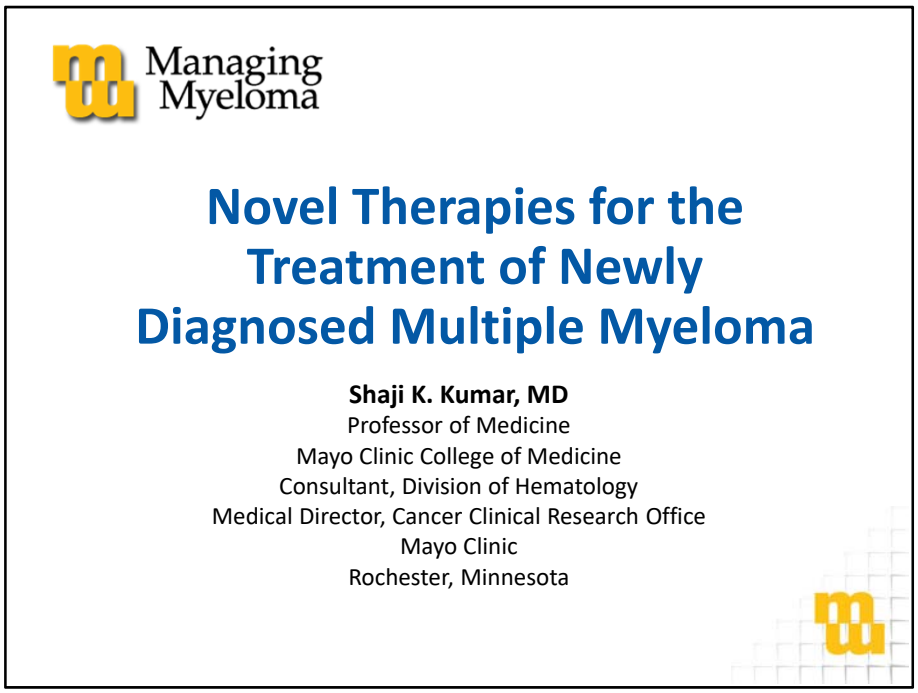
Novel Therapies for the Treatment of Newly Diagnosed Multiple Myeloma



Welcome to *Managing Myeloma*, I am Dr. Shaji Kumar. Today I will review novel therapies for the treatment of newly diagnosed multiple myeloma. In this presentation, I will identify diagnostic criteria and upfront testing strategies which should be considered in the diagnosis of multiple myeloma; summarize the current risk stratification process and methodologies; and select appropriate treatment tailored to individual patient factors based on risk assessment.

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Disclosures

- Research grants for clinical trials to the institution: Celgene, Takeda, Janssen, BMS, Sanofi, KITE, Merck, Abbvie, Medimmune, Novartis, Roche-Genentech, Amgen
- Consulting with no personal payments: Celgene, Takeda, Janssen, KITE, Merck, Abbvie, Medimmune, Genentech, Oncopeptides, Amgen

These are my disclosures.

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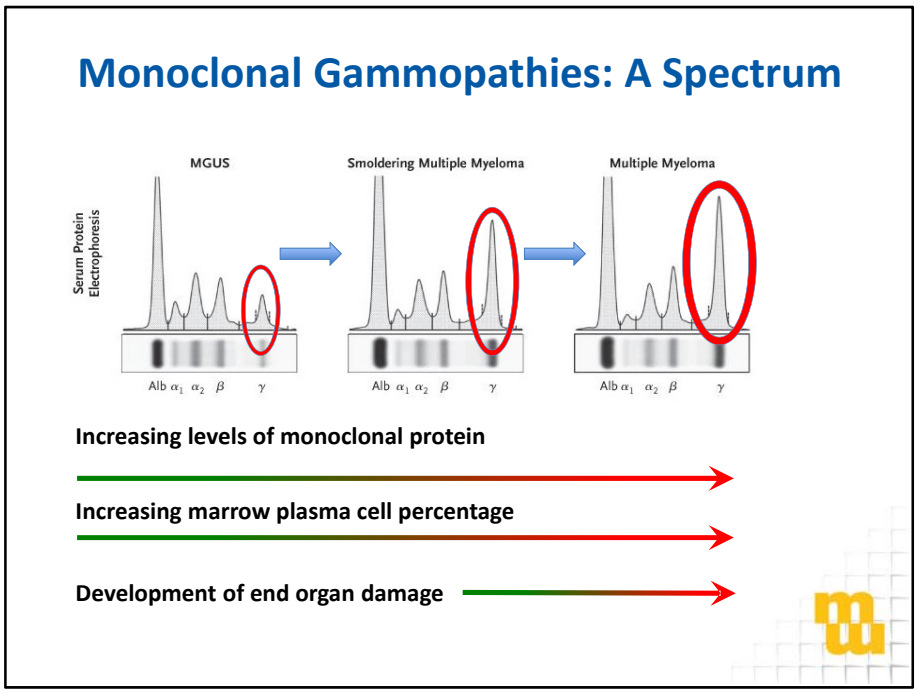

As you know, monoclonal gammopathies constitute a spectrum of disorders starting with monoclonal gammopathy of undetermined significance (MGUS), characterized by the presence of clonal plasma cells with no end-organ damage; all the way to the other end of the spectrum which is active multiple myeloma that needs therapy because there is end-organ damage in the form of hypercalcemia, renal insufficiency, anemia, or bone disease. This progression along the spectrum is characterized by an increasing proportion of bone marrow plasma cell infiltration, as well as increasing monoclonal protein either in the serum or the urine. In between monoclonal gammopathy of undetermined significance and active myeloma, some patients may be diagnosed with what we call smoldering multiple myeloma, where the tumor burden has increased considerably but there is still no end-organ damage. It is important that we make an accurate diagnosis, especially the distinction between smoldering multiple myeloma that we would not treat and active myeloma that requires therapy.

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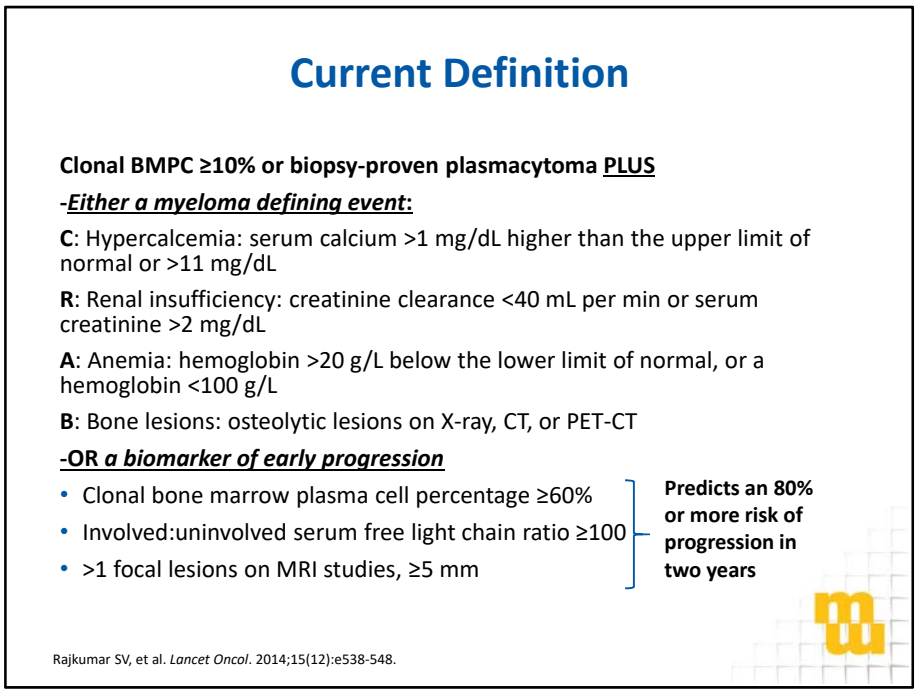

The definition for multiple myeloma was revised a couple of years ago. This revision incorporated what we call myeloma defining events (MDEs) in addition to the traditional CRAB criteria, and also provided some additional clarifications regarding the CRAB criteria itself. Patients should have more than or equal to 10% plasma cells or a biopsy-proven plasmacytoma, in addition to one of the CRAB features as shown here, or a biomarker of early progression. These three biomarkers were incorporated into the diagnostic criteria because they usually represent a clinical situation where the risk of progression to active myeloma or progression to development of CRAB features is almost 80% or higher in the two years from the time of diagnosis of smoldering myeloma. These include the bone marrow plasmacytosis of more than or equal to 60%, involved/uninvolved serum free light chain ratio that is at least 100 or more, and more than one focal lesion on MRI scan which are more than 5 mm in size each. Now, this represents a major change in how we diagnose active myeloma needing therapy because now we are using criteria that predicts the risk of development of CRAB features, not just the presence of CRAB features. We are essentially treating patients before they develop any kind of symptoms.

Diagnostic Approach

- CBC, chemistry
- Monoclonal protein studies: serum PEP, 24-hour urine PEP, immunofixation of serum and urine, serum free light chain (FLC)
- Bone marrow aspirate, flow, FISH
- Serum albumin, beta-2 microglobulin, LDH
- Skeletal evaluation: conventional X-ray, WBLDCT, PET/CT, MRI

NCCN Clinical Practice Guidelines in Multiple Myeloma. Version 4.2018 - February 12, 2018.

For the appropriate diagnosis of patients with myeloma and making the distinction between smoldering myeloma and active multiple myeloma, we need a good number of studies which include the complete blood count as well as serum chemistry. Monoclonal protein studies should include a serum protein electrophoresis and a 24-hour urine protein electrophoresis with immunofixation, and serum free light chain (FLC) assay. Bone marrow studies are important, and the aspirate will provide the percentage of plasma cells and will also allow us to do FISH studies which are designed to detect the cytogenetic abnormalities. The serum albumin, serum beta-2 microglobulin, and serum LDH are important components of the risk stratification system that we use in this disease. Finally, the use of advanced imaging – especially the use of whole-body low-dose CT scan or PET/CT or MRI – allows us to diagnose any lytic disease or bone marrow involvement that is not obvious with conventional x-rays.

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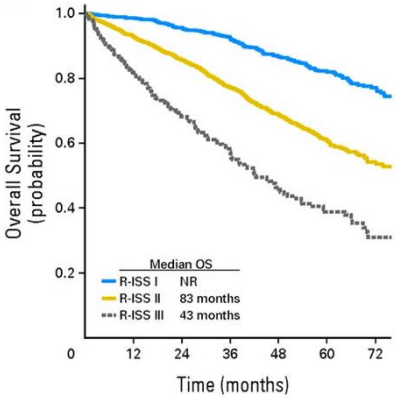
Revised ISS Staging System

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH



Palumbo A, et al. *J Clin Oncol.* 2015;33(26):2863-2869.

The International Staging System (ISS) was revised recently with the incorporation of the FISH abnormalities and serum LDH into the traditional ISS which previously used only the serum beta-2 microglobulin and serum albumin. By combining the traditional ISS staging system with the presence of high-risk cytogenetics by FISH (which essentially means a translocation 4;14, 14;16, or 17p deletion; and a serum LDH that is > than the upper limits of normal), we can identify three groups of patients with very different survival outcomes. Roughly about 60% of these patients would have ISS stage II; and about 20% each would be in stage I or stage III, representing standard-risk disease or high-risk disease, respectively.

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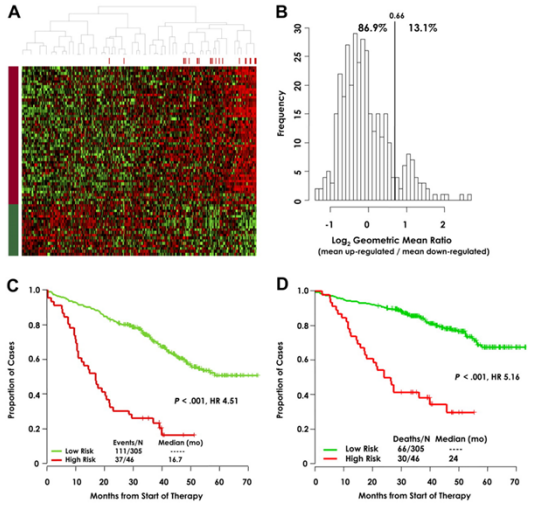
Gene Expression Based Classifications



Signatures

- GEP70
- GEP17
- HOVON
- IFM

Shaughnessy JD, et al. *Blood*. 2007;109(6):2276-2284.

Clearly the ISS staging system does not completely capture the heterogeneity that we see in the outcomes. Additional methodologies such as gene expression-based classifications have been developed. The GEP70 was developed by the University of Arkansas, and more recently there is a signature that was developed by HOVON which is available as a commercial test as well. The gene expression based classifications can allow us to identify about 15% to 20% of patients with high-risk myeloma who tend to have a short overall survival despite the therapies that we have today.

Other Prognostic Factors

- High plasma cell proliferation rate
- Circulating plasma cells
- Extramedullary disease
- Renal insufficiency
- Elevated C-reactive protein (CRP)

There are clearly other prognostic factors that are important in the disease and should be taken into account when you decide on the therapies. These include high plasma cell proliferation rate on the bone marrow aspirate, circulating plasma cells, the presence of extramedullary disease, renal insufficiency, as well as other markers like elevated C-reactive protein.

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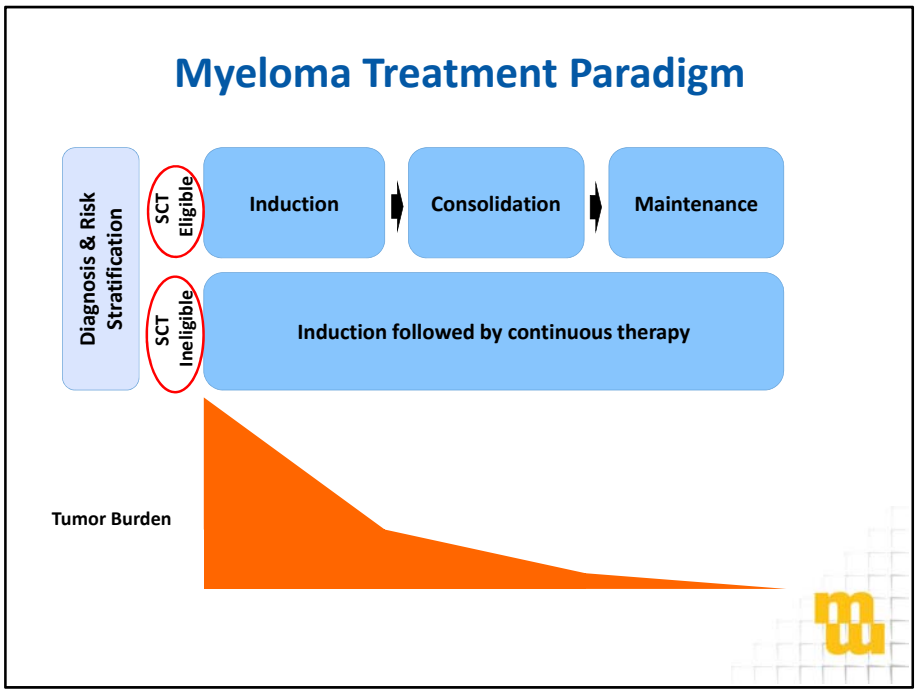

When you think about the treatment paradigm of myeloma, the two most important initial steps are an accurate diagnosis based on the criteria that we just talked about, and risk stratification based on the cytogenetic abnormalities and the ISS staging system. Once we know for sure the patient needs therapy for the myeloma, the next important question is whether the patient would be eligible to go through a stem cell transplant. This is a question that can also be asked after the patient goes through a couple of cycles of therapy as the initial treatment of myeloma is increasingly becoming uniform irrespective of the transplant status. Typically if patients are transplant-eligible, they would undergo what we call an induction therapy which is typically four to six cycles of a combination therapy; followed by consolidation which often includes an autologous stem cell transplant with or without additional chemotherapy-based consolidation; and then follow this with a maintenance strategy that is often continued for a few years or until progression. In patients who are not eligible to go through a stem cell transplant, they often get started again with one or two drugs in combination; and they often stay on one or two drugs for a prolonged period of time. The goal of either of these approaches would be to reduce the tumor burden to the lowest level possible so that we can translate the effect of the therapy to a prolonged duration of response.

So what are the goals of initial therapy? The ideal initial therapy that is used for a patient with newly diagnosed myeloma should be effective in controlling the disease and should achieve rapid disease control. It should reverse the disease-related complications such as renal insufficiency as early as possible. We also want a regimen that is effective without significant toxicity so that patients do not have the risk of early death either from disease or from complications. The regimen should be easily tolerated with minimal or manageable toxicity; and in patients who are eligible to go through a stem cell transplant, it should not interfere with the stem cell collection process itself.

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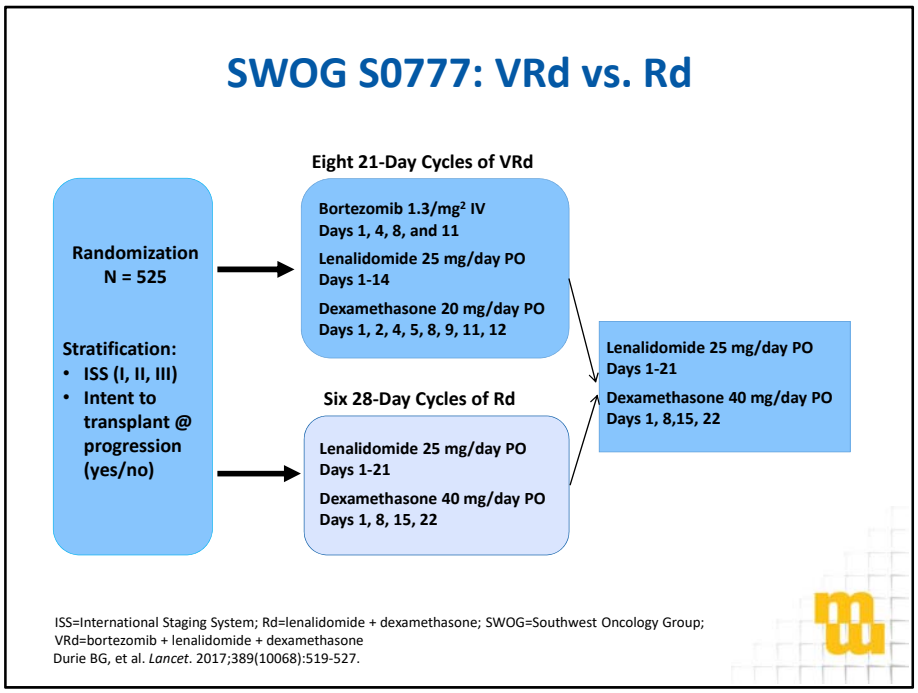

What do we typically use for the newly diagnosed patient today? The most commonly used regimen for newly diagnosed myeloma patients is the combination of bortezomib, lenalidomide and dexamethasone (VRd); and this is based on the results from the large phase 3 trial that randomized patients with newly diagnosed myeloma to VRd or Rd followed by lenalidomide maintenance.

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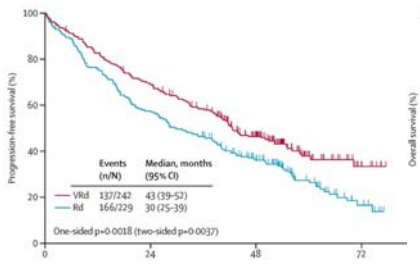
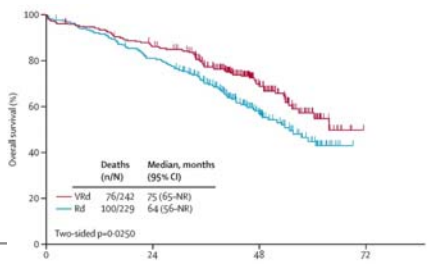
VRd vs. Rd: Survival



Months from registration



Months from registration

Durie BG, et al. *Lancet*. 2017;389(10068):519-527.

This trial demonstrated that using a proteasome inhibitor and an immunomodulatory drug in combination led to not only an improved progression-free survival, but also an improved overall survival.

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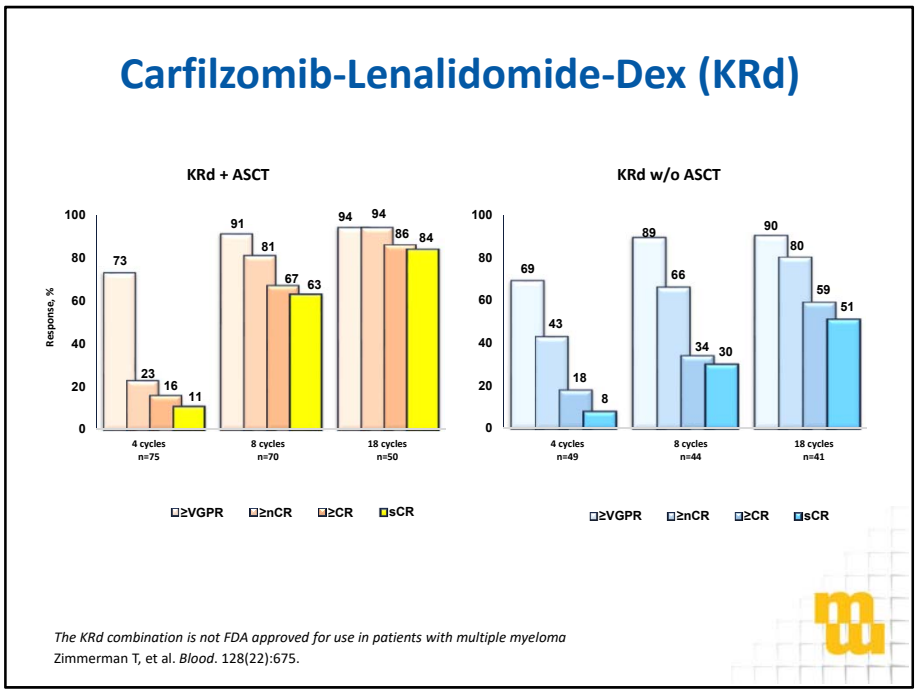

Now, there are clearly other choices as well that can be used for the initial treatment; and these include combinations of bortezomib with thalidomide and dexamethasone, or bortezomib with cyclophosphamide and dexamethasone. Both of those regimens are used less and less often with the data showing the superiority of VRd. The question is then how we can improve upon the current regimen of VRd? There are phase 2 trials that have demonstrated that a newer proteasome inhibitor like carfilzomib can be combined with lenalidomide and dexamethasone, and this regimen can actually give rise to a high response rate including a high proportion of patients with deep responses like VGPR and complete response. This phase 2 trial that is shown here looked at using carfilzomib-lenalidomide-dexamethasone (KRd) with or without stem cell transplant; and you can see that the response rates are quite high while using this regimen. Now, this regimen is being studied in a phase 3 trial comparing it to VRd so I would encourage everyone to use this regimen in the context of a clinical trial until we have the phase 3 data.

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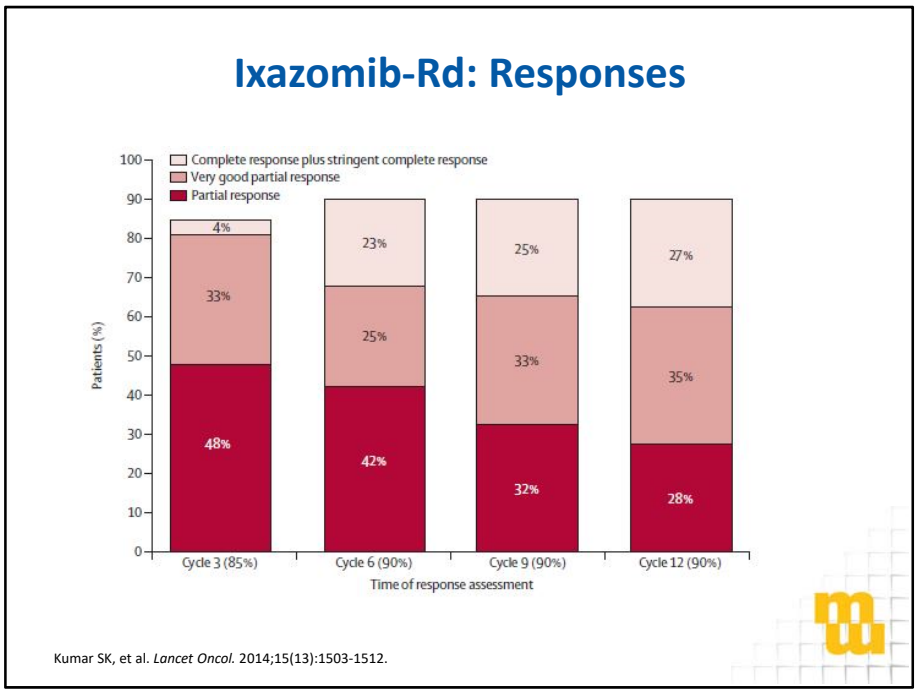
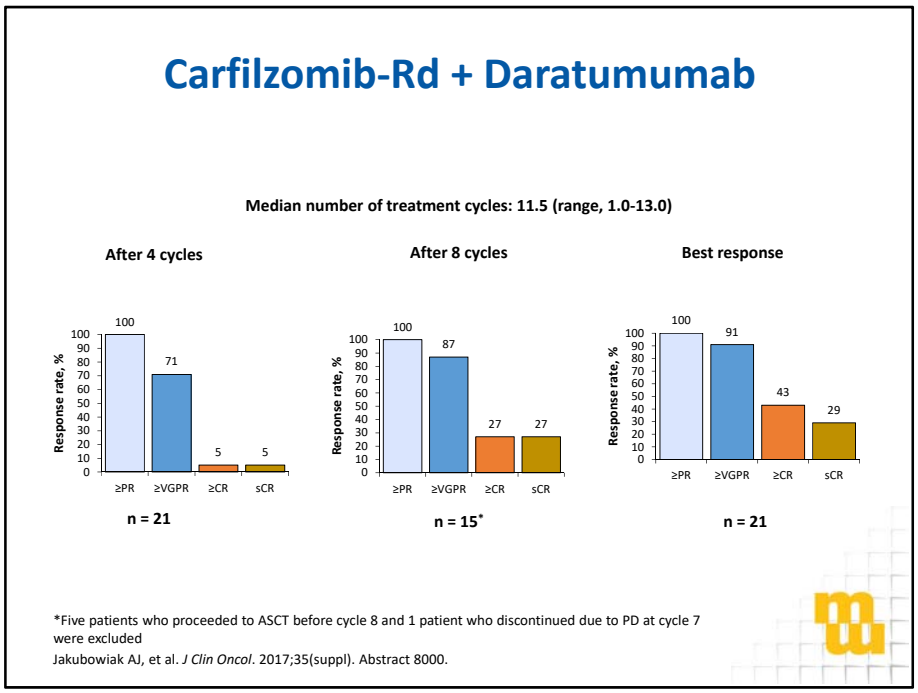


Kumar SK, et al. *Lancet Oncol.* 2014;15(13):1503-1512.

There is another combination that uses an oral proteasome inhibitor which is ixazomib in combination with lenalidomide/dexamethasone. What is unique about this regimen is that it is completely oral, with ixazomib being given once a week for three out of four weeks. We know by using this combination that patients can have responses; over 90% of these patients had a response, with a significant proportion of them getting deep responses that continue to deepen as the patient stays on therapy for longer periods of time.



The important question for the future is whether we add some of the newer classes of drugs like daratumumab which is a monoclonal antibody to this triplet combination? Daratumumab has been studied in combination with KRd in this phase 2 trial. As we can see here, this combination is also quite effective and leads to high response rates and deep responses. How much incremental benefit we get by adding daratumumab to this combination versus using daratumumab at the time of relapse is unclear because those studies are still ongoing, especially the phase 3 trials.

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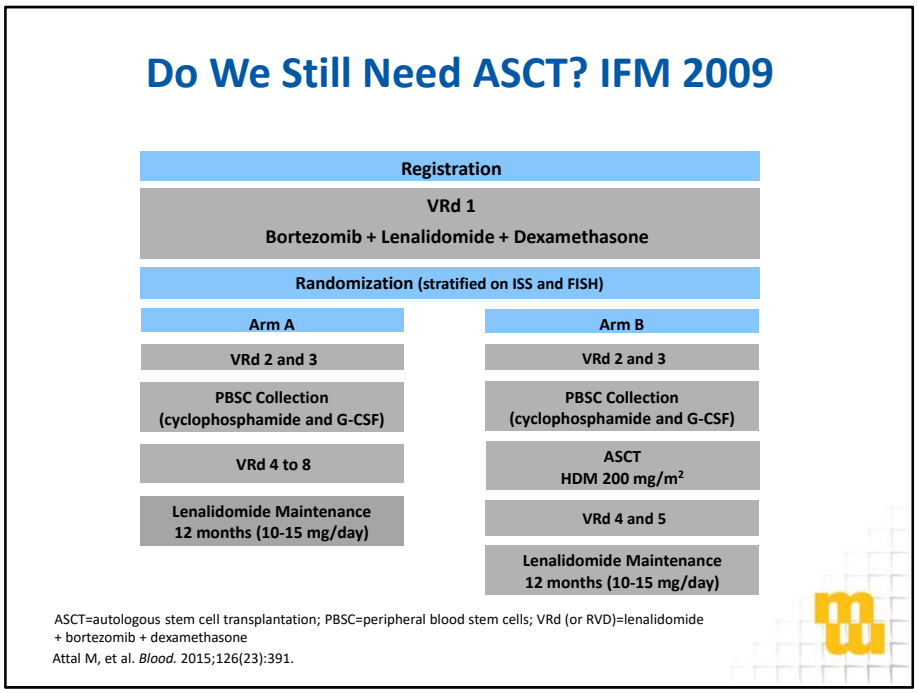

Once you are done with that initial induction therapy for the four to six cycles, and the patients have had a response, the next question is: can we do some kind of consolidation therapy to prolong the duration of response? The recently reported phase 3 IFM trial does demonstrate that transplant still continues to have benefit in the context of newer therapies. This trial randomized patients to either getting an autologous stem cell transplant after VRd induction, or collecting the stem cells and using the transplant at a later date, but continuing additional consolidation with the VRd regimen followed by lenalidomide maintenance.

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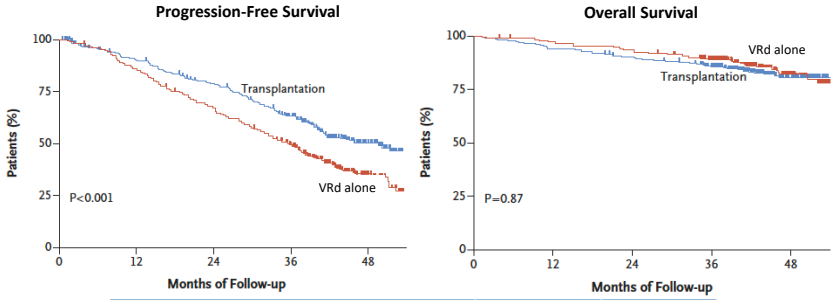
IFM 2009: Survival Outcomes



Outcome	VRd Alone Group (N = 350)	Transplantation Group (N = 350)
Complete response or very good partial response – no. (%)	270 (77)	307 (88)
Minimal residual disease not detected during the study – no./ total no. with complete or very good partial response (%)*	171/265 (65)	220/278 (79)

*MRD was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.
Attal M, et al. *N Engl J Med.* 2017;376(14):1311-1320.

The results of the study clearly showed that the addition of an autologous stem cell transplant significantly improved the progression-free survival. However, overall survival so far appears to be comparable in patients who got an early autologous stem cell transplant or people who decided to defer the transplant to the time of relapse. We need to get some more mature data before we can conclude the impact of early autologous stem cell transplant on overall survival. Until we have the data, I think patients who want to defer stem cell transplant to the time of relapse can certainly consider that as an equally viable approach.

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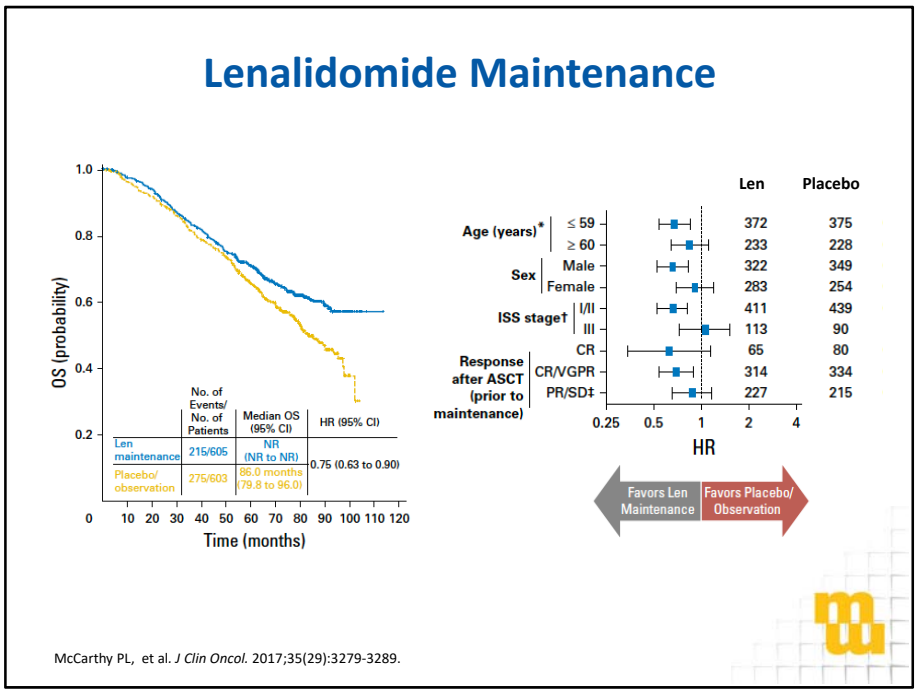

McCarthy PL, et al. *J Clin Oncol.* 2017;35(29):3279-3289.

Once the patients complete the autologous stem cell transplant, then all of these patients should go on maintenance therapy. Currently, meta-analysis of phase 3 trials has shown that lenalidomide maintenance after autologous stem cell transplant clearly improves the overall survival, except in patients who have high-risk disease or ISS stage III.

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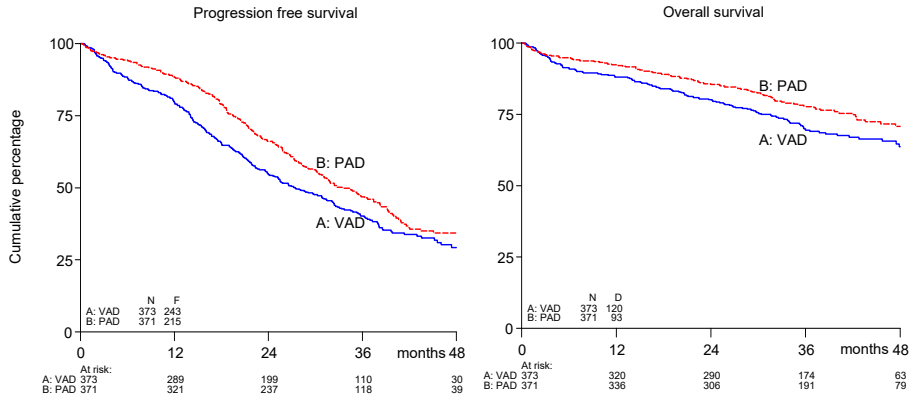
Bortezomib Maintenance



	VAD	PAD	
CR/nCR	34	49	<0.001
≥VGPR	55	76	0.001
≥PR	83	91	0.003

Sonneveld P, et al. *Blood.* 2010;116:40.

For those patients, there is some data from the HOVON trials demonstrating that patients with high-risk disease may benefit from the use of bortezomib, both as part of induction therapy and also subsequently as maintenance post autologous stem cell transplant; and this approach can certainly be considered in the high-risk patients.

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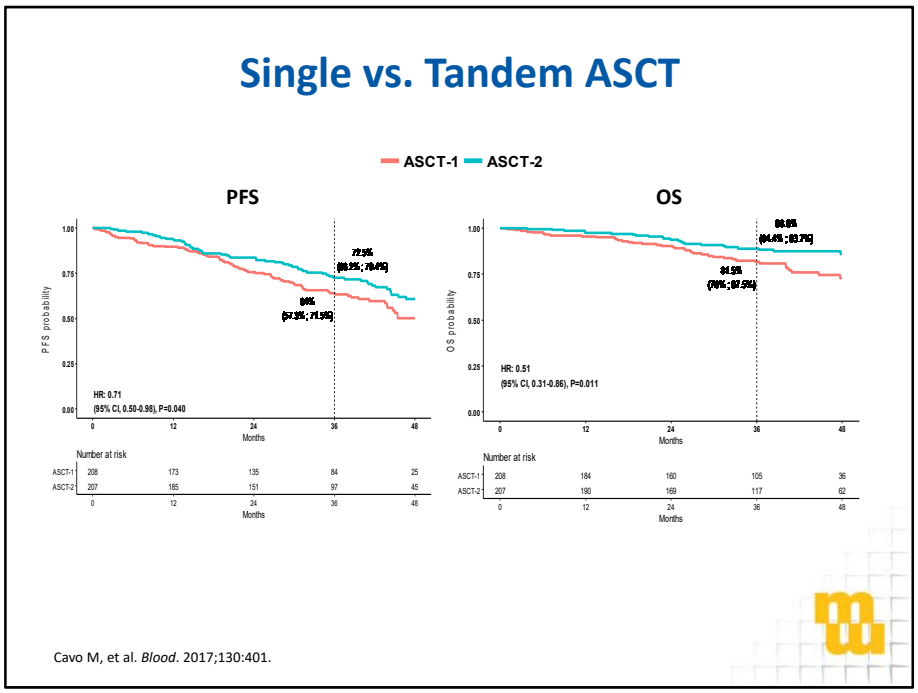

Cavo M, et al. *Blood*. 2017;130:401.

There is also data suggesting that patients with high-risk myeloma doing a tandem autologous stem cell transplant may improve overall survival as demonstrated by this phase 3 trial from HOVON.

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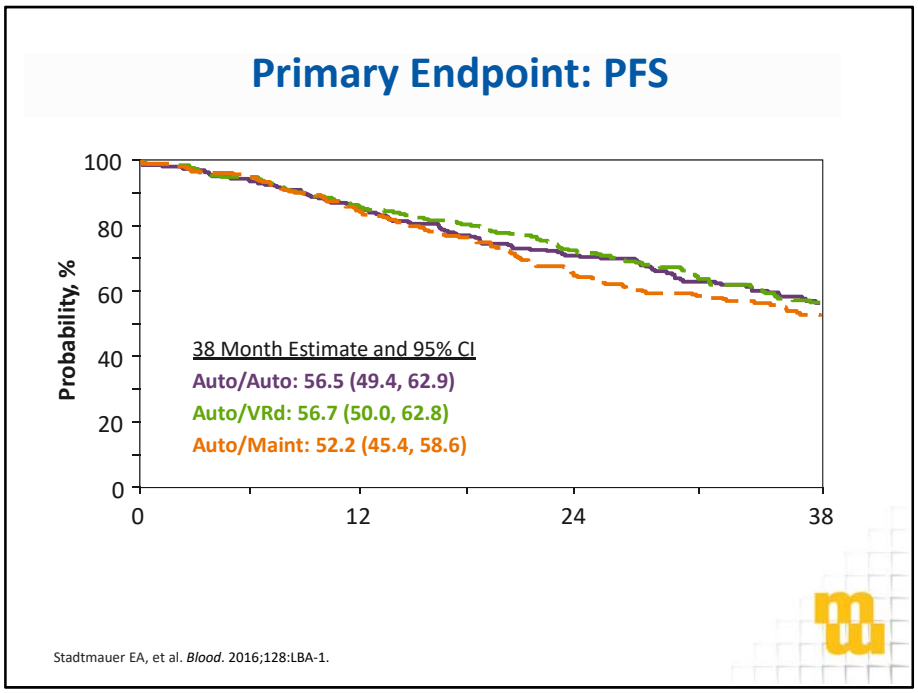

The data from the phase 3 trial that was done in the US which was called the StaMINA trial did not demonstrate any improvement for doing a tandem transplant versus a single transplant. I think it is reasonable to say that if someone got a VRd induction therapy, then doing a tandem autologous stem cell transplant for every patient does not necessarily make sense. But if you have somebody with high-risk disease with 17p deletion or 4;14 translocation, those patients can certainly be considered for a tandem auto transplant and it is a discussion that one would have with the patient.

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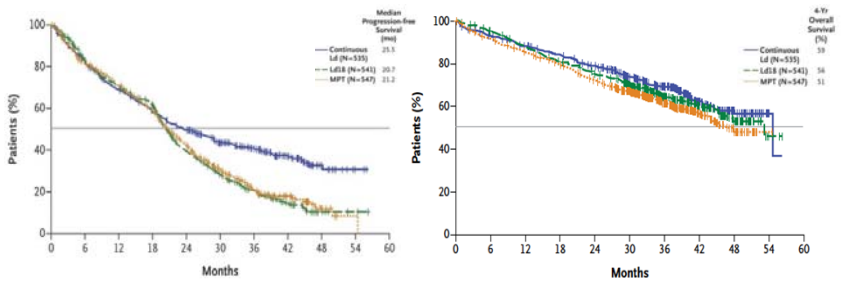
Rd (Continuous or 18 Months) vs. MPT



Rd (or Ld)=lenalidomide + dexamethasone; MPT=melphalan-prednisone-thalidomide
Benboubker L, et al. *N Engl J Med*. 2014;371:906-917.

What about the patients who cannot go through a stem cell transplant? The regimen that we often use in these patients is one of lenalidomide and dexamethasone, and this is based on data from the phase 3 trial comparing len-dex versus melphalan, prednisone, and thalidomide. This trial demonstrated that lenalidomide-dexamethasone given continuously until progression improved the overall survival compared to melphalan-prednisone-thalidomide. It is also interesting to note that, in this study, using lenalidomide-dexamethasone for a limited 18 months also gave a comparable overall survival, and that also needs to be taken into account when you consider this regimen.

RVD Lite

35-day cycle. Lenalidomide 15 days 1-21; bortezomib 1.3 mg/m^2 once-weekly subcutaneously days 1, 8, 15, and 22; and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22 and 23 for patients ≤75 years and days 1, 8, 15, 22 for patients older than 75 years.

Response after 4 cycles (%) (n=30)

ORR (≥PR)	**27 (90.0)**
CR	5 (16.7)
VGPR	11 (36.7)
PR	11 (36.7)
SD	3 (10.0)
VGPR or better	**16 (53.3)**

IMWG Criteria; ORR=overall response rate; CR=complete response; PR=partial response; SD=stable disease; VGPR=very good PR; RVD Lite (also VRd Lite)

O'Donnell E, et al. *Blood.* 2014;124:3454.

We are increasingly starting to use all three drugs in the older patients as well by using lower doses of drugs and also stretching the cycle to a five-week cycle instead of a four-week cycle. This is what we often refer to as the VRd-lite or RVD-lite. This also appeared to give us response rates comparable to the traditional dose and schedule of VRd when used in the older patients.

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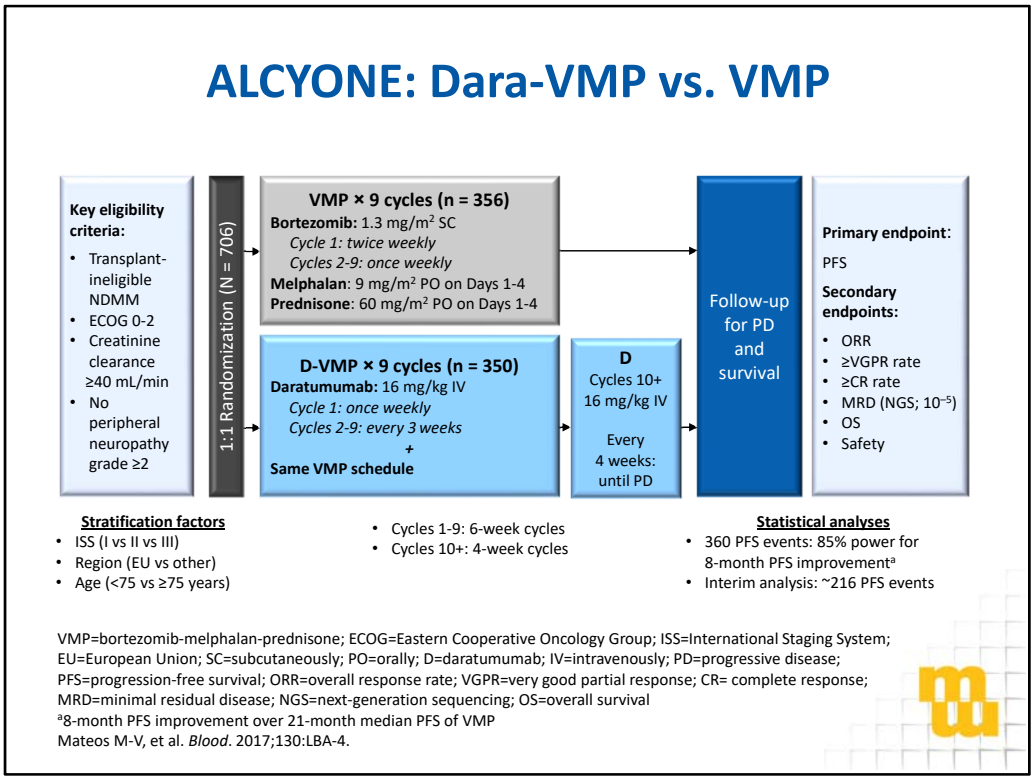

Finally, there are more recent data that have looked at adding daratumumab to bortezomib, melphalan, and prednisone (the ALCYONE trial) which clearly showed that adding the daratumumab to the triplet regimen leads to improved progression-free survival.

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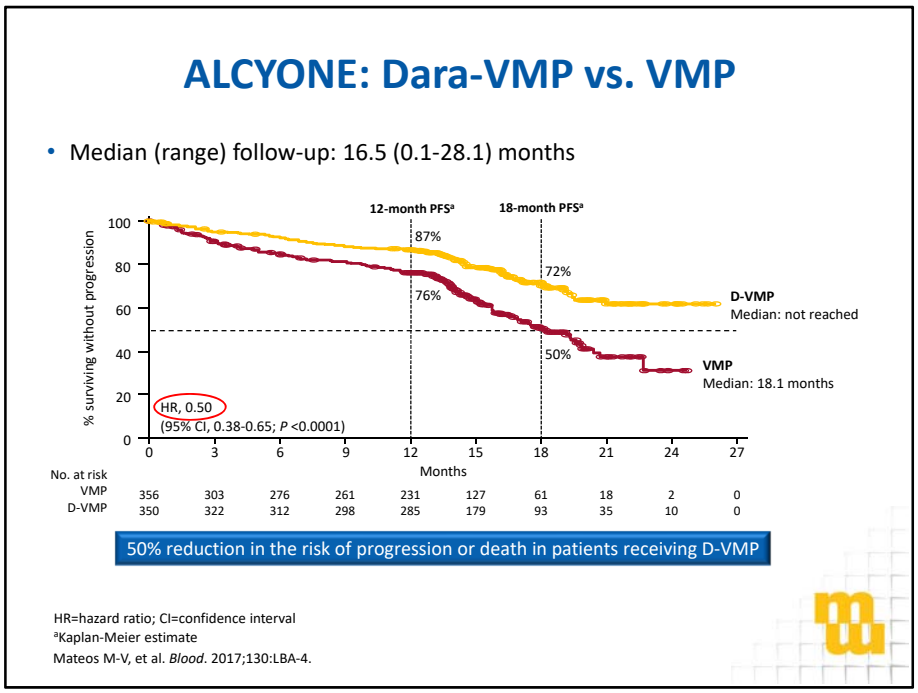
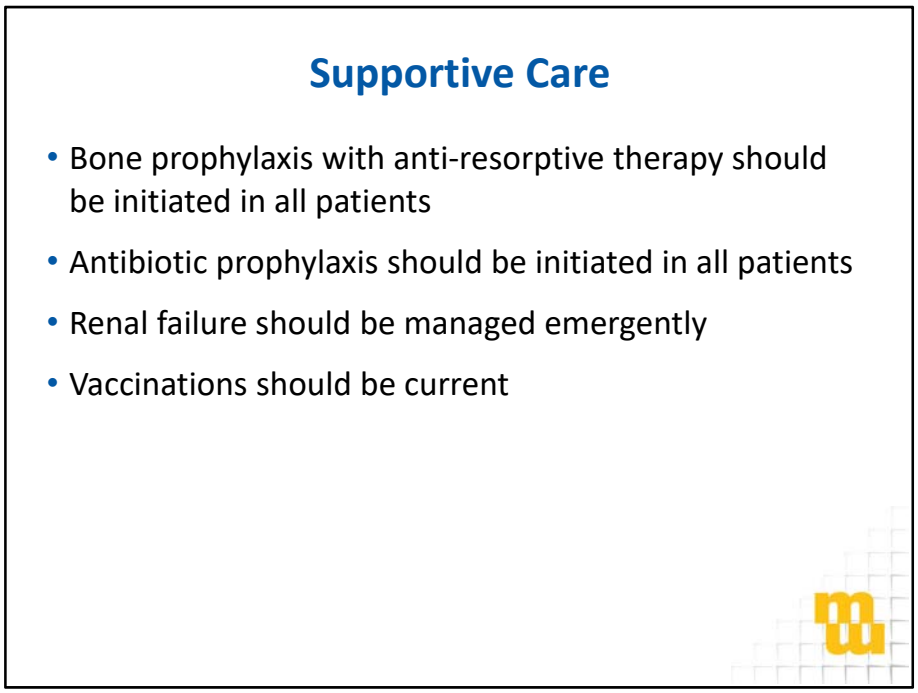


However, we do not have any overall survival data as of this time and that is something that we have to wait for before uniformly adopting a four-drug regimen compared to a three-drug regimen.



In addition to all those initial therapies that are aimed at controlling the disease, we also need to be focusing on supportive care management. These patients have bone disease and should be started on bone prophylaxis with antiresorptive therapy, either bisphosphonate or anti-RANK ligand antibodies; and this should be started in all patients irrespective of whether they have bone disease or not. There is an important role for antibiotic prophylaxis, this is highlighted by the recent phase 3 trial which demonstrated that adding levofloxacin during the first three months after diagnosis can lead to decreased risk of infections. Patients with renal failure should be managed emergently with a focus on decreasing the light chain levels as soon as possible, which provides the maximum opportunity for recovery of renal function. It is also important to make sure these patients have their vaccinations up-to-date.

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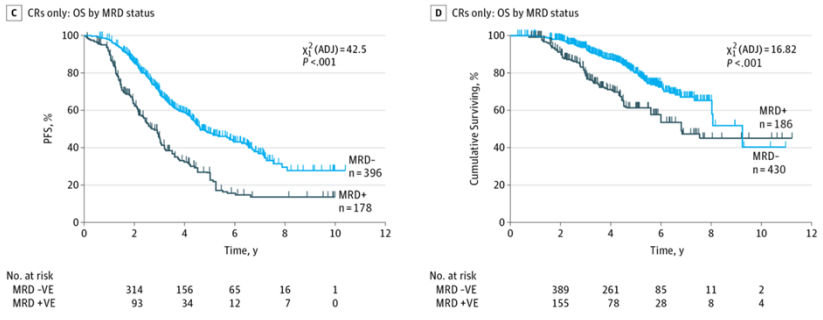
Impact of Minimal Residual Disease (MRD) in CR Patients

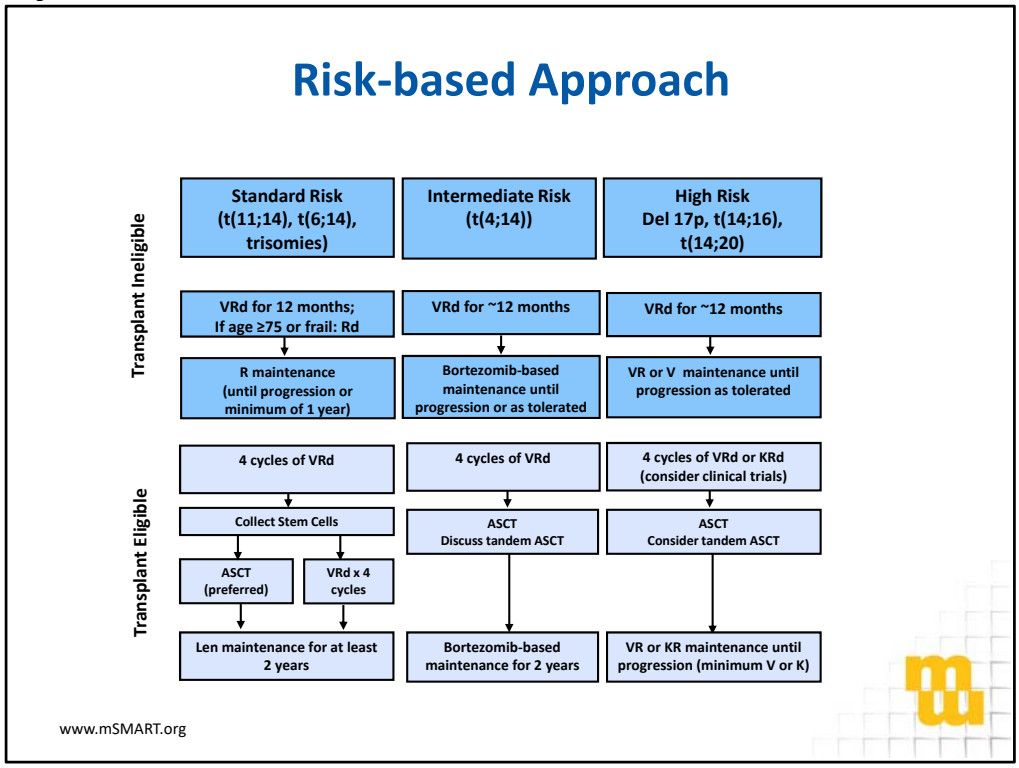


Cannot be used to guide therapy yet

Munshi NC, et al. *JAMA Oncol*. 2017;3(1):28-35.

What is the overall goal of therapy in patients with newly diagnosed myeloma? We already know that if patients get to a minimal residual disease (MRD) state, these patients tend to have better progression-free survival; but that does not automatically mean that we have to try and achieve MRD in every patient. There are studies that are ongoing trying to answer the question of whether MRD should be the target of therapy in all patients. It is reasonable to say based on the available data that in patients with high-risk disease, we should consider treating them to an MRD-negative state because that seems to be best associated with outcome in these high-risk patients, where the current therapy approaches still give us suboptimal results.

Novel Therapies for the Treatment of Newly Diagnosed Multiple Myeloma



There are several risk-based approaches that have been developed. One of them is the mSMART algorithm which classifies patients as standard risk, intermediate risk or high risk based on the presence of cytogenetic abnormalities. All of these patients should be started on initial therapy with the bortezomib-lenalidomide-dexamethasone regimen if you can or lenalidomide-dexamethasone in the standard risk if they cannot tolerate a three-drug regimen. These patients should be placed on lenalidomide maintenance if they are standard risk, or bortezomib-based maintenance if they are high risk. In the transplant-eligible patients, the initial four cycles of induction therapy either with bortezomib-lenalidomide-dexamethasone – or using carfilzomib-lenalidomide-dexamethasone in high-risk patients – should be followed by a single or tandem autologous stem cell transplant. A discussion about a tandem auto transplant should be had with patients who have high-risk disease. High-risk transplant-eligible patients should stay on a bortezomib- or a carfilzomib-based maintenance therapy, and patients with standard-risk disease should stay on lenalidomide maintenance.

Key Points

- It is important to make the correct distinction between smoldering MM and active MM requiring therapy
- Adequate risk assessment is critical
- Novel drug combinations including at least two novel drugs should be standard
- In transplant eligible patients, SCT plays a critical role; post SCT maintenance is important
- Older patients should be treated with a triplet at reduced doses or doublets
  - Prolonged treatment to best plateau is appropriate approach
- Risk based treatment selection is the way of the future

To conclude, I would like to leave you with these key takeaway points. It is important to make the distinction between a smoldering multiple myeloma which does not require therapy and an active myeloma patient who requires therapy to be initiated. Identifying the risk status is very important because that will provide important guidance as to how you treat, what combination to use, and how long you continue these patients on therapy. In transplant-eligible patients, a transplant plays a critical role; and post-stem cell transplant maintenance should be considered the standard of care. All the patients can be treated with a triplet with modified dose and schedule; or in the really frail patients, using a doublet such as lenalidomide-dexamethasone would be appropriate. Risk-based treatment selection is increasingly going to be the vital feature as our risk assessment tools improve, and we have multiple drugs available for use in specific groups of patients.

Thank you for viewing this activity.