Induction Therapy for Newly Diagnosed Multiple Myeloma

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NCCN Guidelines (V2.2023)

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES[a-d]
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/lenalidomide/dexamethasone
Other Recommended Regimens • Daratumumab/lenalidomide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/thalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[f] • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab/bortezomib/thalidomide/dexamethasone • Daratumumab/carfilzomib/lenalidomide/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[g] (VTD-PACE) • Ixazomib/cyclophosphamide/dexamethasone[f] • Ixazomib/lenalidomide/dexamethasone (category 2B)

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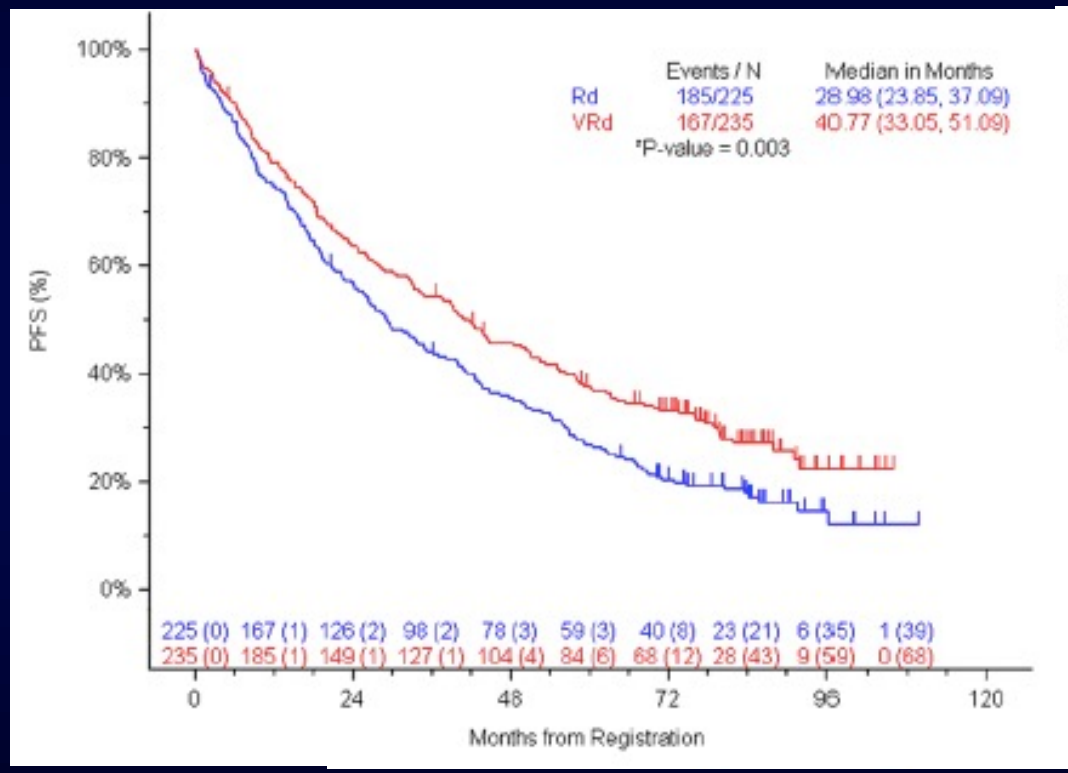
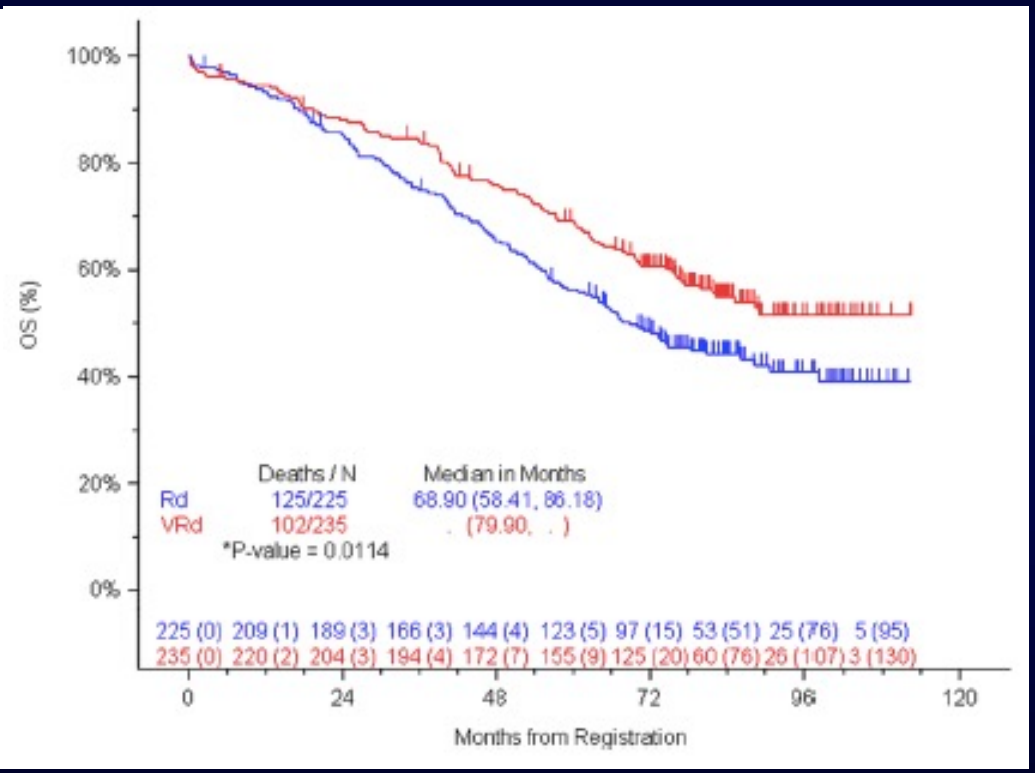
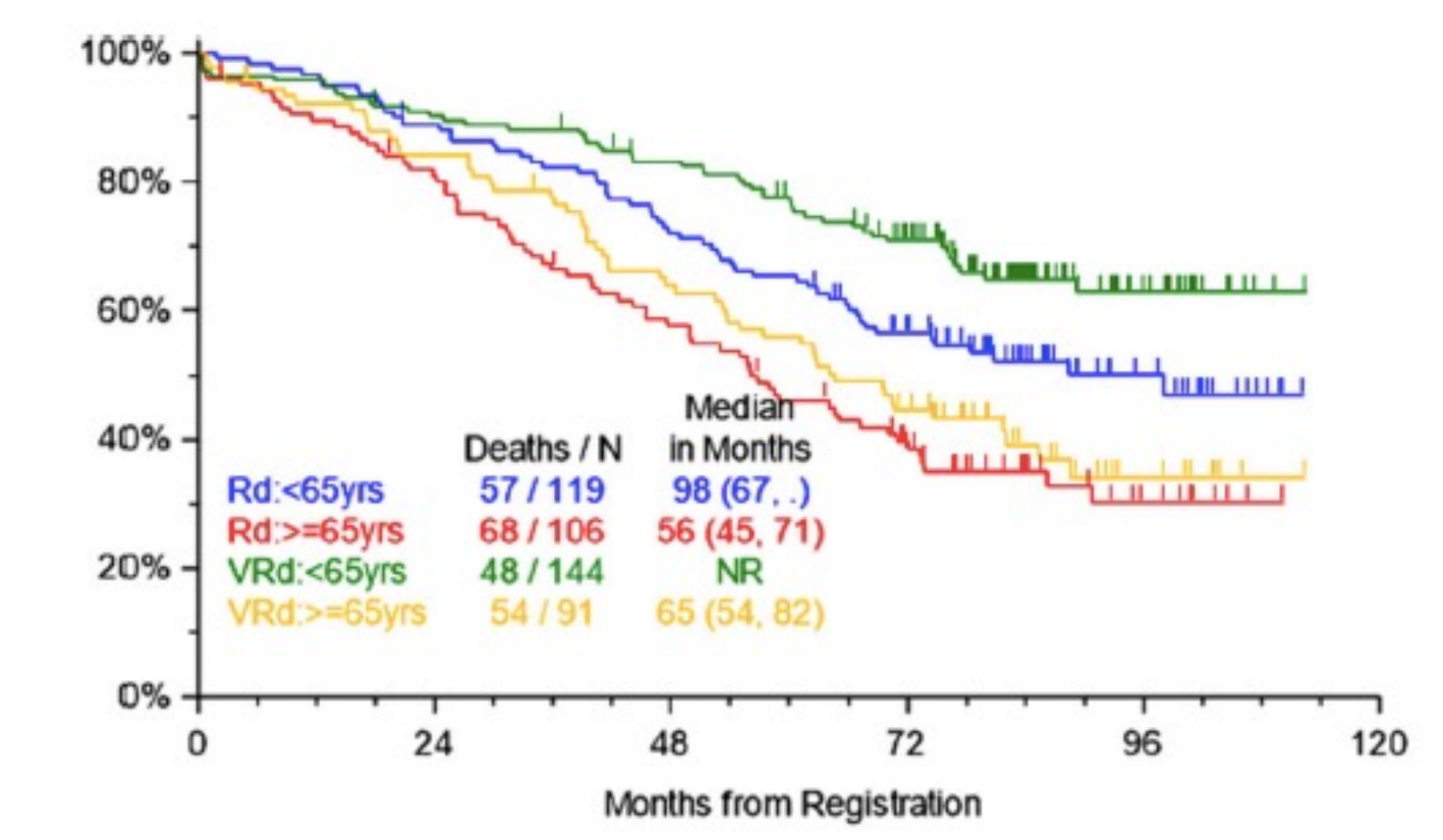
VRd : SWOG S0777





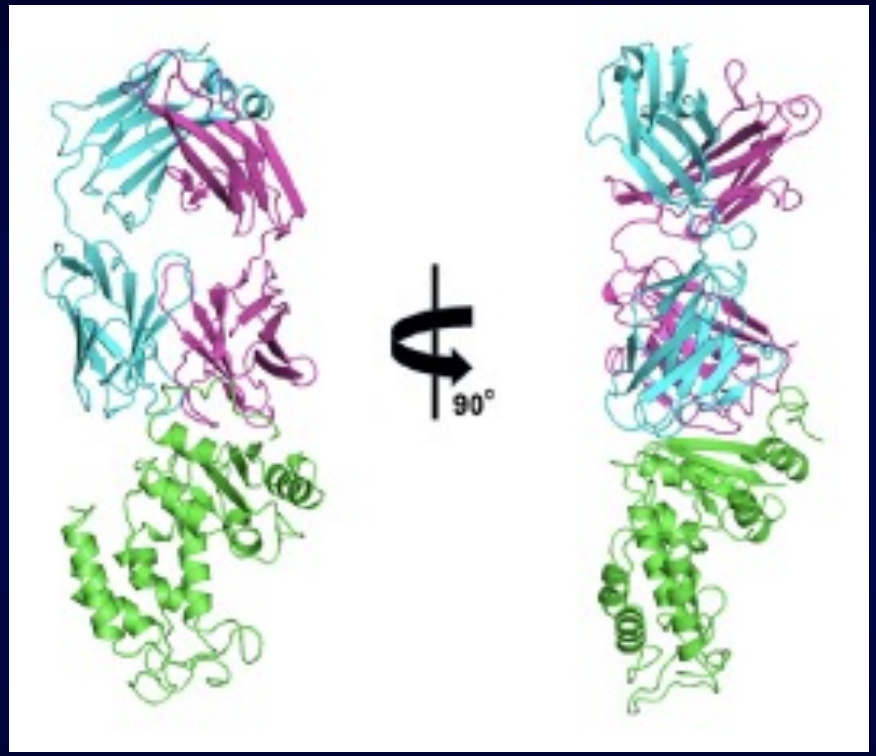
OS by Age



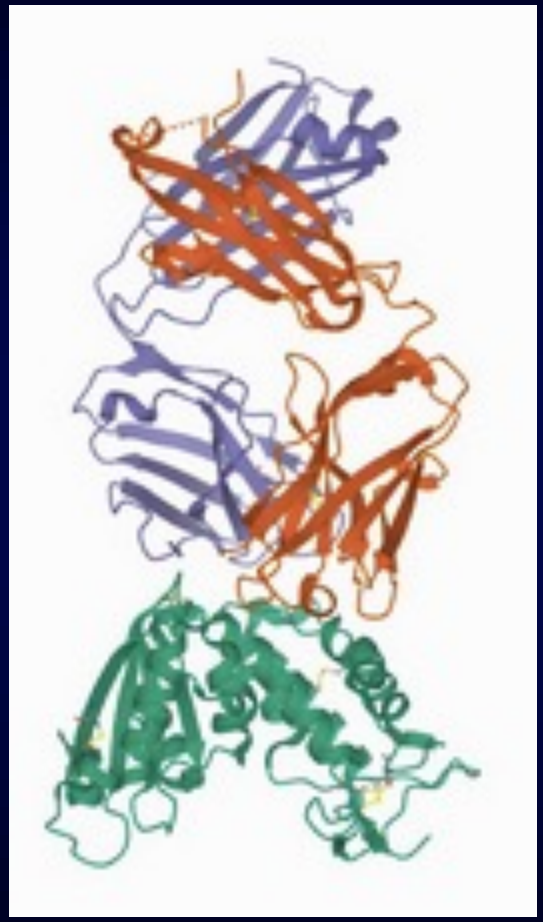
Age < 65 years: HR= 0.640 (0.421,0.973);
stratified, two-sided p= 0.028

Age ≥ 65 years: HR= 0.769 (0.520,1.138);
stratified, two-sided p= 0.168

Daratumumab & Isatuximab



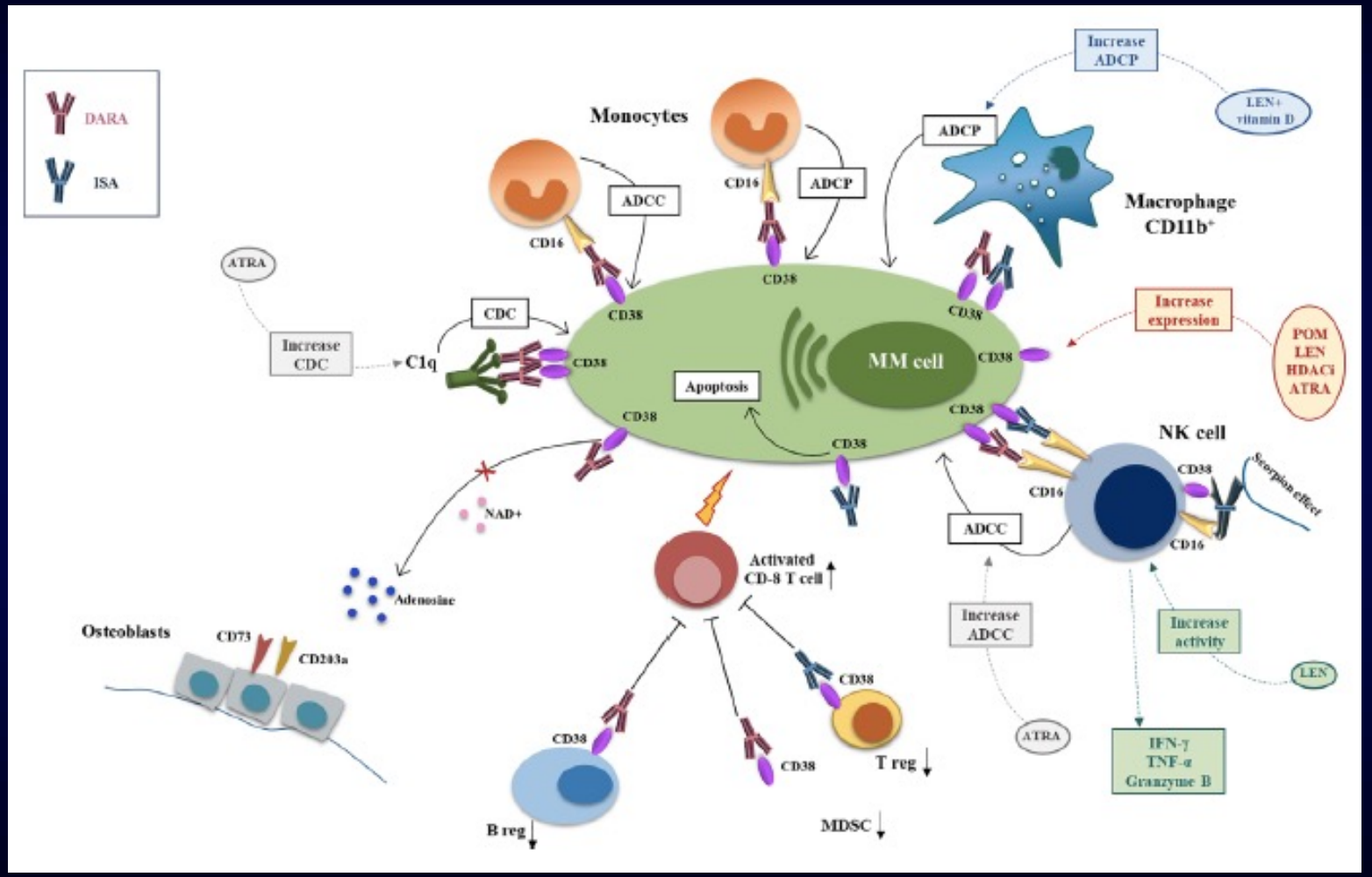
- CD38 bound to Fab of Dara



- CD38 bound to Fab of Isa

Lee, HT et al. Biochem Biophys Res Commun. 536: 26, 2021.
Deckert, J et al. Clin Cancer Res. 20: 4574, 2014.

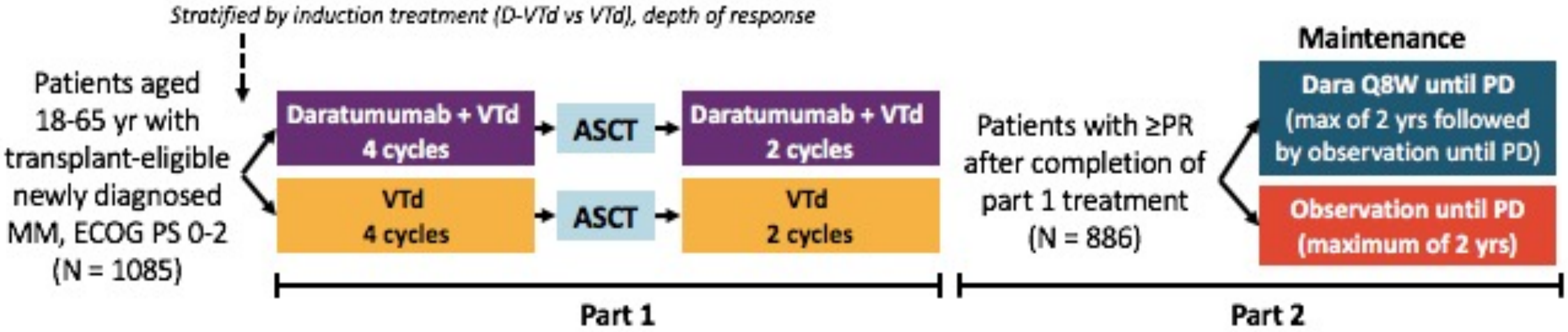
Multiple Mechanisms of Action



Romano, A et al. Front Oncol. 2021 Jul 8;11:684561. doi: 10.3389/fonc.2021.684561.

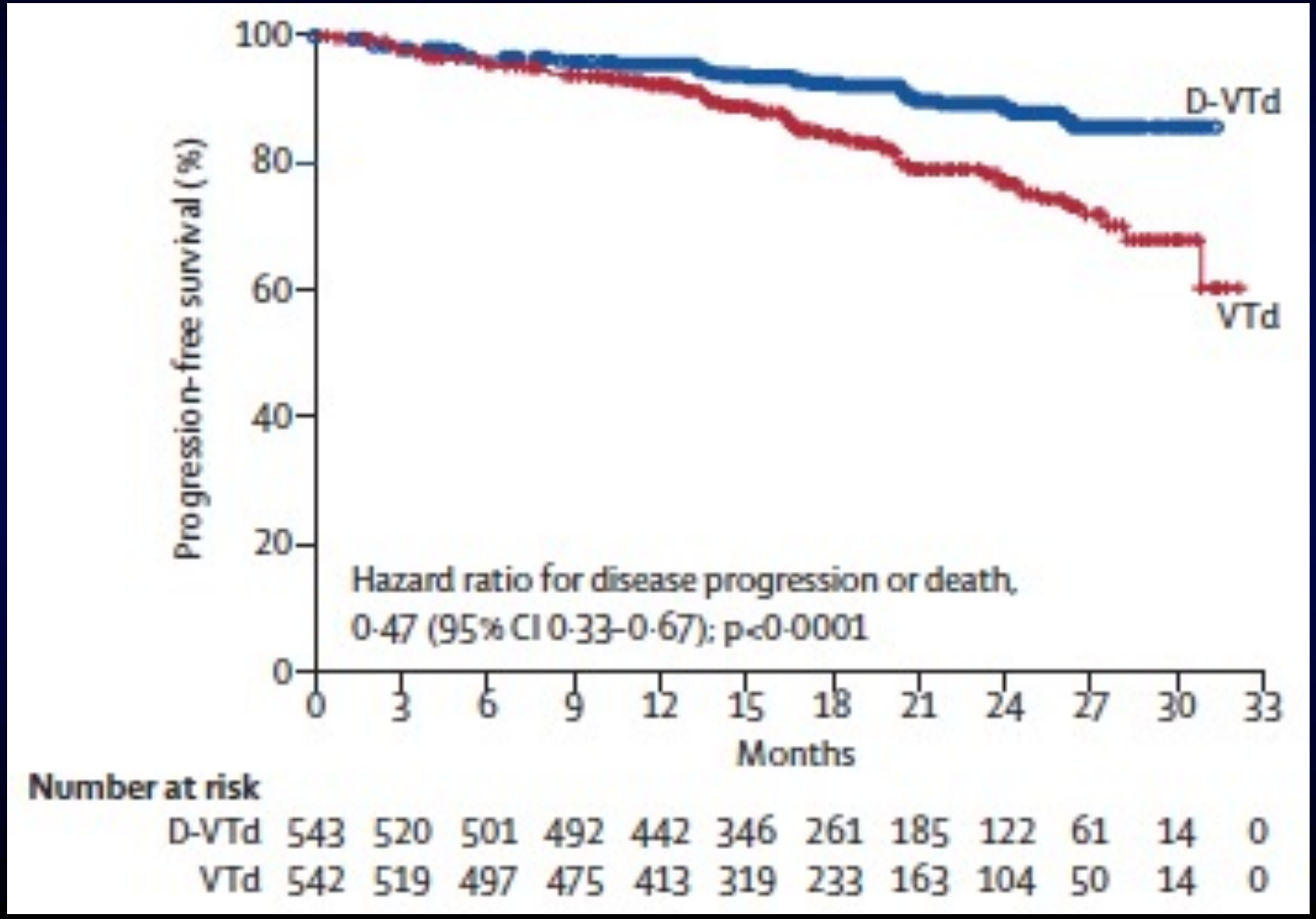
CASSIOPEIA : D-VTd vs. VTd

Bortezomib, thalidomide, and dexamethasone with or without **daratumumab** before and after autologous stem-cell transplantation for newly diagnosed

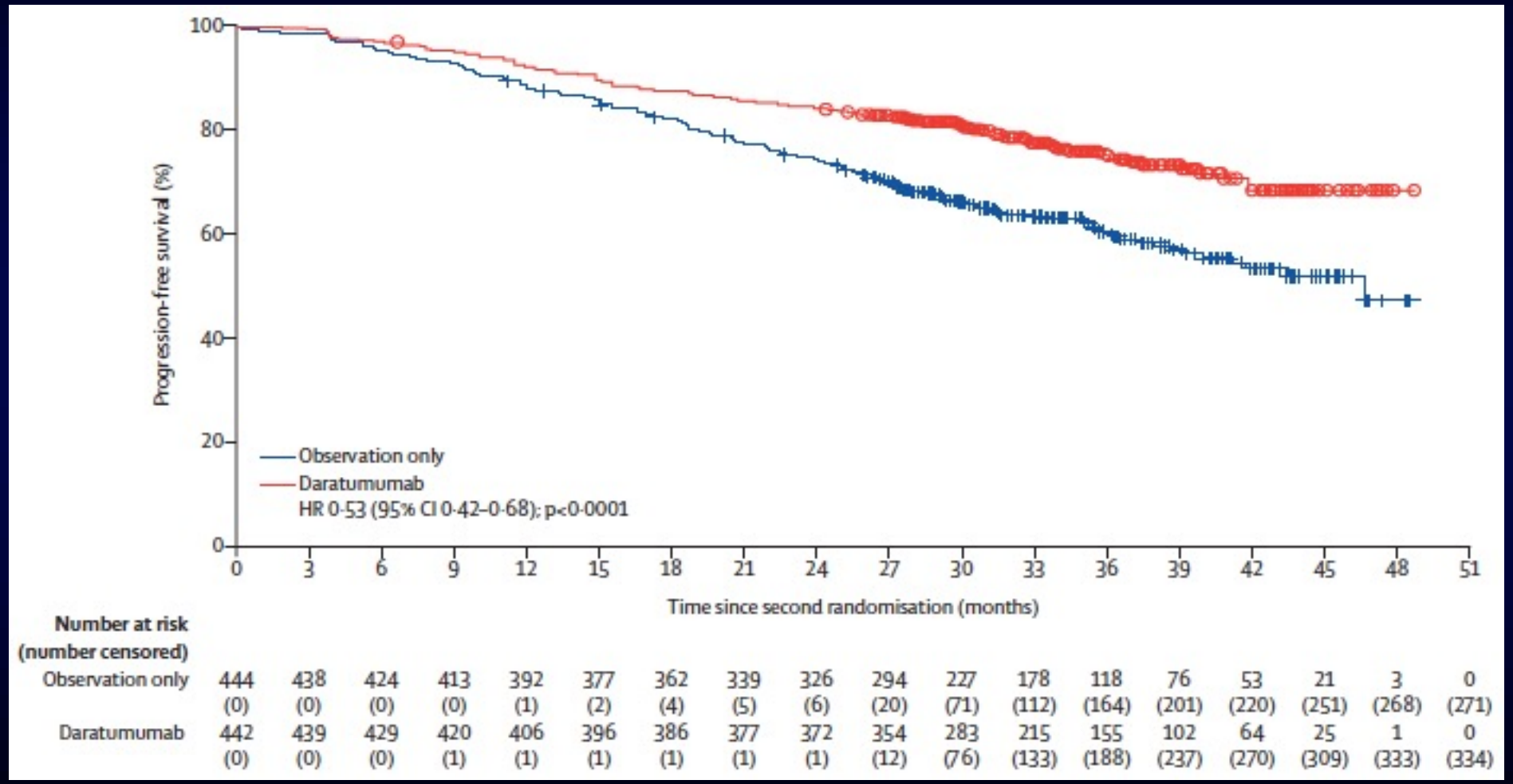


PMID: 31171419 Clinical Trial.

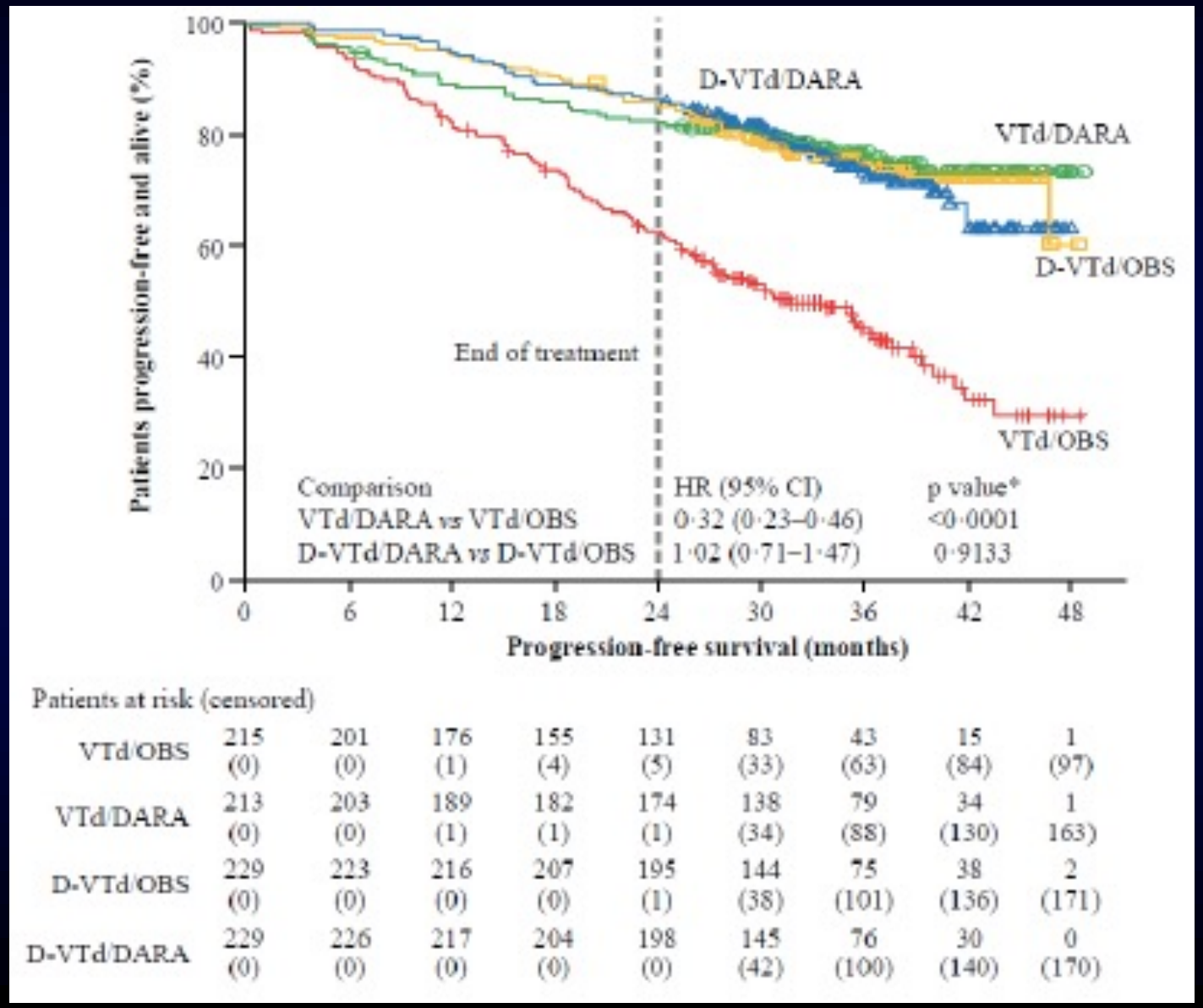
First Randomization Data



Second Randomization Data



Intriguing Question

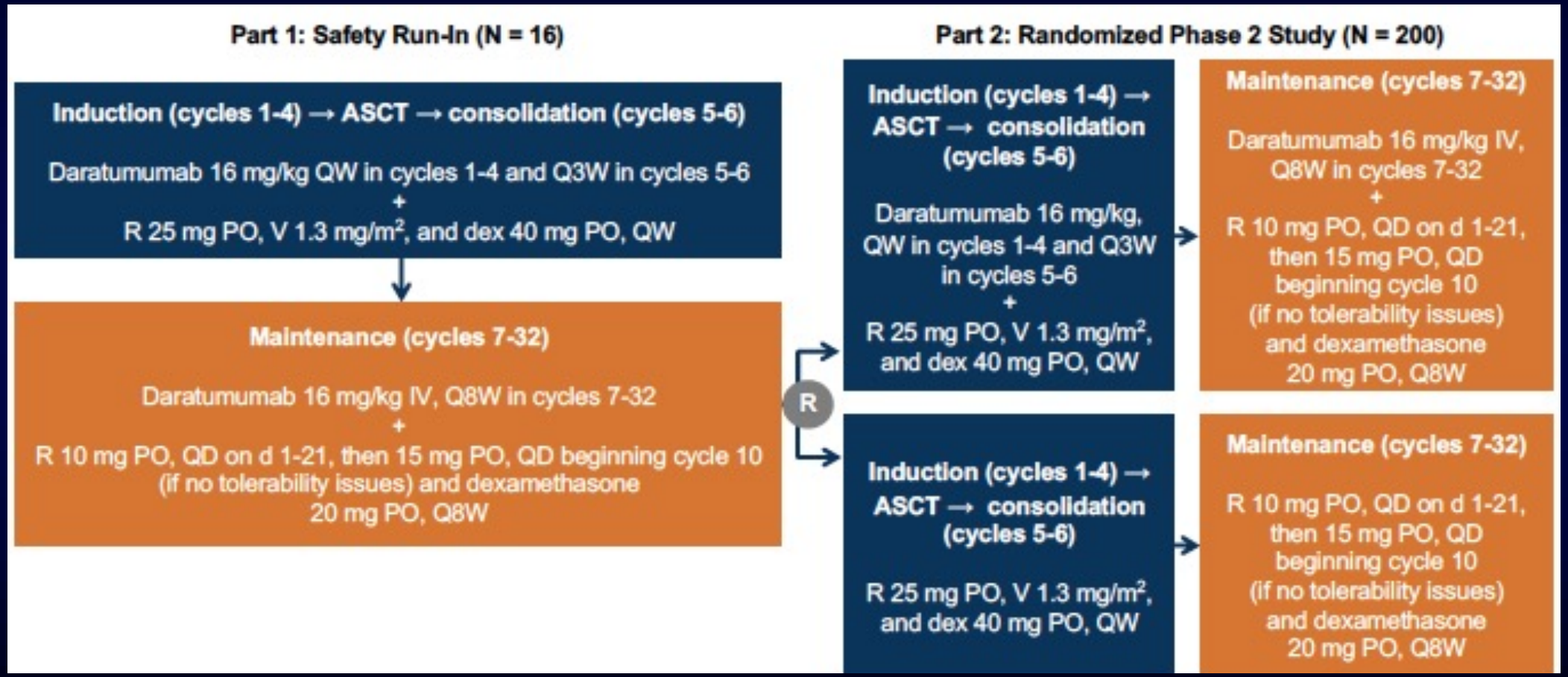


Patients at risk (censored)

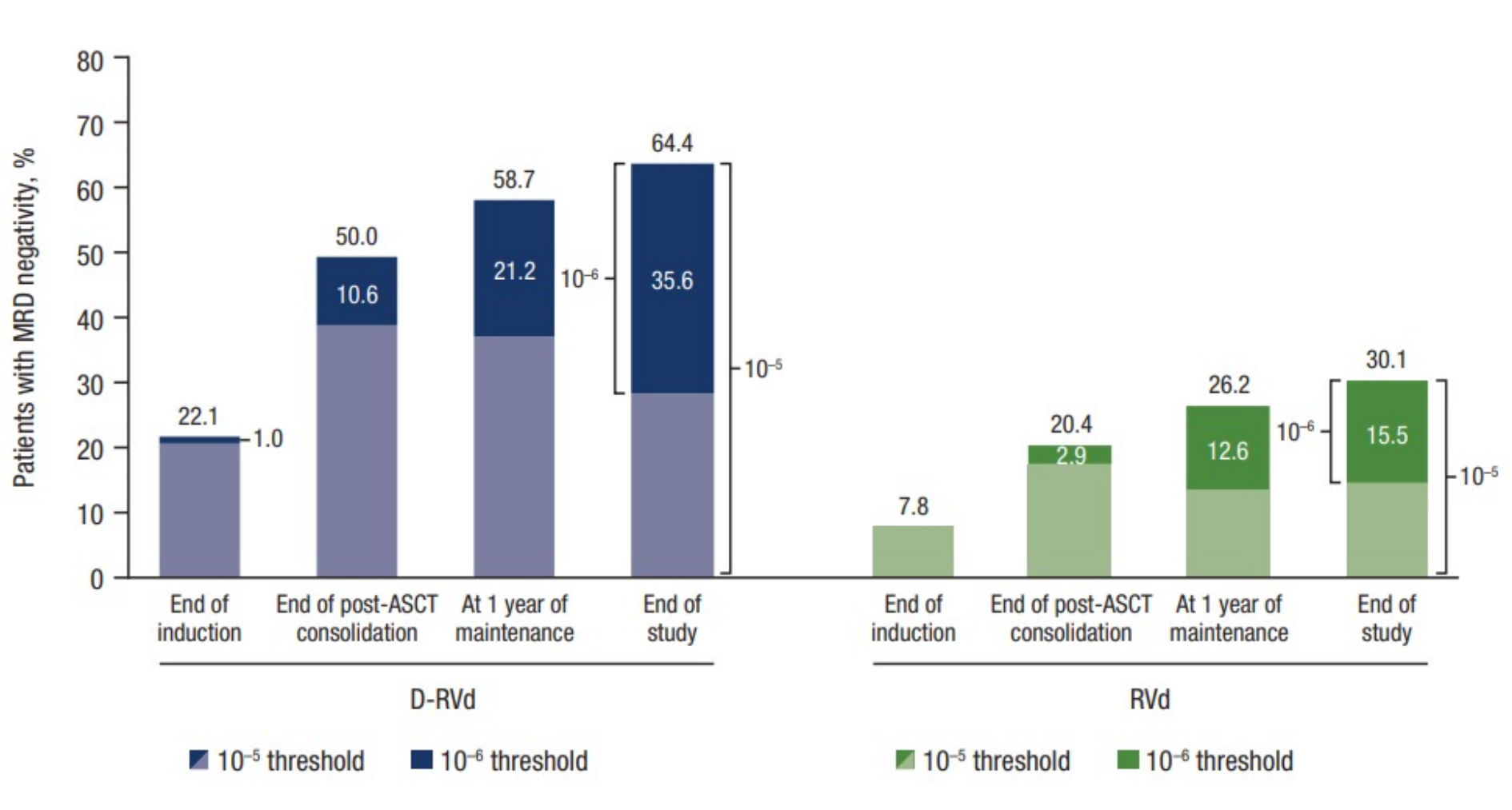
VTd/OBS	215 (0)	201 (0)	176 (1)	155 (4)	131 (5)	83 (33)	43 (63)	15 (84)	1 (97)
VTd/DARA	213 (0)	203 (0)	189 (1)	182 (1)	174 (1)	138 (34)	79 (88)	34 (130)	1 163)
D-VTd/OBS	229 (0)	223 (0)	216 (0)	207 (0)	195 (1)	144 (38)	75 (101)	38 (136)	2 (171)
D-VTd/DARA	229 (0)	226 (0)	217 (0)	204 (0)	198 (0)	145 (42)	76 (100)	30 (140)	0 (170)

- Is Dara needed in both induction & maint., or is one or the other sufficient?

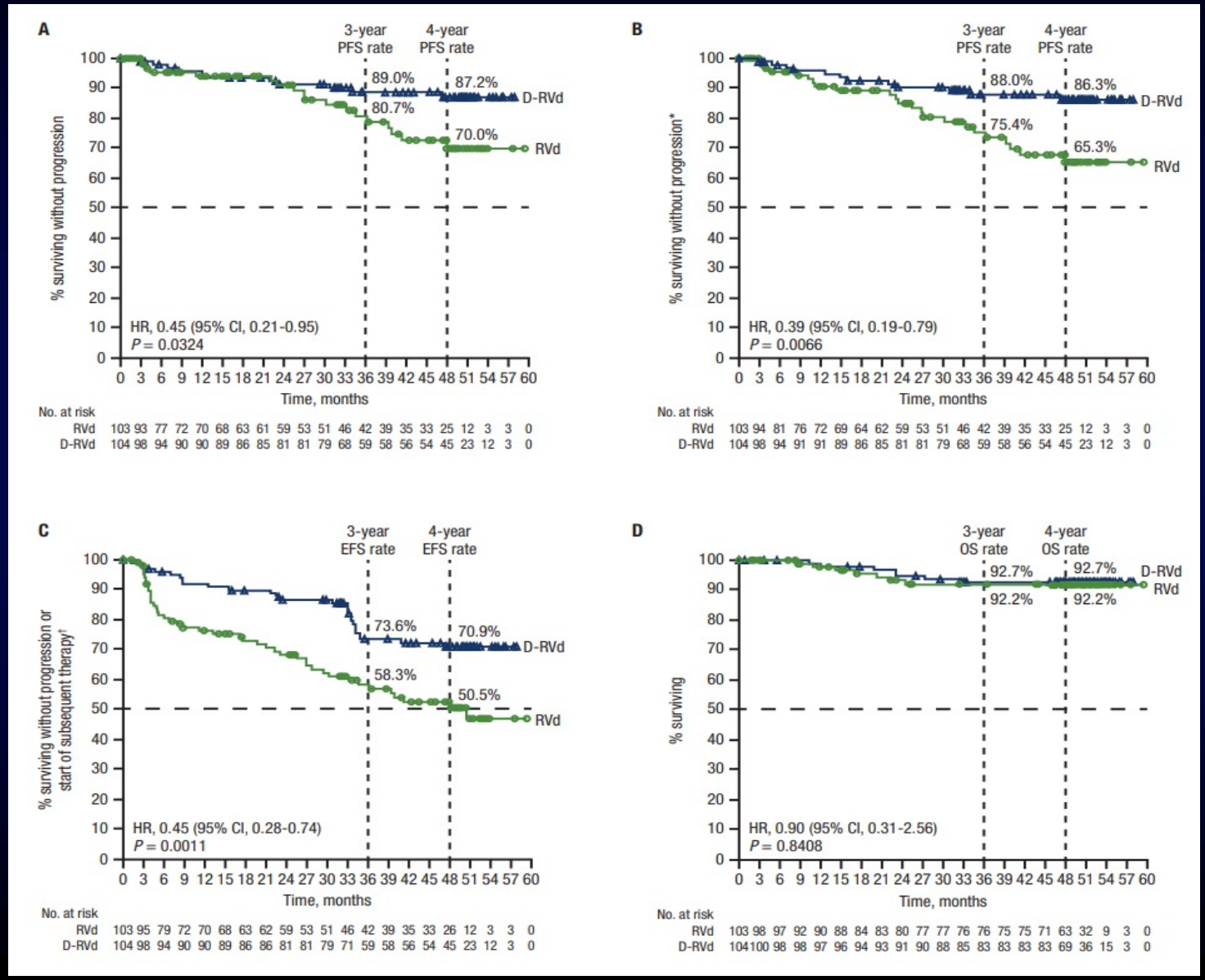
Final Analysis of GRIFFIN



Outcomes Data

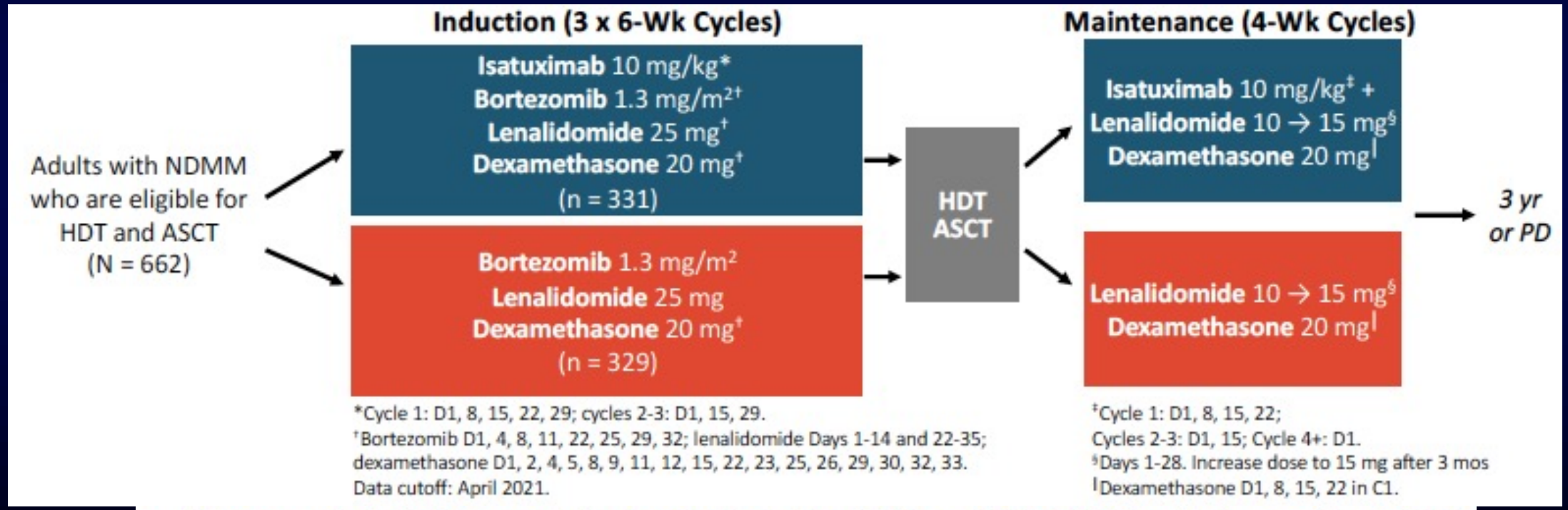


Long Term Outcomes

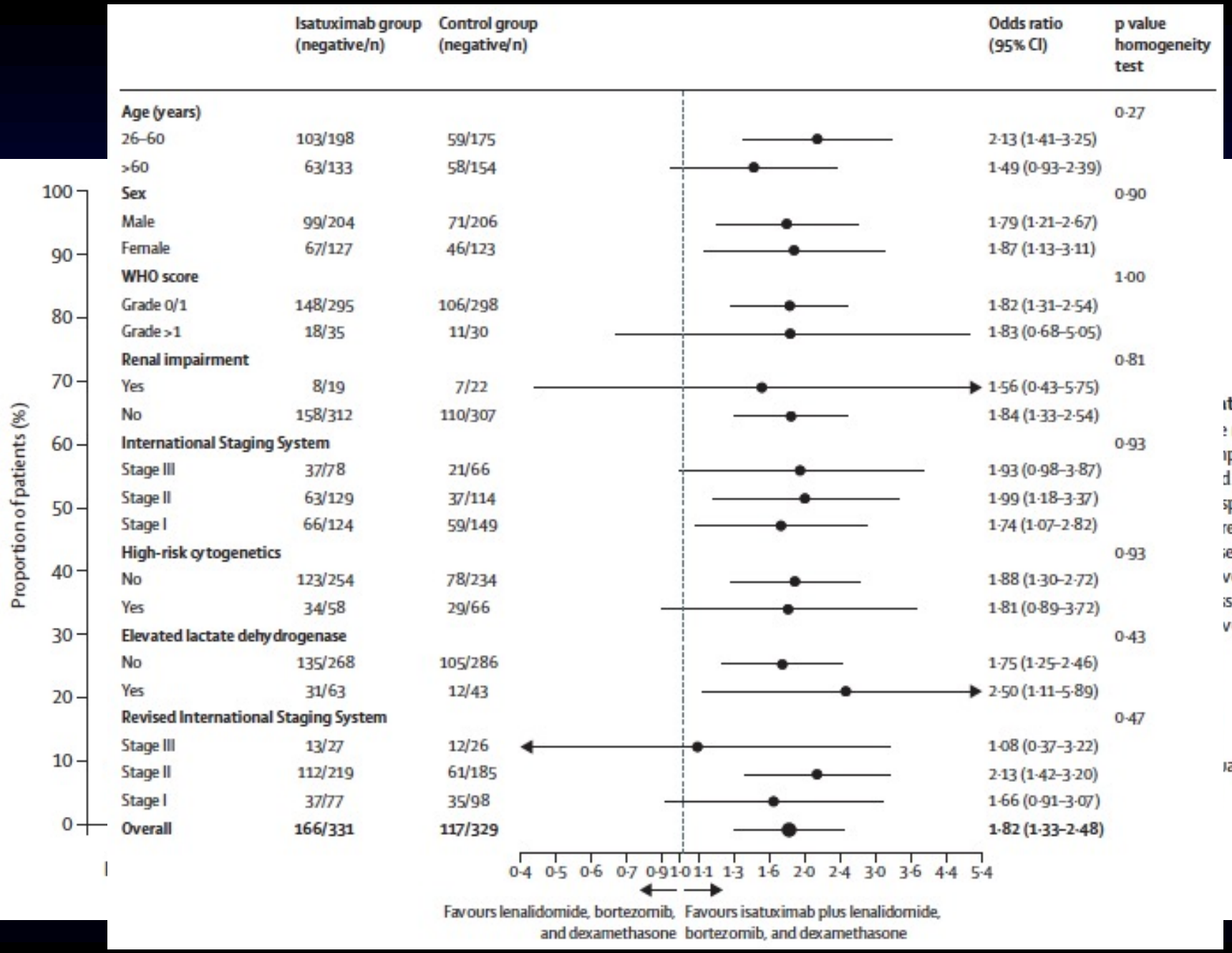


GMMG-HD7 Trial : Isatuximab

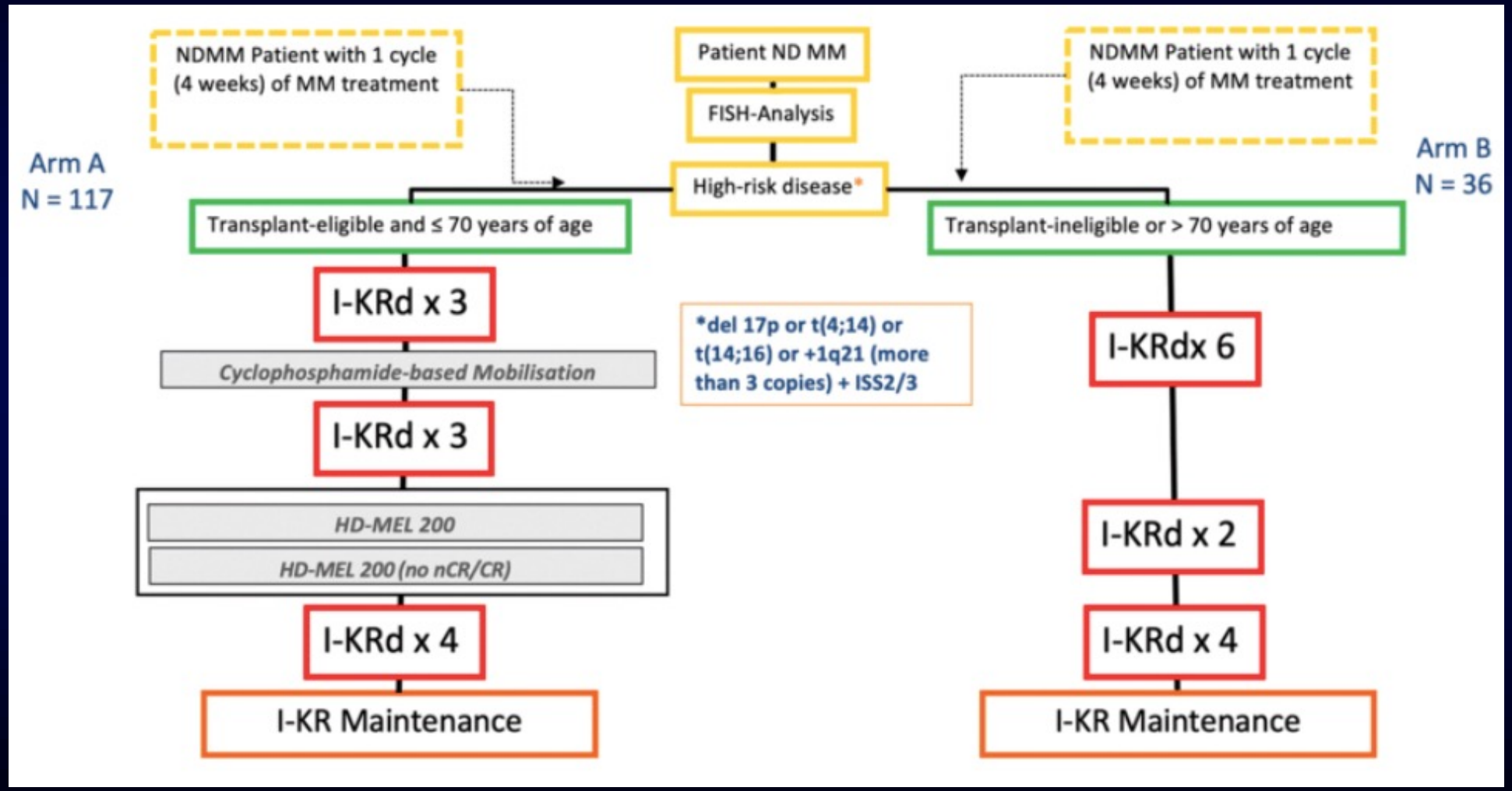
- Addition of Isa to VRd for transplant-eligible myeloma patients



- Primary endpoint: MRD negativity at end of induction (NGF, sensitivity 10^{-5}) stratified according to R-ISS
- Secondary endpoints: CR after induction, safety
- MRD negativity assessed after cycle 3, HDT, 12 mos, and 24 mos as well as at end of study

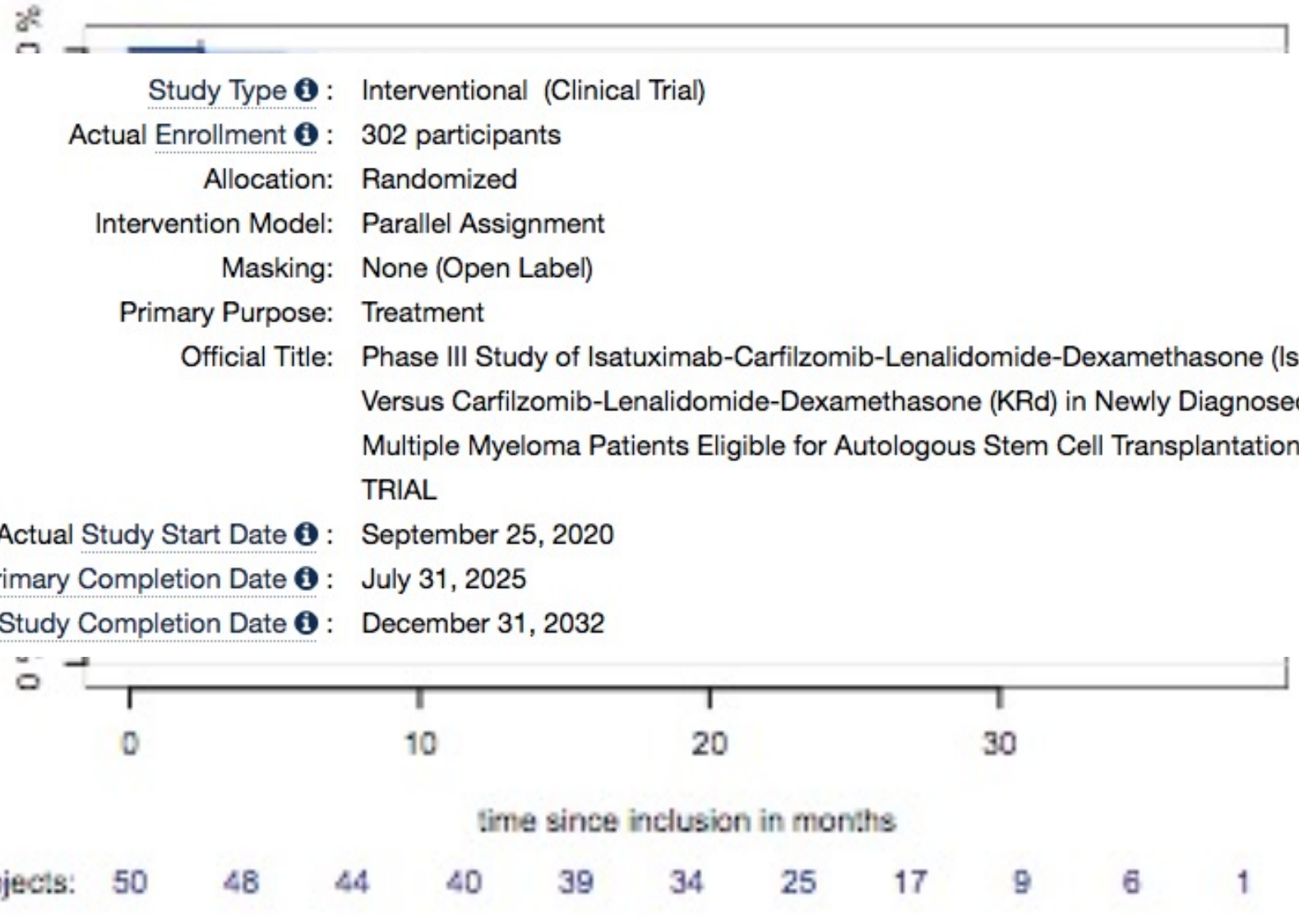

Isatuximab group (negative/n)
Control group (negative/n)
Odds ratio (95% CI)
p value homogeneity test
Age (years)
26–60 103/198 59/175 2·13 (1·41–3·25)
>60 63/133 58/154 1·49 (0·93–2·39)
0·27
Sex
Male 99/204 71/206 1·79 (1·21–2·67)
Female 67/127 46/123 1·87 (1·13–3·11)
0·90
WHO score
Grade 0/1 148/295 106/298 1·82 (1·31–2·54)
Grade >1 18/35 11/30 1·83 (0·68–5·05)
1·00
Renal impairment
Yes 8/19 7/22 1·56 (0·43–5·75)
No 158/312 110/307 1·84 (1·33–2·54)
0·81
International Staging System
Stage III 37/78 21/66 1·93 (0·98–3·87)
Stage II 63/129 37/114 1·99 (1·18–3·37)
Stage I 66/124 59/149 1·74 (1·07–2·82)
0·93
High-risk cytogenetics
No 123/254 78/234 1·88 (1·30–2·72)
Yes 34/58 29/66 1·81 (0·89–3·72)
0·93
Elevated lactate dehydrogenase
No 135/268 105/286 1·75 (1·25–2·46)
Yes 31/63 12/43 2·50 (1·11–5·89)
0·43
Revised International Staging System
Stage III 13/27 12/26 1·08 (0·37–3·22)
Stage II 112/219 61/185 2·13 (1·42–3·20)
Stage I 37/77 35/98 1·66 (0·91–3·07)
0·47
Overall 166/331 117/329 1·82 (1·33–2·48)
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
0·4 0·5 0·6 0·7 0·9 1·0 1·1 1·3 1·6 2·0 2·4 3·0 3·6 4·4 5·4
Favours lenalidomide, bortezomib, and dexamethasone
Favours isatuximab plus lenalidomide, bortezomib, and dexamethasone

GMMG-CONCEPT Trial : Isa + KRd



Interim Analysis

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	302 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Phase III Study of Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone (Isa-KRd) Versus Carfilzomib-Lenalidomide-Dexamethasone (KRd) in Newly Diagnosed Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation (IsKia TRIAL
Actual Study Start Date :	September 25, 2020
Estimated Primary Completion Date :	July 31, 2025
Estimated Study Completion Date :	December 31, 2032



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• Daratumumab/lenalidomide/dexamethasone (category 1)	
Other Recommended Regimens	
• Daratumumab/bortezomib/melphalan/prednisone (category 1)	• Daratumumab/cyclophosphamide/bortezomib/dexamethasone
• Carfilzomib/lenalidomide/dexamethasone	• Ixazomib/lenalidomide/dexamethasone
Useful In Certain Circumstances	
• Lenalidomide/low-dose dexamethasone (category 1)[k]	• Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients
• Bortezomib/dexamethasone	• Carfilzomib/cyclophosphamide/dexamethasone[f]
• Bortezomib/cyclophosphamide/dexamethasone[e]	• Cyclophosphamide/lenalidomide/dexamethasone

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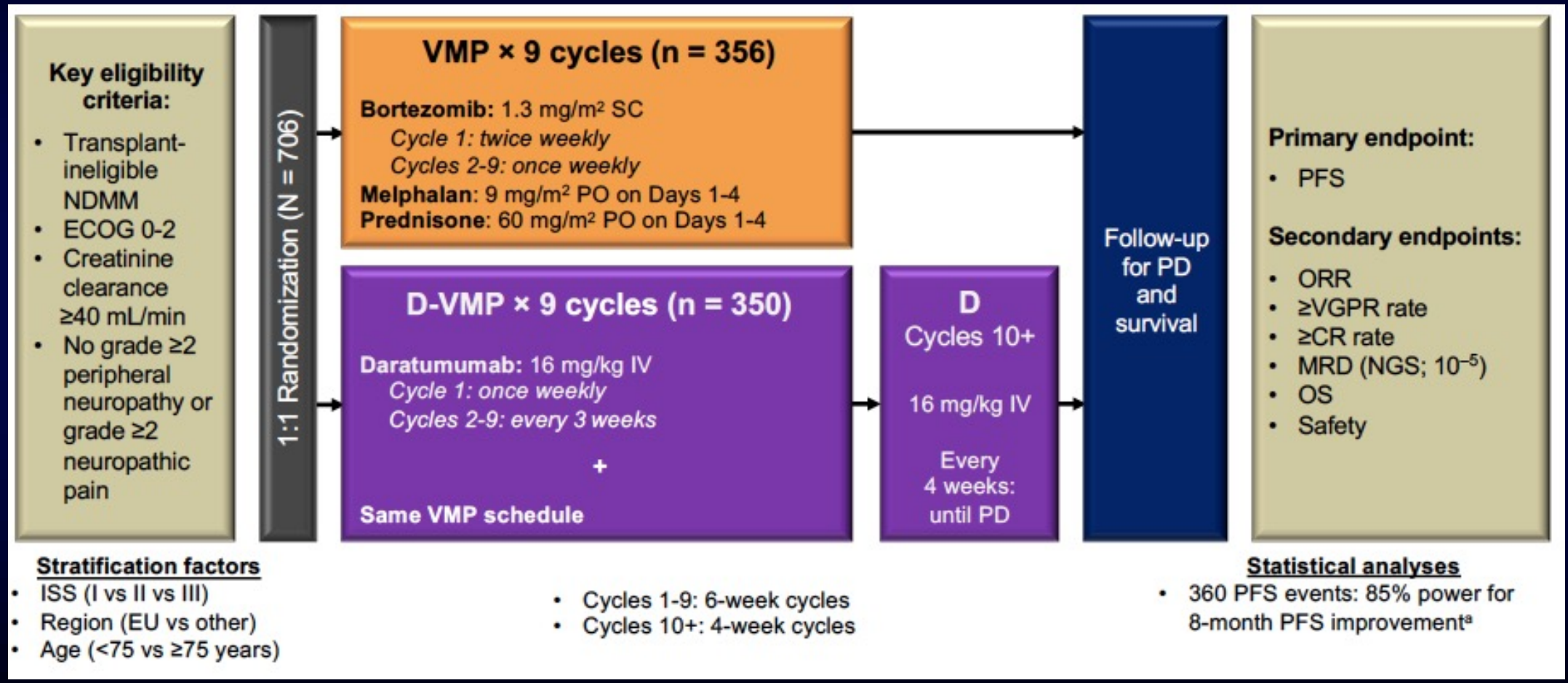
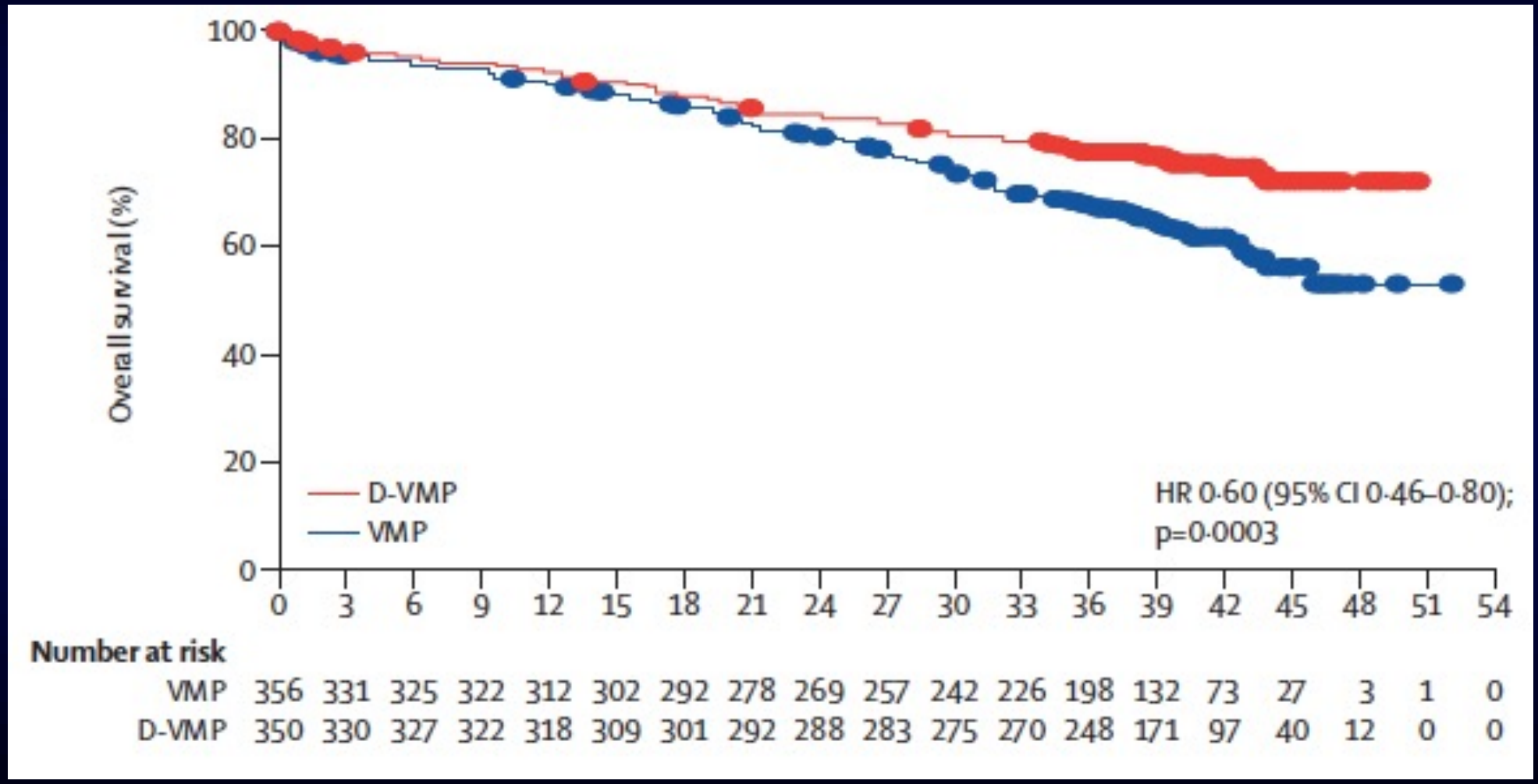
ALCYONE Trial



PFS1, 2, and OS


Overall survival (%)
100
80
60
40
20
0
D-VMP
VMP
HR 0·60 (95% CI 0·46–0·80);
p=0·0003
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54
Number at risk
VMP 356 331 325 322 312 302 292 278 269 257 242 226 198 132 73 27 3 1 0
D-VMP 350 330 327 322 318 309 301 292 288 283 275 270 248 171 97 40 12 0 0

MAIA Study

- Randomized phase III trial

Stratified by ISS (I vs II vs III), region (N America vs other), age (< 75 vs ≥ 75 yrs)

Patients with ASCT-ineligible NDMM, ECOG PS 0-2, CrCl ≥ 30 mL/min (N = 737)

Daratumumab 16 mg/kg IV (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7+) + **Lenalidomide** 25 mg/day PO on Days 1-21 + **Dexamethasone** 40 mg/wk* PO or IV (n = 368)

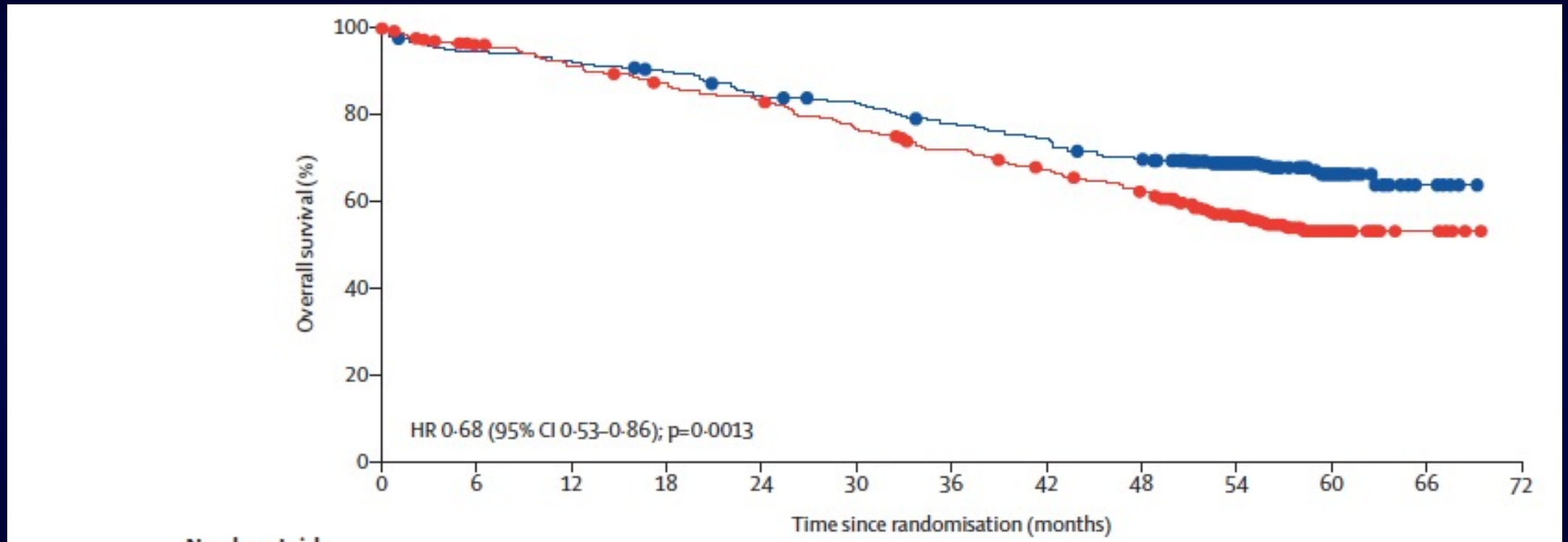
Lenalidomide 25 mg/day PO on Days 1-21 + **Dexamethasone** 40 mg/wk* PO or IV (n = 369)

→ ***28-day cycles until progression***

*Reduced to 20 mg/wk if > 75 yrs of age or BMI < 18.5.

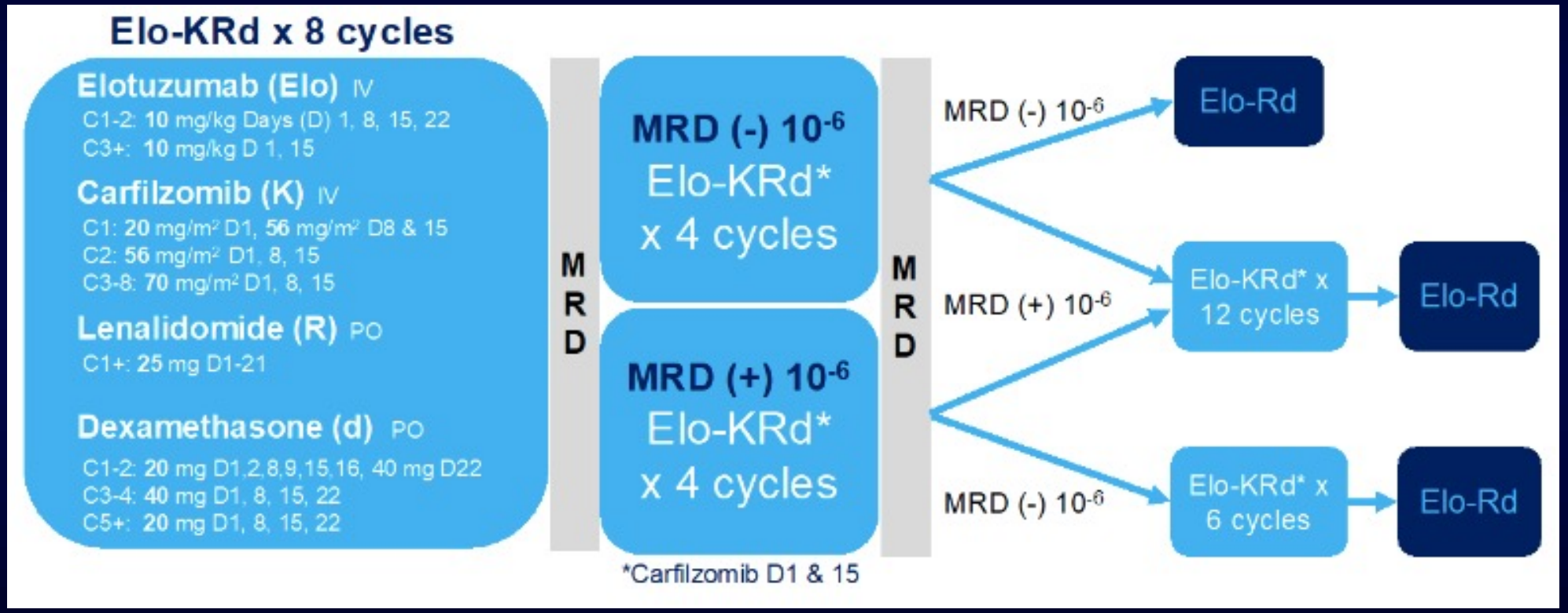
- Primary endpoint: PFS
- Secondary endpoints : ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, safety

PFS & OS Updates

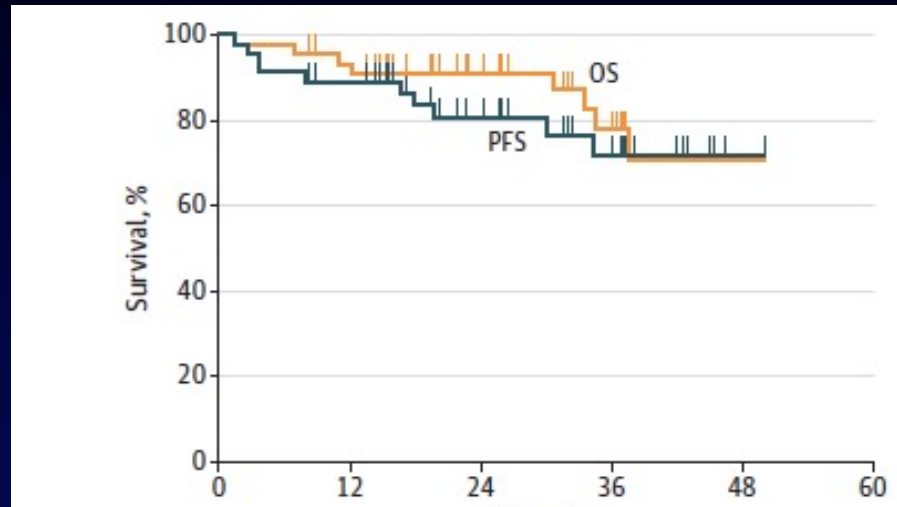


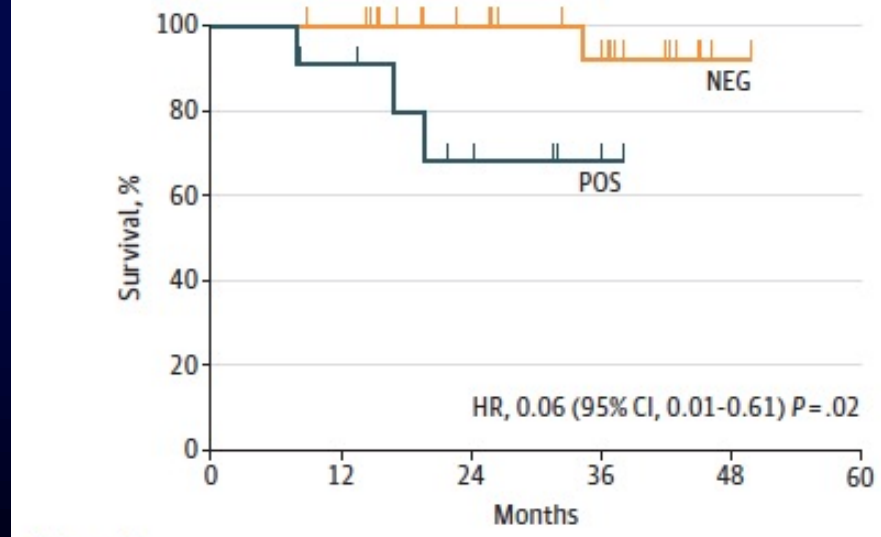
Number at risk (number censored)													
Lenalidomide and dexamethasone	369 (0)	343 (13)	324 (14)	308 (16)	294 (16)	270 (17)	251 (20)	232 (22)	213 (24)	134 (85)	42 (171)	5 (208)	0 (213)
Daratumumab plus lenalidomide and dexamethasone	368 (0)	346 (3)	338 (3)	328 (5)	305 (6)	297 (8)	280 (9)	266 (9)	249 (10)	170 (86)	63 (189)	6 (245)	0 (251)

Using MRD to Guide Therapy



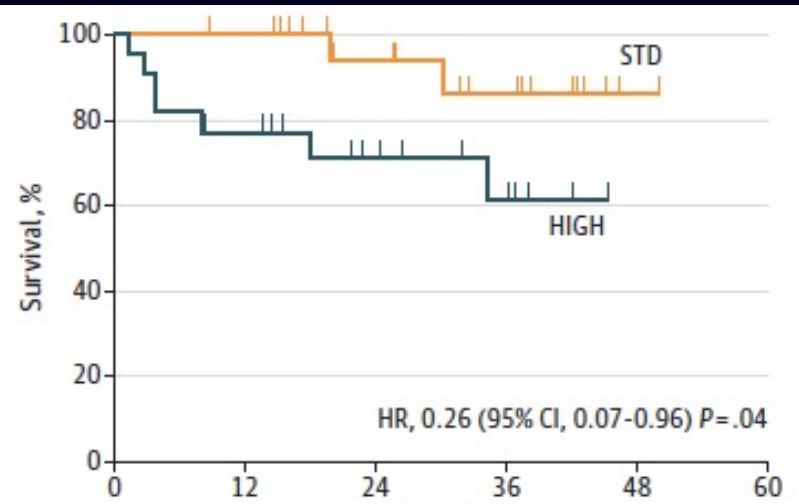
Outcomes

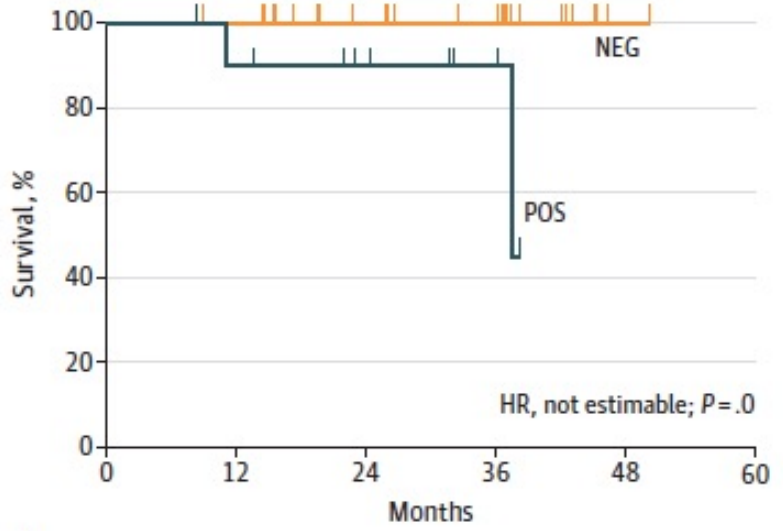




No. at risk

NEG	26	26	18	13	2	0
POS	11	10	6	3	0	0





No. at risk

NEG	26	26	18	14	1	0
POS	11	10	7	4	0	0

Conclusions

- For transplant-eligible patients
  - VRd remains a standard of care
  - Emerging quadruplets with α-CD38 mAbs
  - PERSEUS (Dara) & GMMG-HD7 (Isa)
- For transplant-ineligible patients
  - VRd-lite or DaraRd
  - CEPHEUS (Dara) & IMROZ (Isa)
  - S2209: VRd-lite-R vs. DRd-R vs. DRd-DR

Remaining Questions

- Possibility for molecularly-, risk-, or response-adapted therapy?
- Modifications of current regimen to achieve CR and MRD-negativity in closer to 100%?
- Transition to fixed duration of treatment versus treat to progression to preserve options at time of relapse?

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