Advances in Oncology
Updates and Controversies in the Therapy of Multiple Myeloma

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11/15/2025

NCI Designated Comprehensive Cancer Center

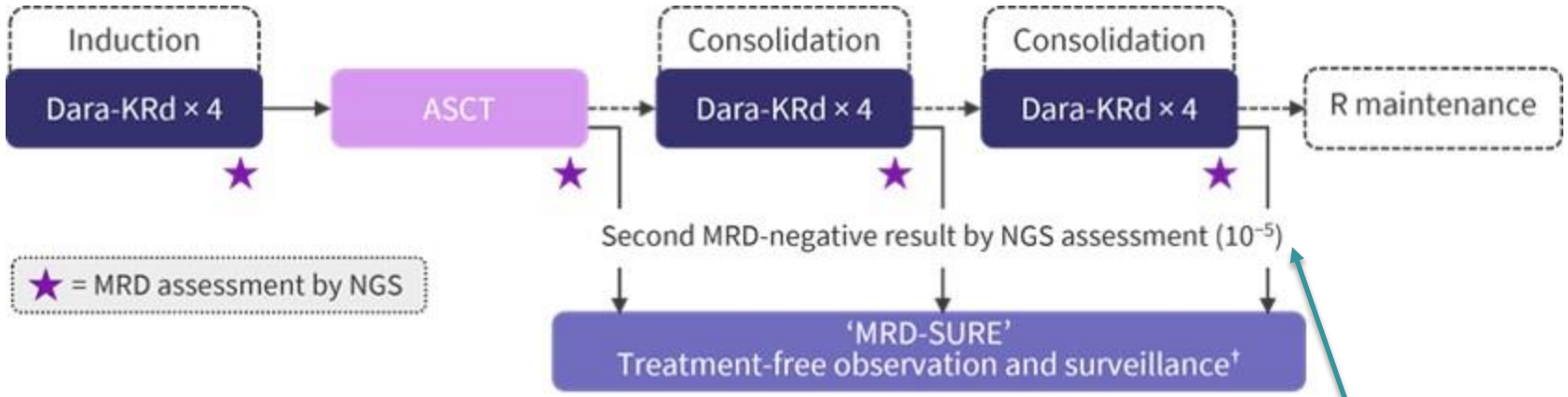
UCDAVIS COMPREHENSIVE CANCER CENTER

Outline

- Newly Diagnosed MM:
  - MASTER Trial Final Analysis
  - IMROZ
- Post-Transplant Maintenance Therapy
  - GRIFFIN + PERSEUS
  - AURIGA
  - FORTE
- How I Approach NDMM

MASTER Trial

- Response adapted approach to newly diagnosed multiple myeloma



Dosing

28-day Dara-KRd cycles
- Dara: 16 mg/m² IV on Days 1, 8, 15, and 22 (Days 1 and 15 for Cycles 3 and 4)
- K: 56 mg/m² IV on Days 1, 8, and 15 (20 mg/m² on first dose of Cycle 1)
- R: 25 mg PO on Days 1–21
- d: 40 mg IV or PO on Days 1, 8, 15, and 22

- One cycle of CyBorD allowed prior to enrollment
- High risk enriched:
  - At least 35% of patients would have t(4;14), t(14;16) or del(17p)
- Post Hoc Analysis:
  - Include +1q and t(14;20)
  - Standard risk (no high risk features)
  - High risk: one high risk
  - Ultra High Risk: ≥ 2 high risk features

Costa et al, Lancet Haem, 2023
Graphic: Multiple Myeloma Hub, accessed 11/2024

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MASTER Trial

	Standard-risk group (n=53)	High-risk group (n=46)	Ultra high-risk group (n=24)	Total (n=123)
Gender				
Men	33 (62%)	24 (52%)	13 (54%)	70 (57%)
Women	20 (38%)	22 (48%)	11 (46%)	53 (43%)
Age, years				
Median (IQR)	60 (50–69)	61 (57–68)	60 (56–66)	61 (55–68)
≥70	12 (23%)	10 (22%)	2 (8%)	24 (20%)
Race/ethnicity				
Non-Hispanic White	42 (79%)	33 (72%)	19 (79%)	94 (76%)
Non-Hispanic Black	10 (19%)	11 (24%)	4 (17%)	25 (20%)
Other	1 (2%)	2 (4%)	1 (4%)	4 (3%)
ECOG performance status				
0–1	42 (79%)	40 (87%)	17 (71%)	99 (80%)
2	11 (21%)	6 (13%)	7 (29%)	24 (20%)
Cytogenetic abnormality				
Hyperdiploidy	27 (51%)	20 (44%)	4 (17%)	51 (41%)
del(13q)	19 (36%)	20 (44%)	18 (75%)	57 (46%)
Gain or amplification of 1q	0	24(52%)	20 (83%)	44 (36%)
del(1p)	3 (6%)	4 (9%)	5 (21%)	12 (10%)
t(11;14)	14 (26%)	7 (15%)	0	21 (17%)
t(4;14)	0	8 (17%)	13 (54%)	21 (17%)
t(14;16)	0	2 (4%)	4 (17%)	6 (5%)
del(17p)	0	12 (26%)	14 (58%)	26 (21%)
ISS				
I	28 (53%)	15 (33%)	5 (21%)	48 (39%)
II	20 (38%)	19 (41%)	8 (33%)	46 (37%)
III	5 (9.4%)	12 (26%)	11 (46%)	29 (24%)
R-ISS				
I	25 (47%)	11 (24%)	0	35 (28%)
II	27 (51%)	23 (50%)	13 (54%)	63 (51%)
III	1 (2%)	12 (26%)	11 (46%)	25 (20%)

- 118 (96%) were evaluable for MRD
- 96 (81%) reached MRD negativity
  - 78% of Standard Risk
  - 86% of High Risk
  - 79% of Ultra-High Risk
- 85 (72%) of MRD negative patients reached CR
  - 76% of Standard Risk
  - 75% of High Risk
  - 58% of Ultra-High Risk
- Of 118 MRD evaluable patients, 71% achieved MRD negativity at 10^{-6}

Costa et al, Lancet Haem, 2023

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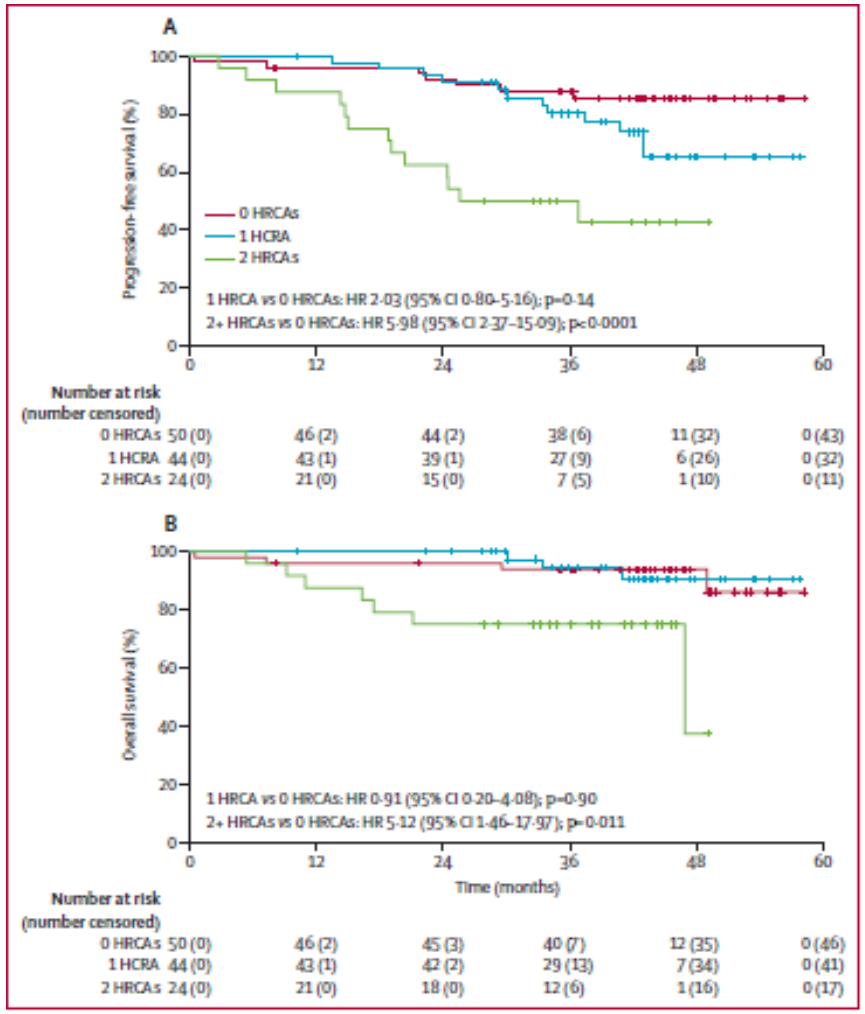

Progression Free Survival (A) at 36 months:

- Standard risk: 88%
- High Risk: 79%
- Ultra-High Risk: 50%

Overall Survival (B) at 36 months:

- Standard Risk: 94%
- High Risk: 92%
- Ultra-High Risk: 75%

Costa et al, Lancet Haem, 2023

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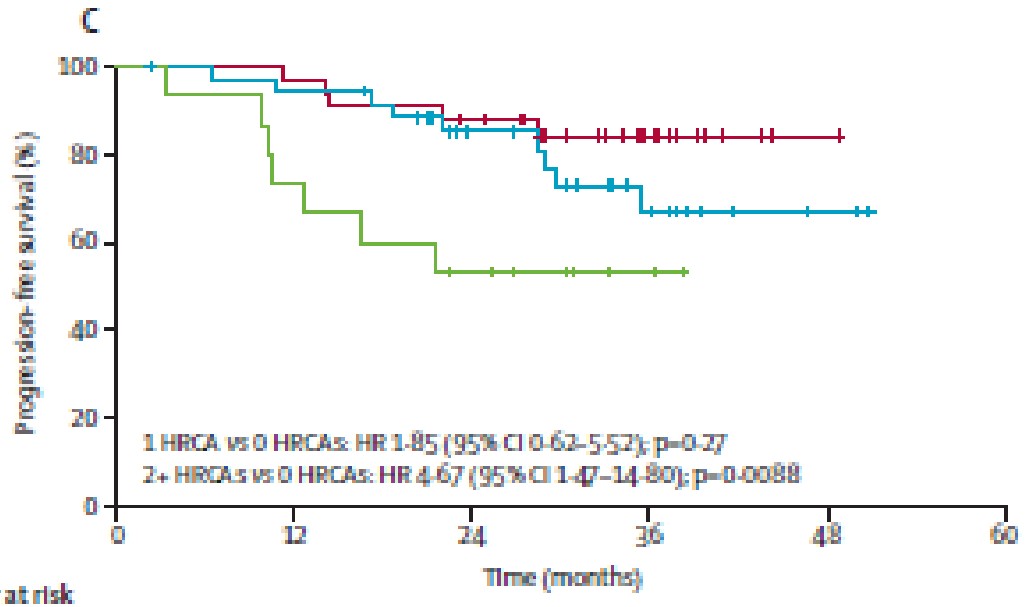
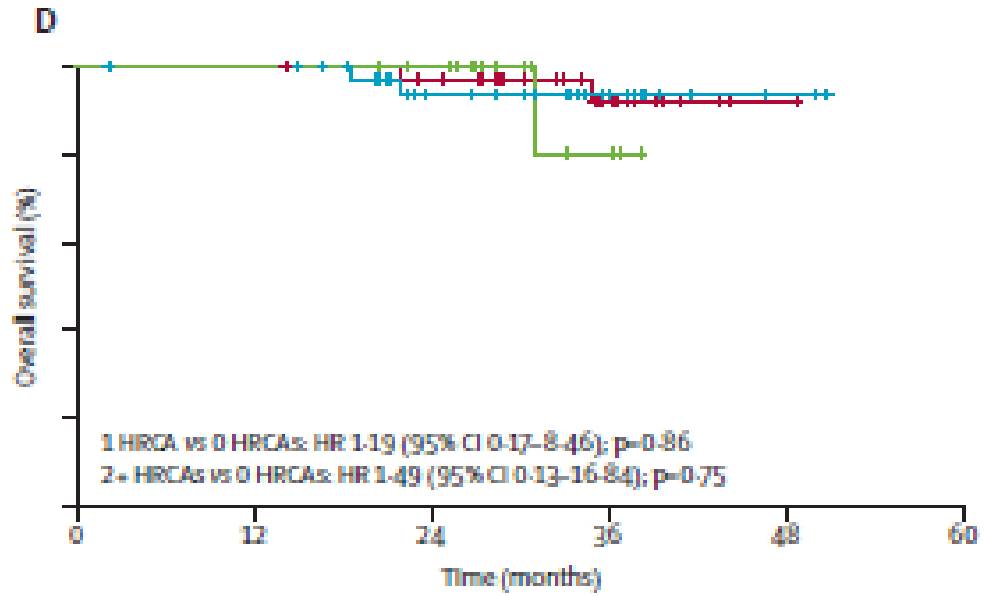
MASTER Trial

MRD-SURE (withdrawal of therapy)

- 84 (71%) met criteria and proceeded onto observation alone
- Land-marked analysis (at beginning of treatment-free observation)





Number at risk (number censored)												
0 HRCAs	33 (0)	32 (0)	28 (1)	13 (5)	1 (27)	0 (28)	33 (0)	33 (0)	30 (2)	14 (17)	1 (30)	0 (31)
1 HCRA	36 (0)	33 (1)	22 (9)	11 (16)	2 (25)	0 (27)	36 (0)	35 (1)	22 (12)	12 (22)	2 (32)	0 (34)
2 HRCAs	15 (0)	11 (0)	7 (1)	2 (6)	0 (8)	0 (8)	15 (0)	15 (0)	13 (2)	3 (11)	0 (14)	0 (14)

Costa et al, Lancet Haem, 2023

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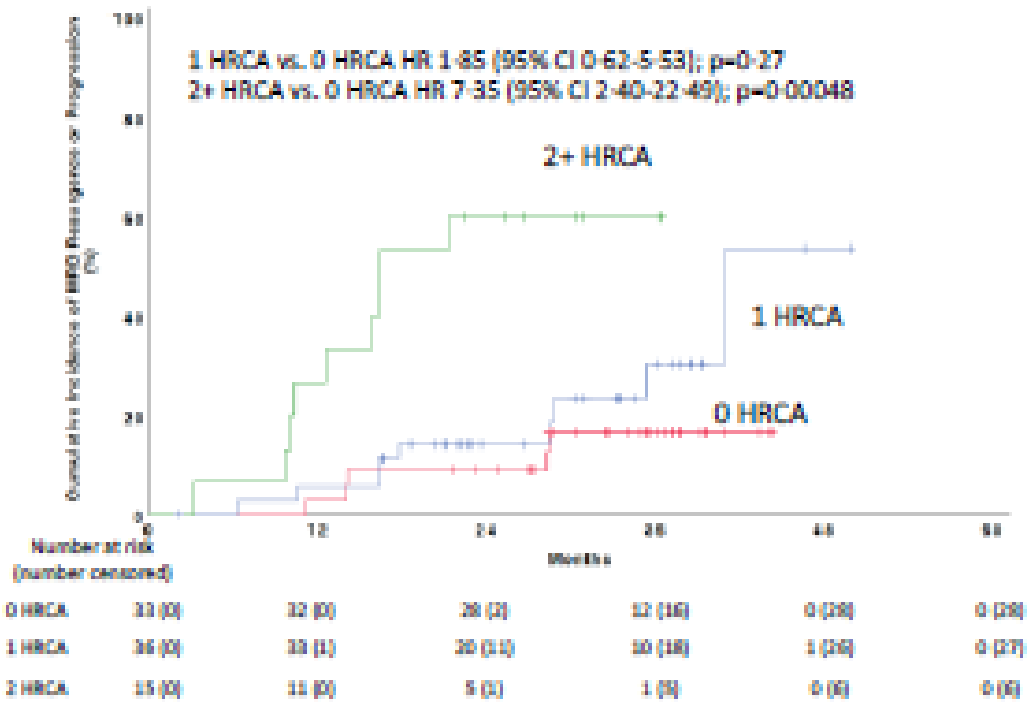
MASTER Trial

B



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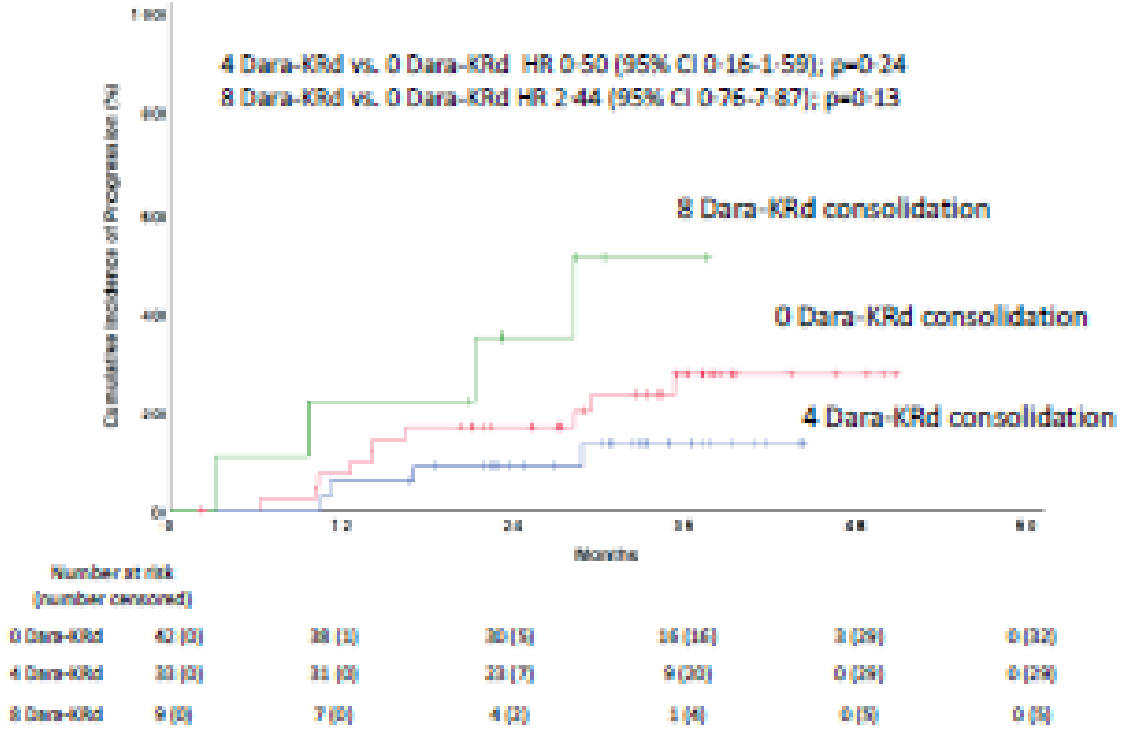

Costa et al, Lancet Haem, 2023

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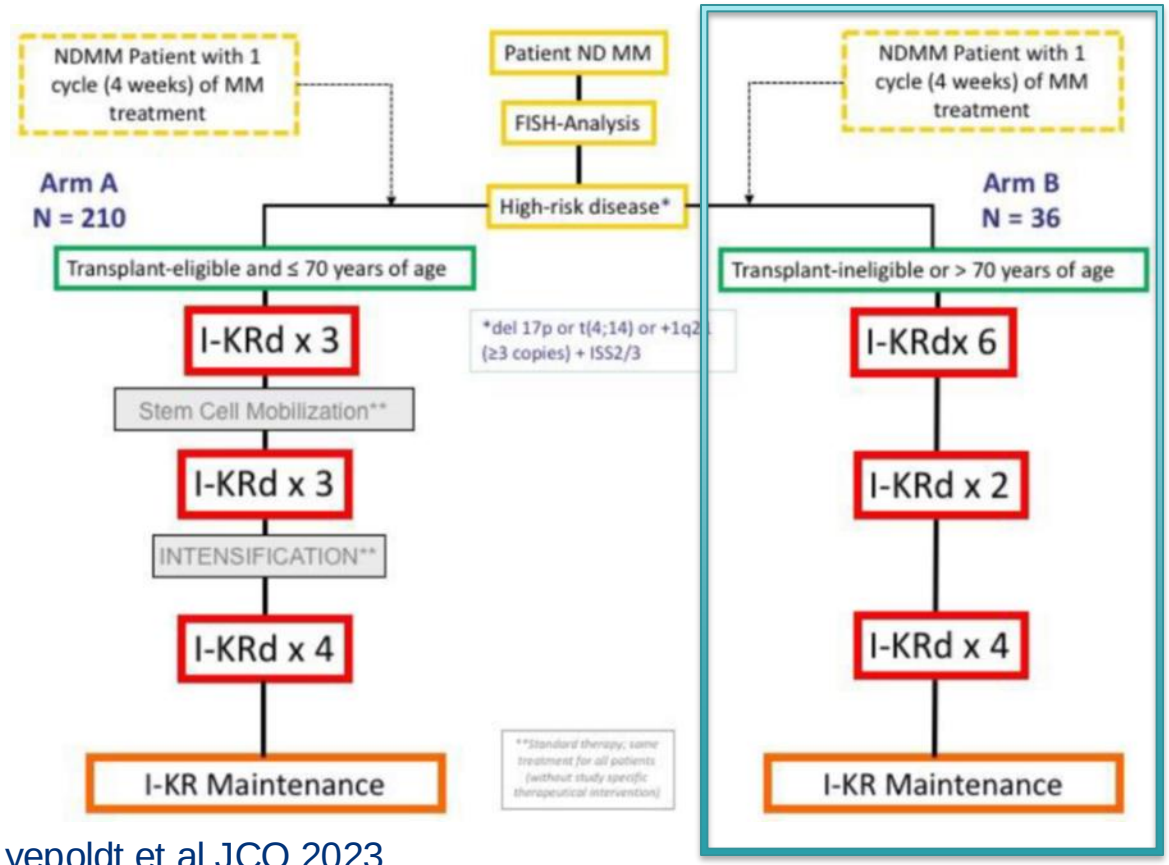
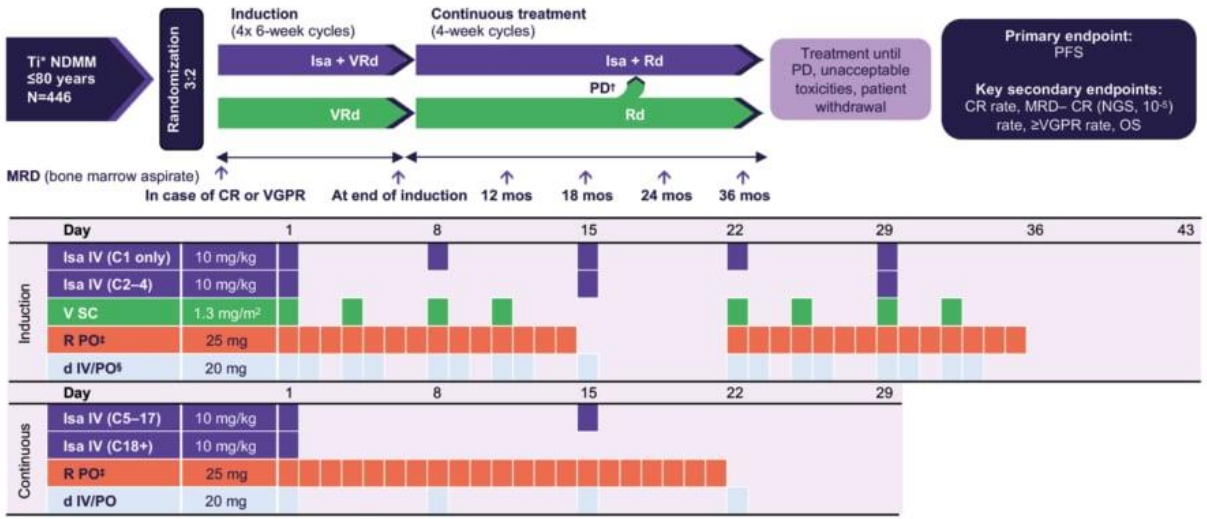
Quadruplet Therapy for Transplant Ineligible Patients:
GMMG-Concept and IMROZ

GMMG-Concept: Isatuximab-KRd for high risk NDMM



IMROZ: Isatuximab-VRd vs VRd in Transplant-Ineligbile NDMM



Lyepoldt et al JCO 2023
Facon et al NEJM 2024

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Quadruplet Therapy for Transplant Ineligible Patients:
GMMG-Concept and IMROZ

- Primary Outcomes:
  - GMMG-Concept: MRD negativity $<10^{-5}$ by next-gen flow
  - IMROZ: Progression Free Survival
    - MRD outcomes: $<10^{-6}$ by next-gen sequencing

	GMMG	IMROZ IVRd	IMROZ: VRd
Age (median (range))	74 (64-87)	72 (60-80)	72 (55-80)
Cytogenetics			
Standard	0	78%	77%
High Risk	100%	15%	19%
Unknown		7%	4%

Lyepoldt et al JCO 2023
Facon et al NEJM 2024

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Quadruplet Therapy for Transplant Ineligible Patients:
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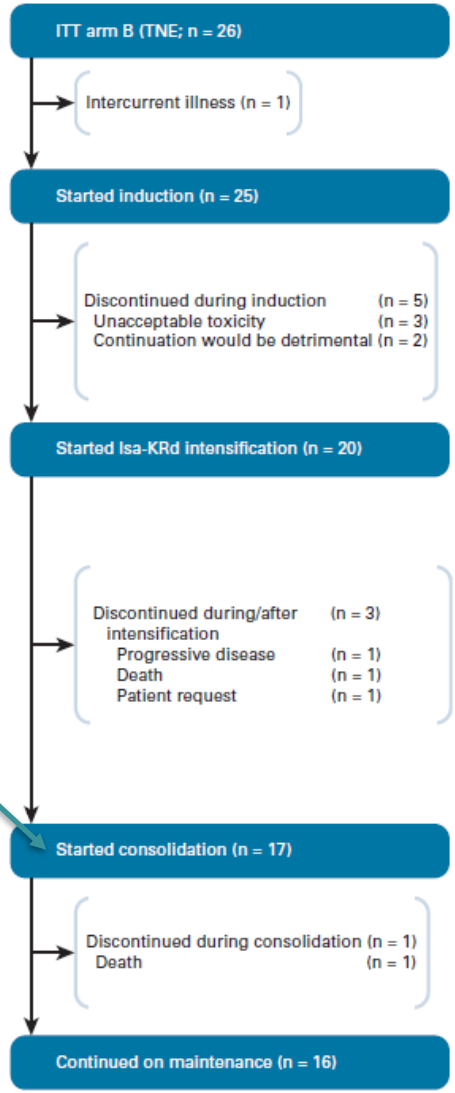
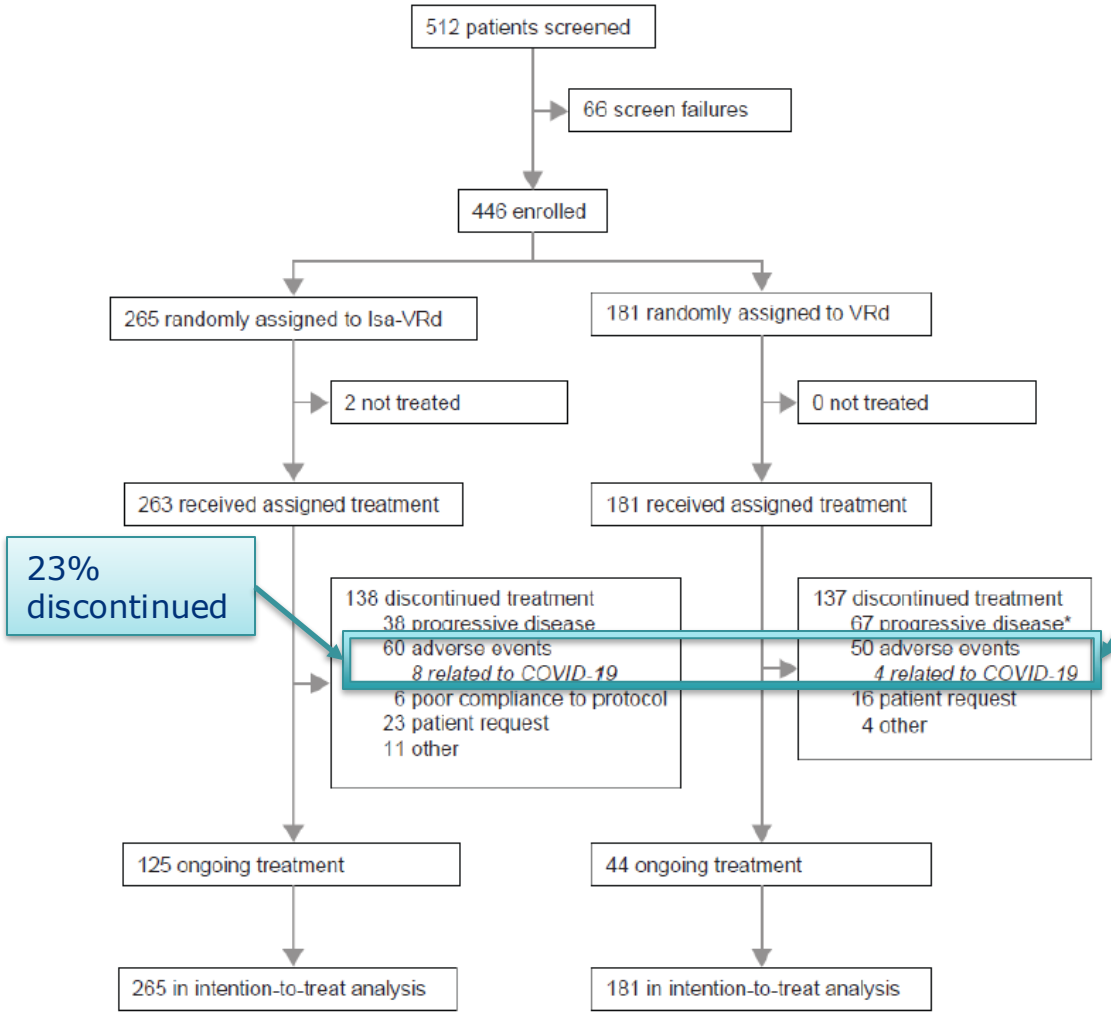


35% discontinued prior to Consolidation



23% discontinued

28% discontinued

Lyepoldt et al JCO 2023
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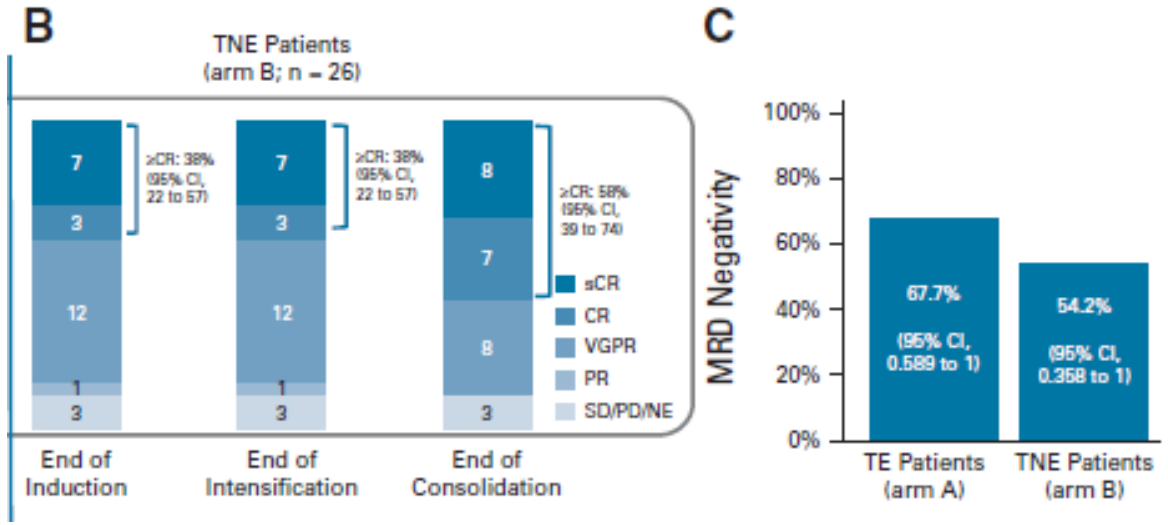
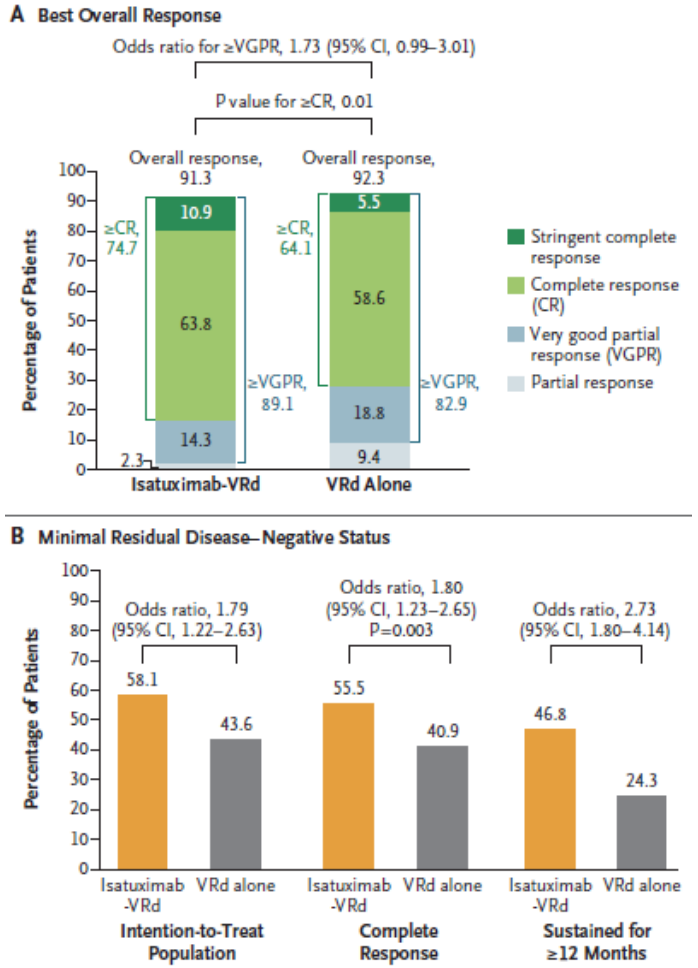
Quadruplet Therapy for Transplant Ineligible Patients:
GMMG-Concept and IMROZ

GMMG-Concept



IMROZ



Lyepoldt et al JCO 2023
Facon et al NEJM 2024

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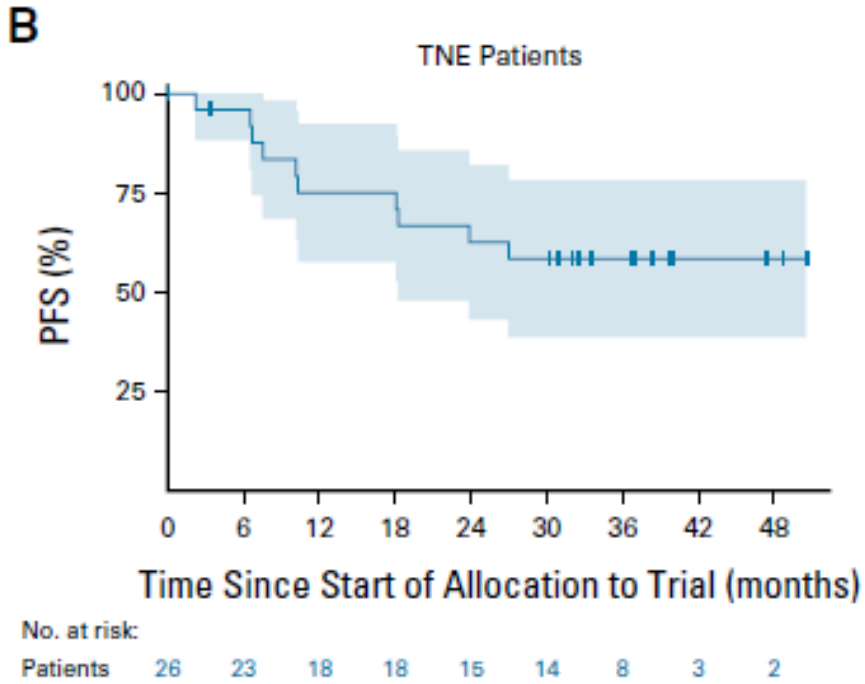
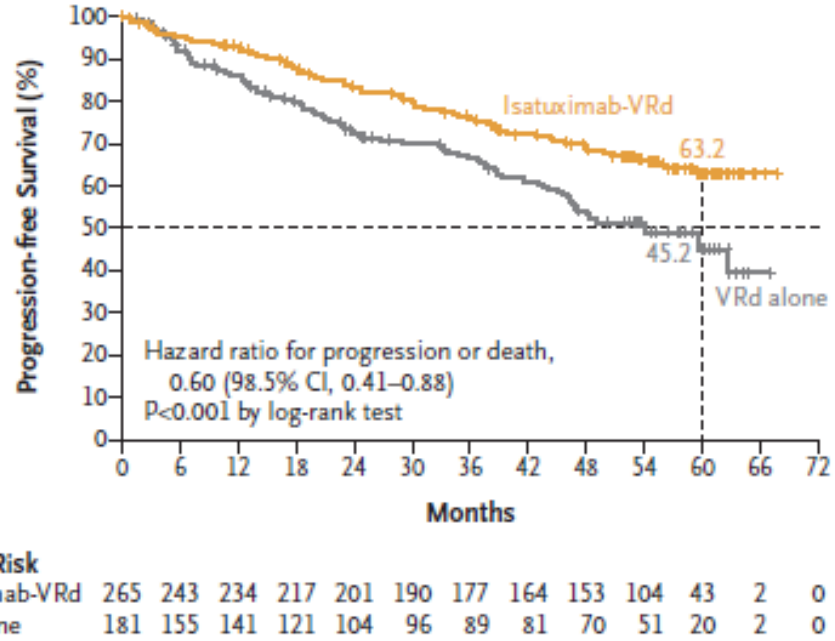
Quadruplet Therapy for Transplant Ineligible Patients:
GMMG-Concept and IMROZ

PFS: GMMG-Concept



PFS: IMROZ



Lyepoldt et al JCO 2023
Facon et al NEJM 2024

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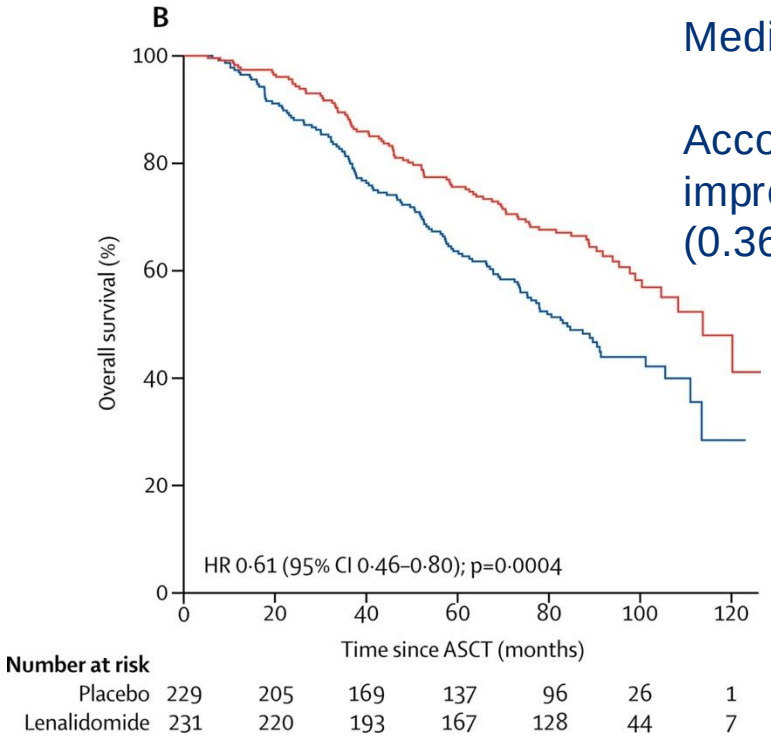
Maintenance Therapy Post SCT

CALGB100104: The Old (Current?) Standard

- Design:
  - Phase III RCT
  - Lenalidomide 10-15 mg vs Placebo continued
- Patients
  - 460 randomized
  - Median age 59
  - Median Create 0.9
  - ISS stage I in 75% of patients
  - PR in 49%, CR in 32% after transplant

Lenalidomide Maintenance: Long term follow up of CALGB100104

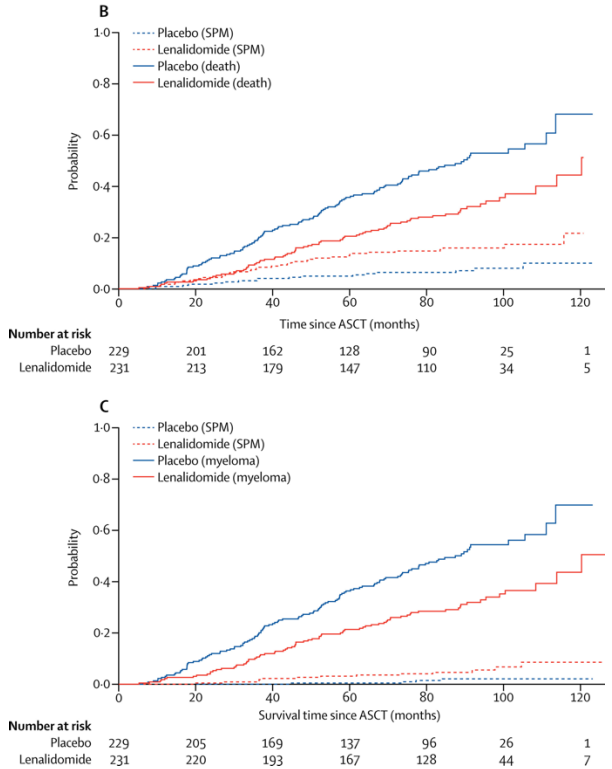
Overall Survival



Median OS 114 mo vs 84 mo

Accounting for cross over improves the HR to 0.52 (0.36-0.73)

Second Primaries: cost of doing business



McCarthy et al, NEJM 2012
Holstein et al, Lancet Haem, 2017
McCarthy et al, ASH 2018

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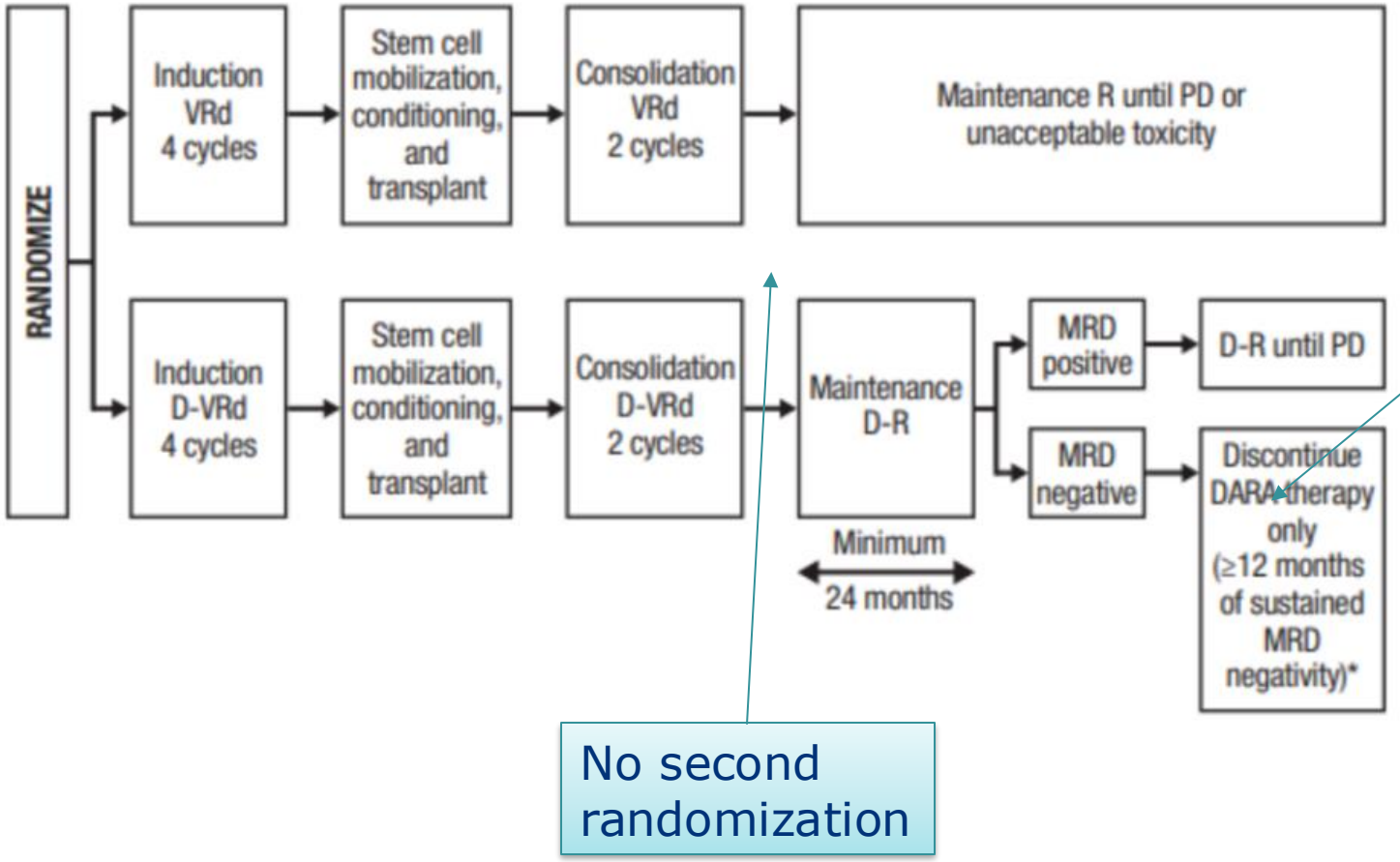

Voorhees et al Blood 2020, Lancet Haem 2023
Sonneveld et al NEJM 2024

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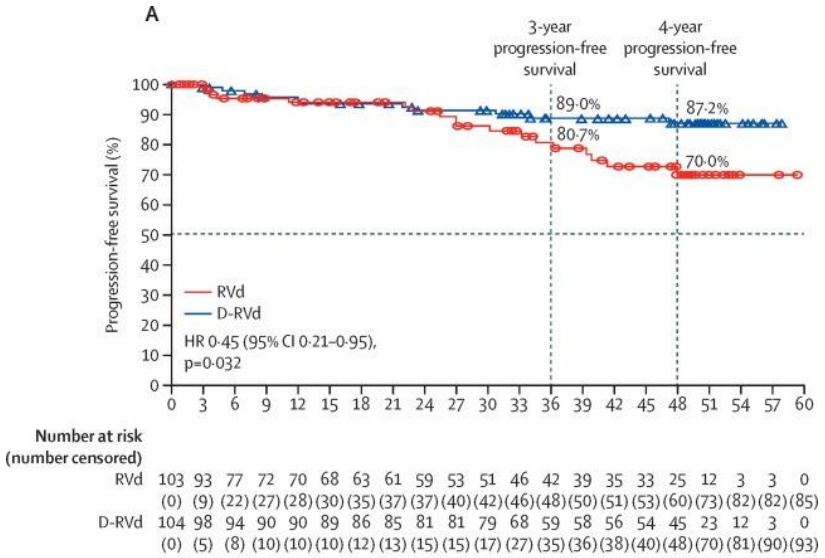
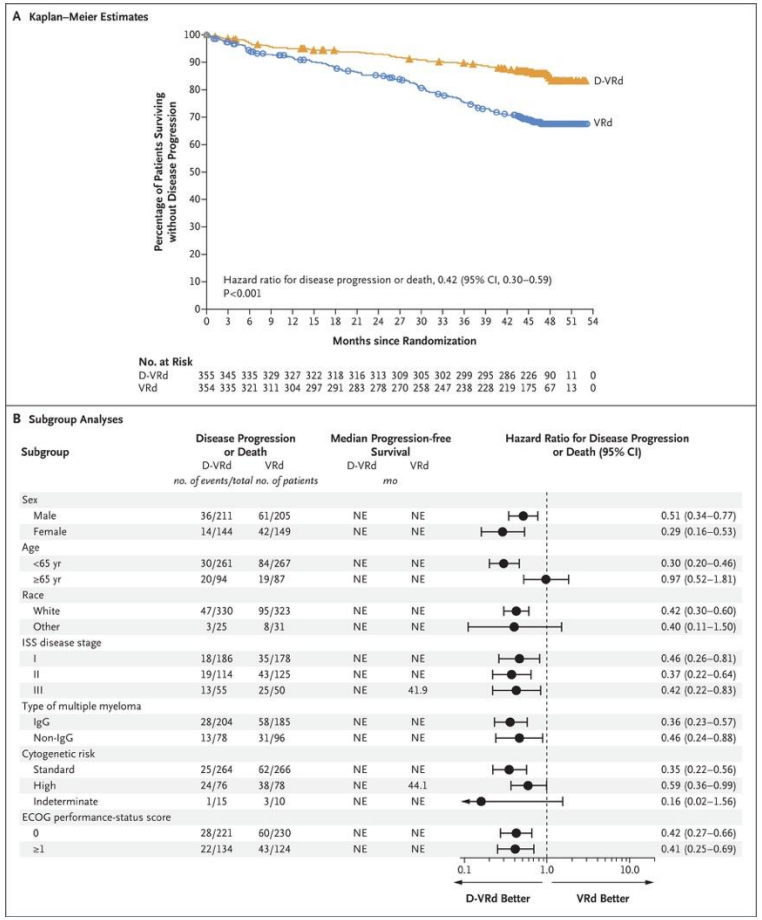
PFS Benefit with Daratumumab Inclusion





Voorhees et al Blood 2020, Lancet Haem 2023
Sonneveld et al NEJM 2024

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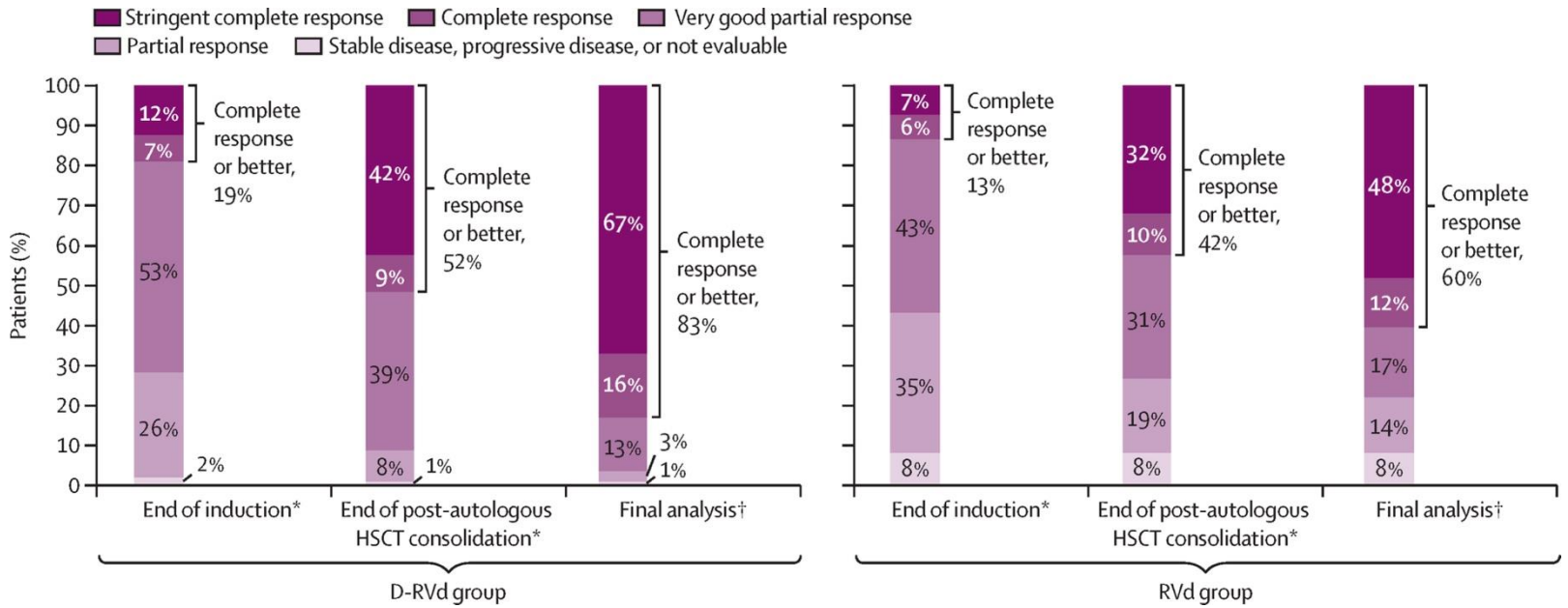
Response over time (GRIFFIN)



Depth of response improves during maintenance, more so in the daratumumab arm

Voorhees et al Blood 2020

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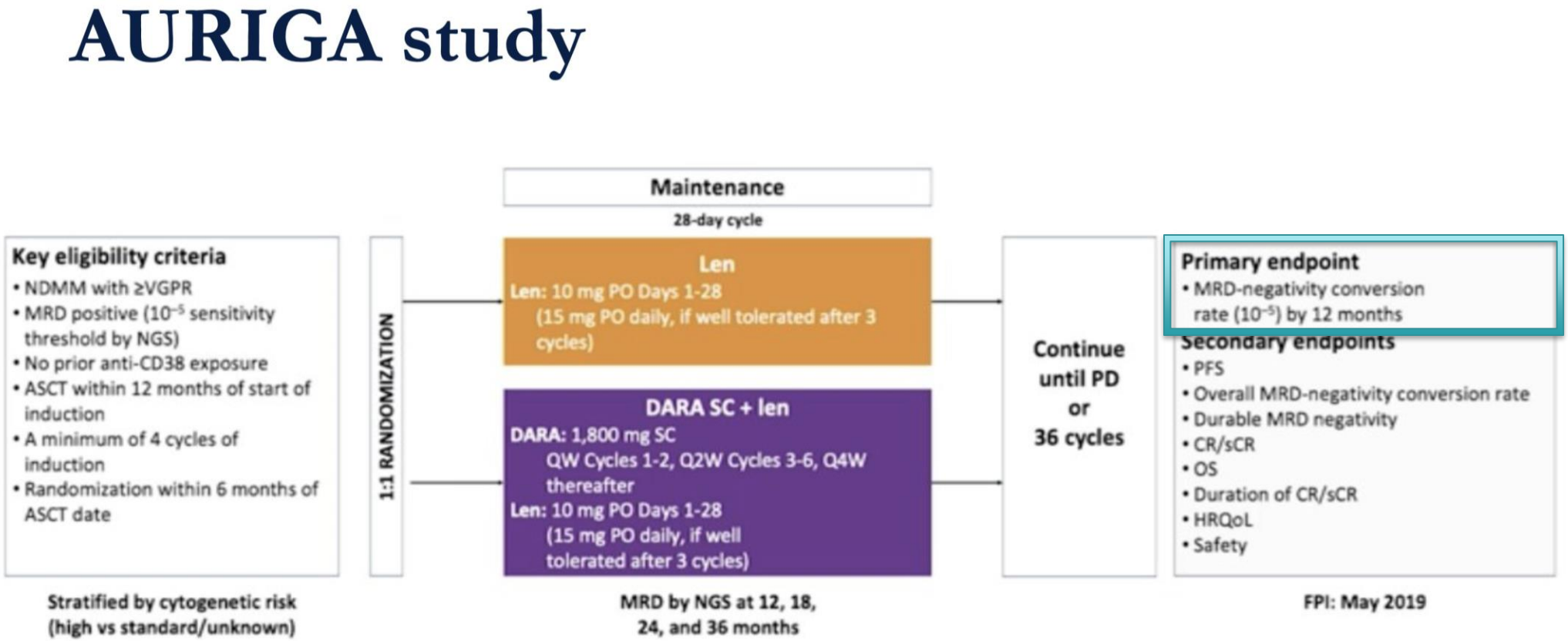
Dara-Len in patients with MRD+ disease post SCT: AURIGA



Badros et al, Blood 2024
Schema from Rahul Banerjee's Twitter Feed

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Dara-Len in patients with MRD+ disease post SCT: AURIGA

Table 1. Patient demographic and disease characteristics in the ITT population

	D-R	R
Age, years	n = 99	n = 101
Median (range)	63 (35-77)	62 (35-78)
Category, n (%)		
<65	61 (61.6)	61 (60.4)
65-70	23 (23.2)	21 (20.8)
≥70	15 (15.2)	19 (18.8)
Sex, n (%)	n = 99	n = 101
Male	61 (61.6)	58 (57.4)
Female	38 (38.4)	43 (42.6)
Race, n (%)	n = 99	n = 101
White	67 (67.7)	68 (67.3)
Black or African American	20 (20.2)	24 (23.8)
Asian	5 (5.1)	1 (1.0)
American Indian or Alaska Native	0	1 (1.0)
Other*	5 (5.1)	5 (5.0)
Not reported	2 (2.0)	2 (2.0)
ECOG PS score, n (%)	n = 99	n = 101
0	45 (45.5)	55 (54.5)
1	52 (52.5)	44 (43.6)
2	2 (2.0)	2 (2.0)
ISS disease stage, n (%)	n = 91	n = 98
I	40 (44.0)	38 (38.8)
II	28 (30.8)	37 (37.8)
III	23 (25.3)	23 (23.5)
Number of induction cycles	n = 98	n = 99
Median (range)	5.0 (4.0-8.0)	5.0 (4.0-8.0)
Cytogenetic risk at diagnosis	n = 92	n = 89
Standard risk	63 (68.5)	66 (74.2)
High risk†	22 (23.9)	15 (16.9)
del(17p)	13 (14.1)	3 (3.4)
t(4;14)	10 (10.9)	12 (13.5)
t(14;16)	6 (6.5)	7 (7.9)
Unknown	7 (7.6)	8 (9.0)
Revised cytogenetic risk at diagnosis	n = 93	n = 89
Standard risk	52 (55.9)	53 (59.6)
High risk‡	32 (34.4)	30 (33.7)
del(17p)	13 (14.0)	3 (3.4)
t(4;14)	10 (10.8)	12 (13.5)
t(14;16)	6 (6.5)	7 (7.9)
t(14;20)	1 (1.1)	2 (2.2)
gain/amp(1q21)	16 (17.2)	22 (24.7)

Badros et al, Blood 2024

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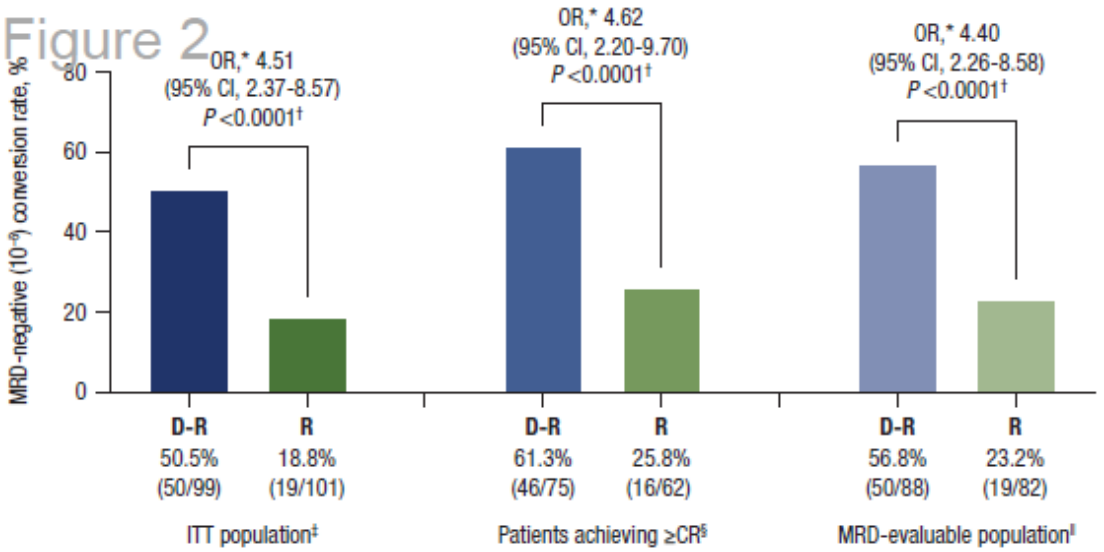
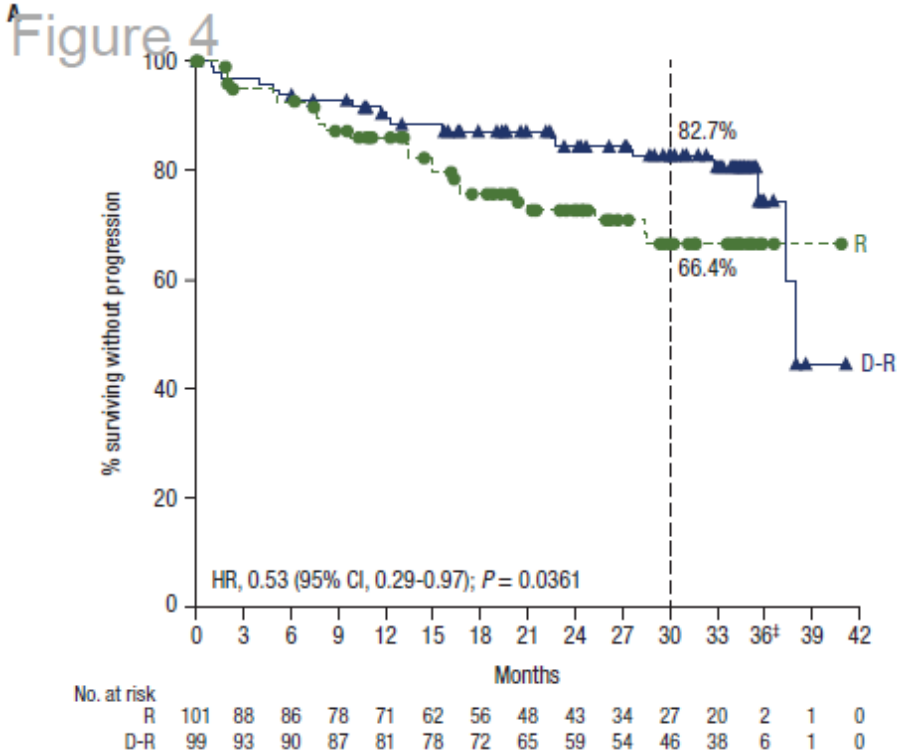
Dara-Len in patients with MRD+ disease post SCT: AURIGA

Primary Outcome: MRD- Conversion Rate



PFS Better in DR vs R
Did not meet stopping rule (yet?)



Badros et al, Blood 2024

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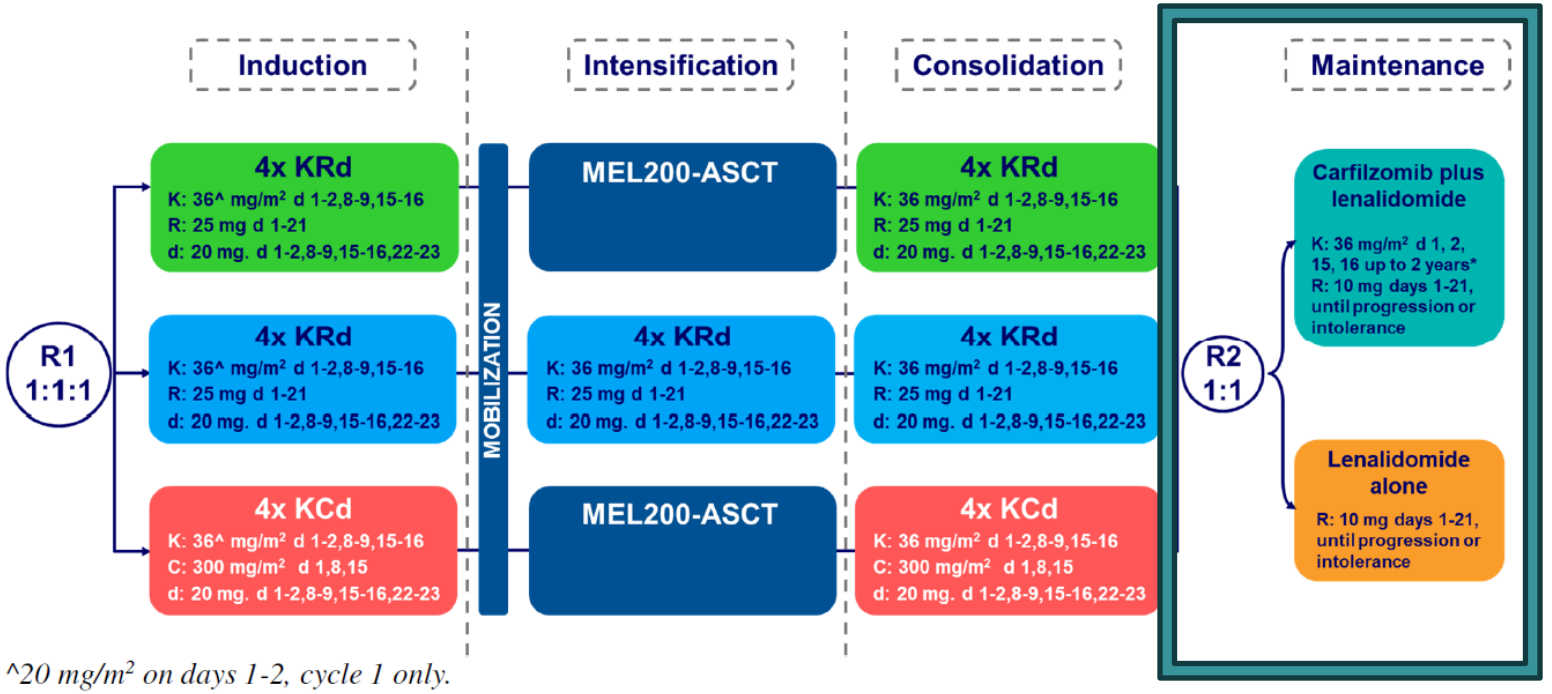
So: Daratumumab is the new standard?

- Maybe?
  - Data for dara inclusion in patients destined for transplant is certainly compelling
  - In MRD+ patients post SCT, we have randomized data supporting doublets
- Multiple questions remain, however:
  - How long?
  - If patients have an adequate response to induction/transplant can we forgo dara?
- Ongoing DRAMMATIC trial is directly addressing daratumumab-lenalidomide vs lenalidomide alone post transplant, agnostic of induction

Carfilzomib + Lenalidomide: the FORTE trial



^*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.*

Abbreviations. R1, first randomisation (induction/consolidation treatment); R2, second randomisation (maintenance treatment); K, carfilzomib; C, cyclophosphamide; R, lenalidomide; -d, dexamethasone; d, days; MEL200, melphalan at 200 mg/m²; ASCT, autologous stem-cell transplantation.

Gay et al, Lancet Onc 2021;
Mina et al Lancet Onc 2022

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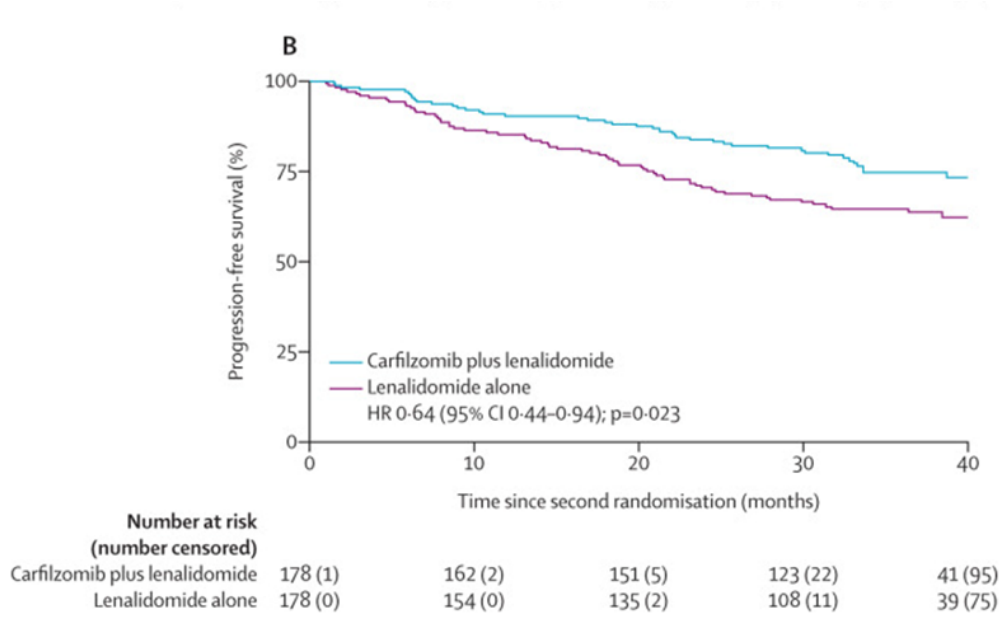
Carfilzomib + Lenalidomide: the FORTE trial

- High risk cytogenetics at randomization 2:
  - KR: 27%
  - R: 28%
- High risk cytogenetics (including amp(1q)) at randomization 2:
  - KR: 56%
  - R: 53%



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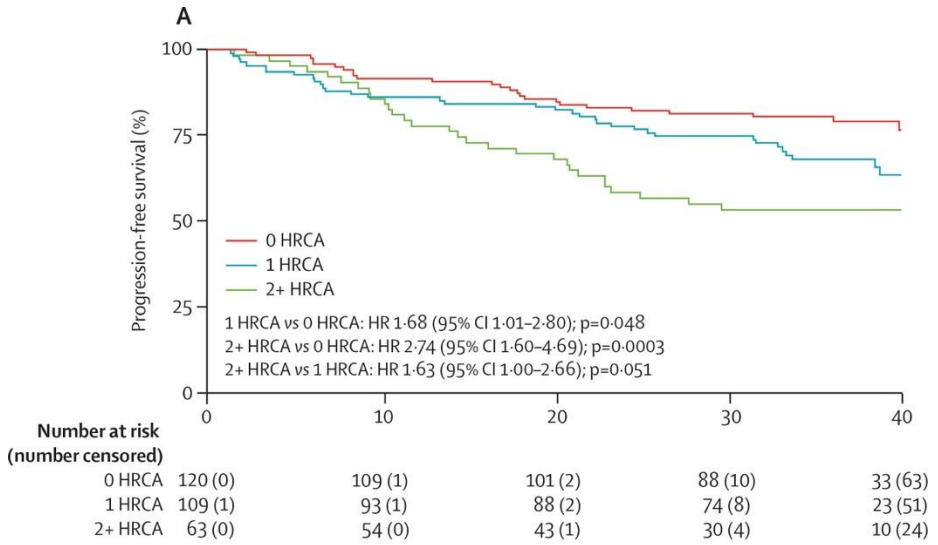

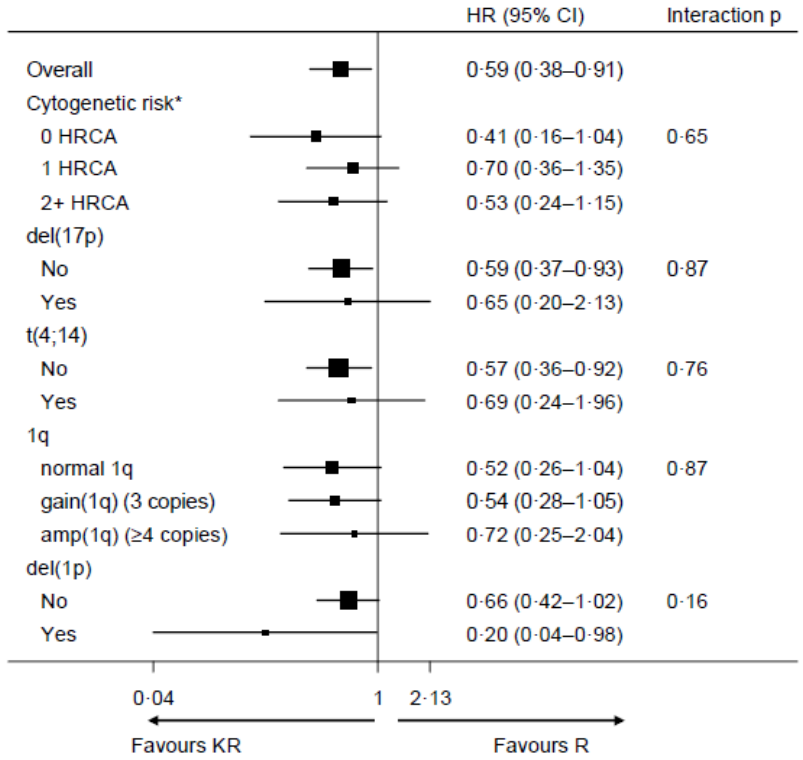

Gay et al, Lancet Onc 2021;
Mina et al Lancet Onc 2022

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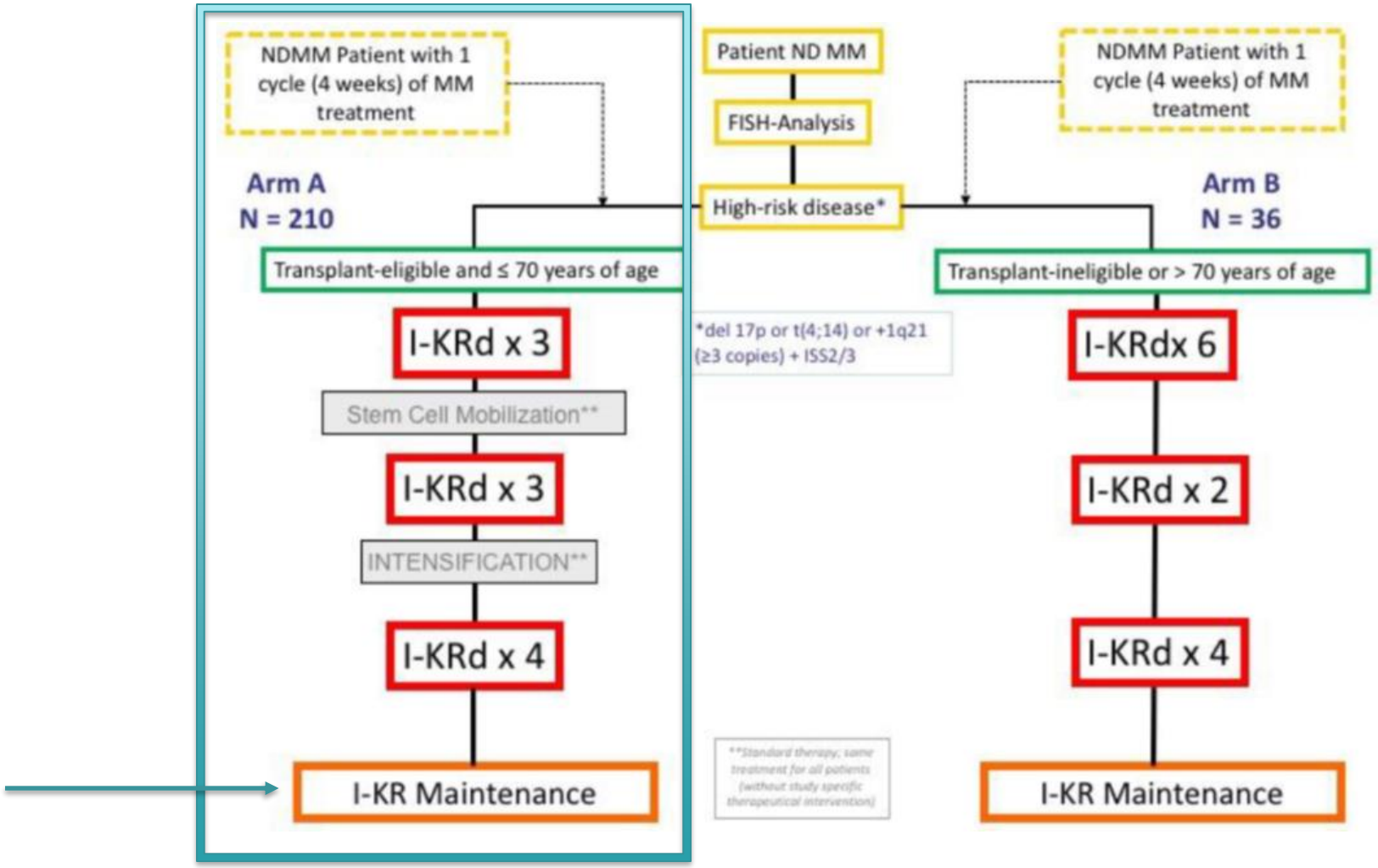
Triplet “Maintenance” in high risk patients:
GMMG-CONCEPT



Leypoldt et al JCO 2023

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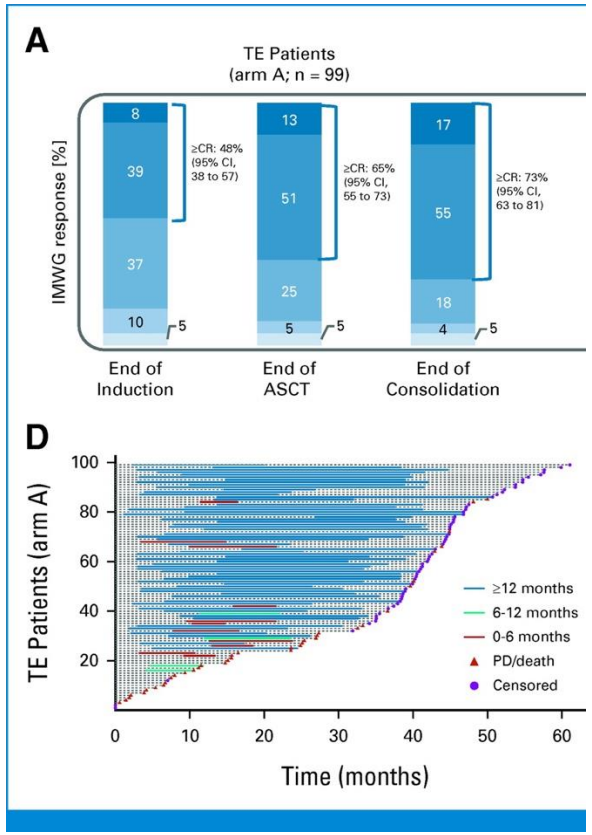
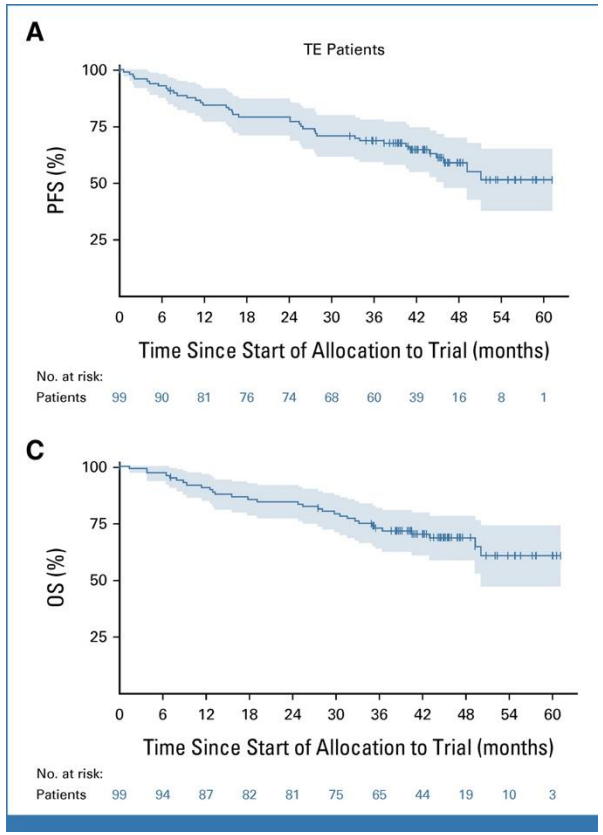


MRD negative:
Ever: 82%
Sustained x6: 73%
Sustained x 12: 63%



Median PFS & OS
not reached
3 yr PFS 69%
2 yr OS 84%

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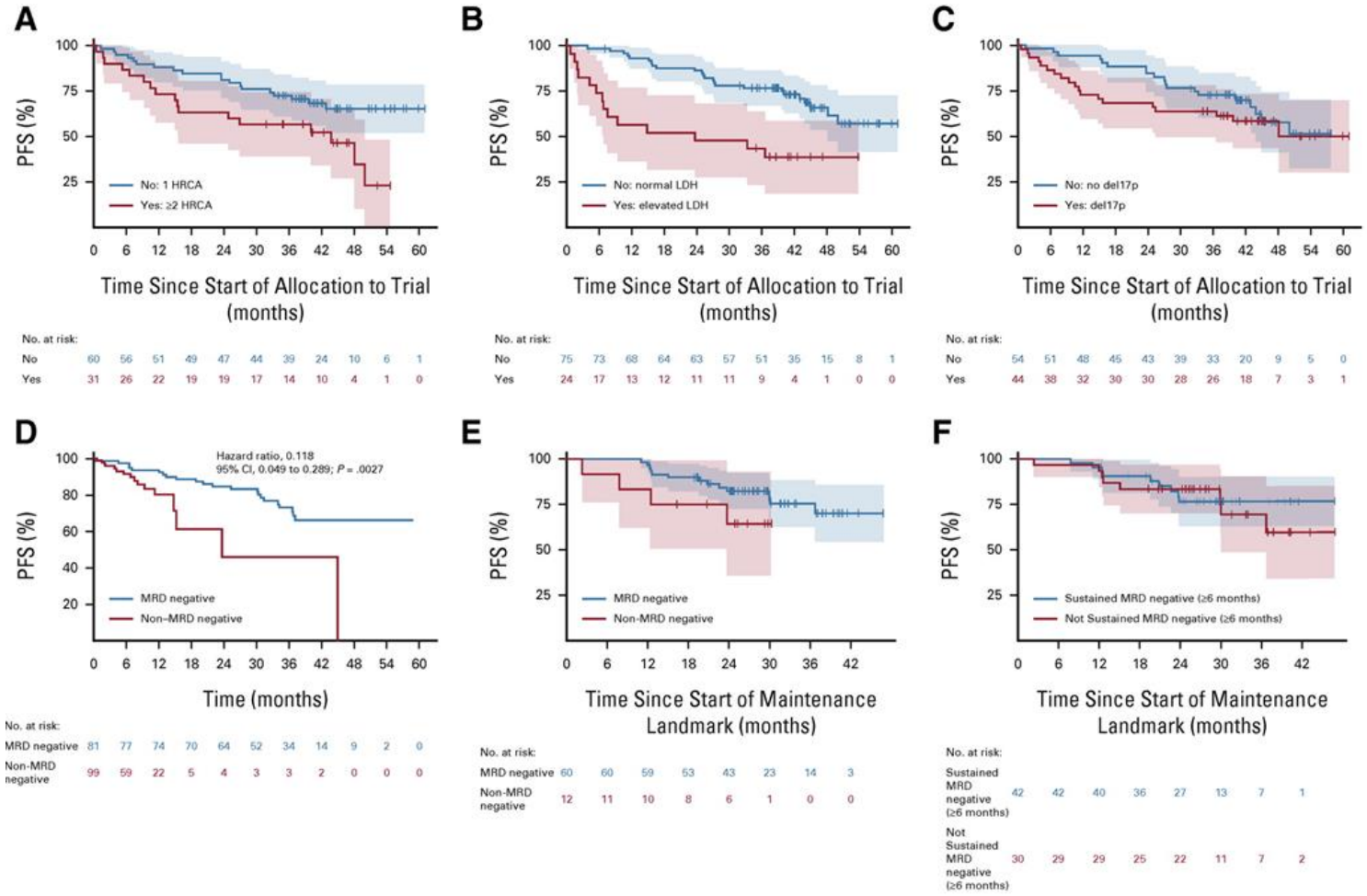
UCDAVIS COMPREHENSIVE CANCER CENTER

Triplet “Maintenance” in high risk patients:
GMMG-CONCEPT



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Summary: Induction: Should all patients get a CD-38 monoclonal antibody?

- Transplant Eligible: Yes
  - Quadruplets are outperforming triplets in terms of PFS and MRD negativity
  - OS data still remains to be seen
- Transplant Ineligible: Maybe
  - If a patient is fit (eg they *could* get a transplant physically but have some other barrier): a quadruplet may be the right choice
  - Unfit/Frail patients: I'm less convinced.
    - GMMG-Concept and IMROZ had high drop out rates due to AE
    - SWOG 2209 is currently enrolling comparing two DRd and VRd-lite in this setting

Maintenance Therapy

- Ongoing maintenance therapy has consistently demonstrated improved PFS, and with long enough follow up, OS benefits in MM patients post-transplant
- Multi-agent approaches appear to improve PFS
- (Un)fortunately – all subgroups appear to benefit
- Fixed duration and response-adapted de-escalation approaches are currently under investigation
  - DRAMMATIC, PERSEUS
- Overall survival data may help us understand the potential long term risks of inducing resistance and ongoing immunosuppression vs PFS benefits, and identify populations most likely to benefit from more aggressive maintenance therapy

My approach to maintenance (off of trial)

- I consider Dara-Len maintenance in all patients
  - "balanced discussion" about potential increased risks (infection) and inconvenience, unknown overall survival benefit
- In high risk patients I consider KR maintenance for 2 years (FORTE)
  - Esp if del(17p) or multiple high risk cytogenetic abnormalities
  - Functional high risk (inadequate response to DVRd induction)
- I do not currently offer triplet maintenance
  - At what point does this cease to be maintenance therapy?
- Do I stop maintenance?
  - Not yet, though MASTER data in standard risk is exciting
  - Ongoing DRAMMATIC trial to help answer this question (with OS endpoint)