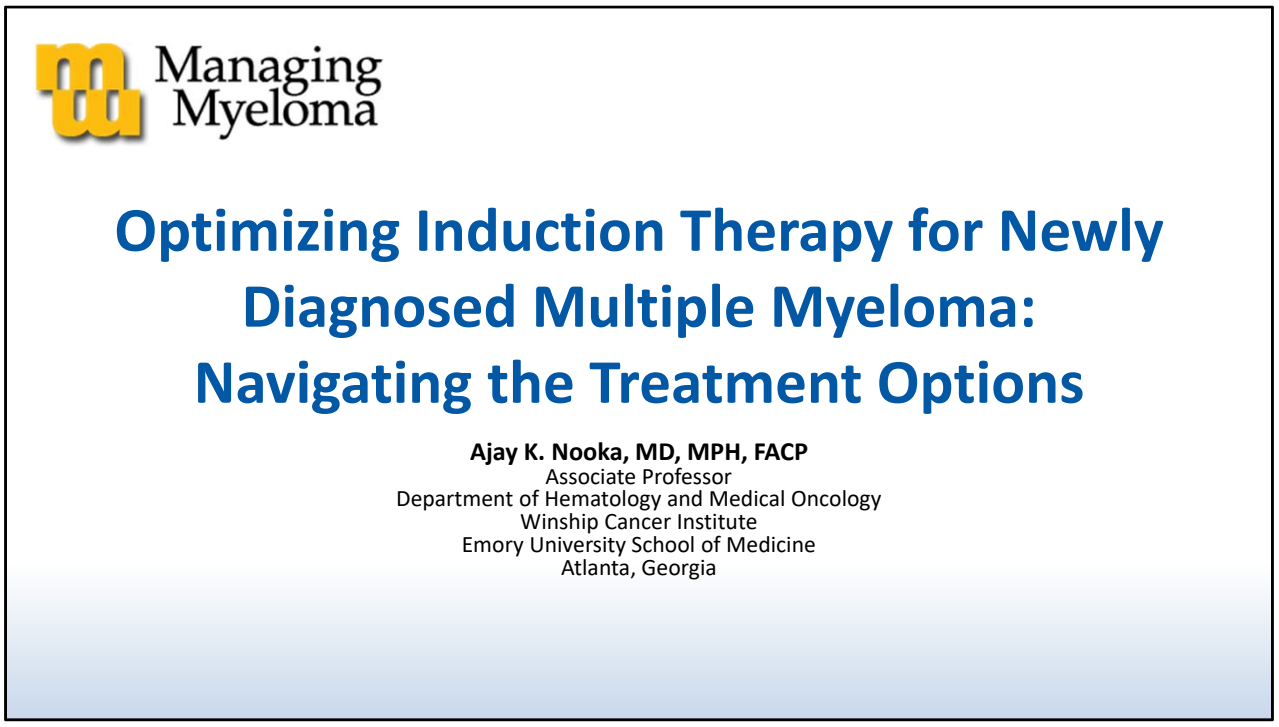
Optimizing Induction Therapy for Newly Diagnosed Multiple Myeloma: Navigating the Treatment Options



Welcome to *Managing Myeloma*. I'm Dr. Ajay Nooka. I'm an Associate Professor at the Emory Winship Cancer Institute. Today, I would like to spend the next few minutes covering the following key aspects of managing a newly diagnosed multiple myeloma patient.

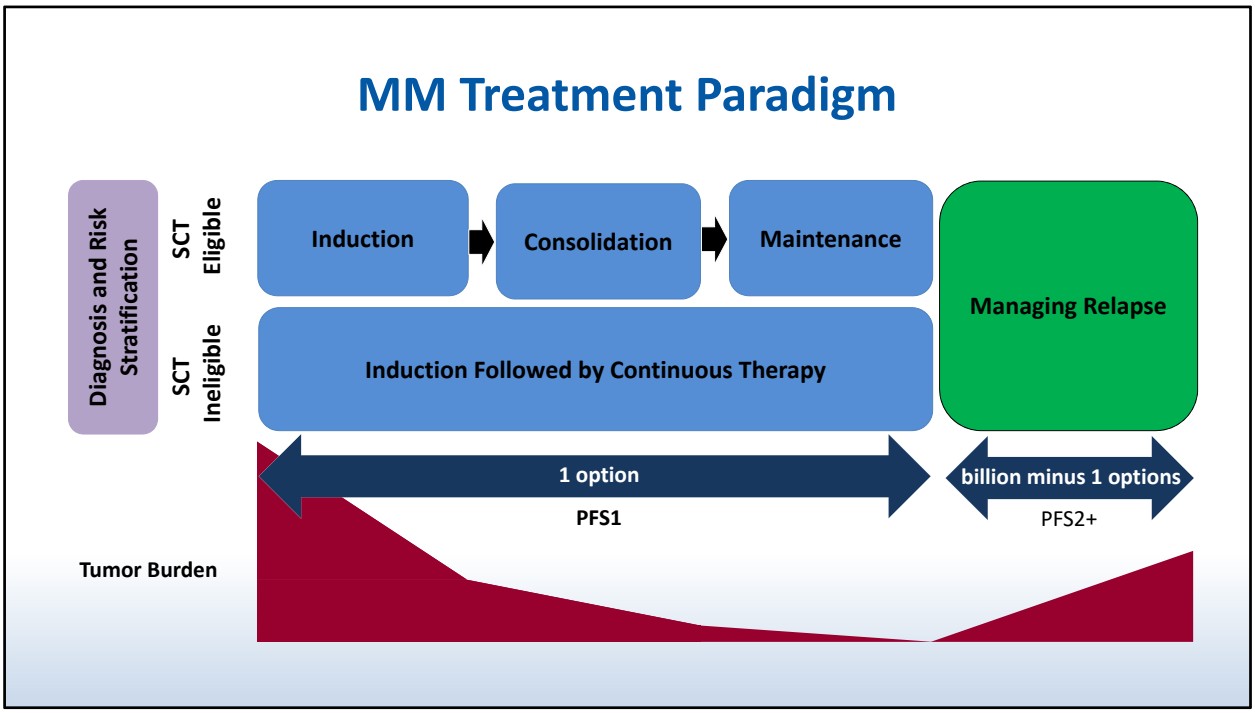
Optimizing Induction Therapy for Newly Diagnosed Multiple Myeloma: Navigating the Treatment Options

Learning Objectives

- Describe predictive measures available for determining risk stratification and patient centered management in newly diagnosed multiple myeloma (NDMM)
- Outline key clinical- and patient-related factors which may influence your selection of induction therapy for NDMM patients who are eligible or ineligible for transplant
- Evaluate safety and efficacy of current emerging multi-drug combinations used in the frontline setting
- Identify the potential impact of monoclonal antibodies on the treatment paradigm for NDMM

I will be reviewing the predictive measures currently available for risk stratification in a newly diagnosed myeloma patient. The key clinical- and patient-related factors that could influence your choice of induction regimen, the safety and efficacy of the current modern day induction regimens in the frontline setting, as well as the role of monoclonal antibodies in the treatment of newly diagnosed myeloma patient in frontline setting.

Optimizing Induction Therapy for Newly Diagnosed Multiple Myeloma: Navigating the Treatment Options



The current concept of myeloma relies on attaining the best depth of response in the initial phases of treatment. Using the most effective induction regimens, followed by an autologous stem cell transplant as a consolidative maneuver, followed by risk adaptive maintenance for delivering the best long-term duration of response. In the transplant ineligible patients, the same concept applies except in the place of transplant, we use a longer duration of induction regimen followed by continuous treatment. If you look at the paradigm of myeloma, half of the myeloma patients' journey revolves around these blue blocks which is what we call the PFS1 benefit. Mathematically speaking, if you have a billion lines of therapy to treat myeloma, billion minus 1 options fall into the green box which is managing relapse and the one line of treatment that could offer the best depth of response or where we can maximize the best efficacy of these treatments falls in the blue lines of therapy.

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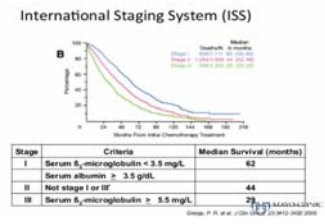
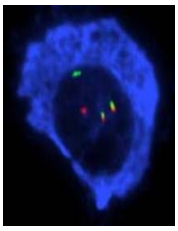
Prognostication

ISS Staging

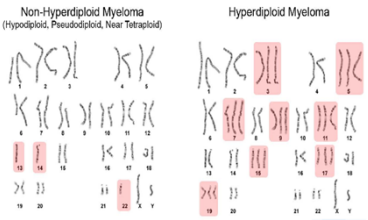


Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29

FISH

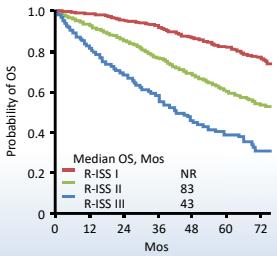


Metaphase Cytogenetics



Revised ISS Staging

Stage	Definition
1	• Serum albumin ≥3.5 g/dL AND β_2-M ≤3.5 mg/L • Normal LDH • No t(4;14), t(14;16), or del(17p)
2	• Not stage I or III
3	• β_2-M ≥5.5 mg/dL PLUS • High LDH, OR • t(4;14), t(14;16), or del(17p)



Greipp P, et al. *J Clin Oncol.* 2005;23(15):3412-3420.; Palumbo A, et al. *J Clin Oncol*. 2015;33(26):2863-2869.

How do we prognosticate newly diagnosed multiple myeloma patients? Historically we used tumor burden as a prognostic factor. It did not turn out to be prognostic, so we moved away to using routinely used lab values to start risk stratifying the patient. The ISS staging system is a prognostic staging system that was developed by the Mayo Clinic based on data from 11,000 patients and stratifying the patients to fall into three groups, the low-risk group, the intermediate-risk group or the high-risk group, and this turned out to be prognostic based on just two lab values, the albumin and the beta-2 microglobulin. We also used genetics for risks stratification. FISH is a very commonly used test using different probes to interrogate for known myeloma chromosomal abnormalities. Unfortunately, they are limited to the probes that we use to interrogate the regions and even though it is a highly sensitive test showing in more than 90% of patients the lesions can be detected. The metaphase cytogenetics is very meaningful yet highly hyperdiploid karyotype shows a highly proliferative neoplasm and a highly proliferative myeloma and it is seen in only 20% to 30% of patients. Unfortunately, majority of the myeloma patients have low proliferative myeloma cells, so may not be the most ideal test that would be comprehensive. Generally, we used FISH and cytogenetics both together for genetic risk stratification. More recently, there is a new staging system that was put out. The Revised International Staging System which combined the ISS as well as the FISH and metaphase cytogenetics to aim at risk- stratifying these patients that could benefit the best R-ISS stage I or the patients who have an ISS stage I that do not have any high-risk features and have a normal serum LDH, and these patients have five-year survival rates of close to beyond 80% and this is a much more robust prognostic staging system than we had any of the staging systems ever before.

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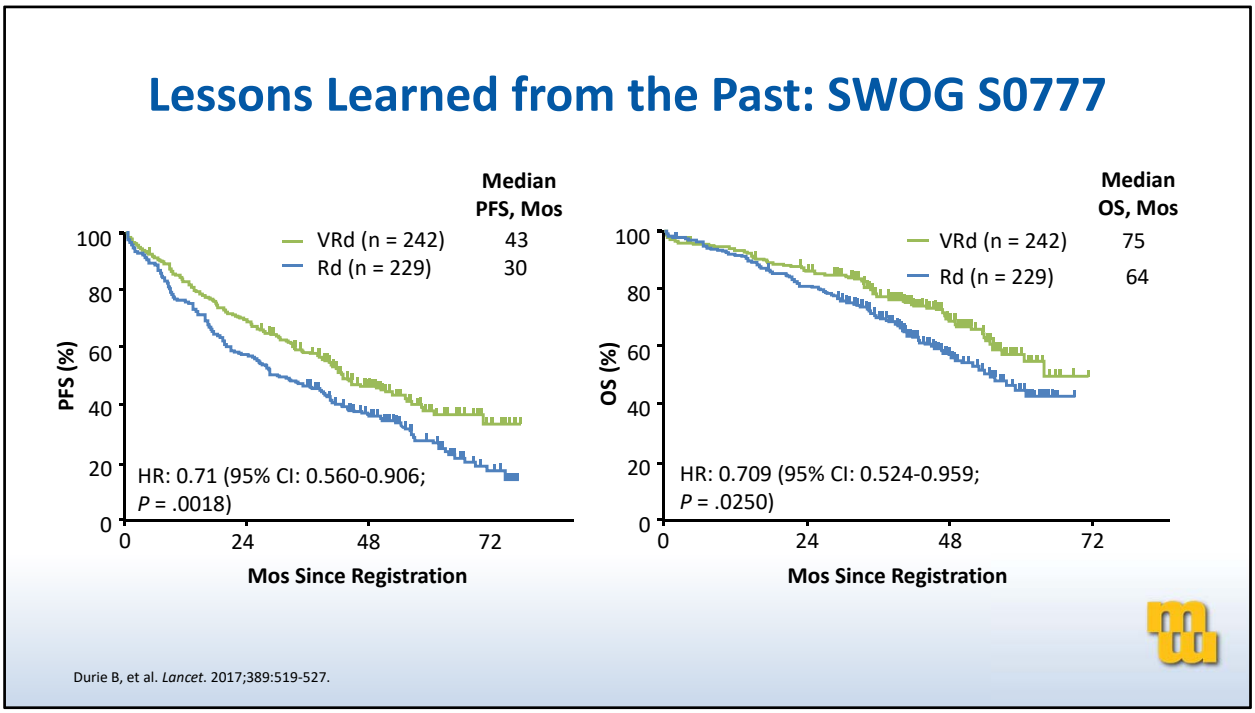
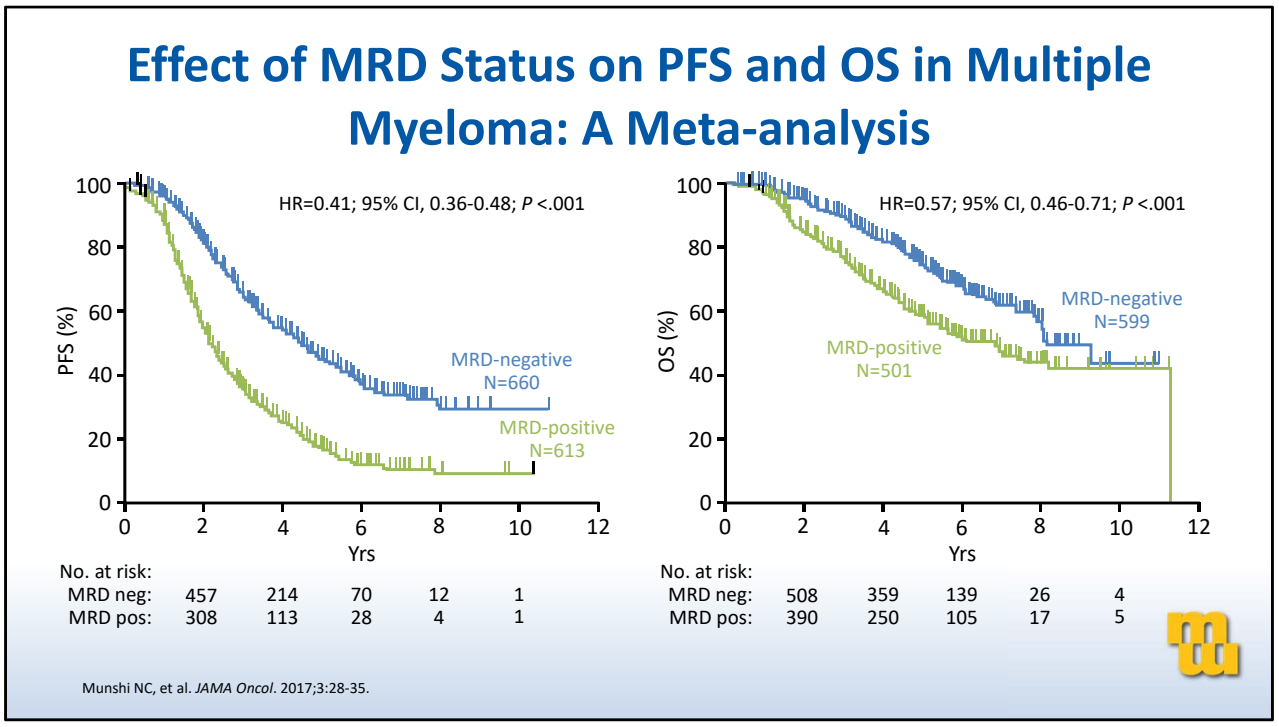


What have we learned from the past clinical trials? Historically, we used lenalidomide and dexamethasone as the standard induction regimen in standard-risk patients, so the SWOG S0777 trial is a very important milestone trial in the history of myeloma therapeutics. The trial randomized patients to receive lenalidomide-dexamethasone versus lenalidomide-dexamethasone plus bortezomib. Bortezomib only given during the first six months of the patient's initial treatment, and it turned out that it had a PFS benefit as well as an overall survival benefit. If you will look closely, the median PFS benefit was more than 13 months and the hazard ratio is 0.71, which is a 29% reduction of the risk of progression or death and similarly, by giving the bortezomib as a part of the treatment regimen in the first six months of treatment has resulted in overall survival benefit of close to a year. So, by using an effective induction regimen, gaining the best depth of response in the first initial months of treatment, you are able to confer a long-term survival advantage based on the trial from the SWOG.



So, the question that comes, what is the depth of response that we should be aiming for? Minimal residual disease has shown to impact both the PFS as well as the overall survival. Nikhil Munshi's group did a meta-analysis of close to 14 studies, looking at the impact of MRD negativity on the PFS and looked for in another 12 studies with 1,000 patients looking at the impact of MRD negativity on the overall survival. It is not surprising to see patients who had an MRD negativity had the best progression-free survival as well as overall survival benefit of the outcomes. When I look closely at those patients who achieved the CR, still MRD negativity turned out to be prognostic both for the PFS and overall survival. Now that we saw the MRD negativity is found to be prognostic, how depth are the sensitivity is what we should be aiming for.

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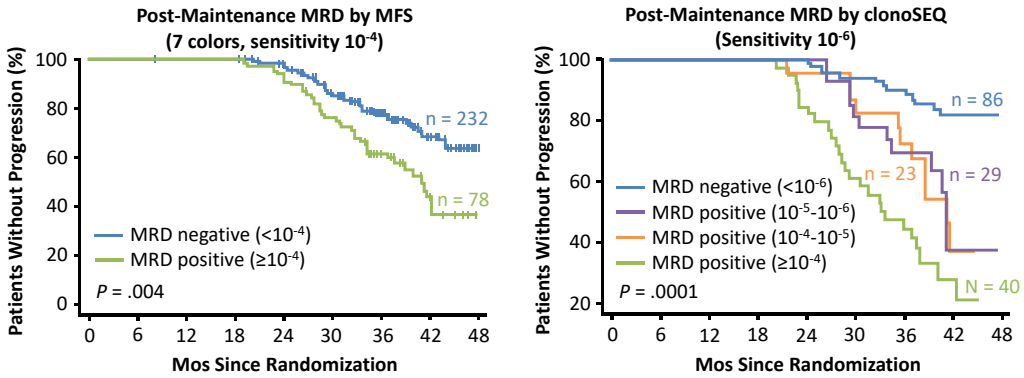
Comparison of NGS and Flow Cytometry in DFCI IFM 2009 Post Maintenance: Sensitivity Matters



- Of 163 MRD-negative patients by flow cytometry (sensitivity 10^{-4}), 84 (51%) were MRD positive by clonoSEQ (sensitivity 10^{-6})
- Patients that were MRD negative by flow and MRD positive by clonoSEQ (NGS) had worse outcomes

Avet-Loiseau H. ASH 2015. Abstract 191.; Perrot A, et al. *Blood.* 2018;132:2456-2464.

This is a very important study from the IFM DFCI evaluating the role of an early versus a delayed transplant, and what the study had done was to give treatment regimen to everyone with lenalidomide-bortezomib-dexamethasone followed by randomizing patients to receive an early transplant versus a delayed transplant. This study to the left that you can see MRD negativity at 10^{-4} has already shown to have a PFS benefit. It is prognostic for a PFS benefit. On the right, are seen at different levels from 10^{-4} to 10^{-6}. The one on the blue curve shows that these patients are the ones that remain in remission for the longest period of time if you achieve a depth of response up to 10^{-6}. In a sense, if you are not able to identify even a one myeloma cell in a million cells, that is termed MRD negativity 10^{-6} which has been shown to be prognostic.

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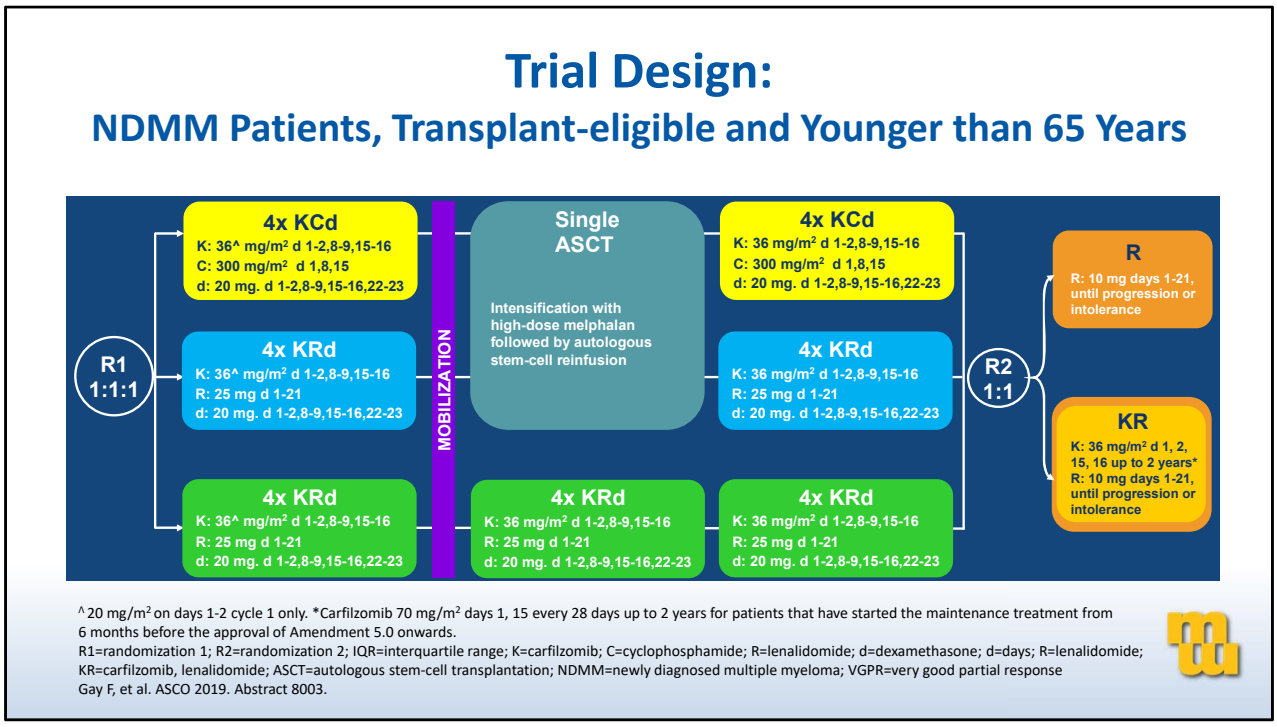

Which brings us to the day of modern induction regimens. Which are the induction regimens that I would go with or which are the favorable induction regimens and what are the downsides of each of these regimens and upsides of each of these regimens? This is a four-day trial that was presented at ASCO 2019. The trial had randomized patients to three arms. The first arm is carfilzomib, cyclophosphamide, and dexamethasone, and patients after receiving four cycles went down to an autologous stem-cell transplant, received four further cycles of carfilzomib, cyclophosphamide, and dexamethasone, and then there is a second randomization to receive maintenance with lenalidomide, which is a standard of care, or carfilzomib and lenalidomide. The second arm received four cycles of carfilzomib, lenalidomide, and dexamethasone, followed by an autologous stem-cell transplant, followed by four further cycles of carfilzomib, lenalidomide, and dexamethasone. The third arm, the most interesting of all, did not receive any transplant. The patients received altogether 12 cycles of carfilzomib, lenalidomide, and dexamethasone.

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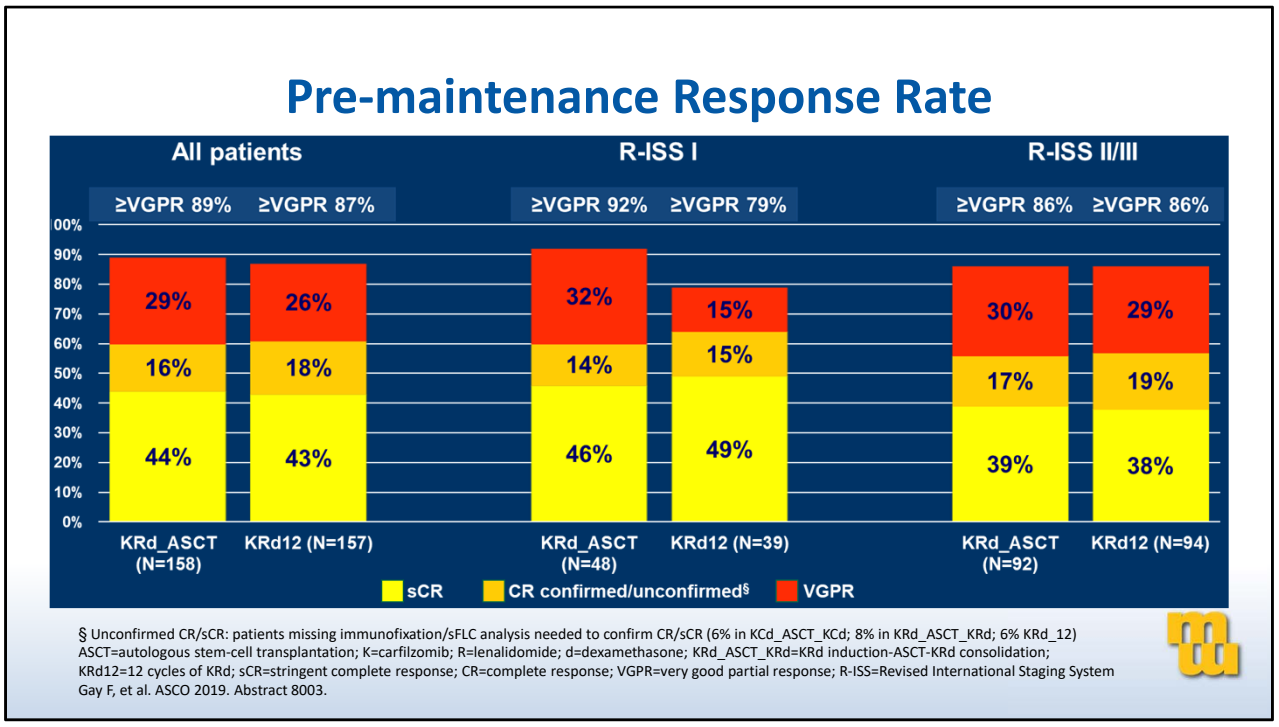

If you look at the pre-maintenance response rates, that is before starting the second randomization, the VGPR rates are almost similar across all patients whether they receive a transplant or not receive a transplant if they are receiving carfilzomib, lenalidomide, and dexamethasone induction. The benefit seems to favor more for the R-ISS stage I patients if the goal for an autologous stem-cell transplant where VGPR rates were seen and 92% versus patients who received 12 cycles of carfilzomib, lenalidomide, and dexamethasone having a 79% VGPR rate. R-ISS stage II and III did not seem to impact much with an autologous stem-cell transplant.

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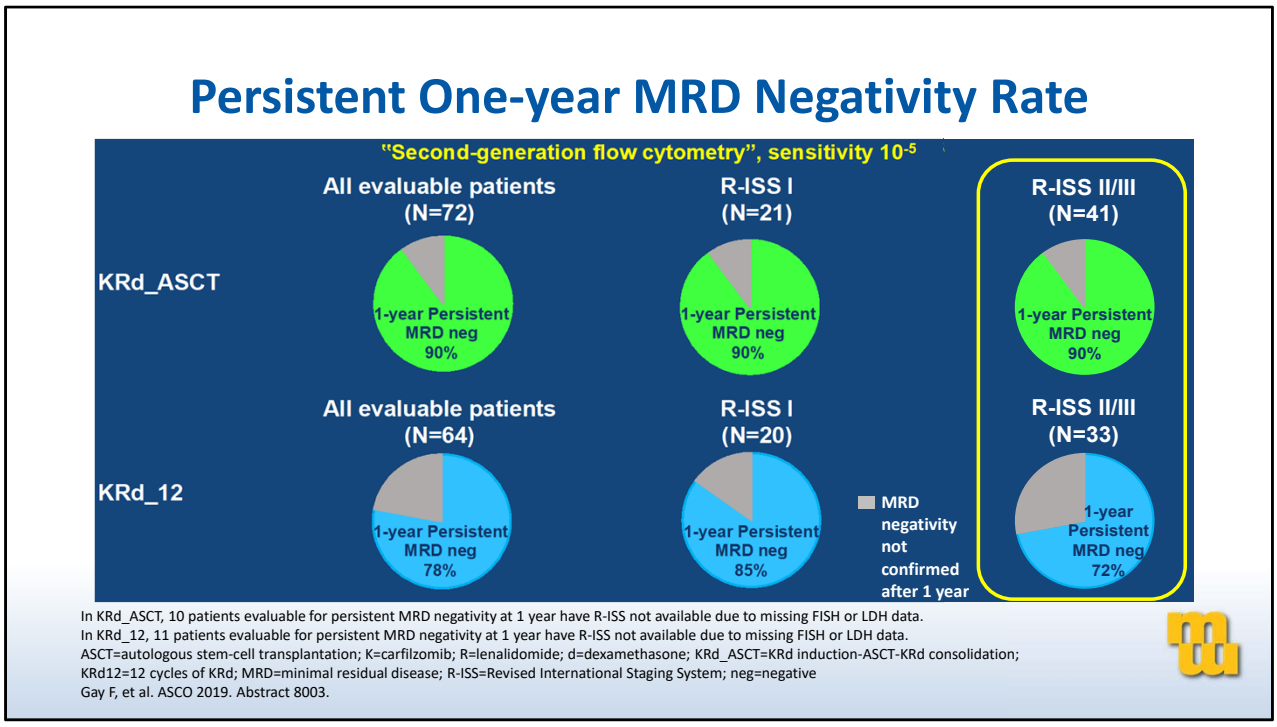

Now, the devil lies in the details, if you look more closely with the persistent one-year MRD negative rates, patients who received KRd plus the stem-cell transplant, even among these high-risk patients of R-ISS stage II or III, they had the one year persistent MRD negative rates at 90%. If you look at those patients who did not receive a transplant, even with the best induction regimen, the MRD negative rates started falling down. At one year, persistent MRD was seen in only 78% of these patients, suggesting the importance of an autologous stem-cell transplant, even in the days of modern-day induction regimens.

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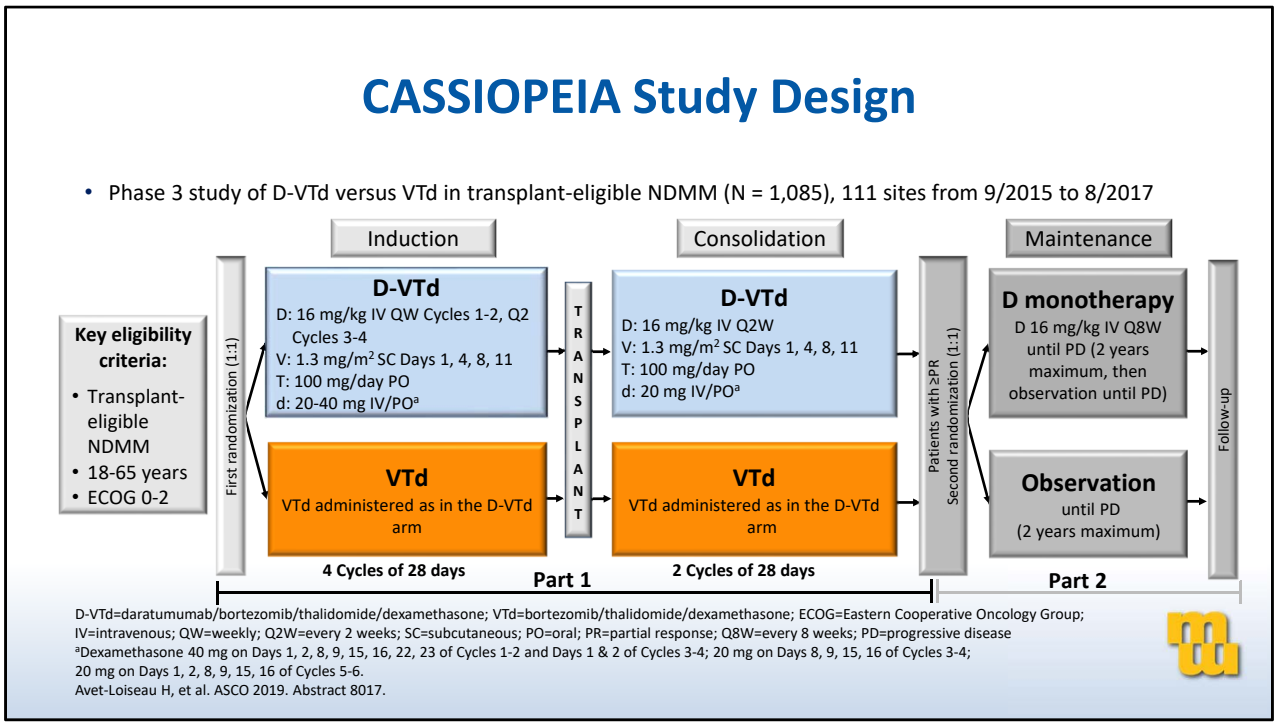

Which brings us to the next trial which is using daratumumab in the induction regimens. As you are all aware, daratumumab is a CD38 monoclonal antibody that is approved for the treatment of relapsed/refractory myeloma in combination with bortezomib, lenalidomide, and pomalidomide, and it is approved in the transplant ineligible patients in combination with lenalidomide-dexamethasone as well as in combination with bortezomib, melphalan, and prednisone, the trials which I would be reviewing in a few minutes. CASSIOPEIA is a trial, that was run by IFM and HOVON, randomized patients received bortezomib, thalidomide, dexamethasone versus daratumumab in combination with bortezomib, thalidomide, and dexamethasone, and thalidomide is the most common immunomodulatory agent that is used outside the United States. So patients would receive four cycles of induction, followed by a transplant, followed by further two cycles of consolidation and there is another second randomization evaluating the role of maintenance. This is a very important study designed for us because it is asking a simple question, is there any role for prolonged maintenance in the light of an effective induction regimen using a monoclonal antibody, using the transplant and gaining those depths of responses? The results for the part 1 study which is the induction followed by transplant followed by consolidation to the primary endpoint of stringent complete response were the ones that were presented recently at ASCO 2019. The study methods primary endpoints stringent complete response rates were 29% versus 20% favoring the daratumumab arm.

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Safety

TEAEs of Interest

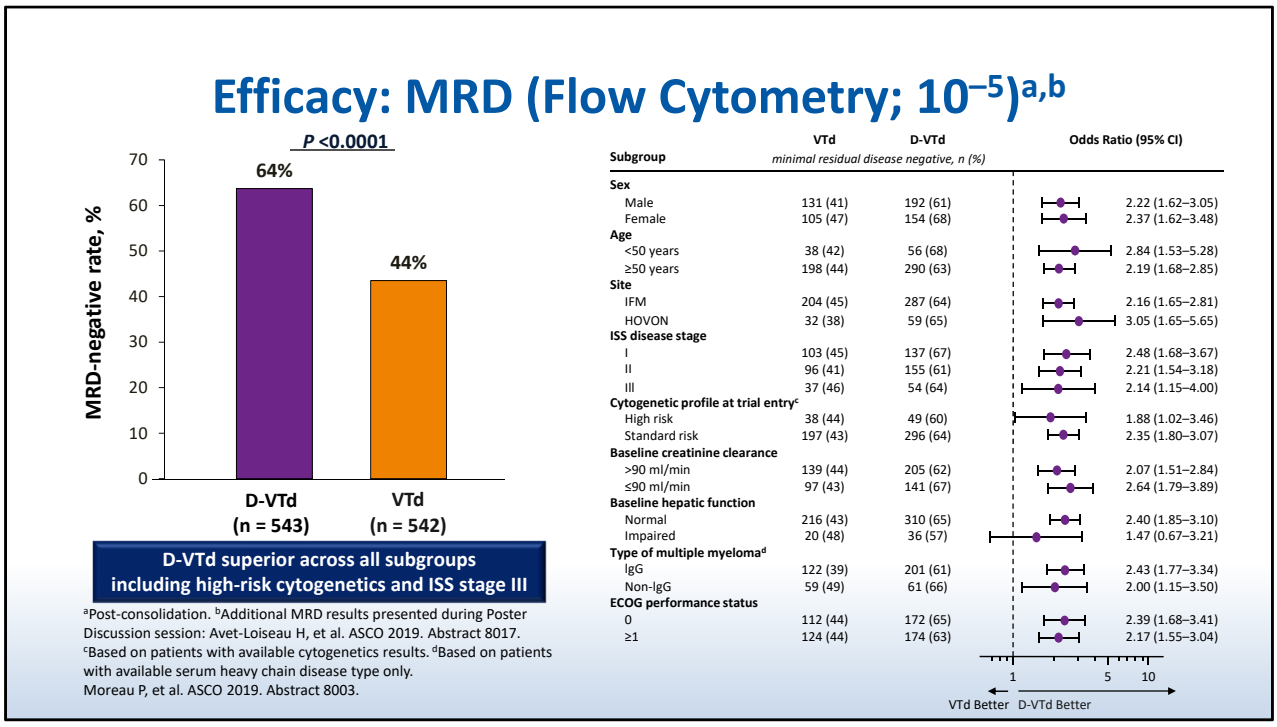
	D-VTd (n = 536)	VTd (n = 538)
Infusion-related reactions, n (%)		
Any grade	190 (35)	–
Grade 3 or 4	19 (4)	–
Infections, n (%)		
Any grade	351 (66)	306 (57)
Grade 3 or 4	118 (22)	105 (20)
Most common serious infection, n (%)		
Pneumonia	19 (4)	9 (2)
Second primary malignancies, n (%)	10 (2)	12 (2)

Stem Cell Collection and Transplantation[a]

	D-VTd	VTd
Patients receiving plerixafor for mobilization, n (%)[b]	110 (22)	39 (8)
$CD34^+$ cells collected, median (10^6/kg)[c]	6.3	8.9
Patients receiving transplant, n (%)[d]	489 (91)	484 (90)
Patients achieving hematopoietic reconstitution, n (%)[e,f]	488 (100)	482 (100)

[a]Additional stem cell collection and transplantation results presented during Poster session: Hulin C, et al. ASCO 2019. Abstract 8042. [b]Among patients who underwent mobilization (D-VTd, n = 506; VTd, n = 492). [c]Among patients who underwent peripheral blood stem cell apheresis (D-VTd, n = 504; VTd, n = 490). [d]In the safety population (D-VTd, n = 536; VTd, n = 538). [e]Among patients receiving transplant (D-VTd, n = 489; VTd, n = 484). [f]Hematopoietic reconstitution requires: neutrophils >0.5 × 10^9/L, leukocytes >1.0 × 10^9/L, and platelets >50 × 10^9/L (without transfusion).
Moreau P, et al. ASCO 2019. Abstract 8003.

Safety wise, there are no major side effects that were predominantly seen with daratumumab except the infusion reactions most of them are grade 1 or 2, and the infection rates grade 3 or 4 are almost similar, secondary primary malignancies are almost similar. More importantly, in a patient who is a transplant eligible patient, daratumumab did not impact the eligibility to collect the stem cells or it did not impact the receipt of a transplant.



From an efficacy perspective, at a depth of MRD negativity 10^{-5}, this is shown to be delivering the best depth of responses with 64% of patients in the daratumumab arm achieving MRD negativity, compared to 44% in the non-daratumumab arm. Towards the right you see the forest plot where almost every subset has gotten a benefit from receiving daratumumab except a few subgroups like the high-risk patients did not seem to benefit as much as the standard-risk patients. I will be discussing it in a minute.

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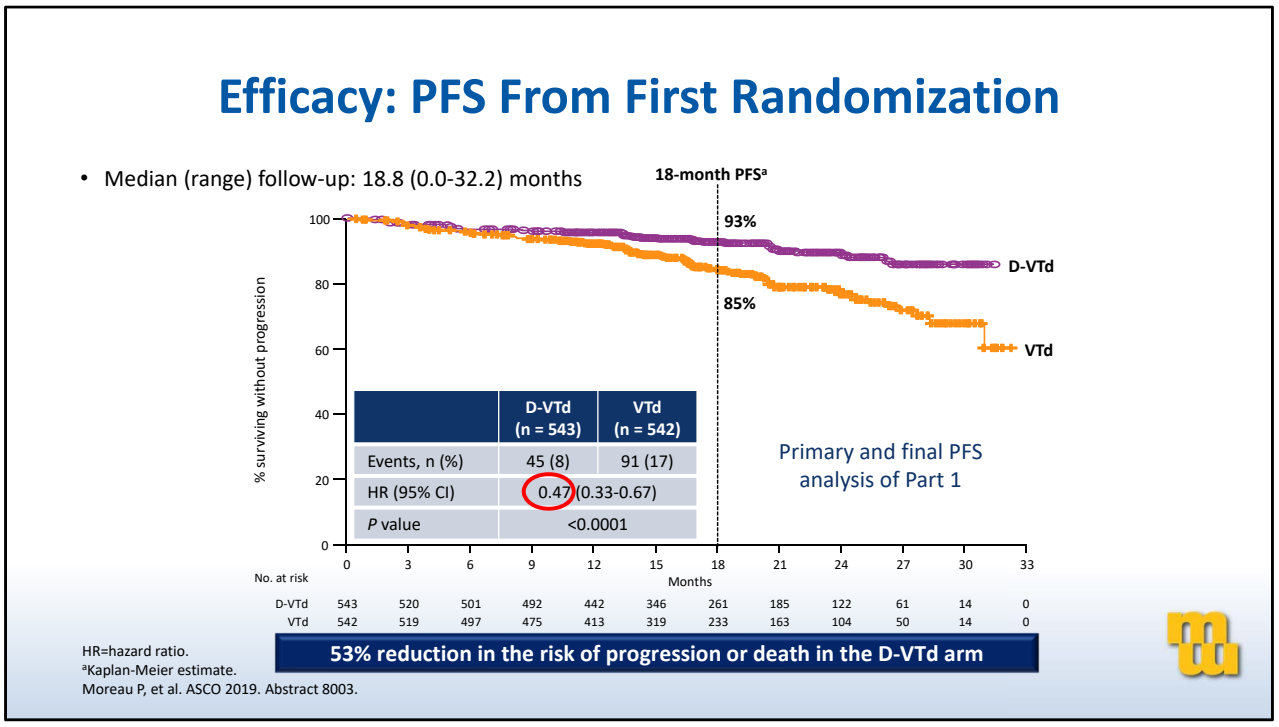

So, if you look at the PFS from the first randomization, the benefit is again towards the daratumumab group, has its ratio of 0.47 which is a 53% reduction of the risk of progression or death.

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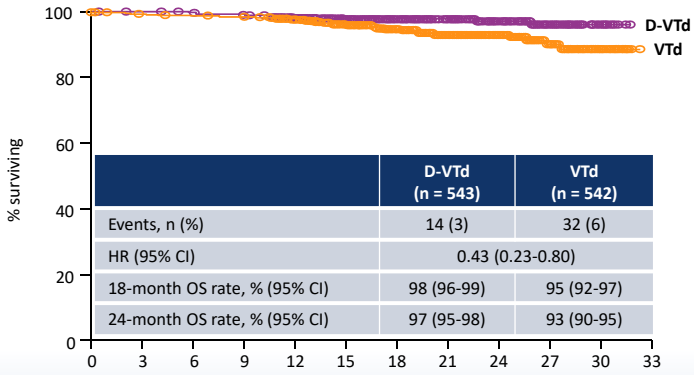
Efficacy: OS

- Median OS was not reached in either treatment arm



	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	14 (3)	32 (6)
HR (95% CI)	0.43 (0.23-0.80)	
18-month OS rate, % (95% CI)	98 (96-99)	95 (92-97)
24-month OS rate, % (95% CI)	97 (95-98)	93 (90-95)

OS data are immature after median follow-up of 18.8 months

No. at risk

VTd	542	535	531	528	480	371	283	206	131	71	17	0
D-VTd	543	539	535	532	485	388	292	212	137	75	17	0

Moreau P, et al. ASCO 2019. Abstract 8003.

Similar benefit was seen from the overall survival. The curves start to separate but it is too early to make any strong conclusions. The curves again are suggesting these are all beneficial towards the daratumumab arm with the high-risk ratio of 0.43.

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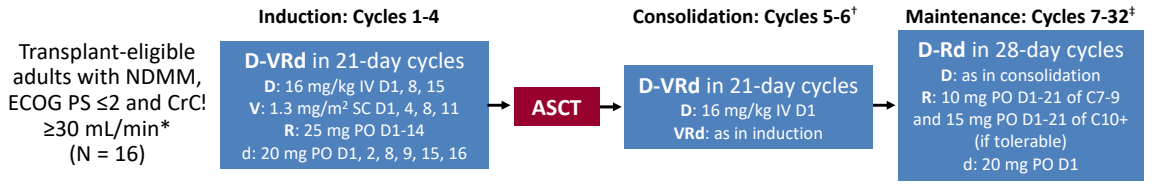
GRIFFIN Safety Run-in Cohort: Daratumumab + VRd

- Preliminary efficacy in safety run-in phase of open-label, randomized phase II trial



*Len dose adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after ASCT. ‡Patients completing maintenance were permitted to continue single-agent len.

Response, %	End of Induction	End of Consolidation	During Maintenance
ORR	**94**	**100**	**100**
sCR	0	25	63
CR	6	38	31
VGPR	50	38	6
PR	38	0	0

Voorhees P. ASH 2018. Abstract 151.

The most commonly used induction regimen in the United States is VRd. Is there any benefit to adding daratumumab to VRd regimen to deepen those responses similar to what we have seen from the CASSIOPEIA trial? The GRIFFIN trial is the one that asked this question, which randomized patients to receive daratumumab plus bortezomib plus lenalidomide and dexamethasone versus bortezomib, lenalidomide, and dexamethasone or the RVD. It is a 200-patient trial. The trial has completed accrual. The results would be anticipated anytime and what we have known so far are the safety run-in cohort results that were presented at ASH last year in 2018, showing that if you are delivering daratumumab in combination with lenalidomide, bortezomib, and dexamethasone, you are able to see a stringent complete response rates in the range of 63%, which is two-thirds of the patients achieving the stringent complete response when you get a four-drug regimen with the monoclonal antibody. So, we are all eager to see the final results for the GRIFFIN study.

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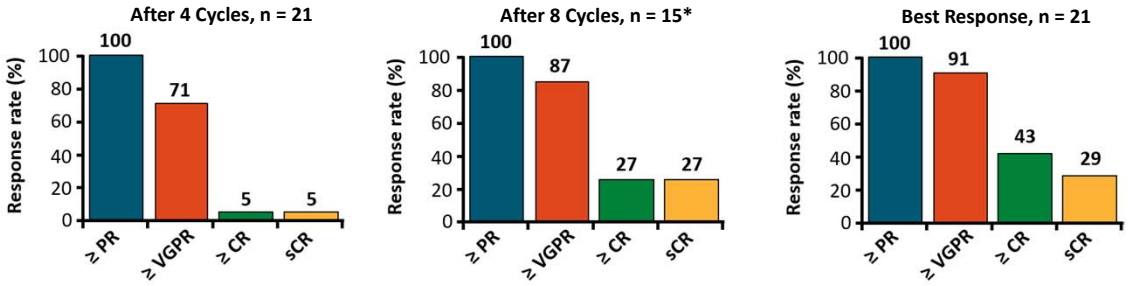
Daratumumab + KRd in Newly Diagnosed MM: Response

- Median number of treatment cycles: 11.5 (range: 1.0-13.0)



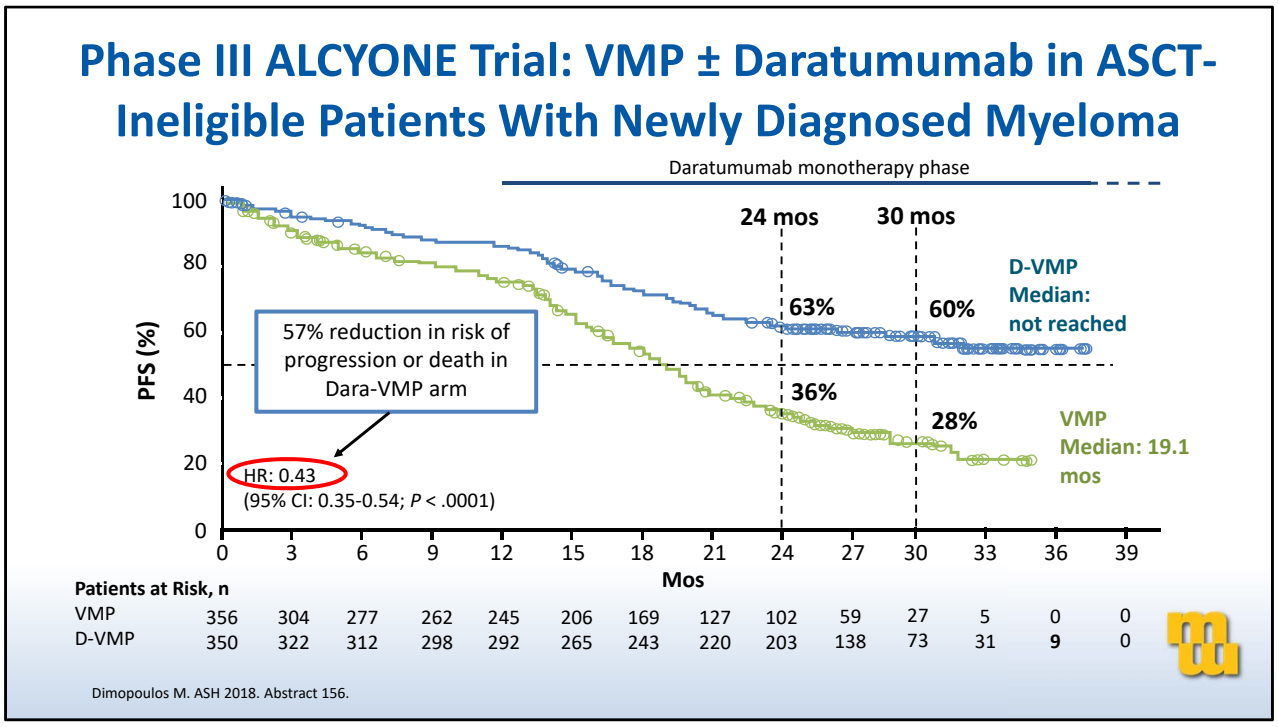
Depth of response improved with duration of treatment

*Five patients who proceeded to ASCT before cycle 8 and one patient who discontinued due to PD at cycle 7 were excluded.

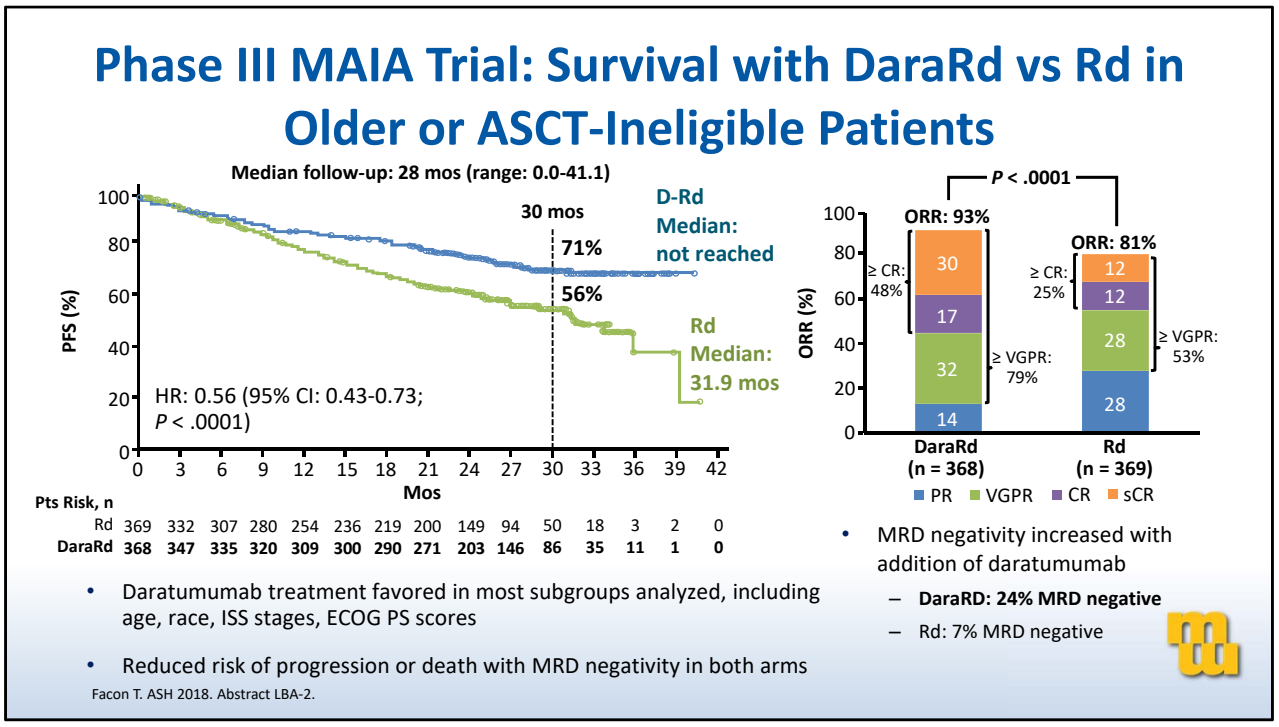
- Median follow-up: 10.8 mos (range: 4.0-12.5)
- OS: 100% at follow-up

Jakubowiak AJ. ASCO 2017. Abstract 8000.

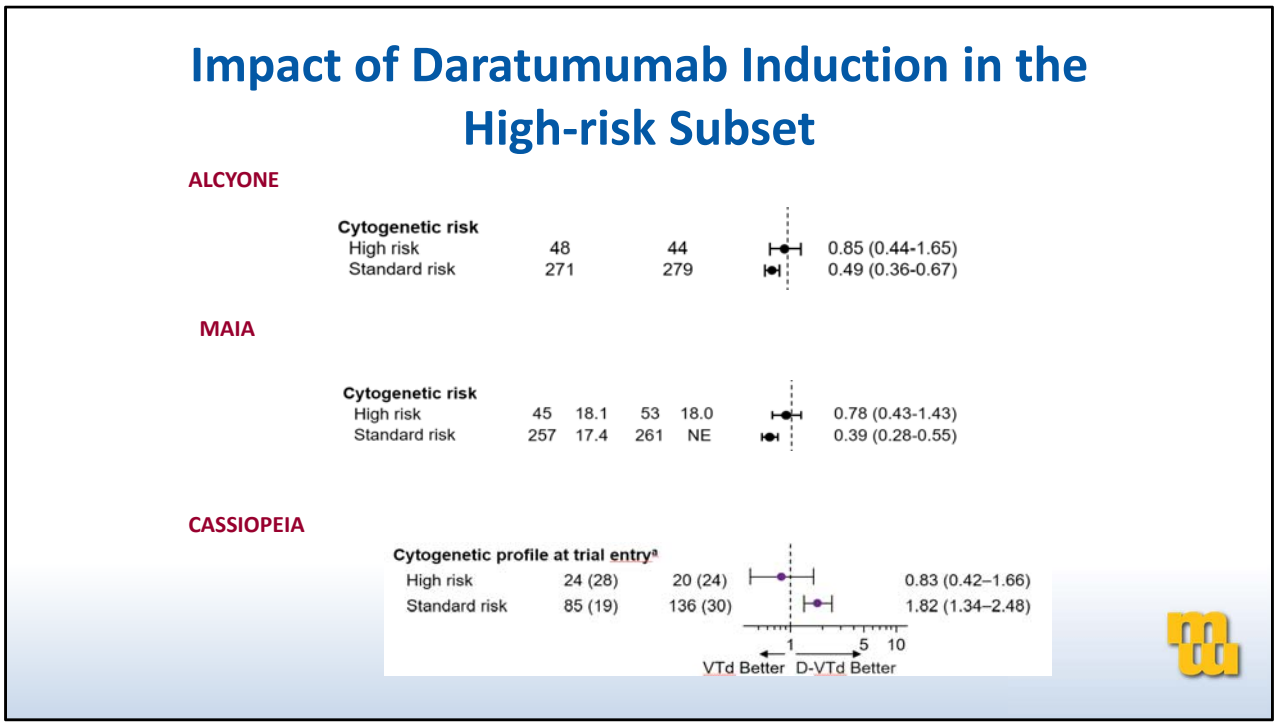
How about daratumumab in combination with carfilzomib, lenalidomide, and dexamethasone in the newly diagnosed setting? This was a study that was presented by Andrzej Jakubowiak, the results showed that VGPR rates are significantly higher as the best response rates in a small patient population. These were 91% VGPR rates and stringent CR rates in half the patients. A very good combination, well tolerated, and this could be further evaluated.



Coming through the transplant ineligible patients, the trials that have led us to the approval of daratumumab in the frontline setting are the ALCYONE trial and the MAIA trial. ALCYONE trial randomized patients to receive bortezomib, melphalan, and prednisone versus bortezomib, melphalan, prednisone, and daratumumab. As you can see from these PFS curves, the curves start to separate very very early on, even within the first few months, the patients start to see a benefit with the daratumumab arm. At the 30 months, the median PFS has not been reached for the daratumumab arm and VMP median was 19.1 months, at 30 months 60% of patients who were in the daratumumab arm did not progress, whereas 28% of the patients who are on the VMP arm did not progress. This study had shown that by giving daratumumab in combination to VMP in transplant ineligible patients, 57% reduction of risk of progression or death can be achieved by adding daratumumab in upfront setting. This study led to the approval of this combination of the United States as well as EU.



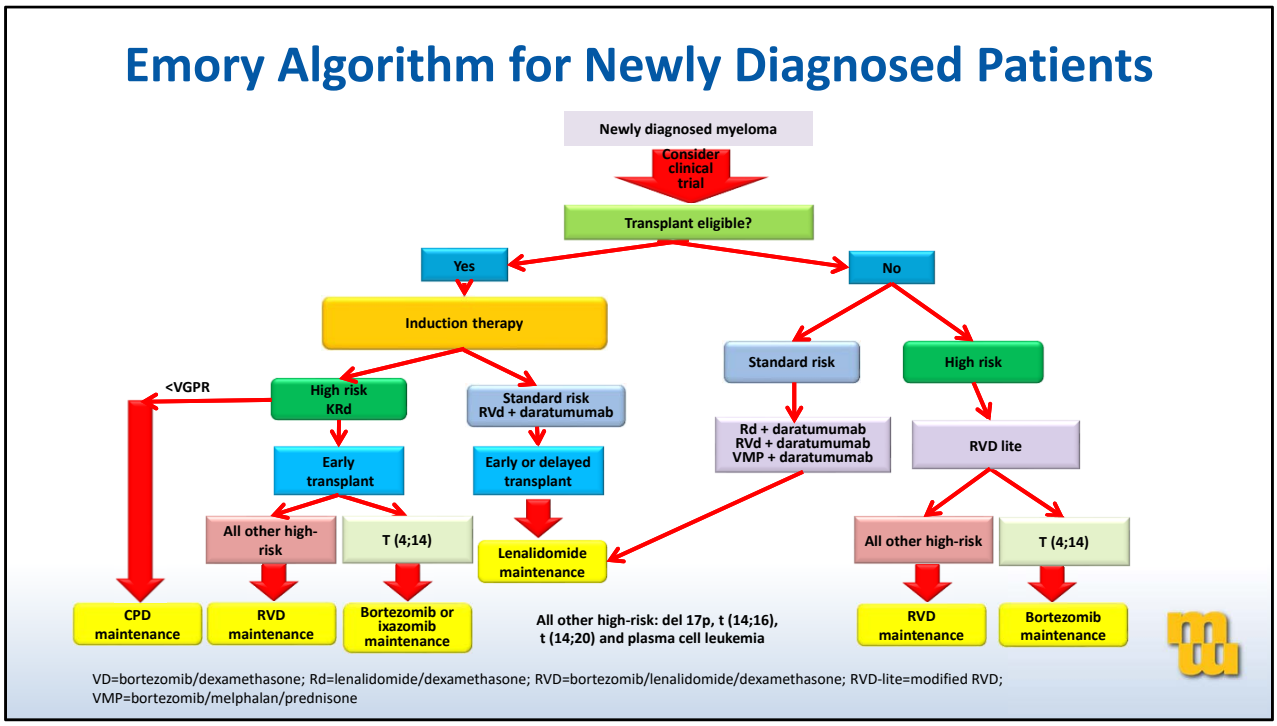
Lenalidomide-dexamethasone is the other combination or the back bone that we commonly use in the United States. MAIA trial asked the question of the benefit of daratumumab if you combine it with the lenalidomide-dexamethasone in the transplant ineligible patients. The trial randomized patients received daratumumab-lenalidomide dexamethasone versus lenalidomide-dexamethasone. At the 30 months, the median PFS for the daratumumab arm has not been reached whereas the median PFS was 31.9 months for the lenalidomide-dexamethasone arm and the overall response rates were significantly higher, and even to the point in the transplant ineligible patients you have in a quarter of the patients achieving MRD negativity 10^{-5}. It shows the efficacy of these modern induction regimens.



So, now are there any subgroups that I have doubts about the benefit of daratumumab in the upfront setting? The first two trials are the ones that were in the transplant ineligible patients, the ALCYONE trial and in the MAIA trial. If you look closely in the first two graphs, the benefit seems to be more for the standard-risk patients, high-risk patients do not receive the same kind of benefit that the standard-risk patients have received. Again, these are not pre-specified analysis. This is a subset analysis that was seen in a small subset of patients, so I would not take this as the final recommendation but these need to be further proved in further studies using daratumumab in the upfront setting. The daratumumab should not be used in the high-risk setting.

If you look in the CASSIOPEIA trial which is using daratumumab induction regimen in the transplant eligible patients, what you see towards the right is daratumumab to be better. Again, it showed the same results as the previous transplant ineligible patients, that standard-risk patients got the better benefit in terms of achieving better and stringent complete responses.

Optimizing Induction Therapy for Newly Diagnosed Multiple Myeloma: Navigating the Treatment Options



Based on the currently available literature, we have changed the algorithm to the following: So, for the patients who are transplant eligible, the most common induction regimen of choice for a high-risk patient that we recommend is carfilzomib, lenalidomide, and dexamethasone followed by early transplant for the FORTE trial and for standard-risk patients for the GRIFFIN trial, RV plus daratumumab with an option to go for earlier delay transplant. In the transplant ineligible patients for the high-risk patients, we will stick on to RVD lite as the choice of induction regimen, but the for the standard-risk patient, lenalidomide-dexamethasone plus daratumumab for the MAIA trial or VMP plus daratumumab for the ALCYONE trial or RVD plus daratumumab for the GRIFFIN trial are still options at this point of time.

Conclusions Regarding Induction Regimens in Newly Diagnosed Myeloma

- RVD experience leads us to believe patients will benefit from a four-drug induction regimen among most patients
- Novel induction therapies are in the horizon, using monoclonal antibodies seems a very enticing approach to deepen the responses with the intent to achieve MRD negativity.
- KRd and transplant will be the ideal induction regimen for high-risk patients
- More data with mabs are needed for the subset with high-risk myeloma
- Cost of the mabs in the upfront setting as well as the TAEs are justifiable
- Time to embrace the change

To conclude, our RVD experience lead us to believe patients will benefit by adding more drugs in the upfront setting to gain the best depth of response. More importantly, the fourth agent that we always look for should not have any overlapping toxicities and here clearly, daratumumab does not have any overlapping toxicities and the monoclonal antibodies seem to be showing a very innovative and enticing approach to gain the best depth of response in terms of MRD negativity. In the high-risk patients, KRd seems to be having the best efficacy as well as safety at this point of time, so we stick to KRd and transplant in the high-risk patients. We need more data to say that daratumumab should not be administered to the high-risk patients. At this point, we are still for further phase 3 trials. I have not discussed a lot about the cost of the monoclonal antibodies in the upfront setting but theoretically, it is seems to be justifiable at this point so as the treatment emergent adverse events. It is time to embrace the change, at least for a majority of the patients. We are seeing significant improvement in the depths of responses and we will be seeing more and more clinical trials that will give us more information.