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NDMM: Are We Done with Auto-SCT?

“Auto-SCT Remains SOC”

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Outline



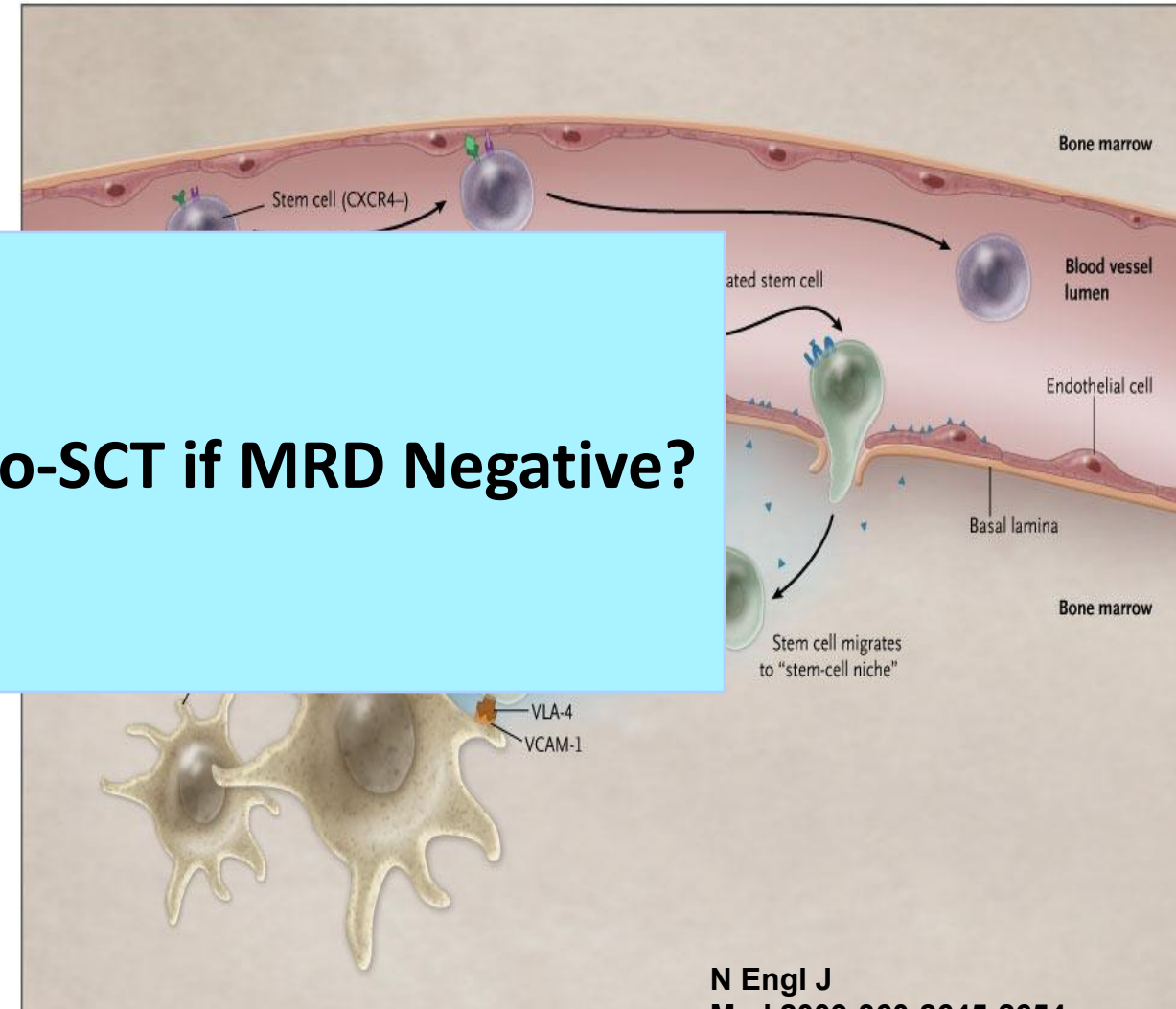
- Introduction
- Historical Review of HDT & ASCT.
- What Guidelines & Experts Recommend.
- Advantages – PFS, MRD, Sustained MRD (PIVOTAL TRIALS)
- Conclusions

Introduction



- ✓ No therapy in MM has been as extensively investigated as HDT & Auto-SCT. If you search the “National Library of Medicine, you will find 27,000 publications covering stem cell transplantation.
- ✓ With the rapid evolution of treatment options, whether this 1983 by Thomas and Powles still has relevance.
- ✓ Most leaders in the field believe that HDT & Auto-SCT remains the standard of care for eligible patient for the time being.

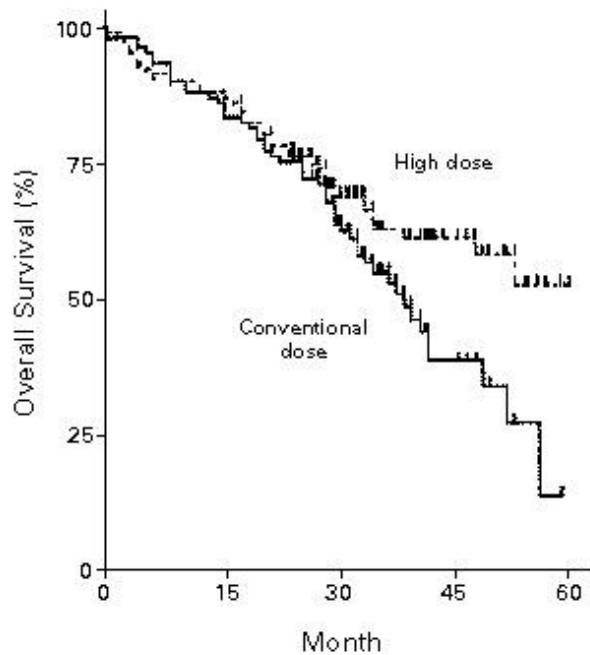
Can we forgo HDT & Auto-SCT if MRD Negative?



N Engl J
Med 2009;360:2645-2654

A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA

MICHEL ATTAL, M.D., JEAN-LUC HAROUSSEAU, M.D., ANNE-MARIE STOPPA, M.D., JEAN-JACQUES SOTTO, M.D., JEAN-GABRIEL FUZIBET, M.D., JEAN-FRANÇOIS ROSSI, M.D., PHILIPPE CASASSUS, M.D., HERVÉ MAISONNEUVE, M.D., THIERRY FACON, M.D., NORBERT IFRAH, M.D., CATHERINE PAYEN, M.D., AND RÉGIS BATAILLE, M.D.,
FOR THE INTERGROUPE FRANÇAIS DU MYÉLOME*



Conventional dose 63 (53-73) 35 (22-50) 12 (1-40)
High dose 69 (58-78) 61 (50-71) 52 (36-67)

TABLE 2. RESPONSE RATES ACCORDING TO TREATMENT GROUP.*

TYPE OF RESPONSE	CONVENTIONAL DOSE (N = 100)	HIGH DOSE (N = 100)
	no. of patients	
Complete	5	22
Very good partial	9	16
Partial	43	43
Minimal	18	7
Progressive disease	25	12

*P<0.001 for the comparison of the various response categories between the two groups by the chi-square test. Seventy-four patients in the high-dose group underwent autologous bone marrow transplantation.

This randomized study demonstrated that high-dose therapy and transplantation improves response rates, EFS, and OS in patients with MM.

Trials Have Consistently Showed Benefit of ASCT



Trial Name	N	MRD Negative 10 ⁻⁵	mPFS (%)	OS (%)
FORTE¹				
KRd	157	69%	69% (4yrs)	85% (4yrs)
KRd + ASCT	158	80%	56% (4yrs)	86% (4yrs)
DETERMINATION²				
RVd	357	40%	46.2 mths.	79.2% (5yrs)
RVd + ASCT	365	54%	67.5 mths.	80.7 (5yrs)
PERSEUS³				
Dara-RVd	355	75.2% (PC)	84.3% (4yrs)	Data immature
RVd	354	47.5% (PC)	67.7% (4yrs)	
EMN24 IsKia⁴				
Isa-KRd	151	45% (PI) & 77% (PC)	95% (1yr)	Data immature
KRd	151	26% (PI) & 67% (PC)	95% (1yr)	
GMMG-HD7⁵				
Isa-RVd	331	66.2% (Post-ASCT)	76% (4yrs)	Data immature
RVd	329	47.2% (Post-ASCT)	69% (4yrs)	
GRIFFIN⁶				
Dara-RVd	104	64%	87.2% (4yrs)	92.7% (4yrs)
RVd	103	30%	70% (4yrs)	92.2 (4yrs)

1) Lancet Oncol 2023; 24: 64–76; 2) New Engl J Med 2022; 387: 132–47; 3) N Engl J Med 2024; 390: 301–13; 4) Nat Med 2026; 32: 1773–82; 5) J Clin Oncol 2025; 43: 1279–88; 6) Lancet Haematol 2023; 10: e825–37.

Guidelines and Recommendations for NDMM Including BMT



Publication	Year Published	Early HDM-ASCT	Deferred HDM-ASCT
EHA-ESMO Clinical Practice Guidelines (Ann. Oncol. 2021, 32, 309–322)	2021	“For patients <70 years without comorbidities, induction therapy follow by HDM-ASCT is the recommended treatment”	Not included
BSH/Myeloma UK Guidelines (Br. J. Haematol. 2021, 193, 245–268)	2021	“Recommended for younger, fitter patients”	“On the IFM2009 trial 21% of patients in the non-ASCT arm were unable to receive ASCT at relapse because of disease refractoriness reinforcing the benefit of upfront ASCT where feasible”
ASTCT Clinical Practice Recommendations (Transpl. Cell Ther. 2022, 28, 284–293)	2022	“The panel recommends early ASCT as consolidation therapy in eligible, NDMM patients after 4-6 cycles of induction”	“The panel recommends mobilization and storage of stem cells in NDMM patients not undergoing ASCT after first line of therapy for future use as a treatment at first relapse”
mSMART Guidelines (https://www.msma.org/mm-treatment-guidelines)	2023	“Preferred for standard-risk patients [t(11;14), t(6;14), trisomies], recommended for high-risk patients”	“An option for SR patients”
Vincent Rajkumar (Expert Opinion) (Am. J. Hematol. 2022, 97, 1086–1107)	2022	“ASCT should be considered in all eligible patients”	“Maybe an option for standard-risk patients”



ORIGINAL ARTICLE

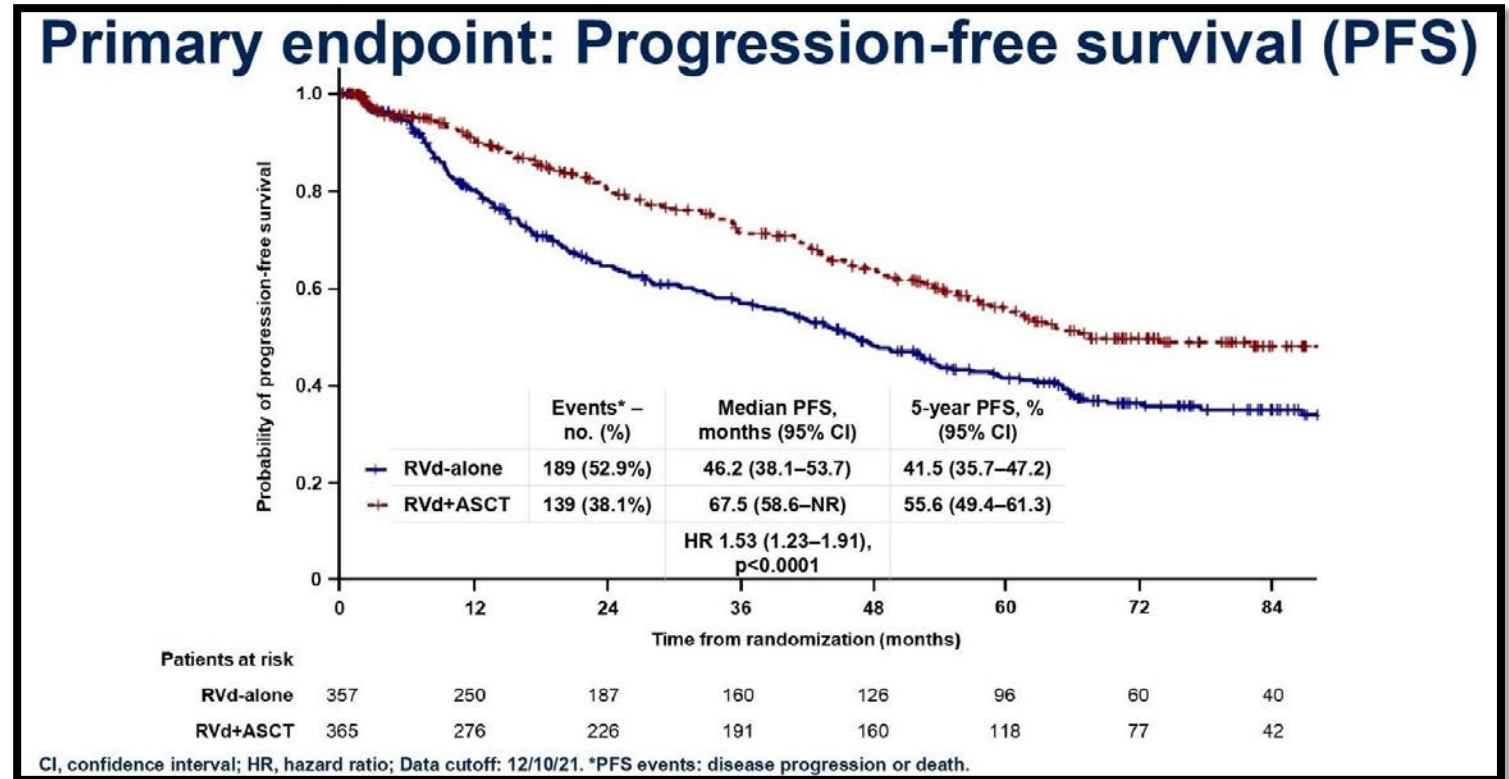
Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

P.G. Richardson, S.J. Jacobus, E.A. Weller, H. Hassoun, S. Lonial, N.S. Raje, E. Medvedova, P.L. McCarthy, E.N. Libby, P.M. Voorhees, R.Z. Orlowski, L.D. Anderson, Jr., J.A. Zonder, C.P. Milner, C. Gasparetto, M.E. Agha, A.M. Khan, D.D. Hurd, K. Gowin, R.T. Kamble, S. Jagannath, N. Nathwani, M. Alsina, R.F. Cornell, H. Hashmi, E.L. Campagnaro, A.C. Andreescu, T. Gentile, M. Liedtke, K.N. Godby, A.D. Cohen, T.H. Openshaw, M.C. Pasquini, S.A. Giralt, J.L. Kaufman, A.J. Yee, E. Scott, P. Torka, A. Foley, M. Fulciniti, K. Hebert, M.K. Samur, K. Masone, M.E. Maglio, A.A. Zeytoonjian, O. Nadeem, R.L. Schlossman, J.P. Laubach, C. Paba-Prada, I.M. Ghobrial, A. Perrot, P. Moreau, H. Avet-Loiseau, M. Attal, K.C. Anderson, and N.C. Munshi, for the DETERMINATION Investigators*

DETERMINATION TRIAL: Primary Endpoint of PFS



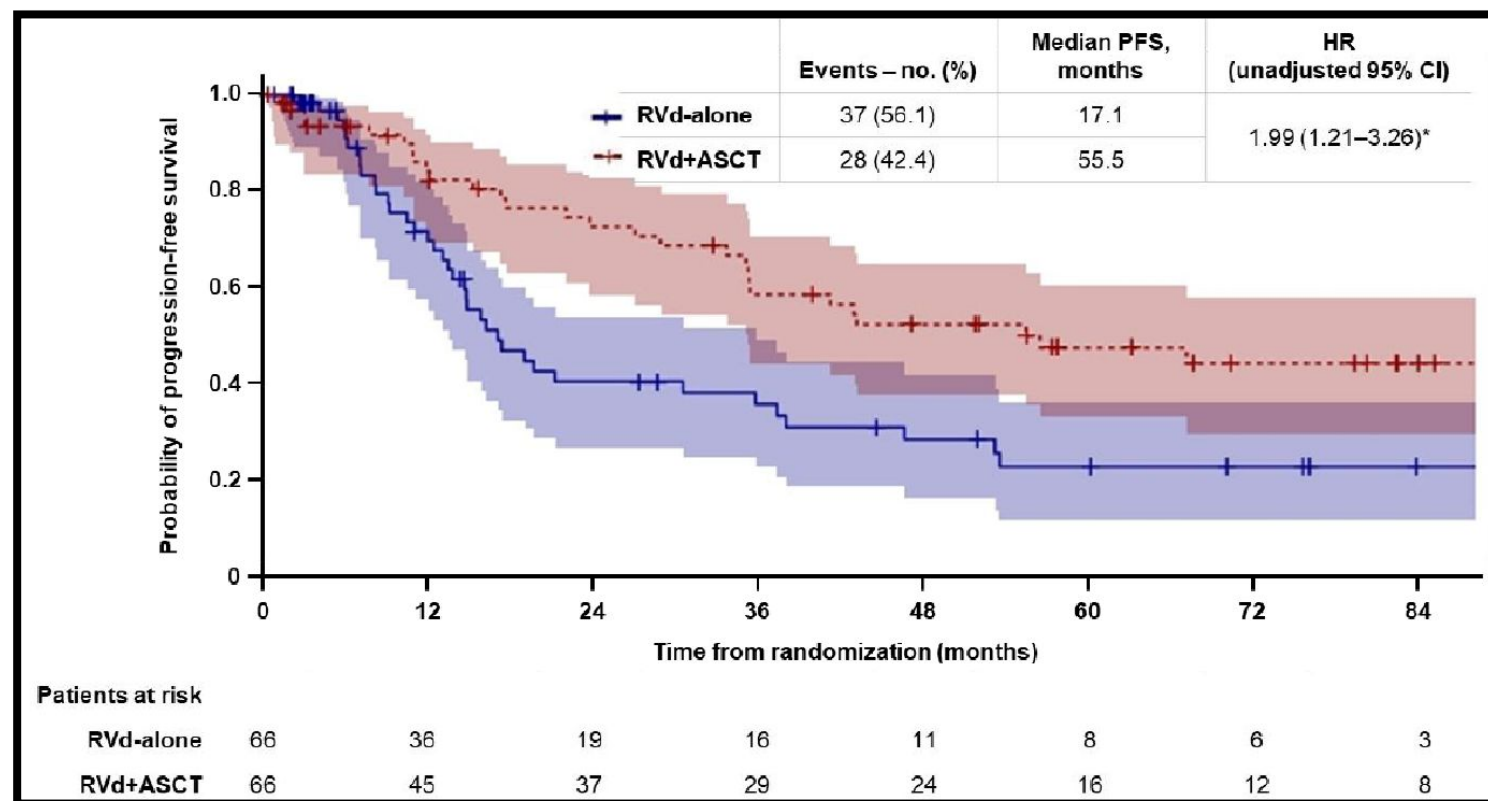
- It's important to know that the DETERMINATION trial was designed with the **primary endpoint of PFS**. The study was not powered/design to formulate a response-adapted treatment approach.
- Per the study design, “the continued use of transplant in first-line treatment would be warranted if the PFS of the high-dose arm were greater than 39 months and the trial will be positive if the PFS of the high-dose arm is greater by at least 9 months than that of the conventional dose arm.



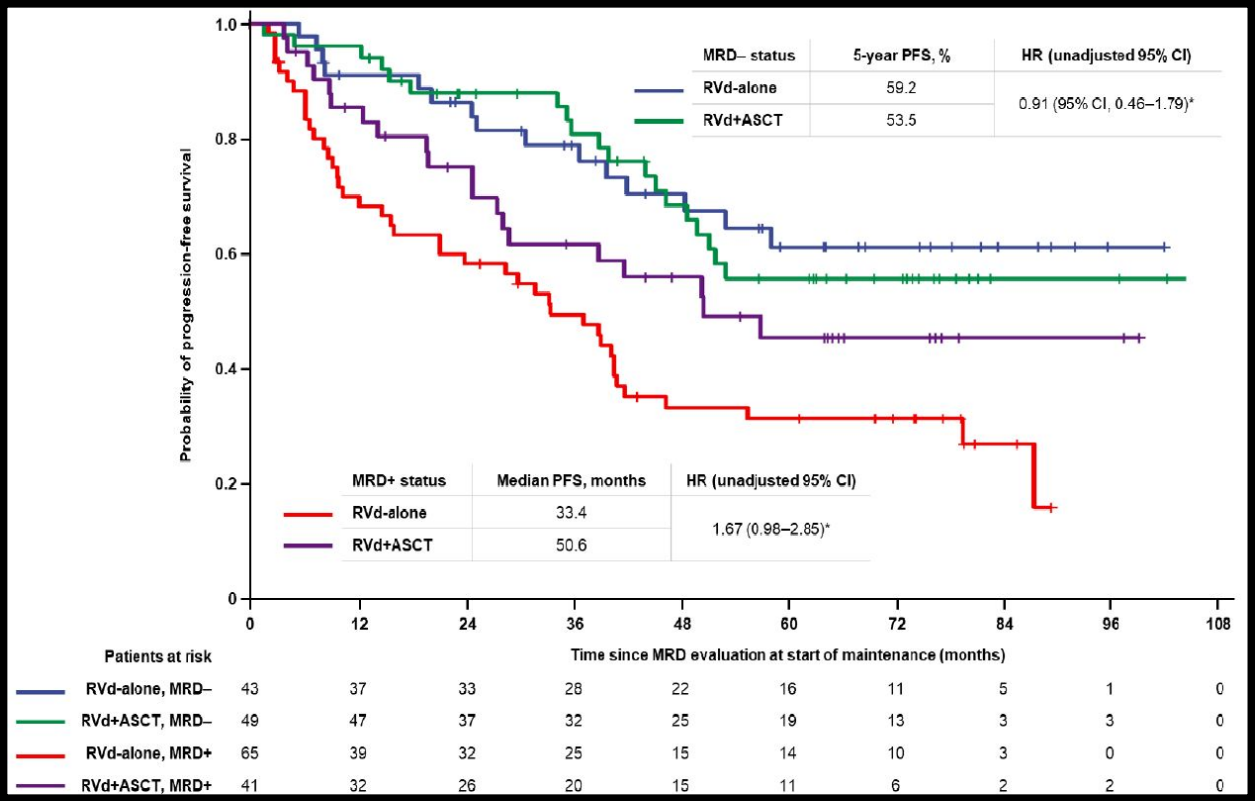
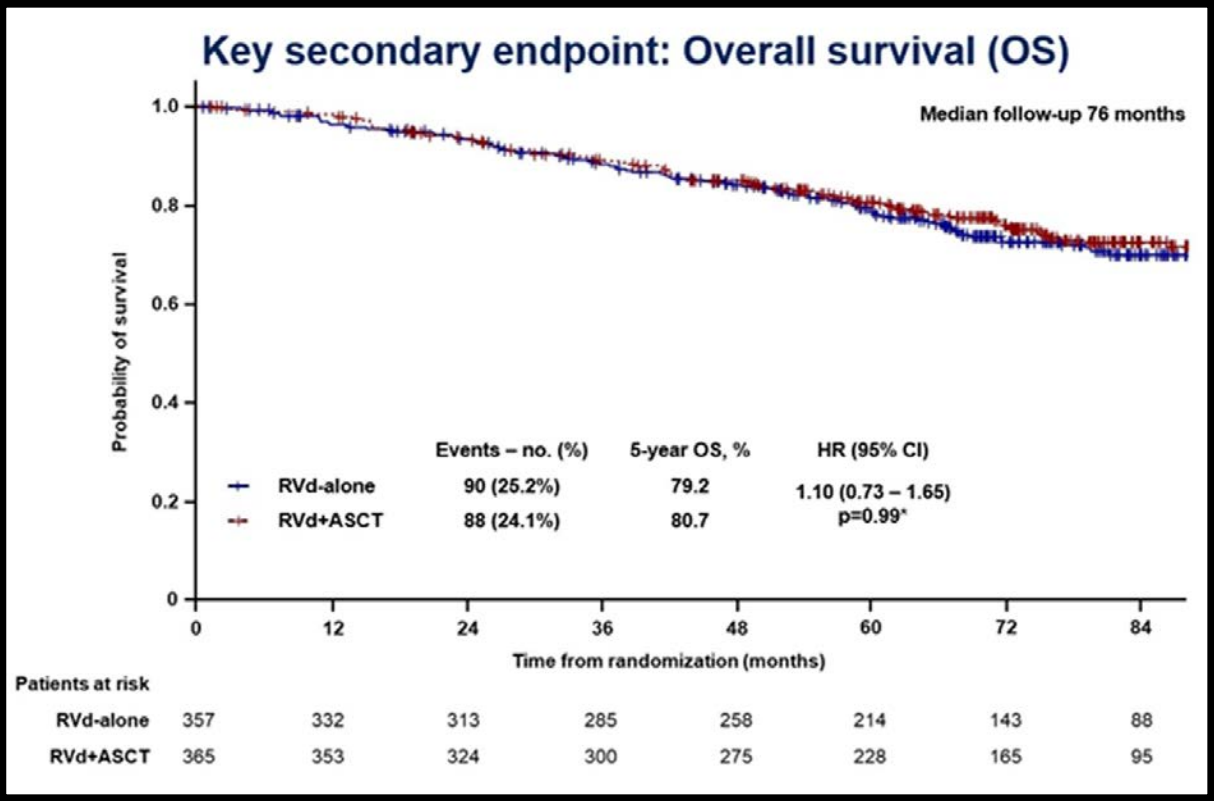
DETERMINATION TRIAL: Primary Endpoint of PFS – High-Risk Disease



- The median duration of PFS among patients with a high-risk cytogenetic profile was 17.1 months in the RVD-alone group and 55.5 months in the ASCT group.

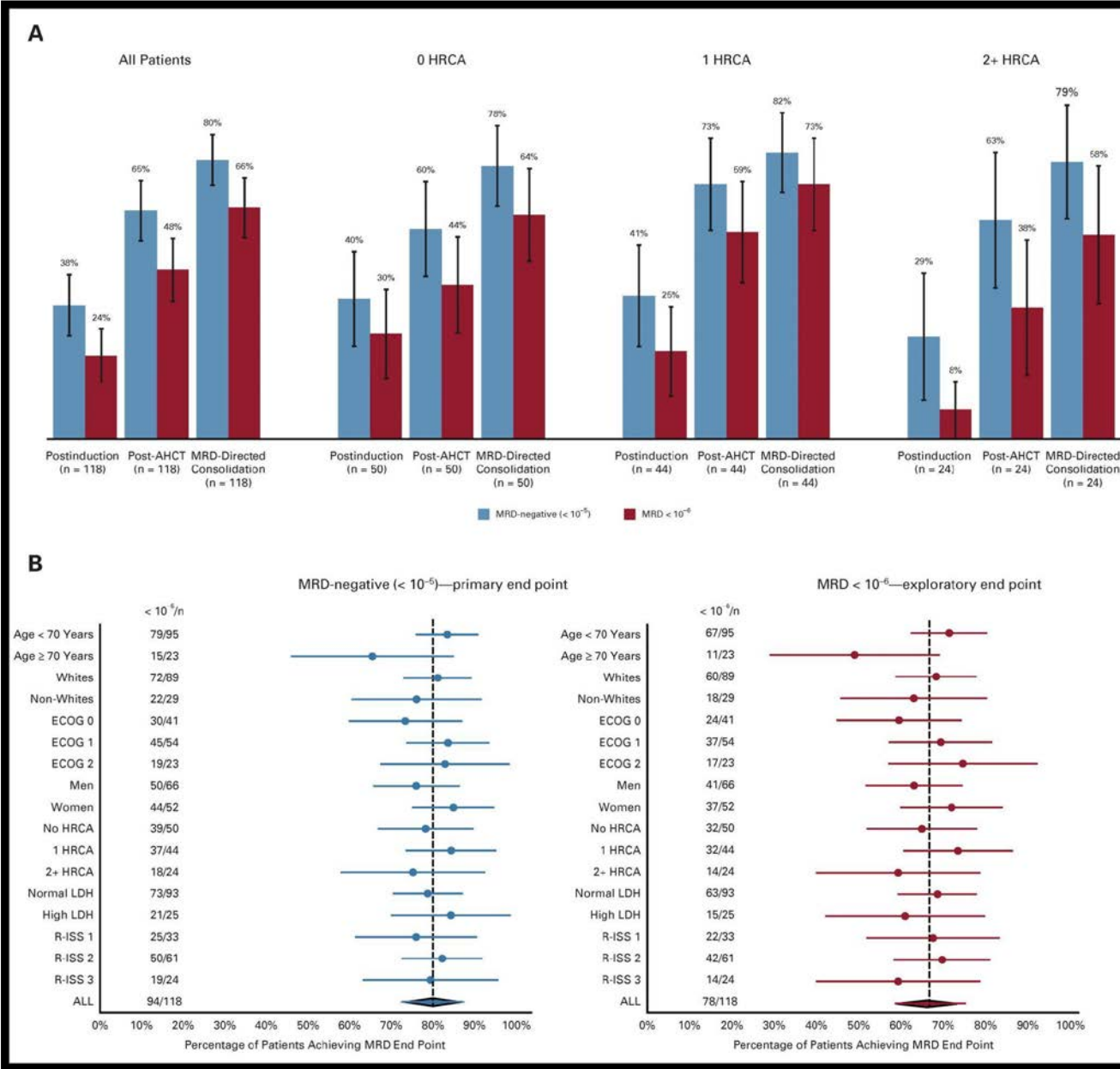
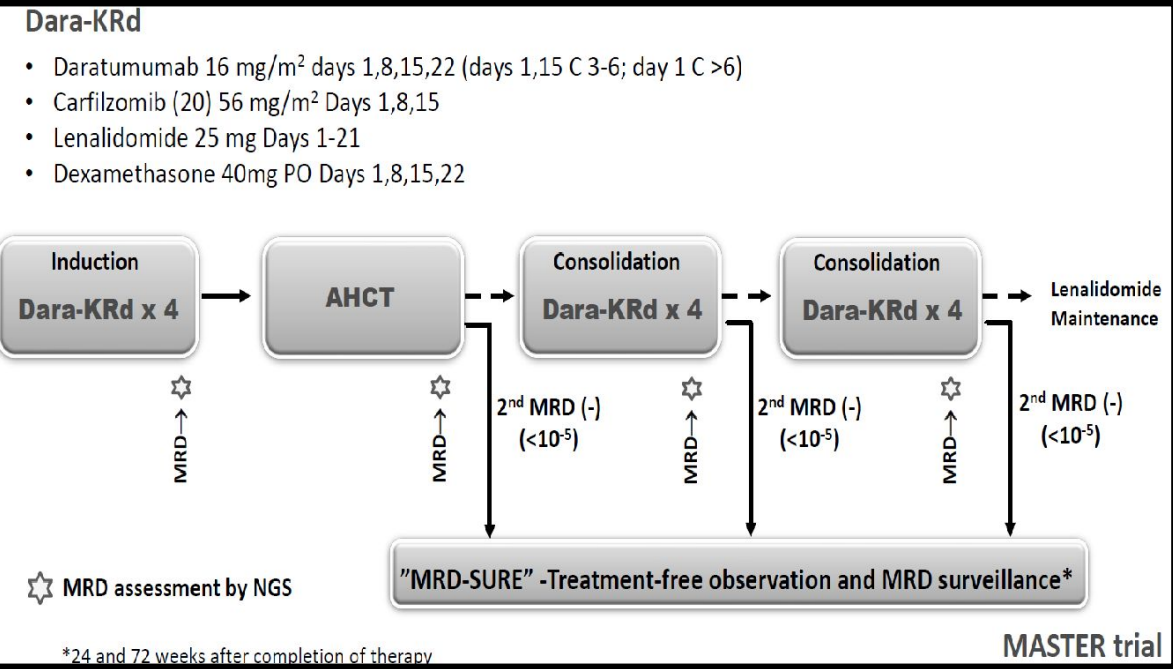


DETERMINATION OS and MRD



The subsequent off-protocol treatments contributed to the lack of difference in OS between the 2 assigned treatment arms

MASTER Trial

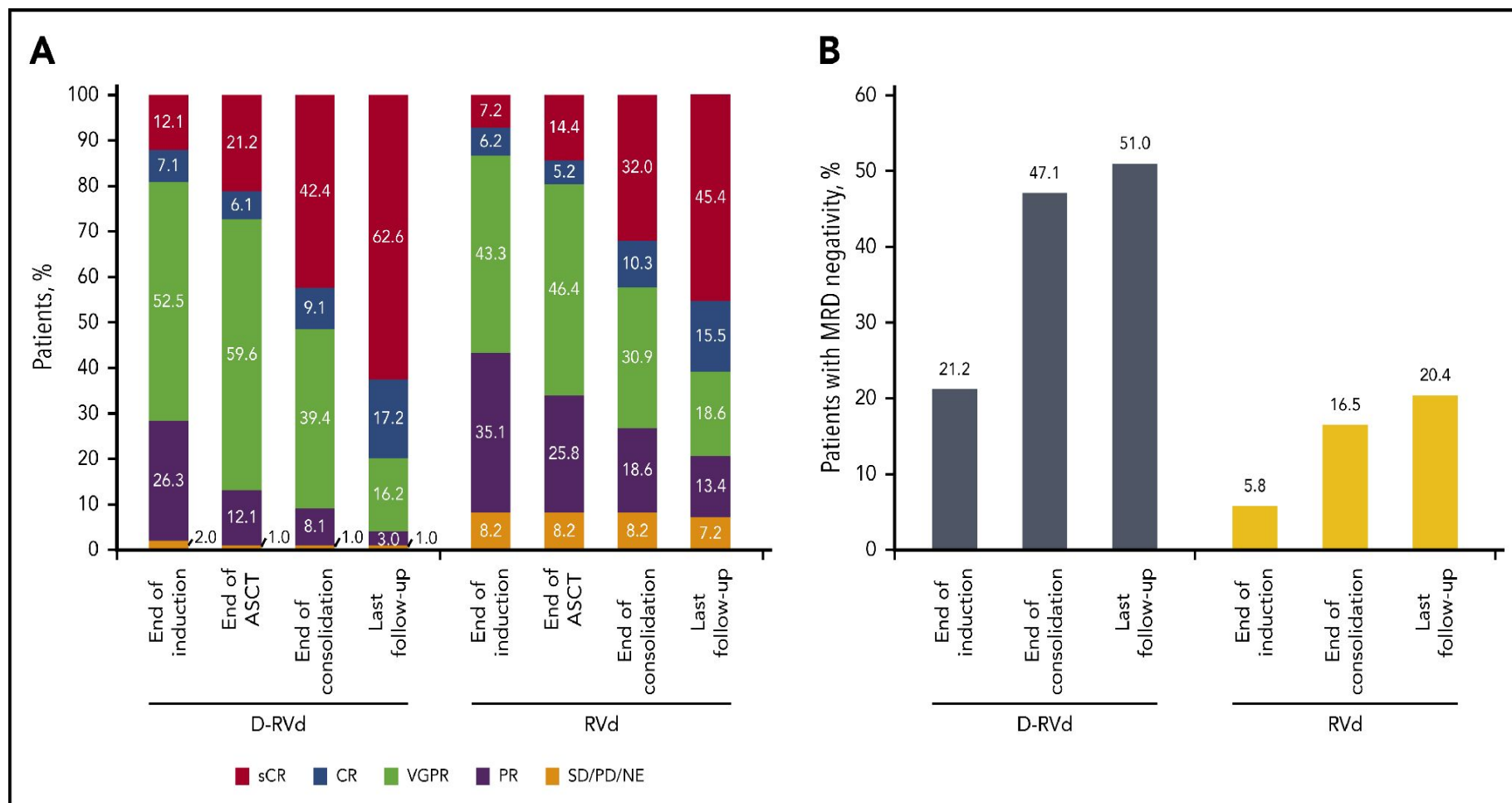


Best MRD Response by Phase of Therapy

GRIFFIN Study



- In GRIFFIN, the addition of daratumumab to RVd in transplant-eligible NDMM patients resulted in improved rates of sCR and MRD negativity.
- Similarly, D-RVd was associated with higher rates of sustained minimal residual disease-negativity lasting at least 12ms (10^{-5} , 46 [44%] of 104).



Sustained MRD – FORTE Trial



Response, %	Induction, intensification, and consolidation			Maintenance	
	KRd plus ASCT (n = 158)	KRd12 (n = 157)	KCd plus ASCT (n = 159)	KR (n = 178)	R (n = 178)
Stringent CR [†]	46	44	32	68	65
MRD negativity ^{‡§}	62	56	43	81	79
1-year sustained MRD negativity [§]	47	35	25	—	—
4-year PFS	69	56	51	—	—
4-year PFS in patients with MRD negativity [§]	83	63	69	—	—
4-year PFS in patients with 1-year sustained MRD negativity [§]	87	92	84	—	—

- Higher rates of sCR, MRD-, and sustained MRD- were reported in the KRd plus ASCT arm.
- KRd plus ASCT consistently increased the rates of sustained MRD- in all cytogenetic subgroups, compared with KRd12.

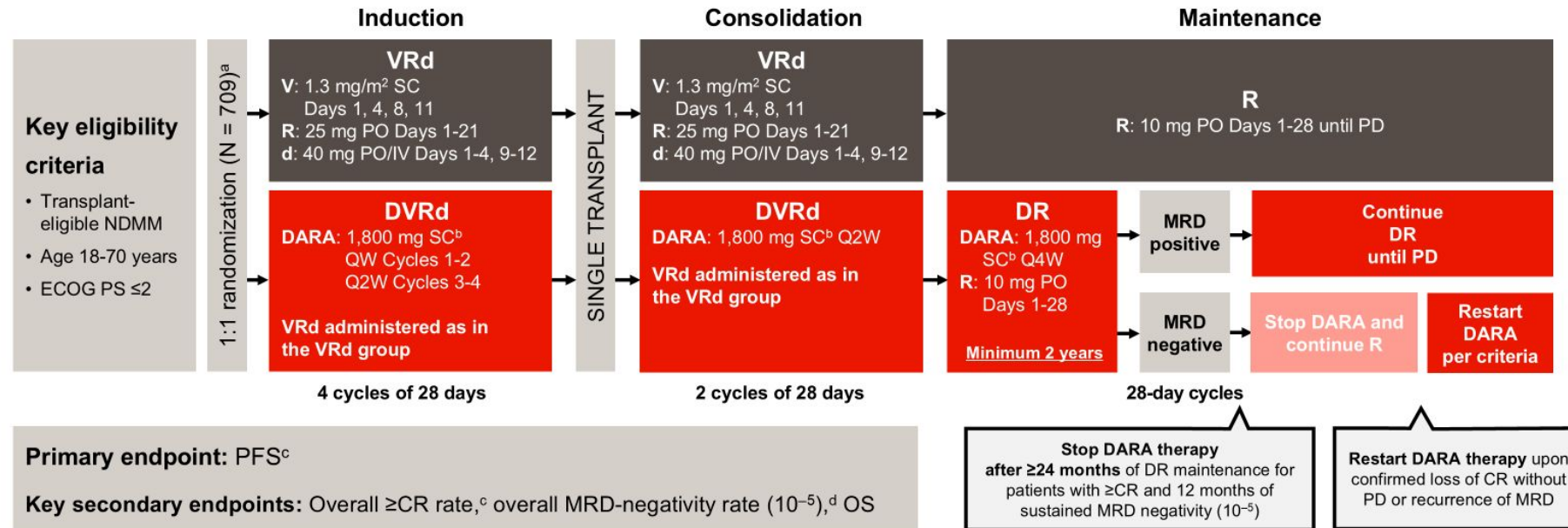
Modeling Long-Term PFS in TE & TIE NDMM Treated With Dara-RVd Based on PERSEUS (TE NDMM) and CEPHEUS (TIE)



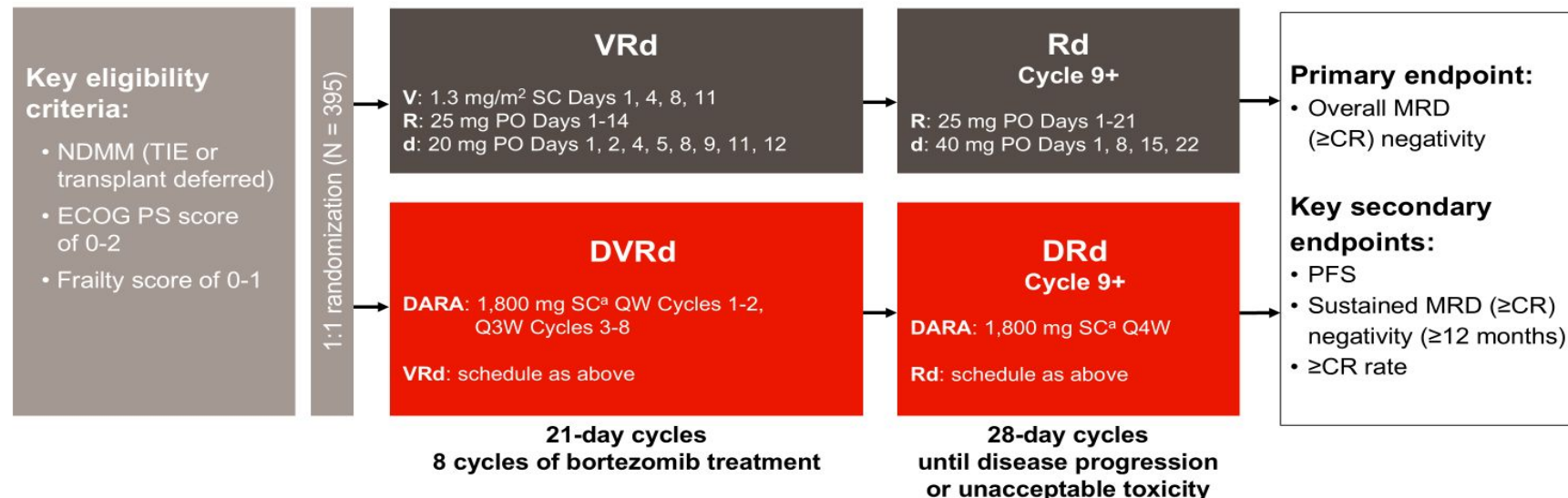
- DVRd treatment significantly improved depth and duration of response and PFS in PERSEUS and CEPHEUS, with the median PFS not reached at the time of follow-up for both trials.
- As the median PFS for DVRd treatment is likely to exceed NDMM study durations, it is important to model the long-term PFS benefits to inform clinical decision making and support economic evaluations for patient access

The objective of this analysis was to estimate long-term PFS outcomes of DVRd in NDMM, based on the PERSEUS (TE NDMM) and CEPHEUS (TIE NDMM subgroup) trials

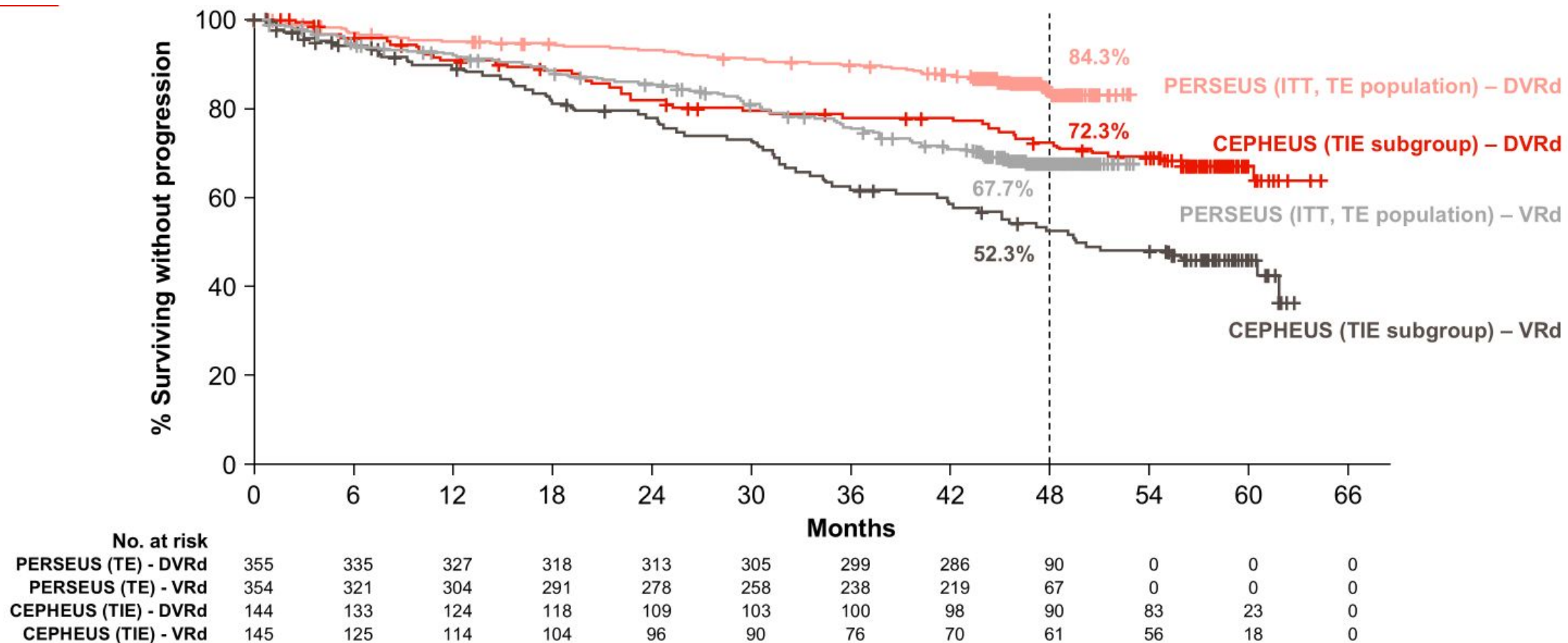
PERSEUS: Study Design (N Engl J Med 2024; 390: 301–13)



CEPHEUS: Study Design (Nat Med 2025; 31: 1195–202)

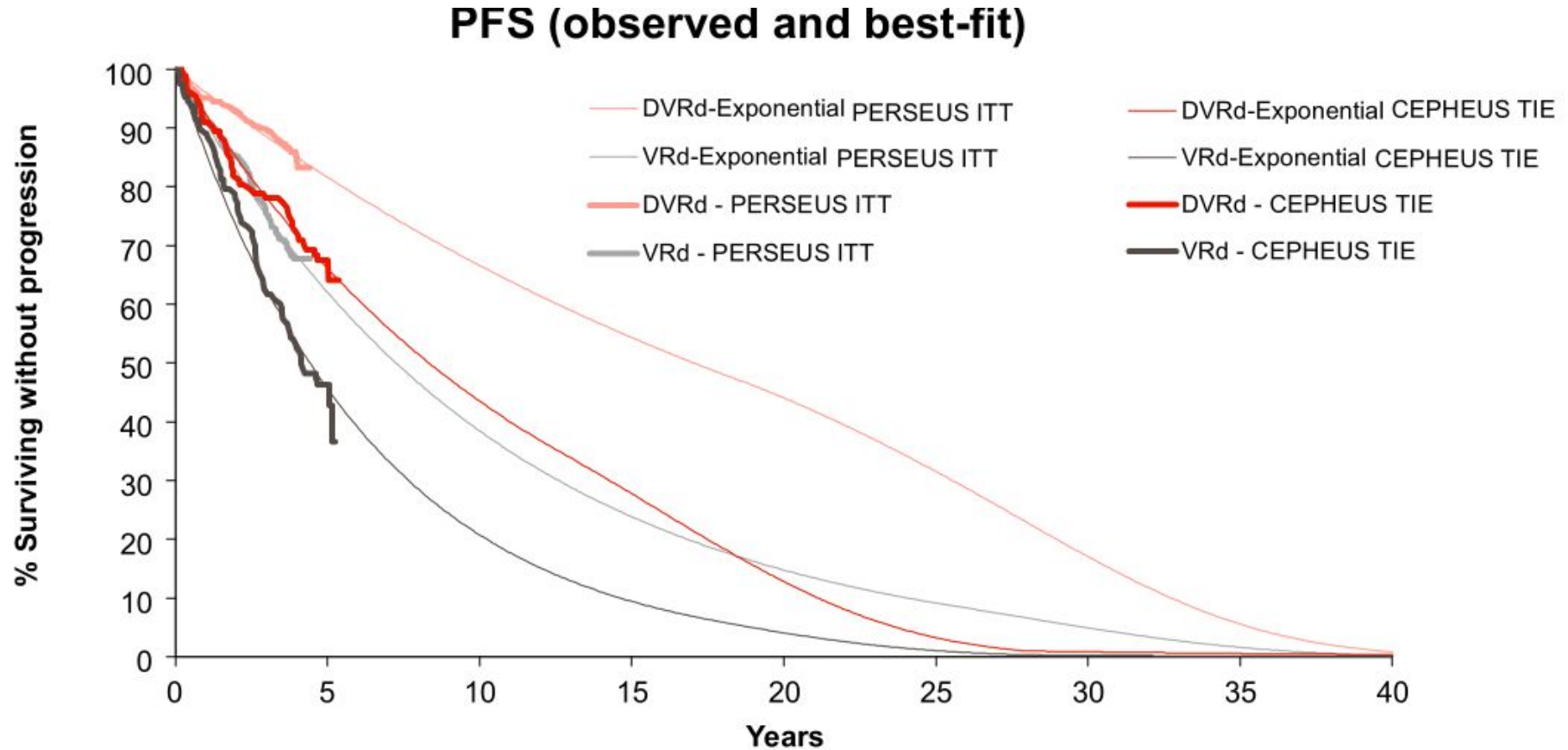


Median PFS With DVRd Not Reached in Both PERSEUS and CEPHEUS Trials



Median PFS with DVRd not reached in TE patients in PERSEUS and TIE patients in CEPHEUS trials

Significantly Longer Projected PFS With DVRd vs VRd for the Best-Fit Distribution



Estimated PFS, DVRd vs VRd

PERSEUS: 205 months (17.1 years) vs 87 months (7.3 years)

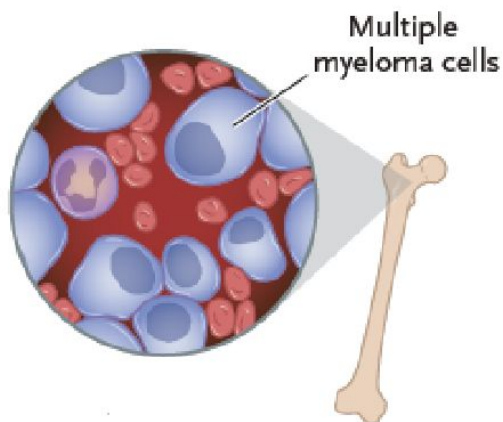
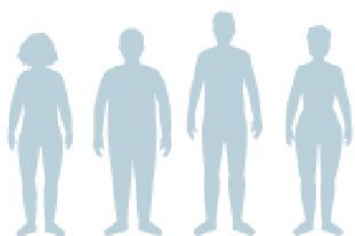
CEPHEUS: 100 months (8.3 years) vs 53 months (4.4 years)

MIDAS Study



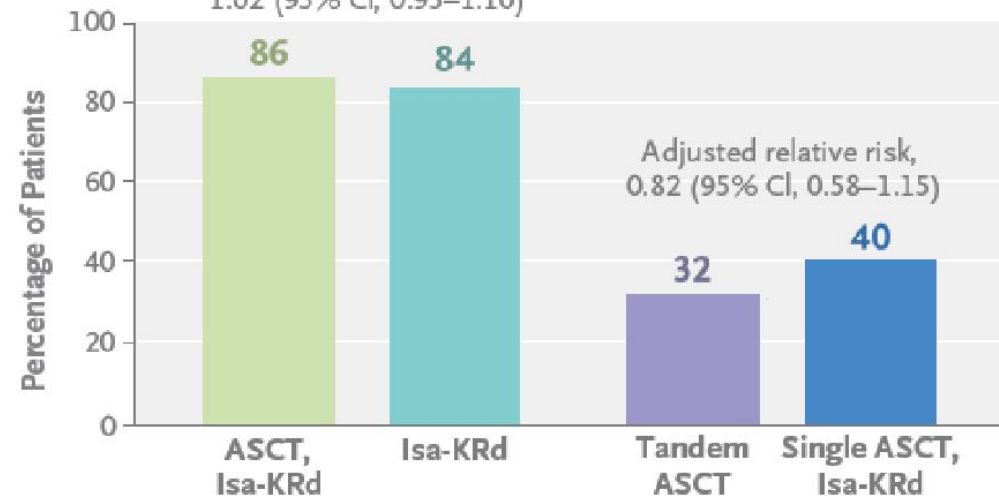
Patients

- 718 adults
- Median age, 59 years
- Men: 57%; Women: 43%

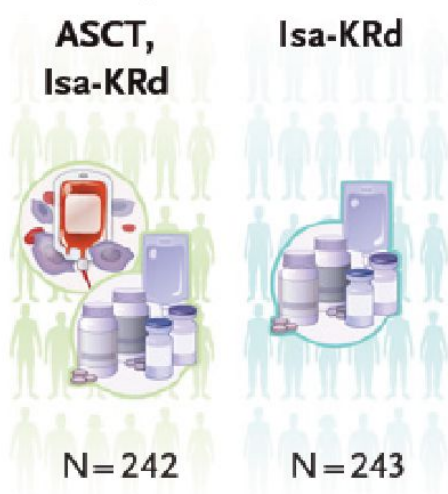


MRD Negativity before Maintenance Therapy

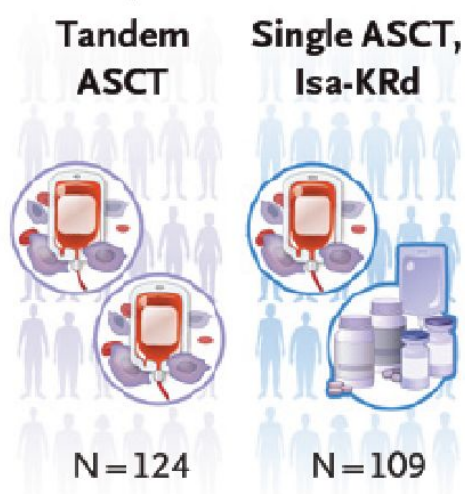
Adjusted relative risk,
1.02 (95% CI, 0.95–1.10)



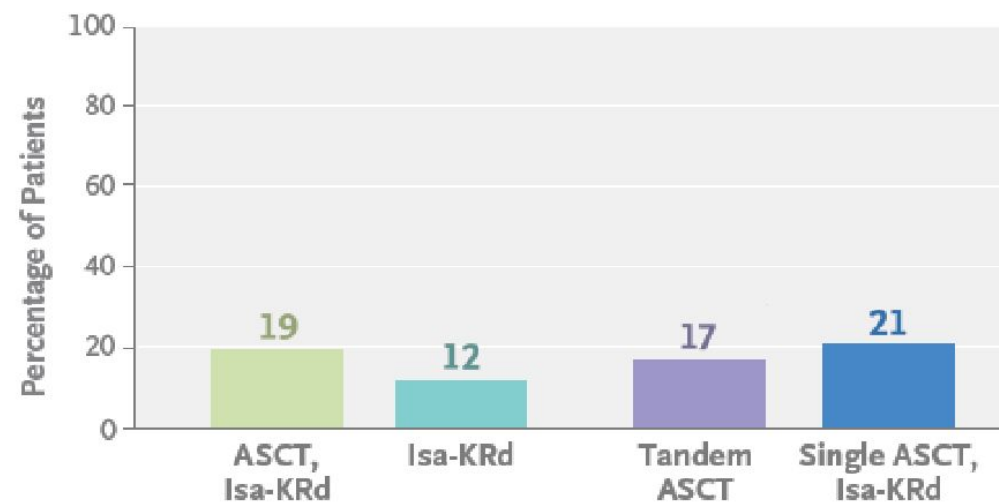
MRD-negative after induction



MRD-positive after induction



Serious Adverse Events



MIDAS Study



- Despite findings that ASCT didn't improve short-term MRD negativity compared to ISA-KRd, using this data to forgo ASCT is premature as no data on PFS/OS (Follow-up was only 17 months).

Non-ASCT vs ASCT Equivalence unproven!

- MIDAS was not powered to show equivalence, so we don't yet know whether ASCT improves **MRD negativity, PFS, or OS.**

- Only a relatively small proportion of the MIDAS population had high-risk cytogenetics—about **8% had an IFM high-risk cytogenetic score >1** in the induction cohort.

ASCT is Cost Effective



- Many of us working at major academic medical centers see a skewed population of patients who are well insured. For these patients, the personal costs are high, but not anywhere near how much an uninsured or international patient would pay for the same treatment.
- The financial toxicity of MM therapy, particularly novel agents, leads to lack of access to newest options and cutting back on dose or schedule which in terms is detrimental for the overall patient's outcome.

	Approximate Drug Cost per Year* (in U.S. Dollars)	Comment
Drugs		
Thalidomide	60,000	
Lenalidomide	168,000	
Pomalidomide	192,000	
Bortezomib	50,000	
Ixazomib	111,000	
Carfilzomib	130,000	260,000 (at 56 mg/m ²)
Daratumumab	120,000	
Elotuzumab	120,000	
Panobinostat	96,000	
Cyclophosphamide	5800	
Melphalan IV	10,000	Per transplant
Dexamethasone	3,400	
Regimens		
VRd	220,000	
KRd	300,000	
VCd	60,000	
DRd	290,000	
D-VRd	340,000	
D-KRd	590,000	
*Source for calculating costs: parenteral drug prices: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2017ASPFiles.html (accessed Feb 12, 2018); oral drug prices: GoodRx.com (accessed February 12, 2018). Abbreviations: VRd, bortezomib, lenalidomide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; DRd, daratumumab, lenalidomide, and dexamethasone; D-VRd, daratumumab, bortezomib, lenalidomide, dexamethasone; D-KRd, daratumumab, carfilzomib, lenalidomide, dexamethasone.		

Risk of secondary malignancies



- Multiple prospective and retrospective analysis of ASCT in MM have fixed the secondary malignancy rate at 3-4%.
- In a CIBMTR analysis, a total of 2356 deaths were noted among the entire cohort of 15,999 patients. The cause of death was MM in approximately 72% of patients aged <40 years, 80% of patients aged 40 to 49 years, 80% of patients aged 50 to 59 years, 72% of patients aged 60 to 69 years, and 68% of patients aged ≥70 years. Around 4% of patients were reported to have died of secondary malignancy (Cancer 2020 Dec 1;126(23):5077-5087)
- Now, this is not an issue restricted to ASCT □ In the MAIA study, secondary primary malignancies accounted for 8.8%. (NEJM 2019;380:2104)

Conclusions



- High-dose therapy/ASCT remains the standard of care for eligible MM patients because of its significant improvement in PFS and higher rate of MRD(-). Extremely important for HR disease even in the era of quadruplets.
- Achieving MRD(-) has demonstrated to be one of the key prognostic factors for long-term PFS/OS in NDMM. SUSTAINED MRD Negativity is the STRONGEST prognostic marker.
- ASCT has been fully standardized to be performed in different settings with similar outcomes and has proven to be safe with a very low associated mortality.
- Whether SR patients can safely forgo ASCT based on MRD(-) status remains unresolved and requires longer follow-up.
- Ongoing studies evaluating CAR-T cells, TCE, and novel cereblon-modulating agents (MajesTEC-5, MajesTEC-4/EMN30, CARTITUDE-6, MagnetisMM-7, EMN26, MASTER-2, FASTER, & EXCALIBER) are expected to further refine maintenance strategies in TE patients.

The background of the image is a dense, repeating pattern of dark blue, almost black, leaves. The leaves are elongated and pointed, with visible veins. They are arranged in a way that creates a textured, organic feel. A semi-transparent dark blue rectangular area is centered over the image, serving as a backdrop for the text.

Thank you

Your Moffitt Myeloma Teams

