NCI Designated Comprehensive Cancer Center

VANDERBILT-INGRAM CANCER CENTER

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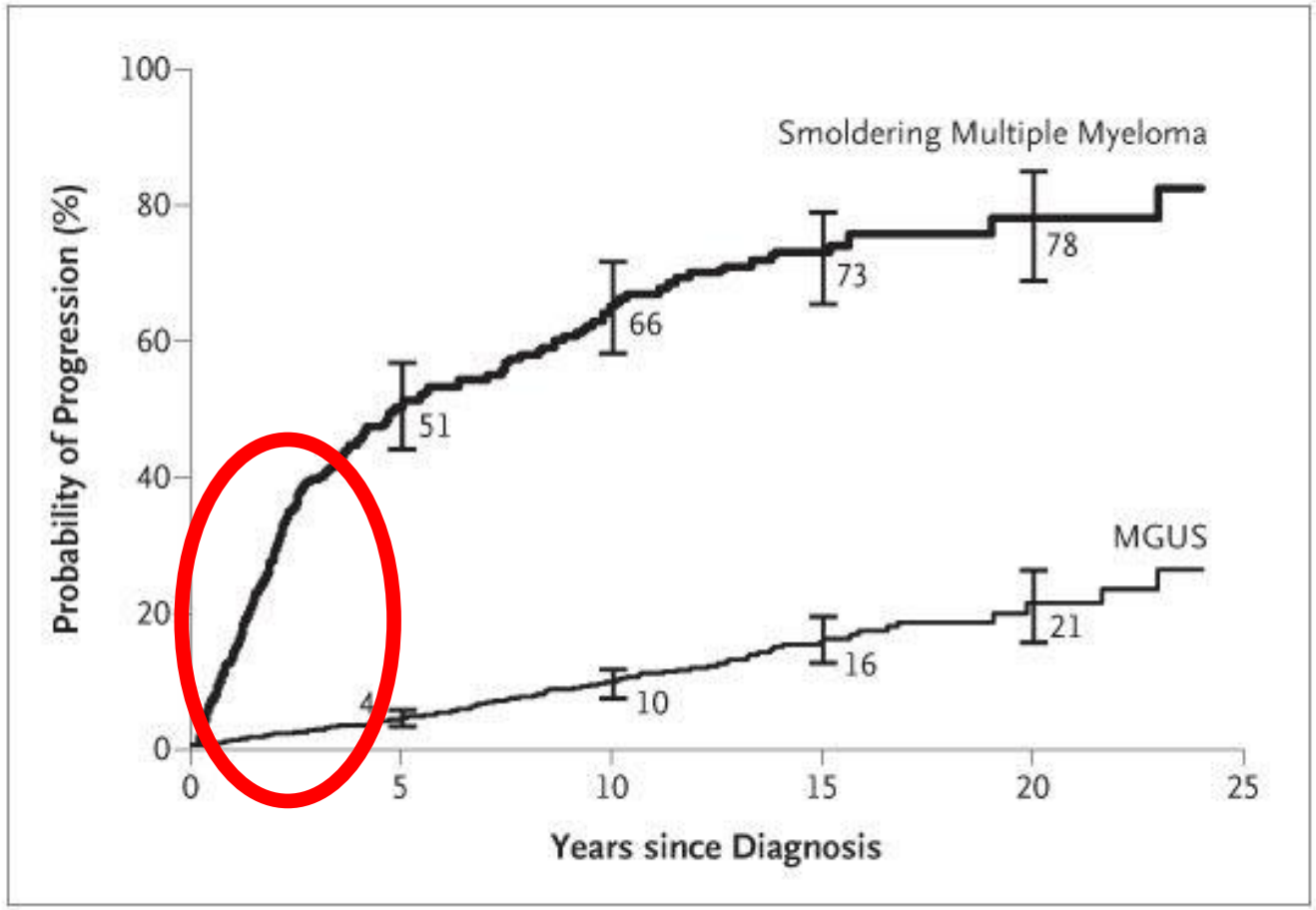
How I Treat Multiple Myeloma in 2023

Outline

- Management of Smoldering Myeloma
- Newly Diagnosed Multiple Myeloma
- High Risk Multiple Myeloma - different treatment?
- Relapsed/Refractory MM

What's the big deal with SMM?

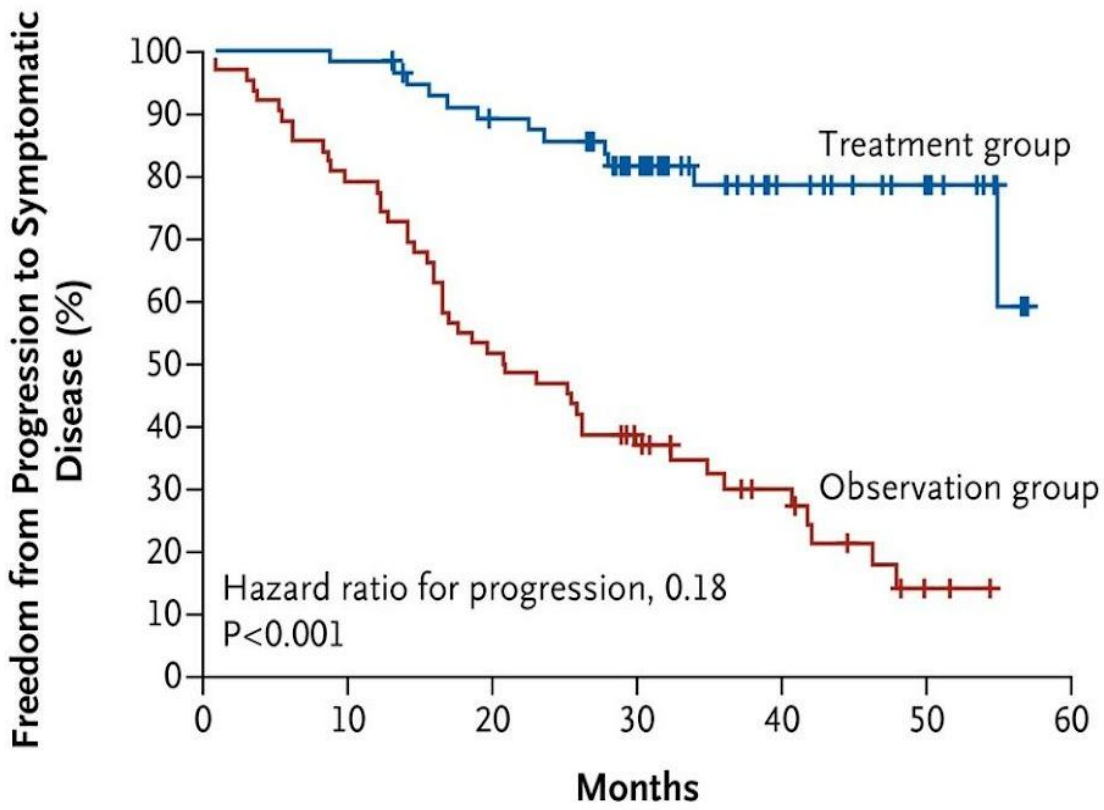
- Myeloma used to be defined by M spike > 3 and BMPC > 10%
- Study by Kyle in 1980 showed that a subset of patients never developed symptoms without treatment
- SMM was then defined and natural history shown here



Kyle et al, NEJM 2007

SMM Goal: Avoid End Organ Damage

- Early studies prior to IMiD looked at use of melphalan and found no OS
- Spanish study looked at lenalidomide-dex vs. observation and found OS
- Limitations:
  - Underpowered
  - No PET/CT at entry
  - No lenalidomide in control arm at PD

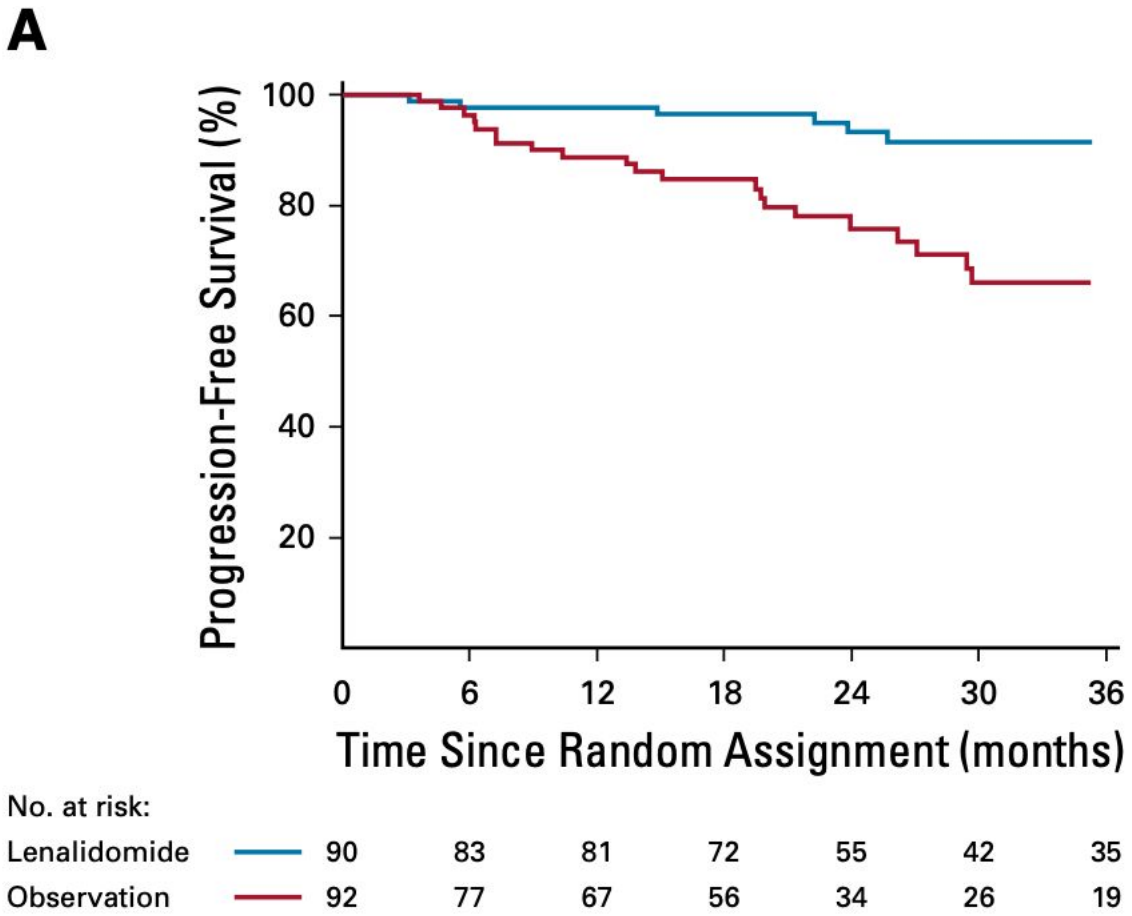


No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

Mateos et al, NEJM 2013

ECOG Trial: Lenalidomide Off Label

- Phase II run in followed by Phase III Randomized Trial
- Len vs. Observation
- Continued until PD or toxicity
- After PFS benefit at interim analysis, patients crossed over to len so no OS benefit observed



Lonial et al, JCO 2020

Lenalidomide SMM…Is it worth it?

- Does PFS actually matter to patients?
- Are patients in control arm having **irreversible** end organ damage?
- Question is still unanswered but could consider in high-risk patients with SMM (Mayo 2-20-20 criteria) or updated PANGEA model
- Concerns:
  - Cost – drug and collect stem cells after ~4 cycles (storage cost)
  - Toxicity
  - Secondary Malignancy
  - Are we fundamentally changing trajectory of disease?

TABLE A6. Basis of Progression

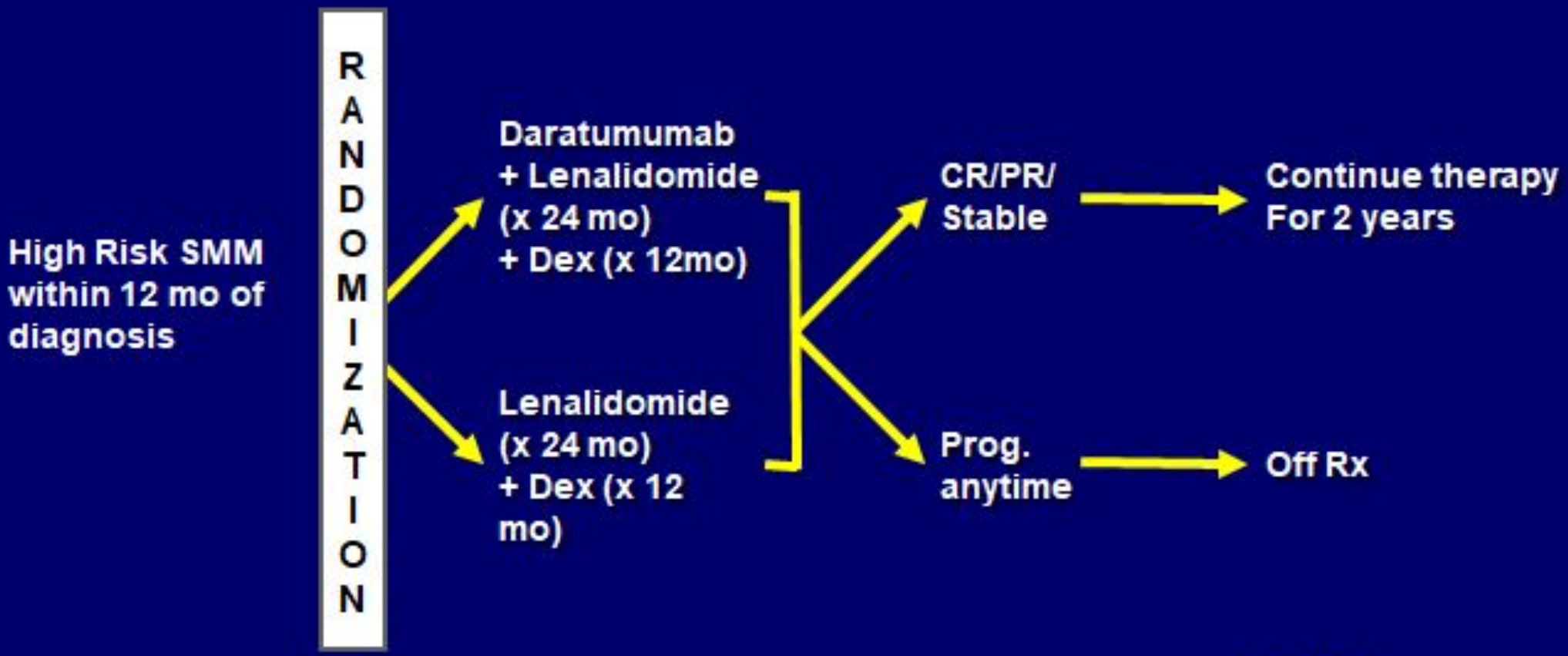
Variable	Phase II Run In	Phase III Randomized Trial		
	Lenalidomide (n = 6 PD cases)	Lenalidomide (n = 7 PD cases)	Observation (n = 21 PD cases)	Total (n = 28 PD cases)
Biochemical				
Serum M	6 (100.0)	7 (100.0)	18 (85.7)	25 (89.3)
Urine M	0 (0.0)	0 (0.0)	4 (19.0)	4 (14.3)
Bone marrow plasma cell %	0 (0.0)	2 (28.6)	6 (28.6)	8 (28.6)
End organ				
Hypercalcemia	0 (0.0)	0 (0.0)	1 (4.8)	1 (3.6)
Anemia	2 (33.3)	4 (57.1)	8 (38.1)	12 (42.9)
Renal failure	0 (0.0)	0 (0.0)	3 (14.3)	3 (10.7)
Bone lesion/soft-tissue plasmacytoma	4 (66.7)	3 (42.9)	11 (52.4)	14 (50.0)

NOTE. Data are given as No. (%). Progression defined per protocol required biochemical and end organ failure. Within these categories, multiple bases of progression may be reported.

Abbreviation: PD, progressive disease.

Lonial et al, JCO 2020

EAA173: Phase III –Daratumumab to Enhance Therapeutic Effectiveness of Revlimid in Smoldering Myeloma (DETER-SMM)(PI: NC)



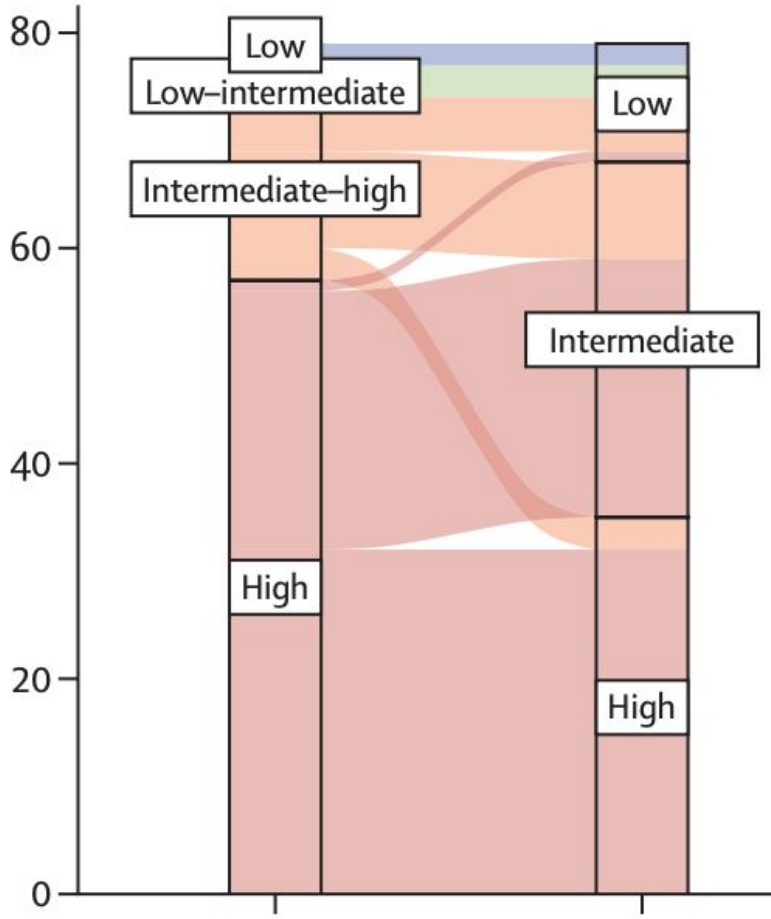
N = 288

PI: Natalie Callander

(Activated 4/30/2019)

Personalised progression prediction in patients with monoclonal gammopathy of undetermined significance or smouldering multiple myeloma (PANGEA): a retrospective, multicohort study

- Pangea model on the left
- Mayo 2-20-20 risk stratification on the right
- Figure shows all patients that progressed to MM from SMM
- PANGEA does a better job at classifying those who are at high risk



Cowan et al, Lancet Hematology 2023

How I Treat Smoldering MM in 2023

- Risk stratify SMM
  - Mayo 2-20-20 or PANGEA model (ideal)

- Low to intermediate risk
  - Surveillance (rise in M spike by 0.5 and decrease Hgb by 0.5 within 12 months warrants full workup – 90% risk of progression to MM)

- High Risk (50% risk of progression to MM at 2 years)
  - **Active surveillance (monthly labs that can be spaced out) – reasonable**
  - Lenalidomide monotherapy based on ECOG trial (unclear if this prevents symptomatic or irreversible organ damage)
  - **<u>Clinical Trial – EAA173 now enrolling at VUMC</u>**

Newly Diagnosed Transplant Eligible MM

1. Risk Stratify patients
   - t(4;14), t(14;16), t(14;20)
   - amp 1q (3 or more copies)
   - del 17p
   - Extramedullary disease or circulating myeloma cells

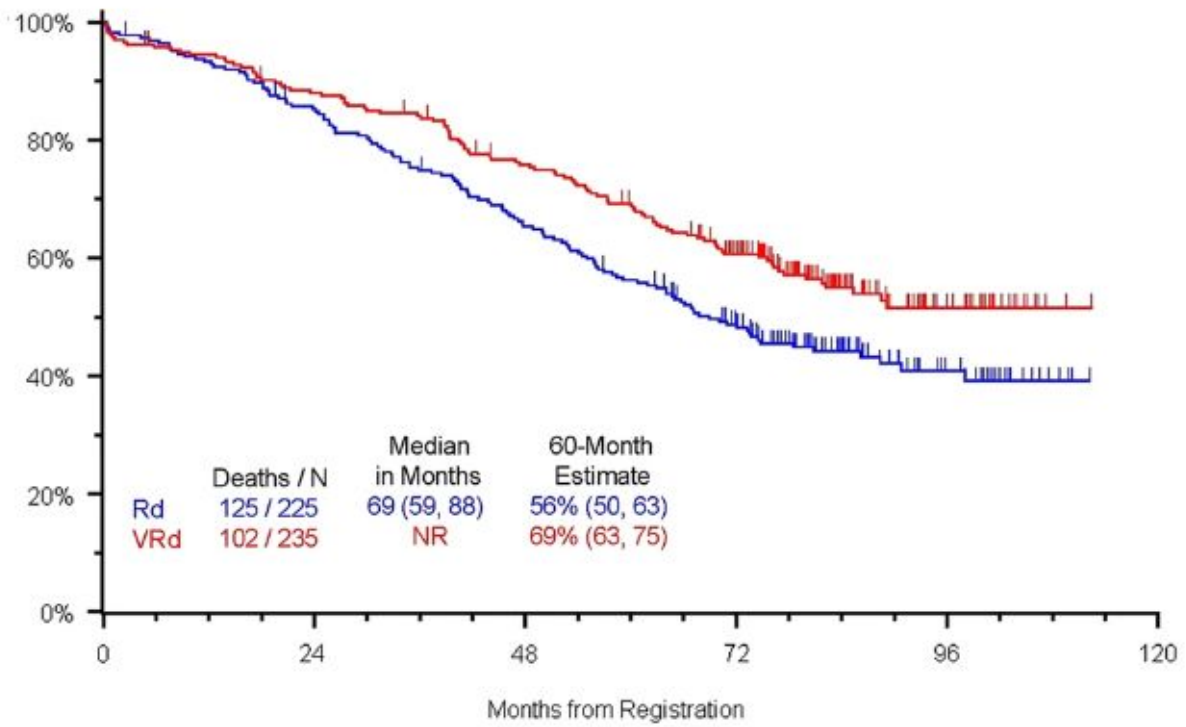
2. Quadruplet regimen for high risk but could use triplet for standard risk

3. Always collect stem cells after 3-4 cycles but can delay transplant for standard risk

4. Maintenance with lenalidomide for all except high risk with PI + IMiD

Argument for VRD Induction

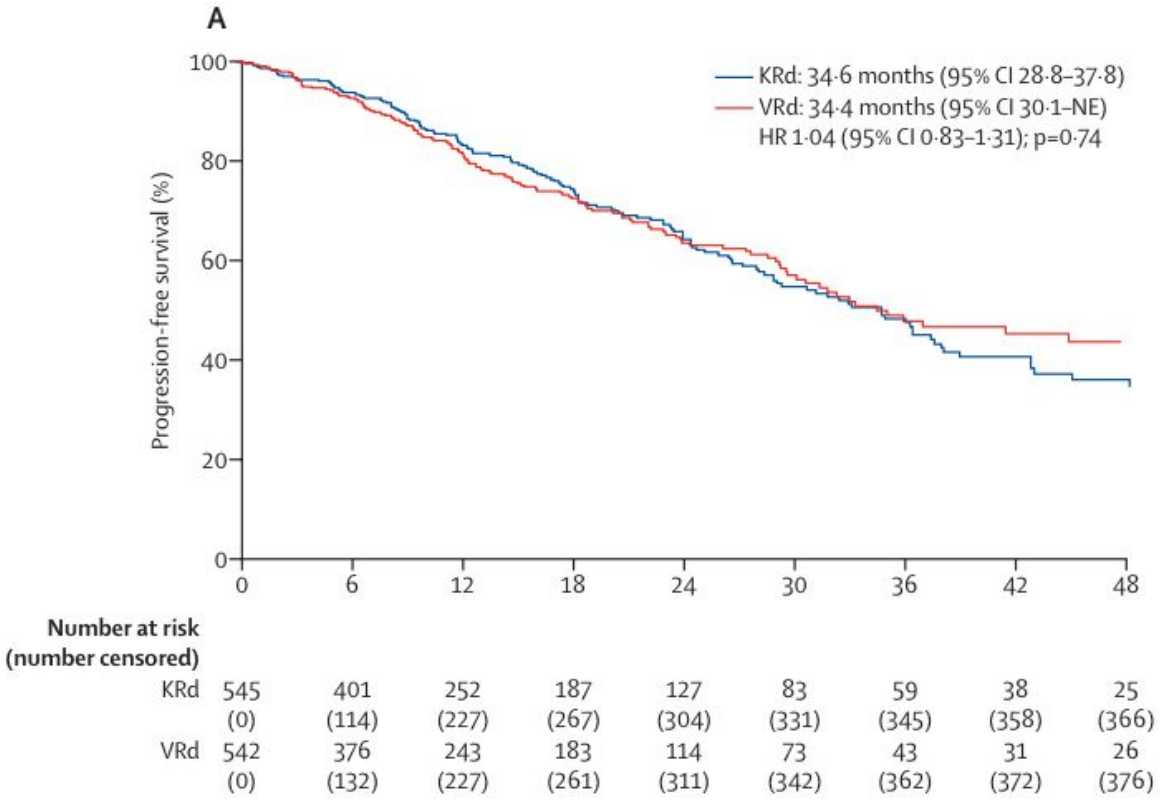
- SWOG 0777 is a randomized phase III RCT showing OS benefit
- Triplet VRD vs. doublet RD
- No quadruplet trials have been powered for OS benefit
- Should we just save the daratumumab?



Durie et al, Blood Cancer Journal 2020

Why not KRD Induction?

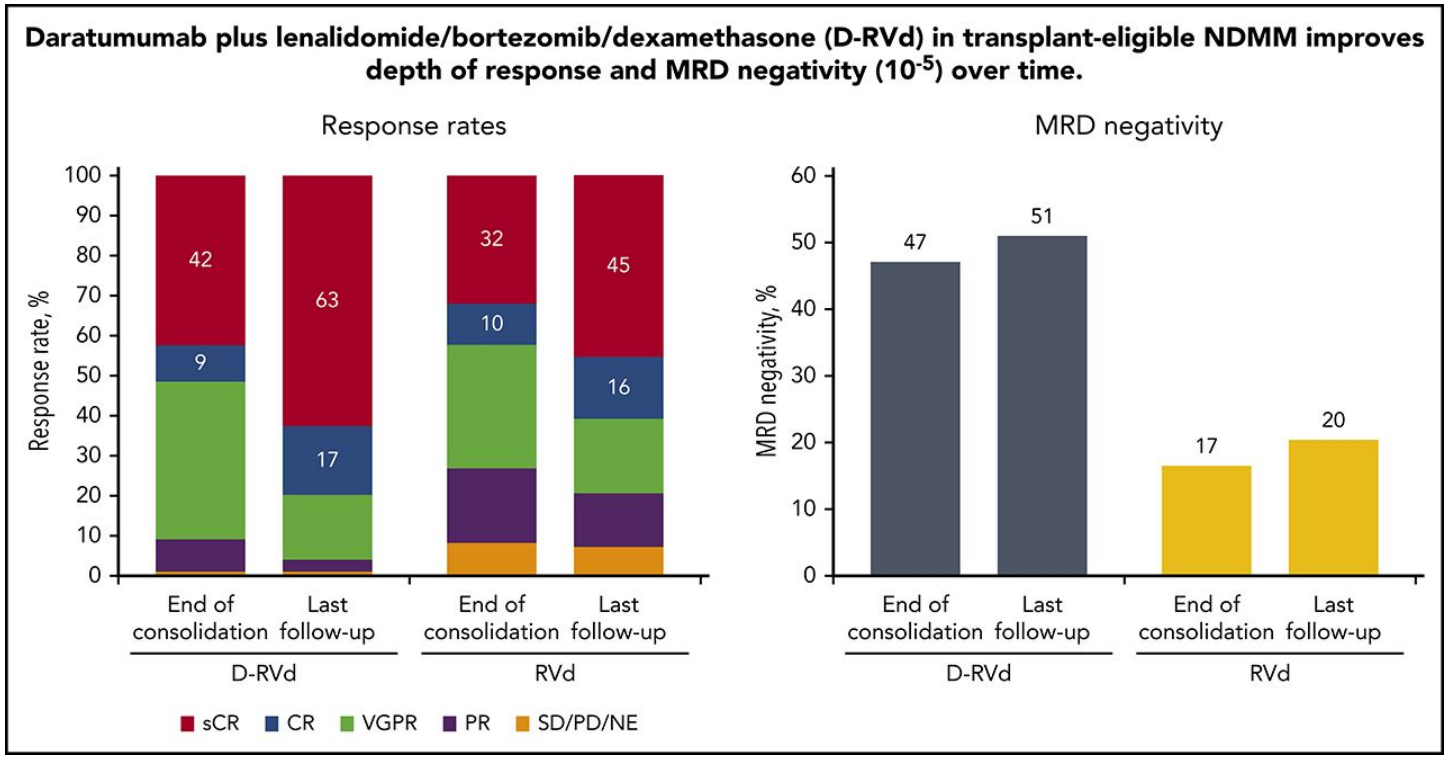
- ENDURANCE phase III RCT compared VRD vs. KRD
- Excluded high risk patients (concurrent elotuzumab trial enriched for high risk)
- No difference in PFS or OS
- More toxicity



Kumar et al, Lancet Oncology 2020

Argument for Dara-VRD: Griffin Trial

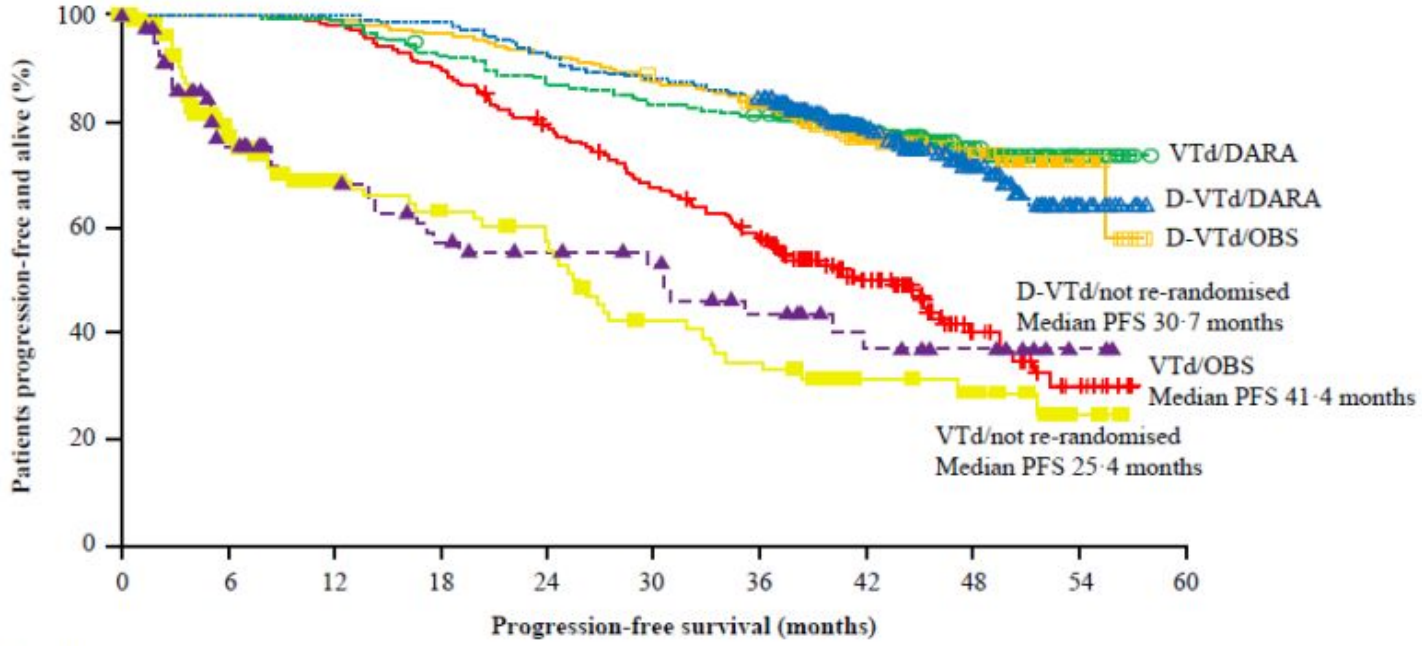
- GRIFFIN phase III RCT compared Dara-VRD vs. VRD
- Continued Dara-R in maintenance if given in induction
- MRD negative sustained at 1 year 44% vs. 14% favoring quadruplet
- PFS or OS benefit???



Voorhees et al, Blood 2020

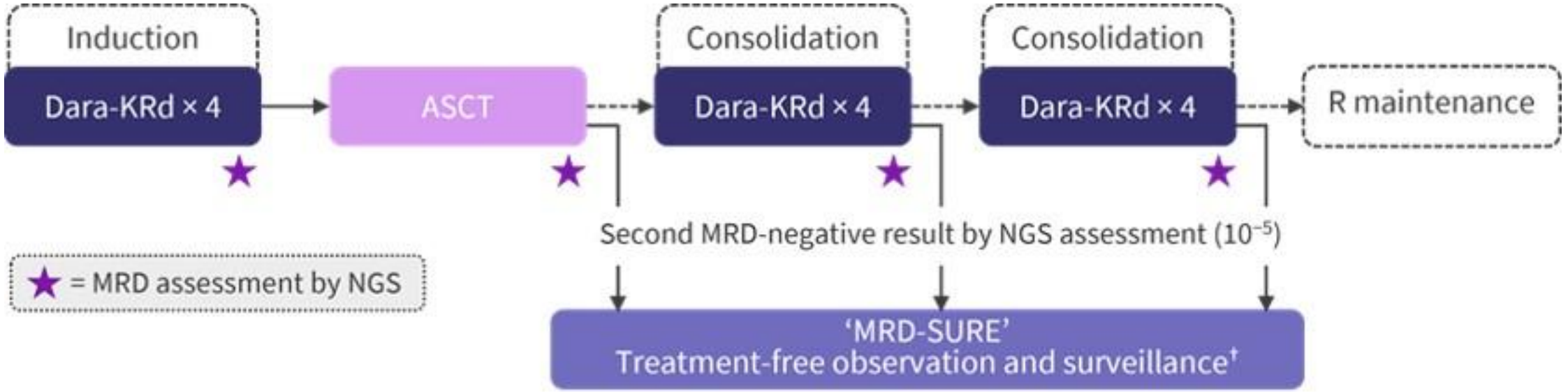
Do we need daratumumab forever?

- CASSIOPEIA phase III RCT compared Dara-VTD vs. VTD in Europe
- Second randomization of Dara vs. observation maintenance (appropriate?)
- Dara maintenance same PFS as observation
- VTD induction but given dara in maintenance seems to have same PFS



Moreau et al, Lancet Oncology 2021

MASTER Trial: Patients off all therapy



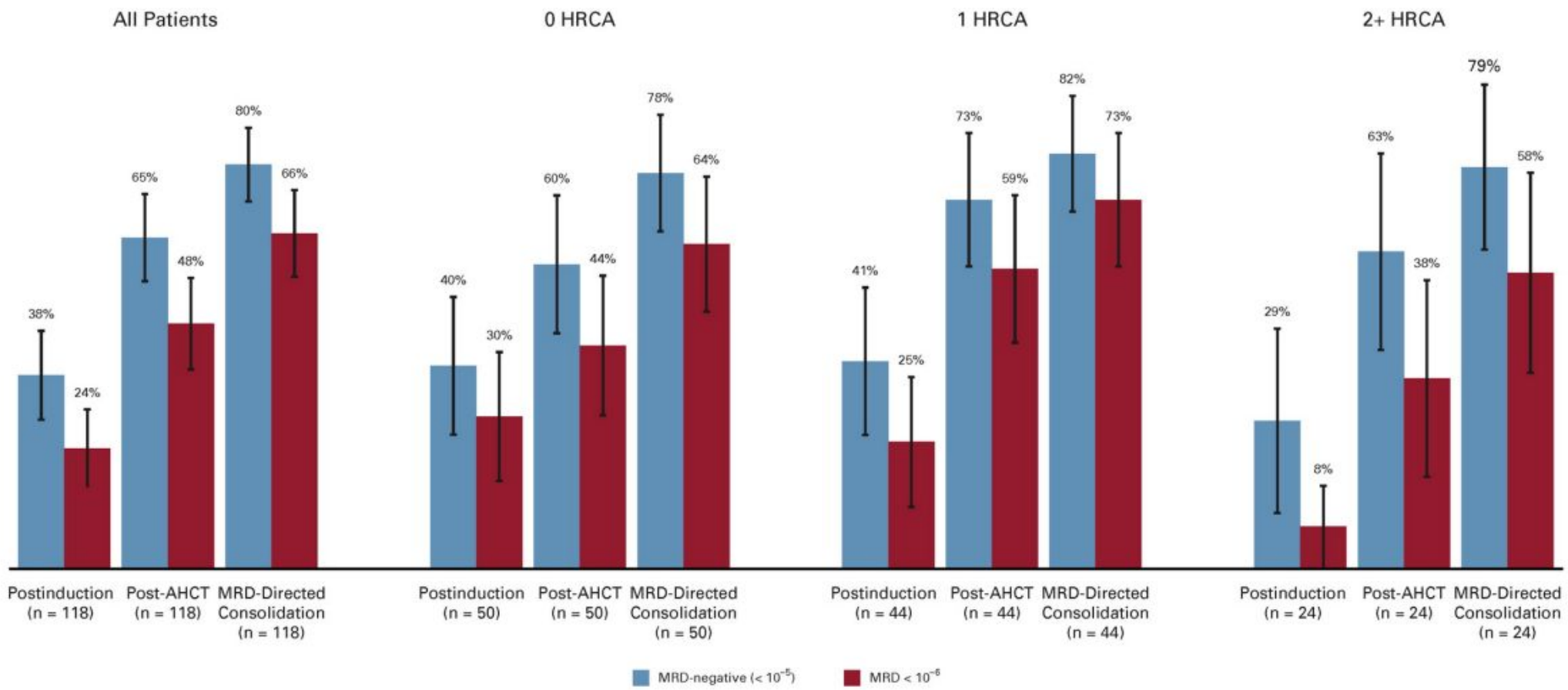
Dosing

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

Costa et al, JCO 2021

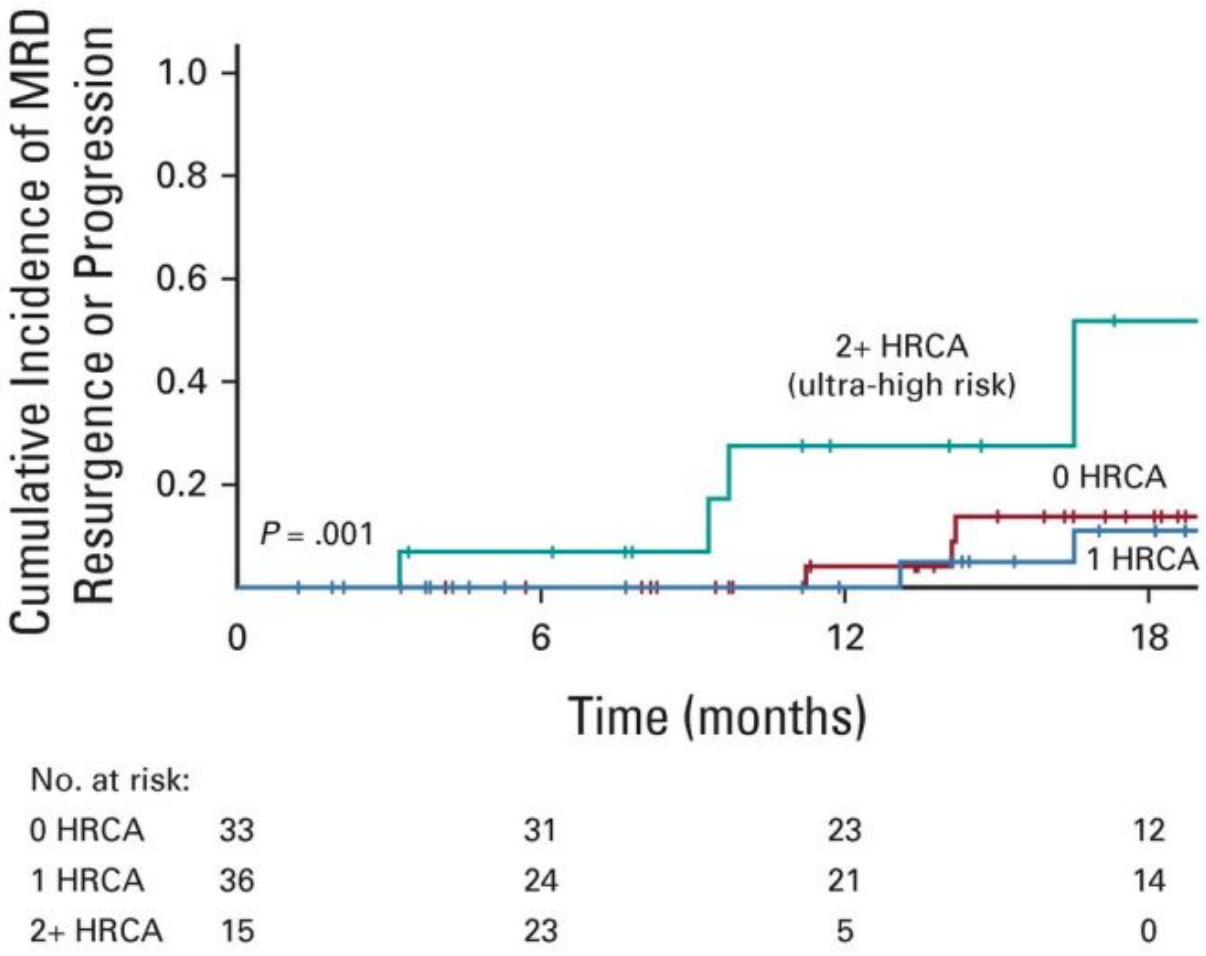
MASTER Trial: Patients off all therapy



Costa et al, JCO 2021

Dara-KRD Compelling But No Phase III

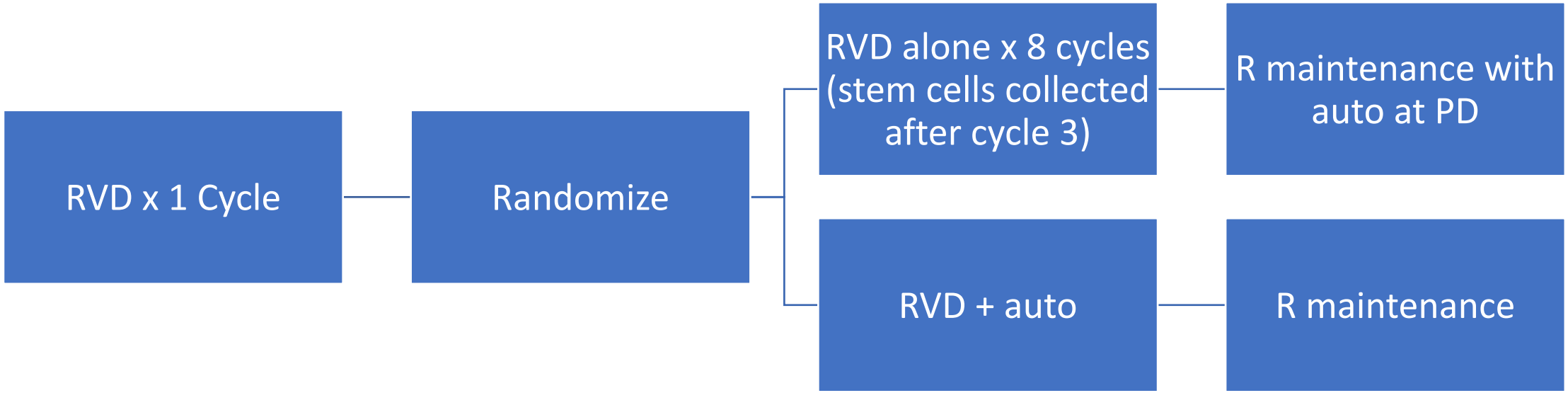
- About 70% of patients achieved MRD negativity during the study
- Sustained MRD achieved for a year or more in most patients
- High risk with ~30% resurgence within 1 year
- Question if MRD is a good surrogate in high risk



Costa et al, JCO 2021

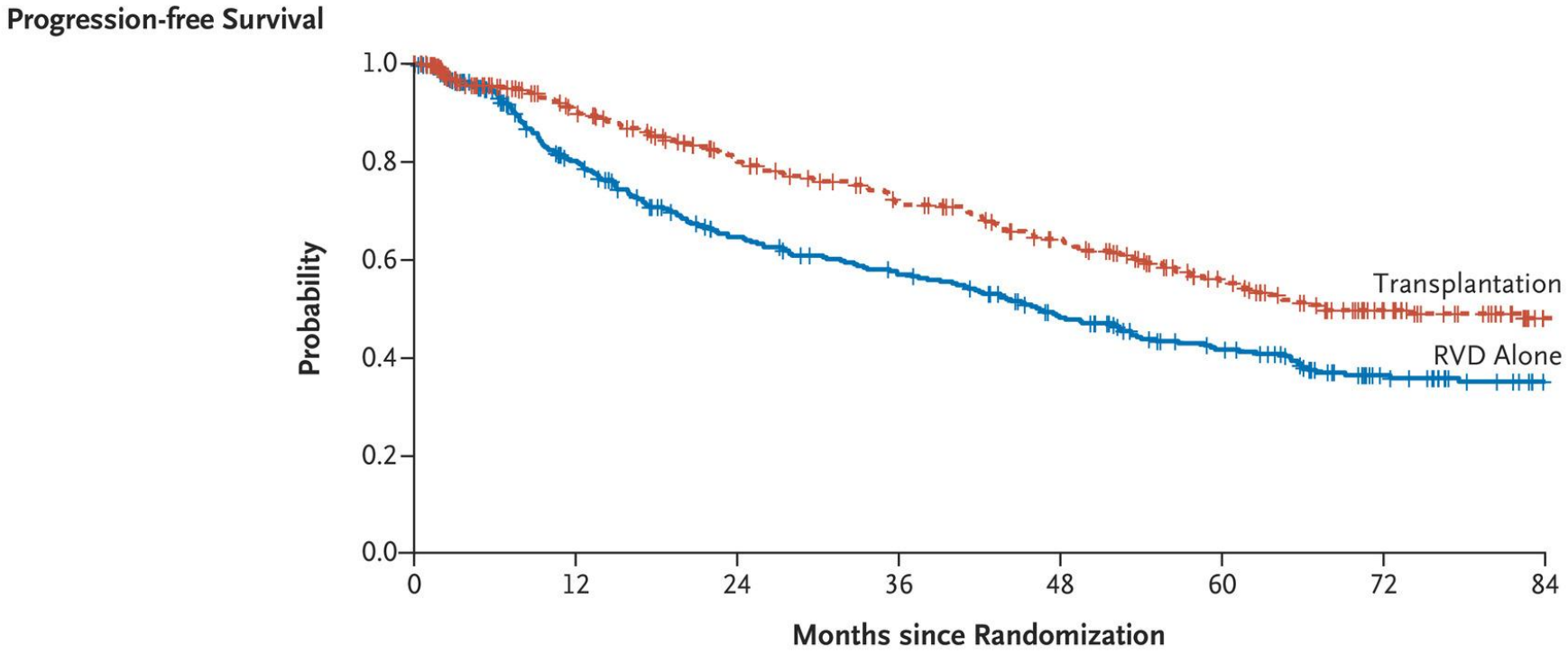
ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma



Richardson et al, NEJM 2022

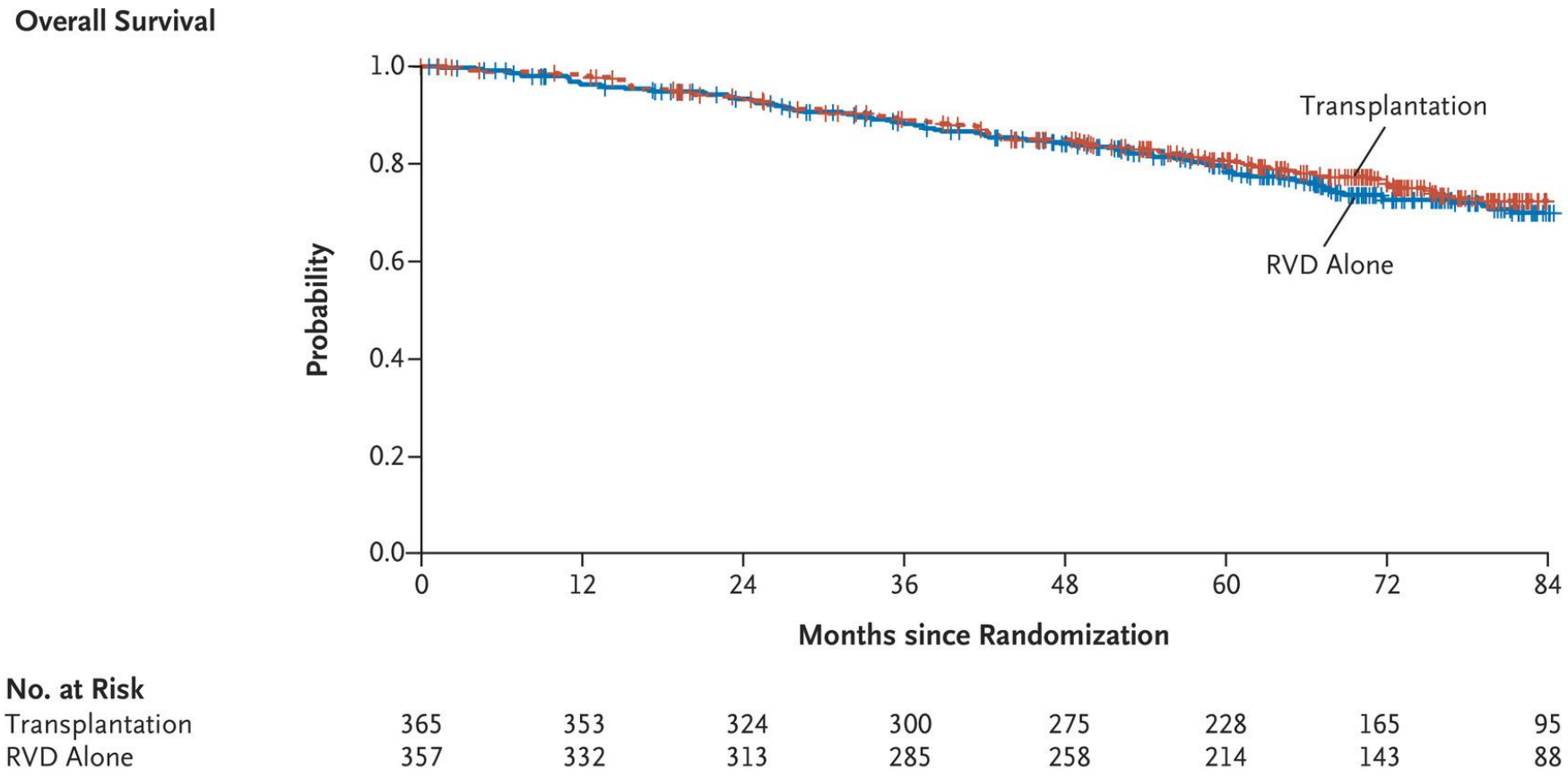
DETERMINATION: Early vs. Delayed SCT



No. at Risk								
Transplantation	365	276	226	191	160	118	77	42
RVD Alone	357	250	187	160	126	96	60	40

Richardson et al, NEJM 2022

DETERMINATION: Early vs. Delayed SCT

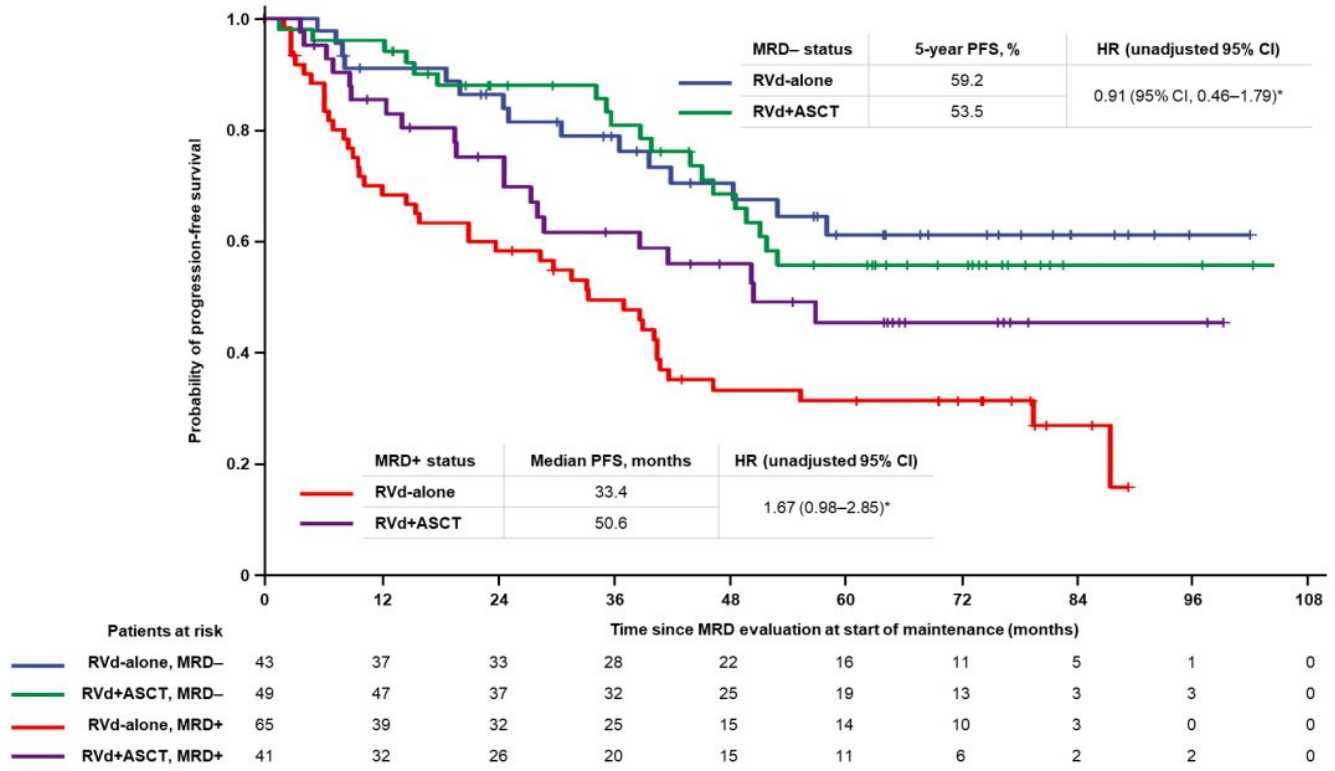


No. at Risk								
Transplantation	365	353	324	300	275	228	165	95
RVD Alone	357	332	313	285	258	214	143	88

Richardson et al, NEJM 2022

DETERMINATION: MRD not a surrogate

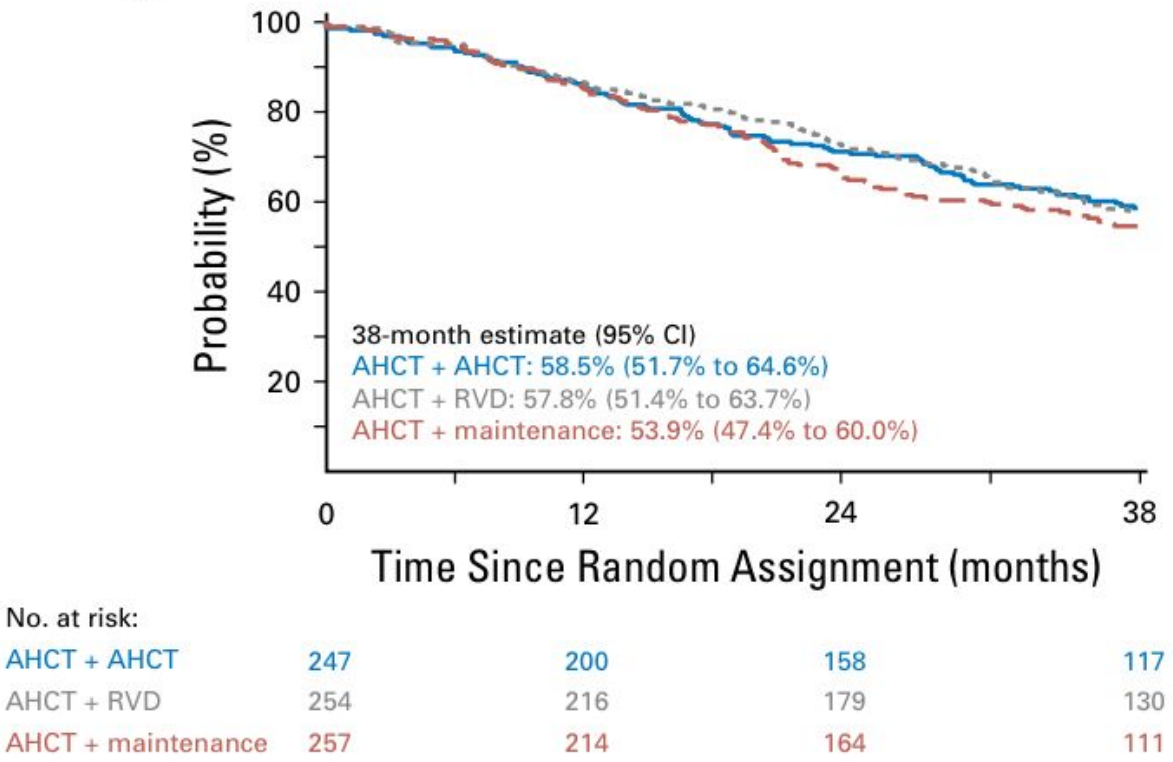
- MRD clearly prognostic and didn't matter how you get there
- Up front transplant had 15% higher MRD negative rates
- There was not a 15% benefit in OS and in fact no difference in OS
- No improvement in QOL and only ~25% needed transplant in control
- Caveat: only ~10% were high risk



Richardson et al, NEJM 2022

Tandem Transplant High Risk?

- RVD induction followed by auto
- Randomized 1:1:1 to tandem vs. RVD consolidation vs. lenalidomide maintenance
- No PFS or OS benefit for tandem or RVD consolidation
- Trial included 30% high risk patients
- Data weak to support tandem for all
- Bispecific Ab is likely the future



Stadtmauer et al, JCO 2019

Context of PI Maintenance in High Risk

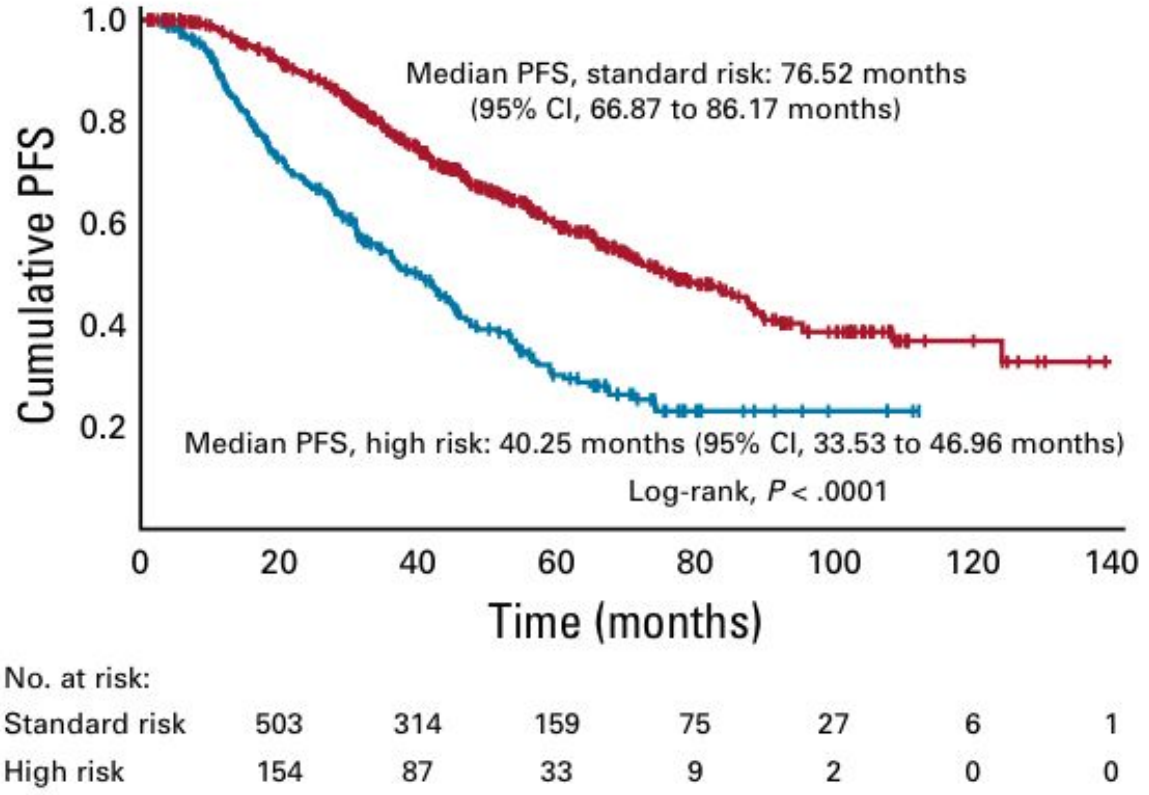
Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial

Pieter Sonneveld, Ingo G.H. Schmidt-Wolf, Bronno van der Holt, Laila el Jarari, Uta Bertsch, Hans Salwender, Sonja Zweegman, Edo Vellenga, Annemiek Broyl, Igor W. Blau, Katja C. Weisel, Shulamiet Wittebol, Gerard M.J. Bos, Marian Stevens-Kroef, Christof Scheid, Michael Pfreundschuh, Dirk Hose, Anna Jauch, Helgi van der Velde, Reinier Raymakers, Martijn R. Schaafsma, Marie-Jose Kersten, Marinus van Marwijk-Kooy, Ulrich Duehrsen, Walter Lindemann, Pierre W. Wijermans, Henk M. Lokhorst, and Hartmut M. Goldschmidt

Sonneveld et al, JCO 2012

PI + IMiD Maintenance for High Risk

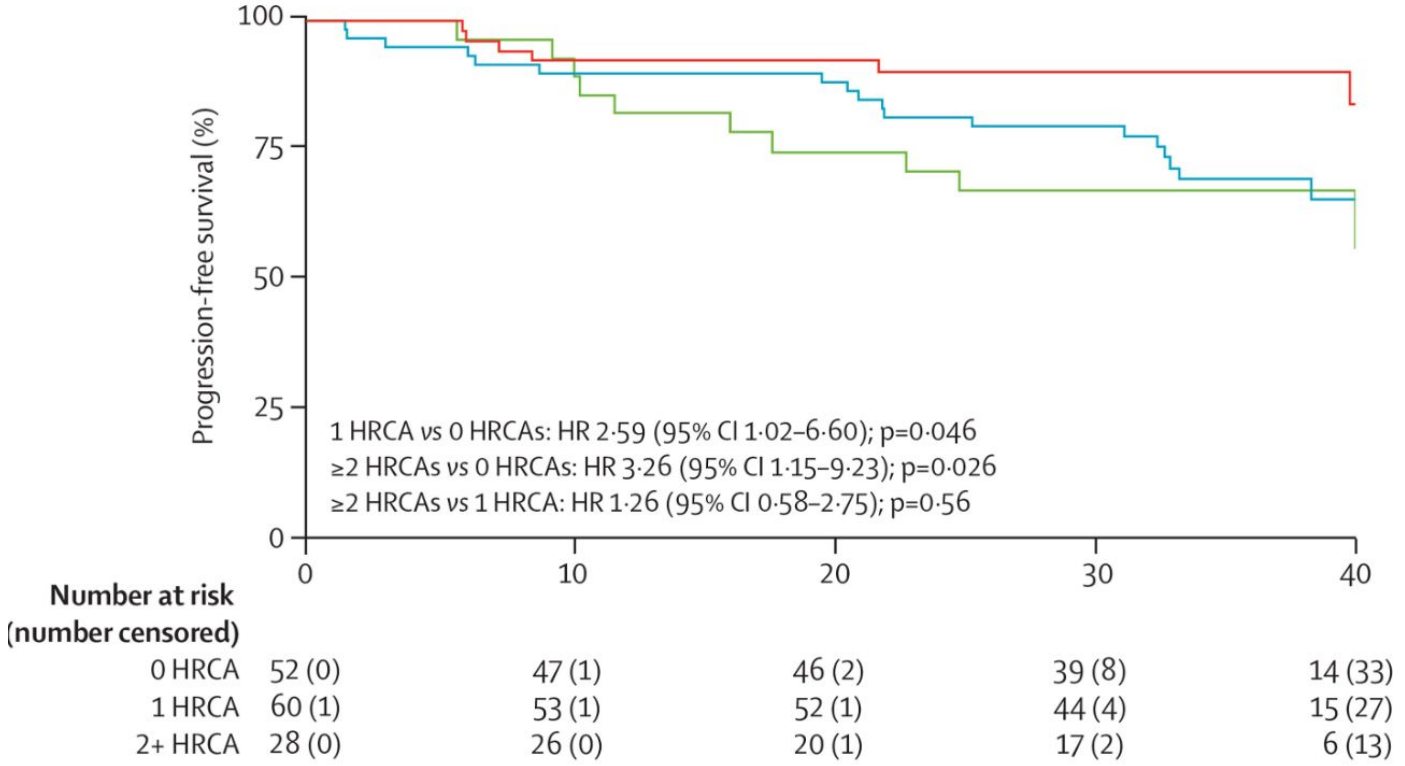
- Emory experience of 1000 consecutive patients with RVD induction followed by auto SCT
- If high risk, given indefinite RVD maintenance
- Median PFS 40 months and OS 78 months
- Historical high risk PFS ~24 months



Joseph et al, JCO 2020

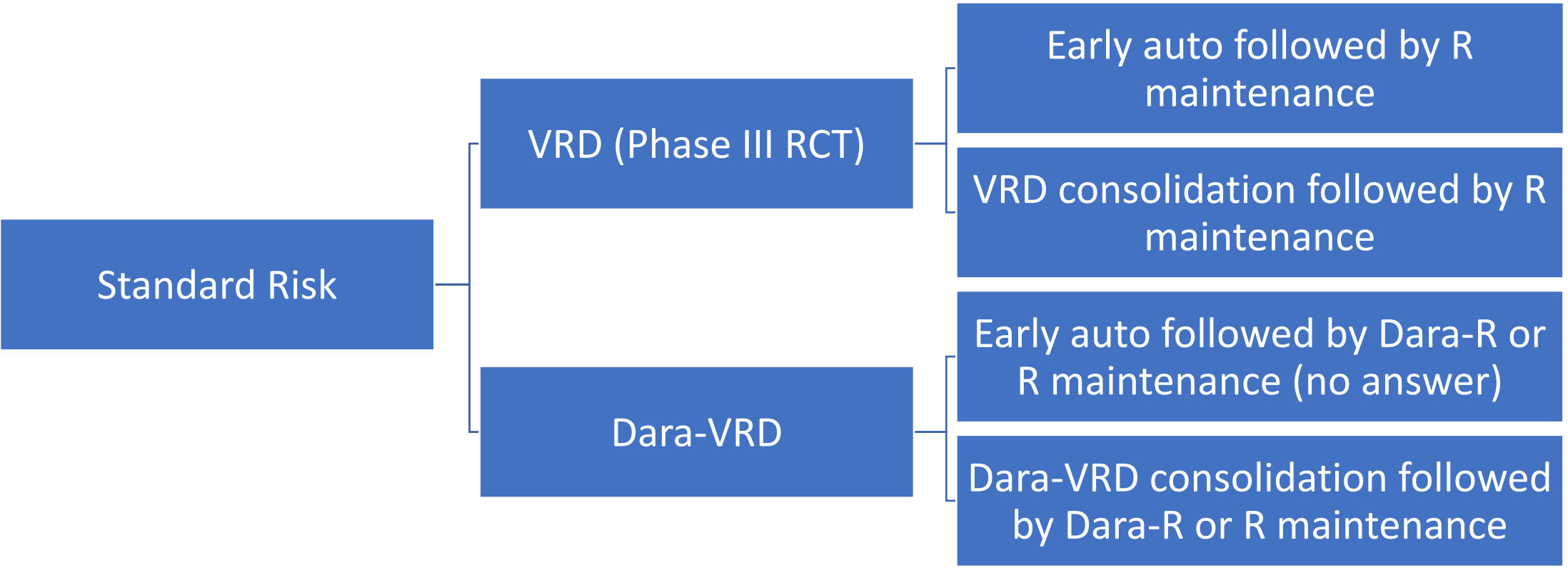
FORTE Trial: KR vs. R Maintenance

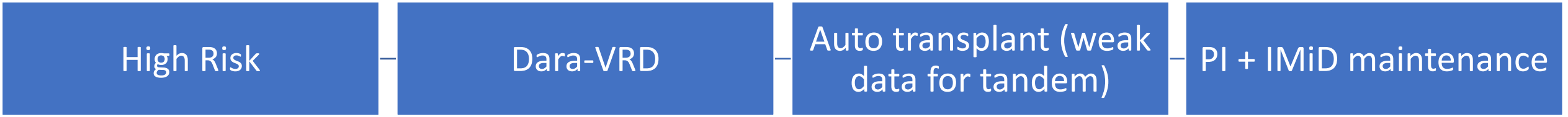
- Randomized different carfilzomib induction regimens
- Second randomization for KR vs. R maintenance
- KR maintenance in high risk with impressive >3 year median PFS



Mina et al, Lancet Oncology 2023

Transplant Eligible Algorithm



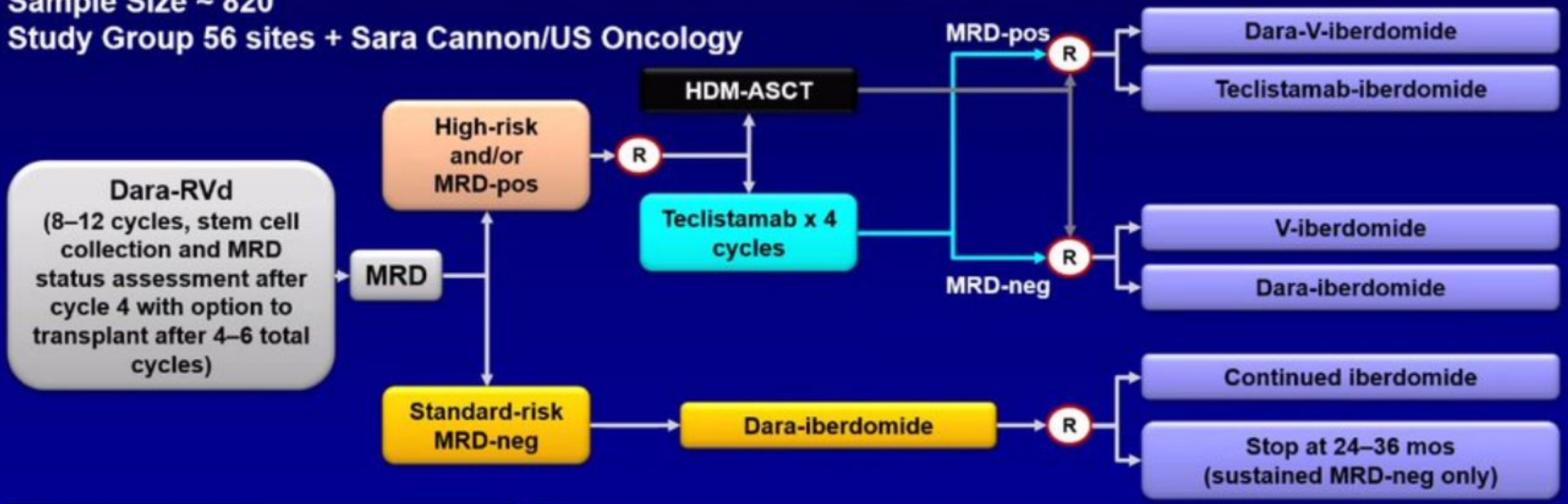


DETERMINATION 2: preferred concept 1

Standard- and high-risk patients with community practice (e.g. US Oncology) access as a focus

Sample Size ~ 820

Study Group 56 sites + Sara Cannon/US Oncology



Primary endpoints:

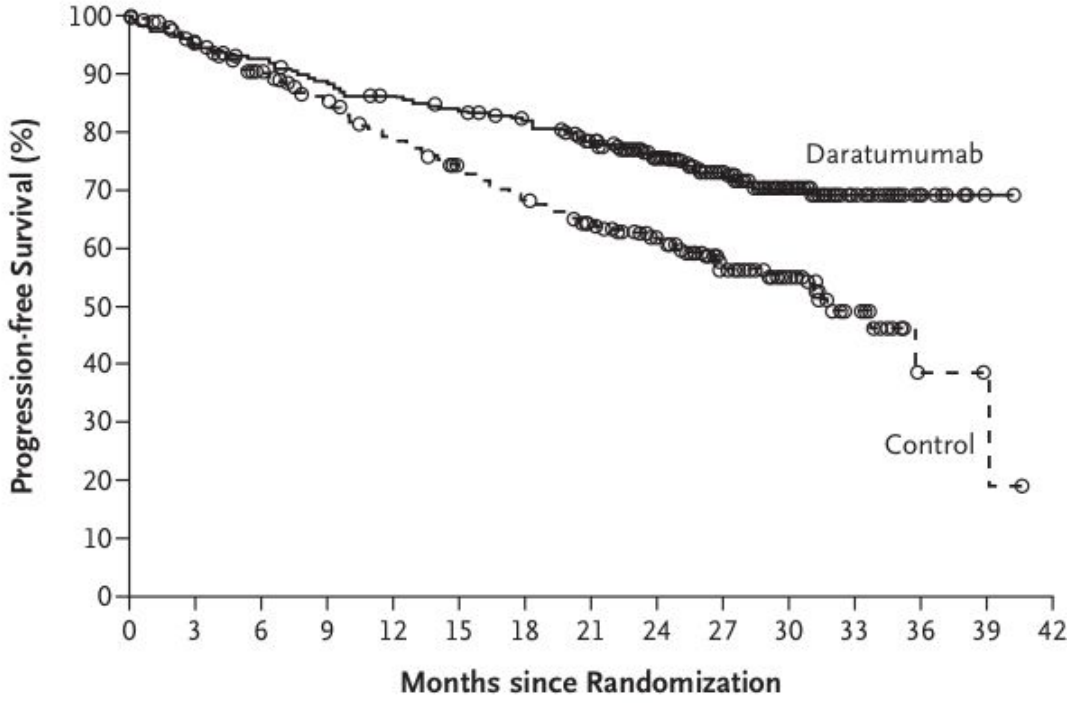
- Standard-risk MRD-neg group: Sustained MRD-neg vs PFS
- High-risk and/or MRD-pos group: Sustained MRD-neg after HDM-ASCT vs teclistamab vs PFS

Questions answered:

- Is anti-BCMA bispecific consolidation superior to HDM-ASCT in deepening response?
- Can novel combinations overcome persistent MRD positivity?
- What is the most efficacious maintenance regimen?
- Can we safely stop maintenance in deep and durable responders without sacrificing PFS?

Transplant Ineligible: MAIA Trial

- Dara-RD indefinite vs. RD
- Improved PFS with no increase in toxicity
- Control arm should have been VRD based on SWOG 0777 trial
- Dara-RD reasonable but so is VRD
- Should we save daratumumab for relapse?

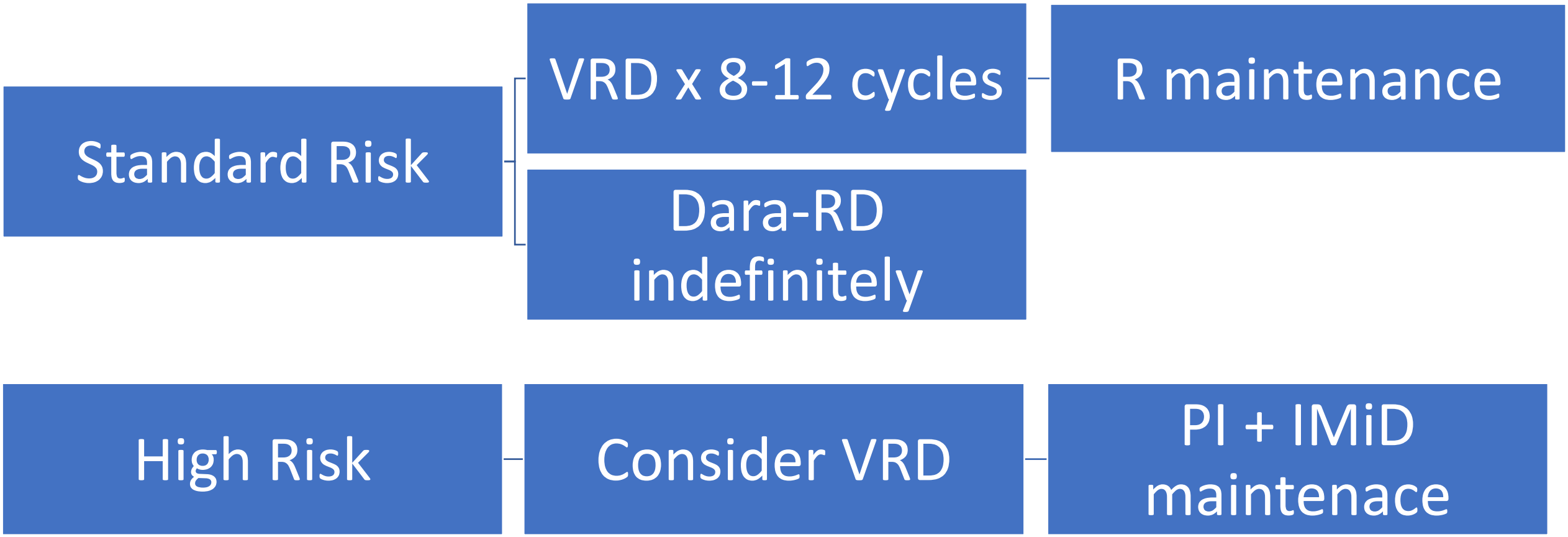


No. at Risk

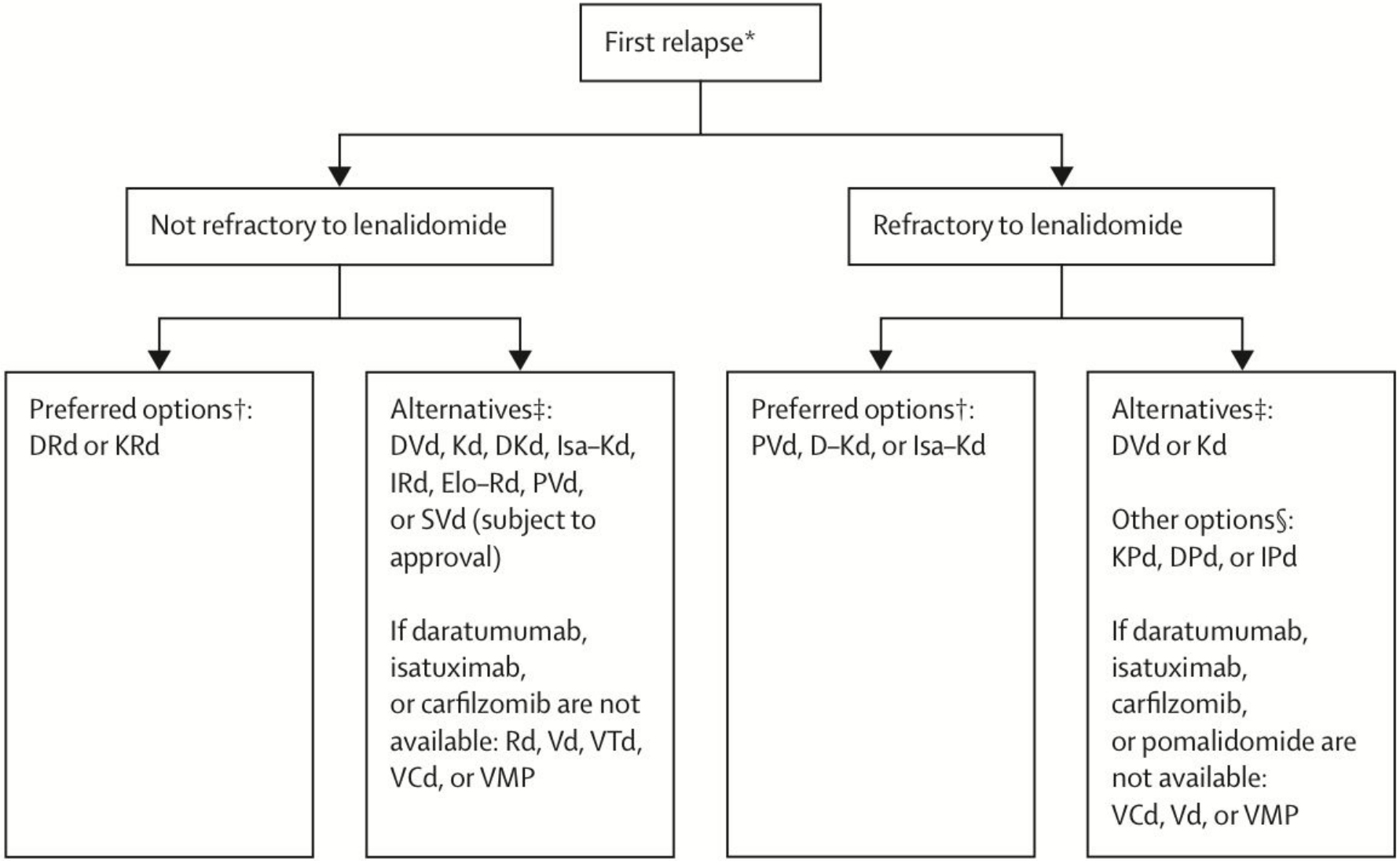
Daratumumab	368	347	335	320	309	300	290	271	203	146	86	35	11	1	0
Control	369	332	307	280	254	236	219	200	149	94	50	18	3	2	0

Richardson et al, NEJM 2022

Transplant Ineligible Algorithm



R/R MM: Choose your own adventure



Moreau et al, Lancet Onc 2021

First Relapse: Dara-KD likely the best

ENDEAVOR trial:

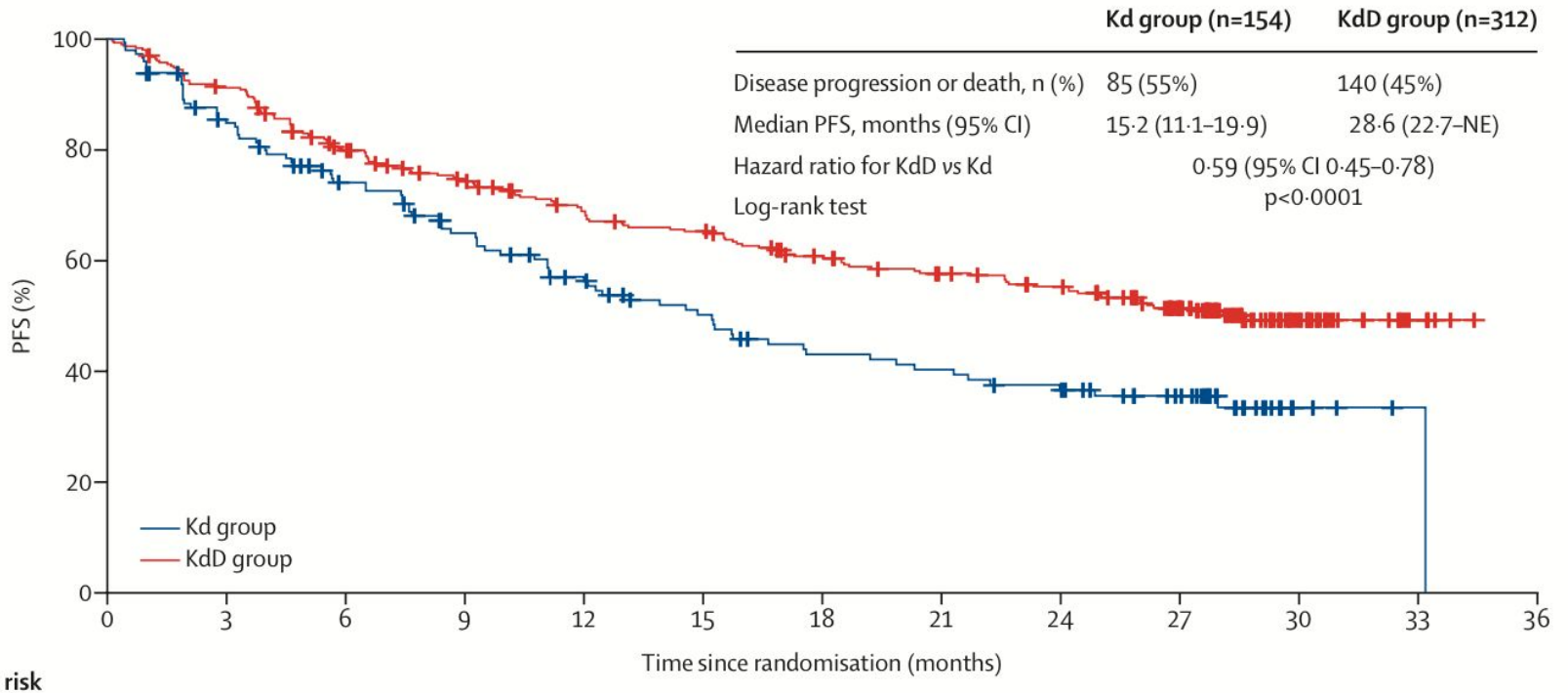
- KD vs. VD with median PFS 18.7 mo vs. 9.4 mo

CANDOR trial:

- Dara-KD vs. Kd with median PFS 28.6 mo vs. 15.2 mo

CASTOR Trial

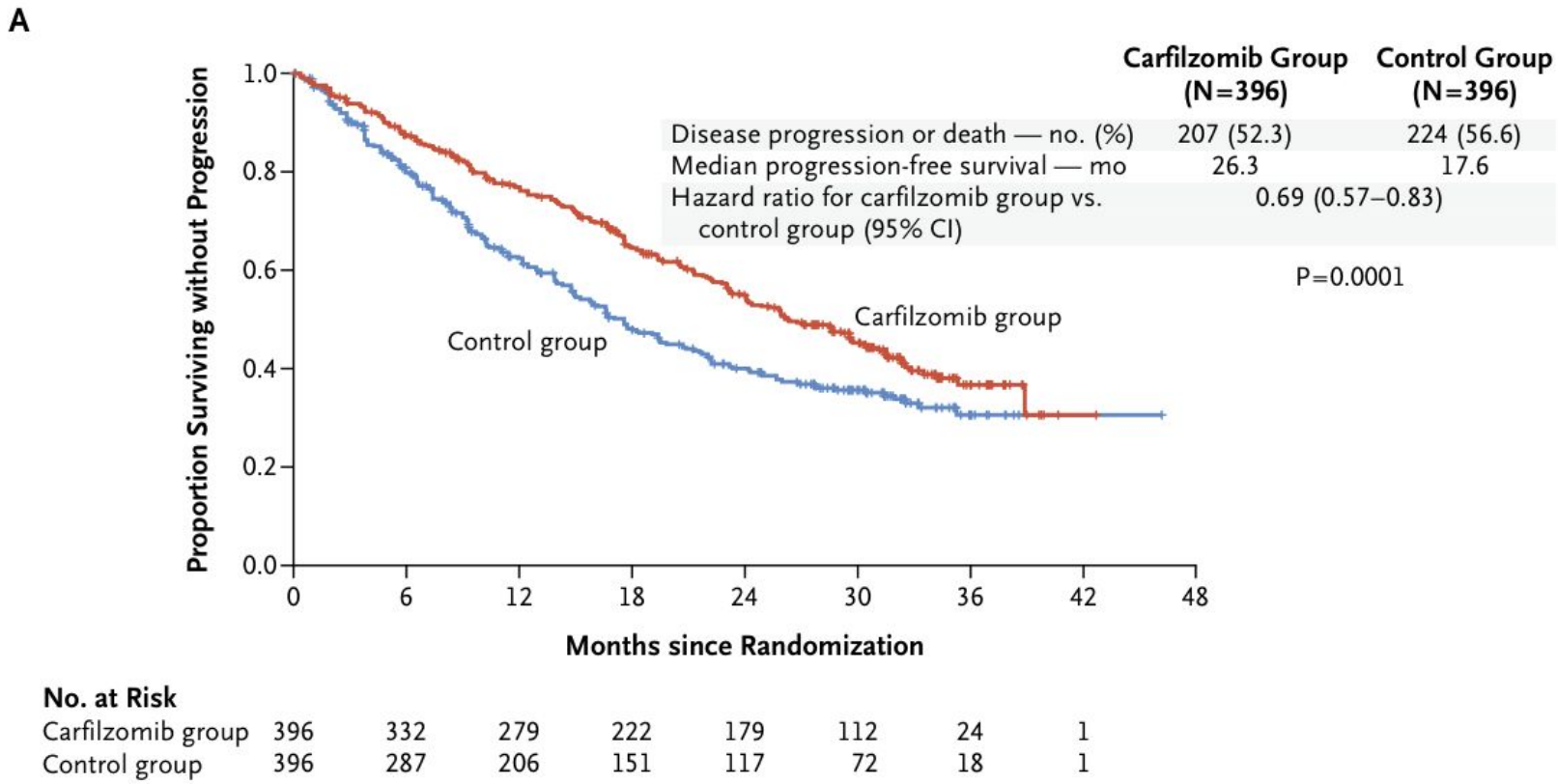
- Dara-VD vs. VD with median PFS 16.7 mo vs. 7.1 mo



Palumbo et al, NEJM 2016
Dimopoulos et al, Lancet Onc 2017
Usmani et al, Lancet Onc 2022

What if refractory to dara at first relpase?

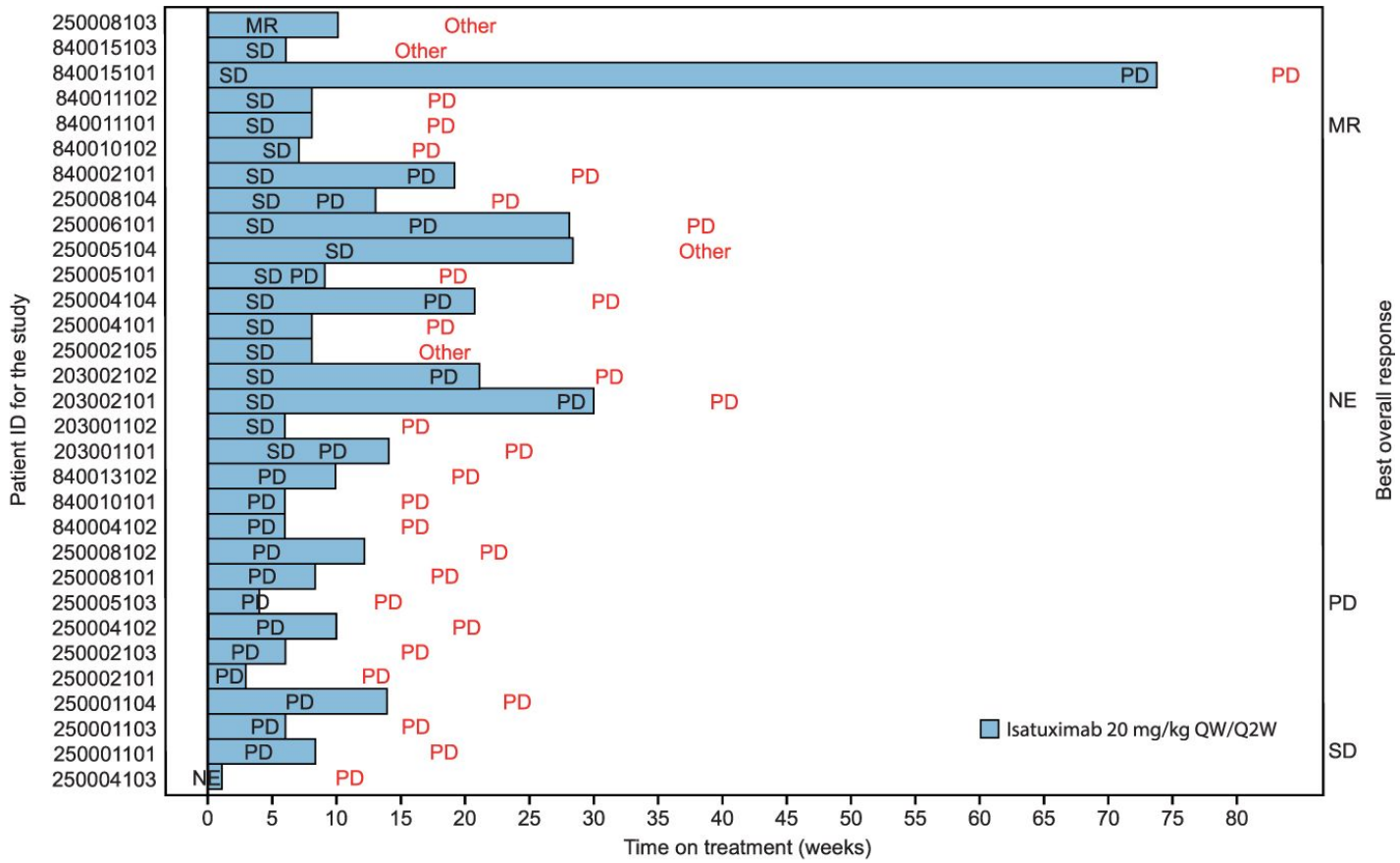
- If we did a quadruplet up front and then continued dara-R maintenance, then we would also be dara refractory
- Ideal would be KRd vs. KPd
- Lenalidomide refractory is relapse while on full dose or maximally tolerated dose



Stewart et al, NEJM 2016

Isatuximab if refractory to daratumumab?

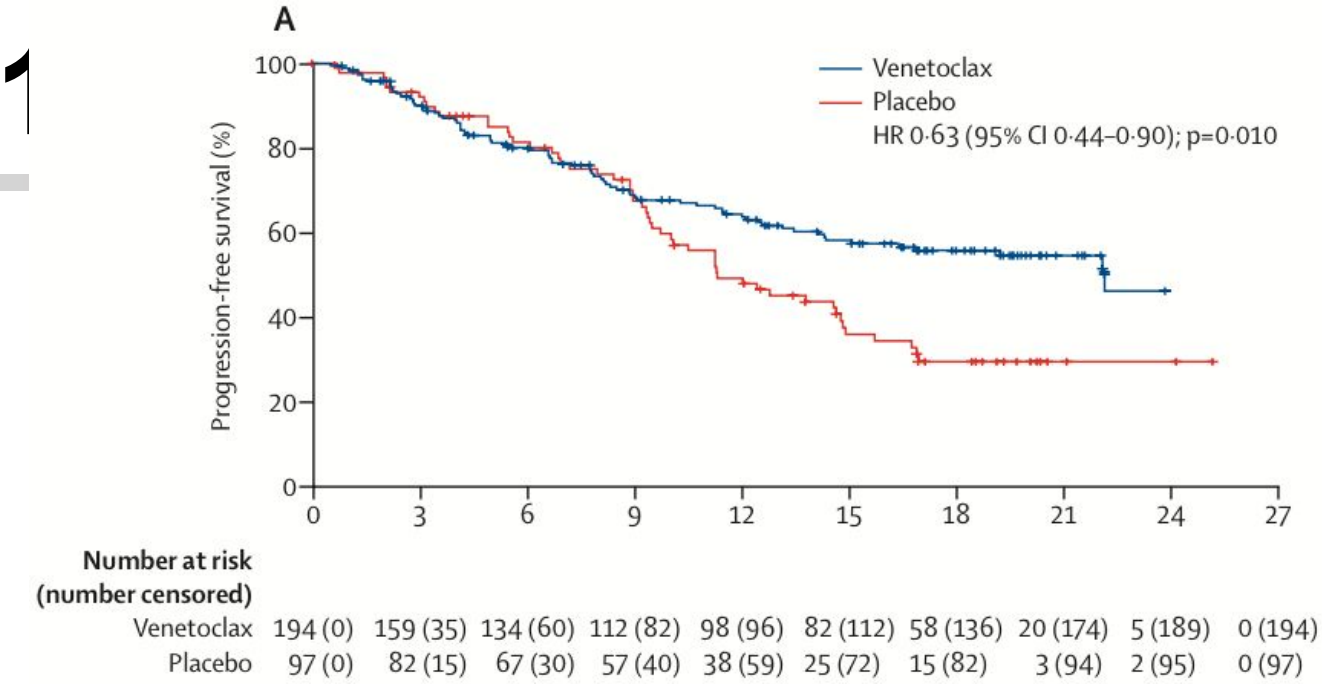
- Does not work well from multiple retrospective studies
- Phase 2 study looking at isatuximab after progression on daratumumab
- **0% response rate**

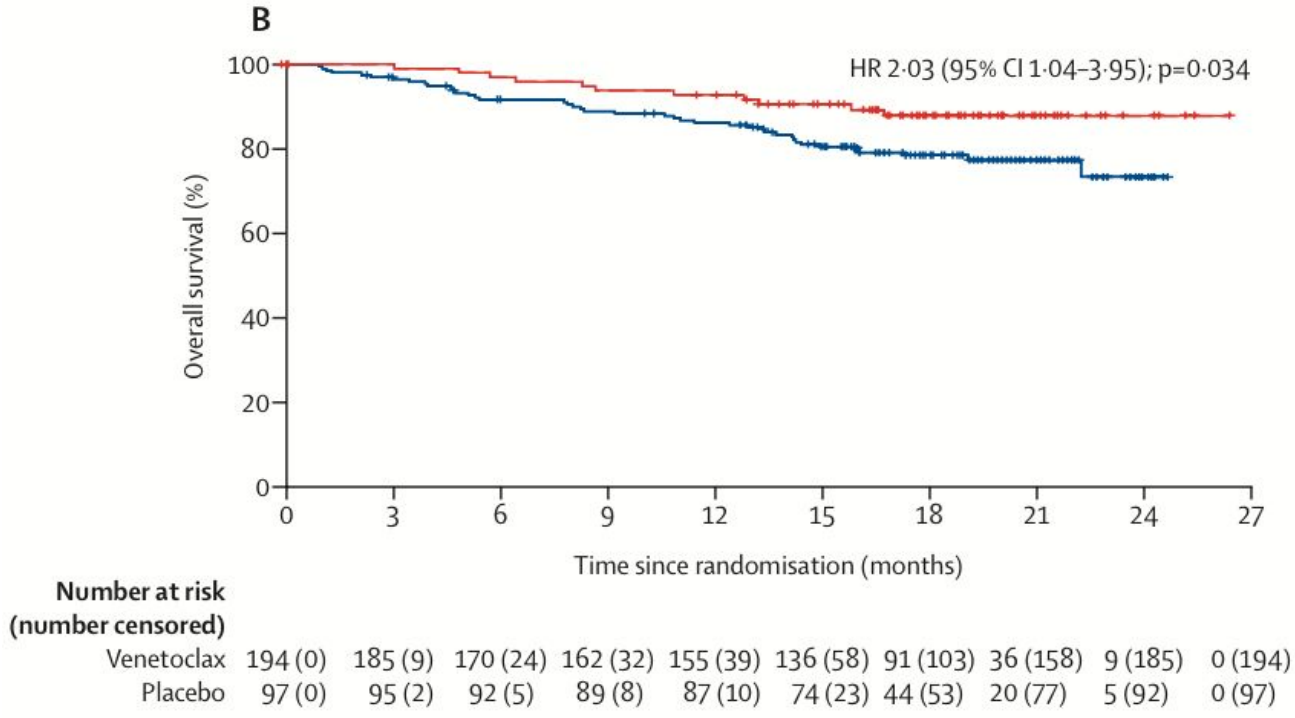


Mikhael et al, Blood Cancer Journal 2021

Venetoclax for t(11;1

- BELLINI phase III RCT compared venetoclax + VD vs. VD in relapsed/refractory MM
- Improved PFS….
- **Increase mortality due to infections** – this is an important lesson as we move towards increased use of bispecifics
- Subgroup analysis and other retrospective studies have shown significant response in t(11;14)





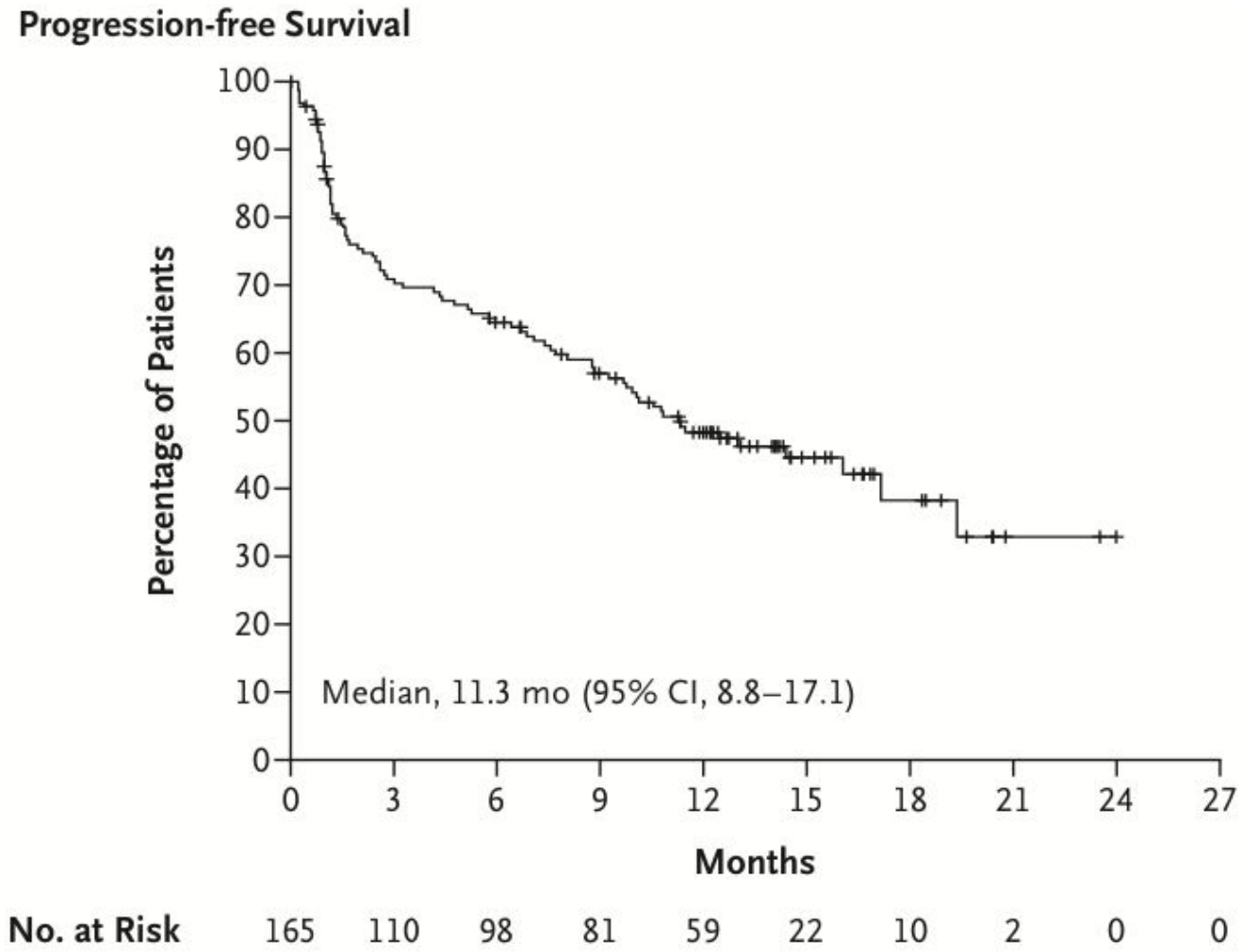
Triple Class or Penta Refractory…

- Venetoclax + PI + Dex for t(11;14) patients

- Bispecific Antibody (off the shelf)
  - Teclistimab (BCMA-CD3)
  - Talquetemab (GPRC5D-CD3)

- CAR-T (slow manufacturing)
  - Ida-cel
  - Cilta-cel

- **Significantly increased risk of severe infections (~50% grade 3+)**



Moreau et al, NEJM 2022

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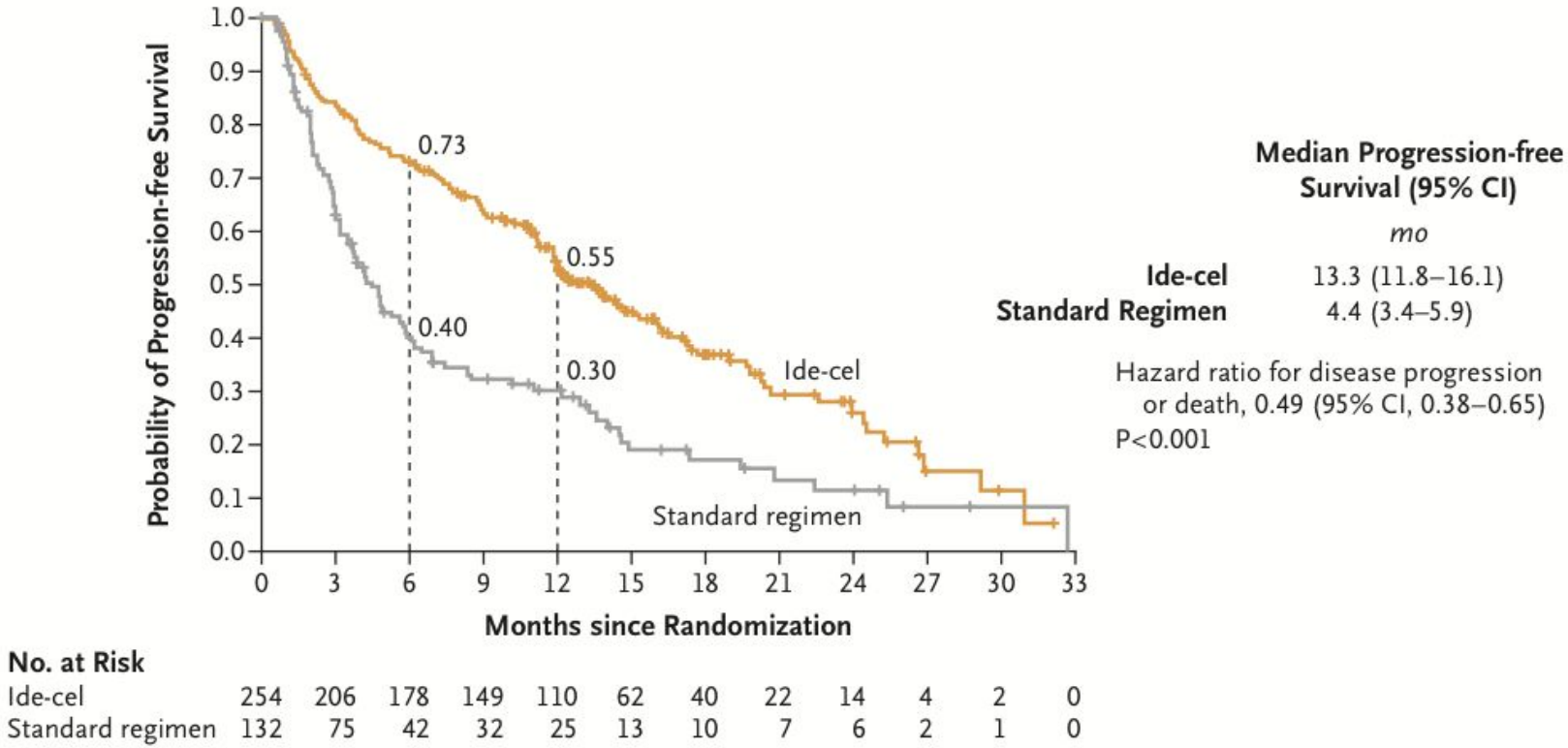

Rodriguez et al, NEJM 2023

Table S6. Minimal Residual Disease Negativity in Patients With At Least a Complete Response (ITT Population).

	Sensitivity level* at 10^{-5}		Sensitivity level* at 10^{-6}	
Patients who achieved CR and MRD-negative status†	**Ide-cel (n=254)**	**Standard regimens (n=132)**	**Ide-cel (n= 254)**	**Standard regimens (n = 132)**
MRD negativity — no. (%)	51 (20)	1 (1)	32 (13)	0
95% CI	15.2–25.0	0–2.2	8.5–16.7	0–0

Table S7. Grade 5 All-causality Adverse Events (Treated Population).

System organ class Preferred term	**Ide-cel (n=250)**	**Standard regimens (n=126)**
	Patients — no. (%)	
Grade 5 all-cause event*	36 (14)	8 (6)

Table S14. Deaths (ITT population).

Parameter	**Ide-cel (n=254)**	**Standard regimens (n=132)**
	Patients — no. (%)	
Overall number of deaths	75 (30)	34 (26)

How to mitigate infection risk?

- IVIG early and and monthly
  - D+30 for CAR-T x 1 year
  - 2nd month of therapy for bispecific until end of therapy
  - Continue until IgG > 400
- Bacterial until ANC > 500 or for 1st month of bispecific
- Revaccination for pneumonia and COVID
- PJP prophylaxis until end of therapy and/or until CD4 > 200

Received: 14 March 2023 | Accepted: 29 May 2023

DOI: 10.1111/bjh.18909

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

HOW I APPROACH

Recommendations on prevention of infections during chimeric antigen receptor T-cell and bispecific antibody therapy in multiple myeloma

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QUESTIONS?