Managing Myeloma

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# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes

**Sagar Lonial, MD, FACP**
Department Chair
Professor of Hematology and Medical Oncology
Emory University School of Medicine
Atlanta, Georgia

Hello, I'm Dr. Sagar Lonial, from the Emory University School of Medicine in the Department of Hematology and Medical Oncology. Welcome to this *Managing Myeloma* update on developments in newly diagnosed myeloma, considerations for improved patient outcomes. We're going to spend the next few moments really talking through changes in the development and treatment of patients with newly diagnosed multiple myeloma.

## Disclosures

- **Dr. Sagar Lonial** has relevant financial relationships related to advisory activities from AbbVie Inc., Bristol-Myers Squibb Company, Celgene Corporation – A Bristol-Myers Squibb Company, GlaxoSmithKline plc, Janssen Pharmaceuticals, Inc., Karyopharm Therapeutics, Novartis AG, and Takeda Oncology. He has received research grant(s) from Bristol-Myers Squibb, Celgene, Janssen, and Takeda. He is on the board of TG Therapeutics, Inc.
- **Dr. Saad Usmani** has relevant financial relationships related to advisory activities and consulting from Endo Pharmaceuticals Inc., Genentech, Inc., Gilead, Oncopeptides, AB, Sanofi, Seattle Genetics, Inc., SecuraBio, 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.

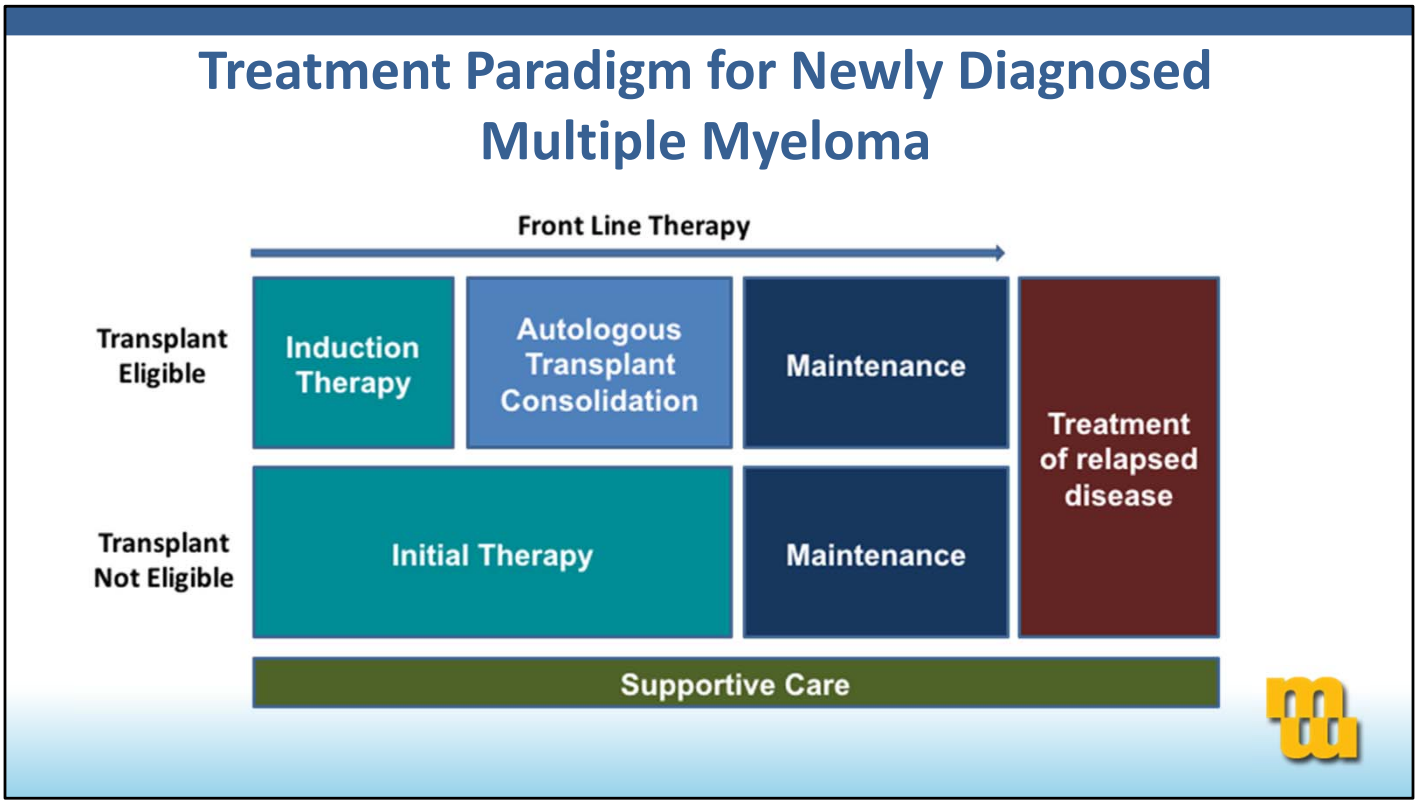
Here are my disclosures, and the disclosures of my co-chair Dr. Saad Usmani.

## Learning Objectives

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

- Personalize initial therapy and maintenance approaches for NDMM based on patient and disease characteristics, and the latest evidence from clinical trials and real-world experience
- Identify the most appropriate therapies for patients with NDMM who have underlying comorbidities and who have treatment-related adverse events that necessitate changing therapeutic strategies
- Utilize patient education and shared decision-making approaches to improve patient satisfaction and outcomes

Learning objectives are listed here. The goal here is to personalize initial therapy and maintenance approaches for newly diagnosed myeloma based on patient and disease characteristics, and the latest evidence from clinical trials; identify the most appropriate therapies for patients with newly diagnosed myeloma who have comorbidities; and utilize patient education and shared decision-making to improve patient satisfaction and outcomes.




Okay, let's go through the treatment paradigm for newly diagnosed myeloma. This really includes both the transplant-eligible and transplant-ineligible patients on the same figure. The concept here really revolves around the fact that transplant-eligible typically will get induction therapy, followed by consolidation with stem cell transplant and then maintenance, whereas non-transplant eligible will get less intensive induction therapy and then go on to maintenance therapy.

Now, this paradigm for the newly diagnosed patients, particularly the transplant eligible, was actually tested in the Phase III DETERMINATION Trial that was presented at ASCO this year and then just published in the *New England Journal of Medicine*. What it does is continue to confirm the ongoing benefit for early high-dose and autologous transplant for the management of patients with newly diagnosed myeloma; with one of the longest progression-free survivals ever reported in a randomized Phase III trial in myeloma of 65 months for the group that received induction with RVd transplant and continuous Len maintenance, compared to only 40 months in the group that received RVd and no transplant and continuous lenalidomide maintenance.

This 22-month improvement in PFS is really quite impressive and really speaks to the continued ongoing benefit of high-dose therapy and transplant in myeloma.

## Staging and Cytogenetic Risk-Assessment

| Stage[1] | R-ISS[1] |
|---|---|
| I | Serum albumin ≥3.5 g/dL$^{-1}$<br>Serum β2M <3.5 mg/L$^{-1}$<br>No high-risk cytogenetics<br>Normal LDH level |
| II | Not stage I or III |
| III | Serum β2M >5.5 mg/L$^{-1}$<br>High-risk cytogenetics: t(4;14), t(4;16), or del(17p)<br>or elevated LDH |

| Risk[2] | mSMART[2] |
|---|---|
| Standard | Trisomies<br>t(11;14)<br>t(6;14) |
| High | t(4;14)<br>t(14;16)<br>t(14;20)<br>Del(17p)<br>*p53* mutation<br>Gain 1q<br>High plasma cell S-phase<br>GEP high-risk signatures |

1. Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869. 2. mSMART website. 2018. Accessed January 8, 2021. Accessed January 8, 2021. https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5b802d8270a6adbc6a79a678/1535126914646/Risk+Strat+3.0rev_svr.pdf

Now, as we begin to think about staging and risk assessment in patients with myeloma, there really are two different ways to look at this. We're going to focus mostly on the left side of this curve of this figure, which is the R-ISS, which uses the old ISS, including serum albumin and beta 2-microglobulin, as well as now, genetics and an LDH. The mSMART criteria here on the right I don't find very helpful. They are a single institution consensus, not validated prospective criteria. The R-ISS really does represent the optimal way to stage and assess risk in modern myeloma therapy.

## NCCN Regimens for Transplant Candidates

| Primary Therapy for Transplant Candidates |
|---|
| **Preferred Regimens**<br>• Bortezomib/lenalidomide/dexamethasone (category 1) |
| **Other Recommended Regimens**<br>• Carfilzomib/lenalidomide/dexamethasone<br>• Daratumumab/lenalidomide/bortezomib/dexamethasone<br>• Ixazomib/lenalidomide/dexamethasone (category 2B) |
| **Useful in Certain Circumstances**<br>• Bortezomib/cyclophosphamide/dexamethasone<br>• Bortezomib/doxorubicin/dexamethasone<br>• Carfilzomib/cyclophosphamide/dexamethasone<br>• Ixazomib/cyclophosphamide/dexamethasone<br>• Bortezomib/thalidomide/dexamethasone (category 1)<br>• Cyclophosphamide/lenalidomide/dexamethasone<br>• Daratumumab/carfilzomib/lenalidomide/dexamethasone<br>• Daratumumab/cyclophosphamide/bortezomib/dexamethasone<br>• Daratumumab/bortezomib/thalidomide/dexamethasone<br>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE) |

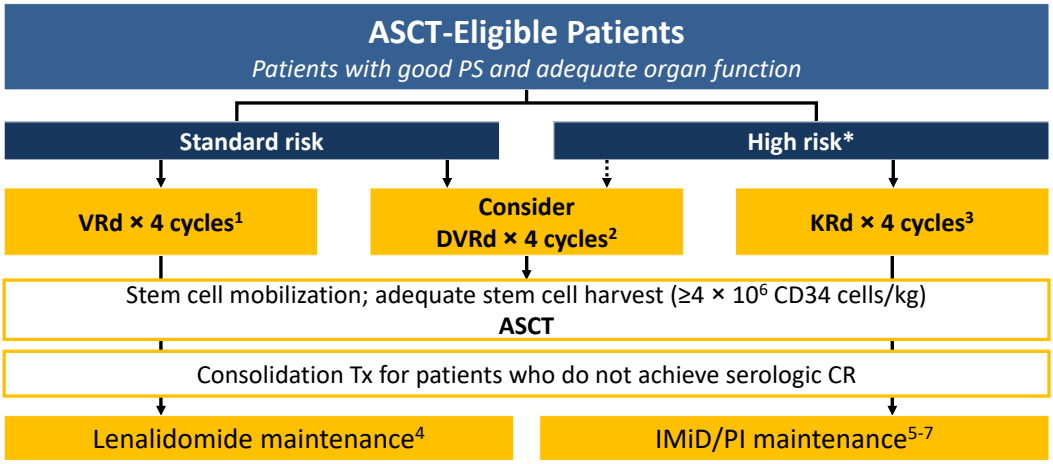
All recommendation are category 2A unless otherwise indicated.
NCCN Guidelines Version 4.2022.

Now, if you begin to look at NCCN regimens for patients who are considered transplant candidates, the preferred regimen, again, is VRd. That is Category 1, based on randomized Phase III data. We will go through some of that data in the next few moments. Other regimens include KRd, Dara RVd, and IRd. In this “Useful in Certain Circumstances” section, I'll tell you, I don't consider any of them really useful anymore. Probably, the one that comes up the most is the VCD, bortezomib, cyclophosphamide, and dexamethasone. I think in modern myeloma therapy, there is now no real reason to use that any longer.

As I said, I don't think VCD is any longer a reasonable regimen to use, and certainly, doxorubicin or any combinations of cyclophosphamide to me, no longer fit in the modern paradigm of disease treatment.

NCCN, National Comprehensive Cancer Network.

## Induction and Maintenance Therapy for Patients With Transplant-Eligible Myeloma




1. Attal M, et al. *N Engl J Med.* 2017;376:1311-1320. 2. Voorhees PM, et al. *Blood* 2020;136(8):936-945. 3. Gay F, et al. ASH 2020. Abstract 294. 4. McCarthy P, et al. *J Clin Oncol*. 2017;35:3279-3289. 5. Nooka AK, et al. *Leukemia*. 2014;28:690-693. 6. Dimopoulos. ASH 2018. Abstract 301. 7. Usmani SZ, et al. *Lancet Haematol*. 2021;8(1):e45-e54. 8. Richardson P, et al. ASCO 2022. LBA4.

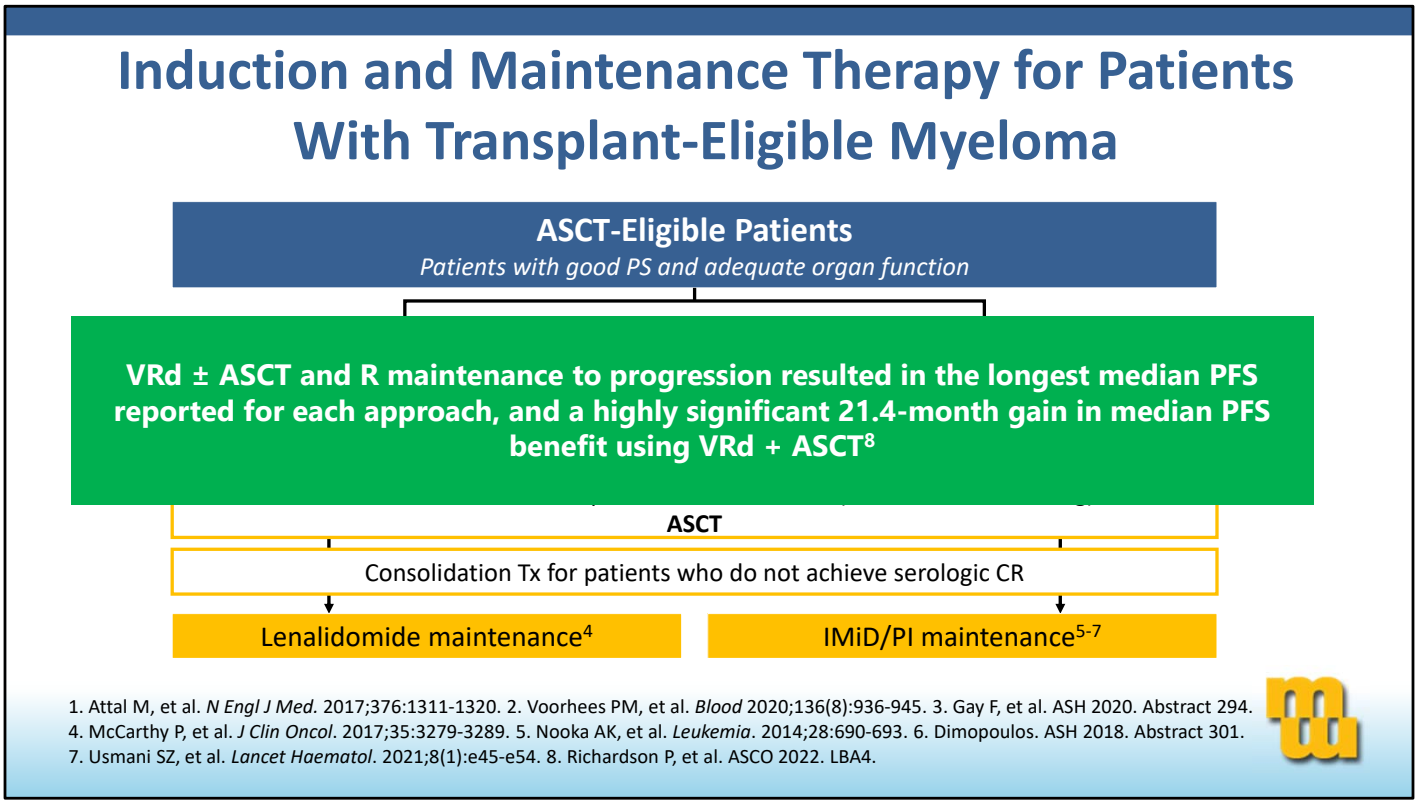
As we think about a simple algorithm, here is something that's been put forward by a number of groups here, and that is VRd x 4 cycles, stem cell collection, transplantation, and then lenalidomide maintenance, for standard-risk myeloma. I'll tell you at our center, we currently do Dara-RVd for standard-risk stem cell collection and transplant followed by single-agent lenalidomide maintenance. I'll show you some of the data that supports that decision.

For high-risk patients, many groups are using KRd as their initial induction, also collecting stem cells and consolidating with a transplant, and then likely using doublet or triplet maintenance with an IMiD and a PI or an IMiD PI and dexamethasone.

*By R-ISS staging (R-ISS II/III) and/or cytogenetics (t[4;14], t[14;16], or del[17p]).

ASCT, autologous stem cell transplant; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD, immunomodulatory drug; KRd, carfilzomib, lenalidomide, and dexamethasone; PI, proteasome inhibitor; Tx, treatment; VRd, bortezomib, lenalidomide, and dexamethasone.

Richardson P, et al. ASCO 2022. LBA4. https://ascopubs.org/doi/pdf/10.1200/JCO.2022.40.17_suppl.LBA4

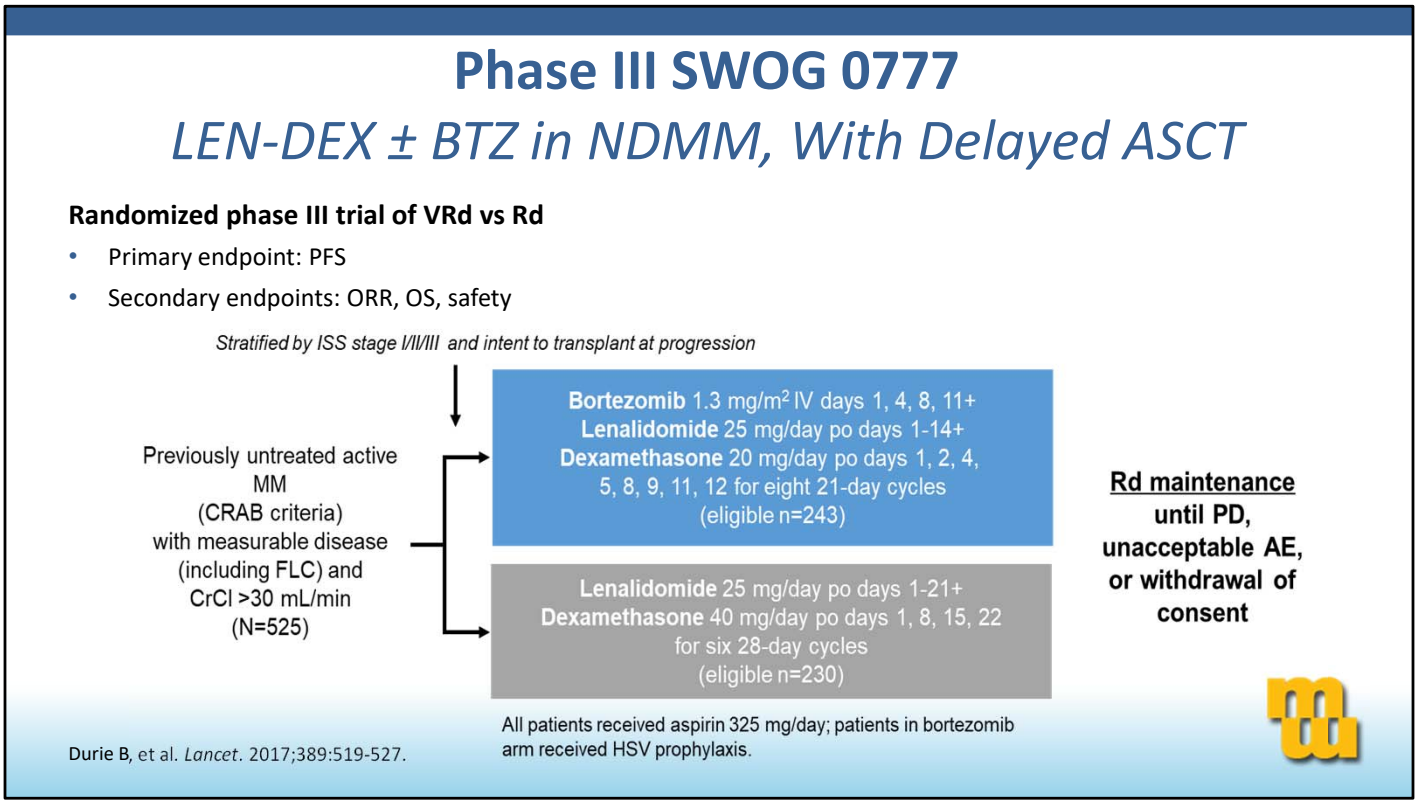



Certainly, at our center, we published data almost eight years ago, now, on VRd consolidation and maintenance in high risk, demonstrating some of the best long-term PFS and OS for that patient group. More recently, we've now switched to KRd induction and KRd consolidation and maintenance for that patient population.

*By R-ISS staging (R-ISS II/III) and/or cytogenetics (t[4;14], t[14;16], or del[17p]).

ASCT, autologous stem cell transplant; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD, immunomodulatory drug; KRd, carfilzomib, lenalidomide, and dexamethasone; PI, proteasome inhibitor; Tx, treatment; VRd, bortezomib, lenalidomide, and dexamethasone.

*RVd ± ASCT and R maintenance to progression resulted in the longest median PFS reported for each approach, and a highly significant 21.4-mo gain in median PFS benefit using RVd + ASCT.[8]*
Richardson P, et al. ASCO 2022. LBA4. https://ascopubs.org/doi/pdf/10.1200/JCO.2022.40.17_suppl.LBA4




Now, the SWOG 777 trial, while most of us in the US had adopted RVd as a standard regimen, this was actually the trial that demonstrated the benefit of the triplet of RVd over lenalidomide and dexamethasone. This was not a trial exclusively done in older frailer patients, this was a trial where transplant was actually deferred.

AE, adverse event; BTZ, bortezomib; HSV, herpes simplex virus; LEN, lenalidomide; NDMM, newly diagnosed MM; ORR, objective response rate; OS, overall response; PFS, progression-free survival; PD, progressive disease; Rd, lenalidomide and dexamethasone.

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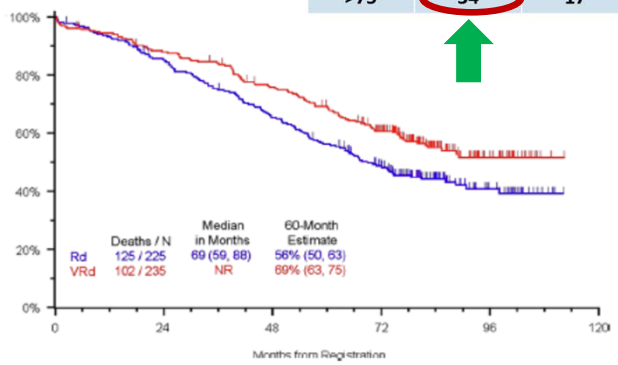
## Updated Analysis SWOG777

Median PFS (months)

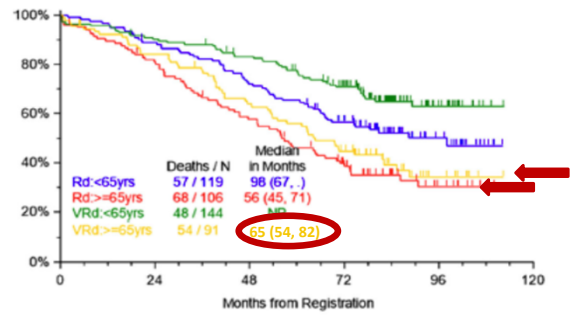
| Age (years) | VRd | Rd |
|---|---|---|
| <65 | 48 | 34 |
| ≥65 | 34 | 24 |
| >75 | 34 | 17 |




OS at 5 years

Median follow-up 84 months

4a. Overall Survival by Age




Age < 65 years: HR= 0.640 (0.421,0.973); stratified, two-sided p= 0.028

Age ≥ 65 years: HR= 0.769 (0.520,1.138); stratified, two-sided p= 0.168

Durie B. ASH 2018. Abstract 1992.; Durie B, et al. *Blood Cancer J*. 2020;10(5):53.

What we demonstrated in this trial was that the progression-free and overall survival was clearly better for the group that got the triplet over the group that got the doublet. But when you began to look at subsets, particularly in the older patient population, greater than 75, what I think you're seeing is that those patients clearly got much more benefit out of the triplet than the doublet, suggesting that even for older or younger patients, the benefit of VRd was improved over lenalidomide and dexamethasone.

More importantly, I think it's important to recognize that when we begin to look at all patients in aggregate, that without a transplant in this trial, the overall progression-free survival was relatively short. That's something that I think we need to continue to remember as we talk about, should we offer choice to patients in terms of transplant now versus transplant later? If you're going to do it, doing it early is better than doing it late. The PFS is significantly longer, and the likelihood of coming back with a transplant and relapse is significantly lower. We see that both from the French trial and the US trial.

## Phase II KRd Studies in NDMM

| Trial | Response | Grade 3/4 AEs |
|---|---|---|
| Jakubowiak, et al.[1] (N = 53) | nCR: 78%<br>sCR: 61%<br>24-month PFS: 92% | Hypophosphatemia: 25%<br>Hyperglycemia: 23%<br>Anemia: 21%<br>Thrombocytopenia: 17%<br>Neutropenia: 17% |
| Korde, et al.[2] (N = 45) | CR/sCR: 56%<br>≥nCR: 62%<br>≥VGPR: 89%<br>≥PR: 98% | Lymphopenia: 76%<br>Anemia: 27%<br>Neutropenia: 33%<br>Thrombocytopenia: 24% |
| Zimmerman, et al.[3] (N = 76) | VGPR: 96%<br>CR: 73%<br>sCR: 69% | Lymphopenia: 28%<br>Neutropenia: 18%<br>Infections: 8% |
| Gay, et al.[4] (N = 474); FORTE trial | **KRd-ASCT (n=158)** / **KRd12 (n=157)** / **KCd plus ASCT (n=159)**<br>≥VGPR 89% / 87% / 76%<br>≥CR 54% / 57% / 66%<br>sCR 46% / 44% / 32% | **KRd-ASC** / **KRd12** / **KCd plus ASCT**<br>**Neutropenia** 21(13%) / 15(10%) / 18(11%)<br>**Derm Toxicity** 9 (6%) / 12 (8%) / 1 (1%)<br>**Hepatic Toxicity** 13 (8%) / 12 (8%) / 0 |

1. Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809. 2. Korde N, et al. *JAMA Oncol*. 2015;1:746-754. 3. Zimmerman T, et al. ASH 2016. Abstract 675.
4. Gay F, et al. *Lancet Oncol*. 2021;22:1705-1720.

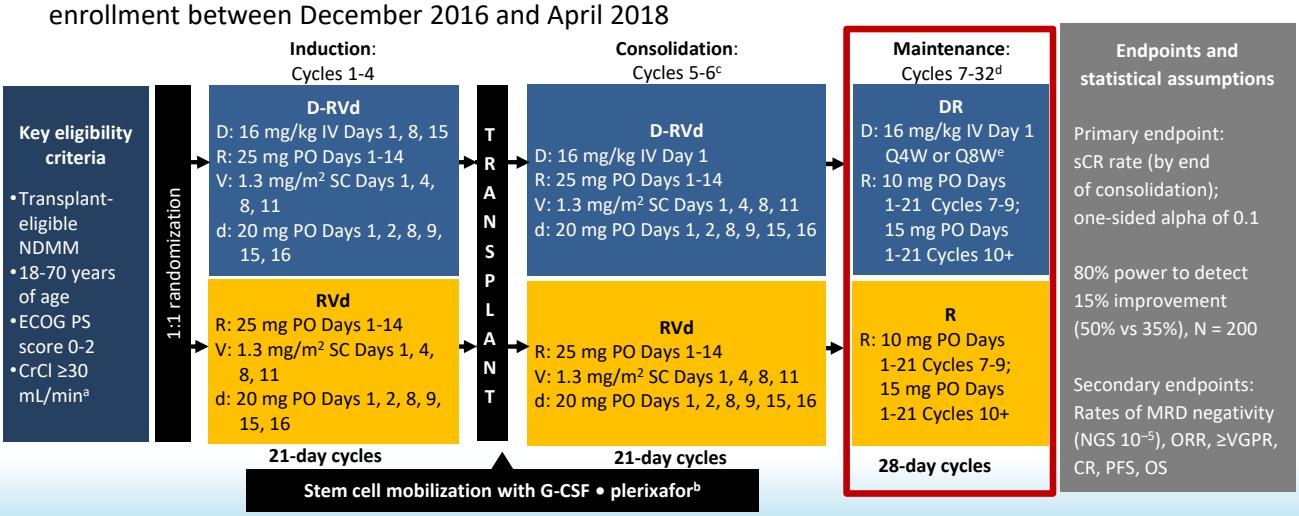
Now, there was a move by several investigators to suggest the KRd was better than VRd. There were multiple small Phase II studies that were done at a number of single institutions that suggested that KRd was going to be better. They suggested it with deeper responses, a better PFS in a Phase II study compared to Phase III trials.

We'll talk about that trial, which is the ENDURANCE trial, which utilized KRd versus VRd without a transplant in patients going on induction therapy for newly diagnosed myeloma of all ages. However, whether you're a believer in VRd or a believer in KRd, what we wanted to do was to look at the incorporation of an anti-CD30 antibody, to see whether this was actually better.

KRd12, 12 cycles of KRd; CR, complete response; nCR, near complete response; PR, partial response' sCR, stringent complete response; VGPR, very good partial response.

## GRIFFIN: Study Design of the Randomized Phase

- Phase II study of D-RVd versus RVd in transplant-eligible NDMM, 35 sites in the United States with enrollment between December 2016 and April 2018



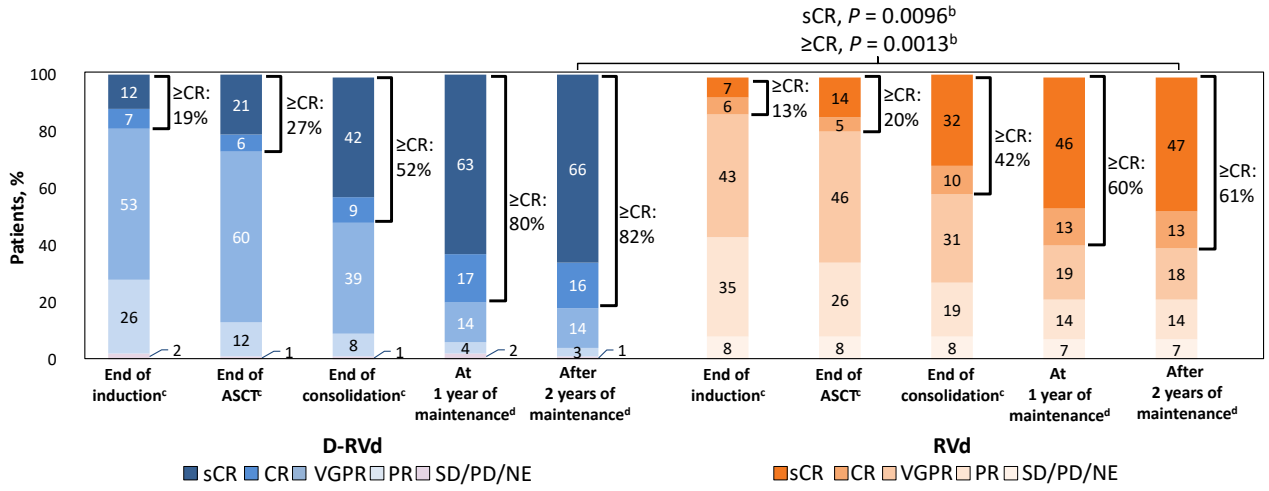

Laubach JP, et al. ASH 2021. Abstract 79.

This was the GRIFFIN trial which is a randomized Phase II trial performed in the US, that took Dara-RVd induction, transplant, Dara-RVd consolidation, and Dara-Len maintenance, versus RVd transplant, RVd consolidation, and Len alone as maintenance therapy. Again, all patients underwent high-dose therapy and autologous transplant.
This is asking a Dara at every phase versus no Dara at every phase of the process.

[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post-transplant. [d]Patients who complete maintenance Cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W based on pharmacokinetic results from study SMM2001 (ClinicalTrials.gov Identifier: NCT02316106). In GRIFFIN, among the D-RVd group who received DR maintenance, 9 patients received DARA Q8W dosing, 57 received DARA Q4W dosing, and 23 switched from DARA Q8W to Q4W dosing.

ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; SC, subcutaneous; G-CSF, granulocyte colony-stimulating factor; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response; PFS, progression-free survival; OS, overall survival.

## GRIFFIN: Responses Deepened Over Time[a]



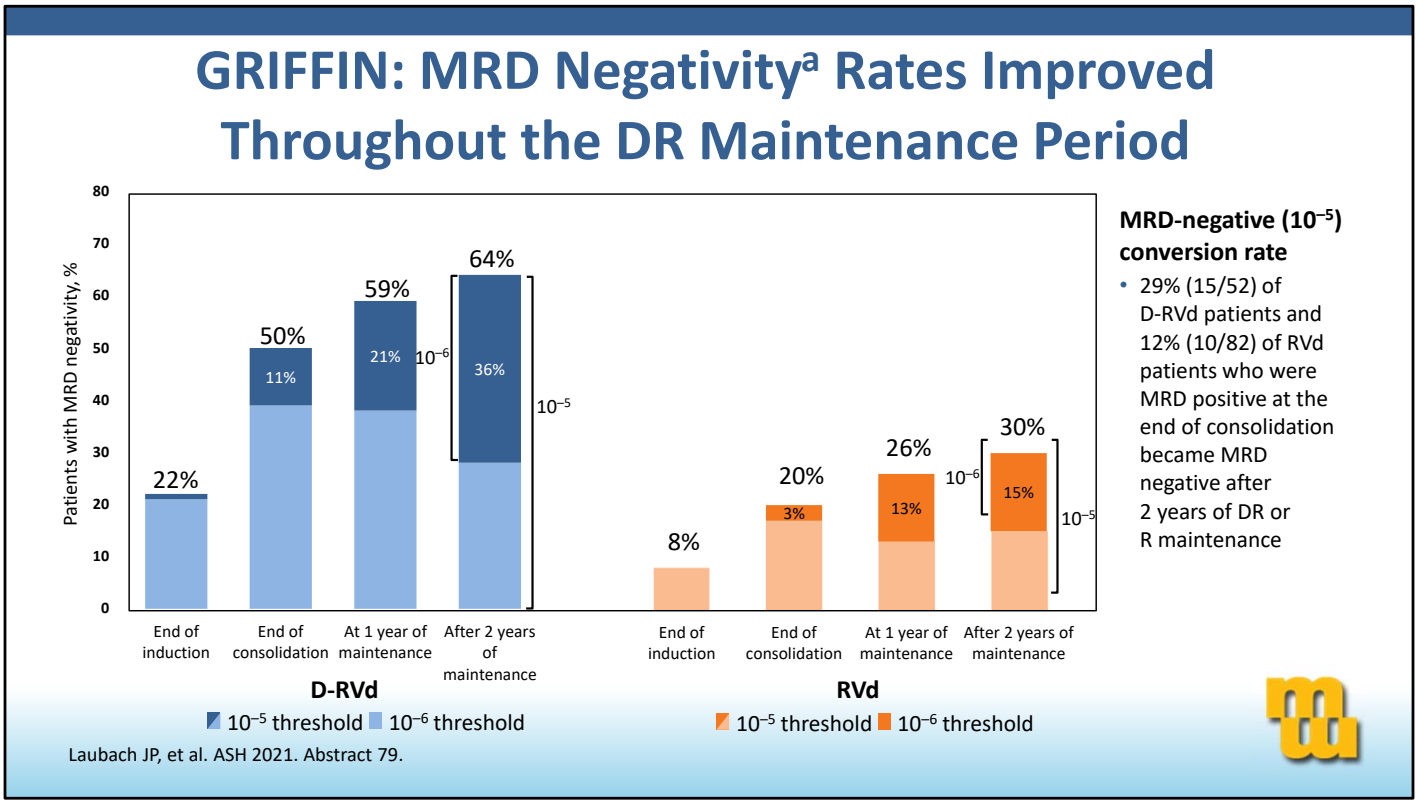

- Response rates for sCR and ≥CR were greater for D-RVd versus RVd at all time points, with the deepest responses occurring after 2 years of maintenance therapy

Laubach JP, et al. ASH 2021. Abstract 79.

What I think you'll see is that the depth of response is significantly better for the group that received RVd plus Dara. You can see that across here, 82% achieved greater than CR, compared to only 61% without daratumumab. This occurred at each step of the way, 19% versus 13%, 27% versus 20%, 52% versus 42%, 60% versus 80%. Again, the depth of response does continue to improve in the post-transplant setting, suggesting the ongoing benefit for transplant, even in patients who receive RVd plus Dara as part of their induction therapy.

[a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran-Mantel-Haenszel chi-square test. [c]Response rates are from the primary analysis cutoff (median follow-up: 13.5 mo), and the response-evaluable population included 196 patients (D-RVd, n = 99; RVd, n = 97). [d]Response rates for the maintenance phase have longer follow-up (median: 38.6 mo), and the response-evaluable population included 197 patients (D-RVd, n = 100; RVd, n = 97). Percentages may not add up due to rounding.

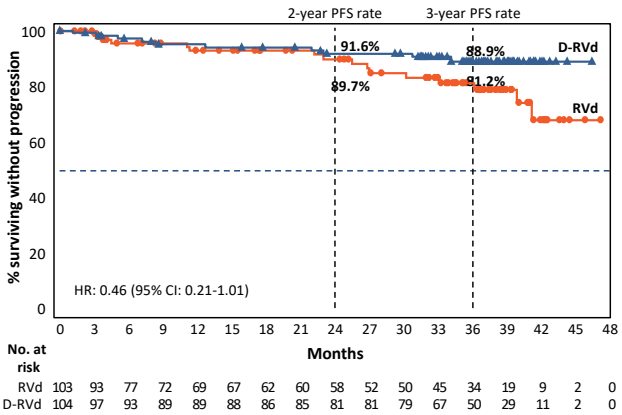
PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable.



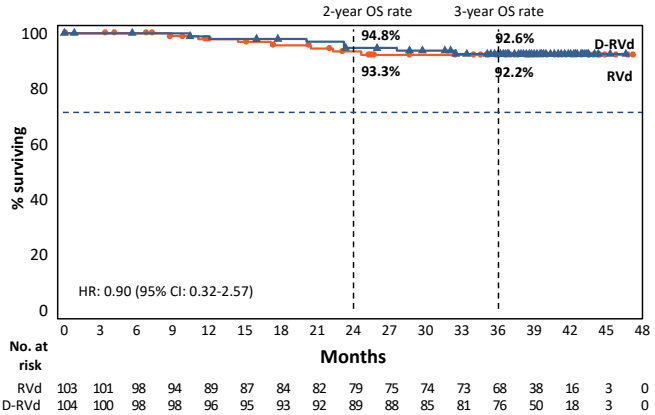

Now, if you look at even deeper measures of response, not just CR, but actually beginning to look at MRD negativity - and I actually like to look at this at $10^{-6}$, which is the light blue and the light orange - what you'll see is that the incidence of MRD negativity at $10^{-6}$ is significantly higher in the group that got Dara compared to the group that did not. In fact, it's basically double, supporting the idea that Dara not only increases CR rate, but it actually increases MRD negativity. This is really important because we're beginning to think about using MRD negativity as a long-term metric of potentially, efficacy of therapy, and also possibly, discontinuation of therapy as well.

[a]The threshold of MRD negativity was defined as 1 tumor cell per $10^5$ white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Bone marrow aspirates were assessed at baseline, at first evidence of suspected CR or sCR (including patients with VGPR or better and suspected DARA interference), at the end of induction and consolidation, and after one and two years of maintenance, regardless of response. Median follow-up was 38.6 months, and MRD-negativity rates are among the ITT population (D-RVd, n = 104; RVd, n = 103).

## GRIFFIN: PFS and OS in the ITT Population




- Median follow-up: 38.6 months
- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR vs RVd/R
- The separation of the PFS curves begins beyond 1 year of maintenance and suggests a benefit of prolonged DR therapy




- Median follow-up:38.6 months
- Median OS was not reached for either D-RVd/DR or RVd/R
- The OS data are not yet mature, with no difference between D-RVd/DR versus RVd/R in estimated 3-year OS rates

Laubach JP, et al. ASH 2021. Abstract 79.

Now, early on, everybody was mentioning that there was no difference in the progression-free survival curves. I think that is really because the control arm of RVd transplant and Len maintenance is so good that it takes longer to really see the benefit of adding Dara. What we're seeing now in a longer follow-up of the GRIFFIN trial is that, at three years, the progression-free survival is beginning to separate, and again, the overall survival has not yet separated as well.

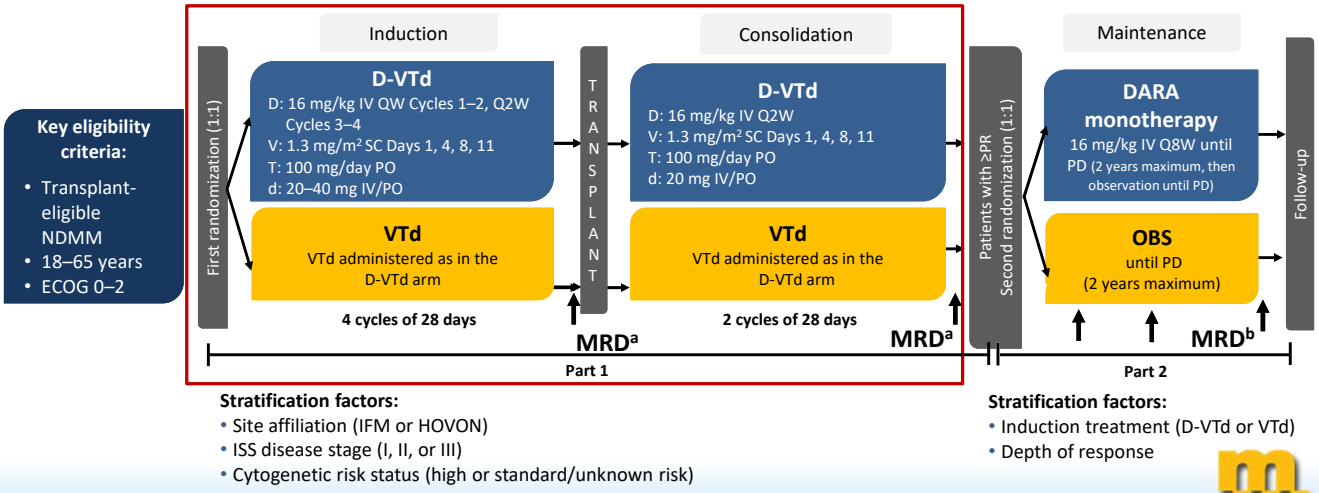
In my mind, the overall survival is not the primary endpoint and honestly, it's not very important. I say that, because in the myeloma world now, the median overall survival for myeloma is between 10 and 14 years. For that reason, expecting what you do in the first 6 to 12 months to change that is really unrealistic. Myeloma has now become like CLL and follicular lymphoma where OS is something you want to make sure is not worse. You shouldn't necessarily see improvements in OS based on what you do in the first year of treatment.

No difference in OS doesn't really bother me one way or another, but certainly, PFS, I think, clearly, is beginning to favor the use of RVd plus Daratumumab.

HR, hazard ratio

## CASSIOPEIA: Induction/Consolidation

- Analyses in Part 1 were conducted in the ITT population (N=1085), which included all first-randomization patients



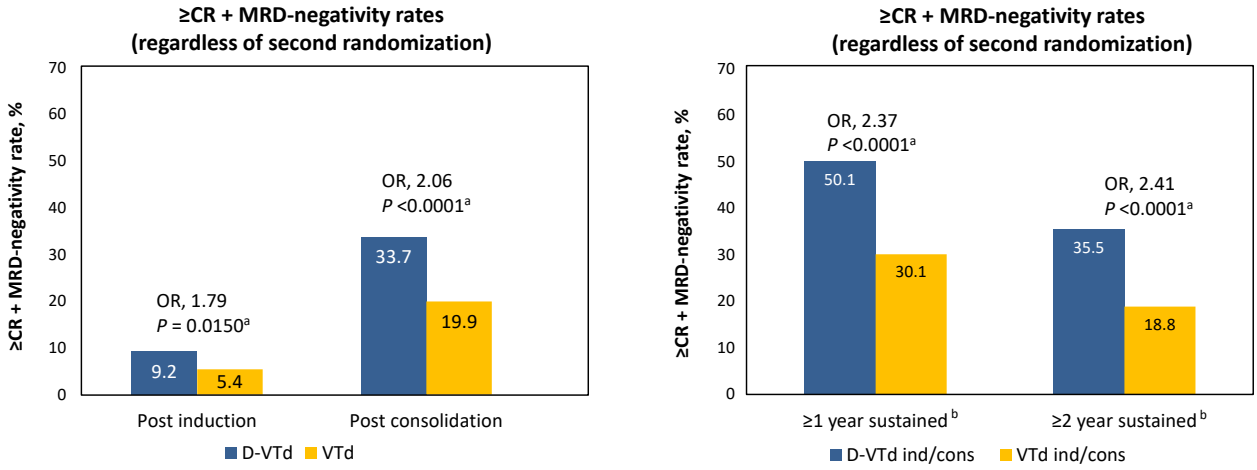

Avet-Loiseau H, et al. ASH 2021. Oral Presentation. Session 82.

What do we know about other trials that are looking at the incorporation of Daratumumab as part of the induction therapy? This was a larger trial done in Europe that uses Dara-VTd transplant and then Dara-VTd consolidation, followed by a second randomization of either Dara monotherapy, or observation. I'll tell you, my spin on the CASSIOPEIA trial is that the only question you can really answer is this right here in the red box because we no longer use observation for patients post-transplant. I really struggled with what to do with the long-term follow-up here. I don't believe the PFS data from this trial, but I do believe the differences in response and depth of response early on that the addition of Dara may contribute to standard therapy in Europe.

[a]MRD analyses were performed at predefined timepoints for all patients, regardless of response. [b]MRD analyses were performed in patients with ≥VGPR at Weeks 25, 52, and 105.

≥PR, partial response or better; IV, intravenous; Q8W, every 8 weeks; OBS, observation; ECOG, Eastern Cooperative Oncology Group; QW, every week; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; IFM, Intergroupe Francophone du Myélome; HOVON, the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology; ISS, International Staging System; PD, progressive disease; ≥VGPR, very good partial response or better.

## CASSIOPEIA: D-VTd Improved Rates of ≥CR + MRD Negativity (MFC; $10^{-5}$) Versus VTd Following Induction and Consolidation




- Post-consolidation MRD-negativity rates among patients who achieved ≥CR were consistent across subgroups, including ISS disease stage and high-risk cytogenetics

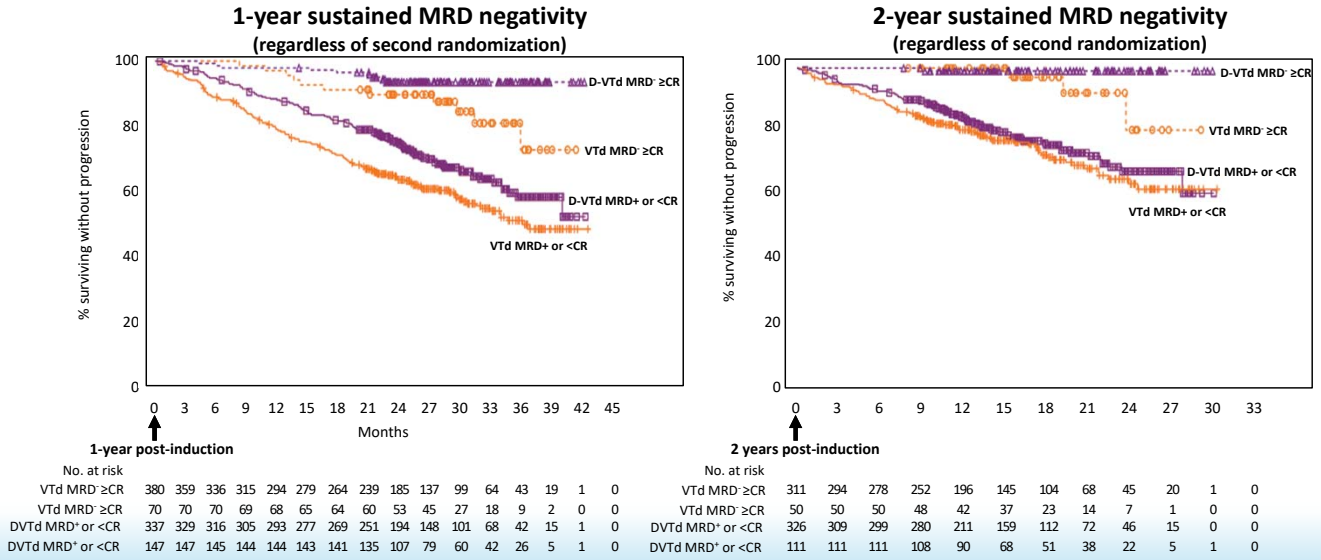
Avet-Loiseau H, et al. ASH 2021. Oral Presentation. Session 82.

That's really, listed here. What you'll see is, greater than CR plus MRD negativity rates 33% versus 19%, and more importantly, sustained MRD negativity is significantly higher in the group that got Dara, 50% versus only 30% in the group sustained for one year, and sustained for two years is 35% versus 18%. Almost double sustained MRD negativity in the group that received Dara as opposed to VTD transplant and no Dara, at all.

[a]Cochran-Mantel-Haenszel estimate of the common odds ratio for stratified tables was used. The stratification factors were study site affiliation, ISS disease stage, and cytogenetics. *P* value was calculated based on a stratified Cochran-Mantel-Haenszel chi-squared test. [b]Patients with ≥12 or ≥24 months of consistent MRD negativity (MRD negative at both the starting and ending point and no positive MRD among them) and ≥CR during the analysis period

MFC, multiparametric flow cytometry.

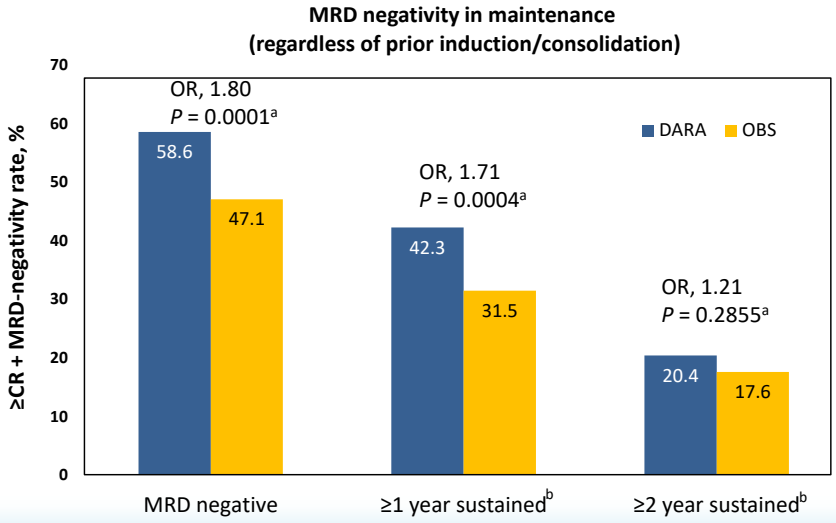
## CASSIOPEIA: Landmark PFS Analysis from Post-Induction ≥CR + MRD Negativity (MFC; $10^{-5}$) Status By Treatment Group




Avet-Loiseau H, et al. ASH 2021. Oral Presentation. Session 82.

Now, if you begin to look at PFS, and this, to me is really quite intriguing, what it says is, it's not just a matter of achieving MRD negativity, it's achieving MRD negativity with the right treatment. The reason I say that is if you look at one- and two-year MRD negativity, what you'll see is that the group that got Dara and MRD negativity had a longer PFS than the group that did not get Dara but also achieved MRD negativity. The sustainability of MRD negativity in the non-Dara group is much shorter. This is really critically important in my mind because it tells you that MRD alone is not the endpoint. It's sustained MRD negativity and what treatments you use to get to MRD negativity overall.

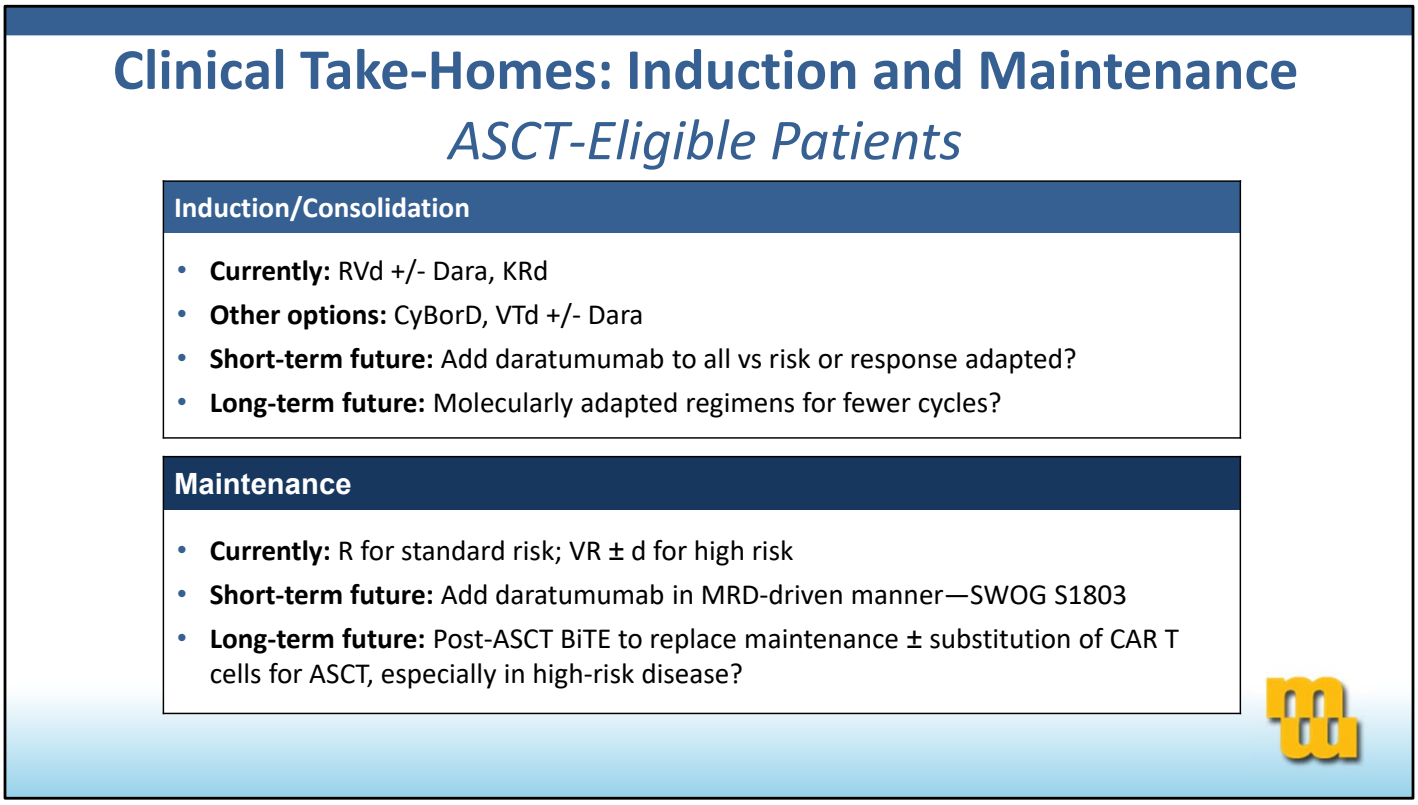
## CASSIOPEIA: Rates of ≥CR + MRD Negativity (NGS; $10^{-5}$) in DARA Versus Observation During Maintenance




Avet-Loiseau H, et al. ASH 2021. Oral Presentation. Session 82.

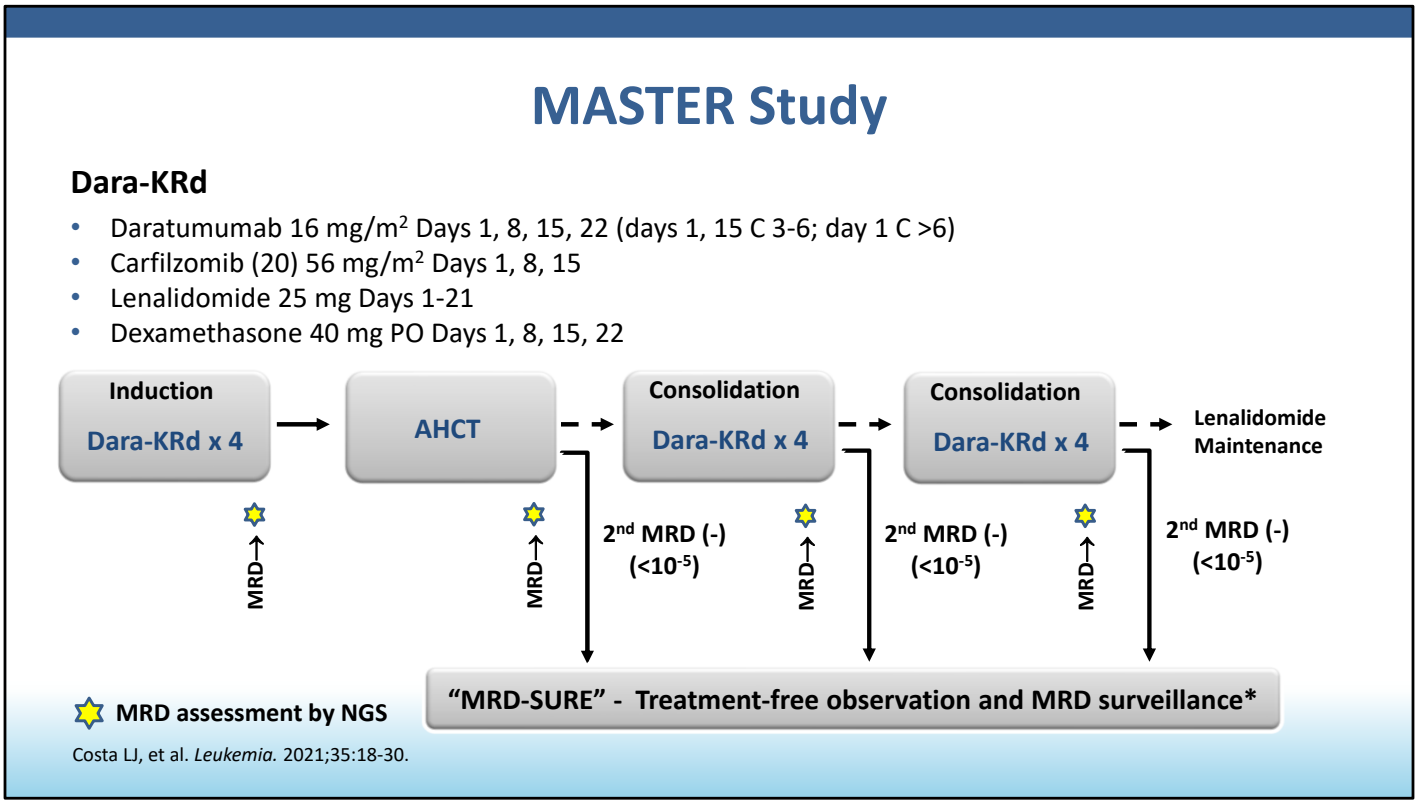
Now, if you begin to look at the MRD negativity and maintenance, and this data I have a lot of trouble with again, for the reasons I told you before, that I'm not sure what to do with patients who got observation.

[a]Cochran-Mantel-Haenszel estimate of the common odds ratio for stratified tables was used. The stratification factors were type of induction treatment (VTd vs D-VTd) and depth of response (as assessed by MRD status and post-consolidation response). *P*-value was calculated based on a stratified Cochran-Mantel-Haenszel chi-squared test. [b]Patients with ≥12 or ≥24 months of consistent MRD negativity (MRD negative at both the starting and ending point and no positive MRD among them) and ≥CR during the analysis period.




More importantly, I think for transplant-eligible patients, the conclusions, at least in my mind, are RVd or KRd or Dara-RVd certainly represent the standards of care for patients in newly diagnosed myeloma. I don't agree with the VCD approach. I don't agree with VTd plus Dara unless you're in a place where you can't use lenalidomide.

I think we are going to be adding Dara for certainly the standard risk. The high risk is certainly a big question. In terms of maintenance, for standard maintenance, I think the DETERMINATION trial demonstrated the benefit of continuous lenalidomide maintenance. I think several trials, including the FORTE trial, have now showed the benefit of an IMiD plus a PI for high-risk maintenance. Again, the question is going to be, do you add Dara for MRD-positive patients post-transplant? That's being addressed here, and how will the bispecifics and CAR-Ts work in terms of consolidation as well? Those are certainly future directions for us to evaluate.




Now, there's another trial that we discussed actually in the Q&A and this was the MASTER trial. Which used Dara-KRd, standard Dara, standard, KRd with 56 once-a-week dosing, which is basically equivalent to 20-20-7 or from an efficacy perspective is similar to bortezomib. What you'll see is they use this MRD assessment by NGS to consider stopping therapy. They called this MRD-SURE at these various time points. These time points were assessed every three months, but more importantly, they were at a depth of $10^{-5}$. It's not what I would consider to be appropriately deep endpoints for thinking about the discontinuation of therapy.

*24 and 72 weeks after completion of therapy

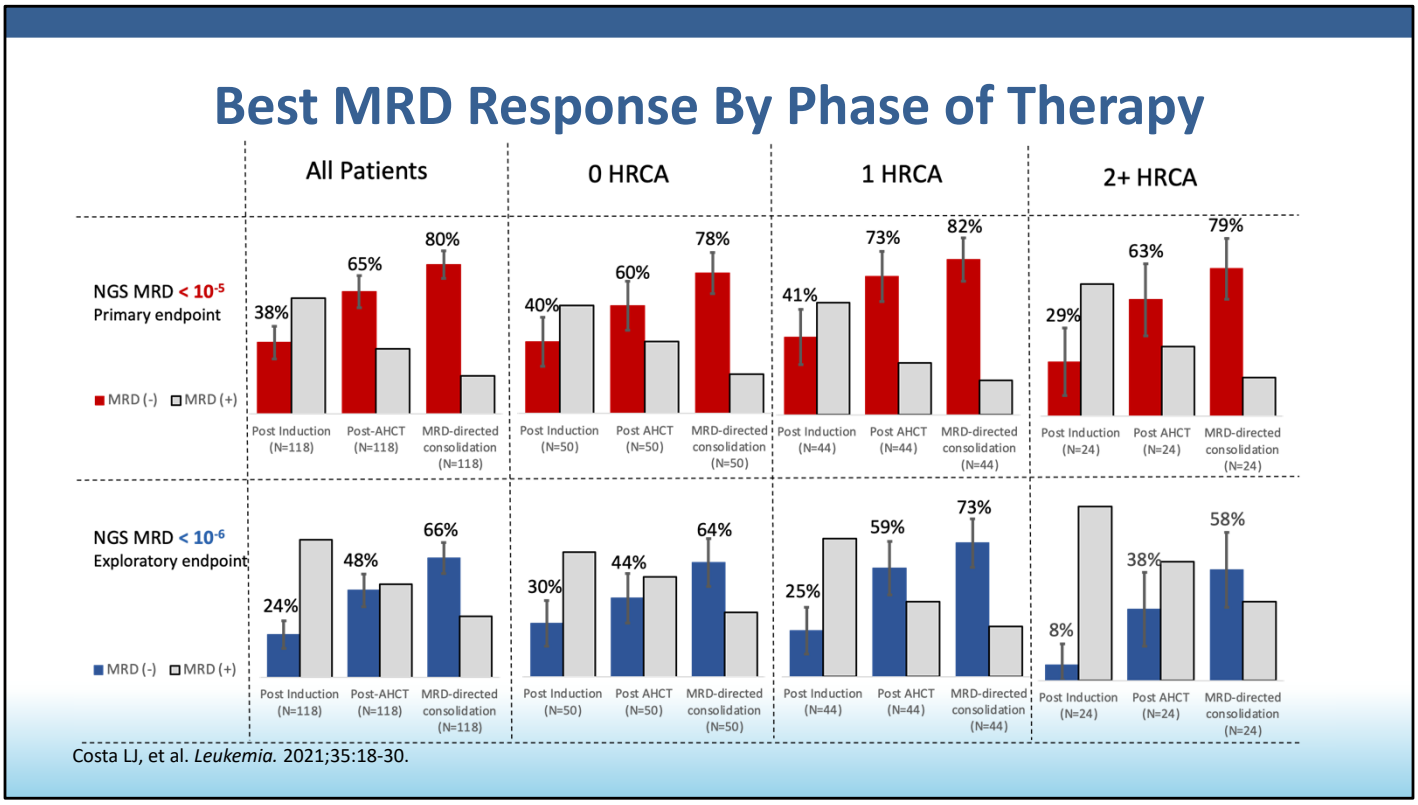
## Safety

| Adverse Event | Any Grade | Grade ≥3 |
|---|---|---|
| | No. of patients (%) | |
| Any | 123 (100) | 91 (74) |
| Hematologic | | |
| Neutropenia | 51 (41) | 43 (35) |
| Lymphopenia | 34 (28) | 27 (22) |
| Anemia | 26 (21) | 13 (11) |
| Thrombocytopenia | 24 (20) | 10 (8) |
| Leukopenia | 22 (18) | 12 (10) |
| Non-Hematologic | | |
| Fatigue | 68 (55) | 11 (9) |
| Bone pain | 68 (55) | 7 (6) |
| Rash maculo-papular | 50 (41) | 5 (4) |
| Nausea | 49 (40) | 0 |
| Constipation | 48 (39) | 0 |
| Upper Respiratory Infection | 45 (37) | 1 (1) |
| Diarrhea | 43 (35) | 5 (4) |
| Insomnia | 35 (28) | 3 (2) |
| Infusion related reaction | 34 (28) | 2 (2) |
| Dyspnea | 34 (28) | 2 (2) |
| Cough | 32 (26) | 0 |
| Hypertension | 32 (26) | 12 (10) |
| Dizziness | 30 (24) | 1 (1) |
| Peripheral sensory neuropathy | 26 (21) | 2 (2) |

Costa LJ, et al. *Leukemia.* 2021;35:18-30.

- 25 TE-SAEs
  - Pneumonia (N=8)
  - Pulmonary embolism (N=3)
  - Fever and neutropenia (N=2)
  - aHUS (N=1)
  - IRR (N=1)
  - Atrial fibrillation (N=1)
  - Other (N=9)
- 3 deaths
  - Unwitnessed sudden death on second week of induction
  - Metapneumovirus pneumonia 9 days after AHCT
  - Unwitnessed sudden death 2 months after AHCT

Now, if you look at Dara-KRd overall, there were some deaths that occurred in this, mostly infection or sudden cardiac death. There were one patient with atrial fibrillation, three patients with PE, but in general, the adverse events are not dissimilar from what you'd expect for a KRd regimen or a daratumumab-based regimen in the context of newly diagnosed myeloma.



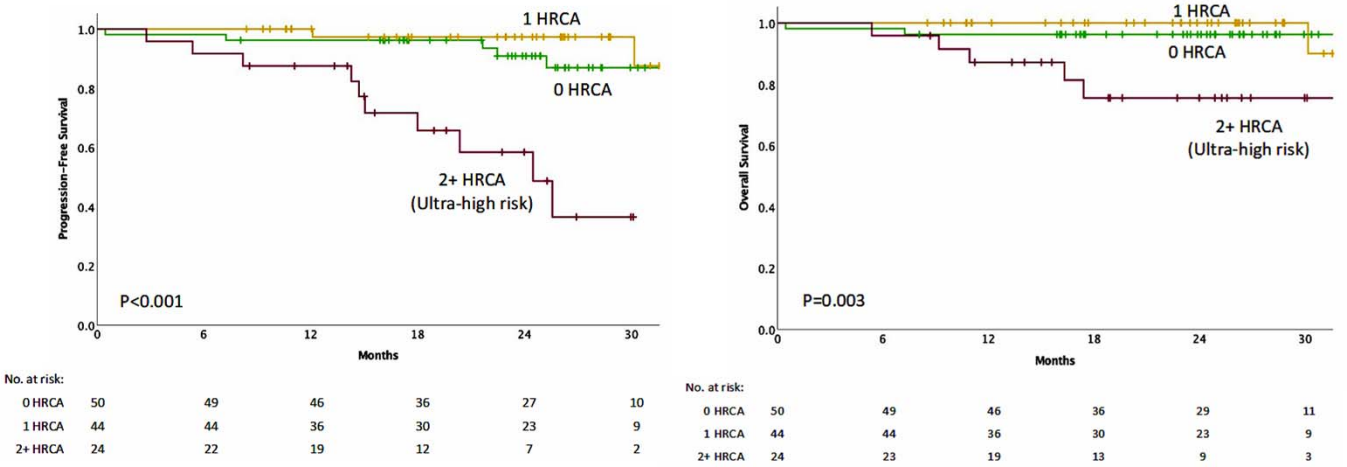

Costa LJ, et al. *Leukemia.* 2021;35:18-30.

If you look at the depth of MRD assessment, you can see here at all patients about 80% achieved MRD negativity at $10^{-5}$, and about 66% achieved it at $10^{-6}$.

If you begin to look at it by risk, what you'll see is that achieving these deep responses was almost independent of risk, which is something that I think all of us are struggling with a little bit honestly, but this was a very small Phase II study. I think it's too small to be able to feel confident that the risk or the likelihood of achieving MRD negativity is similar based on standard-risk versus high-risk.

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

## Progression-Free and Overall Survival




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

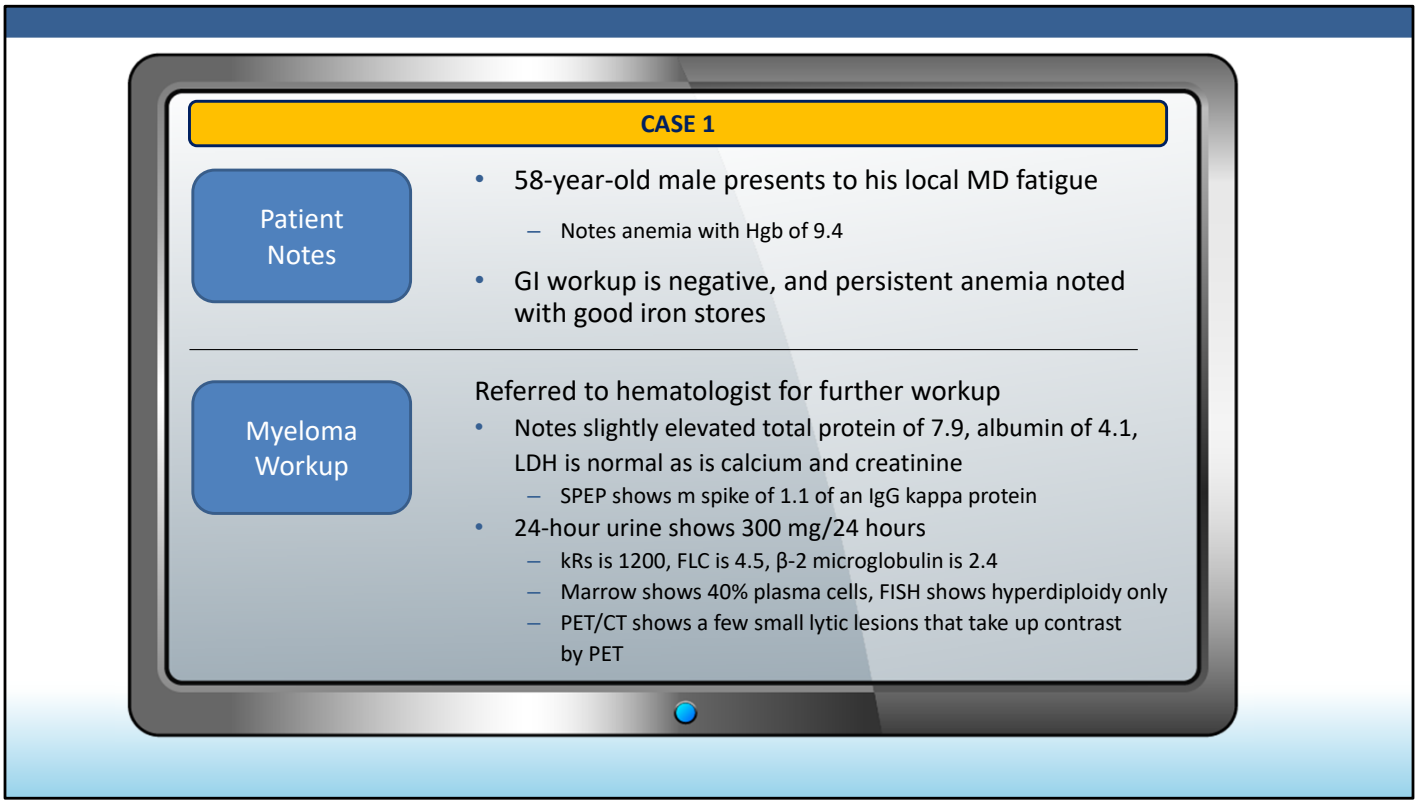
2-year OS: 0 HRCA 96%; 1 HRCA 100%; 2+ HRCA 76%

Costa LJ, et al. *Leukemia.* 2021;35:18-30.

If you look at the progression-free survival, and remember the median follow-up was only 18 months in this trial, what you'll see is that if you had high risk, and many of these patients actually discontinued therapy, that the relapse rate was actually quite high. More importantly, if you didn't have high risk and you discontinued therapy, you were relapsing as well. Again, to me, the idea of seeing two time points, three months apart and $10^{-5}$ really doesn't make sense. Overall survival is not a surprise that it's pretty good for most of these patients, but really PFS is what we're shooting for. In my mind, this tells me that we shouldn't use these two metrics to make decisions about discontinuation of therapy.

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

# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes




Let's go to a case. 58-year-old gentleman who presented to his local physician with anemia, hemoglobin of 9.4. GI workup was negative, persistent anemia noted with good iron stores. He was referred to a hematologist and noted an elevated total protein, normal albumin, LDH and calcium, and creatinine are normal. About 1.1 grams of an IgG kappa, 24-hour urine shows 300 milligrams per 24 hours of a kappa light chain, serum-free light chain showed a kappa light chain of 1200 with a free lambda of 4.5 with a beta-2 of 2.4. Marrow had about 40% plasma cells and FISH showed hyperdiploidy only, and the PET-CT was positive for lytic lesions on exam.

## Case 1 - Polling Question #1

**Based on these findings, what is the R-ISS stage for this patient?**
*(please select your response)*

A. R-ISS Stage 1
B. R-ISS Stage 1a
C. R-ISS Stage 2
D. R-ISS Stage 2a
E. R-ISS Stage 3
F. R-ISS Stage 3a

Based on these findings, what is the R-ISS stage for this patient?

A. R-ISS stage 1
B. R-ISS stage 1A
C. R-ISS stage 2
D. R-ISS 2A
E. R-ISS 3
F. R-ISS stage 3A

Take a moment to answer.

## Case 1 - Polling Question #1

**Based on these findings, what is the R-ISS stage for this patient?**

A. R-ISS Stage 1
B. R-ISS Stage 1a
C. R-ISS Stage 2
D. R-ISS Stage 2a
E. R-ISS Stage 3
F. R-ISS Stage 3a

I will tell you that the correct answer is A, R-ISS stage 1. Those of you that chose the A, B, and C, or 1 versus 1A, that doesn't exist in the R-ISS any longer. That was the Durie Salmon staging. A's do not exist in R-ISS. It's either stage 1, 2, or 3 with a low beta-2, a normal albumin, normal genetics, and a normal LDH, that puts it at an R-ISS stage 1.

## Case 1 - Polling Question #2

**Based on his risk level, please select your induction regimen of choice.**
*(please select your response)*

A. Rd
B. VCd
C. RVd
D. KRd
E. RVd + daratumumab
F. KRd + daratumumab

Rd = lenalidomide and dexamethasone; VCd = bortezomib, cyclophosphamide, and dexamethasone
RVd = lenalidomide, bortezomib, and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone

Based on his risk level, please select your induction treatment of choice.

A. Rd
B. VCd
C. RVd
D. KRd
E. RVd + daratumumab
F. KRd +daratumumab

Take a moment to answer

## Patient Discussion

- Patient is diagnosed with R-ISS stage 1 disease with low B2M and normal genetics/LDH
- Discussion on treatment includes RVd+/- dara as choice of treatment

The patient was diagnosed with R-ISS stage 1 disease with a low beta-2 at normal genetics. Again, at least at our center with standard-risk myeloma, we would use RVd plus Dara. Now the question that often comes up is, well, if you use Dara upfront, are you going to have Dara available in the relapse setting? At least at our center currently, we're not giving Dara as consolidation or maintenance. We're only giving it for that first 4 cycles of therapy and then giving, again, transplant as consolidation and single-agent lenalidomide is maintenance for the high-risk patient. Yes, you can reuse Dara down the road if you need to. We're waiting on longer follow-up from larger trials to really tell us whether the addition of Dara in the consolidation and maintenance phase really offers significant benefit.

More importantly, in the RVd 1000 series that our group published about two years ago now, where we treated 1,000 consecutively patients with RVd transplant and risk-adapted maintenance, what we showed was that for standard-risk patients, the median progression-free survival was almost 80 months. We updated this data at ASCO just a week or so ago. At least in my mind, you really have to show compelling PFS prolongation to justify the addition of Dara to Len in the context of a standard-risk myeloma patient post-transplant.

## Case Discussion Treatment Choice

- Physician and patient decide on D + RVd
- After 4 cycles the patient is in CR with normalization of the FK*

*kappa free serum

Physician and patient decided on Dara plus RVd. After 4 cycles, he's in CR with normalization of his light chains.

## Case 1 - Polling Question #3

**At this point in treatment, what would you recommend?**
*(please select your response)*

A. Recommend stem cell collection and transplant

B. Recommend stem cell collection and delay transplant

C. Continue treatment and not consider transplant

D. Refer for allogeneic transplant due to the patient age

At this point, what would you recommend?

A. Stem cell collection and transplant
B. Stem cell collection and delayed transplant
C. Continue treatment and not consider transplant
D. Refer for allogeneic transplant due to the patient's age

## Case 1 - Polling Question #3

**At this point in treatment, what would you recommend?**

A. Recommend stem cell collection and transplant

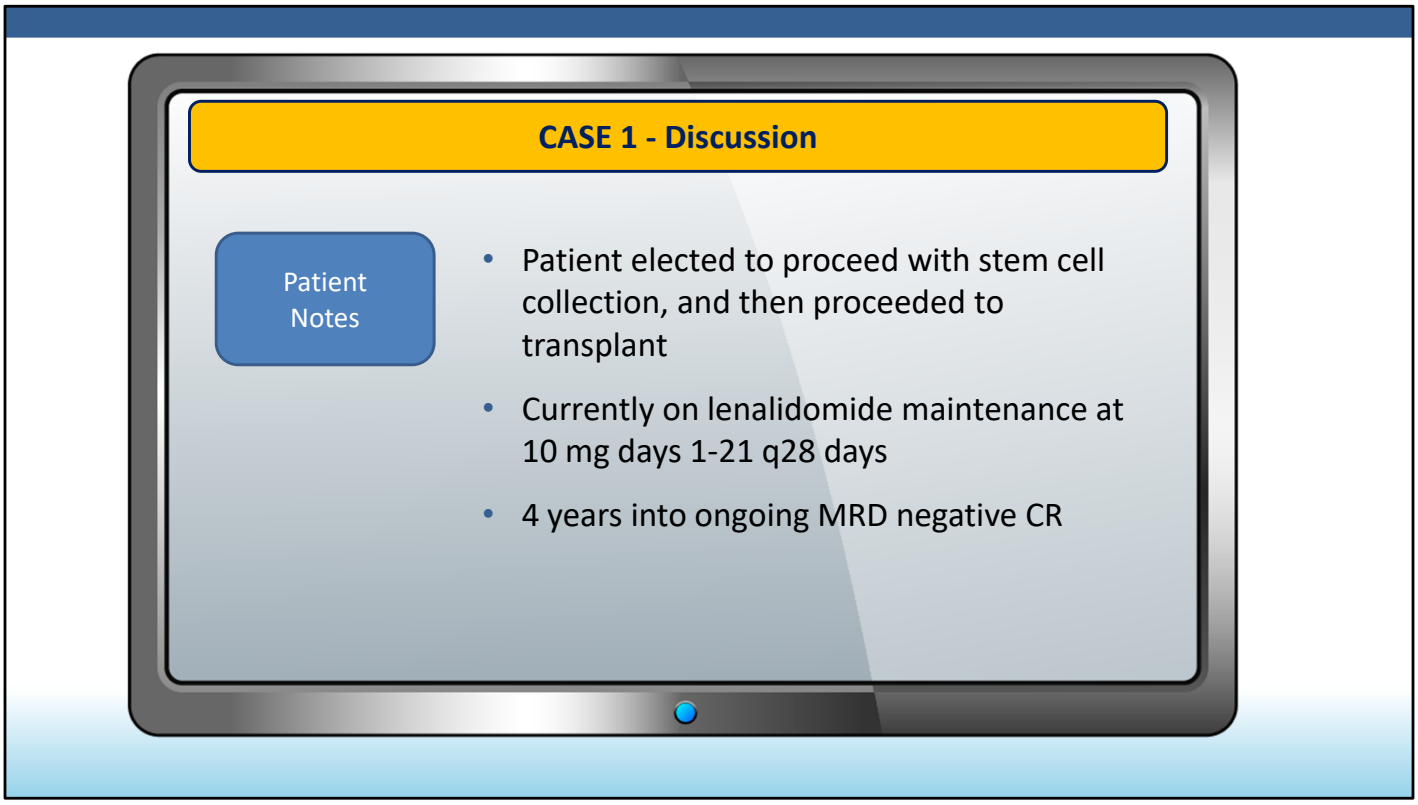
B. Recommend stem cell collection and delay transplant

C. Continue treatment and not consider transplant

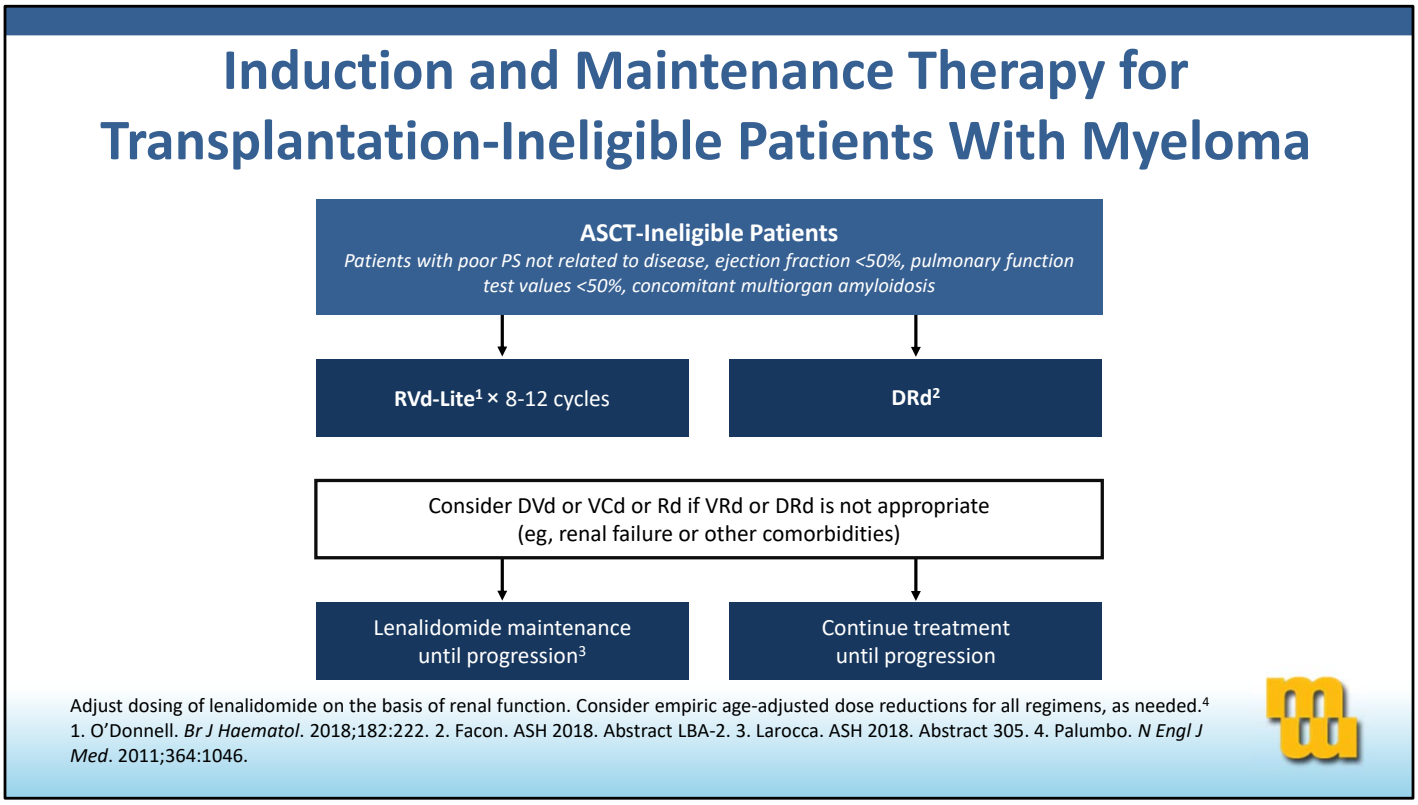
D. Refer for allogeneic transplant due to the patient age

Recommended stem cell collection and transplant, which would've been my vote as well. Recommended stem cell collection and delayed transplant. Again, I think the DETERMINATION study does really support the use of early auto transplant to prolong that first remission to almost 65 months, that's 5½ years now, on average. Again, if you're standard risk, it's almost 80 months. There was a small number of you all that said allo transplant. I don't know many of us are doing allo transplant in patients with myeloma anymore unless you live in Germany where they seem to do a lot of allo transplants in the context of multiple myeloma.

# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes




Patient elected to proceed with stem cell collection, and then transplant currently on Len maintenance, 10 milligrams, days 1-21, Q 28 days, four years is into ongoing MRD negative complete remission.




Let's switch gears a little bit and talk about induction and maintenance therapy for patients with transplant-ineligible multiple myeloma. There really are two paradigms here. One is RVd-lite x 8-12 cycles. That was based in part on a modification between the SWOG study and the group at Mass General, and we'll see that data. The alternative is DRd, which is daratumumab/lenalidomide/dexamethasone. We'll talk about that and the MAIA trial as well. Again, in both of these, lenalidomide or DRd until progression.

Adjust dosing of lenalidomide on the basis of renal function. Consider empiric age-adjusted dose reductions for all regimens, as needed.[4]

## NCCN Regimens for Non-Transplant Candidates

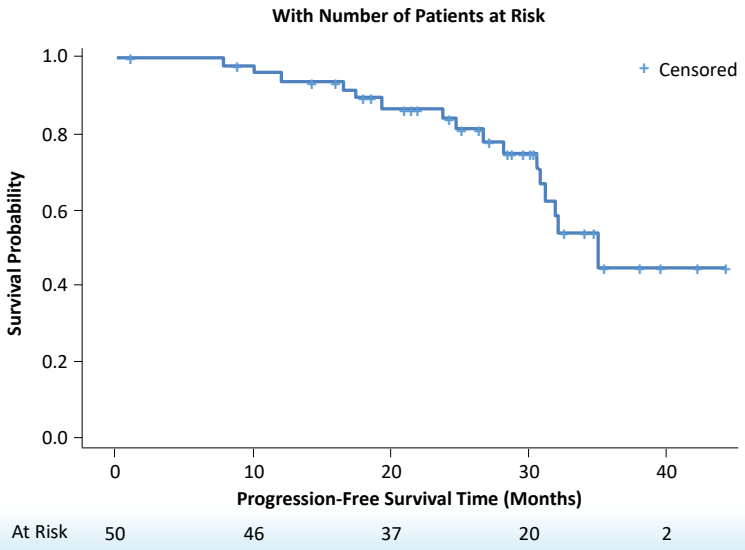
| Primary Therapy for Nontransplant Candidates |
|---|
| **Preferred Regimens**<br>• Bortezomib/lenalidomide/dexamethasone (category 1)<br>• Daratumumab/lenalidomide/dexamethasone (category 1) |
| **Other Recommended Regimens**<br>• Carfilzomib/lenalidomide/dexamethasone<br>• Ixazomib/lenalidomide/dexamethasone<br>• Daratumumab/bortezomib/melphalan/prednisone (category 1)<br>• Daratumumab/cyclophosphamide/bortezomib/dexamethasone |
| **Useful in Certain Circumstances**<br>• Bortezomib/dexamethasone<br>• Bortezomib/cyclophosphamide/dexamethasone<br>• Cyclophosphamide/lenalidomide/dexamethasone<br>• Carfilzomib/cyclophosphamide/dexamethasone<br>• Lenalidomide/low-dose dexamethasone (category 1)<br>• Bortezomib/lenalidomide/dexamethasone (VRD-LITE) for frail patients |

All recommendation are category 2A unless otherwise indicated.
NCCN Guidelines Version 4.2022.

What are the NCCN recommendations again? VRd is a category one, daratumumab/lenalidomide/dexamethasone is a category one, and daratumumab/bortezomib/melphalan/prednisone is a category one based on a trial from Spain. I don't think any of us really do that anymore in the US, but certainly, there is a randomized trial suggesting benefit there. Again, I like to avoid the use of cyclophosphamide at all. I don't think that these ones under useful circumstances really do offer much benefit for patients any longer.

## RVd-Lite

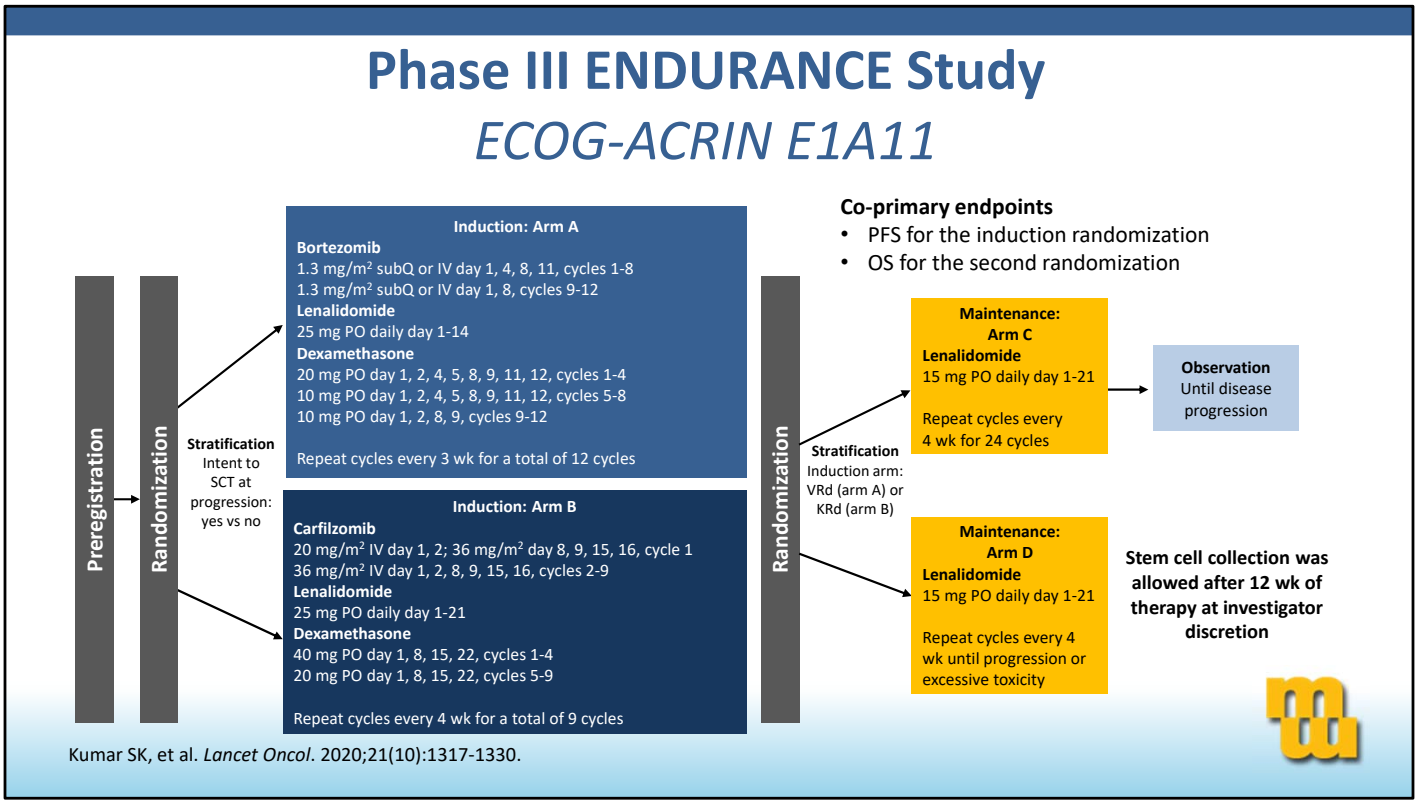
- Regimen (N = 53)
  - Lenalidomide: 15 mg PO days 1 to 21
  - Bortezomib: 1.3 mg/m$^2$ SC 1× weekly on days 1, 8, 15, 22
  - Dexamethasone
    - If ≤75 years, 20 mg 2× weekly
    - If >75 years, 20 mg 1× weekly
- Results
  - 86% ORR
  - 66% ≥VGPR
  - Median PFS: 35.1 months
  - Median OS: NR
  - Median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




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

Here's the data on RVd-lite, which is again from the group at Mass General. They used weekly Len or weekly bortezomib, lenalidomide at 15 milligrams and dose-reduced dexamethasone. High overall response rate, high VGPR, or better. The median PFS in this very small study of only 53 patients was about 35 months. Not dissimilar from what we saw in the SWOG 777 for RVd, but it seems to be a little bit better tolerated than RVd in the SWOG 777, particularly for older patients.

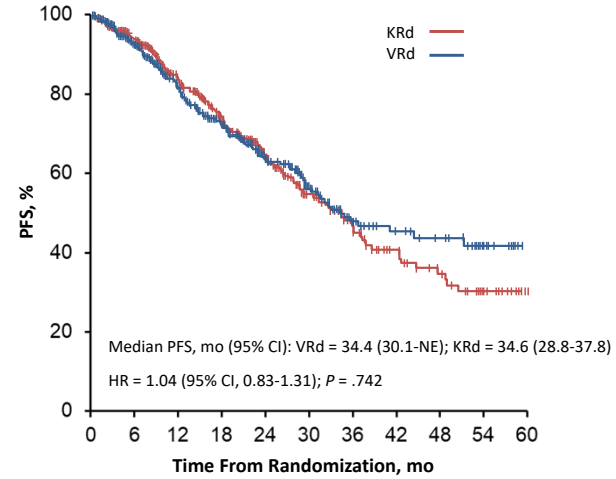
PN, peripheral neuropathy.




What about the ENDURANCE trial? This is the one that I mentioned earlier. This is VRd versus KRd. This question was really trying to prove that KRd was better than VRd in all patients. This was not just older or younger patients. This was all patients. There was no transplant in this. Then there was a second randomization to either maintenance lenalidomide for two years or maintenance lenalidomide continuously until progression. That second randomization, we don't have data, but we do have data on the first one.

## 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 yr, 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)



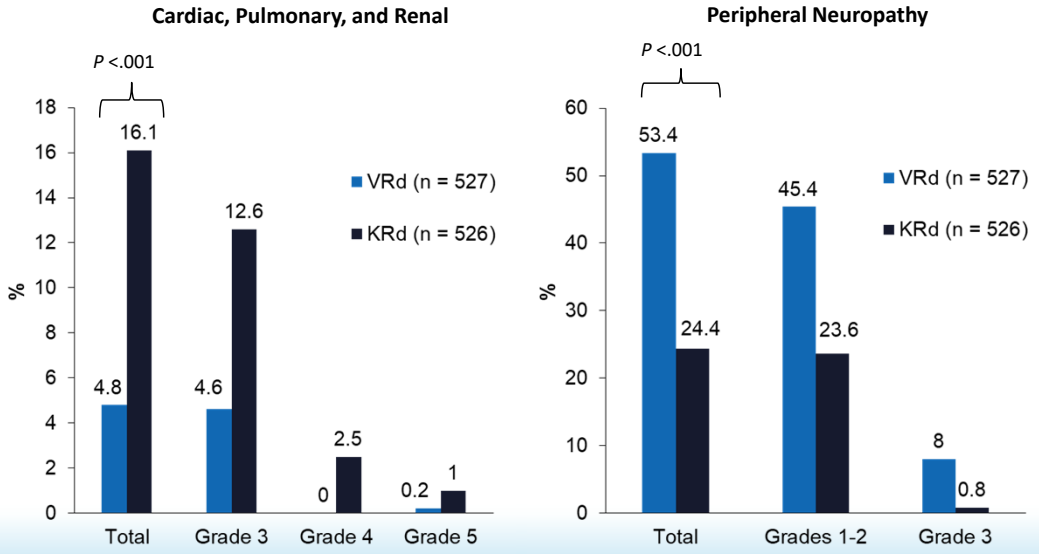

**No. at Risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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. *Lancet Oncol*. 2020;21(10):1317-1330.

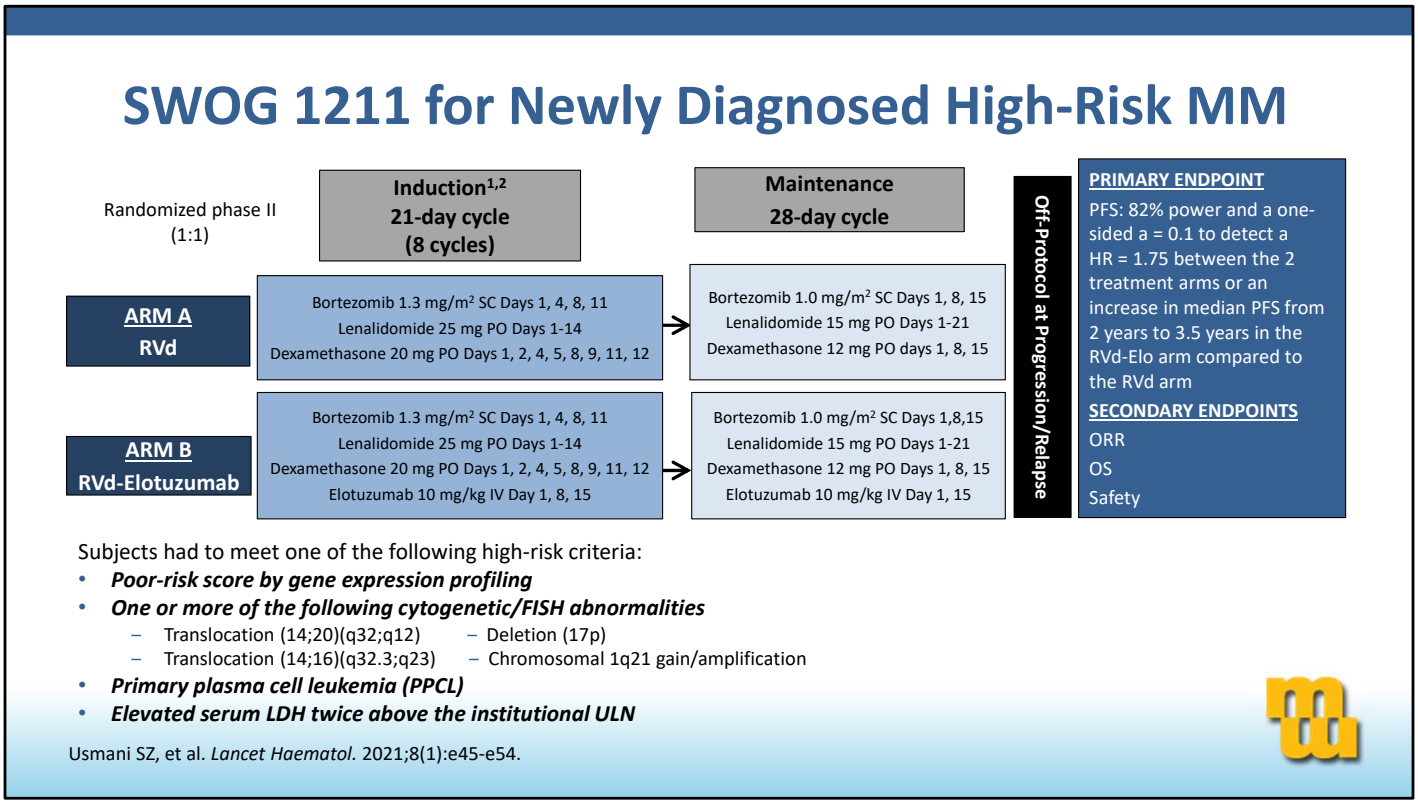
What you see here is that the PFS from induction is no different between VRd and KRd. What it suggests to me is that if you don't use a transplant early on in a standard-risk patient population, there is no real benefit for KRd over VRd. They are equivalent.

## ENDURANCE: Adverse Events of Interest




Kumar SK, et al. *Lancet Oncol*. 2020;21(10):1317-1330.

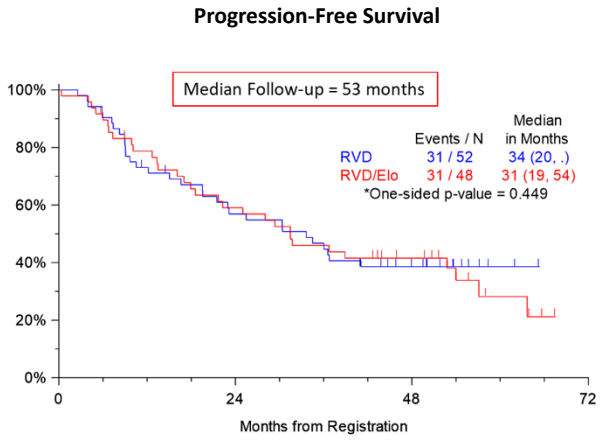
In fact, if you look at adverse events, the real difference was that in KRd, you got cardiac pulmonary and renal toxicity, and in VRd you got peripheral neuropathy. I think most of us are used to using VRd now and so adjusting this is a little bit easier for us. Very few patients got grade 3 and peripheral neuropathy, but certainly, something that can be very challenging for patients overall. On the other hand, what you saw was grade 3 and 4 cardiac, pulmonary, and renal toxicities that can be limiting on therapy in some patients as well.

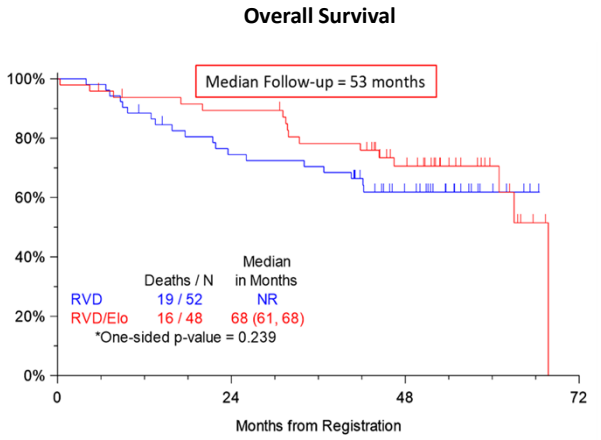



Now, the SWOG-1211 study is a newly diagnosed trial for high-risk myeloma. This was looking at VRd versus elotuzumab-VRd only in high-risk patients. There was an induction phase and then a maintenance phase. Again, no transplant here, which I think in hindsight was likely an oversight because now in Europe we know that they're recommending two transplants for patients with high-risk myeloma, in this one they're recommending no transplant.

1. One cycle of prior therapy allowed prior to enrollment. 2. Stem cell collection allowed after cycle 2 on protocol, ASCT allowed off-protocol at progression/relapse.

## SWOG 1211 Phase II: PFS and OS

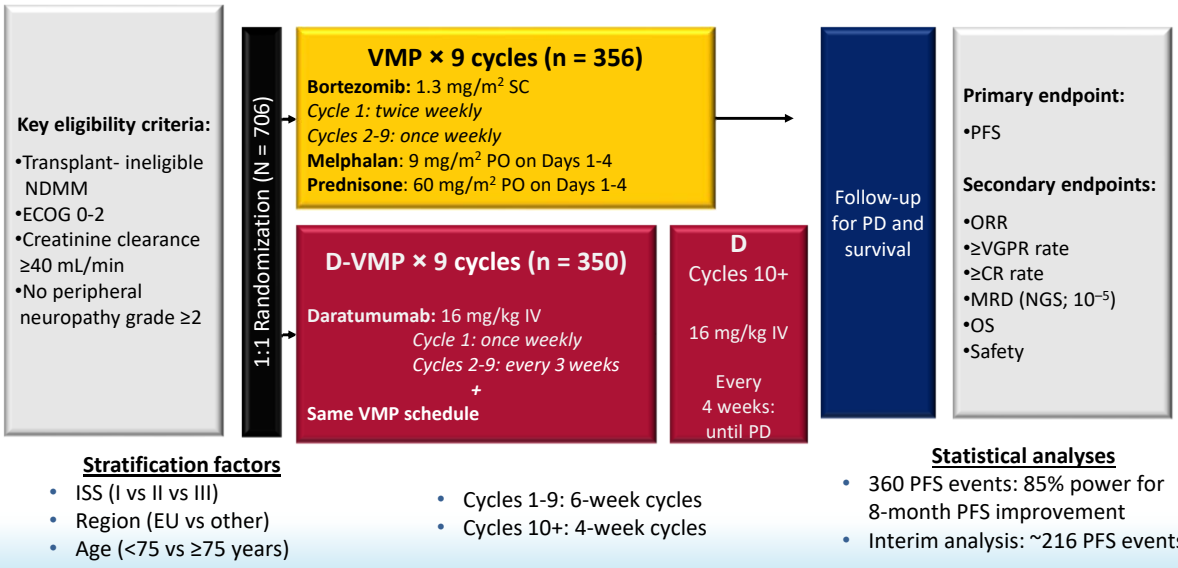



Usmani SZ, et al. *Lancet Haematol.* 2021;8(1):e45-e54.

When we look at differences in progression-free survival, what we see is no difference in PFS. There's a hint towards an improvement in OS, but it's not really statistically significant. In a purely high-risk patient population, the addition of Elo to RVd does not appear to move the needle in terms of progression-free survival or overall survival. Again, median is about 25/26 months, somewhere in that ballpark there. This didn't really raise to the level where we needed it. I think we now know that everybody would recommend transplant for those high-risk patients, particularly in first remission.

## ALCYONE Phase III Study of Daratumumab + VMP in NDMM




**Stratification factors**
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

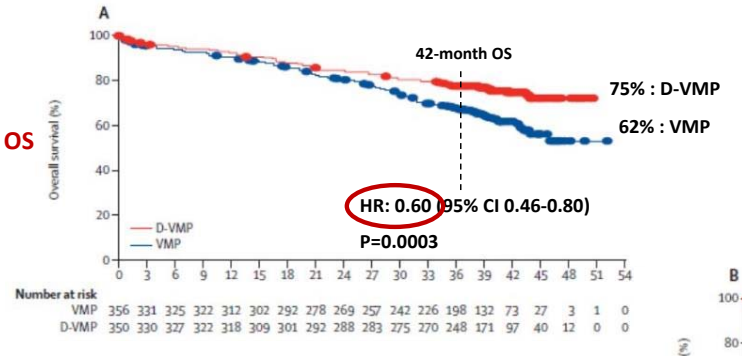
**Statistical analyses**
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

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

Now, the ALCYONE trial was a trial that I mentioned earlier using bortezomib, melphalan, and prednisone versus Dara, bortezomib, melphalan, and prednisone.
This is a complicated trial in that the group that got Dara actually got maintenance therapy. Whereas the group that got VMP did not get maintenance therapy. Remember that was how the VMP regimen was used originally, predominantly out of Spain.

# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes

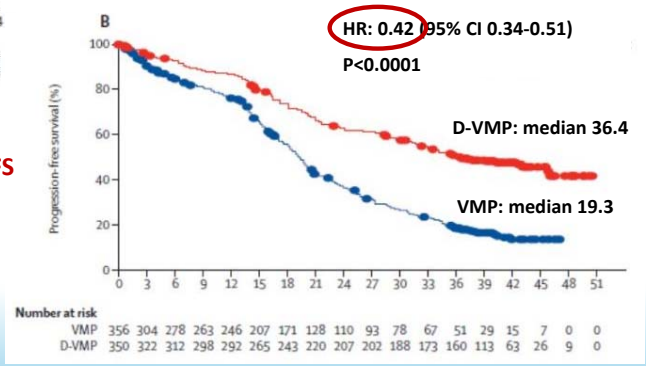
## OS and PFS ALCYONE Trial




OS

Median follow-up: 40.1 months

PFS




Mateos MV, et al. *Lancet*. 2020;395:132-141.;
Mateos MV, et al. ASH 2019. Abstract 859.

If you look at it, clear benefit for the addition of Dara, some of this may be a maintenance effect. Some of this may be Dara in induction, both in terms of progression-free and overall survival with a median follow-up of about 40 months. Clearly better than VMP, but none of us really use VMP anymore.

## Most Common AEs During Tx in the Safety Population

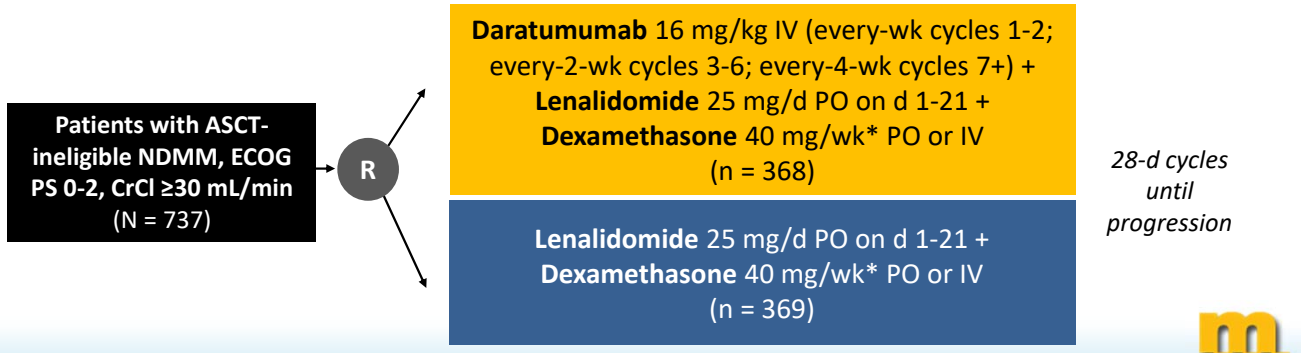
| Event | Daratumumab Group (N = 346) | | Control Group (N= 354) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *Number of patients (percent)* | | | |
| Hematologic AEs | | | | |
| Neutropenia | 172 (49.7) | 138 (39.9) | 186 (52.5) | 137 (38.7) |
| Thrombocytopenia | 169 (48.8) | 119 (34.4) | 190 (53.7) | 133 (37.6) |
| Anemia | 97 (28.0) | 55 (15.9) | 133 (37.6) | 70 (19.8) |
| Non-hematologic AEs | | | | |
| Peripheral sensory neuropathy | 98 (28.3) | 5 (1.4) | 121 (34.2) | 14 (4.0) |
| Diarrhea | 82 (23.7) | 9 (2.6) | 87 (24.6) | 11 (3.1) |
| Pyrexia | 80 (23.1) | 2 (0.6) | 74 (20.9) | 2 (0.6) |
| Nausea | 72 (20.8) | 3 (0.9) | 76 (21.5) | 4 (1.1) |
| Infections | 231 (66.8) | 80 (23.1) | 170 (48.0) | 52 (14.7) |
| Upper resp. tract infection | 91 (26.3) | 7 (2.0) | 49 (13.8) | 5 (1.4) |
| Pneumonia | 53 (15.3) | 39 (11.3) | 17 (4.8) | 14 (4.0) |
| Secondary primary cancer | 8 (2.3) | NA | 9 (2.5) | NA |
| Any infusion-related reaction | 96 (27.7) | 17 (4.9) | NA | NA |

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

If you look at adverse events, the use of Dara does increase the number of infections, and particularly pneumonia. That is something that I think we all need to be aware of and use appropriate prevention and prophylaxis to potentially reduce that risk of complications.

## Phase III MAIA Study: Daratumumab + Rd in NDMM

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

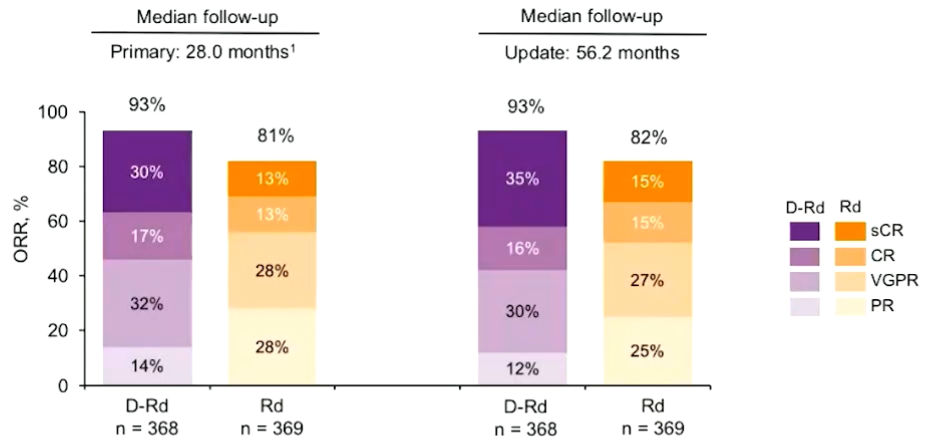



Facon T, et al. *N Engl J Med*. 2019;380:2104-2115.

I think the trial that really sort of changed the landscape for the older, frailer patient was the MAIA trial. MAIA is a randomized Phase III trial of Dara-Len-Dex versus Len-Dex in about 700 patients who were older and transplant-ineligible. Now they use 65 as the cutoff, but I will tell you that about a third of the patients enrolled in this trial were over the age of 75. It really did represent a good spectrum of who patients are in the world of older frailer myeloma.

*Reduced to 20 mg/wk if aged >75 y or BMI <18.5.

## MAIA - Overall Response Rate




- 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 DARA therapy

Facon T, et al. EHA 2021. Abstract LB1901.

Again, what you'll see here are responses, clearly better in the group that got Dara compared to the group that did not, 93 versus 81. If you look at 56-month follow up, 93 versus 82 with much more patients achieving CR and VGPR in the Dara group compared to the group that did not get Dara. In fact, this response rate looks a little better than Len/Dex in the first trial or other trials looking at Len/Dex in older, frailer patients as well.

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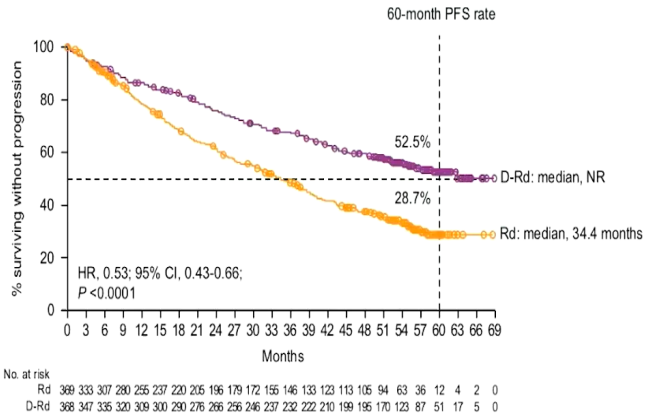
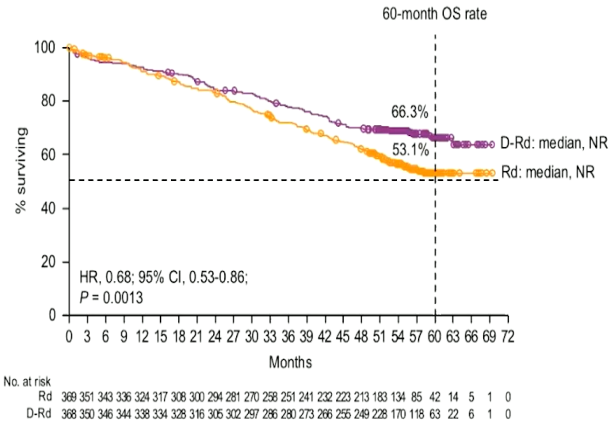
## MAIA - Updated PFS/OS




- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
- These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible

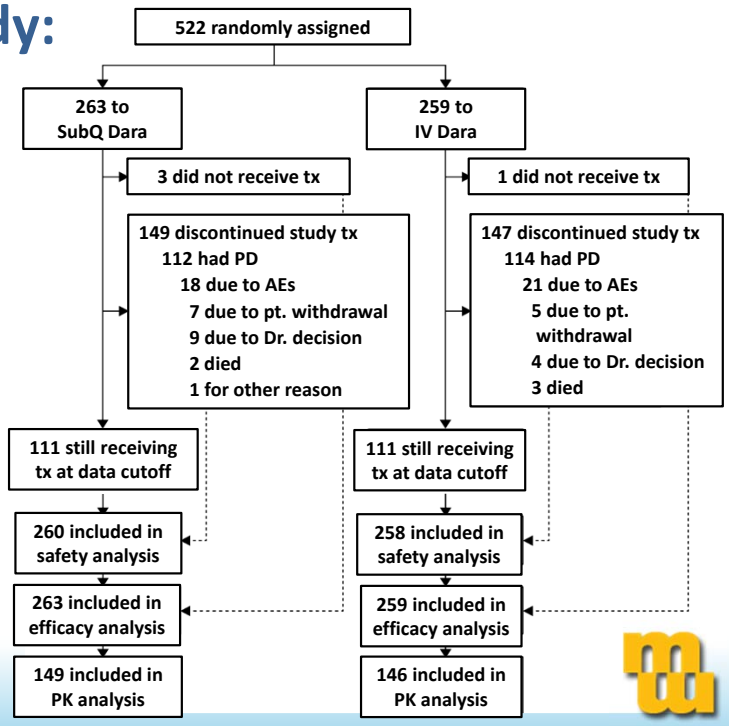



- D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death in patients with NDMM who are transplant ineligible

Facon T, et al. EHA 2021. Abstract LB1901.

If you now begin to look at PFS and OS, big differences favoring to Dara group, both in terms of PFS. Median PFS is about 60 months, so about five years. Again, if you look at the median PFS on the Len/Dex arm, about 34 months, which is about what you'd expect for Len/Dex, but even more importantly, both PFS and OS were better in the group that got Dara-Len-Dex compared to the group that just got lenalidomide and dexamethasone, and at least doing what statisticians tell us never to do, comparing trials against each other, this is far superior to anything that's ever been reported with RVd or VRd in the older, frailer patient population to date.

## Phase III COLUMBA Study: SC Daratumumab

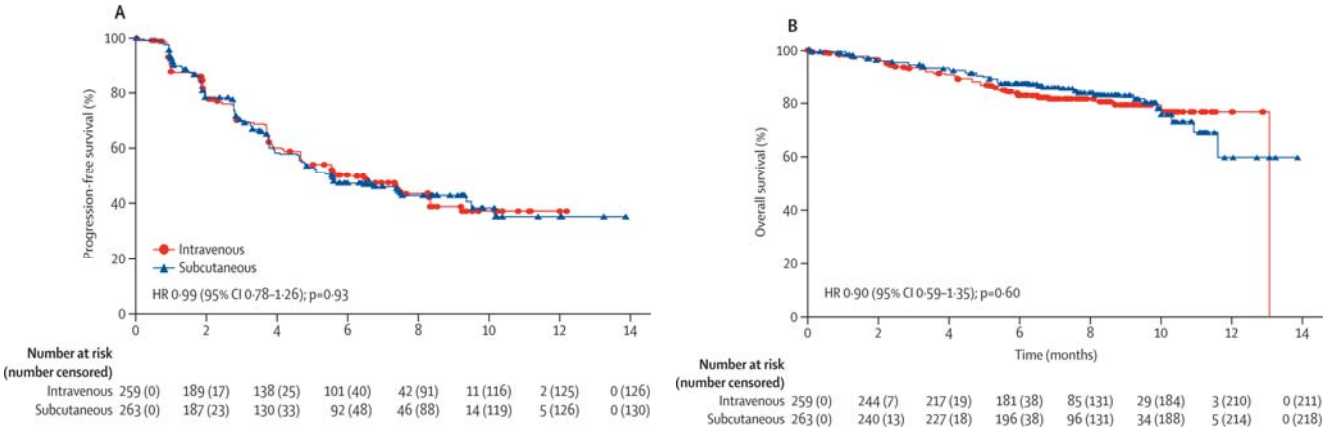



Mateos MV, et al. *Lancet Haematol*. 2020;7(5):e370-e380.

Now, what about the COLUMBA trial? The COLUMBA trial was a randomized Phase III trial looking at SubQ Dara versus IV Dara in an effort to try and make it a lot easier for patients. You can see 522 patients, single-agent Dara, almost all of these were in the relapse setting.

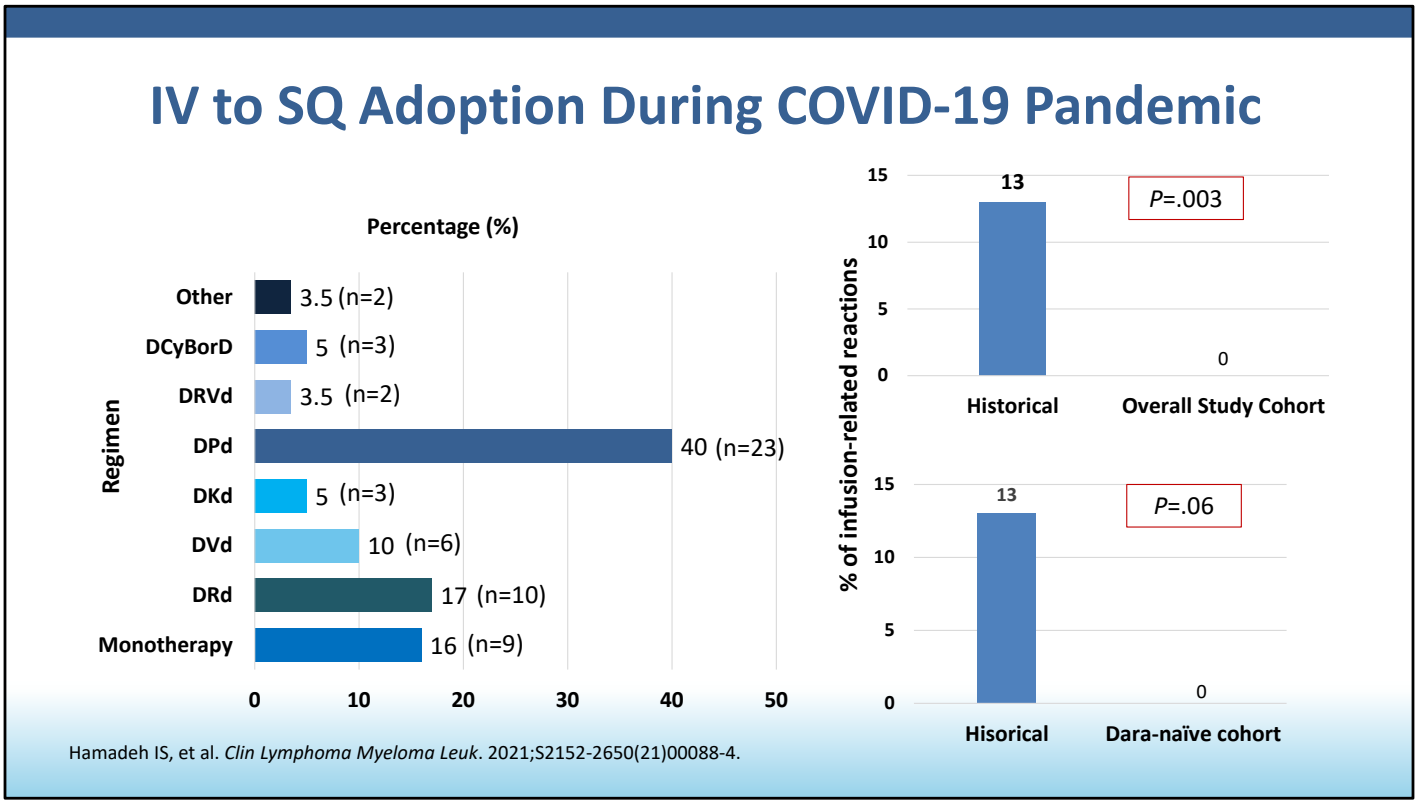
subQ, subcutaneous; Dara, daratumumab; tx, treatment; PD, progressive disease; AEs, adverse events; pt., patient; PK, pharmacokinetics

## Phase III COLUMBA Study: Survival Outcomes




Mateos MV, et al. *Lancet Haematol*. 2020;7(5):e370-e380.

What you'll see here overall is no difference in progression-free survival and no difference in overall survival, telling us that you can easily substitute out SubQ for IV. In fact, the adverse event profile was much better in the SubQ group than in the IV group across the board.




Here it is. IV to SubQ adoption during the COVID-19 pandemic, certainly at our center, we switched immediately after approval, but certainly COVID helped to try and shorten time patients were in the infusion center, to reduce their risk of potentially getting COVID during an infusion center visit across the board.

# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes

The combination of bortezomib, lenalidomide, and dexamethasone (VRd) is one of the standard of care (SOC) first-line treatments for transplant-ineligible newly diagnosed multiple myeloma (TI NDMM)[1]

Ongoing development of novel therapies and combinations strive to improve survival outcomes beyond what is expected from SOC (median overall survival of 75 months with VRd)[1]

Belantamab mafodotin (belamaf) has a multimodal mechanism of action that eliminates multiple myeloma cells via a direct cytotoxic kill as well as by a systemic anti-MM tumor immune response[2–4]

In the DREAMM-2 phase II study, belamaf showed deep and durable responses (very good partial response [VGPR] or better, 19% and duration of response, 11 months [95% CI, 4.25 months to not reached]) in patients with relapsed/refractory multiple myeloma (RRMM)[5,6]

Enhanced anti-myeloma activity has been demonstrated in preclinical work when belamaf has been combined with bortezomib or lenalidomide[2,7]

1. Durie BGM, et al. *Lancet.* 2017;389:519-527. 2. Tai YT, et al. *Blood.* 2014;123:3128-3138. 3. Tai YT, Anderson KC. *Immunotherapy.* 2015; 7:1187. 4. Montes de Oca R, et al. *Mol Cancer Ther.* 2021;20(10):1941-1955. 5. Lonial S, et al. *Lancet Oncol.* 2020;21:207-221. 6. Lonial S, et al. *Cancer*. 2021 doi: 10.1002/cncr.33809 epub ahead of print. 7. GSK data on file.

I think when we talk about transplant-ineligible patients, the combination of VRd is a standard. I think that Dara-Len-Dex certainly has replaced it. There are trials looking at belamaf in combination with Len/Dex using a BCMA-directed therapy. In fact, the DREAMM-2 study demonstrated that belamaf alone had single-agent response rates in refractory myeloma.

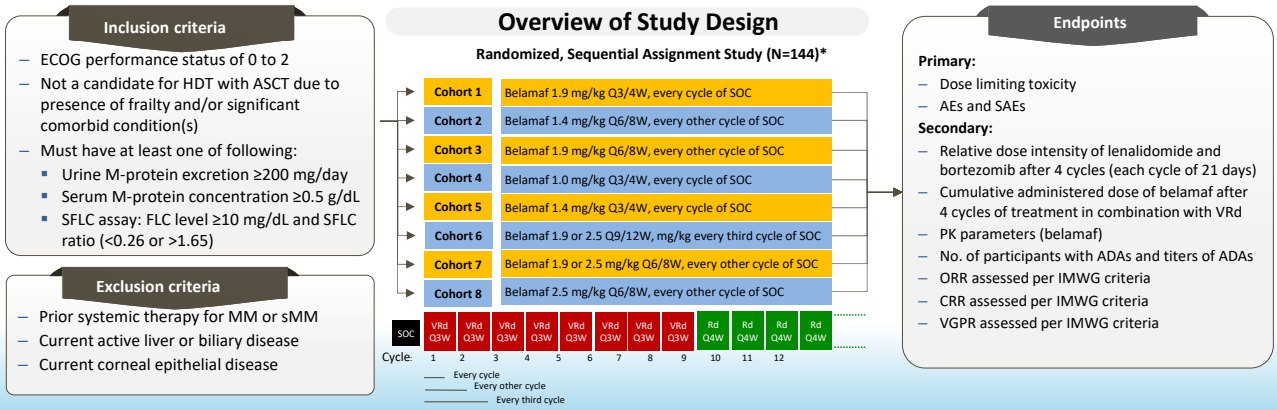
The real question is, can you add it with Len/Dex to try and improve outcomes across the board?

## DREAMM-9: Phase I Study of Belantamab Mafodotin Plus Standard of Care in Patients with Transplant-Ineligible NDMM: Introduction

DREAMM-9 (NCT04091126) is an ongoing phase I, open-label, randomized, dose and schedule evaluation study of belamaf + VRd in patients with TI NDMM. A detailed study design is shown in **Figure 1**

VRd is administered every 3 weeks (Q3W) through Cycle 8 based on SOC dosing, followed by lenalidomide + dexamethasone (Rd) Q4W. Belamaf + VRd is administered until Cycle 8, and thereafter in combination with Rd

**Figure 1. Study Design**




This is data on a trial that Dr. Usmani is leading looking at belamaf in combination with Len/Dex or with VRd with different doses and schedules of belamaf. What I want you to notice is it's not the 2.5 mg/kg given every three weeks. It's 1.9, 1.4, 1.0, and the schedule is changing from Q6, Q8, Q9, Q12, Q3, Q4. Looking at lots of different permutations on this.

*Following evaluation of safety data for Cohort 1, Cohorts 2–5 were opened in parallel and enrolled patients were randomized 1:1:1:1;
† Belamaf will be administered intravenously; ‡Belamaf administered in split doses on Day 1 and 8 of the cycle.

ADA, anti-drug antibodies; AEs, adverse events; ASCT, autologous stem cell transplant; belamaf, belantamab mafodotin; CRR, complete response rate; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; HDT, high dose chemotherapy; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; Q8W, every 8 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; Rd, lenalidomide and dexamethasone; SAE, serious adverse events; SFLC, serum FLC; sMM, smoldering MM; SOC, standard of care; TI NDMM, transplant-ineligible newly diagnosed multiple myeloma; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.

# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes

## Results

### Patient population

At data cut-off, August 11, 2021, 62 patients with TI NDMM have been treated in this study. Here we report data for the first 36 patients; 12 patients in Cohort 1 and 6 patients each in Cohorts 2–5

- 56% (n=20) of the total study population was male, and patients had a median age of 74 years
- 28% of patients (n=10) in the total study population were International Staging System (ISS) stage I, and 61% of patients (n=22) were stage II or III
- 17% of patients (n=6) in the total study population had high-risk cytogenetics (consisting of one or more of the following cytogenetic abnormalities: t(4;14), t(14;16), del17p)

**Demographics, Baseline Disease, and Clinical Characteristics for Patients Treated with Belamaf + VRd**

| | Cohort 1 belamaf 1.9 mg/kg Q3/4W, every cycle of SOC n=12 | Cohort 2 belamaf 1.4 mg/kg Q6/8W, every other cycle of SOC n=6 | Cohort 3 belamaf 1.9 mg/kg Q6/8W, every other cycle of SOC n=6 | Cohort 4 belamaf 1.0 mg/kg Q3/4W, every cycle of SOC n=6 | Cohort 5 belamaf 1.4 mg/kg Q3/4W, every cycle of SOC n=6 | Total Population N=36 |
|---|---|---|---|---|---|---|
| **Age, median (range), years** | 72.5 (63–77) | 74.5 (69–80) | 74.5 (71–78) | 74.0 (72–79) | 74.5 (68–80) | 74.0 (63–80) |
| **18 to <65 years, n (%)** | 2 (17) | 0 | 0 | 0 | 0 | 2 (6%) |
| **65 to <75 years, n (%)** | 5 (42) | 3 (50) | 3 (50) | 5 (83) | 3 (50) | 19 (53) |
| **≥75 years, n (%)** | 5 (42) | 3 (50) | 3 (50) | 1 (17) | 3 (50) | 15 (42) |
| **Sex, n (%)** | | | | | | |
| **Male** | 8 (67) | 2 (33) | 2 (33) | 3 (50) | 5 (83) | 20 (56) |
| **Female** | 4 (33) | 4 (67) | 4 (67) | 3 (50) | 1 (17) | 16 (44) |
| **Race, n (%)** | | | | | | |
| **White** | 10 (83) | 4 (67) | 4 (67) | 5 (83) | 6 (100) | 29 (81) |
| **Black/African American** | 0 | 0 | 0 | 1 (17) | 0 | 1 (3) |
| **Asian** | 2 (17) | 1 (17) | 2 (33) | 0 | 0 | 5 (14) |
| **ISS disease stage, n (%)** | | | | | | |
| **Stage I** | 2 (17) | 2 (33) | 0 | 2 (33) | 4 (67) | 10 (28) |
| **Stage II** | 6 (50) | 3 (50) | 4 (67) | 3 (50) | 1 (17) | 17 (47) |
| **Stage III** | 3 (25) | 1 (17) | 1 (17) | 0 | 0 | 5 (14) |
| **Unknown** | 1 (8) | 0 | 1 (17) | 1 (17) | 1 (17) | 4 (11) |
| **Cytogenetic abnormalities, n (%)** | | | | | | |
| **High risk*** | 4 (33) | 0 | 1 (17) | 0 | 1 (17) | 6 (17) |
| **Other** | 8 (67) | 6 (100) | 5 (83) | 6 (100) | 5 (83) | 30 (83) |
| **Myeloma immunoglobulin, n (%)** | | | | | | |
| **IgA** | 5 (42) | 3 (50) | 0 | 3 (50) | 1 (17) | 12 (33) |
| **IgG** | 7 (58) | 3 (50) | 6 (100) | 3 (50) | 3 (50) | 22 (61) |
| **None** | 0 | 0 | 0 | 0 | 2 (33) | 2 (6) |
| **Light chain, n (%)** | | | | | | |
| **Kappa** | 7 (58) | 2 (33) | 5 (83) | 5 (83) | 4 (67) | 23 (64) |
| **Lambda** | 3 (25) | 3 (50) | 1 (17) | 1 (17) | 2 (33) | 10 (28) |
| **Extramedullary disease, n (%)** | | | | | | |
| **Yes** | 3 (25) | 0 | 0 | 0 | 0 | 3 (8) |
| **Median number of belamaf cycles (range)** | 5.5 (2–9) | 3.0 (2–4) | 3.0 (2–4) | 3.0 (1–9) | 3.0 (2–5) | NA |

What I think you'll see quite nicely actually is that the adverse events really do drop.

*High-risk cytogenetics defined as t(4;14), t(14;16), del17p

Belamaf, belantamab mafodotin; Ig, immunoglobulin; ISS, International Staging System; NA, not applicable; Q3/4W, every 3 weeks for Cycle 1–8 and every 4 weeks afterwards; Q6/8W, every 6 weeks for Cycle 1–8 and every 8 weeks afterwards; SOC: bortezomib, lenalidomide, and dexamethasone in Cycle 1–8 followed by lenalidomide and dexamethasone from Cycle 9 onwards; TI NDMM, transplant-ineligible newly diagnosed multiple myeloma; VRd, bortezomib, lenalidomide, and dexamethasone.

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## Results

**Safety**

- Patients in Cohort 2 and 3 had the lowest number of Grade ≥3 corneal events per the Keratopathy and Visual Acuity (KVA) scale, 3 patients (50%) and 2 patients (33%), respectively
- Corneal AEs related to belamaf led to dose delays in ≥50% of patients across all cohorts and dose reductions in 1 patient in Cohort 1 (8%) and 1 patient in Cohort 3 (17%)
- No patients had a permanent treatment discontinuation related to belamaf-induced corneal AEs

**Summary of Corneal Events Across Cohorts**

| Corneal events | Cohort 1 belamaf 1.9 mg/kg Q3/4W, every cycle of SOC n=12 | Cohort 2 belamaf 1.4 mg/kg Q6/8W, every other cycle of SOC n=6 | Cohort 3 belamaf 1.9 mg/kg Q6/8W, every other cycle of SOC n=6 | Cohort 4 belamaf 1.0 mg/kg Q3/4W, every cycle of SOC n=6 | Cohort 5 belamaf 1.4 mg/kg Q3/4W, every cycle of SOC n=6 |
|---|---|---|---|---|---|
| **Any event, n (%)** | 12 (100) | 3 (50) | 4 (67) | 4 (67) | 5 (83) |
| **Corneal AEs leading to dose reduction of belamaf*** | 1 (8) | 0 | 1 (17) | 0 | 0 |
| **Corneal AEs leading to belamaf dose delay** | 11 (92) | 3 (50) | 3 (50) | 4 (67) | 5 (83) |
| **Grade ≥3 corneal events per KVA scale, n (%)** | 10 (83) | 3 (50) | 2 (33) | 4 (67) | 4 (67) |
| **Median time to onset of Grade ≥3 corneal event (range), days** | 81.0 (63–383) | 126.0 (85–197) | 103.0 (84–122) | 74.0 (42–145) | 57.5 (22–107) |
| **Worse case post baseline, n (%)** | | | | | |
| **≥3 line decline in BCVA (better eye)** | 5 (42) | 1 (17) | 0 | 1 (17) | 1 (17) |
| **≥3 line decline in BCVA (worse eye)** | 8 (67) | 1 (17) | 0 | 1 (17) | 3 (50) |

As you begin to think about alternative doses and schedules, you can see here, corneal adverse events leading to discontinuation are zero in at least three of the groups here.

*There were no permanent discontinuations of belamaf due to corneal AEs.

AE, adverse event; BCVA, best corrected visual acuity; belamaf, belantamab mafodotin; KVA, Keratopathy and Visual Acuity; Q3/4W, every 3 weeks for; Cycle 1–8 and every 4 weeks afterwards; Q6/8W, every 6 weeks for Cycle 1–8 and every 8 weeks afterwards; SOC, standard of care: bortezomib, lenalidomide, and dexamethasone in Cycle 1–8 followed by lenalidomide and dexamethasone from Cycle 9 onwards.

# Developments in Newly Diagnosed Multiple Myeloma: Considerations for Improved Patient Outcomes

## Results

### Efficacy

- Preliminary data on efficacy of belamaf combination treatments are encouraging
- ORR was 100% in Cohorts 1 (12 patients), 3, and 5 (6 patients each), and 83% in Cohorts 2 and 4 (5/6 patients each)
- At least half of patients in each cohort achieved ≥VGPR; the highest rates were seen in Cohorts 1 and 5
  - Based on real-time capture from the clinical database, VGPR were observed in some patients as early as 4 weeks into treatment
  - As of data cut-off, 3/12 patients in Cohort 1, 2/6 patients in Cohort 4, and 1/6 patients each in Cohorts 3 and 5 remained in complete response (CR); with 6/12 patients in Cohort 1 and 1/6 patient in Cohort 5 in stringent complete response (sCR) with a median follow-up of 12.7 and 4.0 months, respectively
- In Cohort 1, as of data cut-off, 9 of 12 patients with best response of ≥VGPR had an MRD assessment; 7 of the 9 patients who achieved ≥VGPR achieved minimal residual disease (MRD)-negative status at the first test after VGPR

**Efficacy Data for Patients Treated with Belamaf + VRd**

| Clinical response | Cohort 1 belamaf 1.9 mg/kg Q3/4W, every cycle of SOC n=12 | Cohort 2 belamaf 1.4 mg/kg Q6/8W, every other cycle of SOC n=6 | Cohort 3 belamaf 1.9 mg/kg Q6/8W, every other cycle of SOC n=6 | Cohort 4 belamaf 1.0 mg/kg Q3/4W, every cycle of SOC n=6 | Cohort 5 belamaf 1.4 mg/kg Q3/4W, every cycle of SOC n=6 |
|---|---|---|---|---|---|
| ORR, n (%; 95% CI) | 12 (100; 73.5–100) | 5 (83; 35.9–99.6) | 6 (100; 54.1–100) | 5 (83; 35.9–99.6) | 6 (100; 54.1–100) |
| sCR, n (%) | 6 (50) | 0 | 0 | 0 | 1 (17) |
| CR, n (%) | 3 (25) | 0 | 1 (17) | 2 (33) | 1 (17) |
| VGPR, n (%) | 3 (25)* | 4 (67) | 2 (33) | 1 (17) | 4 (67) |
| PR, n (%) | 0 | 1 (17) | 3 (50) | 2 (33) | 0 |
| SD, n (%) | 0 | 1 (17) | 0 | 0 | 0 |

In fact, if you look at, more importantly, the response rates, which you're beginning to see is response rates that are beginning to approach 100% overall response rates here, with about half the patients achieving CR, depending upon the dose and schedule of belamaf that was used. Certainly, exciting data coming on the horizon, needs to be validated in larger Phase III trials, but certainly suggests there may be other regimens using immune therapies that would be better than Len/Dex alone in an older, frailer patient population.

*Based on best confirmed response by the investigator.

Belamaf, belantamab mafodotin; CI, confidence interval; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial review; Q3/4W, every 3 weeks for Cycle 1–8 and every 4 weeks afterwards; Q6/8W, every 6 weeks for Cycle 1–8 and every 8 weeks afterwards; sCR, stringent complete response; SD, stable disease; SOC, standard of care: bortezomib, lenalidomide, and dexamethasone in Cycle 1–8 followed by lenalidomide and dexamethasone from Cycle 9 onwards; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.

## Clinical Take-Homes: Induction Therapy

### Transplant-Ineligible Patients

- VRD-lite and DRd are standards of care
- Daratumumab-based combinations are FDA approved and incorporated into treatment guidelines on the basis of phase III evidence
- **Future:** RVd-Dara? RVd-Bela?
- **Long-term future:** Molecularly adapted regimens for fewer cycles?

In terms of take-home messages again, VRd-lite and DRd are standards of care, Dara-based combinations are FDA-approved and are part of the guidelines. I think RVd Bela, RVd Dara for older, frailer patients, I'm not sure a quad really is the right way to go. The Dara-Len-Dex looks so good for standard-risk patients. It's hard not to use it, but certainly for high-risk older patients thinking about alternatives, whether Bela is part of it or not, is certainly an interesting approach. Then, are there ways to discontinue therapy for older patients to reduce the morbidity of treatment on them? This certainly is something that I think we need to look at in a little greater detail as well.

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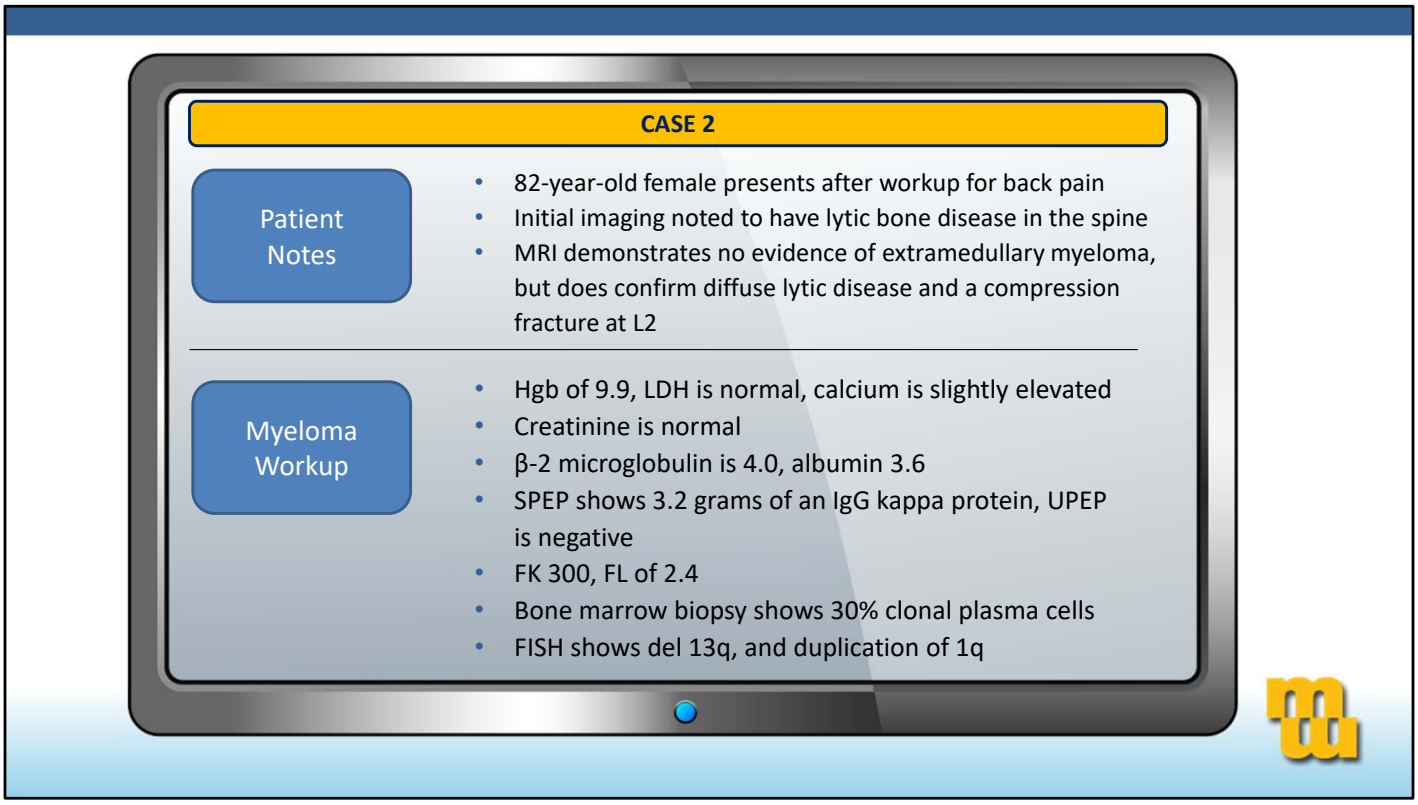



Let's look at Case 2: 82-year-old female presented after workup for back pain. Initial imaging showed lytic bone disease MRI showed no extramedullary myeloma, but did have a compression fracture at L2, hemoglobin was 9.9, LDH was normal. Creatinine is normal. Beta-2 was 4, albumin is 3.6, SPEP had about 3.2 grams of an IgG kappa protein, free kappa was 300, lambda 2.4, 30% clonal plasma cells, FISH shows 1q deletion and duplication of 1q. One extra copy of 1q. Again, the key parts are normal LDH, beta-2 of 4, albumin of 3.6.

## Case 2 - Polling Question #1

**Based on these findings, what is the R-ISS stage for this patient?**
*(please select your response)*

A. ISS Stage 3

B. R-ISS Stage 1

C. ISS Stage 1

D. R-ISS Stage 2

E. R-ISS Stage 3

Based on these findings, what is the R-ISS stage for this patient?

A. ISS stage 3
B. R-ISS stage 1
C. ISS stage 1
D. R-ISS stage 2
E. R-ISS stage 3

Take a moment to answer, please.

## Case 2 - Polling Question #1

**Based on these findings, what is the R-ISS stage for this patient?**

A. ISS Stage 3

B. R-ISS Stage 1

C. ISS Stage 1

D. R-ISS Stage 2

E. R-ISS Stage 3

That is correct. A few of you answered R-ISS stage 3. My guess is that maybe because of the 1q, 1q is not in the R-ISS staging, and this was only one extra copy, not two extra copies of 1q. Deletion 13, remember, is no longer a high-risk feature any longer. It's considered to be standard because it occurs in about 50% of newly diagnosed myeloma.

## Case 2 - Polling Question #2

**What would you choose as the best treatment option at the time?**
*(please select your response)*

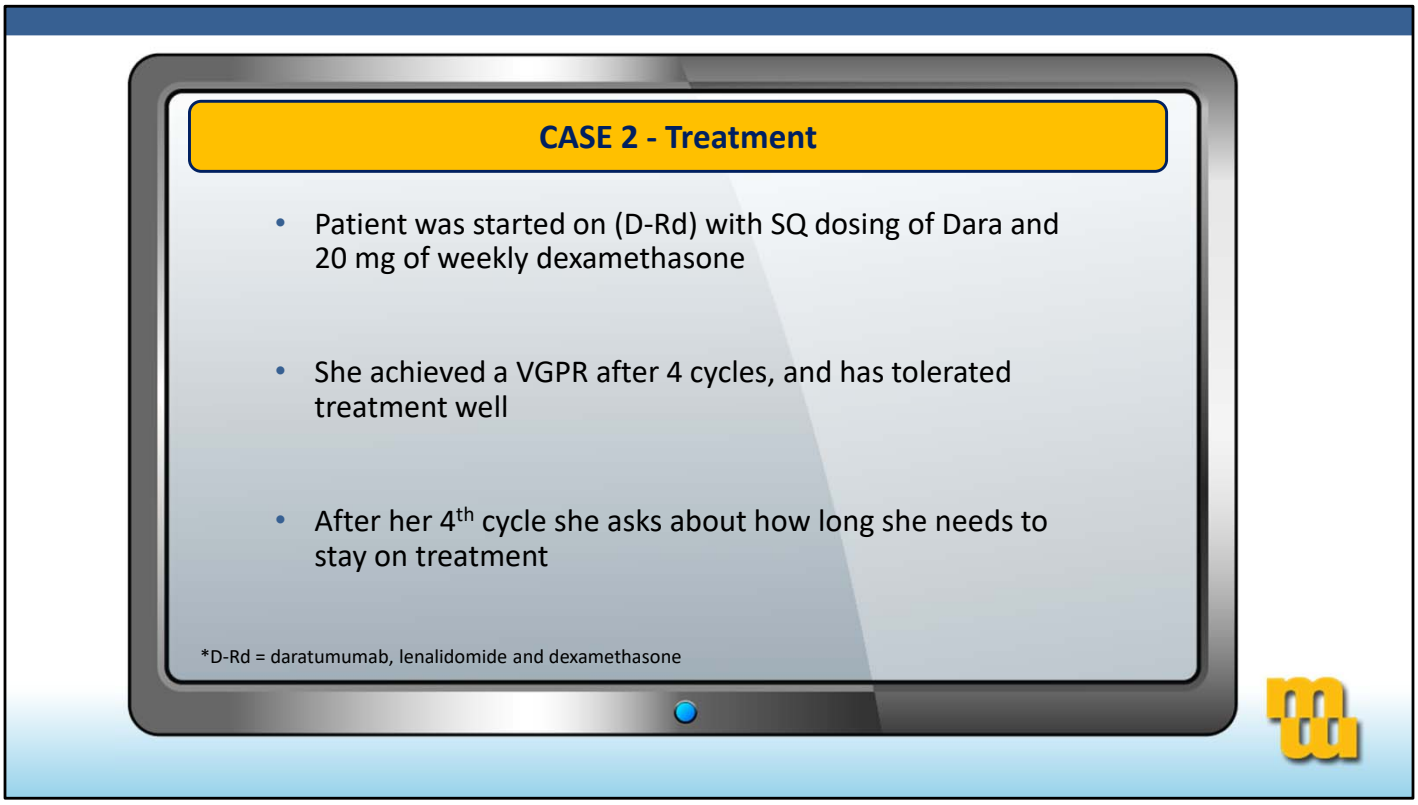
A. Rd
B. MPV
C. MPT
D. VRd
E. DRd
F. KRd
G. VRd + daratumumab

Rd = lenalidomide and dexamethasone; MPV = melphalan, prednisone, bortezomib; MPT = melphalan, prednisone, thalidomide; VRd = bortezomib, lenalidomide, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone

What would you choose as the best treatment option at this time point?

A. Rd
B. MPV
C. MPT
D. VRd
E. DRd
F. KRd
G. VRd + daratumumab

This 82-year-old may be very robust, but certainly a quadruplet in an older, frailer patient may be a little bit challenging for the older, frailer patient.




This actually was my patient. We actually elected, in this case, to use DRd with SubQ dosing of Dara and 20 milligrams of weekly Dex. She achieved a VGPR after 4 cycles and tolerated treatment well. After her 4 cycles, she asked about how long she needs to stay on treatment.

## Case 2 - Polling Question #3

**Based on the MAIA trial, what would be the best response to her question?**
*(please select your response)*

A. Continue with the treatment for 12 months then stop

B. Continue with treatment until reaching CR, go 2 cycles beyond and then stop

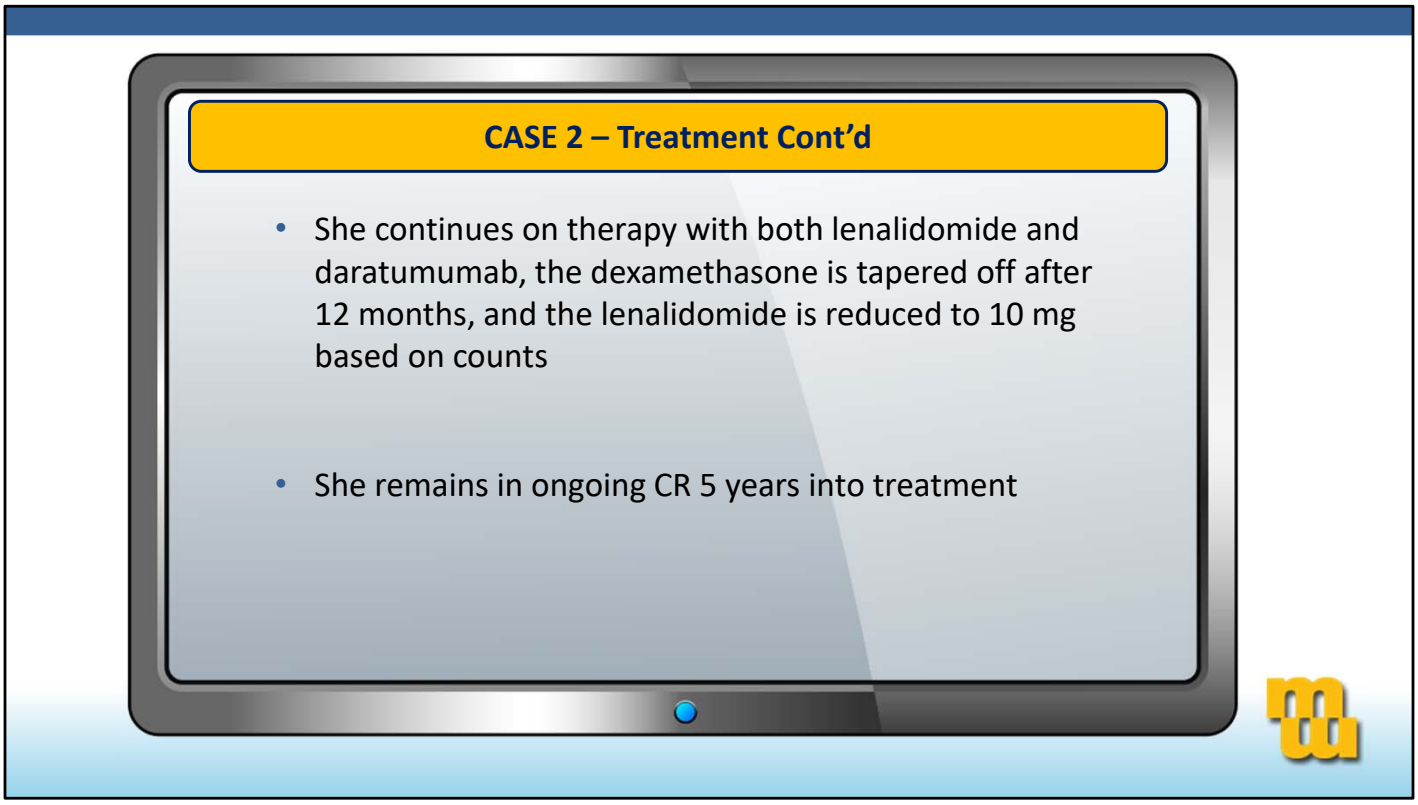
C. Continue with lenalidomide until progression

D. Continue with lenalidomide and the daratumumab until progression

Based on the MAIA trial, what would be your best response to her question?

A. Continue treatment for 12 months and then stop
B. Continue treatment until reaching CR, go 2 cycles beyond it
C. Continue with Len until progression
D. Continue with Len and Dara until progression

What did the MAIA trial do?




Obviously, toxicity plays into all of this, but the MAIA trial continued both Len and Dara until progression. Most patients, if they discontinued anything, they discontinued the Len and stayed on Dara because once you get to once a month, it's so easy, but certainly, this 82-year-old patient that I took care of stayed on both, tapered off her dexamethasone at 12 months, Len was reduced to 10 milligrams based on the counts, and she's in ongoing CR five years into treatment.

Managing Myeloma

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## Questions and Answers on Developments in Newly Diagnosed Multiple Myeloma

**Saad Z. Usmani, MD, FACP**
Chief of Myeloma Service
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

**Do you routinely test for MRD, and are you using MRD as a guide to treatment in your practice? Do you see this as something that community practitioners should consider incorporating into routine practice?**
I am utilizing MRD testing as a prognostic tool right now, post-induction and post-transplant. I am not escalating or de-escalating treatment outside of the context of clinical trials. For patients who are interested in doing that, I am offering them clinical trials where they will be able to do that, whether it is the SWOG-1803 study that's looking at the duration of treatment. There are other frontline strategies where we are giving a certain number of cycles of induction or post-transplant treatment, and stopping treatment, all of those questions are being asked in clinical trials, I'll be offering those as an option.

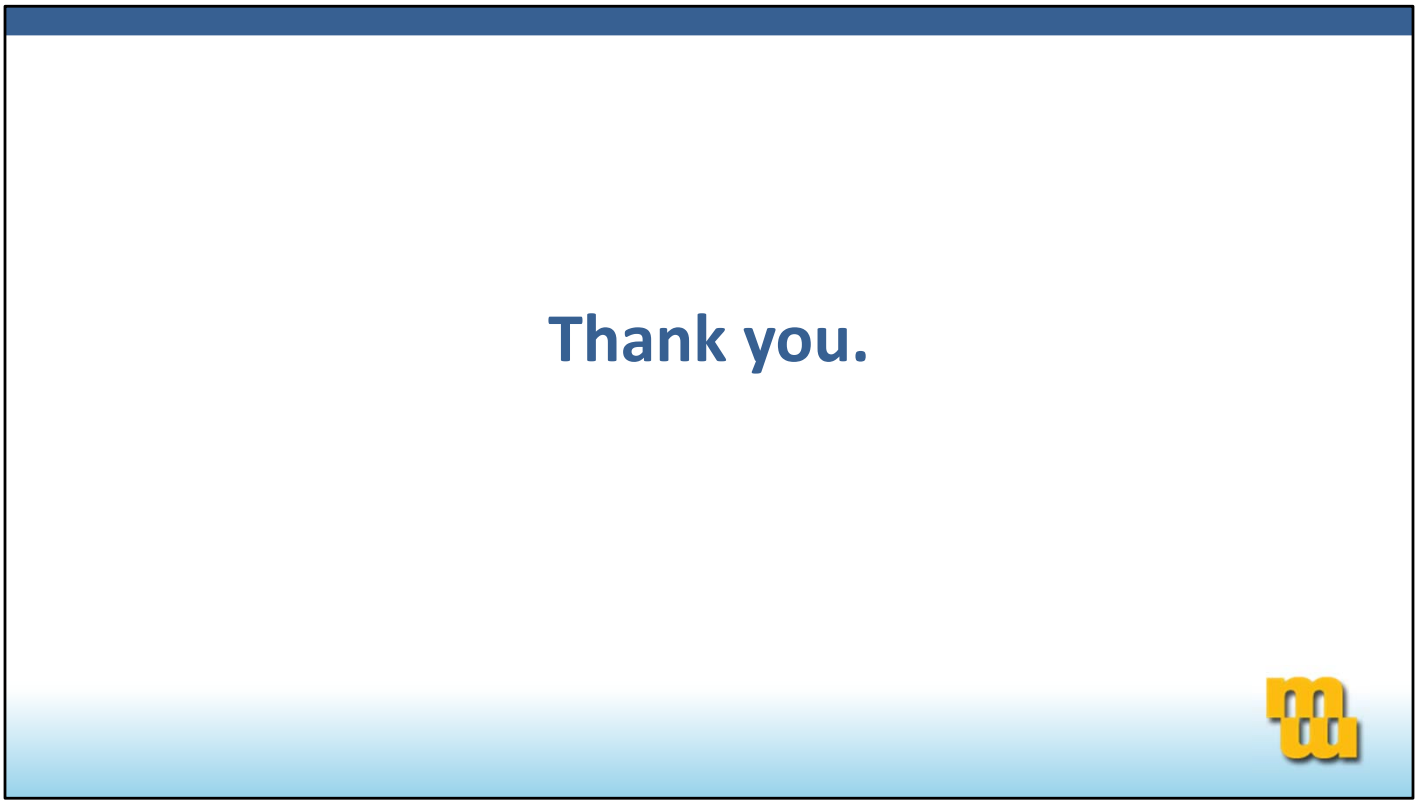
**Should community practitioners be considering incorporating MRD testing in routine practice?**
My answer is, yes, because we do need to provide better prognostic information for our patients. As we move forward, our discussions are moving away from getting patients to CR or better, to getting patients to MRD negative status. Picking the right treatments that get your patients to that MRD negativity status is something that we're going to be talking about a lot more in myeloma. We're already doing this in the academic setting, but something that will routinely be done in the community as well.

**Another question I have is, can you give daratumumab, lenalidomide maintenance after VRD induction with high-risk disease?**
We don't have any data to support that right now. I think the standard of care approach, again, based on single-institution data as well as Phase II data is a PI+IMiD-based post-transplant maintenance for high-risk patients. I've shared some of this data with all of you as well.

**All right, for high-risk patients who are transplant-ineligible, would you suggest RVD or DRD and why?**
All right, this is a very controversial question because we don't have any frontline data in these patients. For high-risk patients, they were only about 14% high-risk patients in the MAIA experience. Again, head-to-head comparisons have not been done. I still favor RVD for high-risk patients because of the PI+IMiD combination having shown to be most efficacious for that subgroup of patients, and the existing data, and the SWOG-1211 study for high-risk patients. However, there is a cooperative group setting study looking at RVD and VRD that will be starting off later this year, being led by the SWOG Myeloma Committee. We probably could get some guiding post or answers for that particular question in the next three or four years, but right now, my personal bias is still towards RVD.

**How would you measure response in multiple myeloma that's primarily bone disease on PET that M-protein is very low?**
For those patients, obviously, looking at PET-CT responses would be something that we do. There are some guidelines around this. The International Myeloma Working Group has published imaging guidelines around this. The paper was published maybe two or three years ago. In my practice, that's something that I follow. It can be a challenge with insurance companies, and we have to do an appeal each time for some patients, but that's the only way to follow the disease in those patients.

**The other question is, do you stop maintenance treatment in high-risk disease after two years?**
My answer is no, because what makes high-risk disease high-risk is the likelihood of falling out of remission. Our current approach is to continue treatment for those patients. At a future timepoint, if we are able to get patients to assess sustained MRD negativity at a very deep level, $10^{-6}$, and it's sustained, we may think about asking that question at clinical trial, "Is it okay to stop treatment for those patients?" The standard of care approach is to continue to give the patients maintenance treatment.




With that, I think we'll stop and thank you very much for your attention and appreciate your joining us today. Thank you, Dr. Usmani, for a great presentation as well. Thank you.