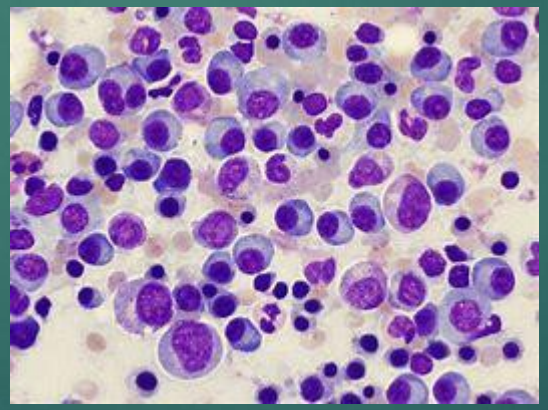
Front-line treatment for transplant-eligible newly diagnosed multiple myeloma (TE-NDMM)



Dr. Eyal Lebel, Hadassah Medical Center

Case 1: Eitan, 49 year-old

- Married+1, works in bio-med industry
- Generally healthy, known MGUS since 2016, no f/u
- Presented Jul 2022 with severe low back pain
- Diffuse bone disease, L1 & L3 compression fractures
- Anemia 10g/dl, Cre. and Ca. normal, proteinuria 3.5 g/24h
- NDMM Igg/K (M-protein 4.5gr/dl, K 1800mg/l ratio 180), 50% clonal PC in BM
- ISS 1, LDH normal, FISH- 17p del in 12%, R-ISS 2

- Started on dexamethasone, had kyphoplasty L1 and L3

What next?

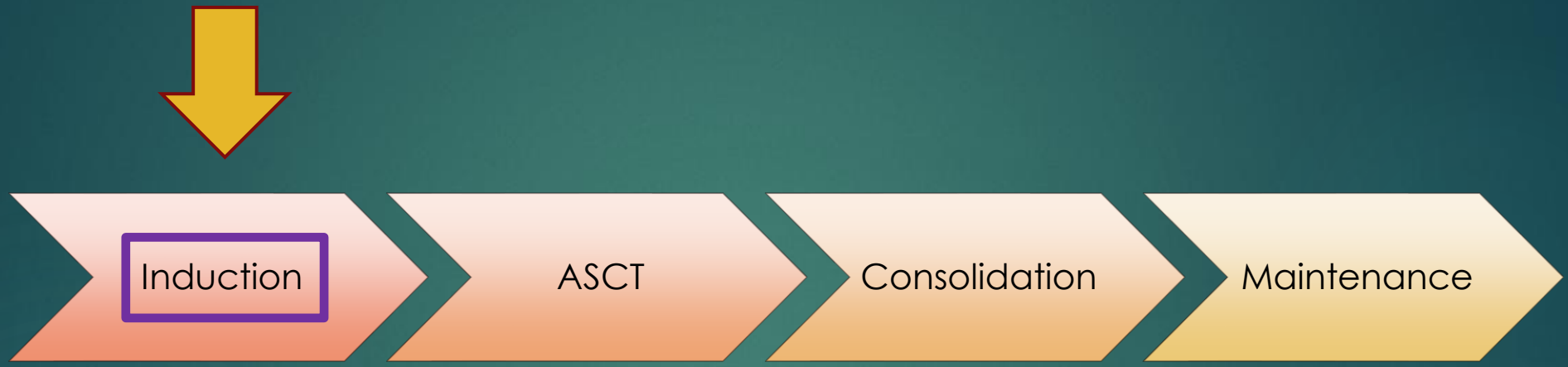
Front-line treatment for TE-NDMM- **Principals**

- **(Relatively)** fit population- give effective regimen (even if intensive)
- Personalize!!

  Disease factors- risk, presentation

  Patient factors- age, comorbidities, preferences
- Supportive care is crucial
- Ongoing adjustments are crucial
- Induction > autologous transplant > consolidation > maintenance

Front-line treatment for TE-NDMM- **paradigm**

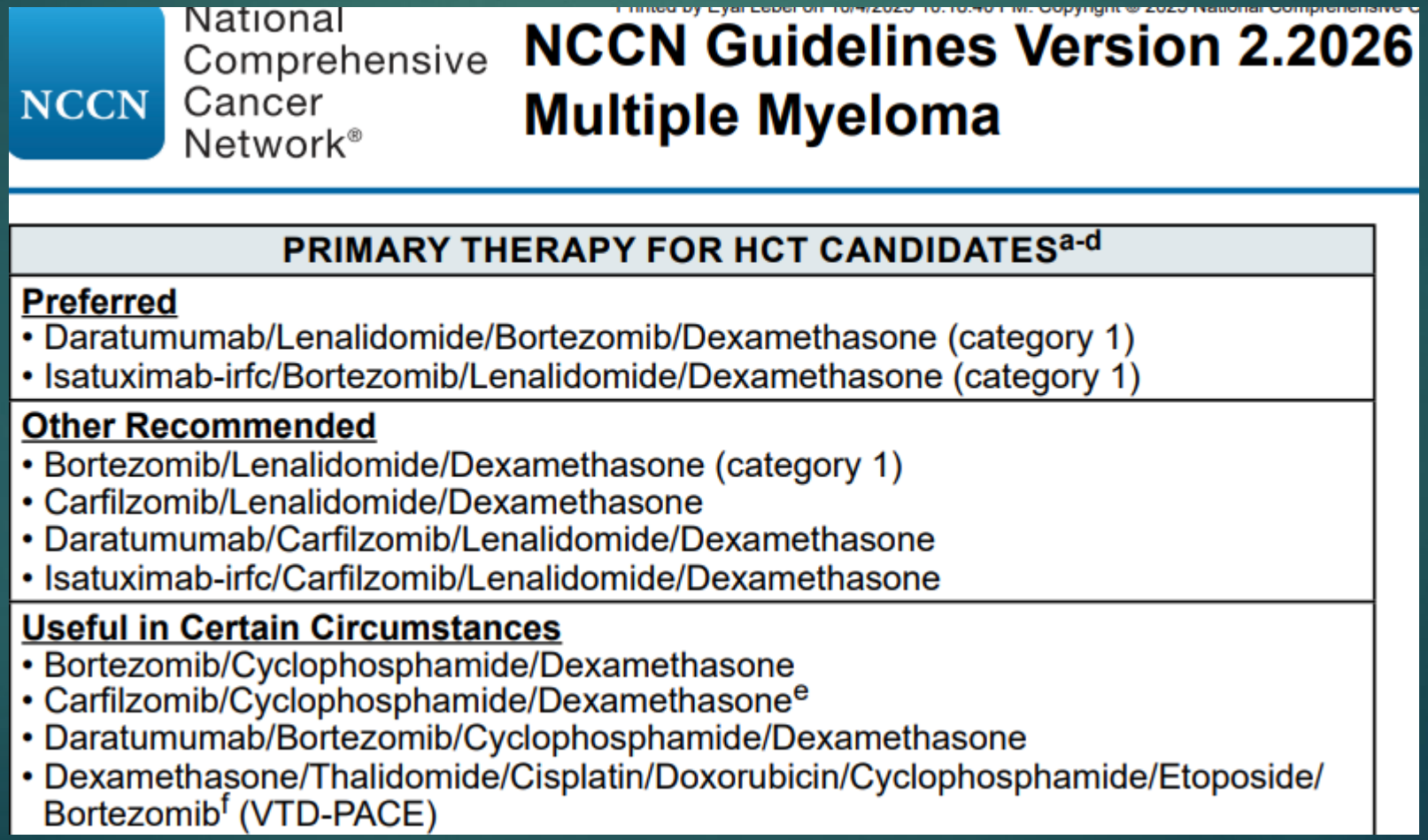


Induction for TE-NDMM

- Goals:
  - Managing emergencies- hyperviscosity, hypercalcemia, acute kidney injury, cord compression
  - Symptom alleviation
  - Disease control
  - Deep response-
    - MRD negativity much more meaningful than sCR
    - Timing of best response- less important
  - Restore the bone marrow function
  - Enabling timely stem-cell collection

Induction for TE-NDMM

- Multi-drug regimen- biologically sensible and proofed in studies
- Quadruple therapy



National Comprehensive Cancer Network®

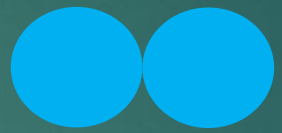
NCCN Guidelines Version 2.2026
Multiple Myeloma

PRIMARY THERAPY FOR HCT CANDIDATES[a-d]
Preferred • Daratumumab/Lenalidomide/Bortezomib/Dexamethasone (category 1) • Isatuximab-irfc/Bortezomib/Lenalidomide/Dexamethasone (category 1)
Other Recommended • Bortezomib/Lenalidomide/Dexamethasone (category 1) • Carfilzomib/Lenalidomide/Dexamethasone • Daratumumab/Carfilzomib/Lenalidomide/Dexamethasone • Isatuximab-irfc/Carfilzomib/Lenalidomide/Dexamethasone
Useful in Certain Circumstances • Bortezomib/Cyclophosphamide/Dexamethasone • Carfilzomib/Cyclophosphamide/Dexamethasone[e] • Daratumumab/Bortezomib/Cyclophosphamide/Dexamethasone • Dexamethasone/Thalidomide/Cisplatin/Doxorubicin/Cyclophosphamide/Etoposide/ Bortezomib[f] (VTD-PACE)

Induction for TE-NDMM- History

- Single agent: HDD

- Doublets- Melphalan-dex, T-D, R-D, V-D



- Triplets- MPT, MPR, VMP, VTD, VCD, VRD, KRD

- Quadruplets:

DARA-VTD, DARA-VRD, DARA-KRD, DARA-VCD, ISA-VRD, ISA-KRD

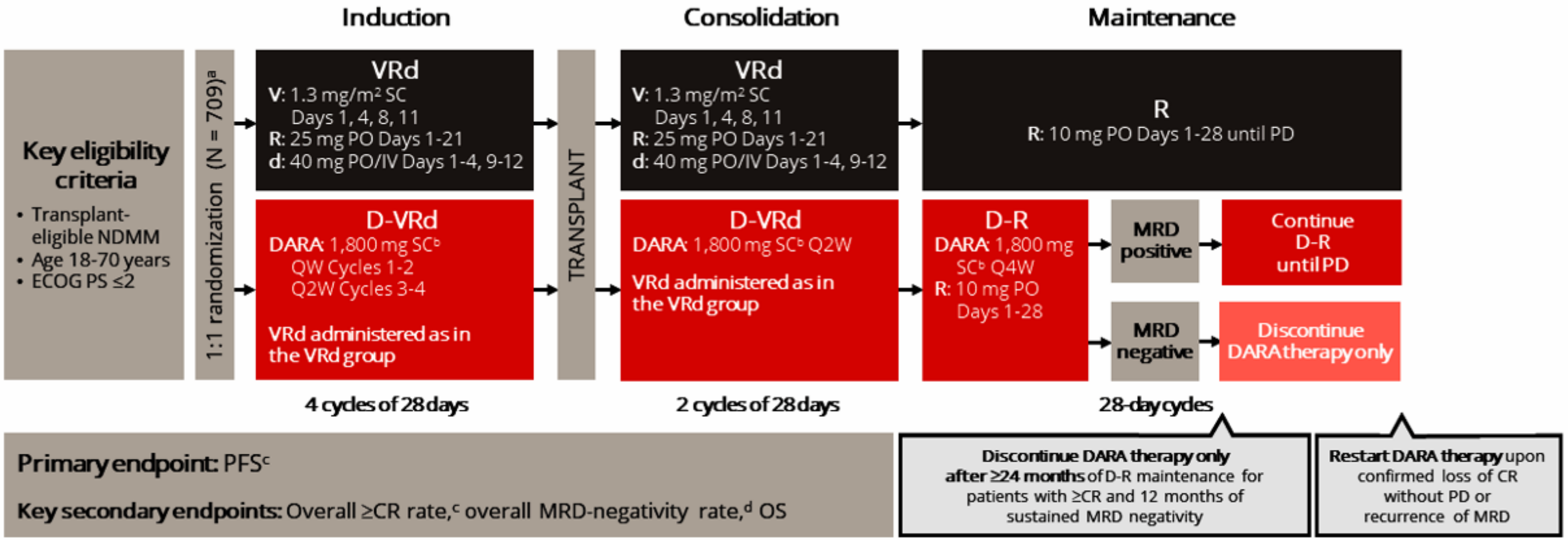
Induction for TE-NDMM- triplets

- VRD is a good backbone
- VTD and VCD – not convincingly worse than VRD in key outcomes
  - VTD – more neuropathy. But overall effective and tolerated
  - Both may be preferred over VRD in kidney disease
- 1/w SC bortezomib is preferred, start with 2/w when urgent control is needed
- KRD – deeper responses but with AE price, and similar PFS (but high-risk not included)
- Triplets+chemo: VTD-PACE / KTD-PACE may be useful in certain circumstances (PCL?), less and less used

Frontline quads with anti-CD38 antibody
new standard for Induction for TE-NDMM

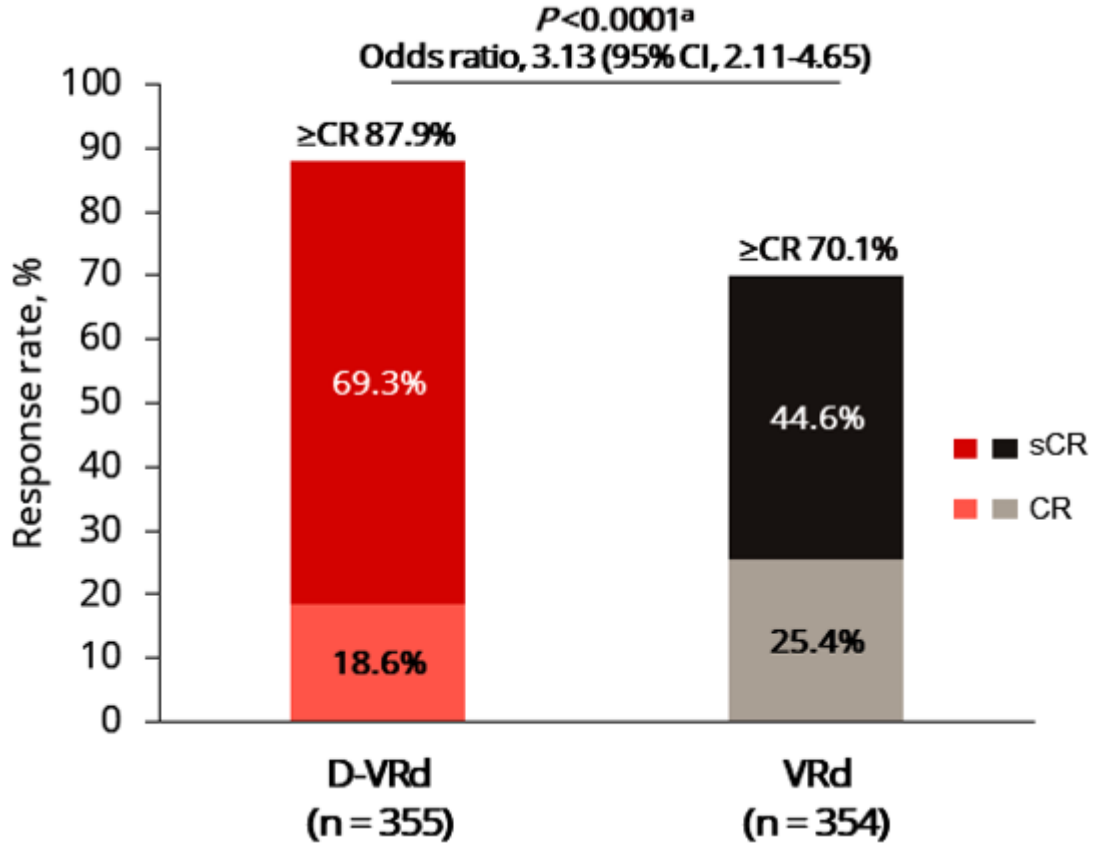
- DARA-VRD was compared to VRD - **GRIFFIN, PERSEUS studies**
- DARA-VTD was compared to VTD - **CASSIOPEA study**
- ISA-VRD was compared to VRD - **GMMG-HD7 study**
- There is good data also on DARA-VCD, DARA-KRD, ISA-KRD

PERSEUS STUDY



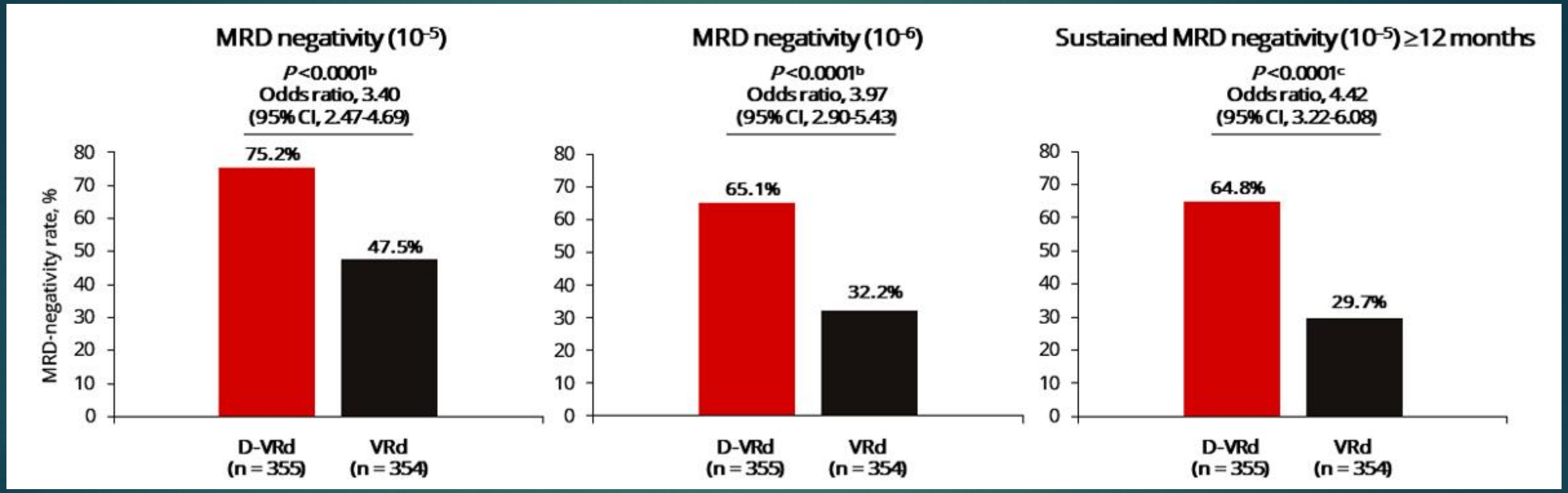
354 patients in each arm (Griffin- 104)

Adding DARA improves the ≥CR rate

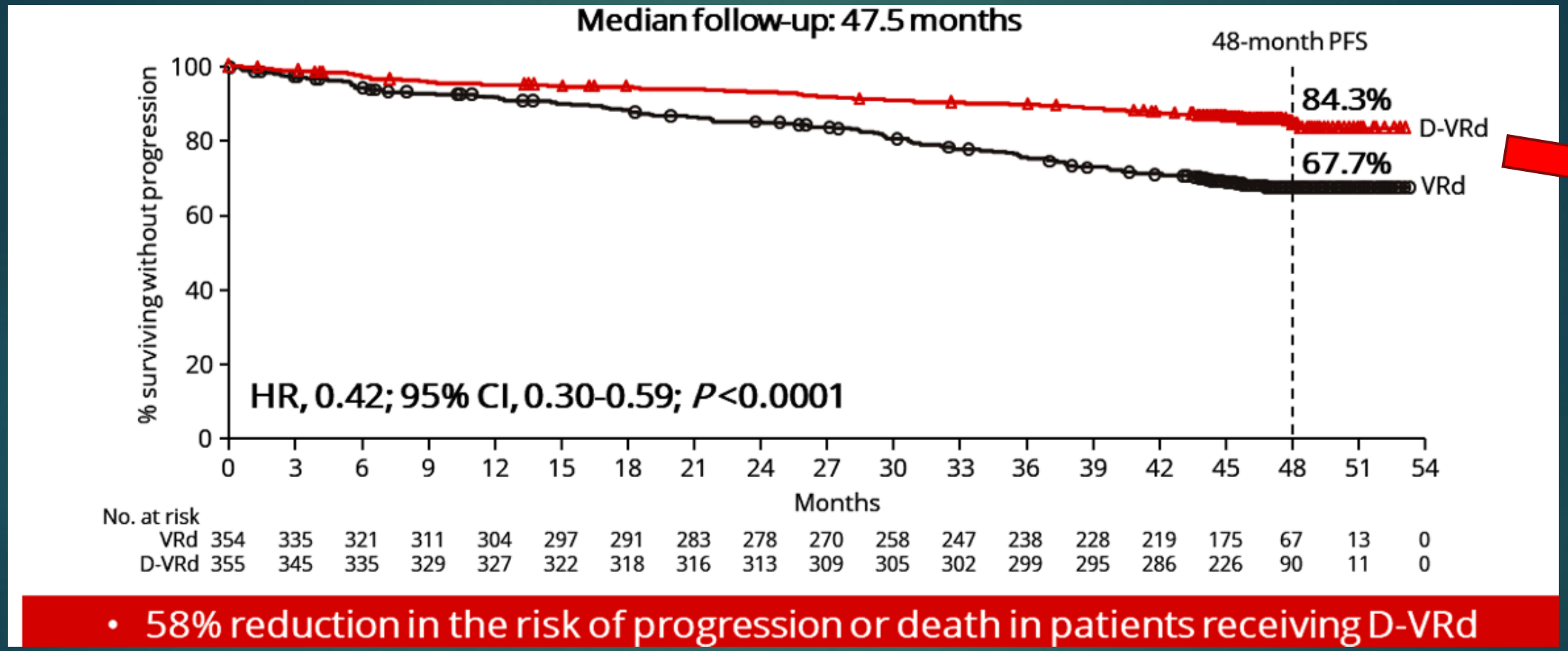


Subgroup	VRd no. of patients with ≥CR/total no. (%)	D-VRd no. of patients with ≥CR/total no. (%)	Odds ratio (95% CI)
Sex			
Male	143/205 (69.8)	185/211 (87.7)	3.08 (1.86-5.12)
Female	105/149 (70.5)	127/144 (88.2)	3.13 (1.69-5.80)
Age			
<65 y	186/267 (69.7)	235/261 (90.0)	3.94 (2.43-6.37)
≥65 y	62/87 (71.3)	77/94 (81.9)	1.83 (0.91-3.68)
Race			
White	226/323 (70.0)	289/330 (87.6)	3.03 (2.02-4.53)
Other	22/31 (71.0)	23/25 (92.0)	4.70 (0.91-24.25)
ISS stage			
I	129/178 (72.5)	167/186 (89.8)	3.34 (1.87-5.95)
II	84/125 (67.2)	101/114 (88.6)	3.79 (1.91-7.54)
III	34/50 (68.0)	44/55 (80.0)	1.88 (0.77-4.58)
Type of MM			
IgG	122/185 (65.9)	178/204 (87.3)	3.54 (2.12-5.90)
Non-IgG	73/96 (76.0)	72/78 (92.3)	3.78 (1.45-9.83)
Cytogenetic risk			
Standard risk	182/266 (68.4)	234/264 (88.6)	3.60 (2.27-5.70)
High risk	59/78 (75.6)	63/76 (82.9)	1.56 (0.71-3.44)
Indeterminate	7/10 (70.0)	15/15 (100)	NE (NE-NE)
ECOG PS			
0	160/230 (69.6)	195/221 (88.2)	3.28 (2.00-5.39)
≥1	88/124 (71.0)	117/134 (87.3)	2.82 (1.49-5.34)

Adding DARA improves the MRD negativity rate



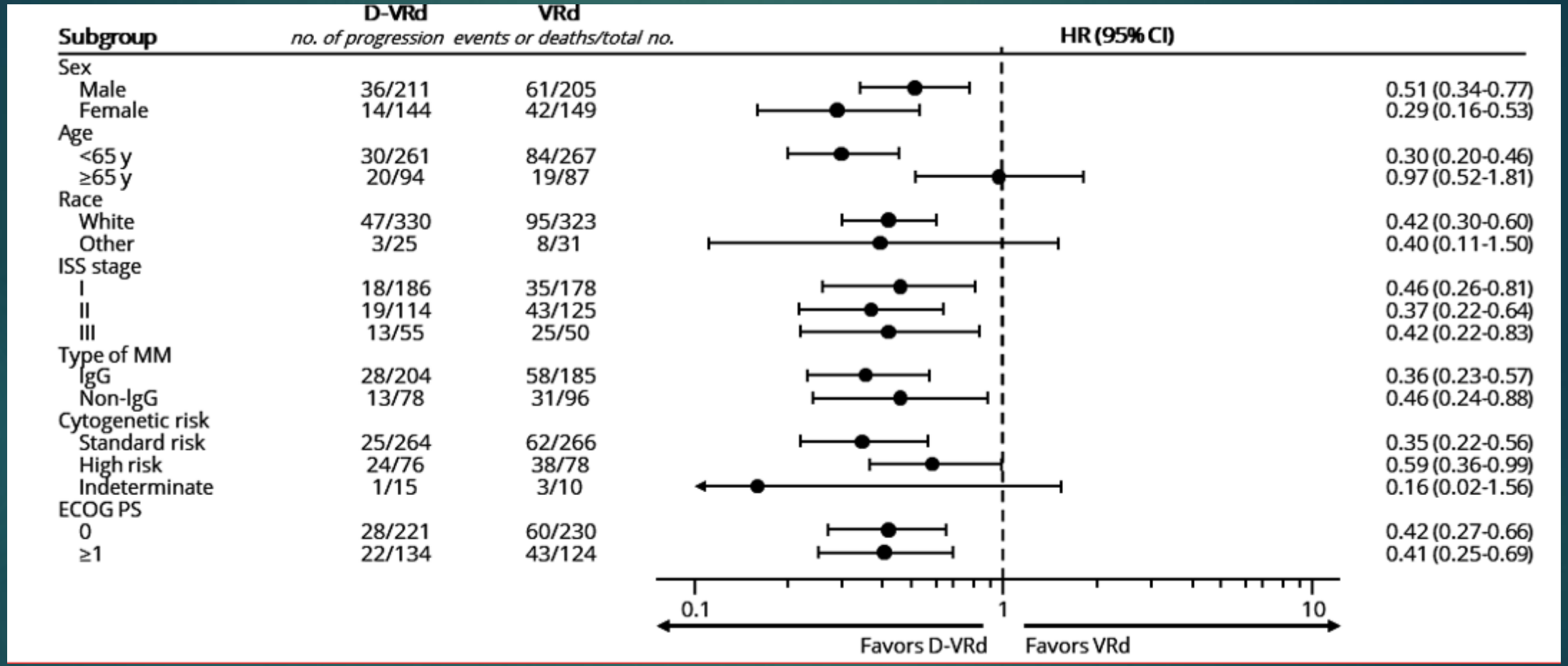
Adding DARA prolongs PFS



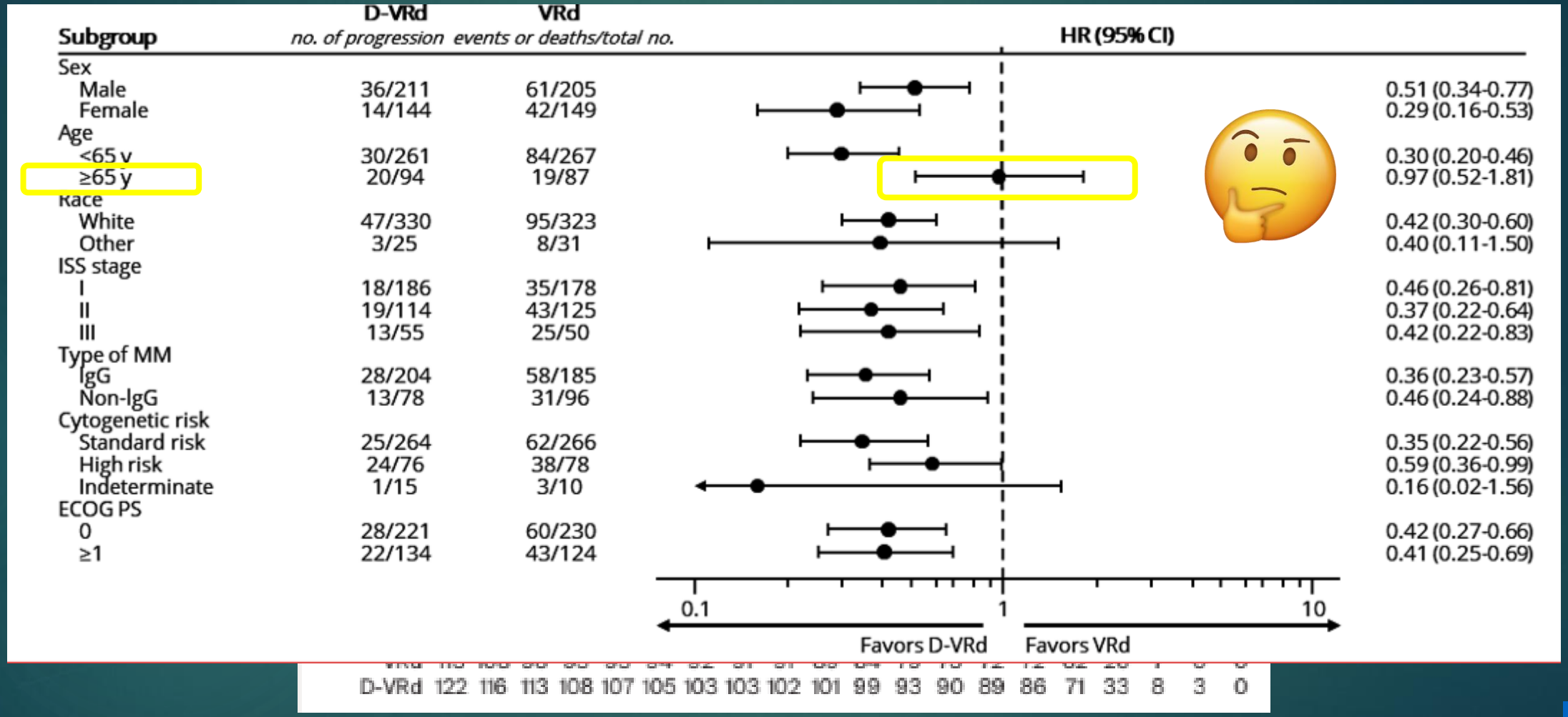
- 58% reduction in the risk of progression or death in patients receiving D-VRd

Modelling showed that in PERSEUS, the best-fit mPFS estimates were 17.1 years (13.2-21.2 years) for daratumumab-VRd + DR maintenance

PFS in subgroups



PFS in subgroups



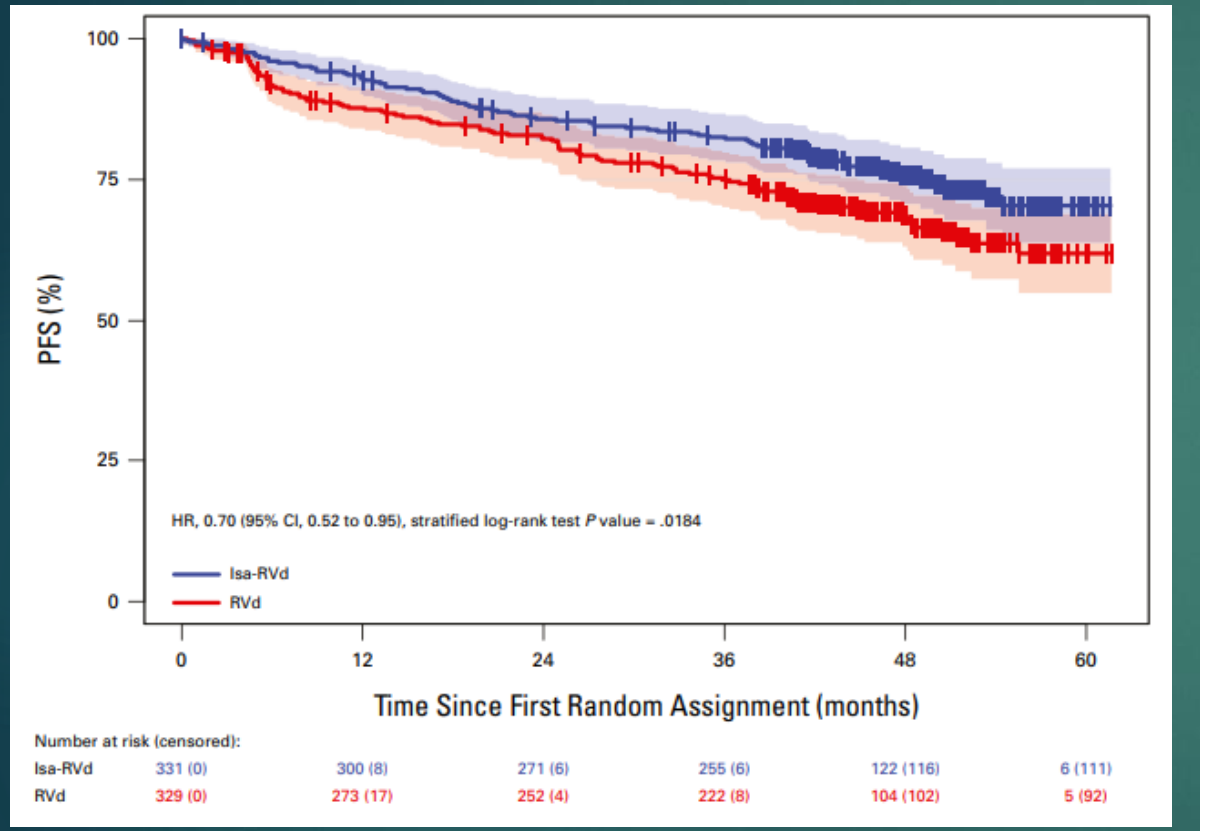
DARA-VRD vs VRD- safety

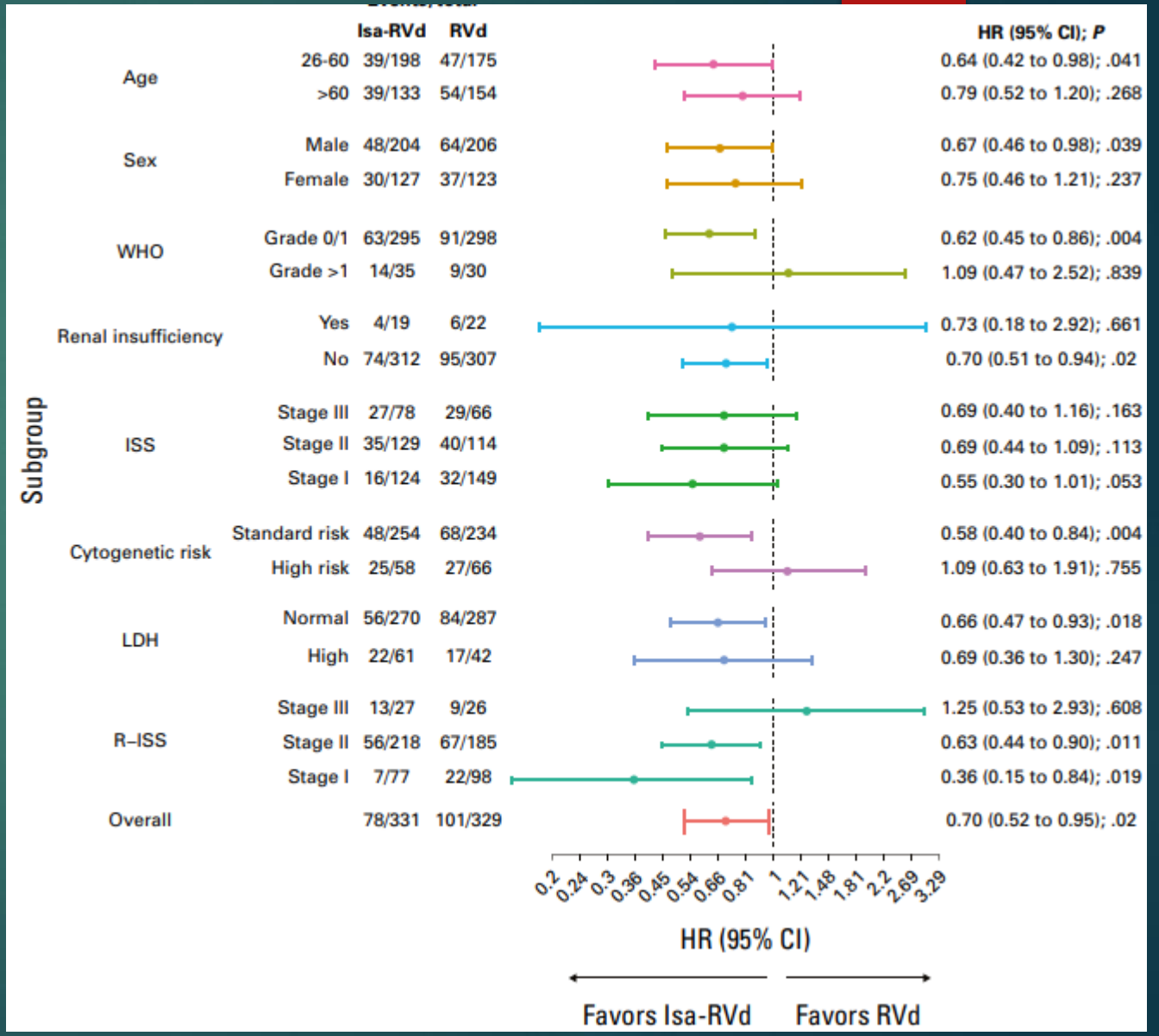
Event, n (%)[a]	D-VRd (n = 351)		VRd (n = 347)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
HEMATOLOGIC				
Neutropenia	**243 (69.2)**	**218 (62.1)**	**204 (58.8)**	**177 (51.0)**
Thrombocytopenia	**170 (48.4)**	**102 (29.1)**	**119 (34.3)**	**60 (17.3)**
Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
NON-HEMATOLOGIC				
Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
Peripheral sensory neuropathy	**188 (53.6)**	**15 (4.3)**	**179 (51.6)**	**14 (4.0)**
Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infections	**305 (86.9)**	**124 (35.3)**	**266 (76.7)**	**95 (27.4)**
COVID-19	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
Upper respiratory tract infection	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)

DARA-VRD vs VRD- summary

- Responses are convincingly deeper with DARA-VRD
- With more patients needing pleraxifor, collection is feasible
- Clear PFS advantage
- More AEs, more infection- but a trend to **less** deaths (9.6% vs 12.4%)

GMMG-HD7: ISA-VRD vs VRD





Kai et al. JCO 2024

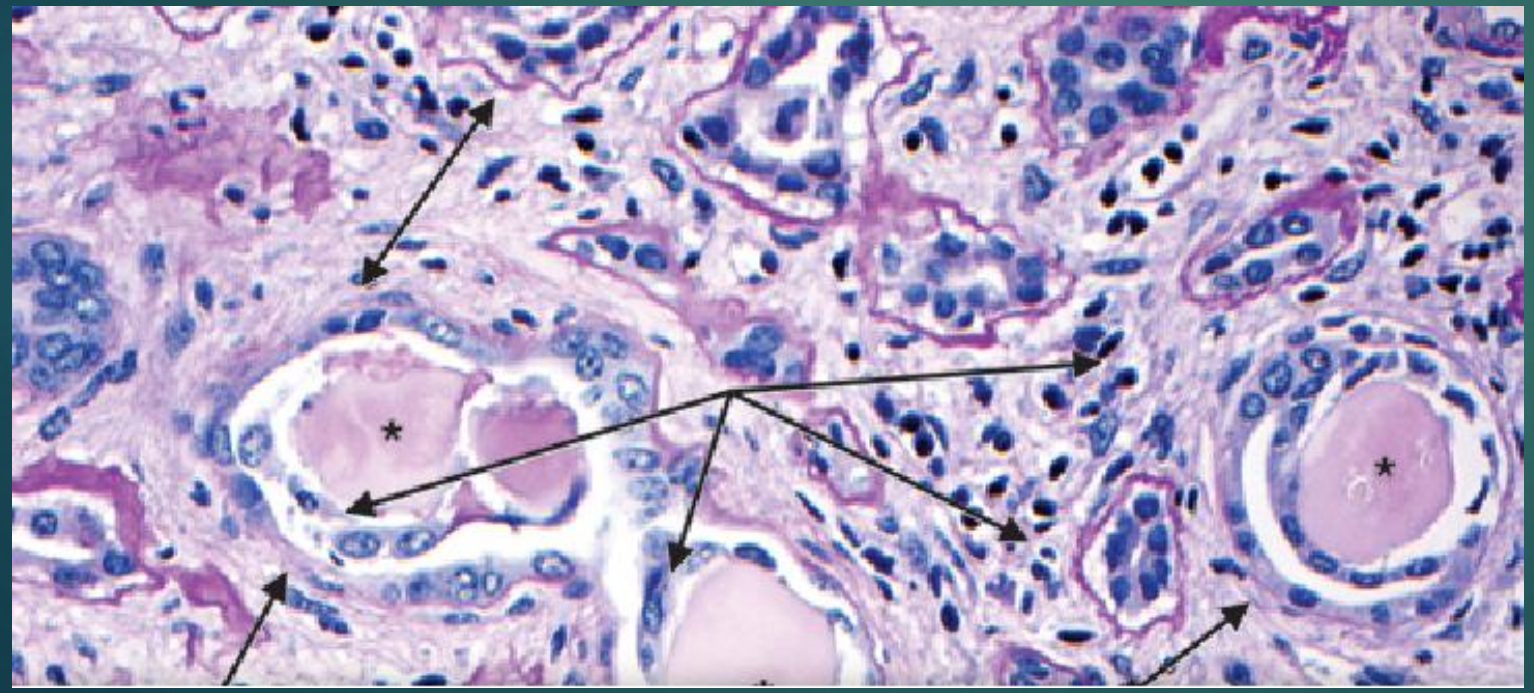
Case 2: Shimon, 63 year-old

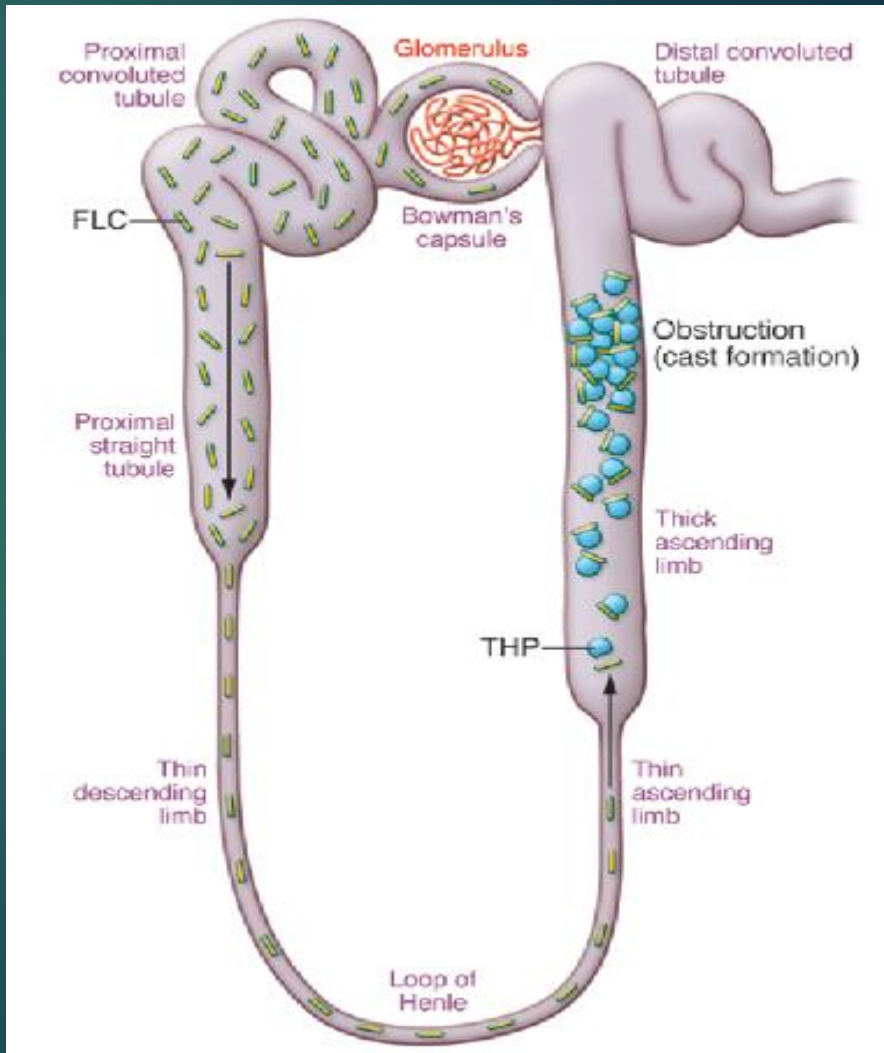
- Generally healthy, heavy smoker
- Admitted May 2022 with weakness, nausea and decreased urine output
- Cre. 10 mg/dl, K 5.8, Ca. Normal, P high
- kappa 2000mg/dl ratio 100, low Ig levels
- Anemia, single rib-based bony lesion
- Free kappa MM confirmed in bone marrow aspirate

What next?

MM presenting with kidney injury

- Main etiology: light chains associated cast nephropathy
- Other etiologies: hypercalcemia, amyloidosis, obstructing masses or direct infiltration, hyperuricemia, dehydration, nephrotoxins

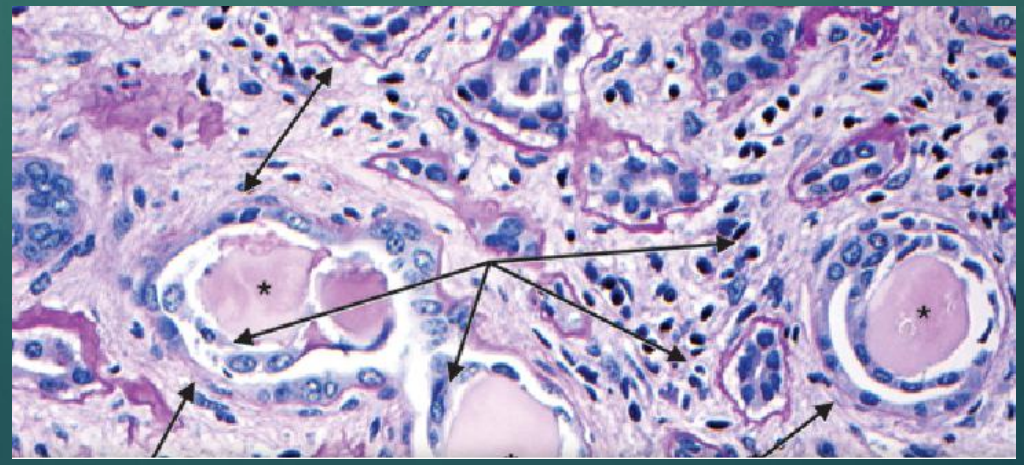




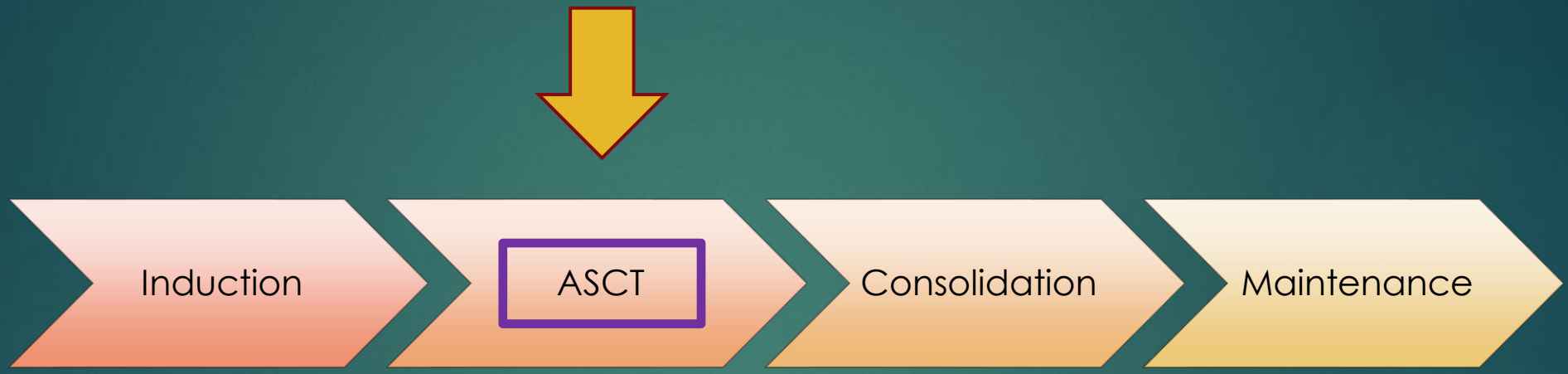
MM presenting with kidney injury

Treatment:

- Urgent effective anti-myeloma therapy- DEXA, BORTEZOMIB, DARA
- LEN problematic- can be used later in stable kidney disease
- Fluids
- Avoidance of nephrotoxins
- Pheresis/high cut-off dialysis- controversial



Front-line treatment for TE-NDMM- **paradigm**



ASCT for MM

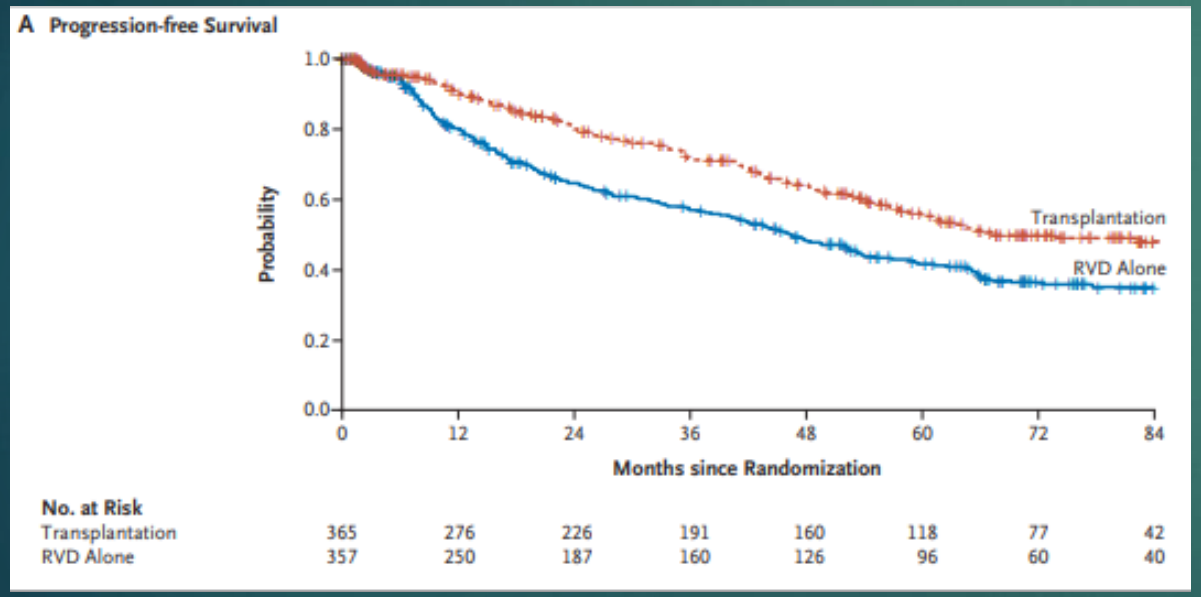
- Since 1983 !!
- Melphalan 200mg/m^2, 140mg/m^2 for severe kidney dysfunction
- Other conditioning, purging- not convincingly better
- Supported by robust data

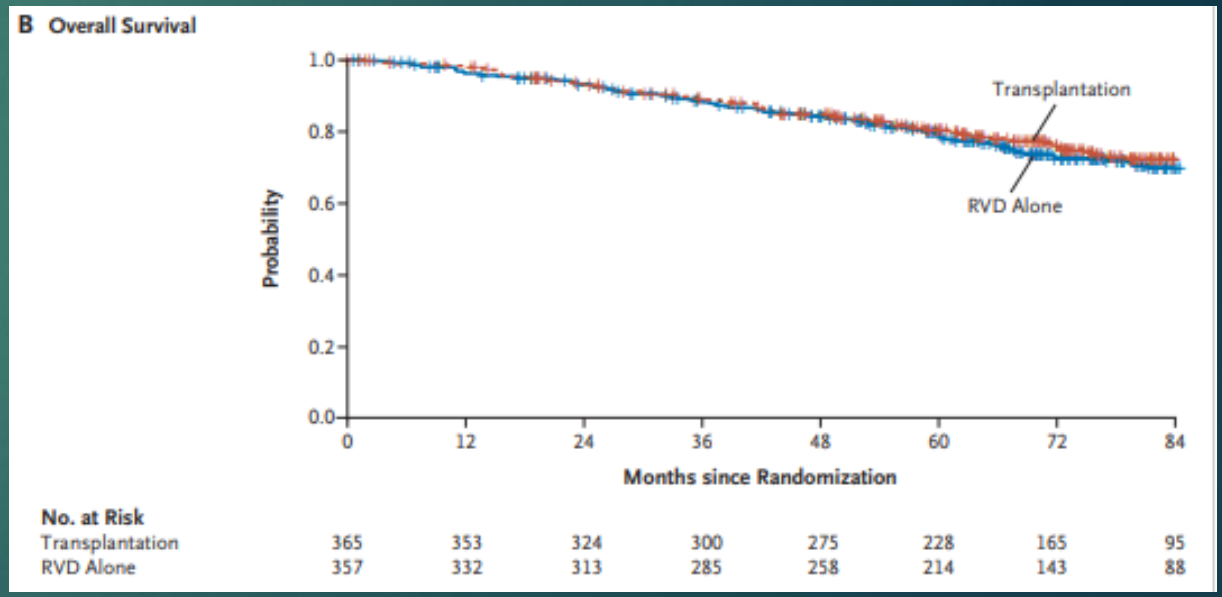
Recently:

ORIGINAL ARTICLE

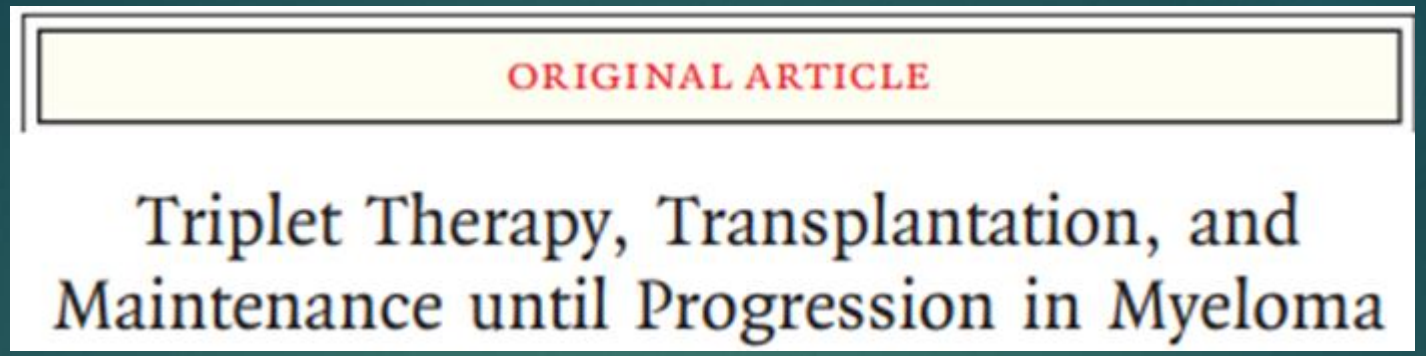
Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

RVD X 8 + R maint. Vs. **RVD X 3 + ASCT + RVD X 2 + R maint.**





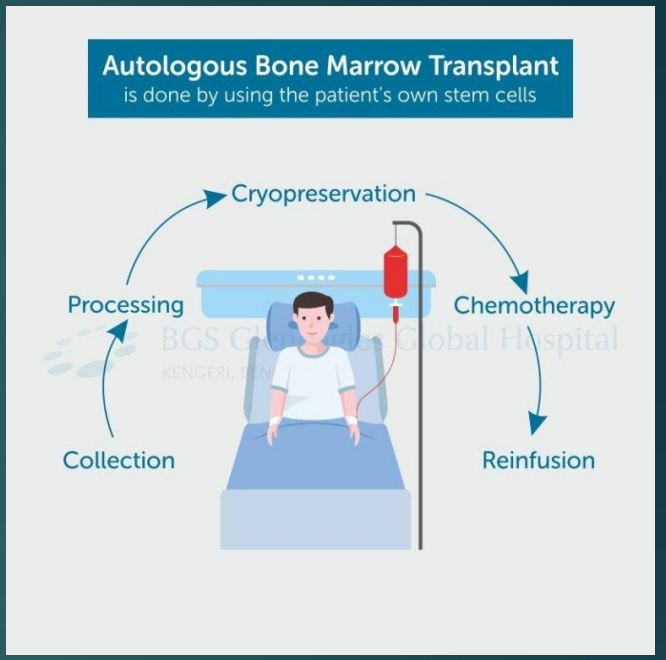
PFS advantage of ~ 2y, without OS advantage



- Short-term toxicities: alopecia, mucositis, infections, bleeding, engraftment syndrome, severe fatigue, 2% mortality
- Long-term toxicities: infertility, secondary primary cancers (SPM)
- In this study: QOL overall similar.
- In this study: SPM similar including invasive, but AML higher post transplant (2% vs. 0%)

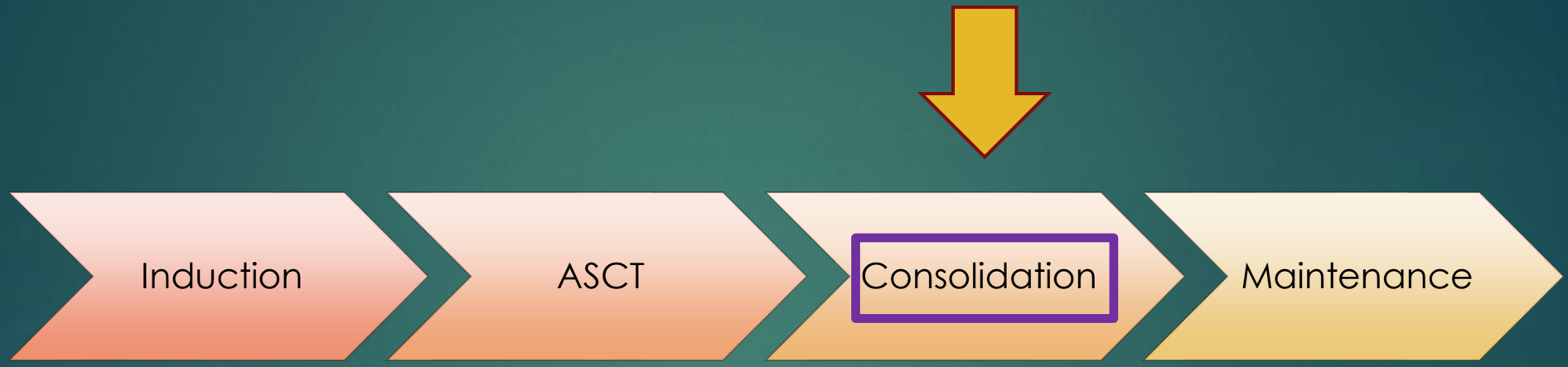
ASCT for MM

- Role of transplant in frontline anti-CD38 era- not studied
- Tandem- possible indications:
  - Patients responsive to transplant but not in CR
  - High-risk patients
  - Much less used today
- Allogeneic transplant
  - Some data support auto-allo vs. auto-auto
  - Much less used today



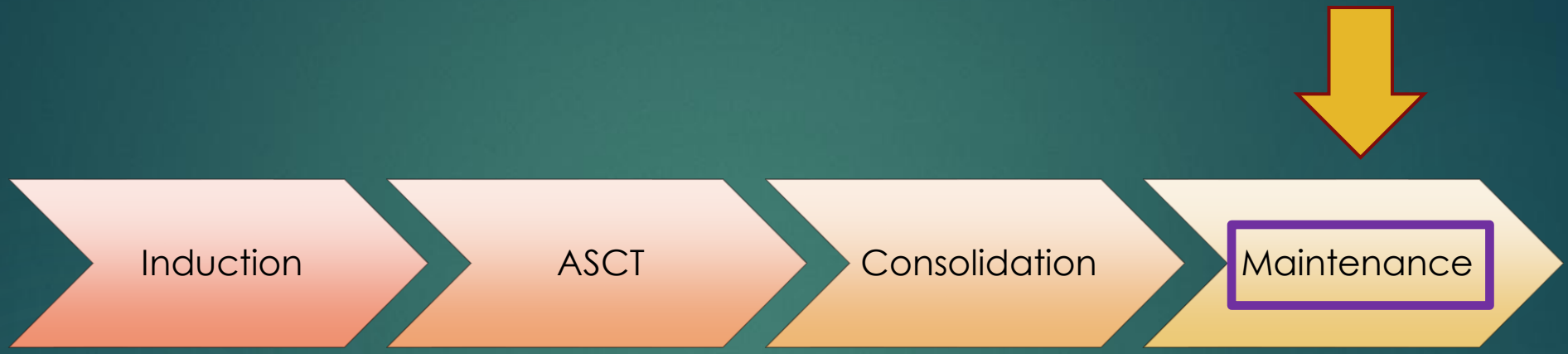
Summary- frontline ASCT for fit patients is still the standard of care

Front-line treatment for TE-NDMM- **paradigm**



- **2-3 cycles same as induction**

Front-line treatment for TE-NDMM- **paradigm**



Maintenance post-transplant

Lenalidomide

- Robust supportive data, 3 large randomized + meta-analysis showing clear PFS benefit
- 10-15mg/day, with or without a week off
- Advantage regardless of previous lenalidomide exposure
- Neutropenia, GI side-effects
- **Secondary primary cancers**: significant increase
  - Solid + heme
  - Promoting p53-mutated myeloid tumors
  - Still- net benefit with LEN maintenance

Maintenance post-transplant

Bortezomib

- Some data support it over LEN in high-risk FISH
- However: data not convincing, neuropathy, frequent visits, new high-risk definitions

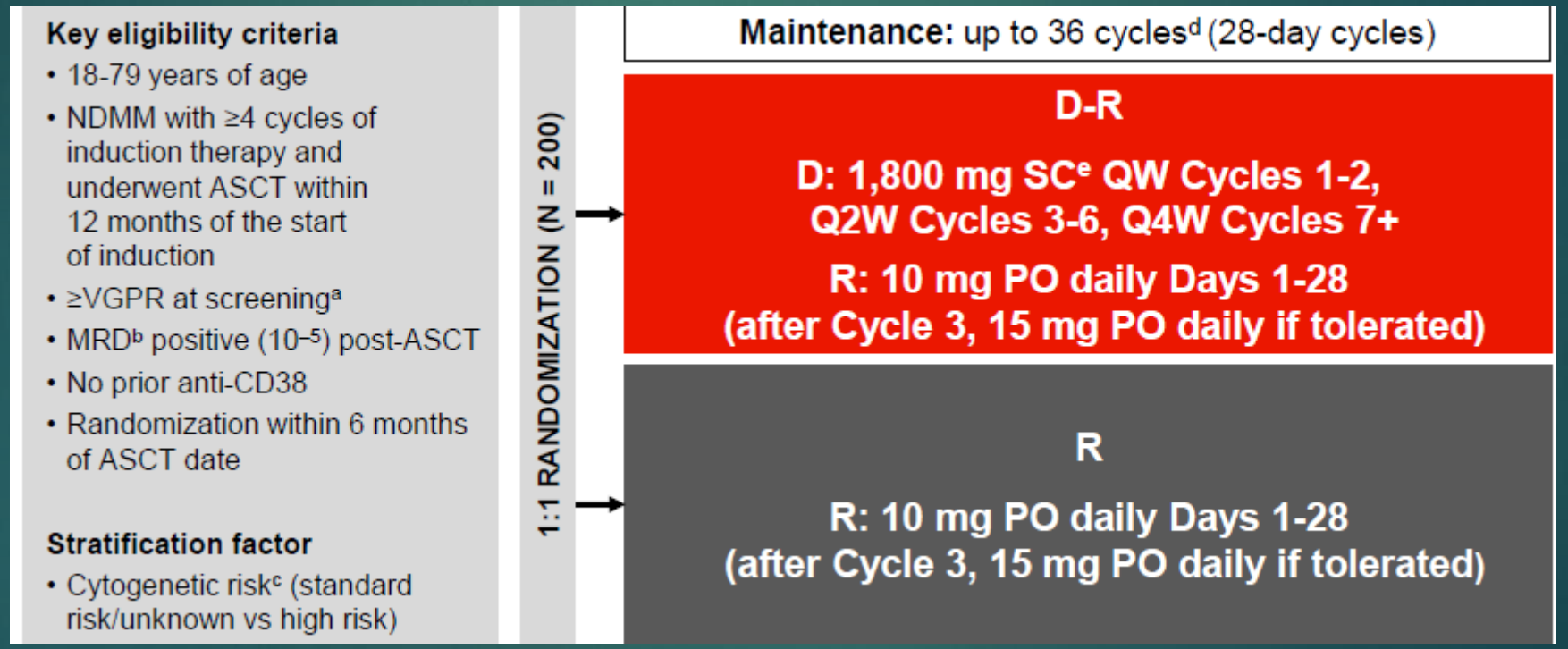
Ixazomib

- Advantage over placebo, much less impressive than lenalidomide
- I+R did not show any additional benefit to R

* There is some data also on **Thalidomide**, **carfilzomib** and **combinations** of PI, IMiD, steroid

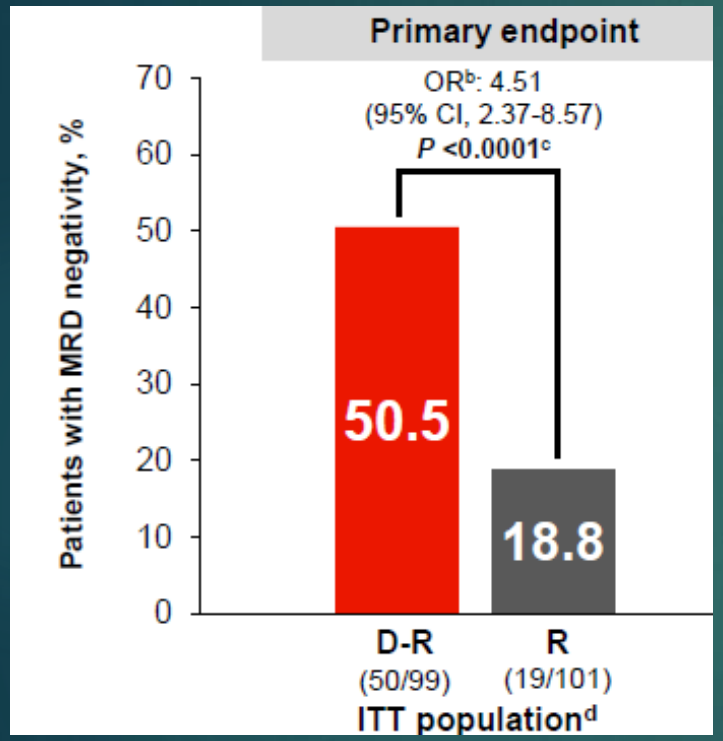
Anti-CD38 Maintenance post-transplant

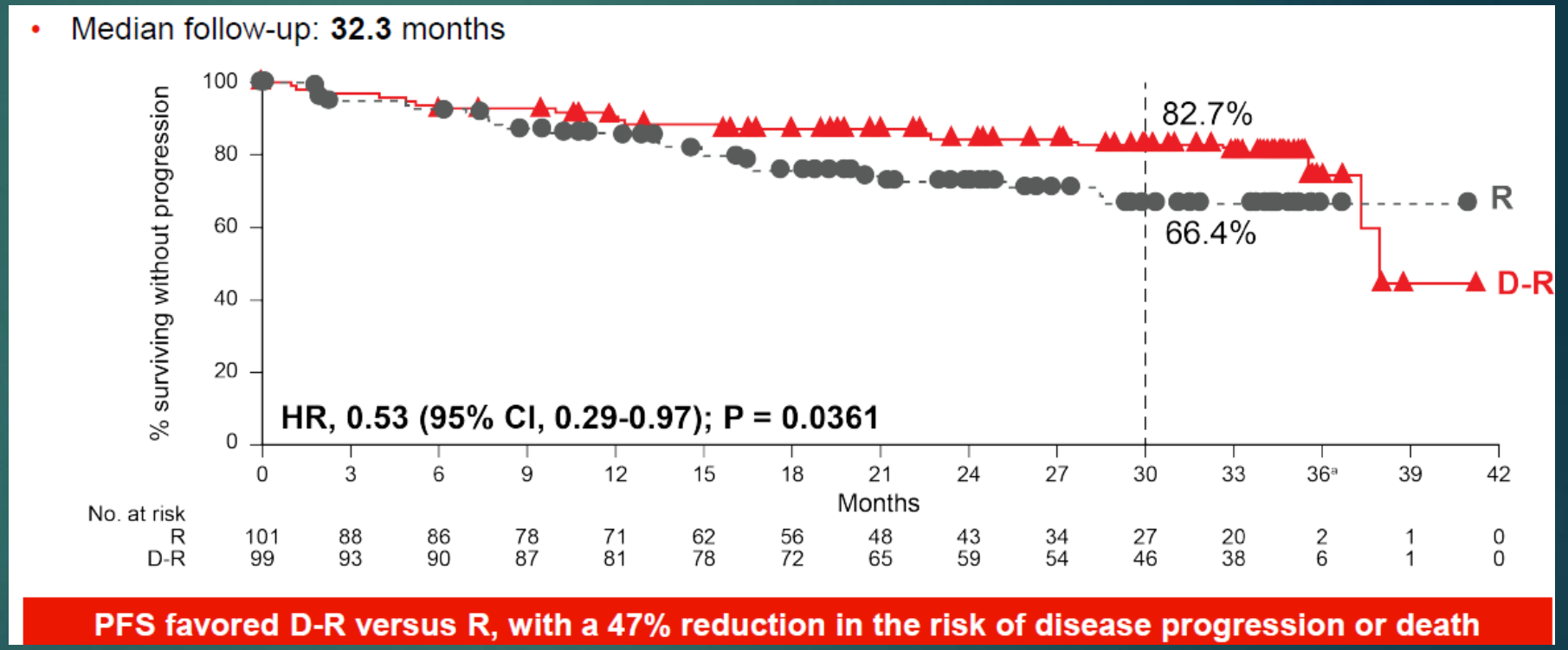
AURIGA study



Anti-CD38 Maintenance post-transplant

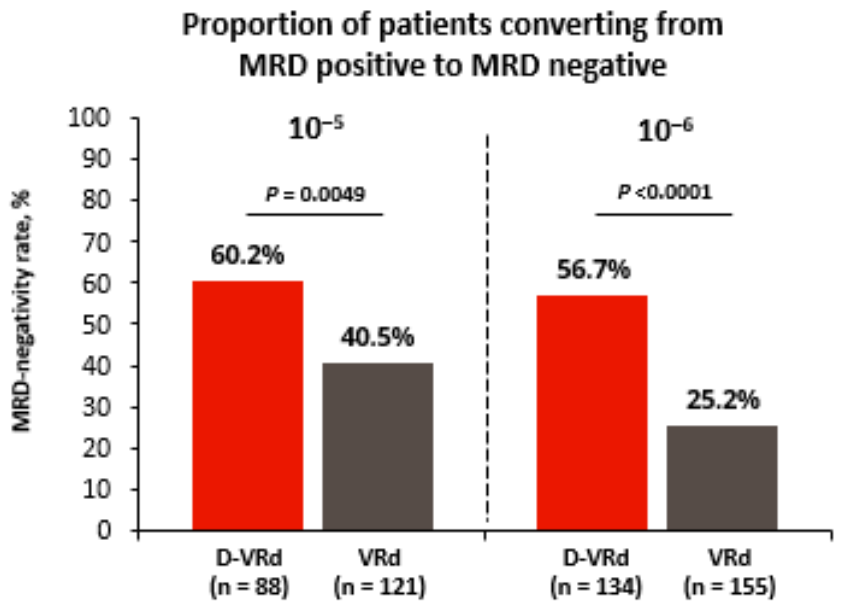
AURIGA study

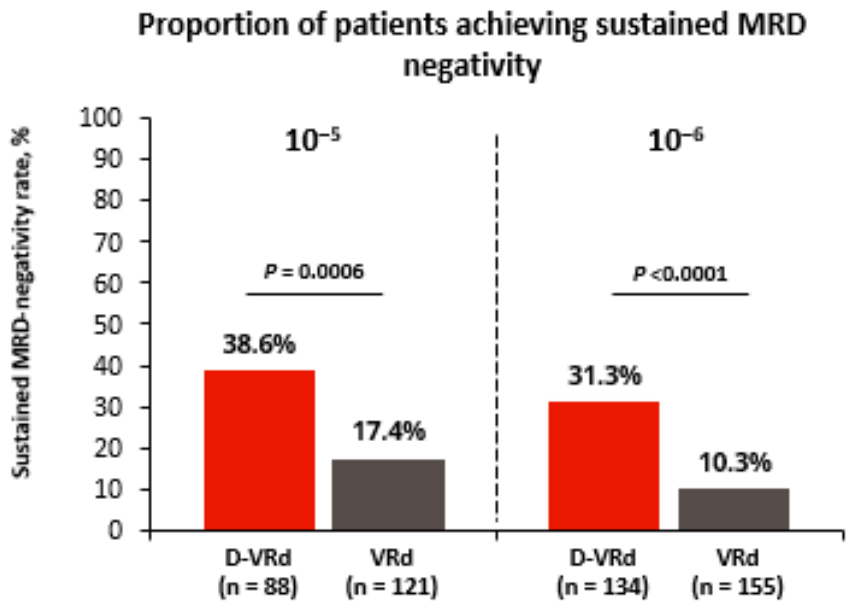




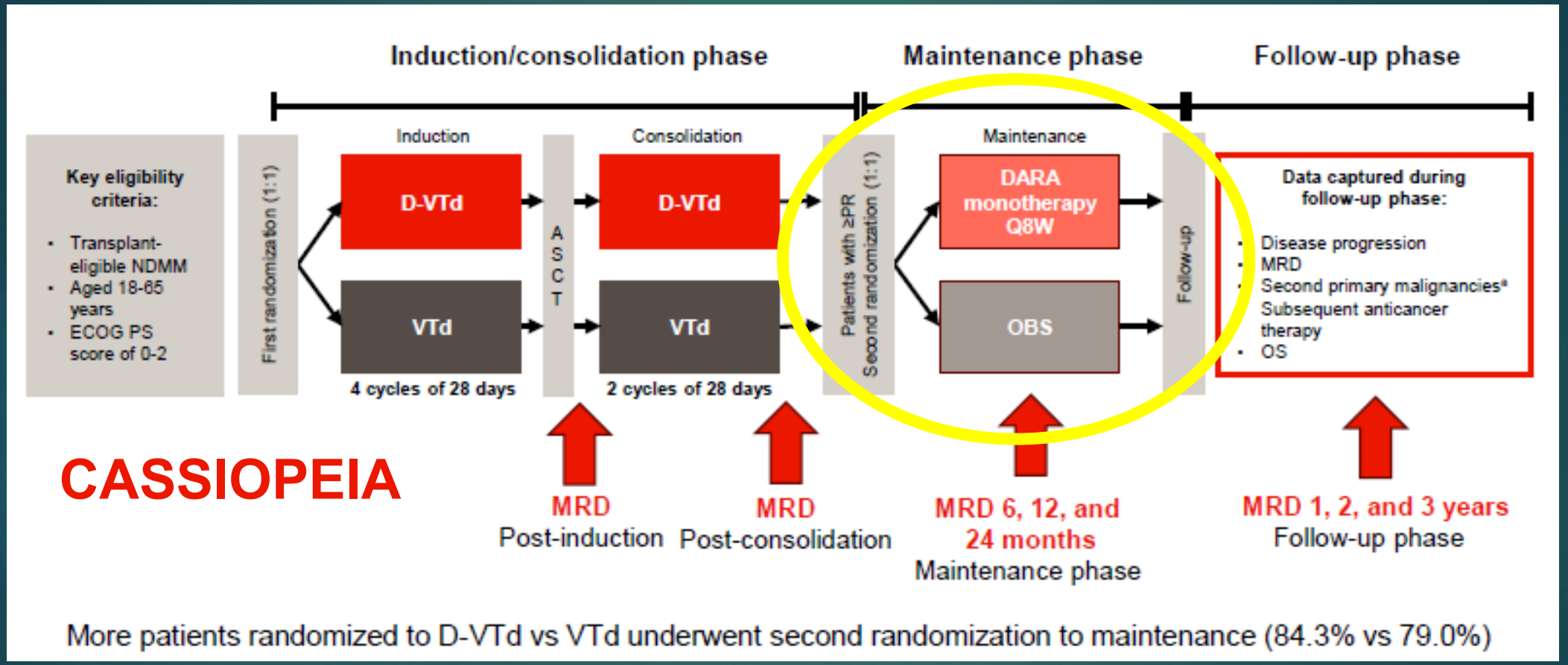
Anti-CD38 Maintenance post-transplant
PERSEUS

PERSEUS: MRD Conversion During Maintenance for Patients Remaining MRD Positive at the End of Consolidation



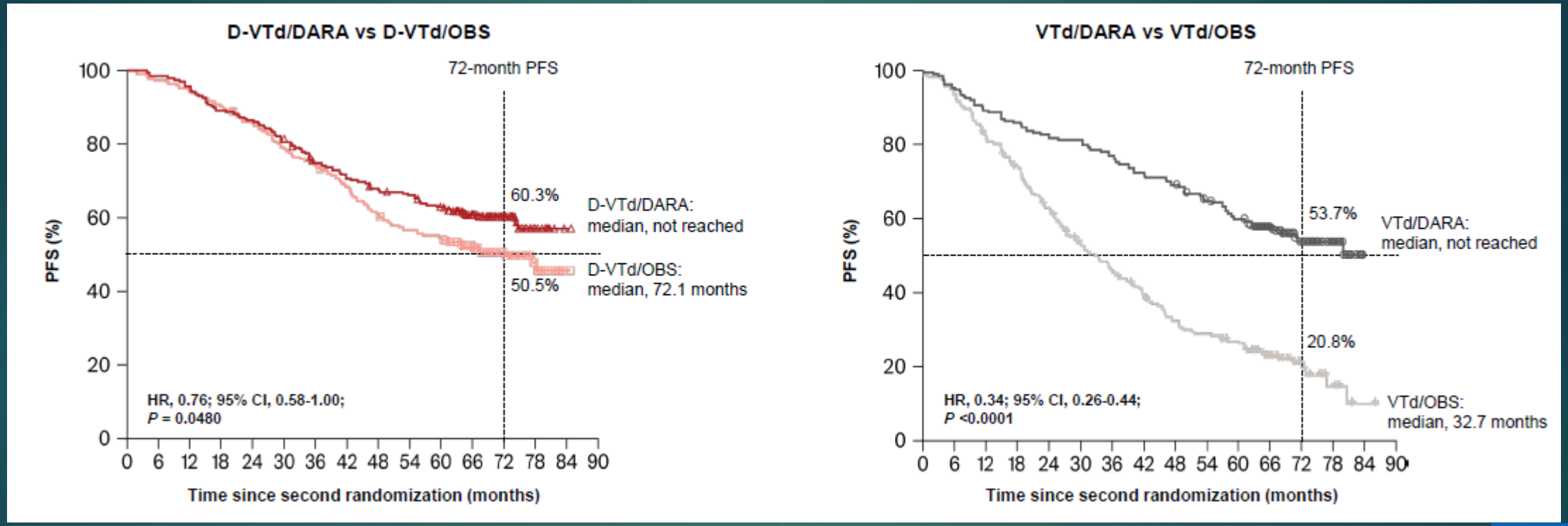


Anti-CD38 Maintenance post-transplant



More patients randomized to D-VTd vs VTd underwent second randomization to maintenance (84.3% vs 79.0%)

Anti-CD38 Maintenance post-transplant
CASSIOPEIA



Second randomization in **GMMG-HD7 (ISA maintenance)** may help

Maintenance post-transplant- **summary**

- lenalidomide until progression is funded and standard
- Anti-CD38 with LEN is probably better

MAINTENANCE THERAPY[g]
Preferred • Lenalidomide[h] (category 1)
Other Recommended • Carfilzomib/Lenalidomide[h] • Daratumumab/Lenalidomide[h]
Useful in Certain Circumstances • Bortezomib ± Lenalidomide[h] • Daratumumab • Ixazomib (category 2B)

Debates:

- Anti-CD38 duration
- Double/triple maintenance, especially for high-risk
- Limited exposure to lenalidomide in high-risk for SPM
- Limited exposure to lenalidomide- tailored by MRD testing

Case 1: Eitan, 49 year-old

- Married+1, works in bio-med industry
- Generally healthy, known MGUS since 2016, no f/u
- Presented Jul 2022 with severe low back pain, admitted
- Anemia 10g/dl, Cre. and Ca. normal, proteinuria 3.5 g/24h
- NDMM Igg/K (M-protein 4.5 gr/dl, K 1800 mg/l ratio 180), 50% clonal PC in marrow
- ISS 1, LDH normal, FISH- 17p del in 12%, R-ISS 2

- **4 X Dara-VRD + ASCT > sCR, MRD negative**
- **DARA+LEN per GRIFFIN/PERSEUS**
- **After 2 years – Stopped Dara > MRD pos > resume Dara > MRD meg.**
- **17p in 12%, is he considered high-risk?**

Case 2: Shimon, 63 year-old

- Admitted May 2022 due to weakness, nausea and decreased urine output
- Free kappa MM, presented with acute severe renal injury Cre. 10 mg/dl, kappa 2000mg/dl ratio 100
- Anemia, single rib-based bony lesion
- ISS 3, normal FISH, R-ISS 2

- **Treated with pheresis, DARA-VCD**
- **Didn't require dialysis**
- **At least VGPR post 2 cycles (BM not done), underwent stem cell collection**
- **Creatinine slowly improved (ASCT delayed…), and plateaued on 2.6 mg/dl**
- **Transplant ??**
- **BM- sCR, MRD negative (flow, 10-5)- transplant deferred**
- **Early progression on DARA only**
- **Good response to IXA-RD but very short**
- **3rd line teclistamab from insurance – doing great, now monthly**

Front-line treatment for (TE-NDMM)- **Summary**

- (Relatively) fit population- give intensive effective therapy
- Personalize !! Adjust !! Support !!
- Induction > autologous transplant > consolidation > maintenance
- Triplet/quadruplet induction- preferred- anti-CD38+PI+IMID+DEX
- Timely stem-cell collection
- ASCT is standard, open to discussion in certain cases treated with anti-CD38
- Anti-CD38 + LEN is becoming the standard for maintenance
- The future: immuneo-therapies will probably be used frontline

Thank you
and good luck!