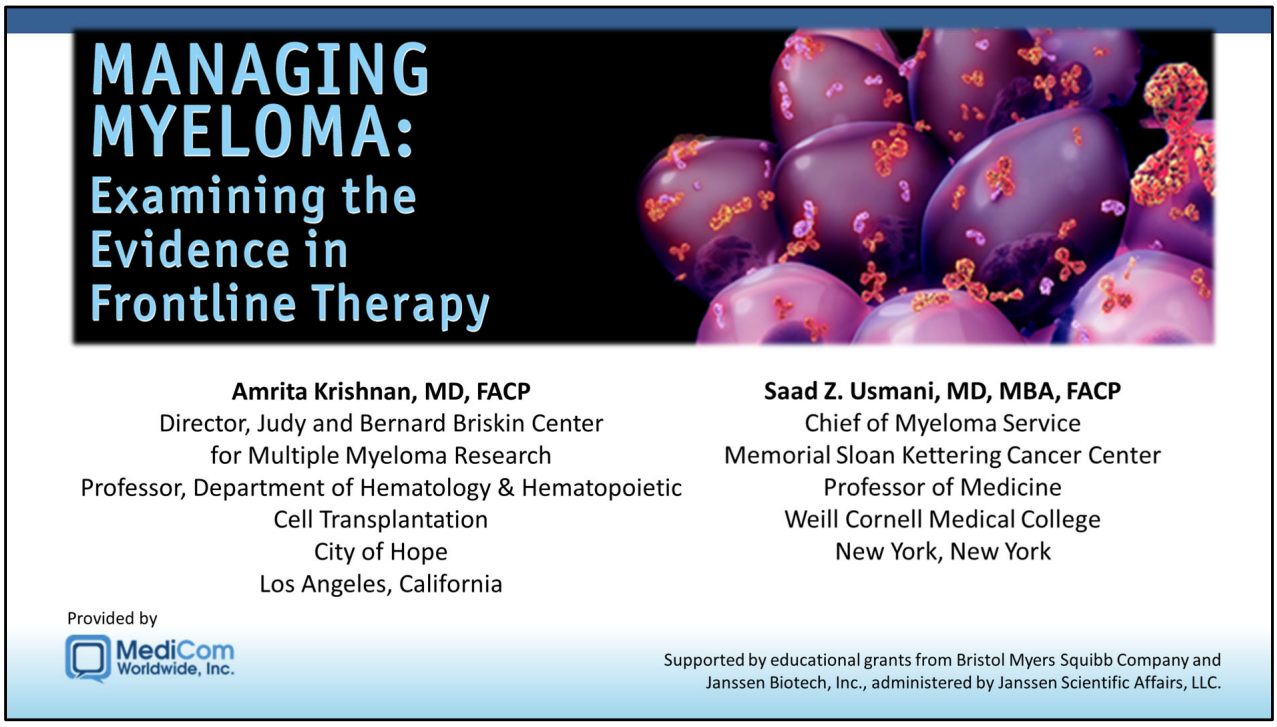
Managing Myeloma:
Examining the Evidence in Frontline Therapy



Saad Usmani: Hello, and welcome to today's program. I'm Dr. Saad Usmani, the Chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center. I am joined by my dear colleague, Dr. Amrita Krishnan, who is Professor of Medicine at the City of Hope in Los Angeles, California.

Faculty Disclosures

- **Dr. Amrita Krishnan** has relevant financial relationships related to consulting activities from AbbVie Inc., Adaptive Biotechnologies, GlaxoSmithKline plc, Regeneron Pharmaceuticals, Inc., and Sanofi. She is on the speakers' bureau for Bristol Myers Squibb Company, Sutro Biopharma, and Takeda Oncology.
- **Dr. Saad Usmani** has relevant financial relationships related to advisory activities and consulting from AbbVie, Inc., Amgen Inc., Bristol Myers Squibb Company, Celgene Corporation - A Bristol Myers Squibb Company, Edo Pharma, Genentech, Inc., Gilead, GlaxoSmithKline plc, Janssen Pharmaceuticals, Inc., Oncopeptides, AB, Sanofi, Seattle Genetics, Inc., SecuraBio, Skyline Diagnostics B.V, Takeda Oncology, and TeneoBio. He has received research grant(s) from Amgen Inc., Array BioPharma, Bristol Myers Squibb Company, Celgene Corporation - A Bristol Myers Squibb Company, GlaxoSmithKline plc, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Pharmacyclics, Inc., Sanofi, Seattle Genetics, Skyline Diagnostics B.V, and Takeda Oncology.

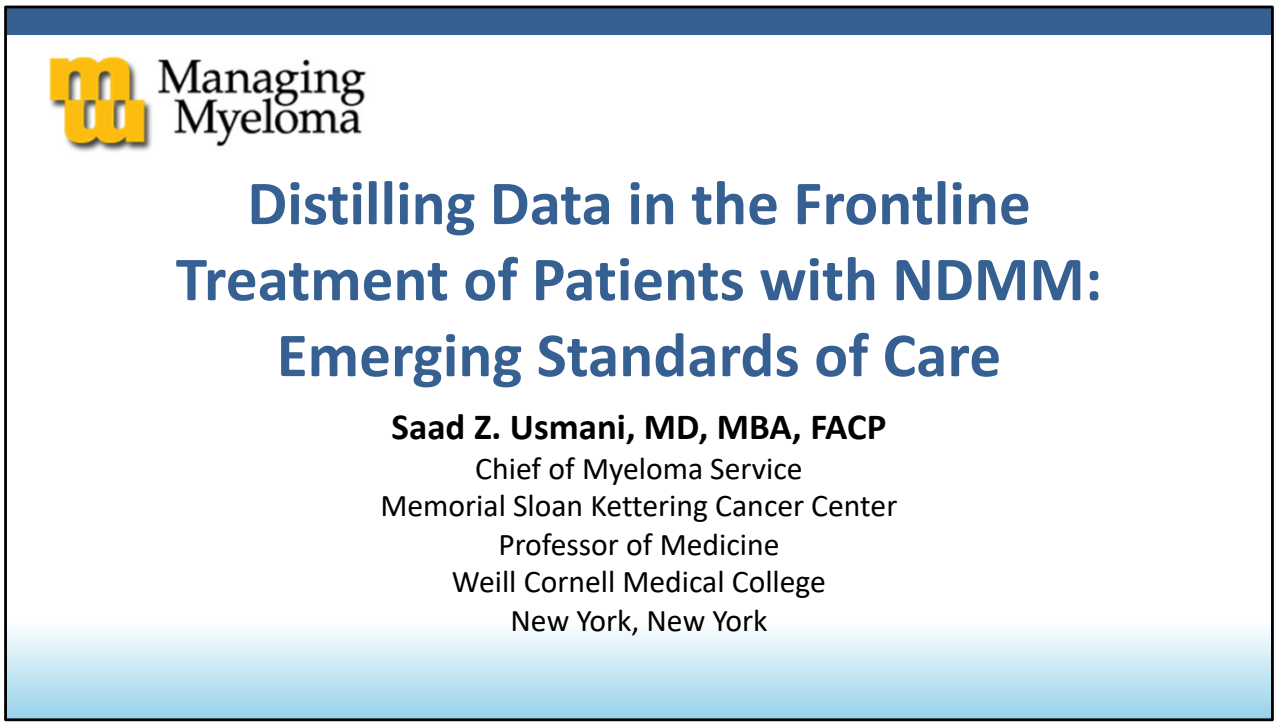
These are our disclosures.

Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Outline practical strategies for implementing new and evolving standards of care into treatment of patients with NDMM
- Summarize clinical data supporting the use of triplet and quadruplet regimens in NDMM patients
- Correlate patient and/or disease characteristics with appropriate triplet or quadruplet regimens in NDMM (transplant eligible and ineligible)
- Identify factors to be considered when developing an optimized treatment sequencing strategy for an individual NDMM patient

Today, our learning objectives will focus on outlining practical strategies for implementing new and evolving standards of care into treatment of patients with newly diagnosed multiple myeloma, summarizing clinical data supporting the use of triplet and quadruplet regimens in newly diagnosed multiple myeloma patients, correlating patient or disease characteristics with appropriate triplet or quadruplet regimens in newly diagnosed multiple myeloma, including both transplant-eligible and ineligible patients, and identifying factors to be considered when developing an optimized treatment sequencing strategy for an individual newly diagnosed multiple myeloma patient.

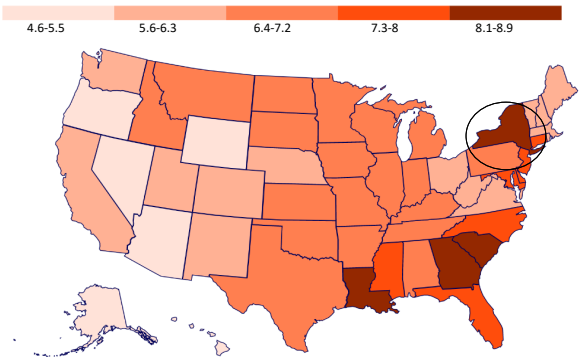


Let's start the first section. The title of this particular section is called Distilling Data in Frontline Treatments of Patients with Newly Diagnosed Multiple Myeloma, and we are focusing on emerging standards of care.

Multiple Myeloma: A Systemic Plasma Cell Malignancy

- Estimated new cases and deaths in 2021 in the United States[1]
  - New cases: 34,920
  - Deaths: 12,410
- Percentage of patients surviving 5 years: 55.6%[2]
- Median age at diagnosis: 69 years[2]
- MM is most common in men and Black adults[2]

State-Level Incidence of MM per 100,000 Between 2012 and 2016[3]



[1]National Cancer Institute. http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/healthprofessional#Section_4. Updated February 11, 2021. Accessed May 6, 2021. [2]National Cancer Institute. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed May 6, 2021. [3]American Cancer Society. https://cancerstatisticscenter.cancer.org/?_ga=2.47184933.325832967.1600196335-611855784.1581698489#!/cancer-site/Myeloma. Accessed May 6, 2021.

Multiple myeloma is a systemic plasma cell malignancy. It's estimated that in the year 2021, there were almost 35,000 newly diagnosed cases and a little over 12,000 patients who died from this disease, and this incidence continues to grow over time. However, the good news is that the percentage of patients who are surviving the disease beyond five years has more than doubled in the last two decades and stands at about 55.6%. The median age of diagnosis is 69 years in general, but it is a bit younger or a little less in terms of age in Black adults. Multiple myeloma is most common in men, and it is the most common hematologic malignancy in the Black population, and they tend to present at an earlier age.

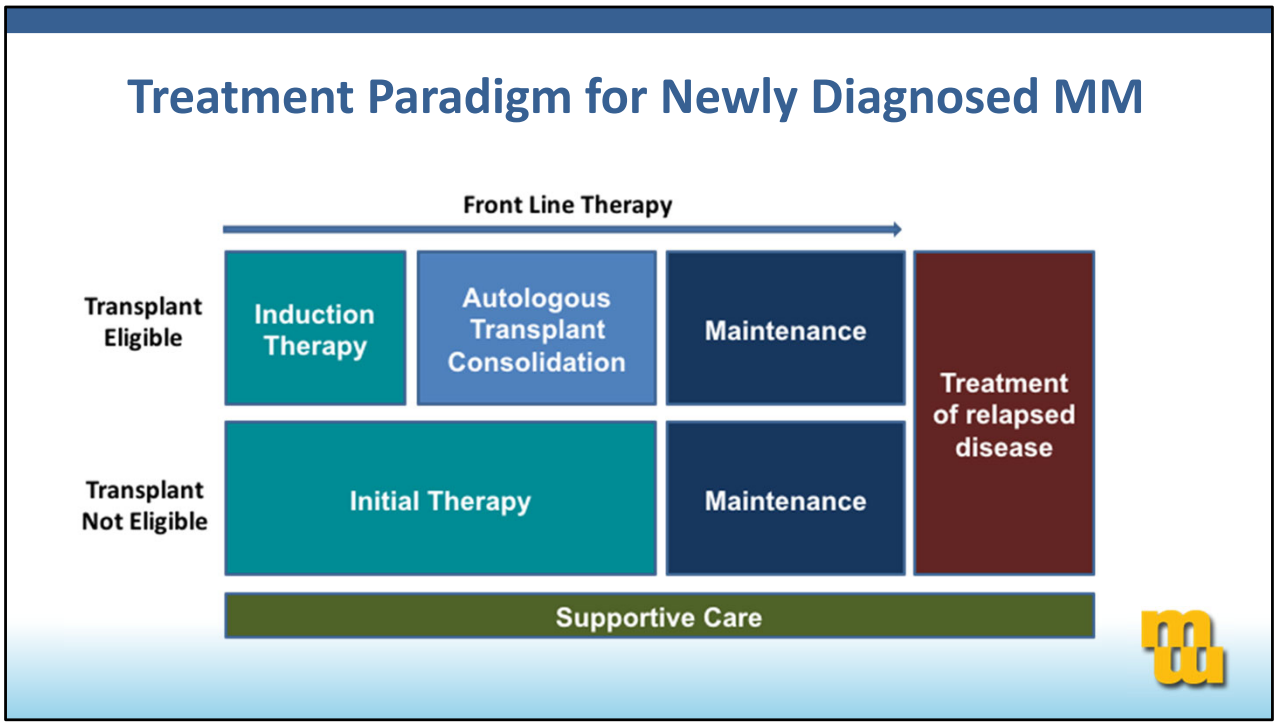
Multiple Myeloma Is Not One Disease

- MGUS to active MM transition period is different among patients. Diagnosis is made at variable timepoints during the transition, so degree of end organ damage is different
- Management strategies have improved MM survival from 2-3 years in the 2000s to >10 years in the 2020s
- Advances in understanding myeloma biology has led to new therapeutic targets
  - MM pathways
  - BM microenvironment
  - Immune regulation and modulation
- Picking the right strategy that gives the highest likelihood of the best depth of response in the first year of diagnosis is extremely important for survival outcomes

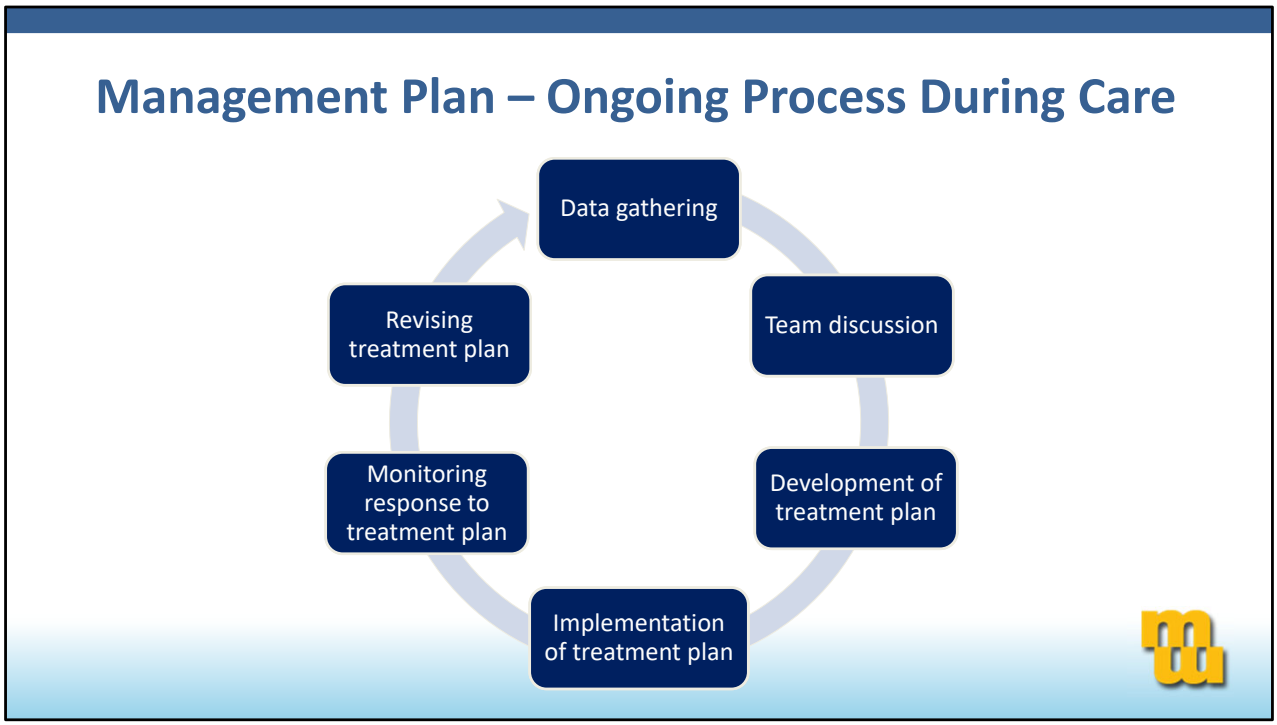
Martinez-Lopez J, et al. *Blood*. 2011;118(3):529-534.; Usmani S, et al. *Leukemia.* 2012;26(11):2398-2405.

One of the things that we like to highlight, if is the fact that myeloma is not one disease. It has many different molecular subgroups, and these molecular subgroups, which we think there are between six to eight different ones, depending on how you define them, they have different biologic behaviors. Those genomic changes are present from the MGUS stage onwards. This MGUS to active myeloma transition is occurring at a different time point in different patients, and it depends on the interaction of the myeloma cells with the bone marrow microenvironment. We see these patients with different degree of end organ damage during this course or journey of MGUS to active myeloma.

The good news is that management strategies and new therapies have improved multiple myeloma survivorship from a median of two to three years back in the early 2000s to over 10 years in the 2020s. Now, we are focused on finding the right strategy for patients that gives them the highest likelihood of the deepest responses especially in their first year of diagnosis. I think all of us in the myeloma community agree, that depth of response, achieving it and sustaining it is very important for survival outcomes.



We have this treatment paradigm that we've lived with now for almost two decades. I'm going to get some opinion from my colleague Dr. Krishnan on this because I think she would agree that this will probably change as we are getting newer cellular therapies and bispecific antibodies into the scheme of myeloma treatment. For newly diagnosed patients even today, we think about them in transplant-ineligible and eligible categories. The idea of that initial induction therapy with or without stem cell transplantation is to get patients into as deep a response as possible, and then the maintenance phase is geared towards maintaining that depth of response. We also pay attention to supportive care in terms of managing bone health, infection risk, overall wellbeing, pain management for our patients. At a time point when the disease does come back, we de-stage patients and reassess and try to find the best available option for the patients at that set point in time.



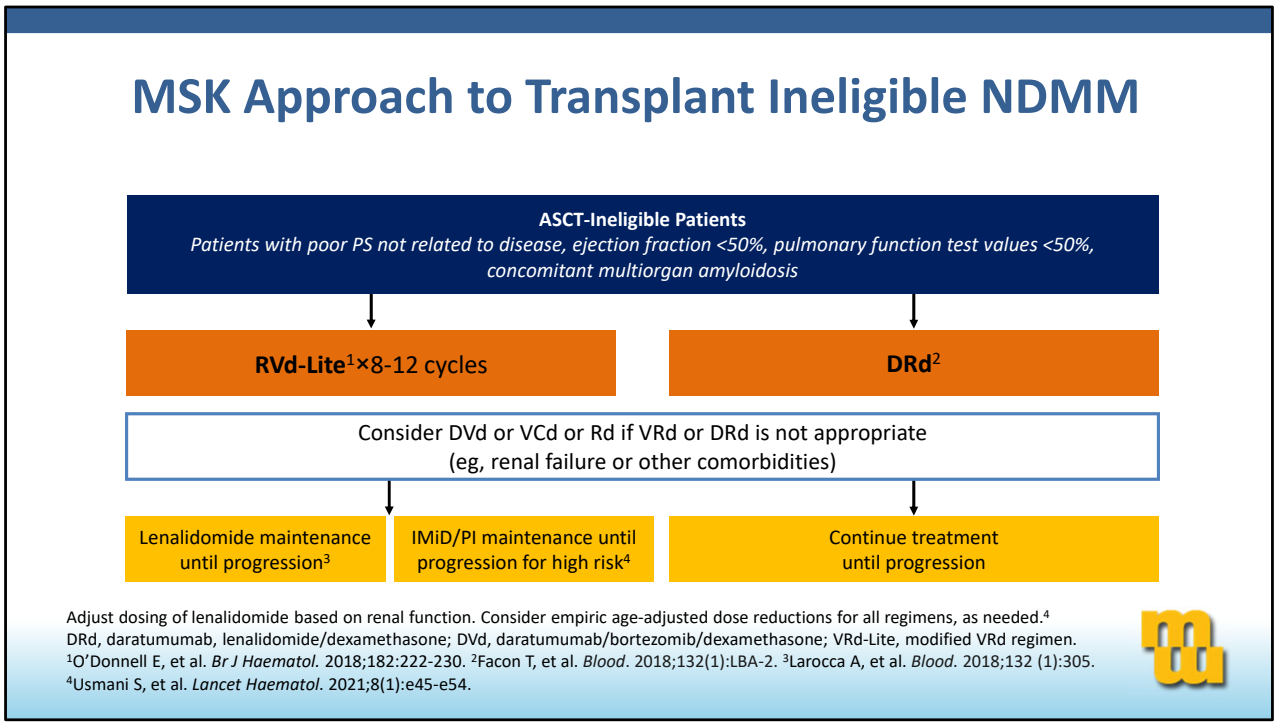
The management plan for our patients even during that early phase of treatment is dynamic. It's not that the train has left the station, and it's not going to change its course. It's a multidisciplinary approach that we typically take for our patients because this patient population is a little bit older in general. When we develop and implement the plan, we are monitoring both the response to treatment as well as the safety or adverse event profile for patients. Then we revise their treatment plan and provide data gathering and continue to implement it. These are some general guidelines on how we are approaching myeloma treatment.

I do want to move to this next section, and this is where, even before I start this section, I would love to get some input from Dr. Krishnan. I'm going to be talking about transplant-ineligible myeloma patients and how we are managing them today based on data. Dr. Krishnan, what do you think? Do you think that we are still going to be thinking about transplant eligibility or ineligibility in the future with all the data that's emerging?

Amrita Krishnan: Thank you Dr. Usmani. I think you may end up adding a third bucket now is T-cell-directed therapy eligible or not. I'm sure you're going to be covering a couple of those studies in regards to some of the bispecific T-cell engagers being used in the newly diagnosed setting and patients not intended for transplant. Also, in terms of CAR T as well, same idea in terms of patients not intended for transplant. I think I agree with you that

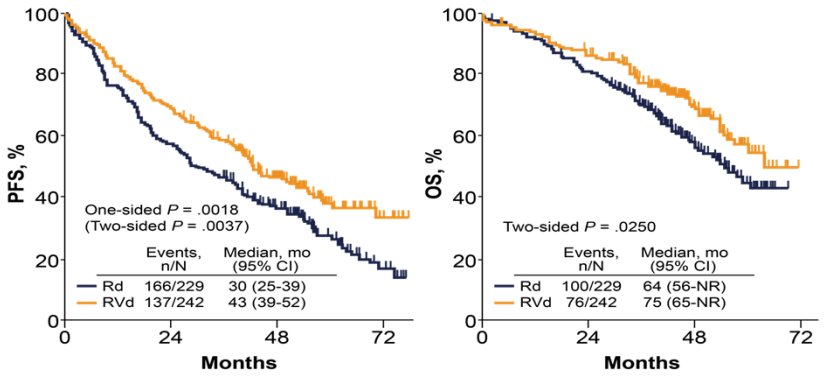
transplant ineligible is probably going to go away, and it may be just not intended for upfront transplant.

Saad Usmani: Yes, I agree with you. I think we are going to probably move in that direction within the next two to three years as some of those trials that I'm going to mention come to the fore.



Saad Usmani: So building on that, currently this is our approach at MSK for our transplant-ineligible patients, and transplant ineligibility is deemed on the basis of performance status or comorbidities for patients, and it's two of these three-drug combinations. It's either RVD lite for 8 to 12 cycles or until response plateau before patients move on to maintenance treatment. If they have standard risk disease, it's lenalidomide only. If it is a high-risk disease, we still try to keep them on the PI maintenance in addition to lenalidomide. Then for patients who start off on the daratumumab-based triplet DRd regimen, we typically tend to continue this treatment once patients have had a response plateau, we may tweak the regimen or discontinue one of the drugs. That really is a patient specific decision that we typically tend to make.

SWOG S0777: RVd Versus Rd in Patients Without Immediate Intent for ASCT1



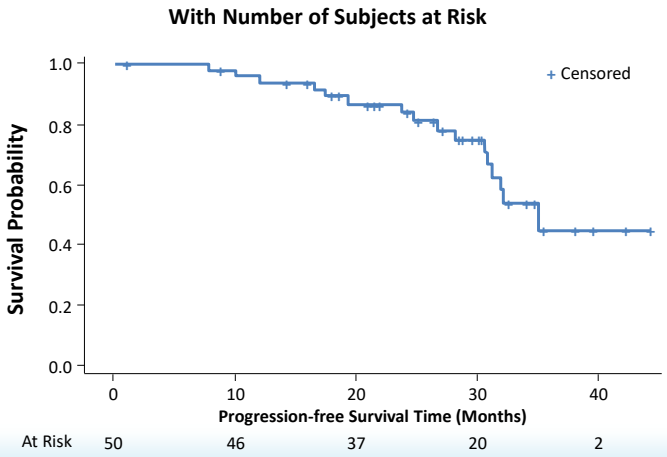
Initial Therapy
RVd for eight 21-d cycles vs Rd for six 28-d cycles in patients not intending to proceed to upfront transplant, followed by Rd in both arms (N = 525)

Durie B, et al. *Lancet*. 2017;389:519-527.

Where do these data come from? I think the RVD data really starts from the SWOG777, which looked at RVD versus Rd as induction for patients without immediate intent for stem cell transplant. This study showed superiority of the PI/IMiD induction compared to just Rd induction for both PFS and OS. One critique of this study is that the median patient population age was in the mid-60s. It included patients who would have been transplant eligible by age or performance status. However, the bottom line is that this regimen validated the practice of using a three-drug combination for our newly diagnosed myeloma patients both in the transplant eligible as well as ineligible settings.

RVd-Lite

- Regimen (N=53)
  - Lenalidomide: 15 mg po days 1 to 21
  - Bortezomib: 1.3 mg/m^2 SC 1× weekly on days 1, 8, 15, 22
  - Dexamethasone
    - If ≤75 years, 20 mg 2× weekly
    - If >75 years, 20 mg 1× weekly
- Results
  - 86% ORR
  - 66% ≥ VGPR
  - Median PFS: 35.1 months
  - Median OS: NR
  - Median follow-up: 30 months
  - Median age: 73 years (range: 65-91)
  - PN: 62%
  - Only 1 patient had grade 3 symptoms

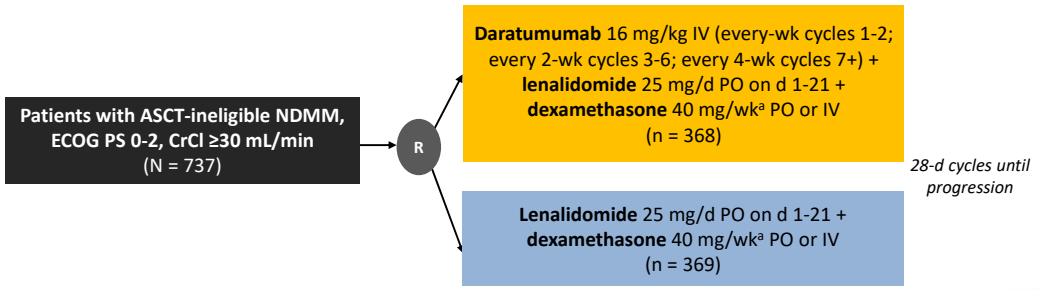


PN, peripheral neuropathy.
O'Donnell, et al. *Br J Haematol.* 2018;182:222-230.

However, the regimen that most of us use for the older patients is the RVD-lite regimen, which was developed or examined at Mass General by our colleagues Doctors Betsy O'Donell and Noopur Raje. It's a single-arm study using lower doses of lenalidomide at 15 milligrams and weekly dosing of bortezomib but showing very similar response rates as well as PFS for this older patient population of median of 73 years. What they had shown in terms of safety is good tolerability. Patients did have peripheral neuropathy with this approach, about two-thirds of the patients. They were grade one and two and reversible according to this report.

Phase 3 MAIA Study: Daratumumab Plus Rd in NDMM

- Stratified by ISS (I vs II vs III), region (North America vs other), and age (<75 vs ≥75 y)
- **Primary endpoint:** PFS
- **Secondary endpoints:** ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, and safety



[a] Reduced to 20 mg/wk if aged >75 y or BMI <18.5.
Facon T, et al. *N Engl J Med*. 2019;380:2104-2115.

I think the more important study which is perhaps more relevant to what we are going to be discussing for this older patient population right now is the daratumumab, lenalidomide, dexamethasone combination. This was an approved regimen that was approved almost three years ago if I remember correctly based on the phase III MAIA trial that compared this three-drug combination to lenalidomide-dexamethasone, which at that time was deemed the standard of care for this patient population based on the first clinical trial.

Demographics and Baseline Characteristics (ITT)

	D-Rd (n = 368)	Rd (n = 369)
Age		
Median (range), y	73 (50-90)	74 (45-89)
Distribution, n (%)		
<65 y	4 (1)	4 (1)
65-<70 y	74 (20)	73 (20)
70-<75 y	130 (35)	131 (36)
≥75 y	160 (43)	161 (44)
Male, n (%)	189 (51)	195 (53)
ECOG PS score,[a] n (%)		
0	127 (35)	123 (33)
1	178 (48)	187 (51)
2[b]	63 (17)	59 (16)
ISS stage,[c] n (%)		
I	98 (27)	103 (28)
II	163 (44)	156 (42)
III	107 (29)	110 (30)

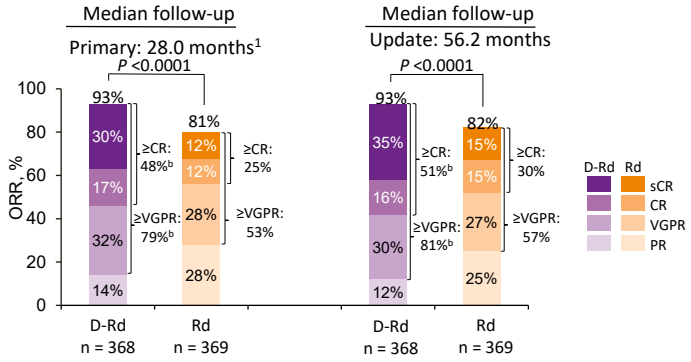
	D-Rd (n = 368)	Rd (n = 369)
Type of measurable disease, n (%)		
IgG	225 (61)	231 (63)
IgA	65 (18)	66 (18)
Other[d]	9 (2)	10 (3)
Detected in urine only	40 (11)	34 (9)
Detected as serum-free light chain only	29 (8)	28 (8)
Cytogenetic profile,[e] n/total n (%)		
Standard risk	271/319 (85)	279/323 (86)
High risk	48/319 (15)	44/323 (14)
Median time since initial diagnosis of MM (range), months	0.95 (0.1-13.3)	0.89 (0-14.5)

Demographics and baseline characteristics were well balanced between arms

ITT, intention-to-treat.
[a]ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [b]Two patients had an ECOG PS score >2 (1 patient each with an ECOG PS score of 3 and 4). [c]ISS stage is derived based on the combination of serum β_2-microglobulin and albumin; higher stages indicate more severe disease. [d]Includes IgD, IgE, IgM, and biclonal. [e]Cytogenetic abnormalities were identified by fluorescence in situ hybridization or karyotype testing; high risk was defined as having a t(4;14), t(14;16), and/or del17p abnormality.
Note: percentages may not add up to 100% due to rounding.

If you look at this patient population, the median age was 73 and 74. In fact, 75 or older age made up 44% of the patient population that enrolled on the study. Really a very relevant older transplant-ineligible patient population here.

MAIA Phase 3 ORR[a]

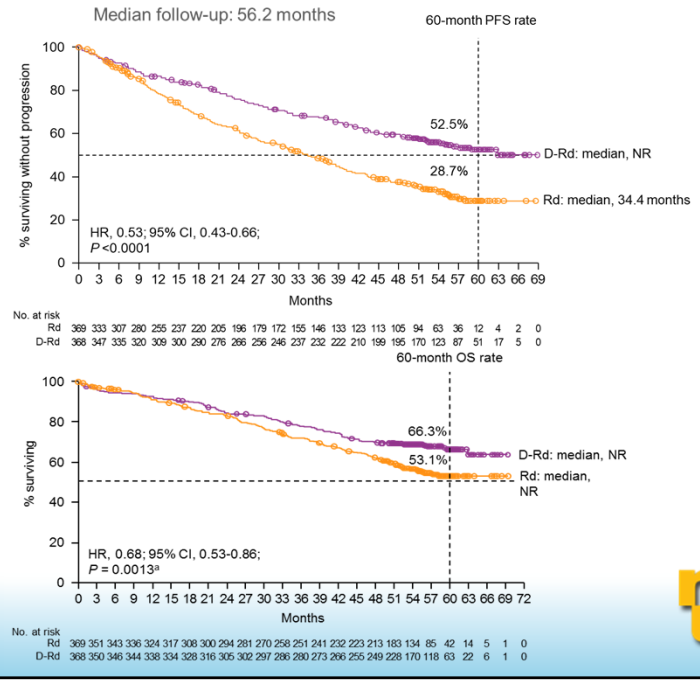


- **D-Rd induced deeper responses, with significantly higher rates of ≥ CR and ≥ VGPR, compared with Rd**
- **With >28 months of additional follow-up, responses deepened with continued daratumumab therapy**

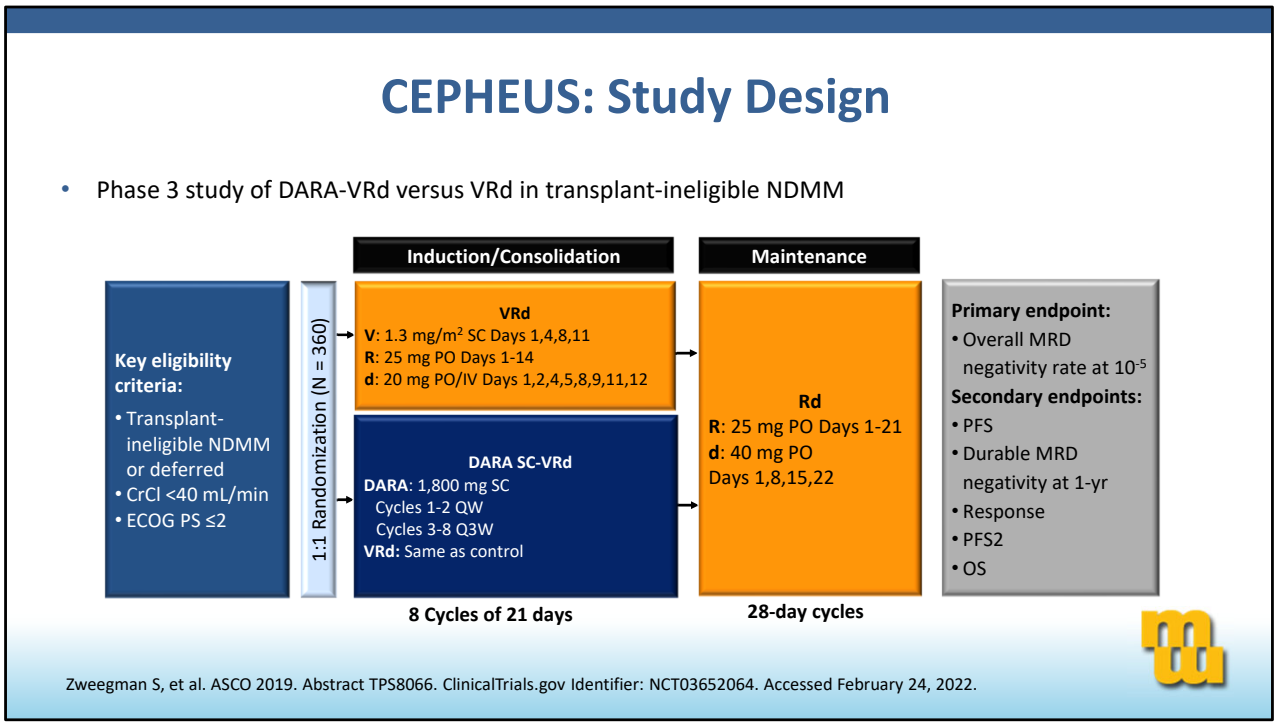
Note: percentages may not add up to the total due to rounding.
[a]ITT population. [b]*P* <0.0001; *P* values were calculated from the Cochran-Mantel-Haenszel Chi-Squared test.
VGPR, very good partial response; PR, partial response; OR, odds ratio.
[1]Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115.

Overall response rates with daratumumab lenalidomide, dexamethasone were 93% with a very high proportion of patients getting to a very good partial response or better. At the almost five-year follow up mark, that percentage was 81%.

MAIA Phase 3 Updated PFS and OS



If you look at the PFS and overall survival at the 56-month median follow up, the median PFS was still not reached for DRd, whereas it was 34.4 months for Rd.
The median OS had not been reached in either arm. It was statistically significant in favor of DRd at that mark with the hazard ratio of 0.68, so demonstrating that DRd is a very effective regimen. Because the median PFS is still not reached this will be a very challenging benchmark for the other clinical trials evaluating patients in this population.

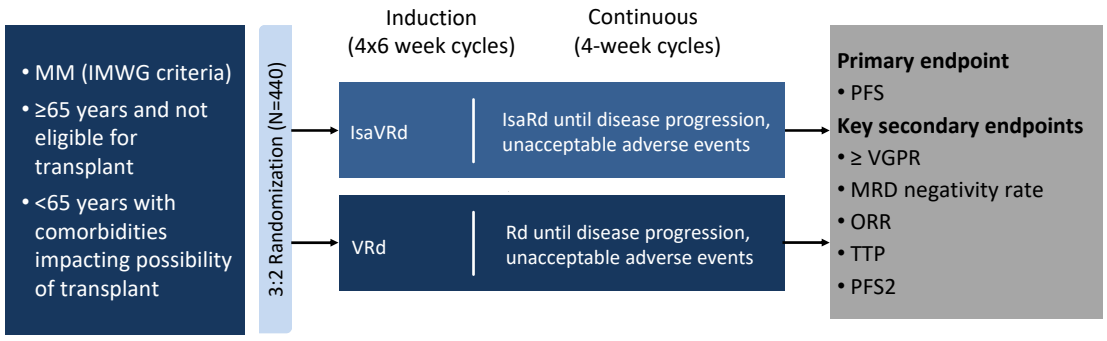


The field is moving on from that, and now this debate of whether we should use a PI or an anti-CD38 monoclonal antibody with lenalidomide, dexamethasone in this older patient population to say, "How about we just combine these therapies together?"

The CEPHEUS trial is fully enrolled. This study began right before the pandemic hit actually, comparing the combination of daratumumab along with VRd as part of induction compared to VRd as part of induction. Then both the arms got Rd. Essentially this is a comparison of the SWOG777 approach versus including daratumumab as part of induction treatment within that SWOG777 approach. This is just an induction question of incorporating daratumumab into the frontline setting.

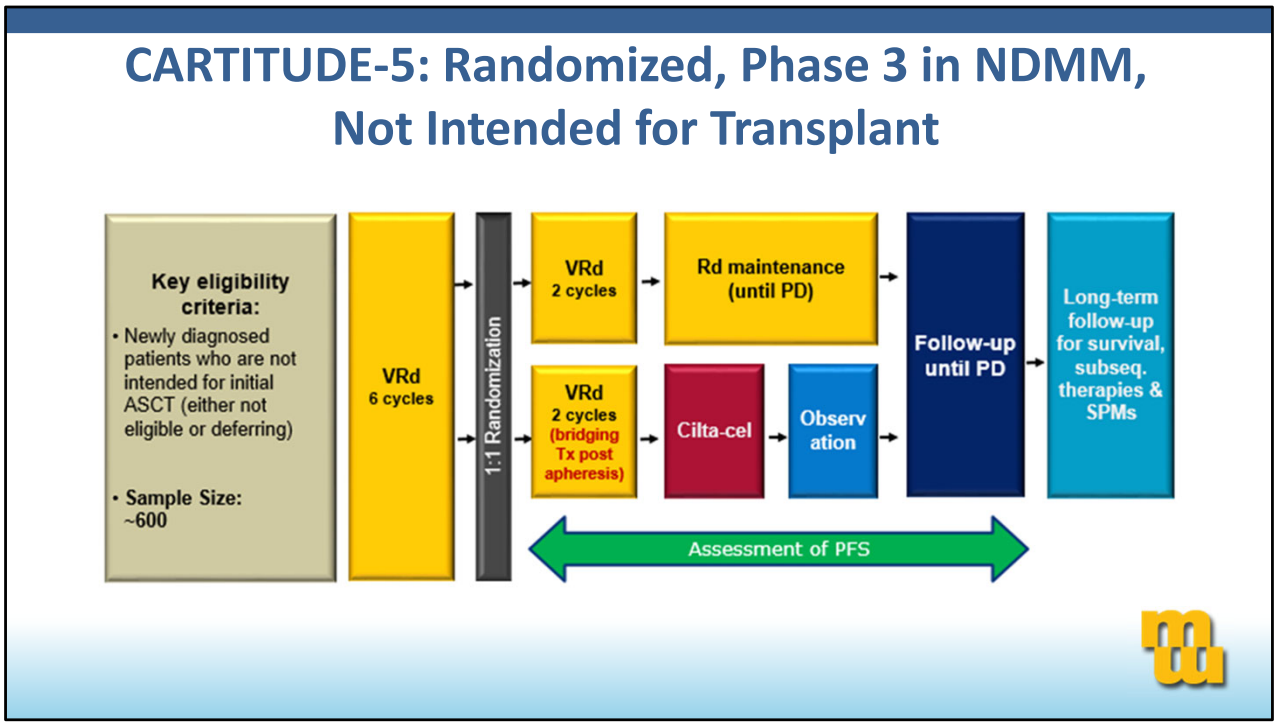
IMROZ: Study Design

- Phase 3 study of IsaVRd vs VRd in patients with transplant-ineligible NDMM

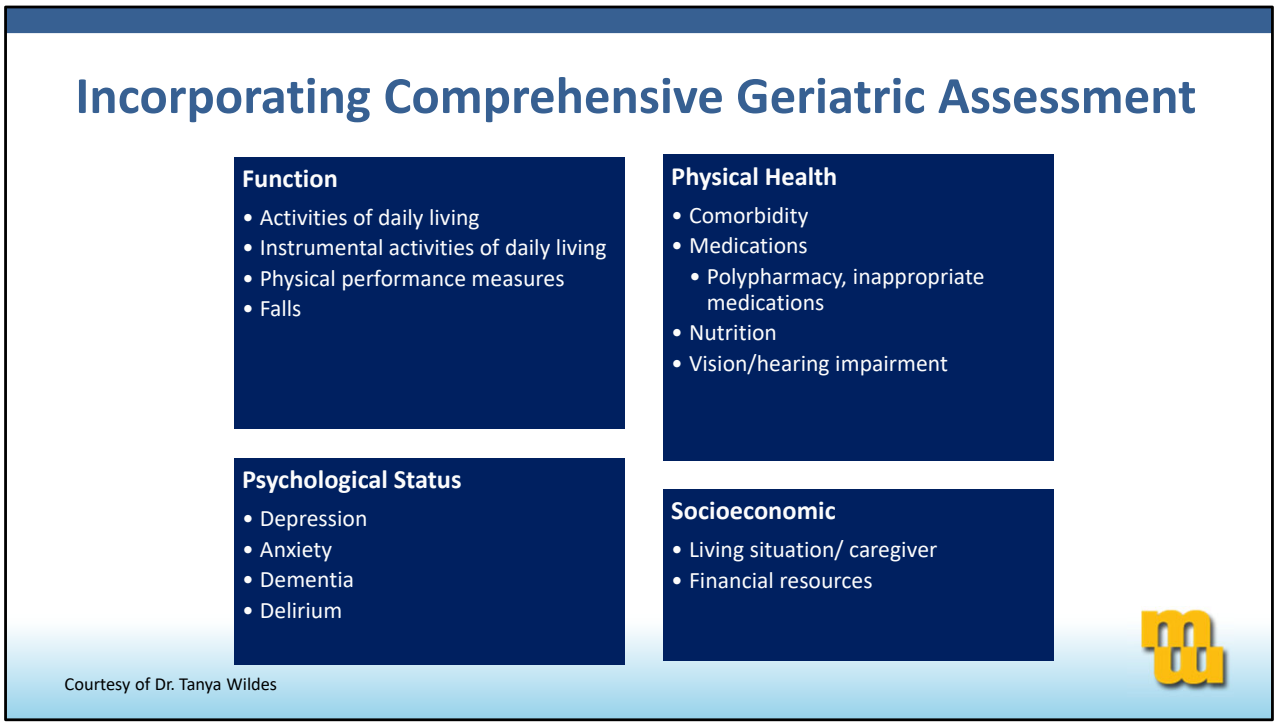


Orlowski RZ, et al. ASCO 2018. Abstract TPS8055.; ClinicalTrials.gov Identifier: NCT03319667. Accessed July 7, 2021.

In a very similar way, the other anti-CD38 monoclonal antibody isatuximab is being studied in the IMROZ trial. Here the therapy, in addition to receiving isatuximab with VRd, the maintenance is continuous with isa, lenalidomide, dexamethasone until relapse or progression, whereas, the standard of care arm on this study is the SWOG777 way of treating patients. Both very interesting studies in a very common patient population out in the community. If we look at the global myeloma care, I think both these trials will be very important.



Then lastly, this is a very exciting study. Dr. Krishnan alluded to this study. This is the CARTITUDE-5 trial, where the standard of care arm is the SWOG777 study again. Patients who are getting VRd as part of their induction treatment, followed by RD as maintenance. In the experimental arm after that phase of VRd induction treatment, the experimental arm gifts the BCMA-directed CAR T-cell therapy Cilta-cel, which all of us know is very active in both late relapse labs and even in early relapsed multiple myeloma. I think this whole discussion around transplant ineligibility, and how we're approaching newly diagnosed multiple myeloma will likely change in the next few years based on these clinical trials. I do want to highlight before I turn things over to Dr. Krishnan to talk about the transplant-eligible patient population approach on this discussion that we've been having within the myeloma community about the older, frail patients and how to extrapolate data from these transplant-ineligible studies for those patients.



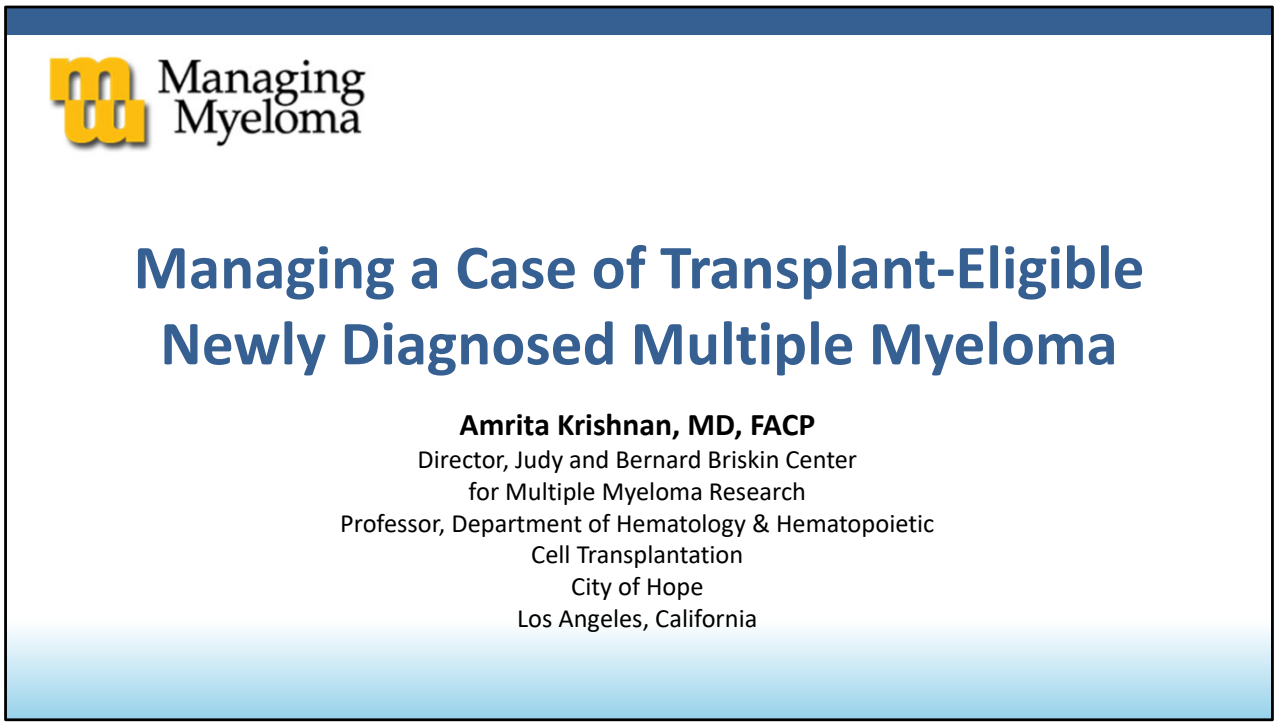
Many programs are starting to incorporate comprehensive geriatric assessments and partnering with their geri-oncology colleagues in evaluating the older myeloma patients. This is a slide courtesy of Dr. Tanya Wildes, who has been a champion for older myeloma patient care, where she and her colleagues evaluate patients with comprehensive geriatric assessments, and then utilizes those attenuated regimens in those patients. We're seeing some clinical trials emerge through the US cooperative group mechanism as well.

Dr. Krishnan, before you go to your talk, what are your thoughts around this? Are you thinking about incorporating this schema or approach in your older patients?

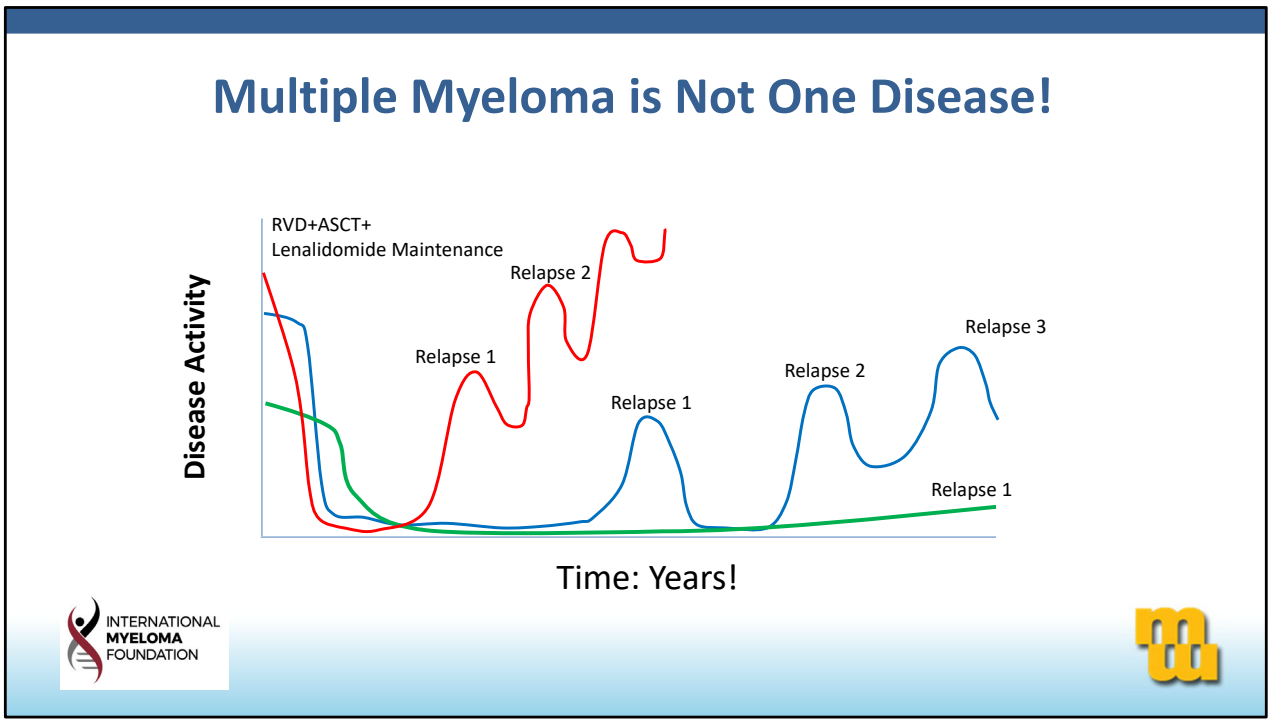
Amrita Krishnan: We certainly have a center for geriatric oncology at City of Hope as well. I think the challenge has been, to be honest, in regard to the resources and to be able to do the geriatric assessment. I think everyone agrees it's very important but how to do it in a way that one is fairly efficient, number two, that you adequately supported to be able to do it. I think that's where it's still a work in progress. There's a lot of ideas now in terms of using technology to assist with that. My colleague Dr. Nathwani has published using an iPad screening for geriatric assessment. Anything we can do to help make it streamlined, I think, will help us use it more.

Saad Usmani: I completely agree with you. We need more people like Dr. Wildes and Dr.

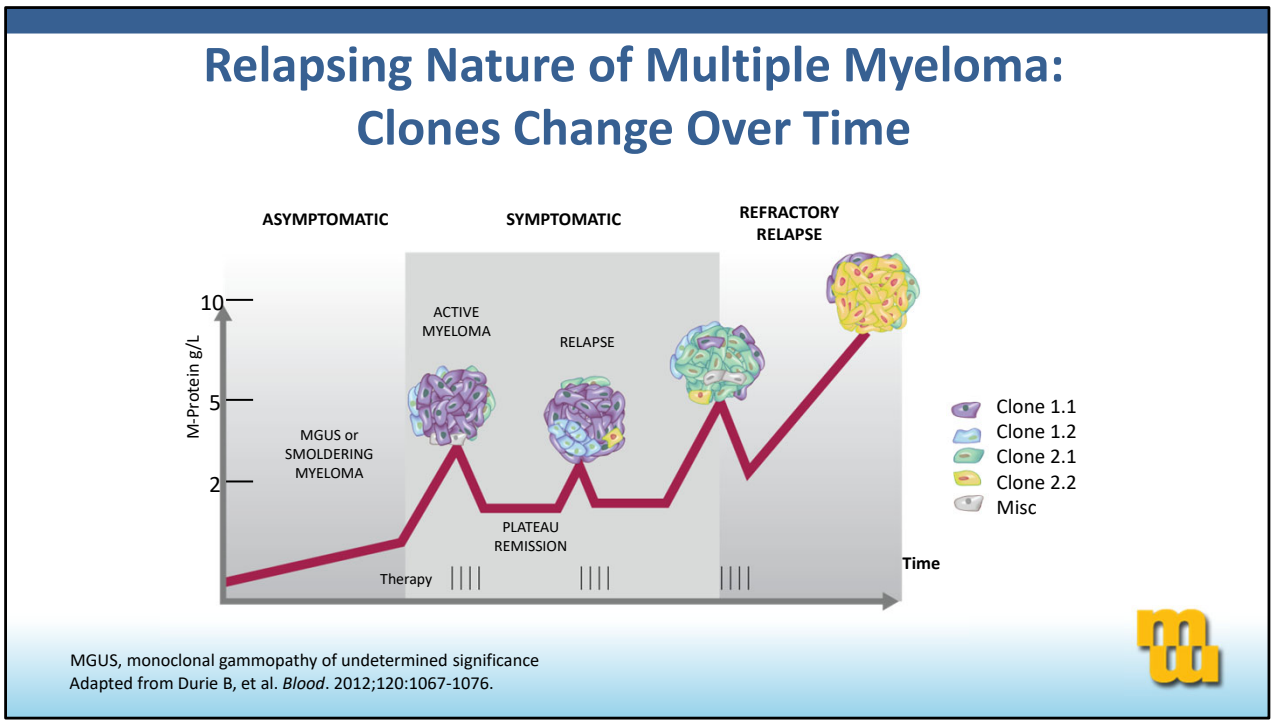
Nathwani to be doing this work in our respective teams and really taking this on. With that being said, Dr. Krishnan, I'll turn things over to you to talk about approaches towards transplant-eligible patients.



Amrita Krishnan: Thank you, Dr. Usmani. Some of my themes will be pretty similar to yours, which tells you that this idea of transplant eligible and non-eligible is fading away and some other regimens that will look also very familiar because, again, those groups are starting to merge closer and closer together. You've already outlined this well.



Everyone's myeloma is different. It's not one disease. The pace of disease can be different. We've all had patients who've been in remission 10-15 years versus those who continue to relapse. It's not always driven just by cytogenetics. It makes us realize there's a lot more in regards to adequately treating myeloma that we need to understand. Certainly, the immune microenvironment is a big part of that and in part why we're so interested in these other T-cell-based therapies.

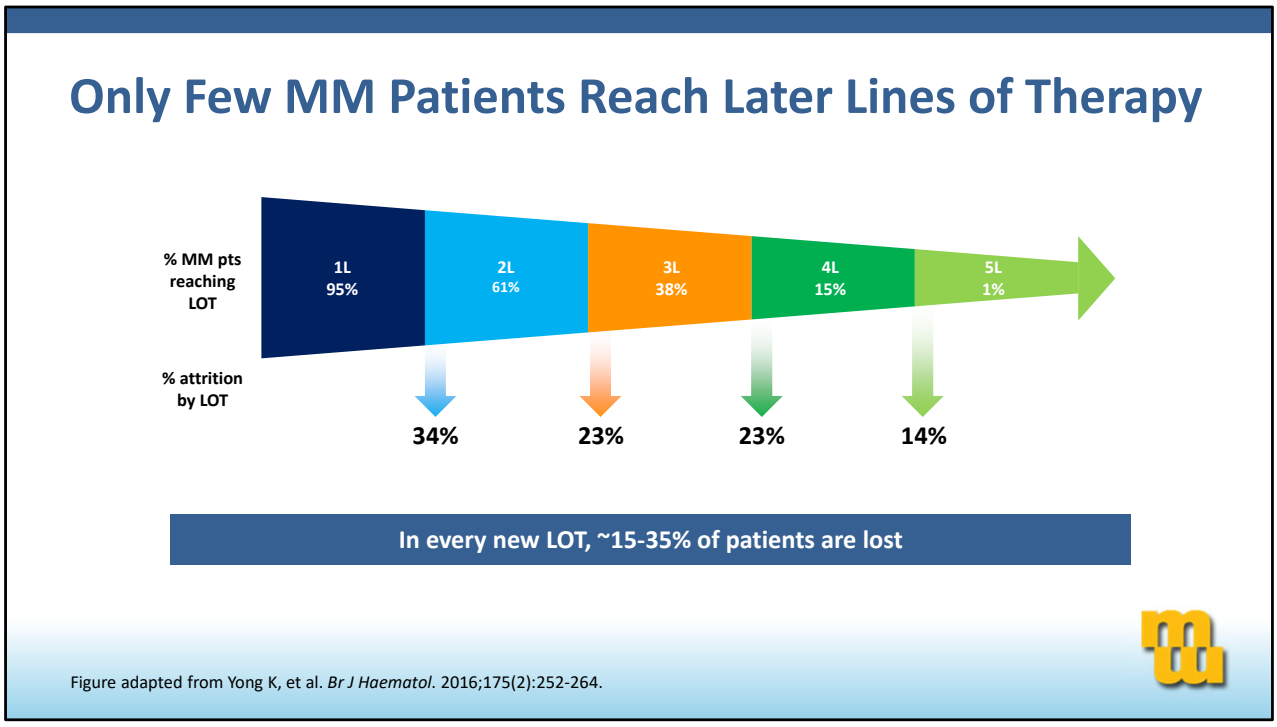


Also, obviously, the idea of clonal evolution of myeloma that you alluded to as well, as patients progress through the various stages of their myeloma is important as we think about targeted therapies. In fact, even more so if we're going to really focus on BCMA-targeted therapies and this idea of relapse post those therapies. Is it a new clone? Is it a BCMA-resistant clone, for example. Those are all very interesting concepts that we're learning more about.

Stage and Risk Stratify Newly Diagnosed MM

- It will influence:
  - PROGNOSIS
  - Clinical trial selection
  - THERAPY
- Rationale
  - Provides less toxic, less costly therapy, retaining future options
- It is already happening!
  - t(4:14) – treated with bortezomib based regimen
  - t(11;14) – responsive to venetoclax
  - p53 deletion – treated with bortezomib and for prolonged periods
- Only true concern is the potential to “undertreat” standard risk MM
  - But this has never been proven – in fact, the TOTAL THERAPY experiment demonstrated that intense therapy does not cure MM

First of all, I think you won’t disagree with the slide because this is your slide. Thank you for sharing that. In terms of, again, the idea that why do we stratify patients to help in terms of the prognosis for them? Even more importantly now, I think I would say we're using stratification to help guide therapy in regards to, as we'll talk about the MASTER study, is ideas of stopping therapy after patients achieve a deep remission, for example. Also, in terms of are we going to use a quadruplet versus a triplet induction? How intense are we going to be about our maintenance therapy? All those decisions now are in part based on risk stratification. Ultimately, we hope to be more biomarker-driven. Some of that we're doing. You alluded to that in the high-risk population using proteasome inhibitors. Eventually, one hopes to see that in terms of patients with t(11;14) the use of BCL2 inhibitors more and more maybe even in the frontline setting, for example. We all acknowledge patients with p53 deletion, and especially those with more than one high-risk chromosome abnormality remain a big challenge for us.

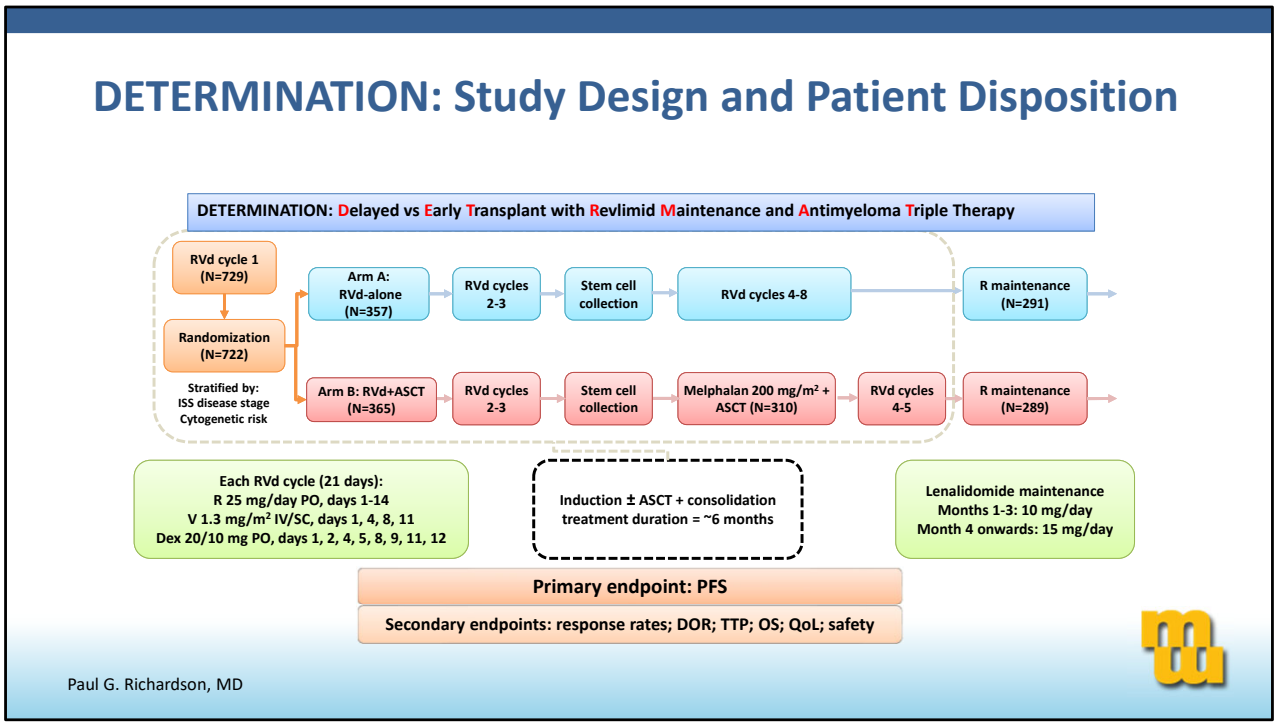


I think you spoke to this very well. Our first shot is our best shot, and that's I think what we need to keep doing in regards to being aggressive at our initial induction therapy because many patients never make it to those later lines of therapy. That's also why there's an interest in moving many of these new therapies earlier and earlier in the course of the disease.

Goals of Therapy

- Induce deep remissions
- Long remissions
- Improve symptoms
- QOL; stop therapy
- ?CURE

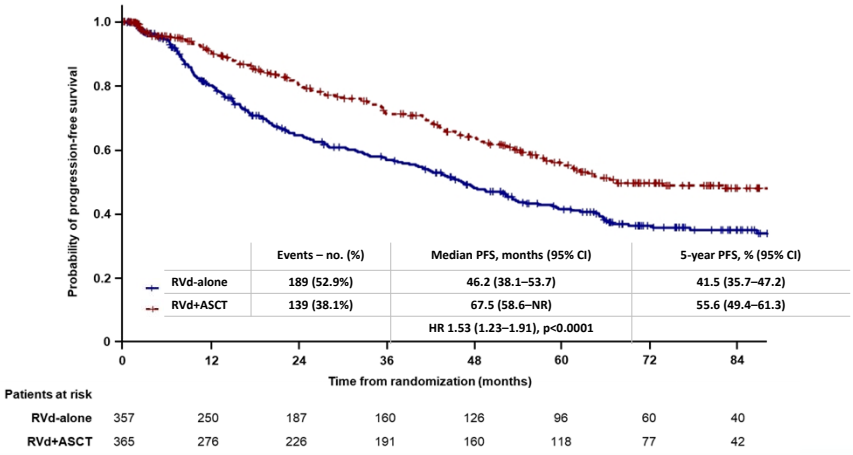
You already said this, and I completely agree. The goal of our therapy is to get a response quickly, to get a deep response, and a long response. Ultimately, we want to make sure that those responses translate into better quality of life. Ultimately, we want to cure the disease, and one could argue that cure means being able to stop therapy as well.



Let's talk about this idea of transplant. We had a long discussion earlier about not intended for transplant. Here, we have the phase III randomized study.

Looking at, I really don't think of it as a transplant versus no transplant, but more as an early versus delayed transplant trial using RVD induction and patients being randomized to RVD versus RVD followed by transplant, followed by RVD consolidation, and both arms getting lenalidomide maintenance until disease progression.

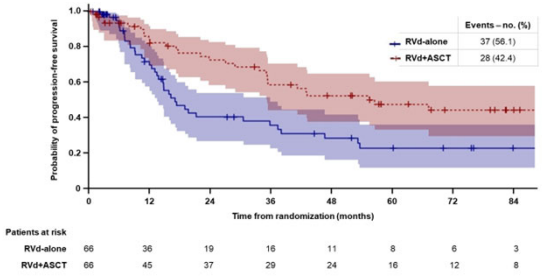
Primary Endpoint: Progression-free Survival (PFS)



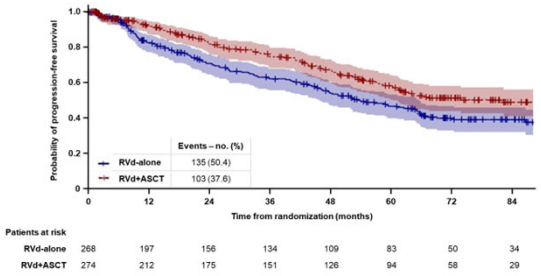
CI, confidence interval; HR, hazard ratio; Data cut off: 12/12/21
Paul G. Richardson, MD

The primary endpoint of the DETERMINATION study was progression-free survival, and you could see that it was clearly met with an improved progression-free survival of 67 months in the autologous transplant arm.

PFS by Stratification Factor – Cytogenetic Risk



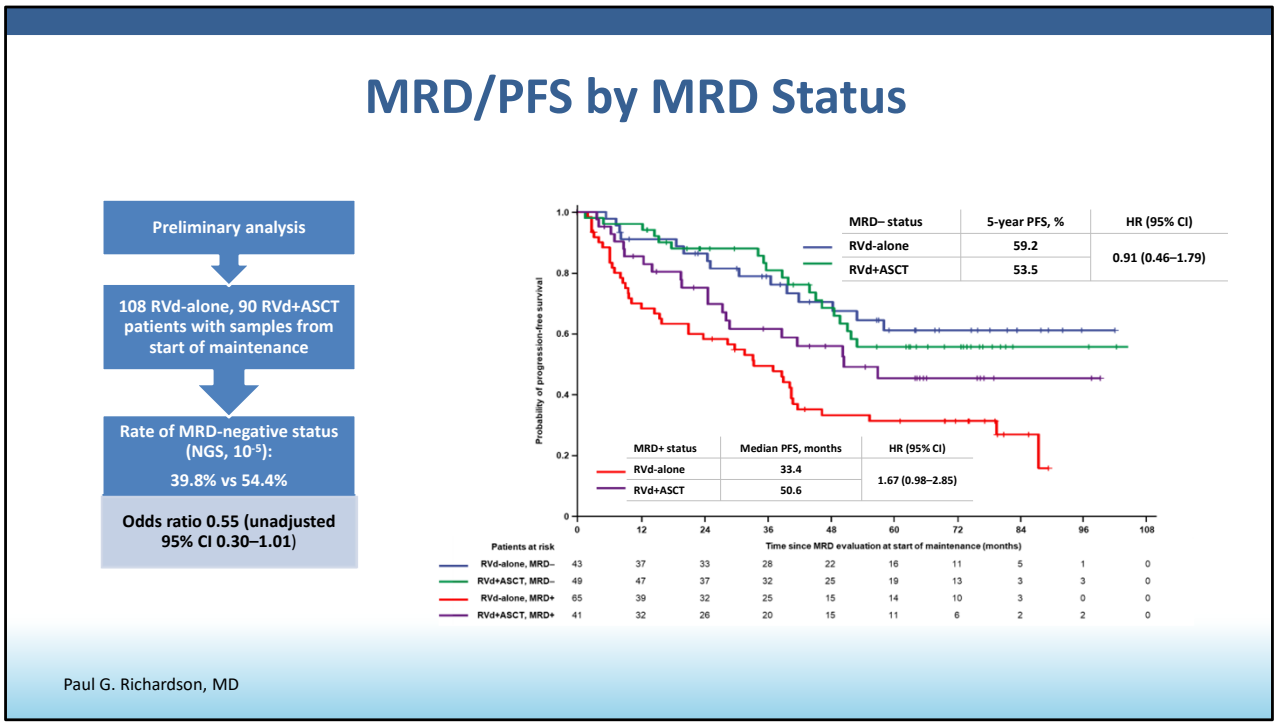
Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	



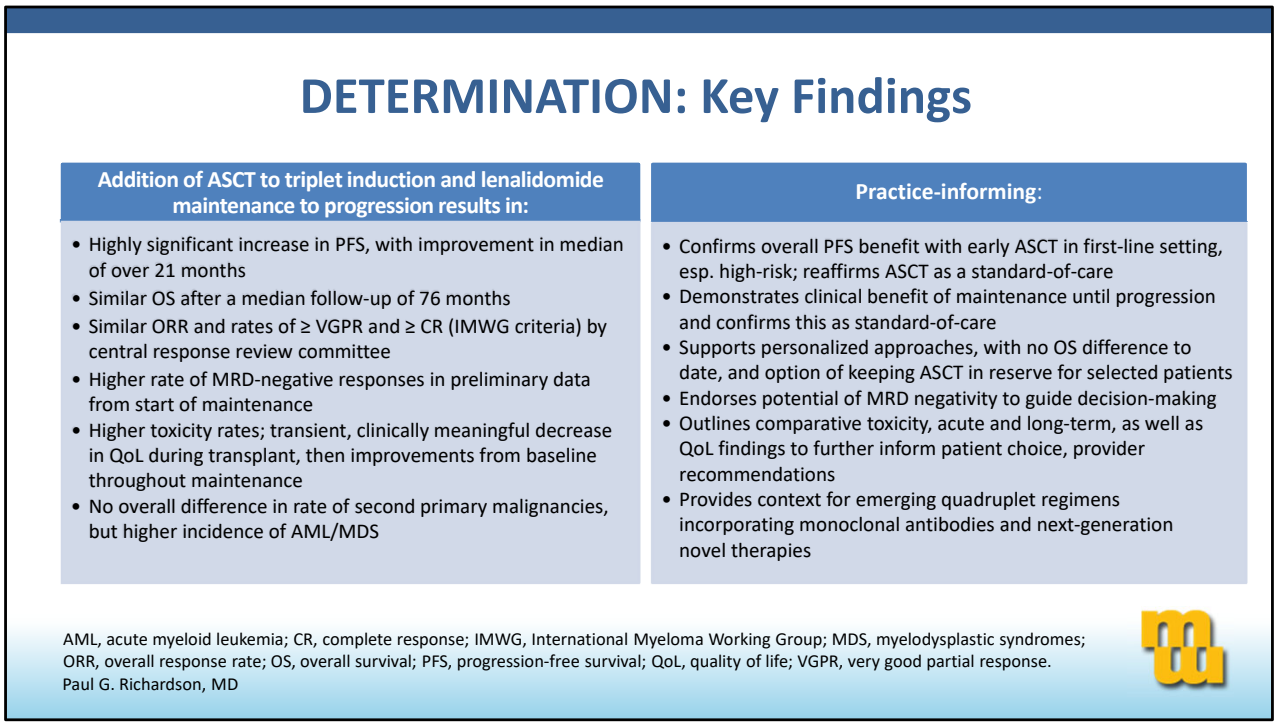
Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

Paul G. Richardson, MD

If you look at cytogenetic risk, and again, back to our initial point of risk stratification, you can see even more so for those high-risk patients, transplant seems to benefit them with a PFS of 55 versus 17 months only in the RVD alone arm. Even in standard-risk patients, you could see a benefit again in terms of PFS to early transplant.



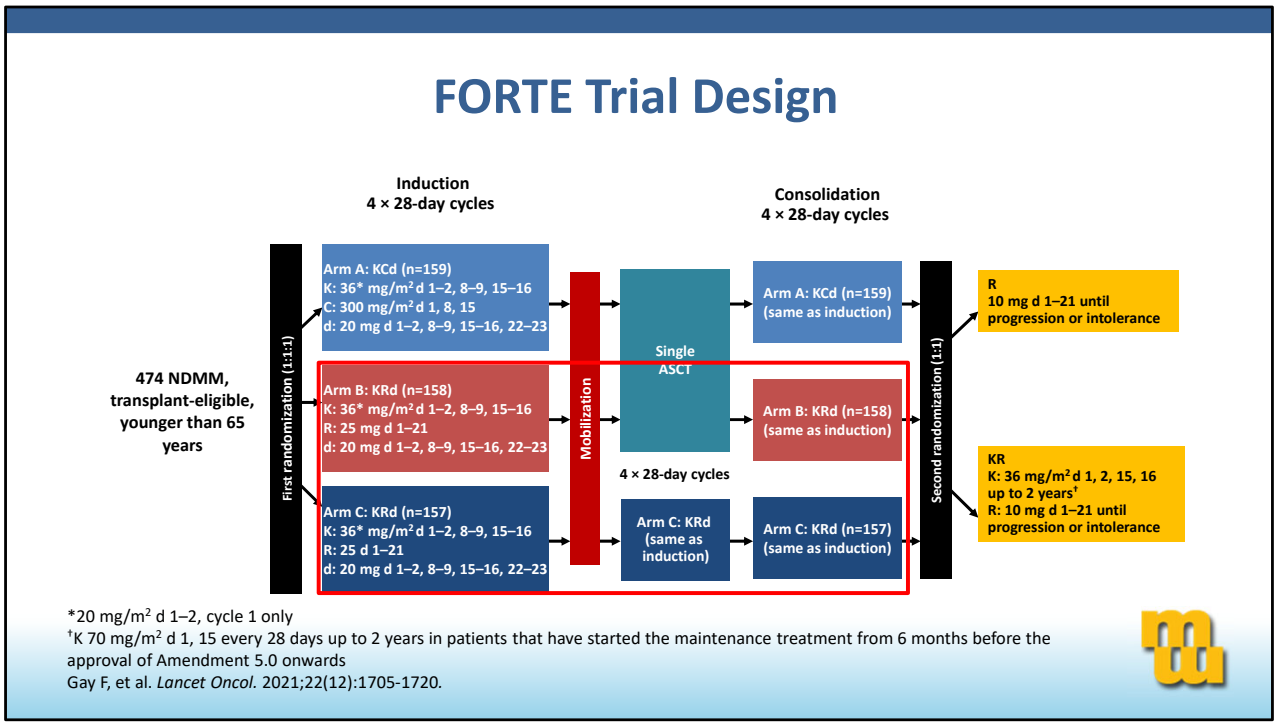
If you look in terms of this idea of getting a deep remission, that holds true as well. The patients who became MRD-negative seem to have the longest PFS. One could argue that that holds true, whether or not you get a transplant for sure. My bias would be your chance of becoming MRD-negative is certainly higher in the transplant arm versus the non-transplant arm.



This is a summary slide from the ASCO presentation by Dr. Richardson in regards to the DETERMINATION key findings that it met the primary endpoint of an overall progression-free survival benefit with early transplant and the upfront setting. To remind you, this study used lenalidomide until disease progression, and this continued to support that idea. Though that may be one area where the field is continuing to evolve. To acknowledge, there is no overall survival difference right now with a median follow up of 76 months. Nonetheless, I would purport that one, this trial was not designed for that, it was designed for PFS. Number two, survival of myeloma patients is continuing to improve and evolve, and demonstrating OS benefits is much more challenging and may not necessarily always be what drives our decision-making process. I would also point out the important point that there was no difference in the overall rate of second primary malignancies in both arms. There was a slightly higher incidence of AML MDS in the transplant arm. Overall, that rate was not statistically significantly different. Again, another area where the field's evolving in terms of trying to understand who is at higher risk for getting these second malignancies and the idea of CHIPs, for example, at baseline may also help guide our therapy.

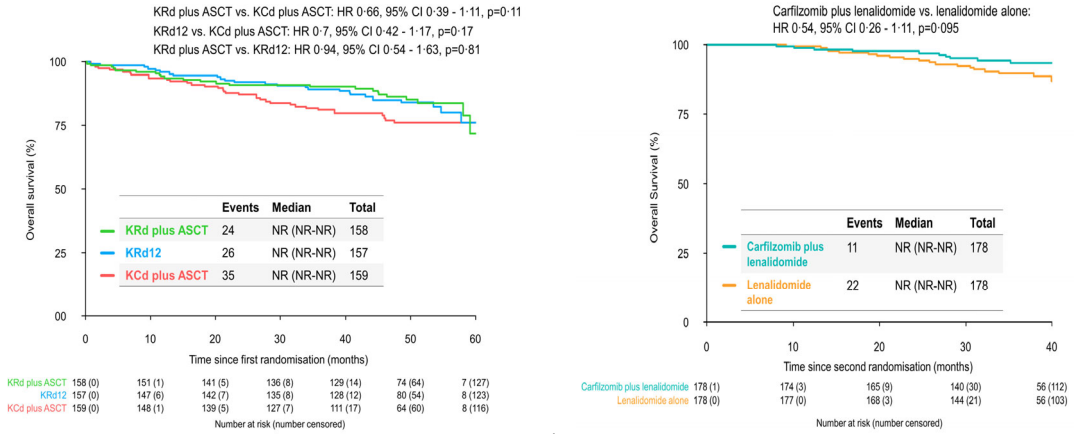
K Is the New V

Now, of course, the field doesn't end there. VRd was the gold standard when this trial was done. That's rapidly evolving and one could argue that K is the new V now.



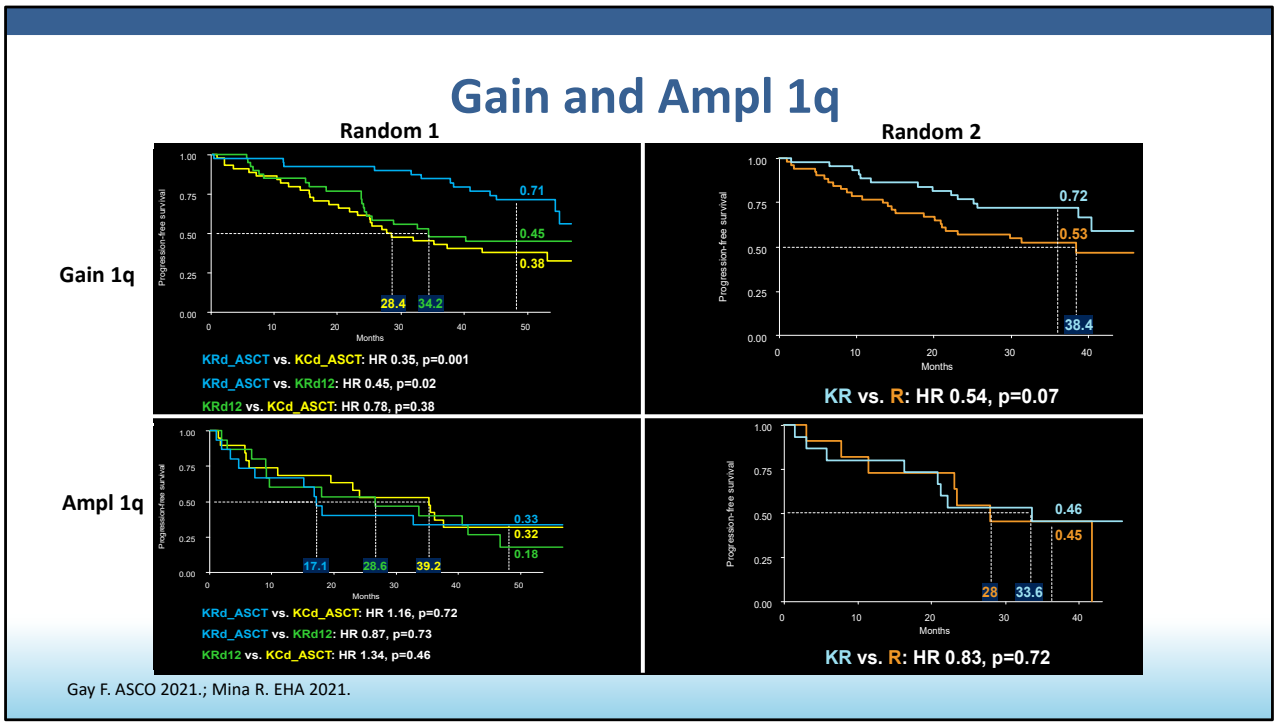
We certainly have data from Dr. Gay and colleagues in terms of the FORTE study looking at KRd plus or minus transplant. You could see certainly KRd superior to KCd.

Overall Survival: Random 1 and Random 2



Random 1, first randomization (induction/consolidation treatment); Random 2, second randomization (maintenance treatment); OS, overall survival; ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, *P*-value; KR, carfilzomib-lenalidomide maintenance; R, lenalidomide maintenance; HR, hazard ratio; CI, confidence interval; p, p-value.
Gay F, et al. *Lancet Oncol.* 2021;22(12):1705-1720.

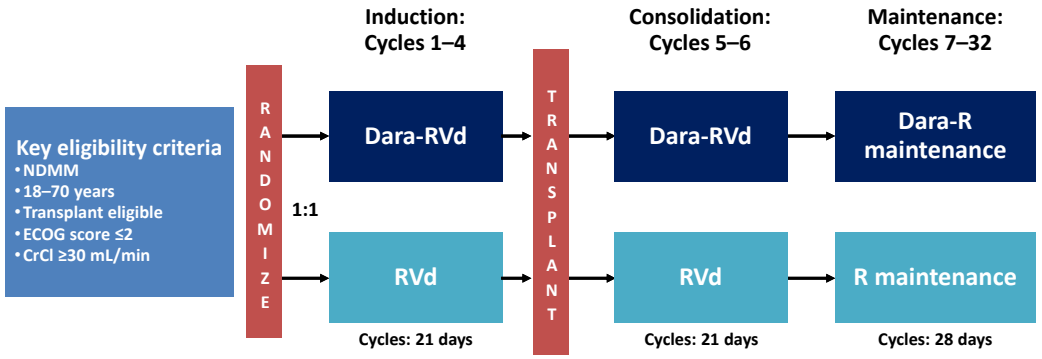
There was a second randomization in this study to KR versus R, same theme here that OS is not different, but this is relatively early follow-up. Certainly, there was a PFS benefit to the KR arm.



Gay F. ASCO 2021.; Mina R. EHA 2021.

Especially in those challenging patients, the high-risk groups. Those who had gain of 1q. In terms of 17p, the one group that remains the big challenge was amplification of 1q. Four or more copies. Even those patients did not seem to benefit from the KR versus R maintenance. Again, suggesting we still have room to think about newer therapies for these very high-risk patients.

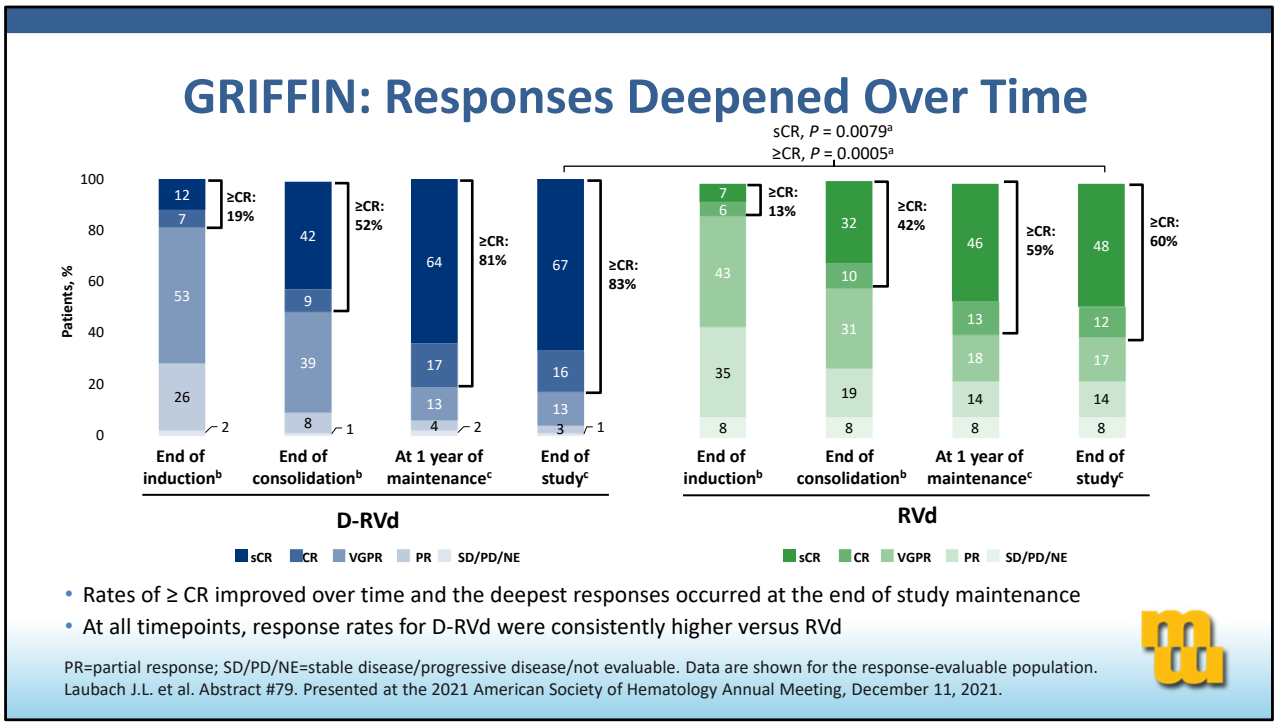
GRIFFIN: Phase 2, Randomized, Open-Label Study of Dara-RVd vs VRd in Transplant-Eligible NDMM



Primary end point: sCR rate after consolidation

Laubach J.L. et al. Abstract #79. Presented at the 2021 American Society of Hematology Annual Meeting, December 11, 2021.

Now, Dr. Usmani talked about quadruplet induction in the non-transplant setting. Here, we have it in the transplant setting with the GRIFFIN study, dara-RVd versus RVD, a phase II randomized study.



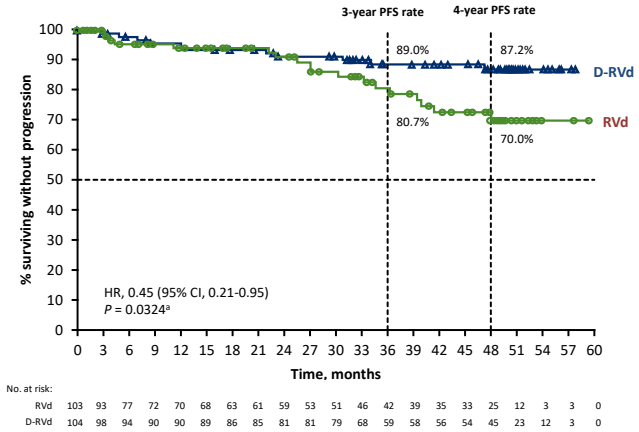
- Rates of ≥ CR improved over time and the deepest responses occurred at the end of study maintenance
- At all timepoints, response rates for D-RVd were consistently higher versus RVd

PR=partial response; SD/PD/NE=stable disease/progressive disease/not evaluable. Data are shown for the response-evaluable population.
Laubach J.L. et al. Abstract #79. Presented at the 2021 American Society of Hematology Annual Meeting, December 11, 2021.

You can see that the quadruplet arm had a much higher response rate and even more importantly greater depth of response. Those responses deepened over time.

GRIFFIN: PFS in the ITT Population

- Median follow-up: 49.6 months
- Median PFS was not reached in either group
- PFS was longer for D-RVd/D-R versus RVd/R, with a clinically meaningful 55% reduction in the risk of disease progression or death
- The separation of the PFS curves occurred beyond 1 year of maintenance



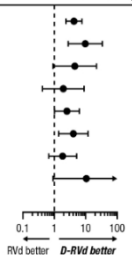
[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, and III) and baseline CrCl (30-50 mL/min or >50 mL/min) at randomization.
An HR <1 indicates an advantage for D-RVd. *P*-value is based on the log-rank test stratified with ISS staging and baseline CrCl at randomization.
Laubach J.L. et al. Abstract #79. Presented at the 2021 American Society of Hematology Annual Meeting, December 11, 2021.

Now, we also have a progression-free survival benefit for the quadruple arm compared to the triplet RVD arm at 87% versus 70%, suggesting, at least in my mind, that the majority of patients, we are now moving towards a quadruplet-based induction.

Final Analysis of Griffin Among Clinically Relevant Subgroups

A.

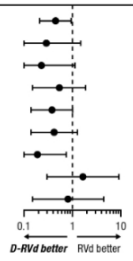
	D-RVd MRD negativity (10^{-5}), n/N (%)	RVd MRD negativity (10^{-5}), n/N (%)	Odds ratio (95% CI)
ITT (overall)	67/104 (64.4)	31/103 (30.1)	4.23 (2.35-7.62)
Age ≥65 years	19/28 (67.9)	5/28 (17.9)	9.71 (2.78-33.92)
ISS stage III disease	10/14 (71.4)	5/14 (35.7)	4.50 (0.91-22.15)
High cytogenetic risk[a]	7/16 (43.8)	4/14 (28.6)	1.94 (0.42-8.92)
Revised high cytogenetic risk[b]	23/42 (54.8)	12/37 (32.4)	2.52 (1.01-6.32)
gain/amp1q	21/34 (61.8)	8/28 (28.6)	4.04 (1.38-11.81)
1 HRCA[c]	17/32 (53.1)	11/29 (37.9)	1.85 (0.67-5.15)
≥2 HRCA[c]	6/10 (60.0)	1/8 (12.5)	10.50 (0.91-121.39)
gain/amp1q + 1 HRCA[c]	6/9 (66.7)	0/6	NE (NE-NE)



A. MRD-negativity (10^{-5})

B.

	D-RVd n/N	D-RVd Median PFS (mo)	RVd n/N	RVd Median PFS (mo)	Hazard ratio (95% CI)
ITT (overall)	11/104	NR	18/103	NR	0.45 (0.21-0.95)
Age ≥65 years	2/28	NR	5/28	NR	0.29 (0.06-1.48)
ISS stage III disease	2/14	NR	6/14	33.1	0.23 (0.05-1.13)
High cytogenetic risk[a]	5/16	NR	5/14	36.1	0.54 (0.15-1.88)
Revised high cytogenetic risk[b]	7/42	NR	10/37	47.9	0.38 (0.14-1.01)
gain/amp1q	6/34	NR	7/28	47.9	0.42 (0.14-1.27)
1 HRCA[c]	3/32	NR	8/29	47.9	0.19 (0.05-0.75)
≥2 HRCA[c]	4/10	33.9	2/8	NR	1.65 (0.30-9.18)
gain/amp1q + 1 HRCA[c]	4/9	33.9	2/6	38.7	0.81 (0.15-4.47)



B. PFS in clinically relevant subgroups

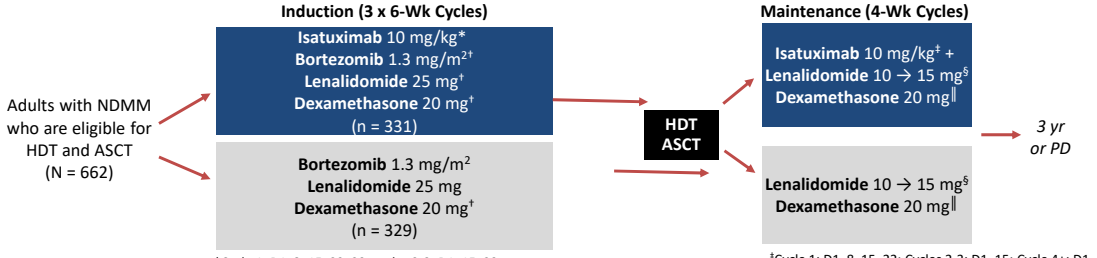
MRD=minimal residual disease; ISS=International Staging System; HRCA=high-risk chromosomal abnormalities; CI=confidence interval; NE=not evaluable; PFS=progression-free survival; D-RVd=daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd= lenalidomide/bortezomib/dexamethasone; NR=not reached.
[a]High-risk cytogenetics are defined based on FISH testing as ≥1 of the following: del17p, t(4;14), or t(14;16).
[b]Revised high-risk cytogenetics are defined based on FISH testing as ≥1 HRCA: del17p, t(4;14), t(14;16), t(14;20) or gain/amp1q (≥3 copies of chromosome 1q21).
[c]HRCA include chromosomal abnormalities per the revised definition.

Chari, A et al. *Blood*. 2022;140 (Suppl 1):7278–7281. https://doi.org/10.1182/blood-2022-162339

I think this is the other big question has always come out is the idea in terms of subgroups, especially those high-risk subgroups, and there does seem to be a benefit for that quadruple in those high-risk patients, including those with 1q abnormalities. Again, I think the same concept we've been seeing with CD38 antibodies, it can help improve outcomes for high-risk patients, but it can't bring them back to the same as standard risk.

GMMG-HD7: Study Design

- Open-label, randomized, multicenter phase 3 trial



*Cycle 1: D1, 8, 15, 22, 29; cycles 2-3: D1, 15, 29.
†Bortezomib D1, 4, 8, 11, 22, 25, 29, 32; lenalidomide Days 1-14 and 22-35; dexamethasone D1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33.
Data cutoff: April 2021.

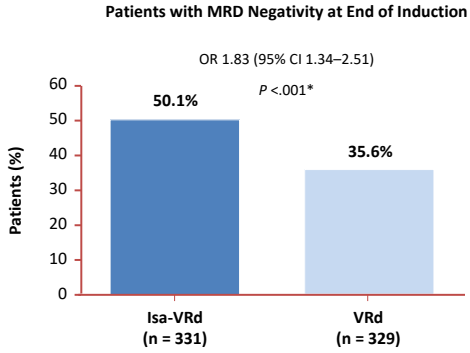
‡Cycle 1: D1, 8, 15, 22; Cycles 2-3: D1, 15; Cycle 4+: D1.
§Days 1-28. Increase dose to 15 mg after 3 mos
‖Dexamethasone D1, 8, 15, 22 in C1.

- 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

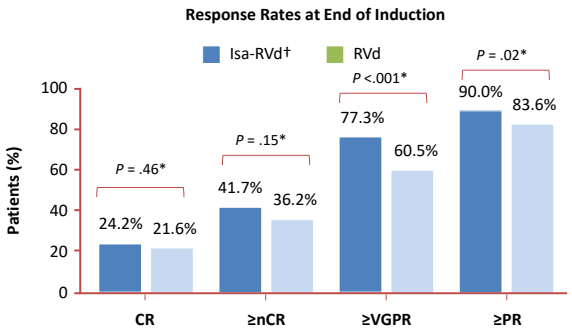
Goldschmidt H. Abstract #463. Presented at the 2021 American Society of Hematology Annual Meeting, December 12, 2021.

Of course, that is not the only anti-CD38 antibody there. We also have isatuximab. Here, we have the GMMG-HD7 study of isatuximab-RVD versus RVD.

GMMG-HD7: MRD Negativity (Primary Endpoint) and Response Rates at End of Induction



- Not assessable/missing* MRD status low: Isa-VRd, 10.6%; VRd, 15.2%

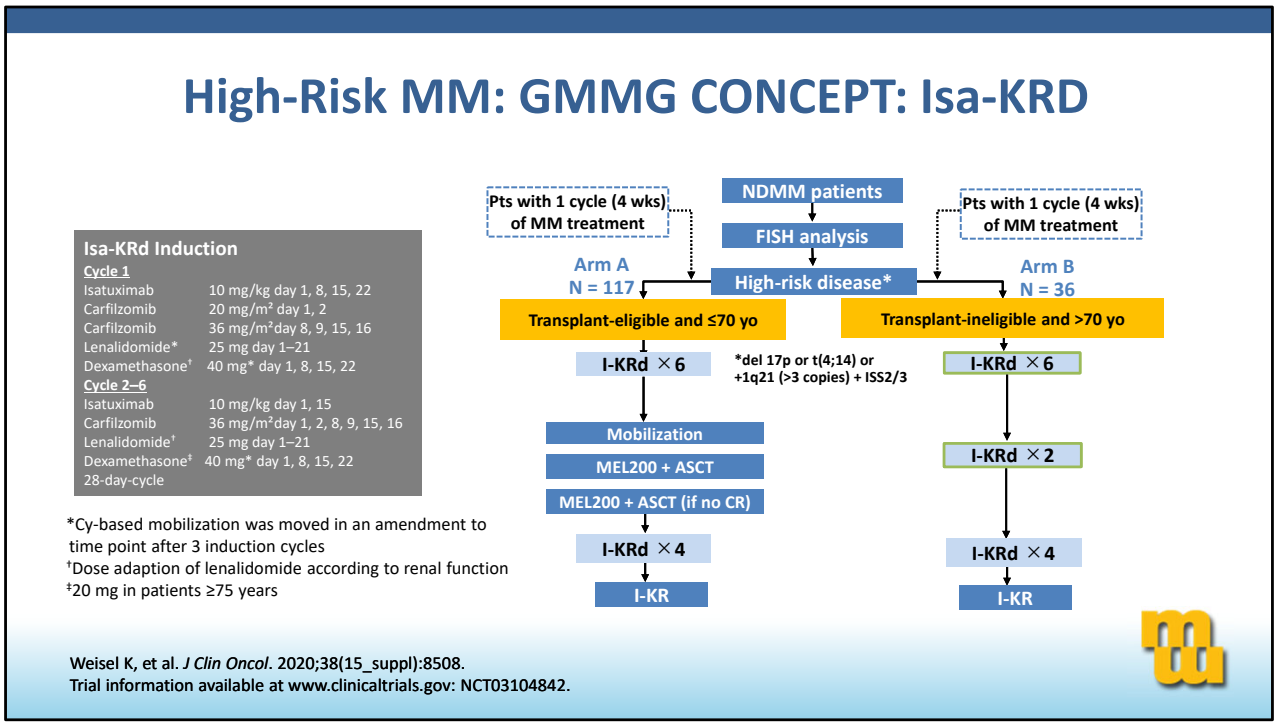


- Significant increase in ≥VGPR with Isa-VRd
- Significant increase in ORR

*Due either to loss to follow-up, missing bone marrow samples, or technical failures in measurement counted as nonresponders.

Goldschmidt H. Abstract #463. Presented at the 2021 American Society of Hematology Annual Meeting, December 12, 2021.

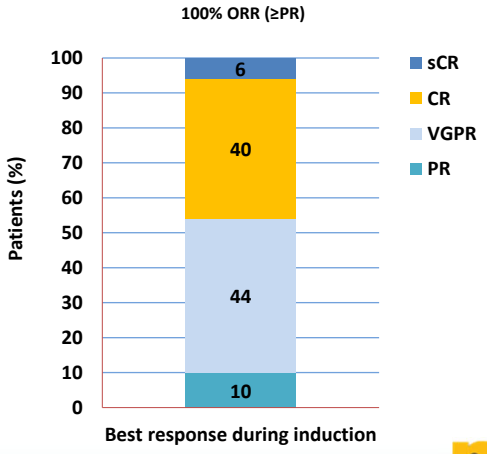
You see a same similar theme in terms of higher rates of response and deeper responses in the quadruplet arm at 50% MRD negative at the end of induction versus 35% in the VRd arm alone.



I think this is the one that I find the most interesting because it puts it all together in regards to using KRd and using an anti-CD38 antibodies. Isatuximab-KRd in the German CONCEPT study, there's both a transplant arm and a non-transplant arm using, again, intensive induction, intensive consolidation, and intensive maintenance as you can see here.

ISA-KRD: Results Post Six Induction Cycles

- All evaluable patients: n=50
- ≥ VGPR: 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n=4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable

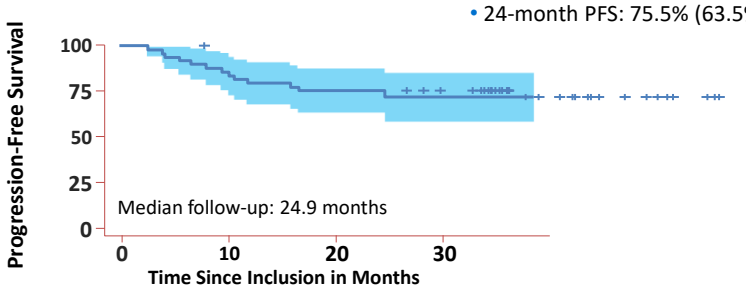


Results of MRD assessments after induction treatment are not reported and available yet.
Leypoldt LB, et al. *Leukemia*. November 3, 2021 [Online ahead of print].

What you see is a small numbers of patients in the early paper, 50 patients, but a 100% response rate with 90% of patients getting a VGPR or better.

Progression-Free Survival

- 12-month PFS: 79.6% (68.3%; 90.9%)
- 24-month PFS: 75.5% (63.5%; 87.6%)



Subjects: 50 48 44 40 39 34 25 17 9 6 1

Planned Interim Analysis of the GMMG-Concept Trial Updated Progression-Free Survival to be Reported at ASH December 11, 2022

Leypoldt LB, et al. *Leukemia*. November 3, 2021 [Online ahead of print].

This trial initial PFS was very encouraging, 79% at 12 months.

ISA-KRD: Planned Interim Analysis of the GMMG-CONCEPT Trial

Interim analysis (IA) of the primary endpoint MRD negativity after consolidation for TE-patients and the corresponding final analysis of transplant non-eligible (TNE) patients

All evaluable patients: n=125

TE –ITT Population: MRD assessment (n=93)

- 67.7% (n=63) MRD negative
- 3.2% (n=3) MRD positive
- 24.7% (n=23) time point not reached
- 4.3% (n=4) missing
- 4 patients not assessable, 2 patients did not start

TNE-ITT Population: MRD assessment in 24 patients

- 54.2% (n=13) MRD negative
- 0% MRD positive
- 45.8% (n=11) time point not reached

The primary endpoint was significantly reached in both study arms (*P*=0.0004 for TE-ITT-IA and *P*=0.012 for TNE-ITT)
Weisel K, et al. ASH 2022. Abstract 759.

This trial's going to be updated at ASH this year. This is what we know so far from the abstract that's been released, that in the transplant population now, we have a 68% MRD negative rate and 54% in the non-transplant population.

ISA-KRD: Results Post Consolidation
Planned Interim Analysis of the GMMG-CONCEPT Trial

	TE-ITT (n=99)
Overall Response Rate	94% (n=94)
≥ CR	72.7% (n=72)
VGPR	18.2% (18)
PR	4% (n=4)
PD	1% (n=1)
Time point not reached	4% (n=4)

	TNE-ITT (n=26)
≥ CR	57.7% (n=15)
VGPR	30.8% (n=8)
Unknown	3.8% (n=1)
Time point not reached	7.7% (n=2)

Weisel K, et al. ASH 2022. Abstract 759.

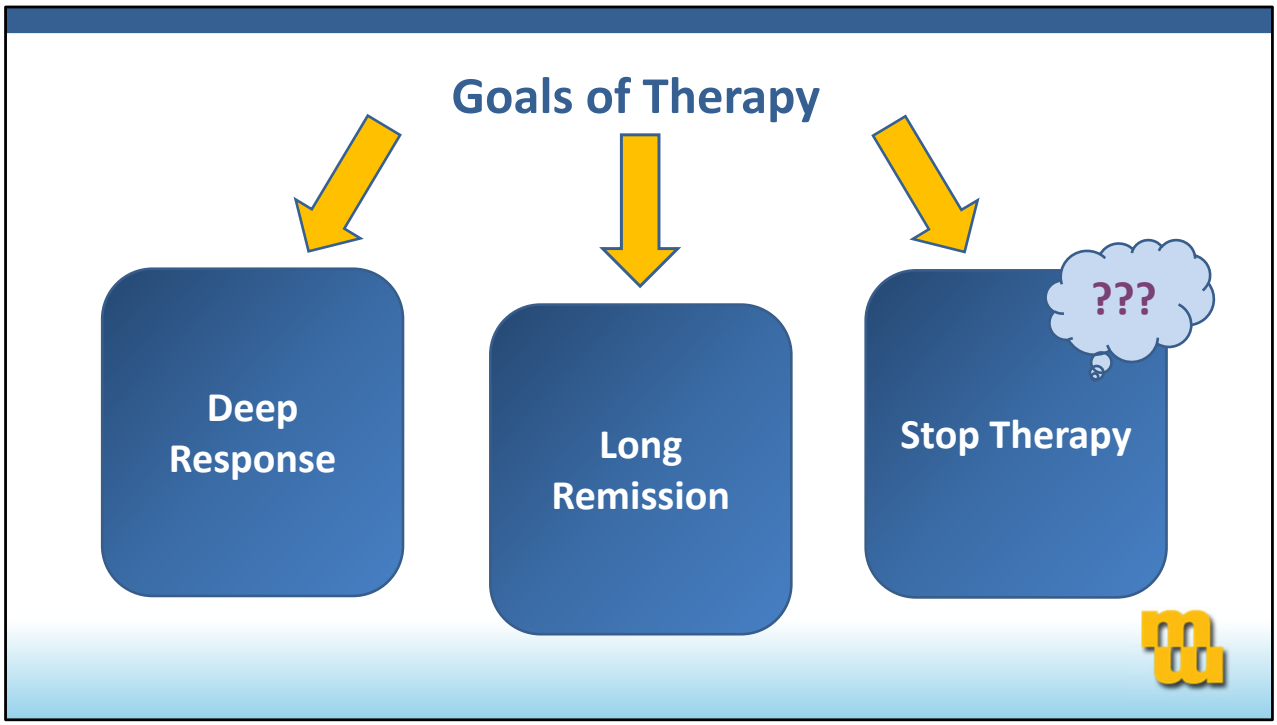
An overall response rate 94% in the transplant-eligible population.

Planned Interim Analysis of the GMMG-CONCEPT Trial: Safety Analysis

- In total, 85.2% (n=104) developed ≥ grade 3 treatment-emergent adverse events (TEAEs)
- Serious TEAEs occurred in 64.8% (n=79) of patients
- TEAEs leading to discontinuation of study treatment occurred in 5 patients

N=122
Weisel K, et al. ASH 2022. Abstract 759.

What we're really waiting for is in regards to the PFS, and they've left that as a teaser that they're going to present the updated PFS results at the ASH meeting.



We certainly will await that, but I would say that one can see here that quadruplet induction helps us get closer to our goal of a deep response and hopefully a long response. Ultimately, we also want to stop therapy.

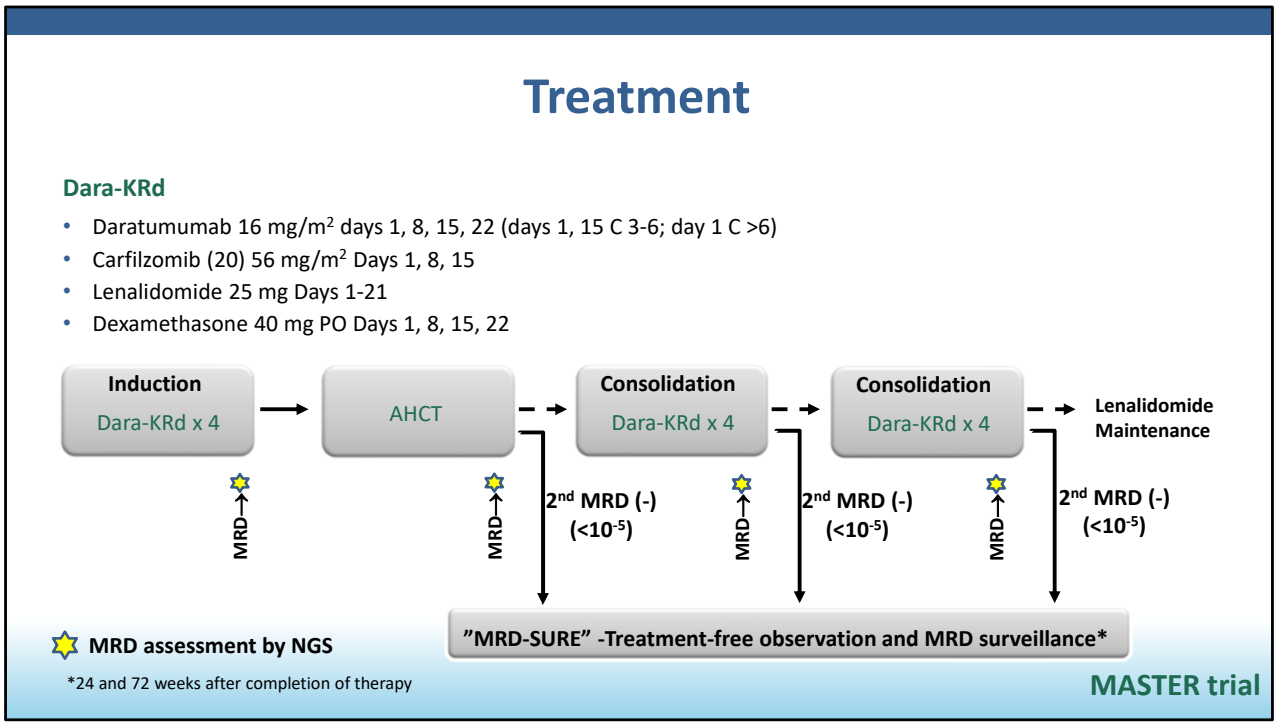
Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation-Final Primary Endpoint Analysis of the MASTER Trial

Luciano J. Costa[1], Saurabh Chhabra[2], Natalie S. Callander, MD[3] , Eva Medvedova[4], Bhagirathbhai Dholaria[5], Rebecca Silbermann[4], Kelly Godby[1], Binod Dhakal[2], Susan Bal[1], Smith Giri[1], Anita D'Souza[2], Timothy Schmidt[3], Aric Hall[3], Pamela Hardwick[1], Robert F. Cornell[5], Parameswaran Hari[2]

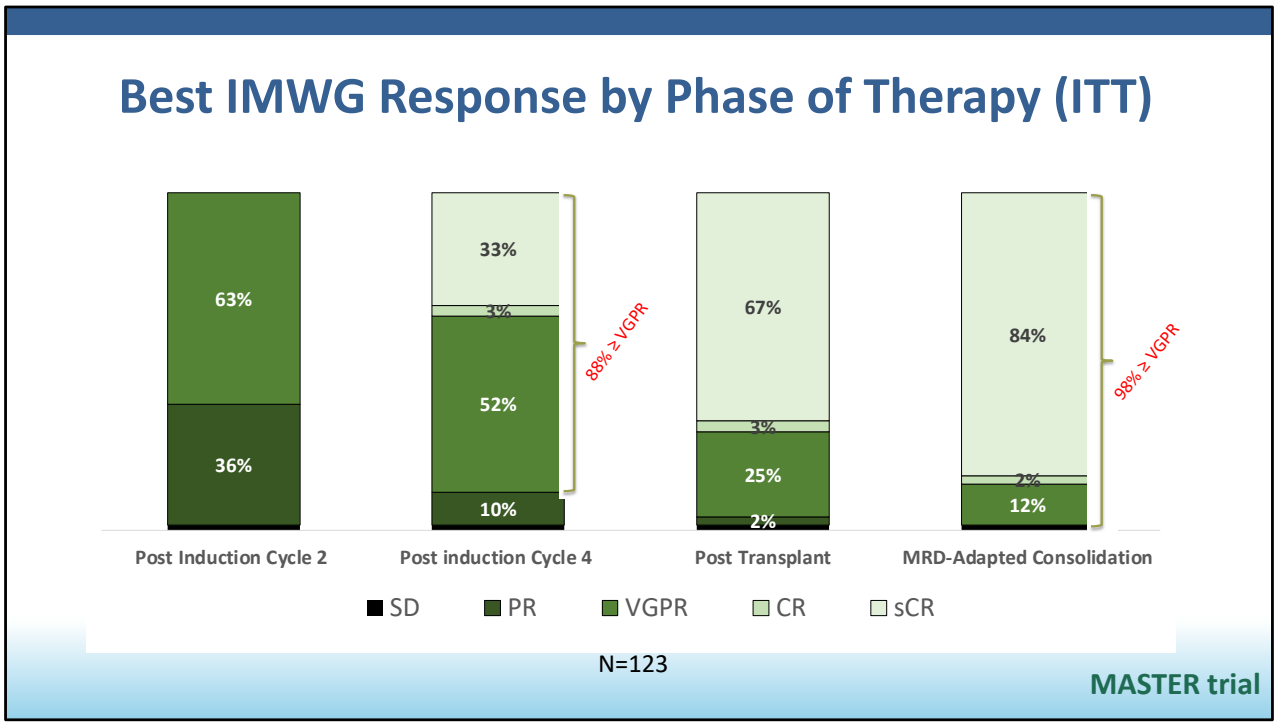
1- University of Alabama at Birmingham; 2- Medical College of Wisconsin; 3- University of Wisconsin at Madison;
4- Oregon Health and Science University; 5- Vanderbilt University

COMMIT- Academic Consortium to Overcome Multiple Myeloma through Innovative Trials

We have the MASTER study of using MRD to help guide us in regards to stopping therapy.

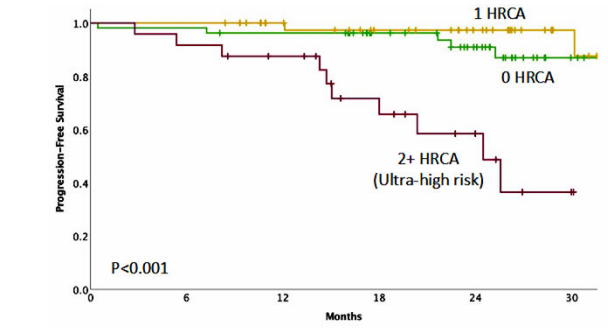


Very intensive induction, daratumumab KRd transplant, daratumumab KRd consolidation, and then lenalidomide maintenance with MRD at multiple time points. I do point out that the MRD is to 10^{-5}.



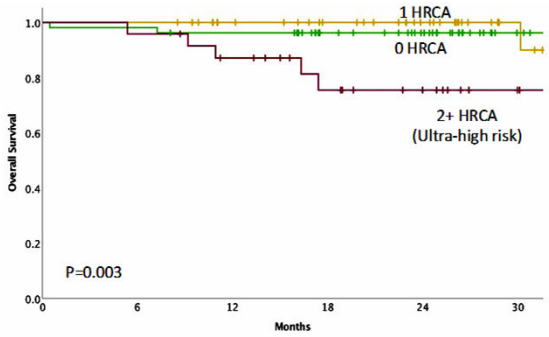
You can see that certainly with this intensive regimen, you get very high response rates and high depth of response as well, 98% of patients' VGPR are better by the time they get to consolidation.

Progression-Free and Overall Survival



No. at risk:						
0 HRCA	50	49	46	36	27	10
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	22	19	12	7	2

2-year PFS
0 HRCA 91%
1 HRCA 97%
2+ HRCA 58%



No. at risk:						
0 HRCA	50	49	46	36	29	11
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	23	19	13	9	3

2-year OS
0 HRCA 96%
1 HRCA 100%
2+ HRCA 76%

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

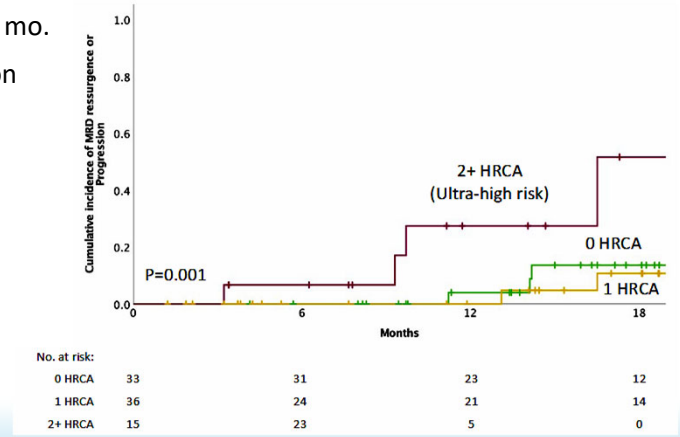
MASTER trial

You can see that certainly a very encouraging progression-free survival in patients with zero or one high-risk cytogenetic abnormality.
Challenging still in regards to those ultra high-risk patients with two or more high-risk cytogenetic abnormalities.

MRD-SURE

- 84 patients achieved MRD-SURE
- Median follow up in MRD-SURE: 14.2 mo.
- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA – 4%
  - 1 HRCA – 0%
  - 2+ HRCA – 27%
- **None** of patients entering MRD-SURE died from MM progression

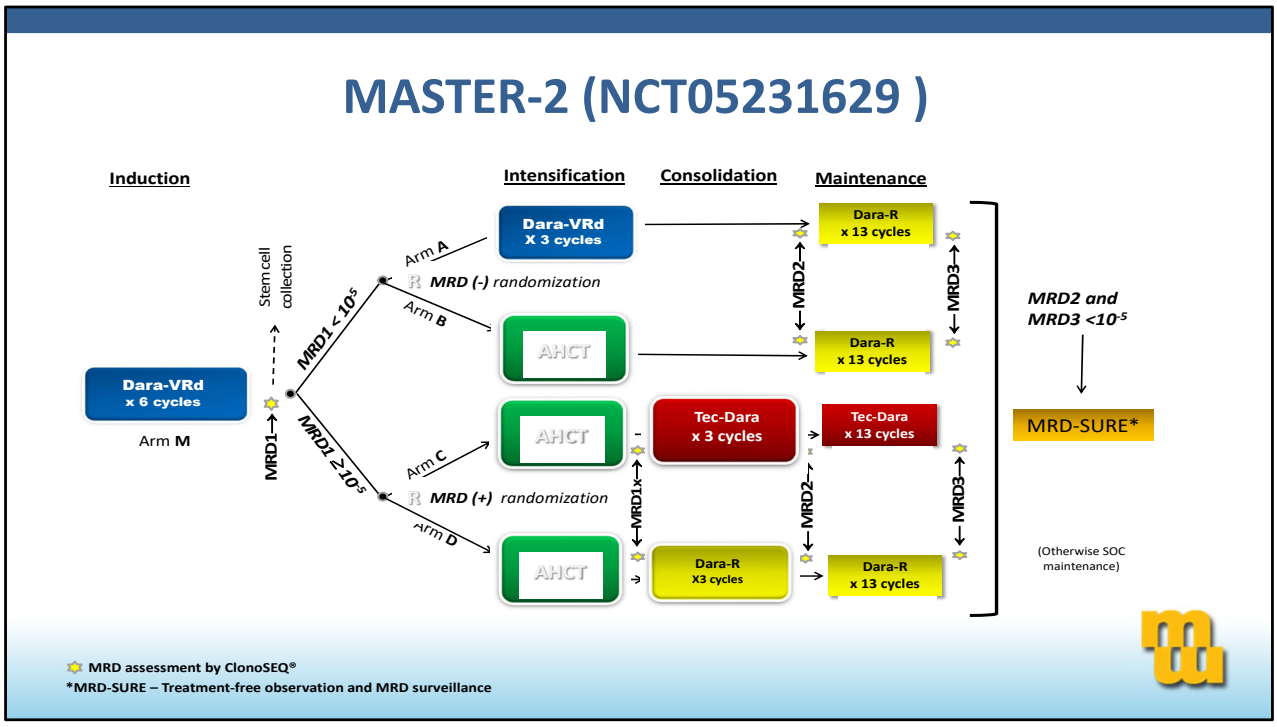
Cumulative incidence of MRD resurgence or progression



HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

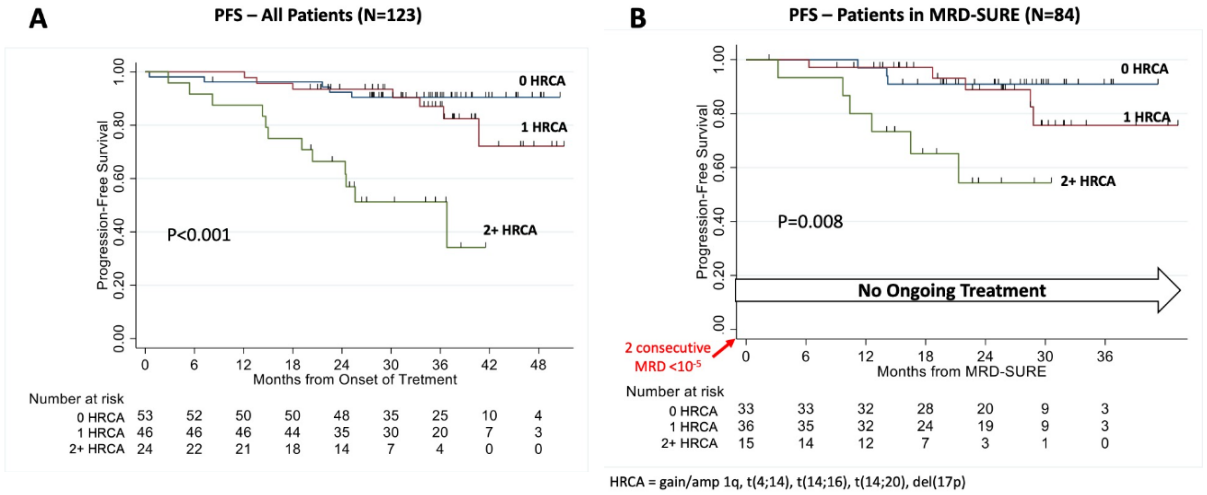
MASTER trial

I think this is probably the most important point of this to me is even if you become MRD negative in a high-risk cytogenetic, ultra high-risk patients, unfortunately, stopping therapy in that group of patients, they have a very high rate of MRD resurgence or progression. It says that for that group of patients, we still need to think about new treatment approaches.



Here is one of the teasers of one of the proposed new treatment approaches. The MASTER 2.0 which you can see here, is now incorporating T-cell engagers as part of that consolidation approach. Again, interesting, and we'll see the future of how that may influence us being able to stop therapy.

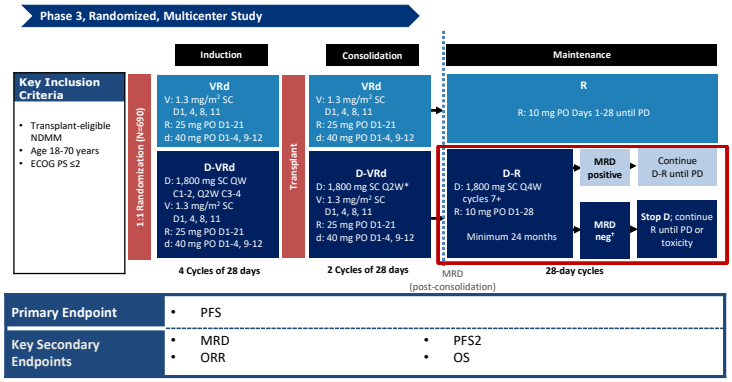
Outcomes of MRD-Adapted Treatment Modulation in Patients with NDMM Receiving Dara-KRd and Autologous Transplantation: Extended Follow-up of the MASTER Trial



HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20), del(17p)

This is the extended follow up from the MASTER studies showing the same idea, again, that the two more high-risk genetic abnormalities still have a very much lower PFS even in those who become MRD negative.

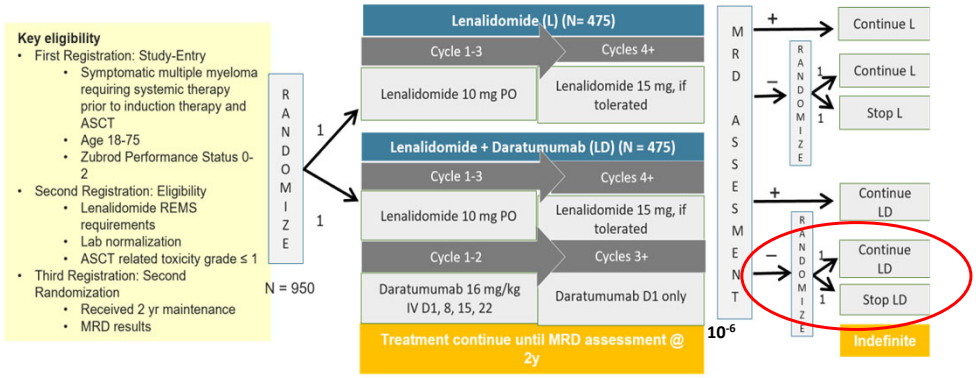
PERSEUS: A Phase 3 Study Comparing D-VRd vs VRd in Patients Transplant-Eligible NDMM: Ex-US Study



*Patients with a post-ASCT recovery period >12 weeks off DARA SC should restart DARA SC Q2W for 2 cycles, then Q4W thereafter.
†If ≥1 year of sustained MRD negativity, restart DARA SC (QW for 8 weeks, Q2W for 16 weeks, Q4W thereafter) at the time of loss of MRD negativity or relapse from CR.
C, cycle; CRAB, calcium, renal, anemia, bone; D, daratumumab; d, dexamethasone; D#, day; MM, multiple myeloma; PD, progressive disease; QW, every week; Q2W, every 2 weeks; R, lenalidomide; SC, subcutaneous; V, bortezomib.
Sonneveld P, et al. ASCO 2019. Poster presentation. Abstract TPS8055. NCT03710603.

We still are interested, though, in stopping therapy. We have the PERSEUS study. We're waiting to get a readout on that. The primary input was PFS. The interesting part of this study was the randomization to Rev (lenalidomide) or daratumumab, Rev maintenance. Then MRD assessment, and then patients being able to come off of at least the daratumumab but maintained on both arms, maintained on Rev to see at least if you can deescalate. It doesn't completely stop therapy, but again, another idea of using MRD to help guide our therapy.

DRAMMATIC: SWOG S1803



Primary endpoint

- Overall survival (OS) and will be compared between patients randomized to L vs LD

Peter Voorhees

Then the SWOG, a dramatic study, in fact does stop therapy. Patients get any induction, get a transplant, get randomized to lenalidomide, daraumumab or lenalidomide alone. At two years, they have another MRD assessment. Those patients who are MRD negative are randomized to either continuing or stopping therapy on their assigned arm. This, it would say, in a true randomized fashion will help us answer this question about can you stop therapy if you get a deep response?

Again, I'd like to acknowledge all my colleagues at our Briskin Myeloma Center. It truly takes a village to treat myeloma. Thank you.

Saad Usmani: Thank you so much, Dr. Krishnan for such an outstanding overview of everything that's going on in a very busy transplant-eligible patient population. I think there are other strategies that will likely be incorporated, things that we have not included is how the bispecifics are planned in that frontline strategy. Perhaps, in another year or two, we're going to be talking about some of that information.

Amrita Krishnan: I would tell you, certainly for MajesTEC-7, for example, in regard to Tec (teclistamab), daratumumab, lenalidomide versus daratumumab, lenalidomide, dexamethasone, I think will be a very interesting study for us.

Saad Usmani: I completely agree.

Conclusions

- Risk stratification is important in directing therapy for NDMM
- High-risk patients have improved PFS with upfront HCT consolidation c/w RVD alone as per the DETERMINATION study
- Addition of daratumumab appears to benefit patients with 1q gain/ amplification and IHRCA in the updated analysis of GRIFFIN
  - But ultra high-risk ≥2hRCA do not have the same benefit and new approaches are needed
  - Even ultra high-risk who achieve MRD SURE as per the MASTER trial have a high rate of disease recurrence

Just to summarize things for our audience the field is fairly dynamic right now. I think one thing that we agree upon as a principal is trying to get patients into as good a response as possible with the optimal strategy from the time they're diagnosed onwards. Does not matter if they're transplant eligible or not. Even that definition is going to be changing in the future as CAR T-cell therapies and even the bispecific antibodies, which we did not talk about much during this conversation that these are strategies that are making their way into the frontline treatment, and the conversation will likely evolve around our optimal strategies for those frontline treatments. Then the other point, Dr. Krishnan, I'm going to highlight it, is we will try to move towards more tailored treatment between standard and high-risk patients, and even thinking about defining duration of treatment for patients. Dr. Krishnan, any other thoughts from our discussion so far?

Amrita Krishnan: I think just the speed of which the field is moving is pretty remarkable that we had our first bispecific specific T-cell engager approved in October 2022. We're already talking now about trials, using it in the frontline setting. I think that is fantastic for patients. I think some of this is a learning curve, though, the same way when some of the other drugs first came out. For example, with T-cell engagers and the infection risk. Again, as we use it in the frontline setting, I think this idea of stopping therapy after fixed duration will be also important because we obviously want to maximize benefit and minimize risk.

Conclusions

- Risk stratification is important in directing therapy for NDMM
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Saad Usmani: Then just thinking about we have the ASH meeting with a lot of new data being presented, and many of us are going to be there live. For the last few years, we've seen a lot of focus on BCMA as a target of different modalities. What do you think are the more exciting things that you're going to be looking forward to at ASH Dr. Krishnan?

Amrita Krishnan: I think the data on the FcRH5 targeting the drug cevostamab is going to be very interesting. That's probably underrepresented target. I think the nice thing about the cevo is the data that's going to be presented at ASH of discontinuing and continued responses in patients even when they're off therapy, which is very encouraging for us. Obviously, GPRC5D is the other new kid on the block. Now, we actually have two bispecific T-cell engagers targeting GPRC and also CAR T targeting GPRC5D. I think that certainly is a great interest. The future discussions are going to be how do you sequence these bispecific T-cell engagers, and how do you sequence CAR T in that mix as well?

Saad Usmani: I agree. It was actually good to see several GPRC5D targeting strategies. Then, for BCMA, I was also intrigued by some of the combination data that's going to be shared beyond just the antibody-antibody combinations. I think there's a BCMA anti-CD38 IMiD combination data that's also being shared. I'm really looking forward to that because that lays the platform for frontline strategies for some of the patient populations that we talked about in our discussion.