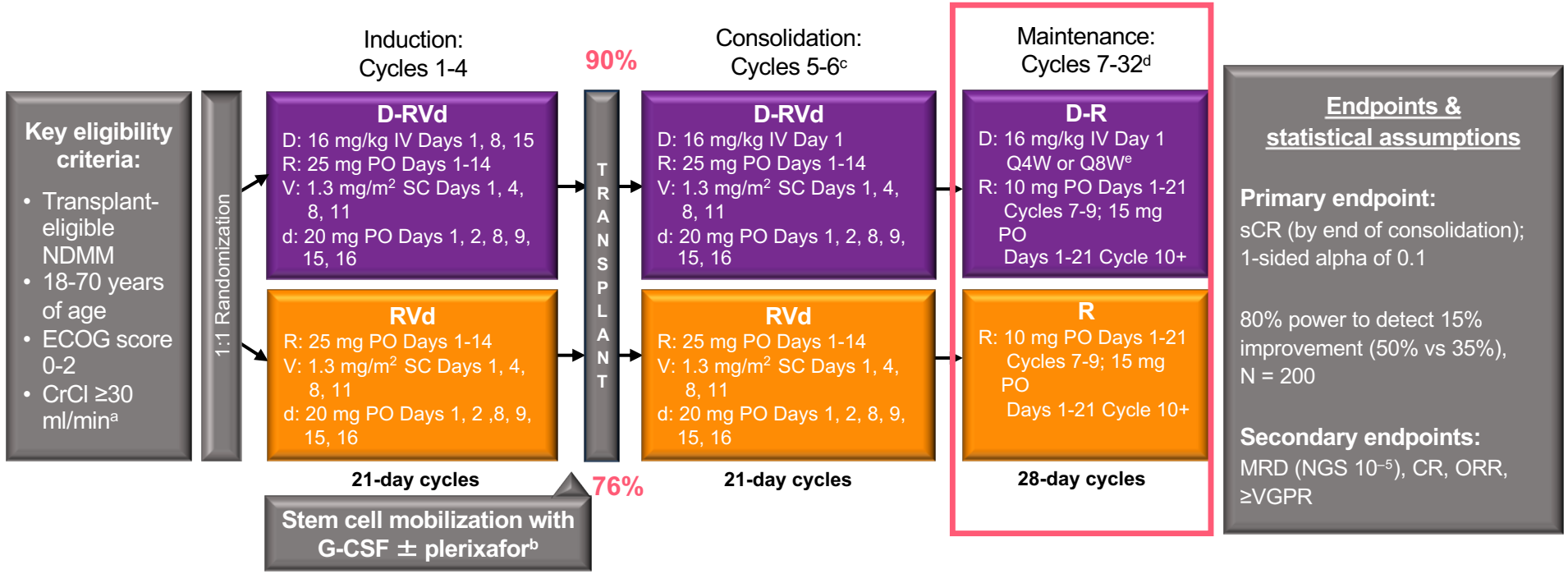
EMN12: Younger patients (18-65 years)



Efficacy: Response following 4 cycles of KRd induction for the first 15 patients aged ≤65 years

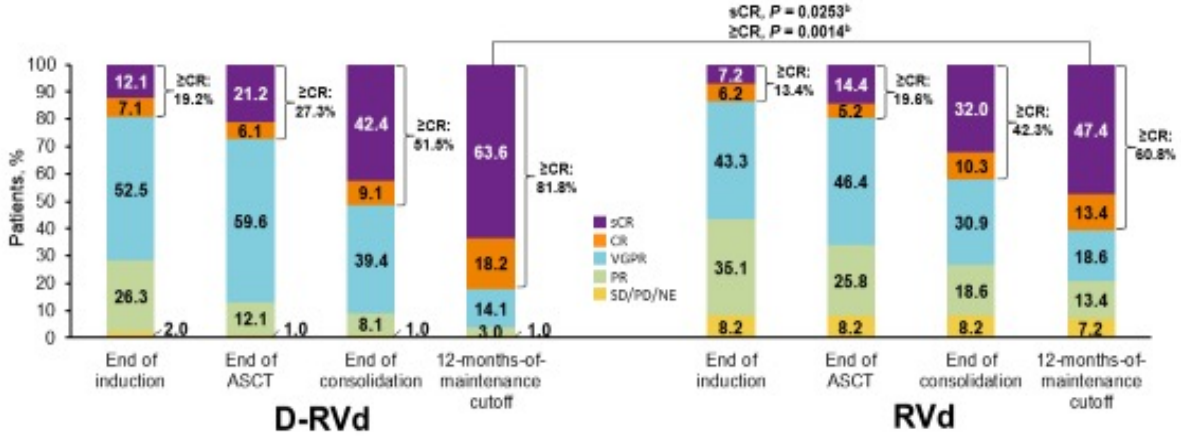


Phase 2 GRIFFIN Trial of D-RVd vs RVd in Transplant Eligible NDMM



- Median age ~60; ISS3 14%, High risk 15%
- Lower ASCT rate in RVd arm due to early discontinuations

Phase 2 GRIFFIN Trial: Responses Deepened Over Time

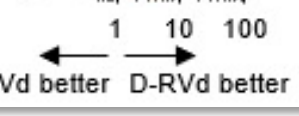


- Results for end of induction, ASCT, and consolidation are based on a median follow up of 13.5 months at the primary analysis
- Median follow up at 12-months-of-maintenance therapy cutoff was 27.4 months

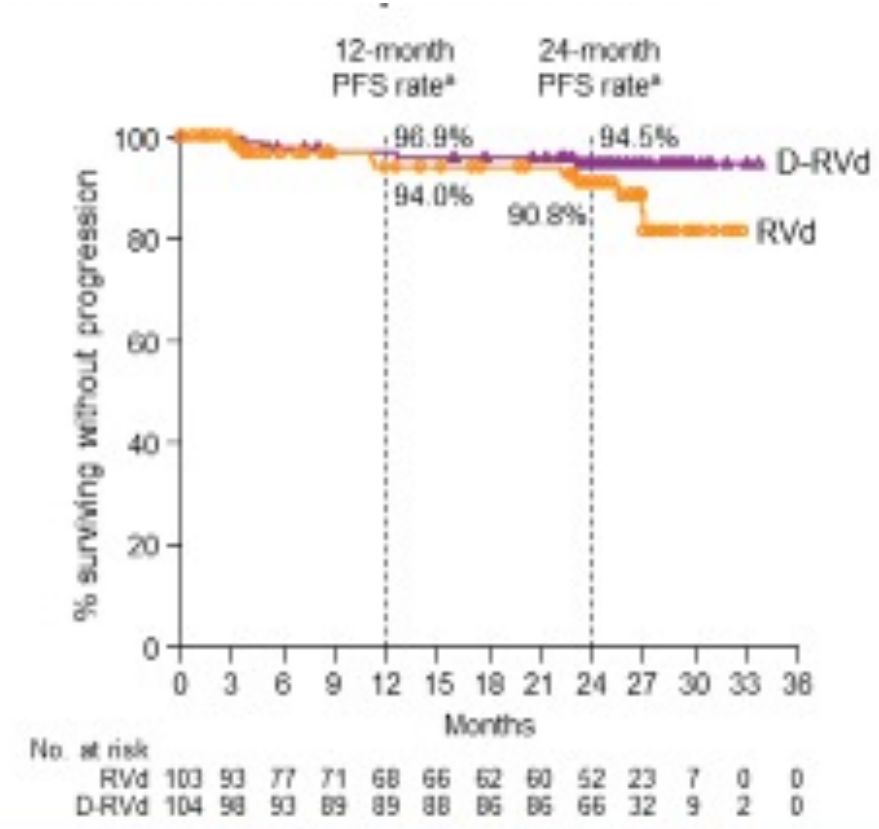
[a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test.

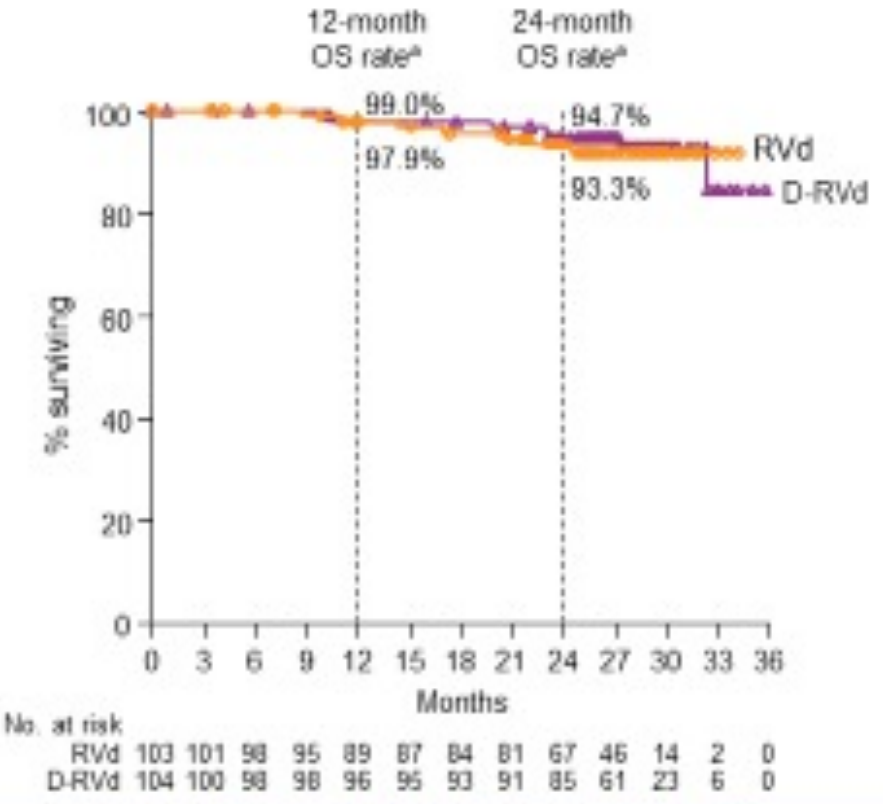
MRDneg

	RVd MRD negative, n (%)	D-RVd MRD negative, n (%)	Odds ratio (95% CI)
Sex			
Male	14/60 (23.3)	33/58 (56.9)	4.34 (1.96-9.58)
Female	14/43 (32.6)	32/46 (69.6)	4.73 (1.93-11.59)
Age			
<65 years	23/75 (30.7)	46/76 (60.5)	3.47 (1.77-6.79)
≥65 years	5/28 (17.9)	19/28 (67.9)	9.71 (2.78-33.92)
ISS disease stage			
I	10/50 (20.0)	32/49 (65.3)	7.53 (3.03-18.69)
II	13/37 (35.1)	23/40 (57.5)	2.50 (0.99-6.27)
III	5/14 (35.7)	10/14 (71.4)	4.50 (0.91-22.15)
Type of MM			
IgG	13/52 (25.0)	35/55 (63.6)	5.25 (2.28-12.09)
Non-IgG	15/51 (29.4)	28/46 (60.9)	3.73 (1.60-8.69)
Cytogenetic risk			
High risk	4/14 (28.6)	7/16 (43.8)	1.94 (0.42-8.92)
Standard risk	24/83 (28.9)	56/82 (68.3)	5.29 (2.72-10.29)
ECOG PS score			
0	8/40 (20.0)	25/39 (64.1)	7.14 (2.59-19.69)
1-2	20/62 (32.3)	40/62 (64.5)	3.82 (1.81-8.04)



Phase 2 GRIFFIN Trial: PFS and OSS (ITT)





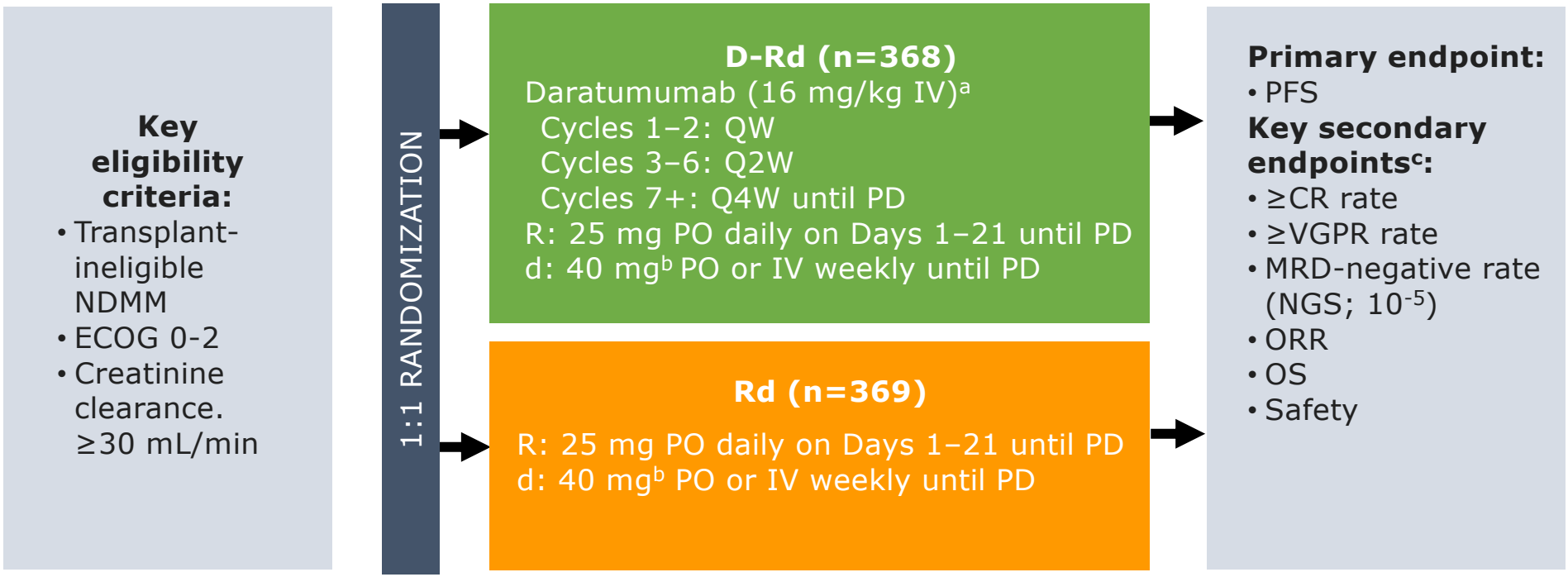
Median PFS and OS were not reached for D-RVd and RVd

Durability of PFS and OS benefits are suggested by the GRIFFIN safety run-in cohort (>40 months median follow-up; ASH 2020 poster 3243)

MAIA (D-Rd vs Rd) Study in TIE-NDMM

Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N=737)

TIE-NDMM



Stratification factors:
- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥75 years)

Cycle: 28 days

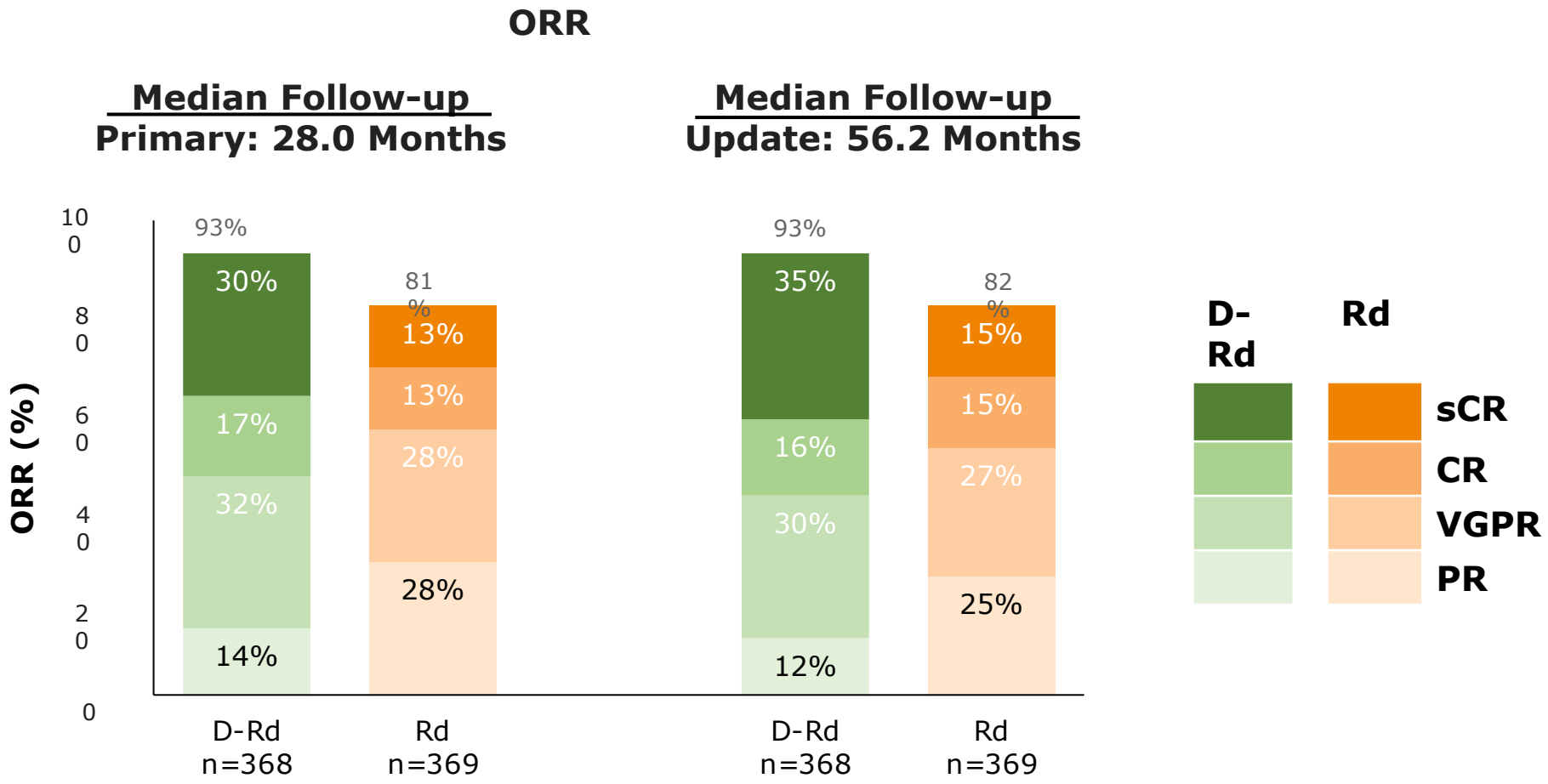
[a]On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
[b]For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c]Efficacy endpoints were sequentially tested in the order shown.

BMI, body mass index; CR, complete response; D, daratumumab; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; IV, intravenous; MRD, minimal residual disease; NA, North America; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PO, by mouth; QW, every week; R, lenalidomide; TIE, transplant ineligible; VGPR, very good partial response.

Falcon T et al. *N Engl J Med.* 2019:380(22):2104-2115.

MAIA: Overall Response Rate

TIE-NDMM

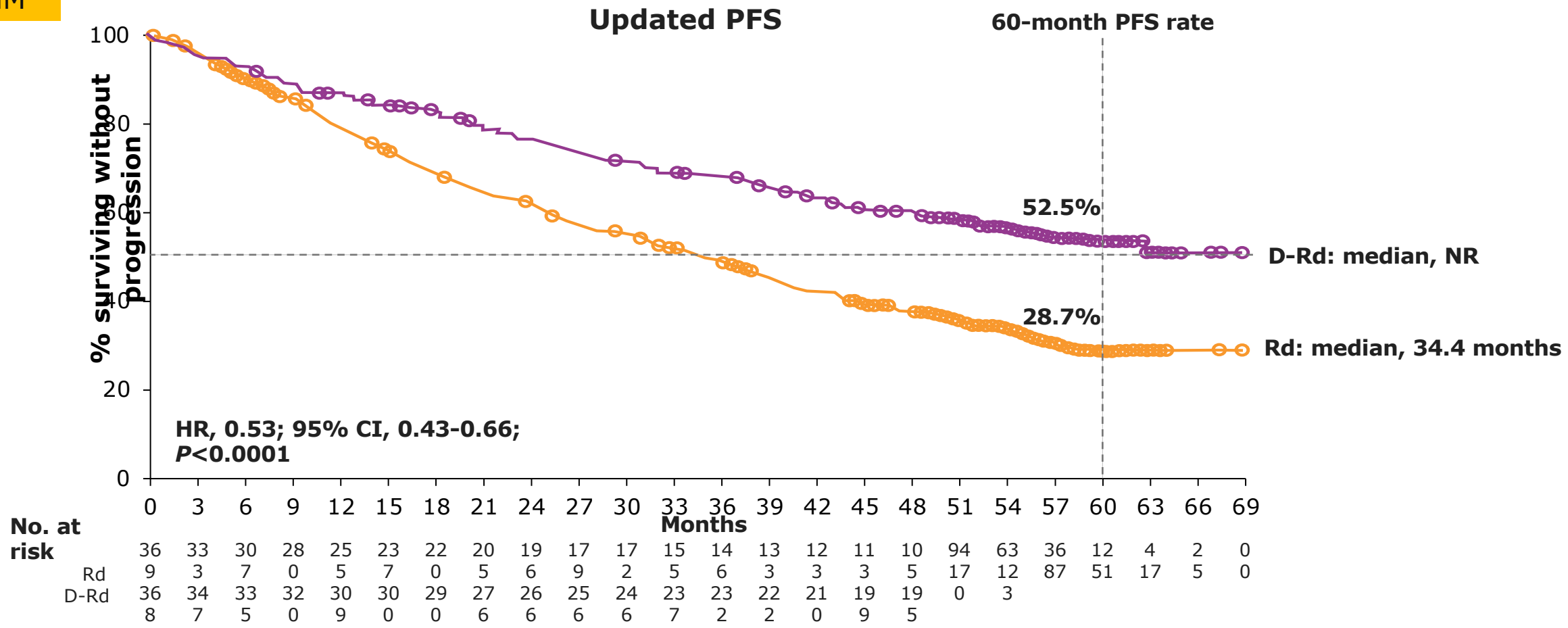


- D-Rd induced deeper responses with significantly higher rates of ≥CR and ≥VGPR, compared with Rd
  - With >28 months of additional follow-up, responses deepened with continued DARA therapy

PR, partial response; sCR, stringent complete response.
*ITT population.
Falcon T et al. *N Engl J Med.* 2019:380(22):2104-2115. Facon T et al. 2021. EHA Abstract LB1901.

MAIA: Progression-Free Survival
NEW 60-month Data

TIE-NDMM



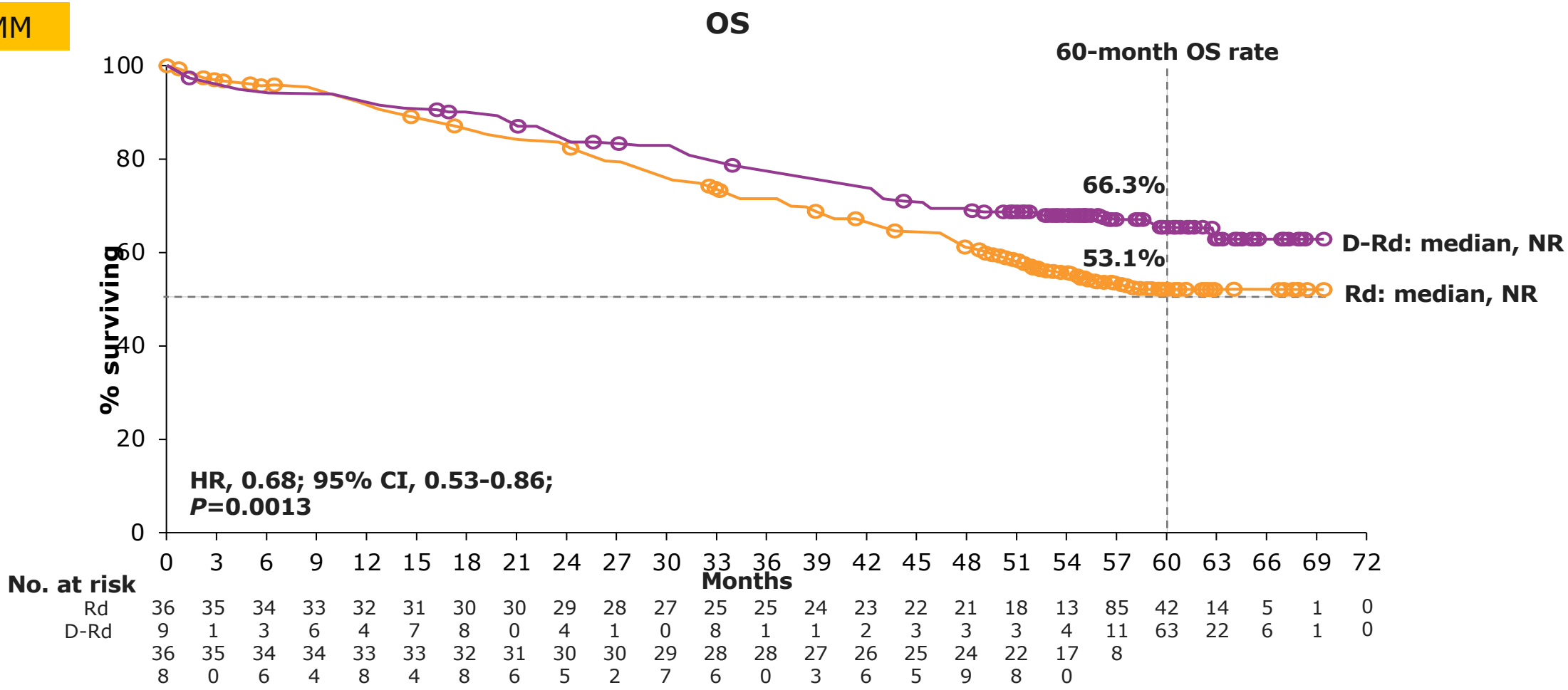
- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
  - These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible

HR, hazard ratio; NR, not reached.

Facon T et al. 2021. EHA Abstract LB1901.

MAIA: Overall Survival

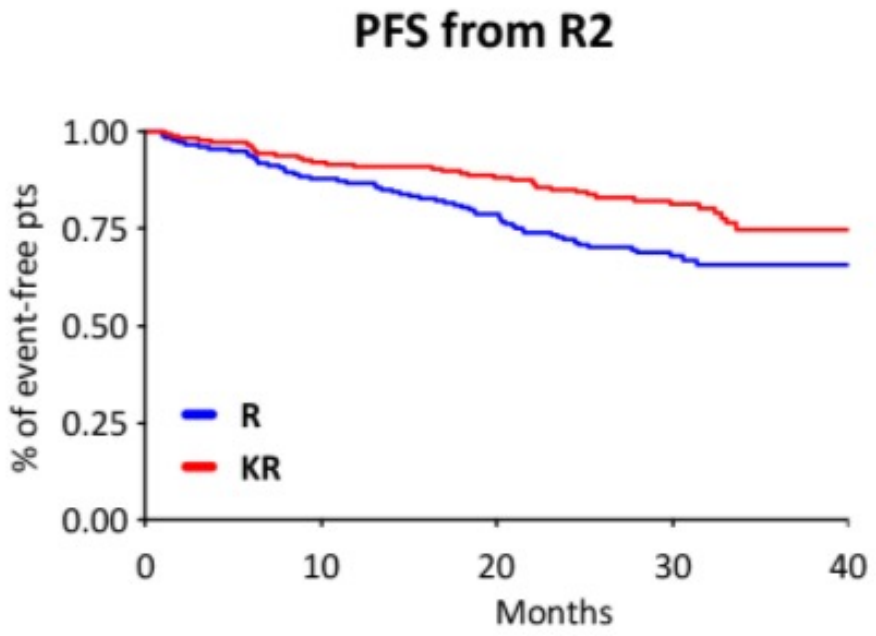
TIE-NDMM

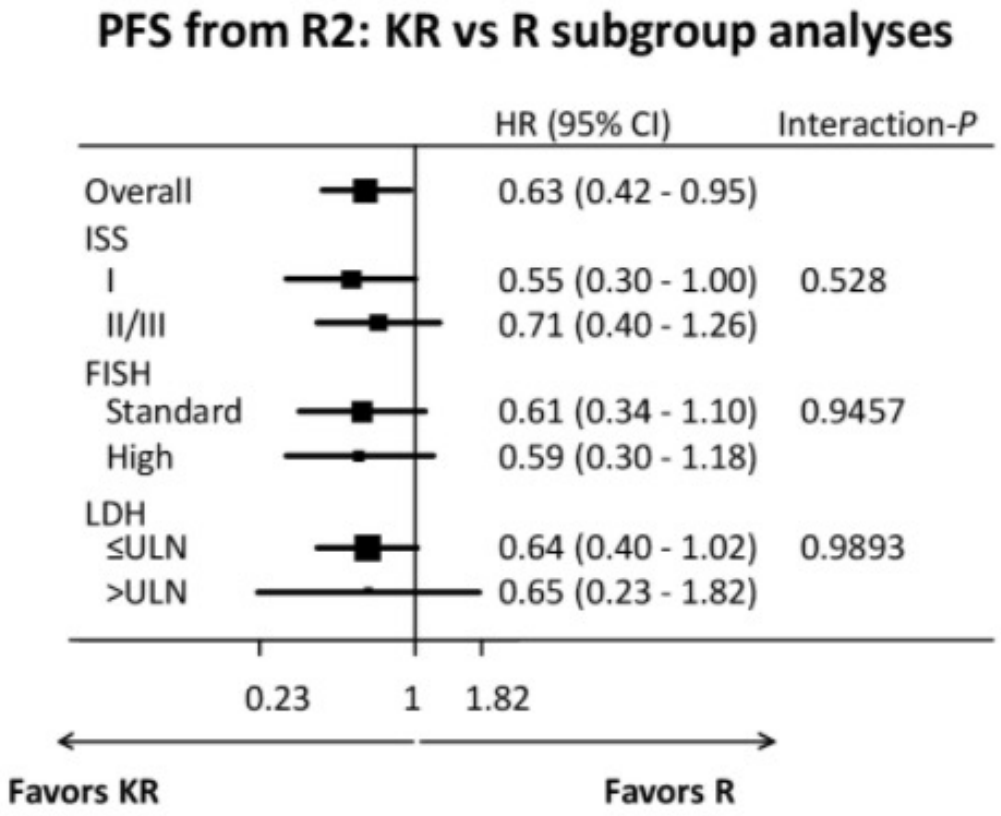


D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

Facon T et al. 2021. EHA Abstract LB1901.

FORTE: KR versus R maintenance

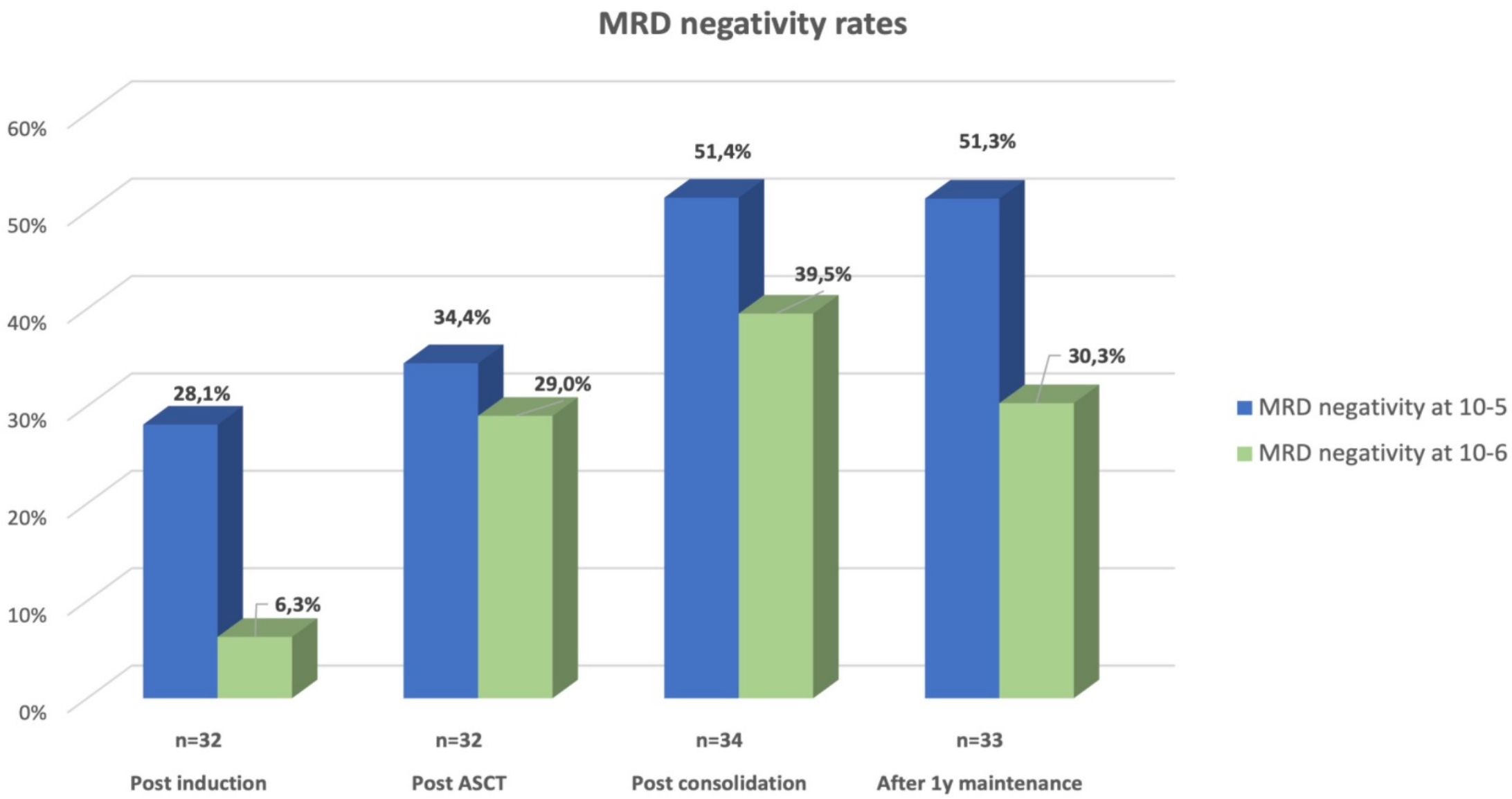




3-year PFS from R2 (ITT, KR vs R): 75%, KR vs 66%, R (HR 0.63; P=0.026).

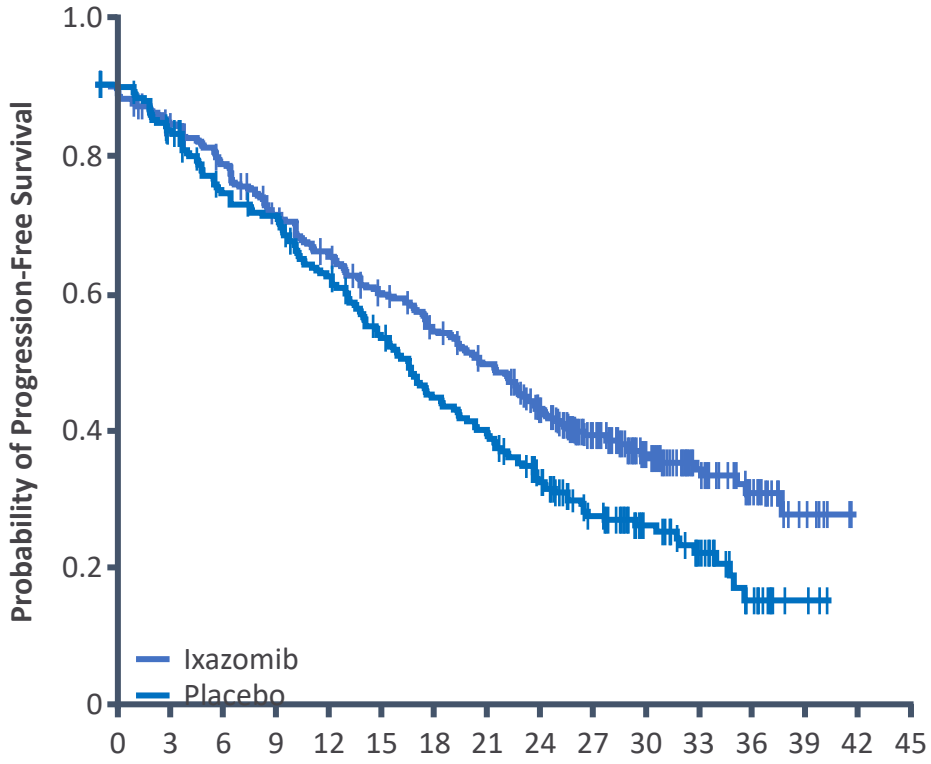
Gay F, et al. ASH 2020. Abstract 141.

464 Daratumumab Plus Ixazomib, Lenalidomide, and Dexamethasone As Extended Induction and Consolidation Followed By Lenalidomide Maintenance in Standard-Risk Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM) Patients (IFM 2018-01): A Phase II Study of the Intergroupe Francophone Du Myélome (IFM)



Improvement in overall PFS with ixazomib vs. placebo

- There was a significant 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs. placebo maintenance:
  - Median 26.5 months vs. 21.3 months
- With only 14% of deaths reported, at a median follow-up of 31 months, median OS has not been reached in either treatment arm and follow up continues
- Improved Depth of response resulted in better PFS



No. of patients at risk:

Ixazomib	395	363	340	311	279	255	238	213	187	135	93
56	35	9	3	0							
Placebo	261	238	210	195	174	153	130	117	100	69	46
32	15	3	0	0							

Meletios A Dimopoulos et al, Blood 2018 132:301
Dimopoulos MA et al. Lancet 2019 Jan 19;393(10168):253-264.
Goldschmidt et al. leukemia 2020; 34(11): 3019–3027

466 Ixazomib Plus Lenalidomide/Dexamethasone (IRd) Versus Lenalidomide /Dexamethasone (Rd) Maintenance after Autologous Stem Cell Transplant in Patients with Newly Diagnosed Multiple Myeloma: Results of the Spanish GEM2014MAIN Trial