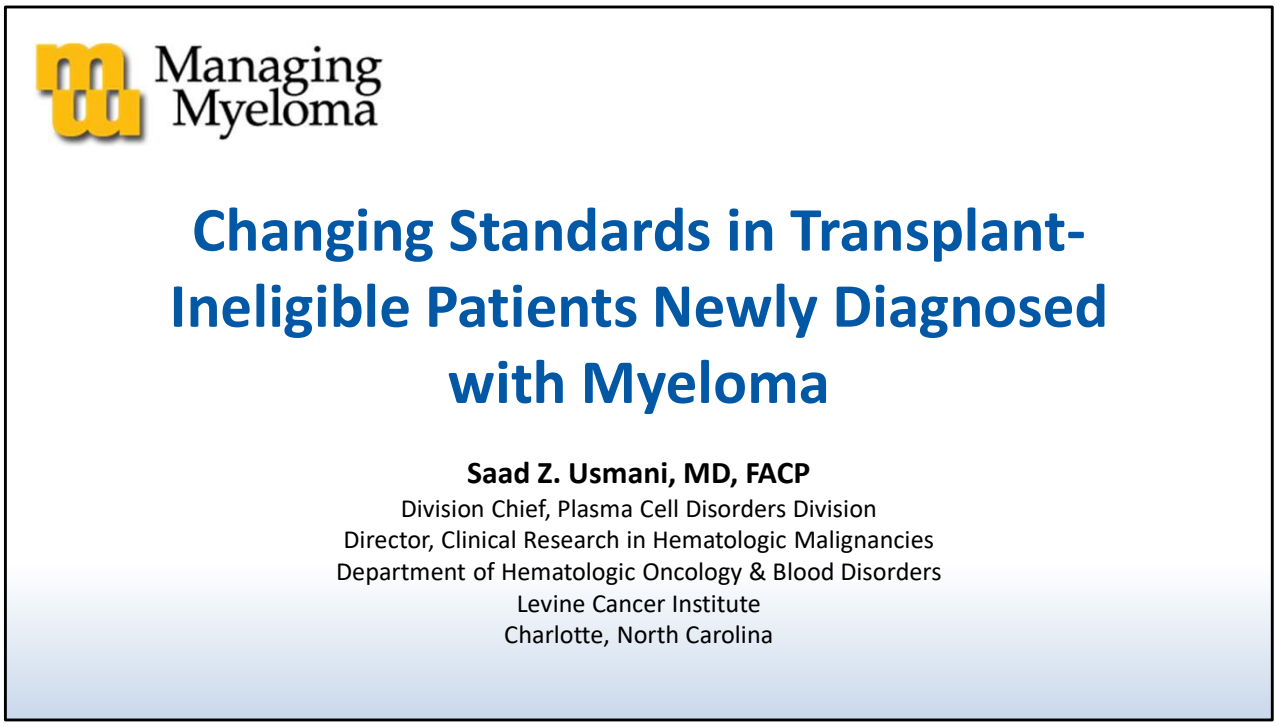
Changing Standards in Transplant-Ineligible Patients Newly Diagnosed with Myeloma



Hello, and welcome to *Managing Myeloma*. I'm Dr. Saad Usmani, and today I will be discussing current developments in frontline treatment of multiple myeloma, specifically, including patients who are transplant ineligible.

Changing Standards in Transplant-Ineligible Patients Newly Diagnosed with Myeloma

Disclosures

- Dr. Saad Usmani has received honoraria related to speakers' bureau activities from Celgene Corporation – A Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Sanofi, and Takeda Oncology, as well as formal advisory activities from AbbVie Inc., Amgen Inc., Bristol-Myers Squibb Company, Celgene, GlaxoSmithKline plc, Janssen, Merck & Co., Inc., Sanofi, Seattle Genetics, Inc., Skyline Diagnostics B.V., and Takeda Oncology. He has received grant support related to research activities from Amgen, Array BioPharma, Bristol-Myers Squibb, Celgene, Janssen, Merck, Pharmacyclics, Inc., Sanofi, Skyline Diagnostics, Seattle Genetics, and Takeda Oncology.

Here are my disclosures

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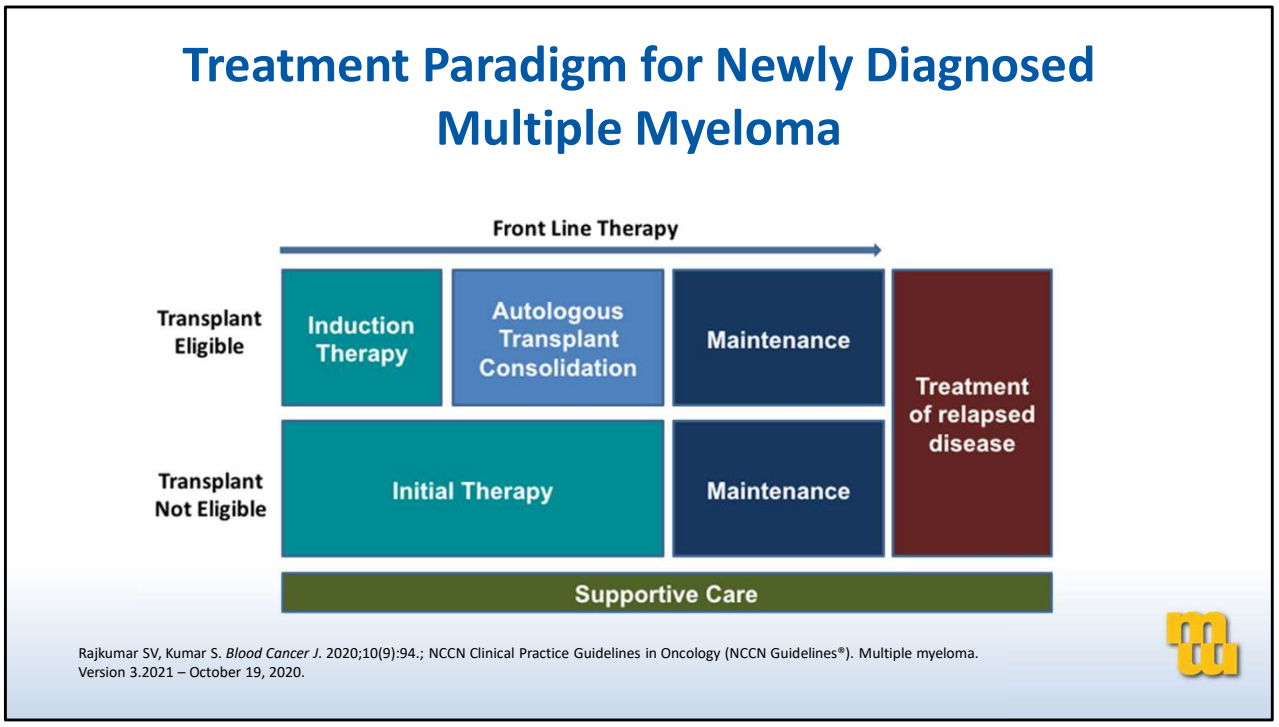

One thing that we all appreciate is that the paradigm for newly diagnosed myeloma treatments has evolved over the past decade. Generally, when patients are newly diagnosed, we are taking them through induction therapy with three drugs. We evaluate them for transplant eligibility, and the ones who are transplant eligible go on to receive high-dose melphalan with autologous stem-cell transplantation, and this is followed by maintenance treatment. Whereas for the transplant-ineligible patients, they continue therapy to response plateau or tolerability and then move on to maintenance treatment. And during this whole time period, we're also providing them supportive care for infection control and prevention, bone health, pain management, and trying to alleviate the sequelae of disease at the time of presentation. And after patients enjoy a period of disease-free interval, if they relapse, we go through the same exercise of evaluating their disease burden and making their treatment choices while paying attention to the supportive care.

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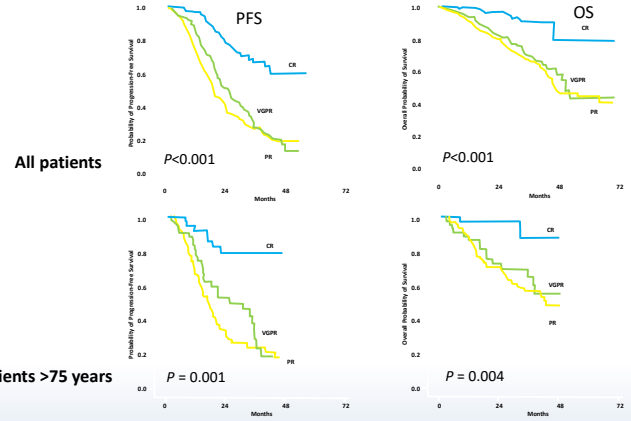
Deeper Response = Better Outcome

Retrospective Analysis: Three Randomized Trials of GIMEMA and HOVON (N = 1175)

First-line treatment: MP (n = 332), MPT (n = 332), VMP (n = 257), VMPT-VT (n = 254)



MP=melphalan-prednisone; MPT=melphalan-prednisone-thalidomide; VMP=melphalan-prednisone-bortezomib; VMPT=melphalan-prednisone-bortezomib followed by bortezomib-thalidomide maintenance.

Gay F, et al. *Blood.* 2011;117:3025-3031.

One of the very important lessons we've learned over time is that deeper responses in the frontline setting are important, not just for transplant eligible patients as well as for transplant-ineligible patients. This particular publication is over nine years old, but had looked at three randomized trials looking at transplant-ineligible patients, demonstrating that patients who achieve a complete response have better PFS as well as overall survival. And within this paper, the authors looked at patients who were 75 or older and found the same to be true. Depth of responses are important for all myeloma patients regardless of how old they are or what comorbidities they may have, because they do correlate with survival outcomes for newly diagnosed patients.

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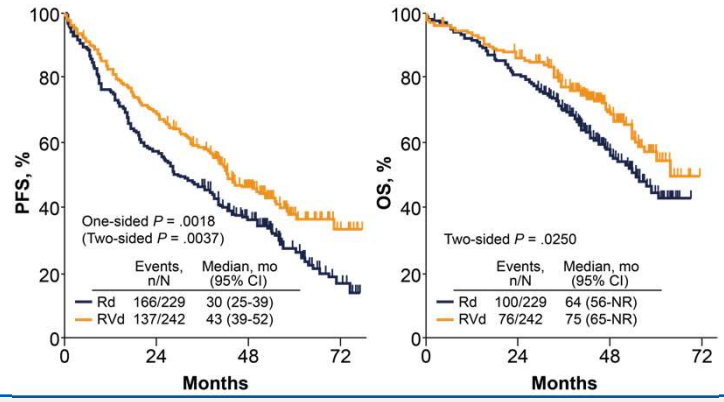
SWOG S0777: RVd Versus Rd in Patients Without Immediate Intent for ASCT



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.

Let me walk you through where we have come from and where we're heading in myeloma therapy. I had mentioned that three-drug combinations are preferred for transplant-ineligible patients. A lot of this data stems from the SWOG 777 trial that had looked at the combination of RVd for induction versus Rd for induction in patients without immediate intent for autologous stem-cell transplant, demonstrating superior PFS as well as overall survival in favor of the three-drug combination. By the time this study actually read out, many of us in clinical practice were utilizing three-drug combinations for most of our patients, but this simply affirmed the fact that we actually were doing the right thing and need to expand this three-drug combination practice to all myeloma patients in the frontline setting. There are always going to be exceptions with older frail patients, and I'll get to some of those discussions towards the end of my talk. But this kind of sets the stage of where we are with standard of care.

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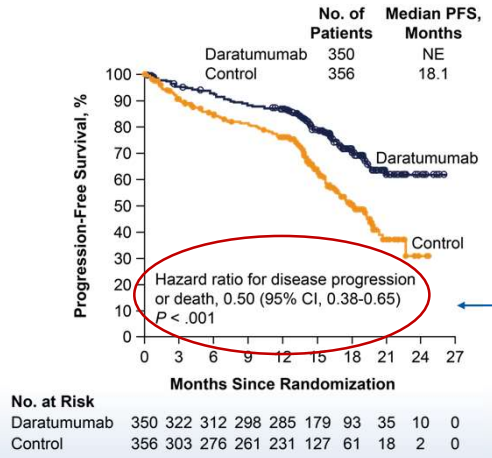
Daratumumab Plus VMP in NDMM (ALCYONE): PFS Outcomes



Prespecified subgroup analyses of PFS showed that the superiority of daratumumab + VMP was consistent across all subgroups, including

- Patients aged ≥75 y
- Those with poor prognosis: ISS disease stage III, renal impairment, or high-risk cytogenetic profile

50% reduction in risk of progression or death in daratumumab/VMP arm

May 2018: daratumumab + VMP is FDA approved for the treatment of patients with NDMM who are ineligible for ASCT

Mateos MV, et al. *N Engl J Med*. 2018;378:518-528.

And then we are entering a phase where now we have had anti-CD38 monoclonal antibody daratumumab move from the late relapse setting to early relapse, and now newly diagnosed setting. ALCYONE was the first trial that randomized patients with transplant-ineligible disease to either receiving VMP as standard of care versus dara-VMP for nine cycles, and then daratumumab was continued in the experimental arm beyond that as a maintenance every four weeks. Even though VMP is not a treatment of choice in the US, it is still a valid regimen in Europe. And what was good to see in this study beyond the fact that adding daratumumab to the frontline induction improves depth of response as well as progression-free survival, but this study actually demonstrated an improvement in overall survival as well.

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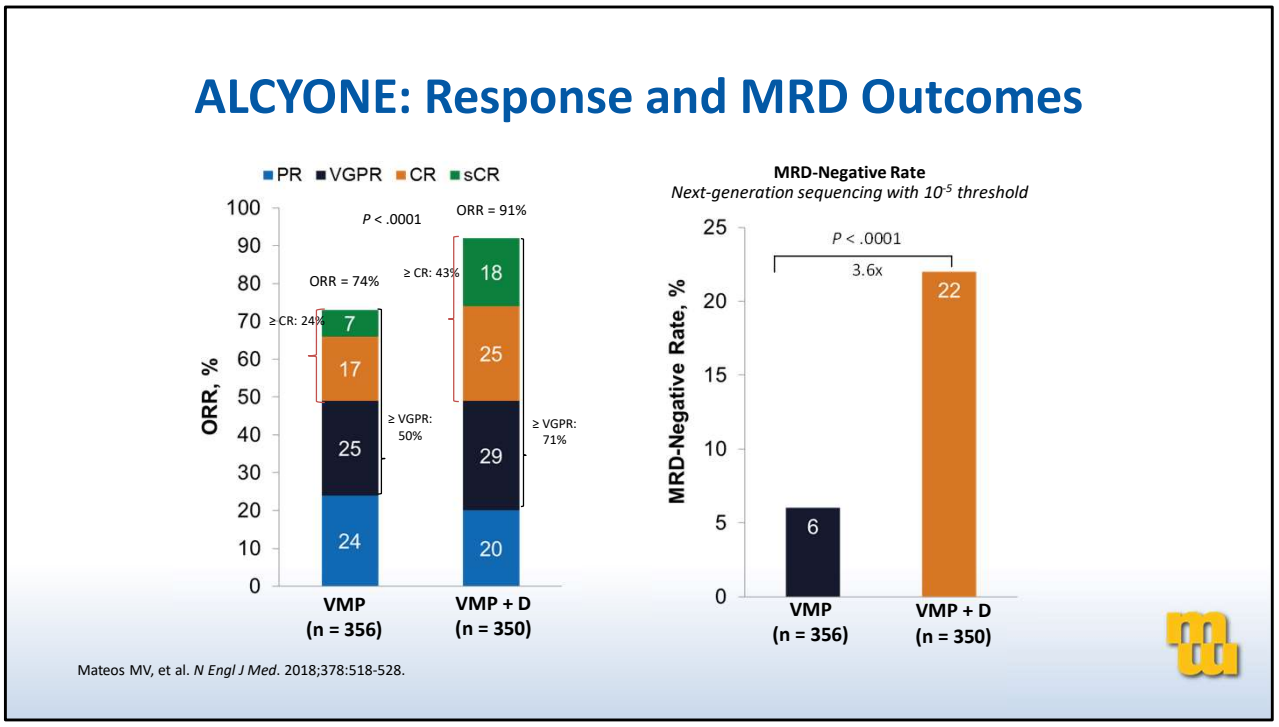

Let me walk you through the responses here. The overall response rate in the dara arm was 91% with 71% of patients achieving VGPR or better. Whereas the overall response rate in the VMP arm was 74% with about 50% of patients reaching VGPR. But MRD negativity was over threefold higher in the daratumumab arm at 10^{-5} and this translated into a PFS benefit.

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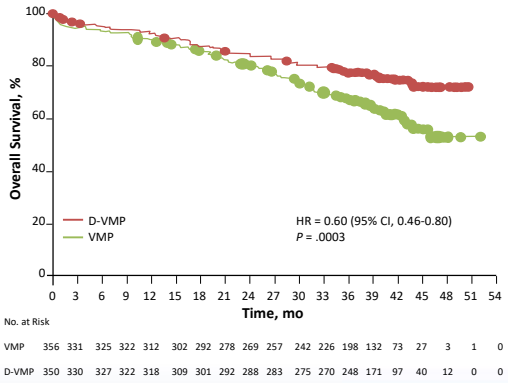
ALCYONE Update: Daratumumab + VMP as Primary Therapy in Nontransplant Candidates

- D-VMP prolonged OS in patients with NDMM ineligible for stem-cell transplantation
- With more than 3 years of follow-up, the D-VMP group continued to show significant improvement in progression-free survival, with no new safety concerns



Mateos MV, et al. *Lancet*. 2020;395(10218):132-141.

And after a median follow-up of over three years, there was overall survival benefit being observed in the daratumumab arm and this is now published in *Lancet* earlier this year with Maria-Victoria Mateos being the first author. So demonstrating the first trial that has incorporated daratumumab in the frontline setting in the transplant-ineligible candidates showing overall survival benefit.

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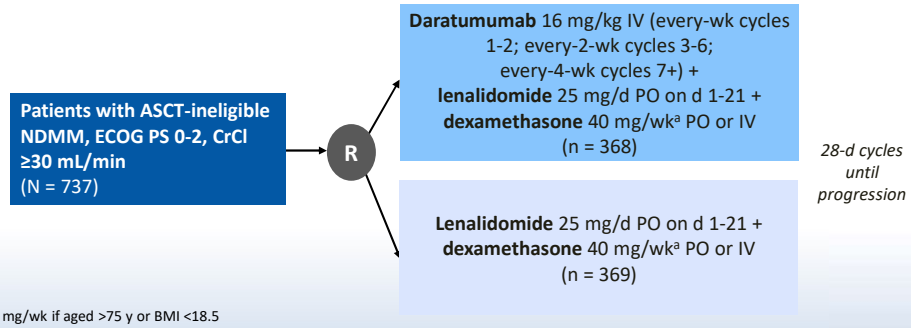
Phase 3 MAIA Study: Daratumumab Plus Rd in NDMM

- 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.

Perhaps the more relevant clinical trial to the US practice is the MAIA study which compared daratumumab/len/dex to len/dex. And this study continued treatment on both arms until disease relapse progression or intolerance, and a total of 737 patients were enrolled in this study and, of note, 44% of the patients enrolled in the study were 75 or older.

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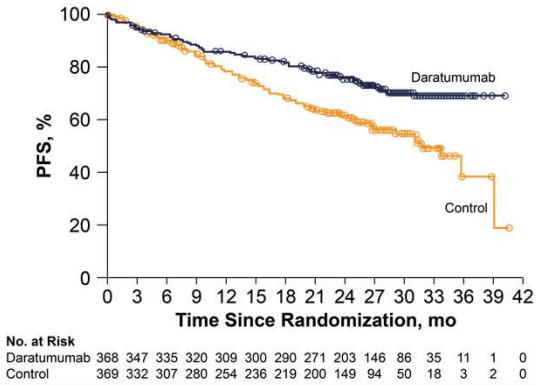
Phase 3 MAIA Study: PFS



	Patients, n	Median PFS, mo
Daratumumab	368	NR
Control	369	31.9
HR for progression or death: 0.56 (95% CI, 0.43-0.73)		
P < .001		

Based on these findings, the FDA approved daratumumab + Rd for use in transplant-ineligible patients with newly diagnosed MM[2]

Facon T, et al. *N Engl J Med*. 2019;380:2104-2115.

This trial demonstrated a PFS benefit in favor of the DRd arm. The median PFS on the DRd arm has not been reached and the control arm was about 32 months. And based on these results, they have approved the combination of dara/len/dex for transplant-ineligible patients, and this paper was published last year in the *New England Journal of Medicine.* So this regimen is probably the most relevant to the US practice as we think about the older myeloma patients.

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Phase 3 MAIA Study: Response and Safety

- Most common grade 3/4 AEs: neutropenia (50.0% vs 35.3%), anemia (11.8% vs 19.7%), lymphopenia (15.1% vs 10.7%), and pneumonia (13.7% vs 7.9%)

Response, %	Daratumumab	Control
ORR	92.9	81.3
≥ CR	47.6	24.9
MRD negativity ($<10^5$)	24.2	7.3

P < .001 for all comparisons

Facon T, et al. *N Engl J Med*. 2019;380:2104-2115.

The overall response rates and depth of response including CR or better as well as MRD negativity rates were statistically significantly higher in the daratumumab arm. The most common grade 3 or 4 adverse events included hematologic toxicities, such as neutropenia, anemia, and pneumonia. Bearing in mind that this is a transplant-ineligible patient population, paying attention to infection control and providing patients appropriate dose adjustments and growth factor support is going to be an important key for this particular regimen.

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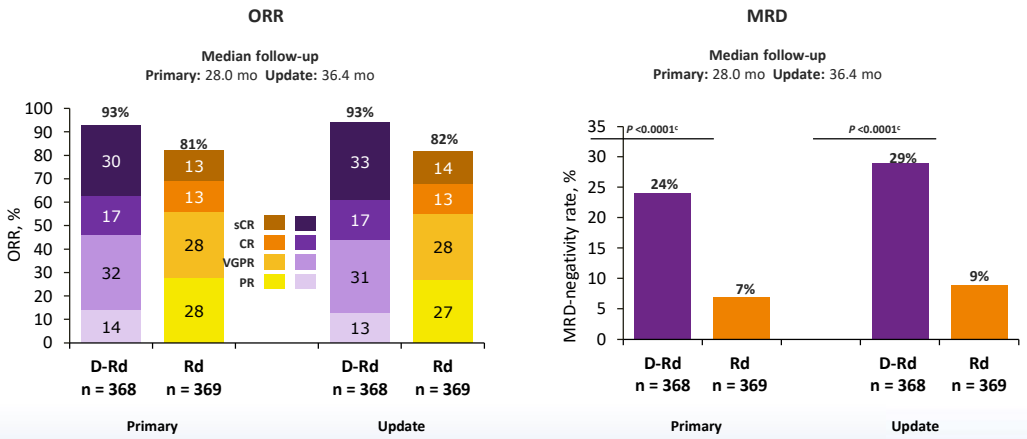
MAIA Updated Efficacy: Depth of Response



ORR=overall response rate; sCR=stringent complete response; VGPR=very good partial response; PR=partial response
Bahlis N, et al. *Blood.* 2019;134(Supplement_1):1875.

Now, looking at the overall response rate, what we find that with subsequent follow-up, so for the original paper the median follow-up was 28 months, but with a follow-up of 36.4 months, these data were reported at ASH last year, demonstrate deepening of responses. MRD negativity rates went up from 24% to 29% in the daratumumab arm of the MAIA trial. These are important data and help us inform that a dara-based triplet is a very reasonable option for older myeloma patients.

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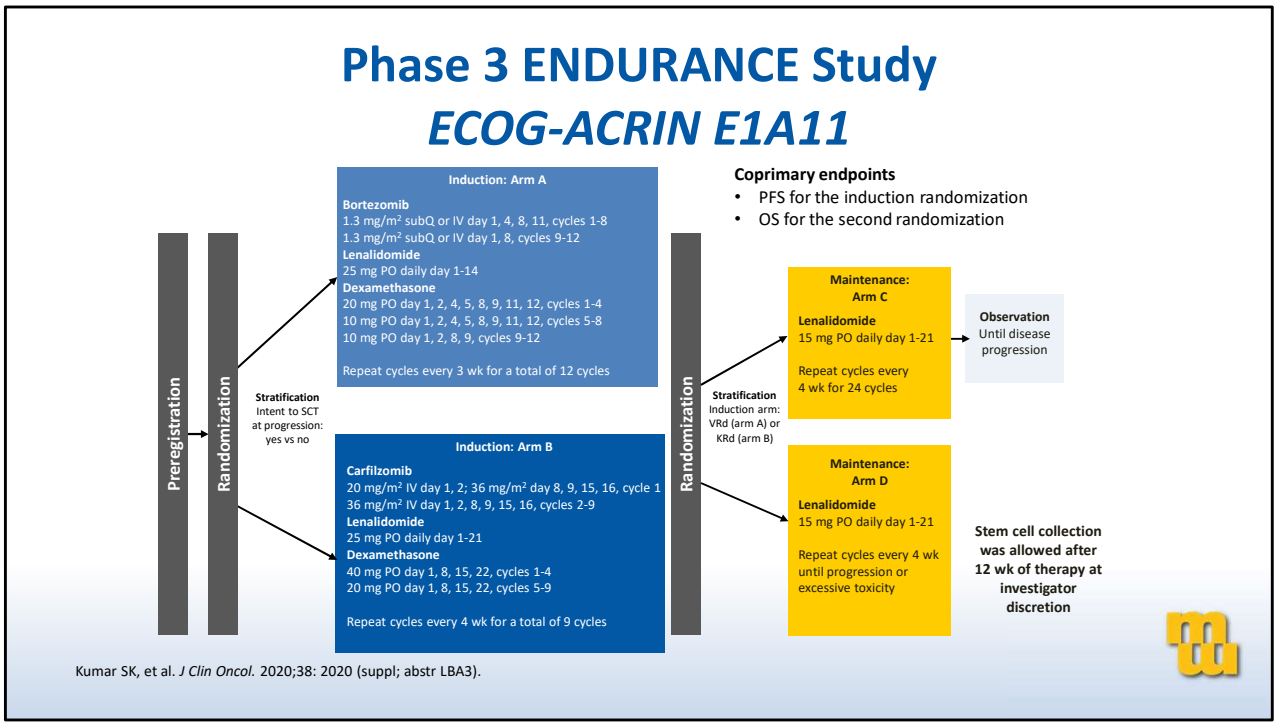

Kumar SK, et al. *J Clin Oncol.* 2020;38: 2020 (suppl; abstr LBA3).

Now, another very important question that was answered this year was, which proteasome inhibitor should we use for newly diagnosed patients who have standard risk disease? So the ENDURANCE trial, which was the ECOG-ACRIN E1A11 study was a randomized phase three study, the largest of its kind that's been done in the US cooperative group setting, comparing VRd as induction or KRd, carfilzomib/len/dex as induction, and the second randomization was to either continuing maintenance for 24 months or continuing maintenance until relapse progression or intolerance. Now, the initial report that was presented at ASCO looked at data from the first randomization so really trying to answer the question, which proteasome inhibitor is better for standard risk patients in the newly diagnosed setting.

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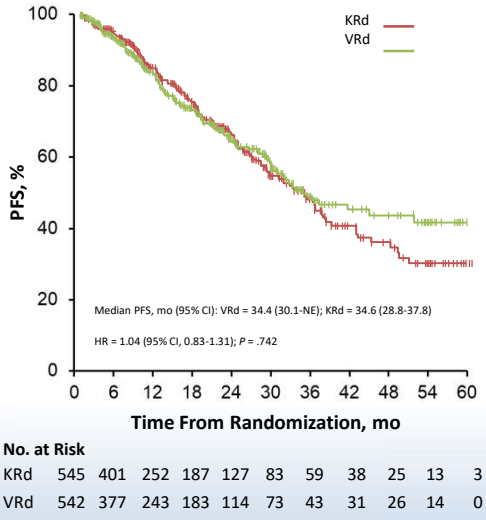
ENDURANCE: PFS From Induction Randomization

- Second interim analysis of PFS (January 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow-up of 15 mo (13-18)
- For patients aged ≥70 y, median PFS (95% CI) for VRd = 37 mo (29-NE) and KRd = 28 mo (24-36)
- With censoring at SCT or alternative therapy: median PFS (95% CI) for VRd = 31.7 mo (28.5-44.6) and KRd = 32.8 mo (27.2-37.5)



No. at Risk

KRd	545	401	252	187	127	83	59	38	25	13	3
VRd	542	377	243	183	114	73	43	31	26	14	0

Kumar SK, et al. *J Clin Oncol.* 2020;38: 2020 (suppl; abstr LBA3).

And at the interim analysis, there were no differences observed in the two arms of the study. I do want to highlight that patients who were 70 years or older had a median PFS on the VRd arm of 37 months compared to 28 months and this is relevant to our patient population, that standard of care. So, the PI perhaps does not make a big difference. Another way of looking at this data overall is patients who have reasons why they cannot get bortezomib as the proteasome inhibitor. It's okay for carfilzomib to be used in place such as, you know, patients who already have pre-existing neuropathy as an example.

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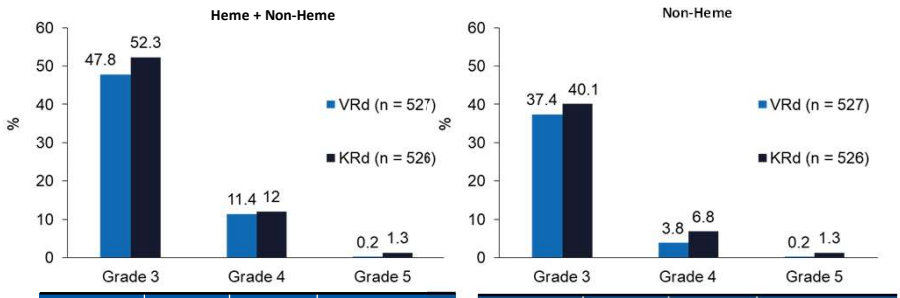
ENDURANCE: Treatment-Related Adverse Events



Step 1 Treated Patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-VRd	Chi Square *P*
Grades 3-5	313 (59.4)	345 (65.6)	6.2	.038
(95% CI)	(55.1-63.6)	(61.3-69.6)	–	–
Grades 4-5	61 (11.6)	70 (13.3)	1.7	.394
(95% CI)	(9.0-14.6)	(10.5-16.5)	–	–

Step 1 Treated Patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-VRd	Chi Square *P*
Grades 3-5	218 (41.4)	254 (48.3)	6.9	.024
(95% CI)	(37.1-45.7)	(44.0-52.6)		
Grades 4-5	21 (4.0)	43 (8.2)	4.2	.004
(95% CI)	(2.5-6.1)	(6.0-10.9)		

Kumar SK, et al. *J Clin Oncol.* 2020;38: 2020 (suppl; abstr LBA3).

As one would expect, treatment-related adverse events, looking at the pattern, we find that numerically the numbers are higher on the KRd arm in terms of grade 3 toxicities for both heme as well as non-heme adverse events.

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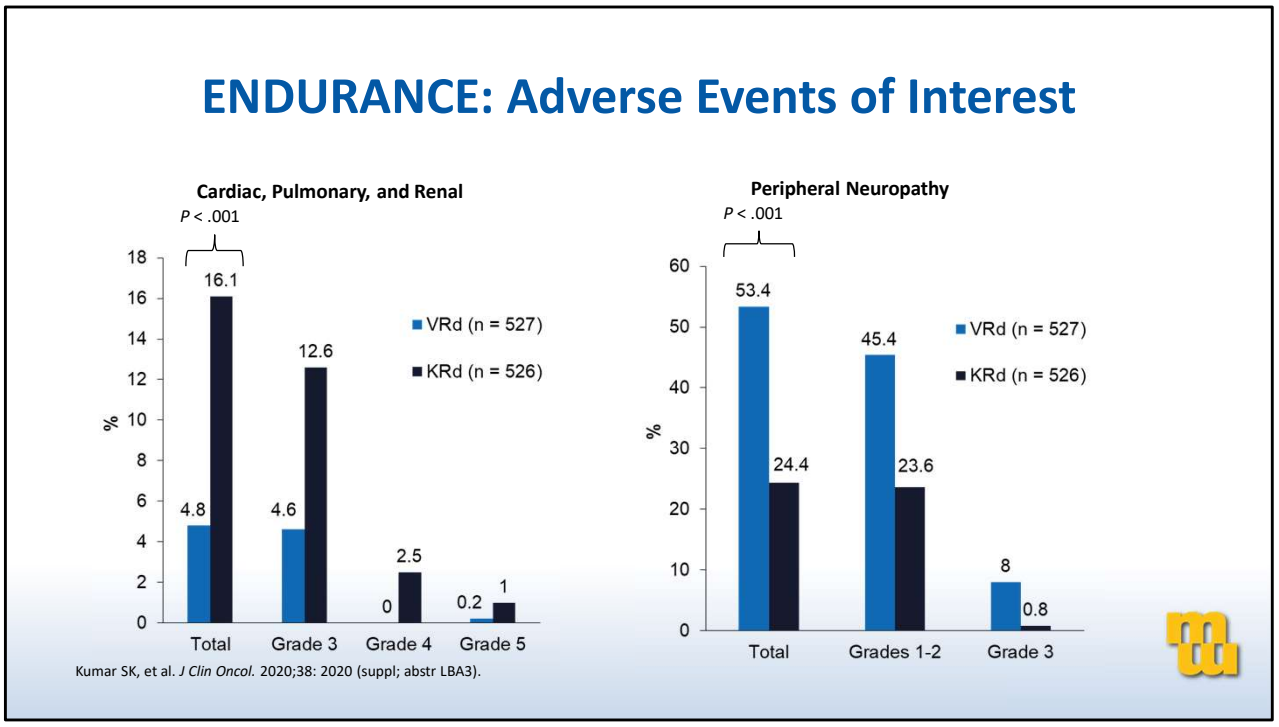

More importantly, cardiopulmonary and renal issues were seen more commonly in the KRd arm, whereas neuropathy was seen more commonly on the VRd arm again. Making the point that based on this trial, you know, one can pick and choose the PI based on the patient's presentation and features.

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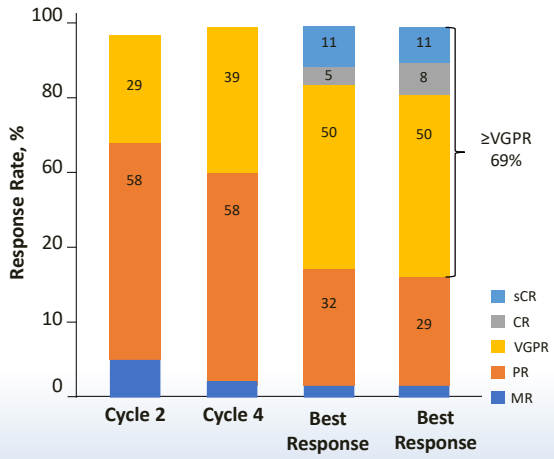
IRd Plus Daratumumab Appears to Be Active and Well-Tolerated in ASCT-Eligible Myeloma



Kumar S, et al. ASH 2018. Abstract 304.

- IRd + daratumumab in patients with newly diagnosed myeloma appears to have excellent efficacy with rapid responses that deepen quickly over the initial cycles of therapy
- Well tolerated with
  - Limited dose modifications
  - No discontinuation for toxicity and **no influence on the ability to collect stem cells**

Another interesting regimen that's emerging, and I'm looking forward to these data, is the combination of ixa-len-dex or IRd, which is an all-oral combination along with daratumumab. And the data I'm showing you on this slide is a phase 1/2 experience that was presented by my colleague, Shaji Kumar, a couple of years ago at ASH. As you can see, this is an efficacious regimen, but perhaps the depth of response doesn't appear to be as good as the other database regimens that we've seen in the newly diagnosed setting. But something to keep in mind, this is not ready for primetime, but something that may actually be utilized for both transplant eligible as well as ineligible patients in the future.

Assessing Fitness and Frailty in Older MM Patients

- Advantages:
  - Dose adjustment of chemotherapy
  - Appropriateness for autologous stem cell transplant
  - Avoidance of polypharmacy
  - Better physical and mental well-being
  - Better quality of life
  - Identification of socioeconomic barriers
- Disadvantages:
  - None

Wildes TM, et al. *J Am Geriatr Soc.* 2019;67(5):987-991.

One thing that I want to cover, which is quite important for this transplant ineligible patient population, is the assessment of fitness and frailty in older myeloma patients. Historically we've done the eyeball test, but there has been a drive now to develop a multidisciplinary kind of an approach for patients who are older. And you can see that there are a lot of advantages we have if we take this approach. After assessing fitness and frailty, we can make appropriate dose adjustments of chemotherapy, have a better assessment of appropriateness for autologous stem-cell transplant, many of the older patients have other comorbidities and we can avoid polypharmacy, improve their physical and mental well-being, improve their quality of life, and also in the process identify socioeconomic barriers to care in this older patient population. Honestly, I don't see a lot of disadvantages. It only improves the level of care we provide to patients.

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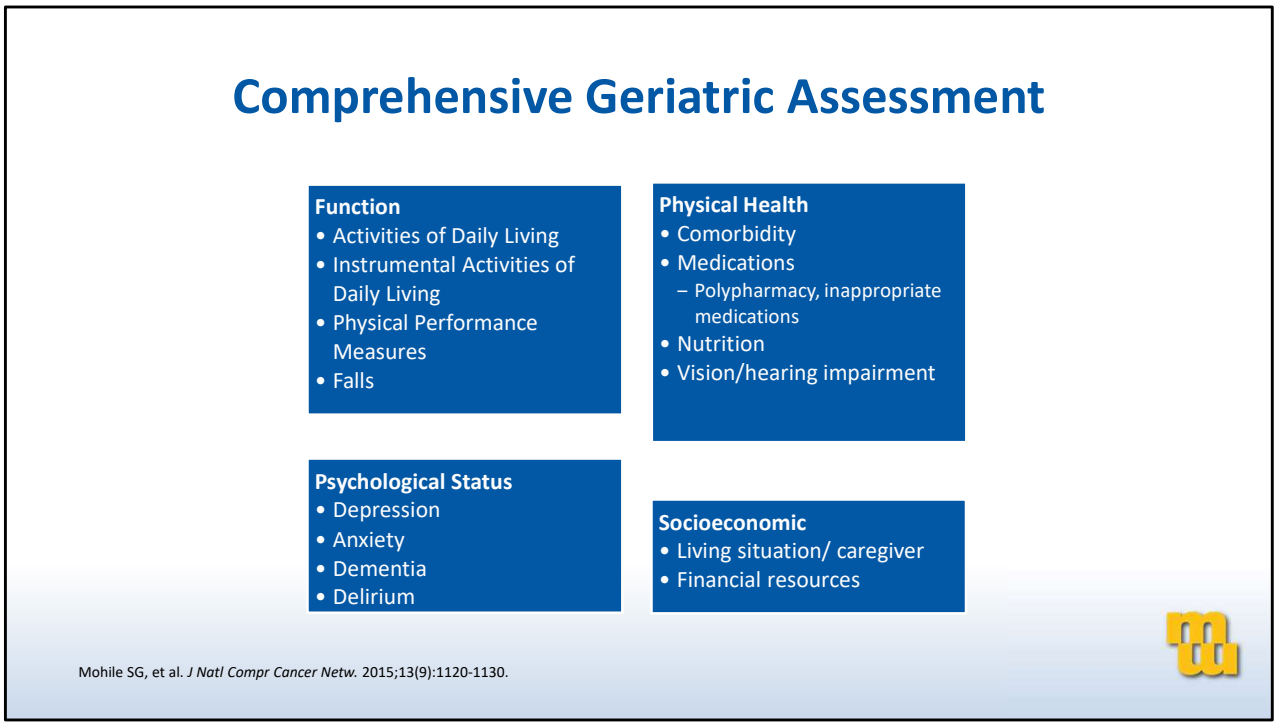

When it comes to comprehensive geriatric assessment, one can look at functional status, psychological status, physical health as well as socioeconomic issues, and all of those things need to be incorporated in this assessment. And that's why having a geri/onc assessment along with other specialties is important, and some of the programs around the country like WashU and Ohio State have pioneered some of this work and program like ours have followed suit in incorporating these assessments and doing this in a more recognized and comprehensive fashion.

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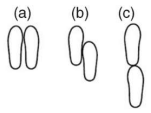
Physical Performance Tests

Short Physical Performance Battery

(1) Stance
(a) feet side-by-side
(b) semitandem stance
(c) tandem stance



0–4 points

(2) Gait velocity
(4 m distance)

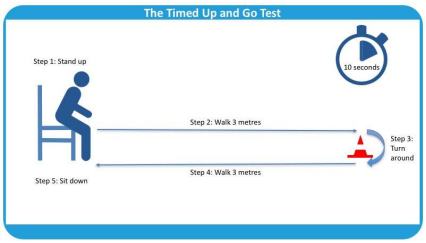
0–4 points

(3) Sit-to-stand time
(5x)

0–4 points

Σ:0–12 points

Timed Up and Go



Guralnik JM, et al. *N Engl J Med.* 1995;332(9):556-561.; Podsiadlo D, et al. *J Am Geriatr Soc.* 1991;39(2):142-148.

Physical performance tests can be easily done with a short physical performance battery looking at stance, gait velocity, and sit-to-stand time. And another simple test that can be done is the timed up and go, looking at how much time it takes for an individual to get up from the chair, walk a certain distance, and come back. And these are established physical performance tests that are incorporated in a geriatric assessment.

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Cognitive Screens

Test	Scoring	Duration	Cut Point/Score	Link
Mini-Mental State Evaluation-2 (MMSE-2)[1]	11 items, scores range from 0 to 30	10 min	>24	www.minimental.com
Mini-Cog©[2]	3-item recall test; clock drawing test (CDT serves as recall distractor	3 min	0-2 positive screen for dementia	www.mini-cog.com
Montreal Cognitive Assessment (MoCA)[3]	Total score of 30; evaluates 8 function domains	10 min	<26	www.mocatest.org
CDT[4]	10-point scale	Depends on manner of administration	Depends on instructions	https://www.sralab.org/rehabilitation-measures/clock-drawing-test

[1]Folstein MF, Folstein SE. Mini-Mental State Evaluation, 2nd edition. Available at: https://www.parinc.com/Products/Pkey/238. Accessed November 16, 2020. [2]Mini-Cog© Screening for Cognitive Impairment in Older Adults. Available at: https://mini-cog.com/. Accessed November 16, 2020. [3]Montreal Cognitive Assessment. Available at: https://www.mocatest.org/. Accessed November 16, 2020. [4]Shirley Ryan Ability Lab Web site. Clock Drawing Test. Available at: https://www.sralab.org/rehabilitation-measures/clock-drawing-test. Accessed November 16, 2020.

And, going to the cognitive screens, there are several well-validated exams such as MMSE, Mini-Cog, MoCA, and CDT. In our program, we look at the first two for our patients doing the comprehensive assessment.

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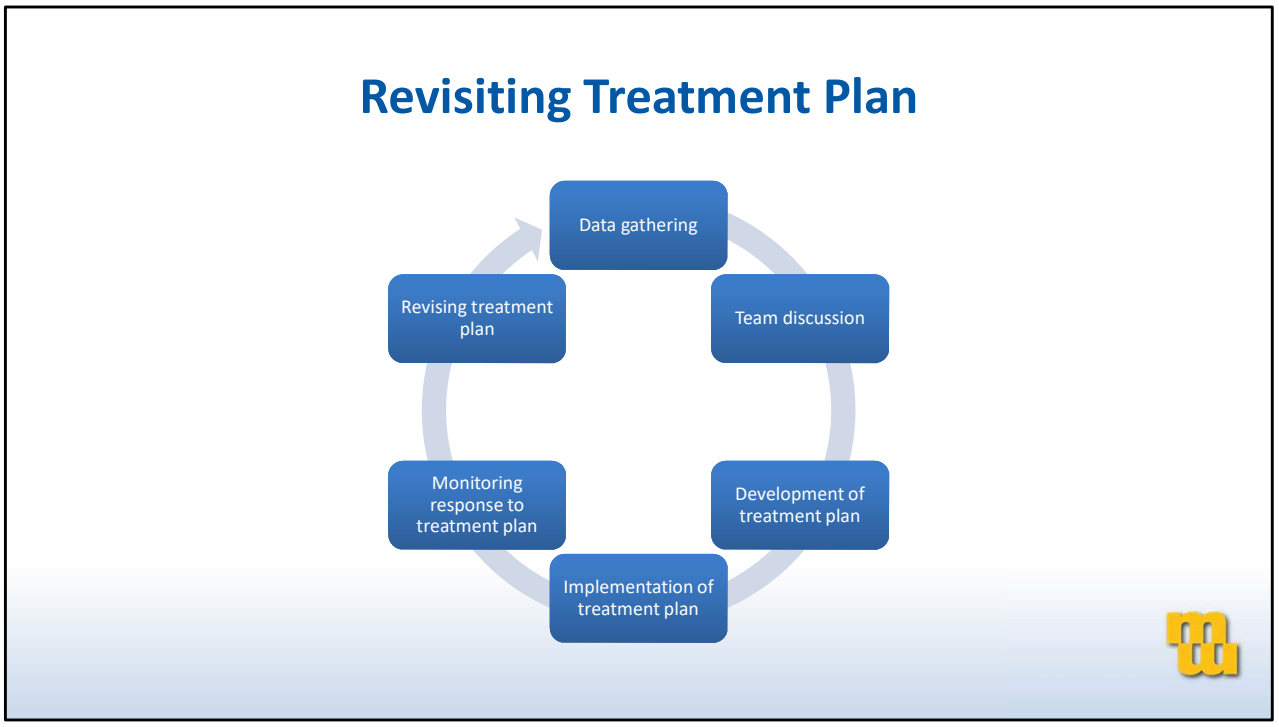
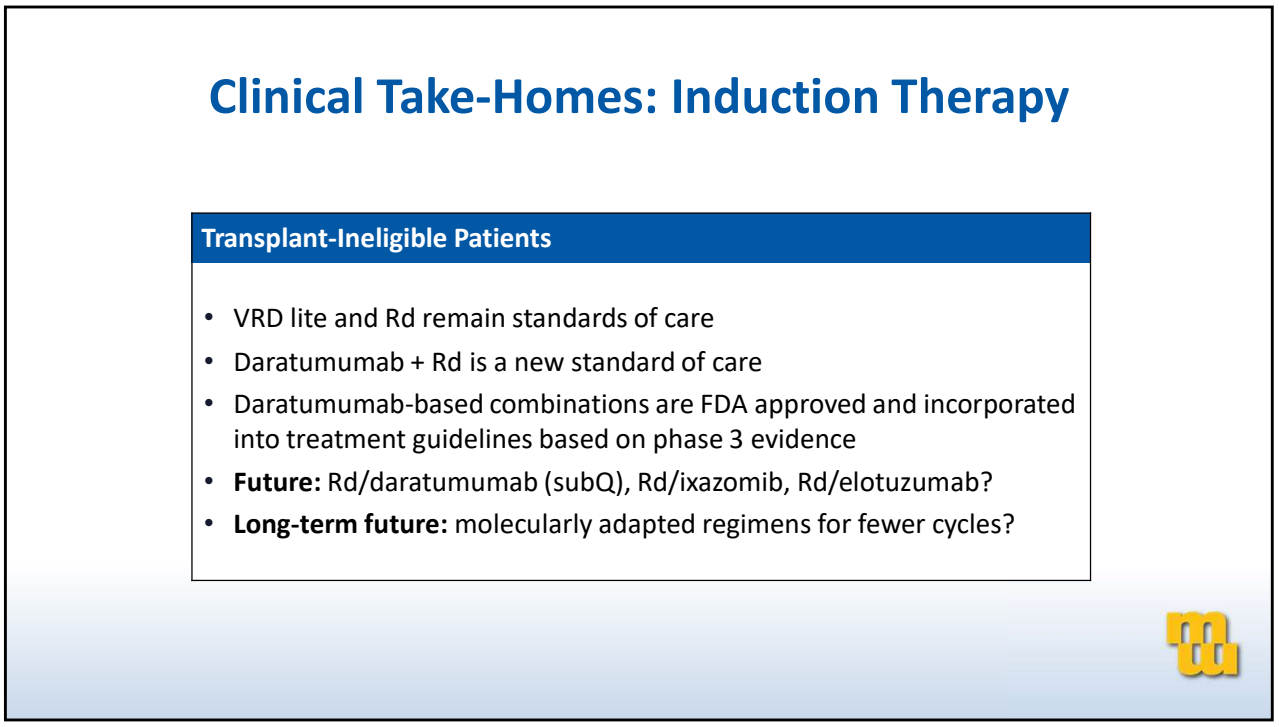


And essentially, we have to revisit the treatment plan. We gather the data, have the treatment discussion, come up with a treatment plan on what would be the best dosing and treatment schedule for patients, we implement that plan. But then we also, see how the patient handles it. Revise the plan based on the patient's tolerability, gather the data again, have the treatment discussion, and implement the new plan. This is a very dynamic process. Yes, it is labor intensive, but it means the world to our older myeloma patients.

Changing Standards in Transplant-Ineligible Patients Newly Diagnosed with Myeloma



The key takeaways that I would say for the transplant-ineligible patients is that the VRd lite or VRd combinations are still standard of care. I think Rd is still a valid standard of care for transplant-ineligible patients. Dara/len/dex is a new standard of care. And for patients who are being considered for Rd alone, dara/Rd probably provides a very good option that improves depth of response and PFS. The downside there would be the higher incidence of infections, and this is where medicine becomes art in managing our patients. Again, looking at the comprehensive geriatric assessment, doing dynamic assessments, and dose reducing or modifying the schedule of treatment becomes an art. There are several daratumumab-based combinations that have moved up based on phase 3 evidence into the frontline setting, and we'll be hearing more about those regimens with the passage of time. I think the benefit of overall survival seen in the ALCYONE study is very encouraging and hopefully that also pans out in the MAIA trial as well. Now, subcutaneous formulations of daratumumab are available and they are going to be a game changer for the older patient population. So this becomes a very important quality of life advance for the older patients.

Eventually, I think we are going to have molecularly adapted regimens. For example, translocation 11;14, patients may have drugs like venetoclax come to the fore for them but, you know, that's something simply looking at future directions there. And then MRD negativity and sustained MRD negativity may be used as guiding post to limit the number of cycles of treatment or limit the number of cycles of maintenance as you saw from the second randomization of the ENDURANCE trial that I had shown you on the previous slide. So, with these clinical take home messages,

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Conclusions

- Therapeutic advances have led to prolonged survival in MM, but it remains a chronic disease
- Treatment of myeloma requires a long-term strategy
- Key is delivering the best ‘package’ of treatment at a given stage
- Optimal combinations and sequencing is key
- Risk stratified approach in clinic
- Future will be developing more individualized approaches

I would like to conclude my talk by saying that we have made a lot of progress over the past 15 years. Therapeutic advances have prolonged survival in multiple myeloma, but it remains a chronic disease and it's not curable at the current time. The idea here is to provide a long-term strategy and deliver the best package of treatment for your patient at any given stage. I think risk-stratification for older patients is important and incorporating geriatric assessments will help develop more individualized approaches for these patients.

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In the end, I would like to thank our patients and their caregivers; my mentor, Dr. Barlogie; my clinical team as well as lab research team as well as collaborators.
Thank you.