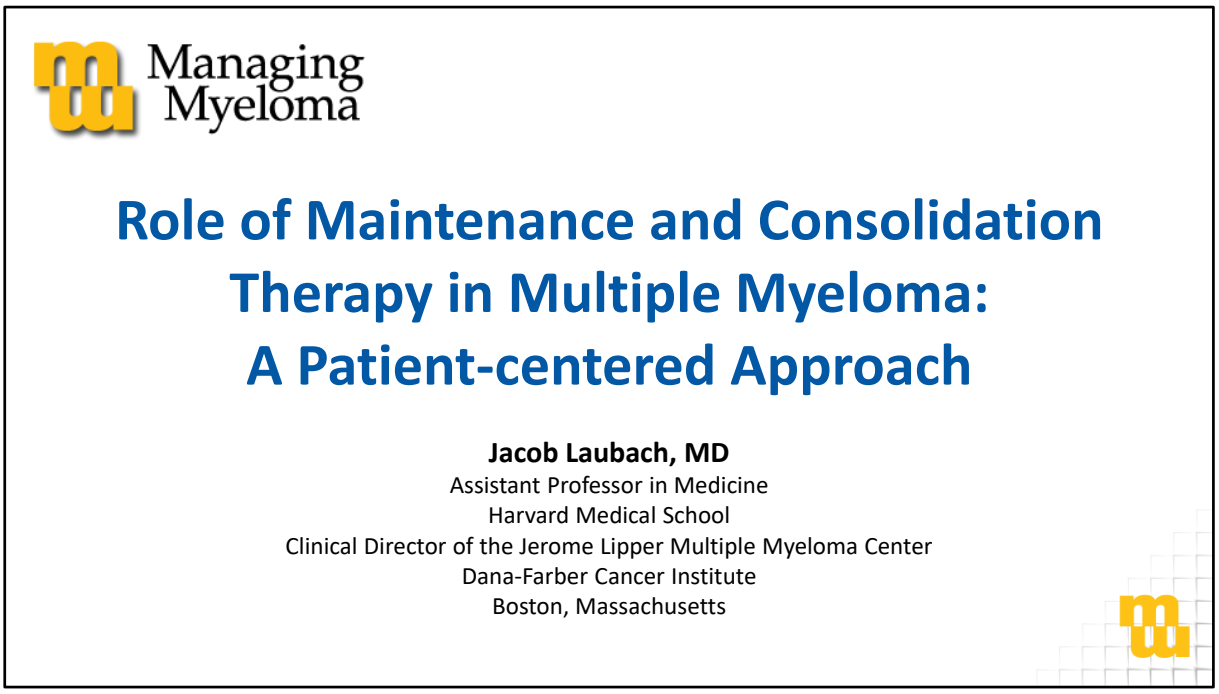
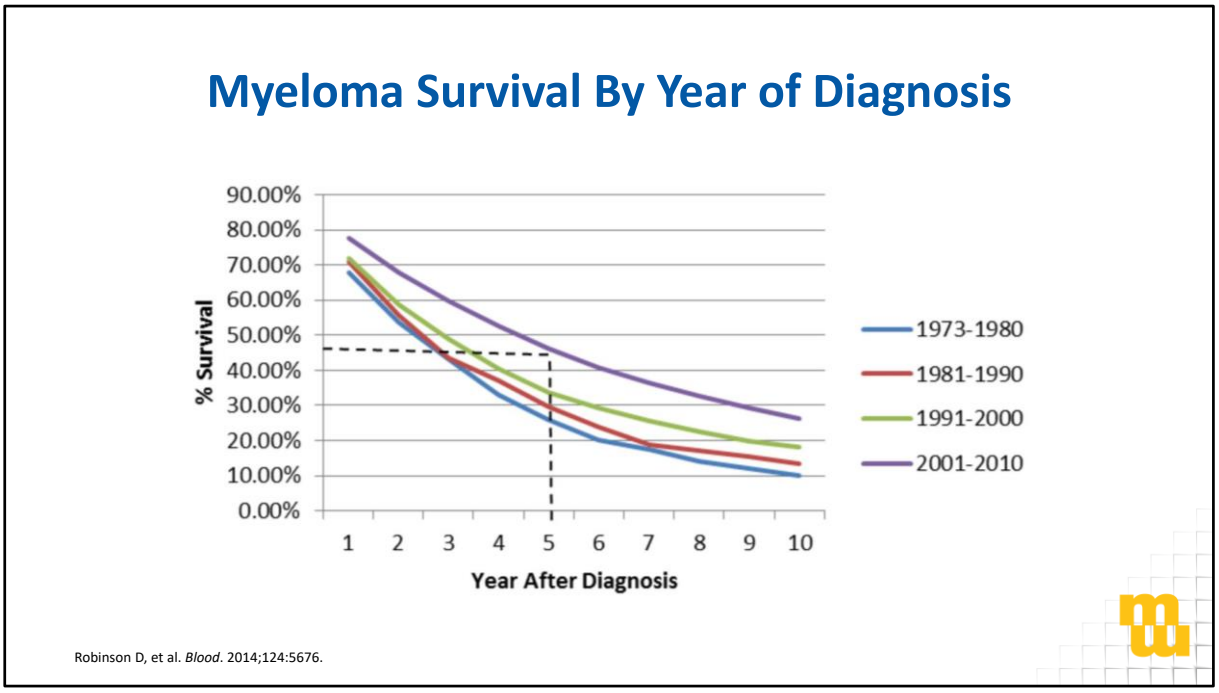
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



Welcome to *Managing Myeloma*. I am Dr. Jacob Laubach. In today's presentation, I will review the role of maintenance and consolidation therapy in multiple myeloma, specifically using a patient-centered approach. In this video, I will provide you with background on identifying patients who may benefit from maintenance and consolidation therapy, and summarize treatment options available based on individual patient profile and treatment history. We will also cover data from recent clinical trials related to patient outcomes. Let's begin.

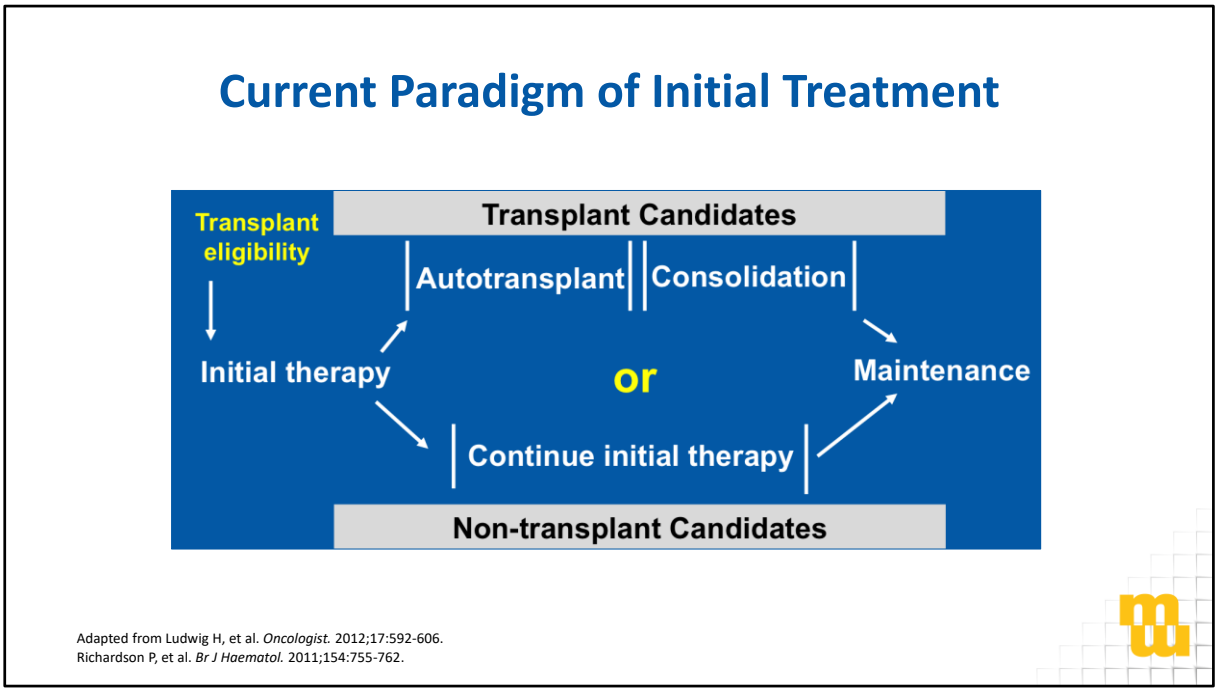
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



Robinson D, et al. *Blood*. 2014;124:5676.

As is well known, myeloma outcomes have improved dramatically over the course of the past decade or so with the availability of new, better treatment options for patients. It is anticipated that outcomes for patients will continue to improve in the coming years.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



This is the current paradigm for the initial treatment of multiple myeloma. Patients are evaluated for their eligibility for autologous stem cell transplantation, which remains a standard of care for newly diagnosed multiple myeloma. Those who are transplant-eligible receive induction therapy, with regimens incorporating two or preferably three drugs, followed in many instances by autologous stem cell transplantation, and thereafter by consolidation and maintenance therapy. Those who are transplant ineligible also receive induction therapy, with regimens incorporating two or, at times, three drugs for a period of time before transitioning to maintenance therapy.

Rationale for Maintenance Therapy

- Preserve response in patients with complete response or better
- Deepen response in patients with < complete response
- Lengthen response duration and survival
- Improve quality of life
- Minimize disease and treatment-related symptoms

The rationale for maintenance therapy is as follows: It allows us to preserve response in patients with a complete response or better, to deepen response in individuals who have achieved less than a complete response, to lengthen the response duration and overall survival, improve quality of life, and minimize disease- and treatment-related symptoms.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Patient Cases

- 70-year-old gentleman presents with fatigue and is found to be anemic with renal impairment
  - Diagnosed with ISS III IgG lambda myeloma
  - Receives 5 cycles of cyclophosphamide, bortezomib, and dexamethasone; achieves very good partial response prior to autologous stem cell transplantation (ASCT)
- 76-year-old woman presents with shoulder and sternal pain and is found to have a sternal mass and numerous lytic bone lesions
  - Diagnosed with ISS II IgA kappa myeloma; FISH showing additional copies of 1q, trisomy 9, monosomy 13, and del17p
  - Receives 8 cycles of lenalidomide, bortezomib, and dexamethasone; achieves very good partial response
- 43-year-old gentleman presents with back pain and is found to have diffuse lytic bone lesions along with anemia, hypercalcemia, and renal impairment
  - Diagnosed with ISS II kappa light chain myeloma; noted on FISH to have both del13q and del17p
  - Receives 6 cycles of lenalidomide, bortezomib, and dexamethasone followed by ASCT

I am going to present three patient cases from individuals in my own practice. The first is a 70-year-old gentleman who originally presented with fatigue and was found to be anemic with renal impairment. He was diagnosed with ISS III IgG-lambda multiple myeloma. He received five cycles of therapy with cyclophosphamide, bortezomib, and dexamethasone, and achieved a very good partial response prior to undergoing autologous stem cell transplantation. We will discuss later what choice was made in his care regarding maintenance therapy. In another case, a 76-year-old woman presented with shoulder and sternal pain and was found to have a sternal mass and numerous lytic bone lesions. She was diagnosed with ISS II IgA-kappa multiple myeloma, with FISH analysis showing additional copies of 1q, trisomy 9, and monosomy 13, as well as deletion 17p. She received eight cycles of lenalidomide, bortezomib, and dexamethasone and achieved a very good partial response. Once again, later in our presentation, we will discuss choices that were made with respect to maintenance therapy in her case. Finally, we will discuss a 43-year-old gentleman who presented with back pain and was found to have diffuse lytic bone lesions along with anemia, hypercalcemia, and renal impairment. He was diagnosed with ISS II kappa light chain multiple myeloma and, on FISH analysis, was found to have deletion 13q and deletion 17p. He received six cycles of therapy with lenalidomide, bortezomib, and dexamethasone, followed by autologous stem cell transplantation.

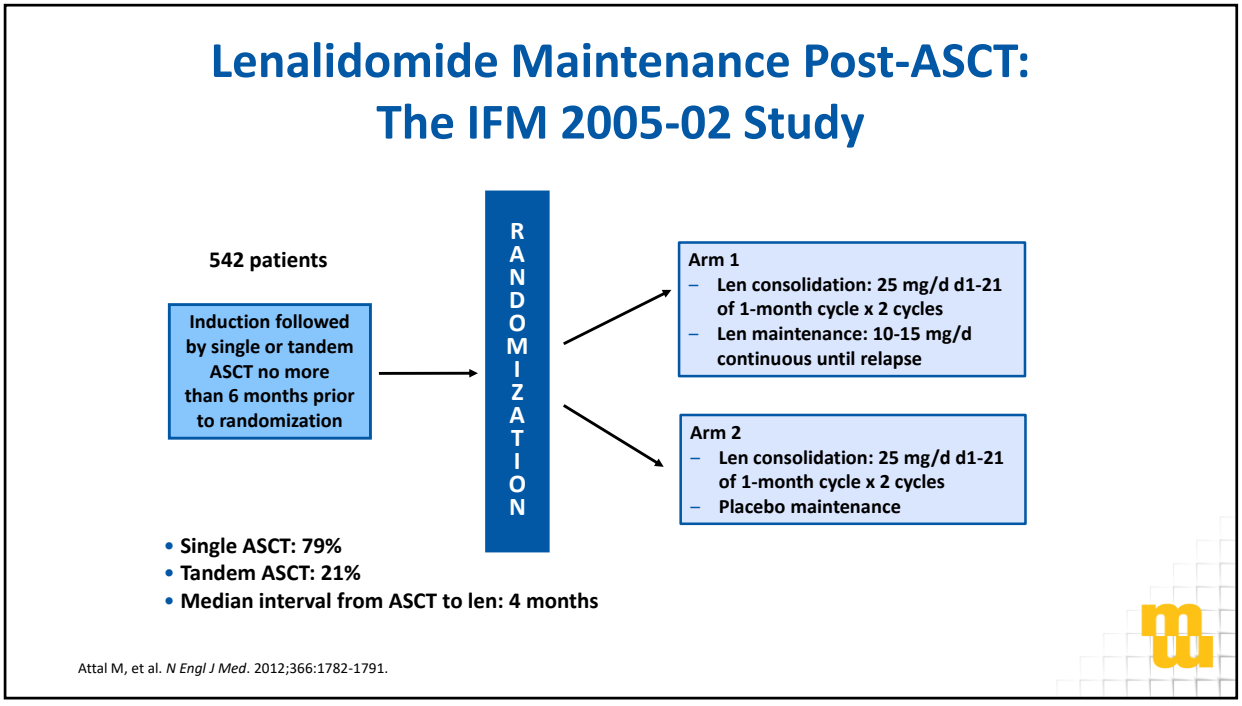
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Important Clinical Considerations

- Which maintenance agent is most suitable for a particular patient based on prognostic factors, prior therapy, coexisting medical conditions, and patient preferences?
- Optimal duration of maintenance
- Monitoring for maintenance-related toxicity and supportive care considerations
- Impact of maintenance on management at the time of disease relapse

With regard to maintenance therapy, there are a number of important clinical considerations to consider. First, which maintenance agent is most suitable for a particular patient based on prognostic factors, prior therapy, coexisting medical conditions, as well as patient preference? Second, what is the optimal duration of maintenance therapy? Third, it is critically important to monitor for maintenance-related toxicities and provide appropriate supportive care. Finally, what is the impact of maintenance therapy on management of the disease at the time of relapse?

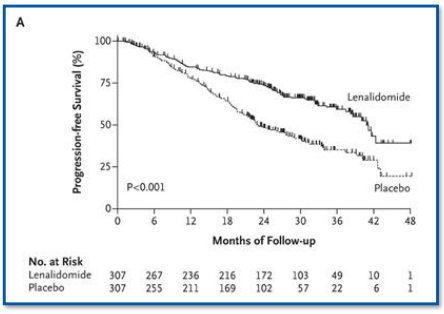
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

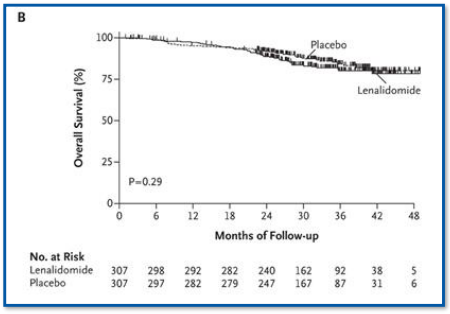


Fortunately, with regard to maintenance therapy in multiple myeloma, this is an area where we are guided by the results of numerous high-quality phase III clinical trials. The IFM 2005-02 study was an evaluation of lenalidomide maintenance in the post-transplant setting. In this study, which was conducted across 78 sites in France, Belgium and Switzerland, 542 patients were randomized in the aftermath of either a single or tandem autologous stem cell transplantation to either lenalidomide consolidation followed by lenalidomide maintenance or, in the second arm of the trial, lenalidomide consolidation followed by placebo.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Impact of Len Maintenance on PFS and OS





Median PFS lenalidomide group: 41 months

Median PFS placebo group: 23 months

HR 0.5; *P* < 0.001

3-year OS lenalidomide group: 80 months

3-year OS placebo group: 84 months

HR 1.25; *P* = 0.29

Attal M, et al. *N Engl J Med*. 2012;366:1782-1791.

The incorporation of lenalidomide maintenance as part of the patient's overall treatment strategy led to a significant improvement of progression-free survival, with a median progression-free survival of 41 months in the group of patients who received lenalidomide maintenance, versus 23 months for those who received placebo. There was no difference, in this trial, in overall survival at three years.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Incidence of Second Primary Cancers

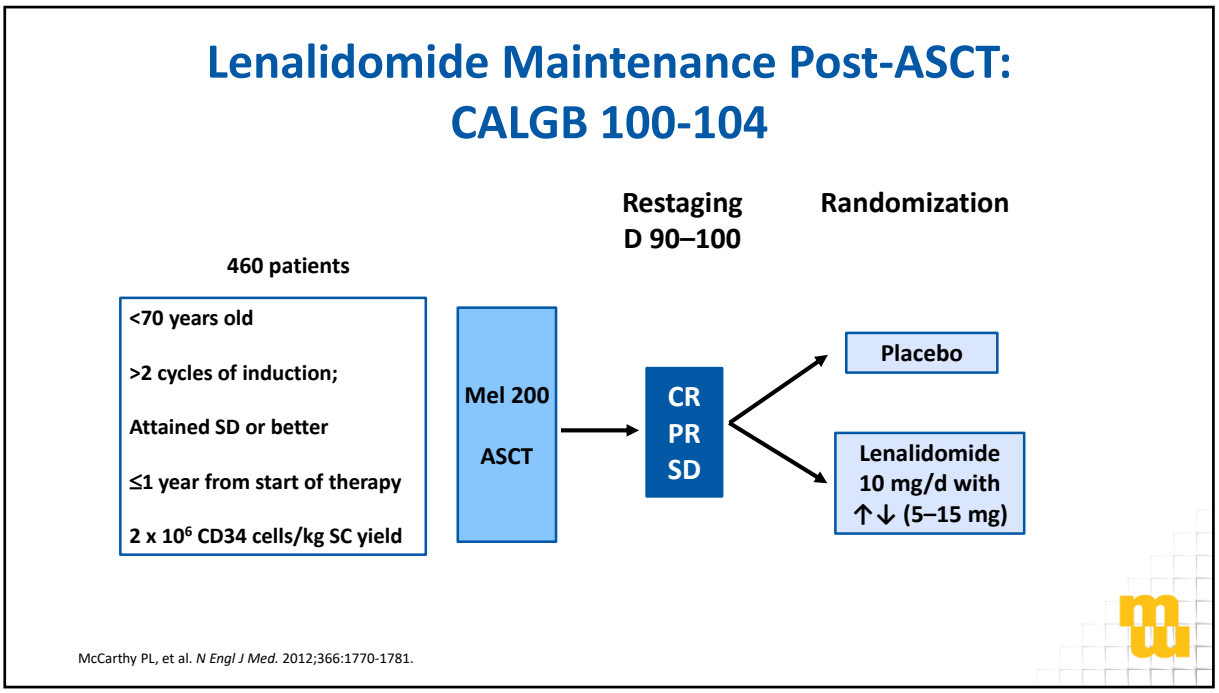
Types of Lesions in Patients with at Least One Second Primary Cancer.*

Type of Lesion	Lenalidomide Group (N=306)	Placebo Group (N=302)	Total (N=608)
	number of patients (percent)		
Hematologic cancers	13 (4)	5 (2)	18 (3)
AML or MDS	5	4	
ALL	3	0	
Hodgkin's lymphoma	4	0	
Non-Hodgkin's lymphoma	1	1	
Solid tumors	10 (3)	4 (1)	14 (2)
Esophageal	1	0	
Colon	3	0	
Prostate	2	1	
Breast	2	0	
Lung	0	1	
Sinus	1	0	
Kidney	1	1	
Melanoma	0	1	
Nonmelanoma skin cancers	5 (2)	3 (1)	8 (1)
Total	26 (8)	11 (4)	37 (6)

Attal M, et al. *N Engl J Med*. 2012;366:1782-1791.

Of note, an increased incidence of second primary cancers, both hematologic cancers as well as solid tumors, was observed among patients who received lenalidomide maintenance in this study.

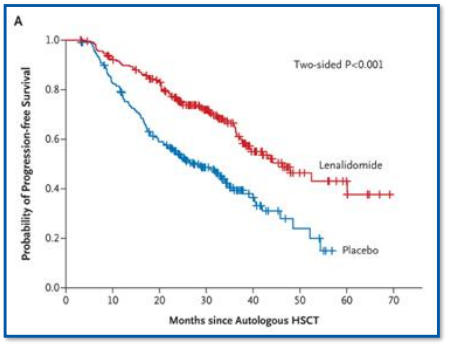
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



A second trial of lenalidomide maintenance in the post-transplant setting was the CALGB 100-104 trial. In this study, which was conducted across sites in North America, 460 patients who were less than 70 years of age, had received two cycles of induction therapy, and achieved at least stable disease or better were randomized to receive either lenalidomide maintenance starting at a 10-mg dose, or placebo.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

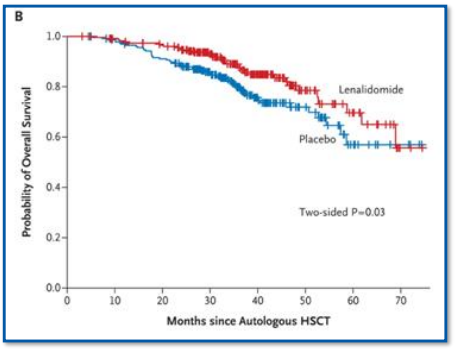
Impact of Len Maintenance on PFS and OS



Median PFS lenalidomide group: 46 months

Median PFS placebo group: 27 months

***P* < 0.001**



3-year OS lenalidomide group: 88%

3-year OS placebo group: 80%

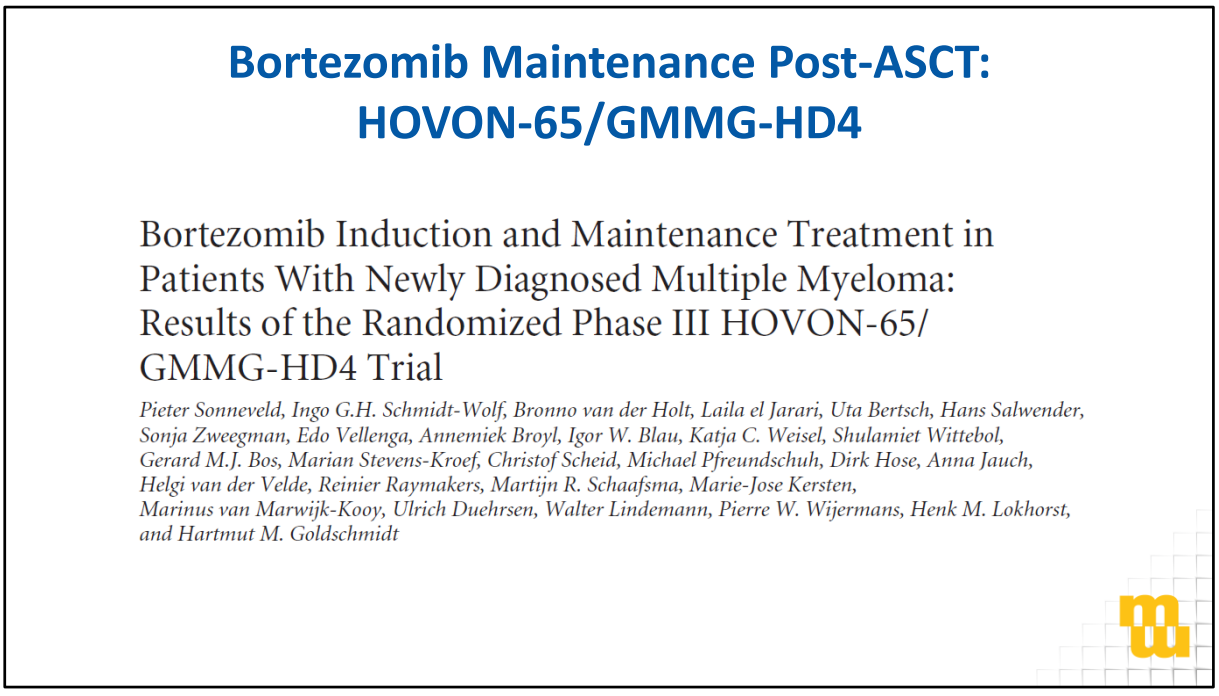
HR 0.62; *P* = 0.03

PFS=progression-free survival; OS=overall survival; HR=hazard ratio
McCarthy PL, et al. *N Engl J Med.* 2012;366:1770-1781.

Once again, there was a significant improvement in progression-free survival associated with the use of lenalidomide maintenance, with a median progression-free survival of 46 months, versus 27 months in those who received placebo. In this study, importantly there was also an overall survival benefit at three years, with 88% of patients living who received lenalidomide, versus 80% of patients who received placebo.

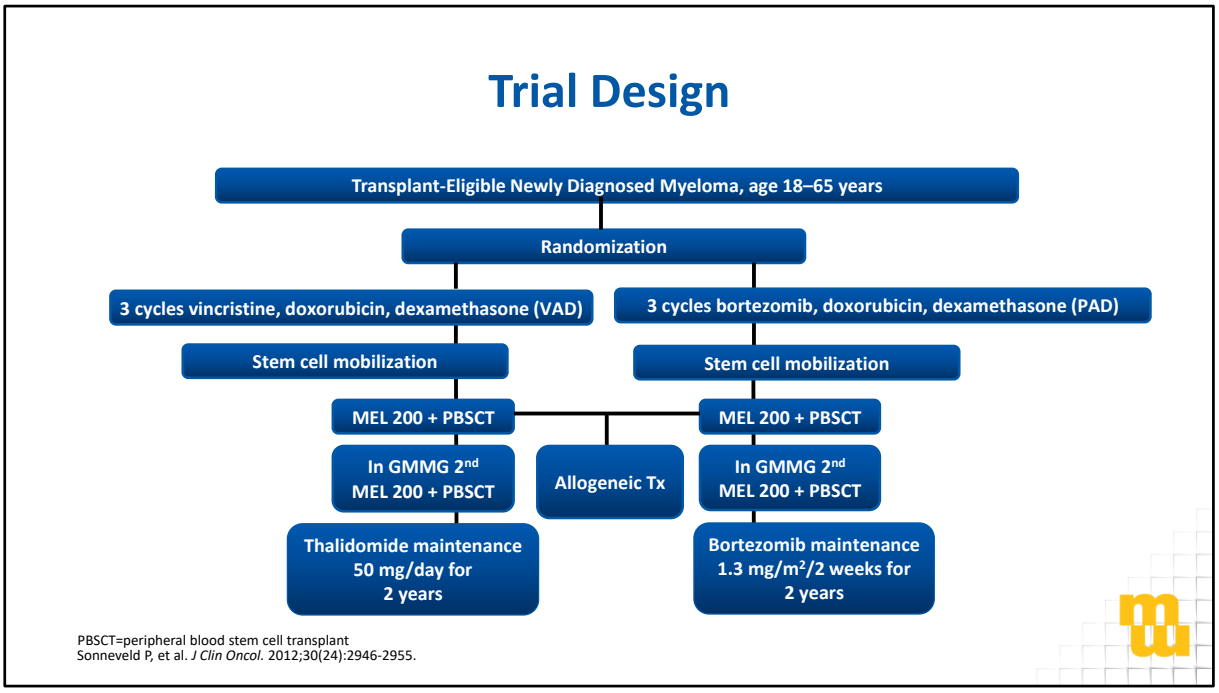
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Bortezomib Maintenance Post-ASCT: HOVON-65/GMMG-HD4



Bortezomib has also been evaluated as a post-transplant maintenance option. However, there are no specific randomized phase III trials that were designed to specifically isolate the impact of bortezomib maintenance. This was an important study by the HOVON and GMMG groups, in which bortezomib was incorporated in the management of patients with newly diagnosed disease from the time of induction therapy through maintenance therapy in the post-transplant setting.

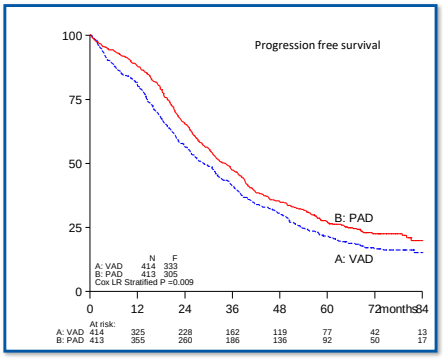
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



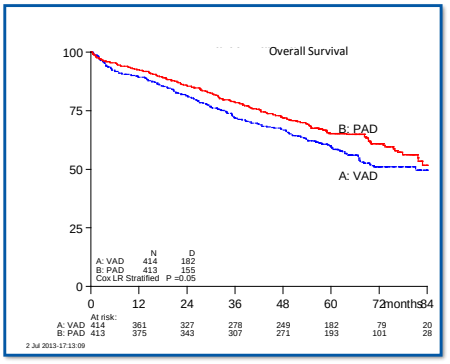
In this trial, transplant-eligible patients with newly diagnosed multiple myeloma between the ages of 18 and 65 were randomized to receive either: three cycles of vincristine, doxorubicin (Adriamycin) and dexamethasone (VAD, a previous standard of care in the field); or three cycles of bortezomib, doxorubicin (Adriamycin) and dexamethasone. In either case, this was followed by stem cell mobilization in either a single or tandem autologous transplantation. Patients who had received the VAD treatment then received either: maintenance therapy with thalidomide at 50 mg daily for two years; or bortezomib maintenance with bortezomib administered intravenously at 1.3 mg/m^2 every other week for two years.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Progression-free Survival



Cox HR 0.76 CI .64 – .90, *P* = .001



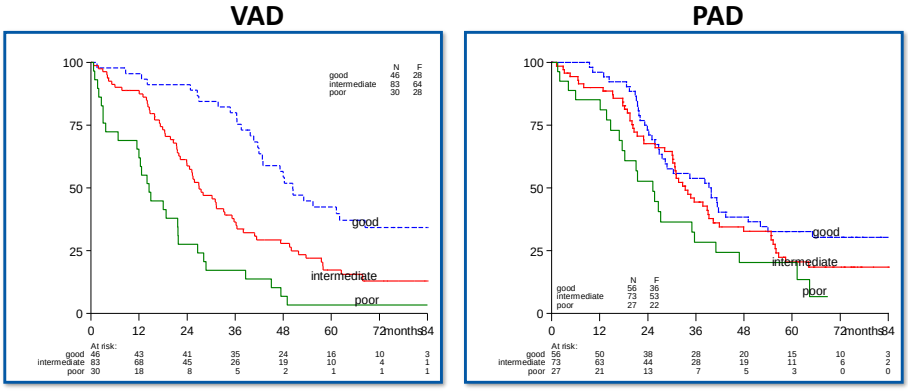
HR 0.78 CI .64 – .90, *P* = .01

Sonneveld P, et al. *J Clin Oncol.* 2012;30(24):2946-2955.

The incorporation of bortezomib as a component of maintenance therapy in this trial, as well as induction therapy, led to significant improvement in both progression-free and overall survival. It also proved to be quite feasible and safe.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Progression-free Survival By Risk Group Based on FISH + ISS



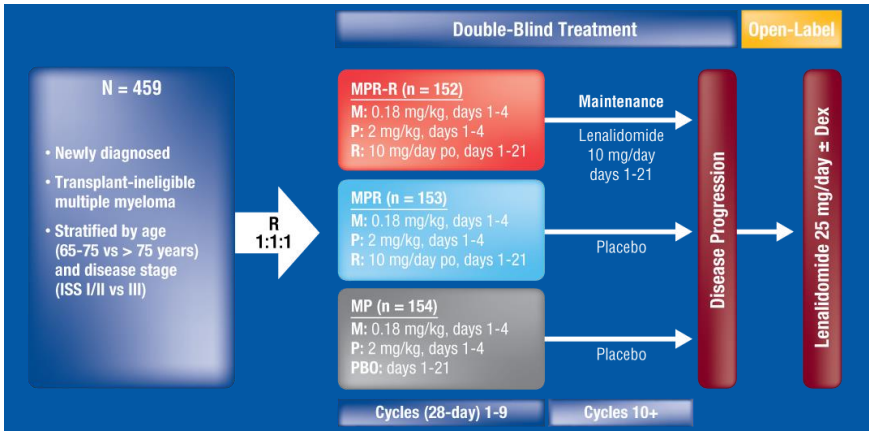
Good Risk: no t(4;14)/del17p/add1q and ISS I
Intermediate Risk: either t(4;14)/del17p/add1q and ISS I or no t(4;14)/del17p/add1q and IISS II/III
Poor Risk: t(4;14)/del17p/add1q and ISS II/III

Sonneveld P, et al. *J Clin Oncol.* 2012;30(24):2946-2955.

Importantly, there appeared to be a benefit to the incorporation of bortezomib in terms of overcoming high-risk disease characteristics, as defined by both ISS stage and FISH. As you can see, the progression-free survival curves in the study in the VAD group showed significant differences according to risk groups. Whereas, in the group of patients treated with bortezomib, the progression-free survival curves cluster together, indicating that those with high-risk disease had better outcomes overall than in those patients who received VAD.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

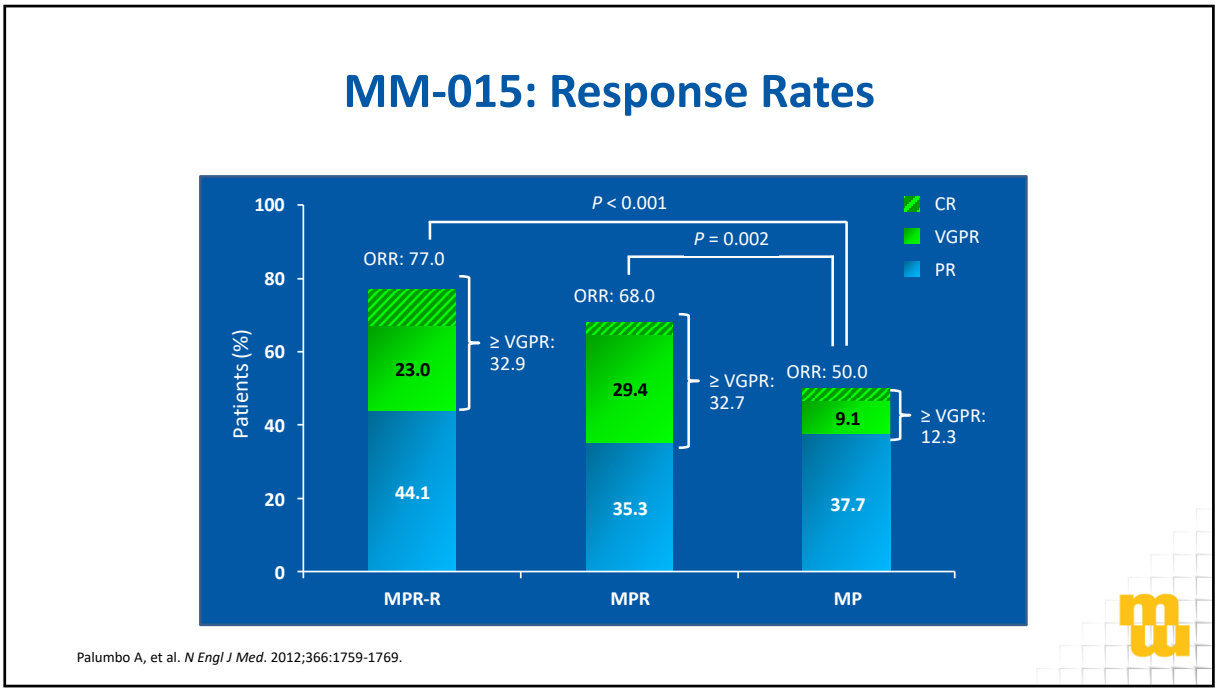
Lenalidomide Maintenance for Transplant-ineligible Patients: The MM-015 Study



MP=melphalan and prednisone; MPR=melphalan, prednisone and lenalidomide; MPR-R=MPR followed by lenalidomide maintenance
Palumbo A, et al. *N Engl J Med*. 2012;366:1759-1769.

Other clinical trials have evaluated the impact of lenalidomide maintenance in transplant-ineligible patients. The MM-015 study, for example, randomized 459 transplant-ineligible patients to receive either standard melphalan and prednisone (MP); melphalan, prednisone and lenalidomide (MPR); or melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR-R). Patients were treated in nine 28-day cycles, followed by either placebo in the groups shown in blue and gray, or maintenance therapy in the MPR followed by lenalidomide maintenance group.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

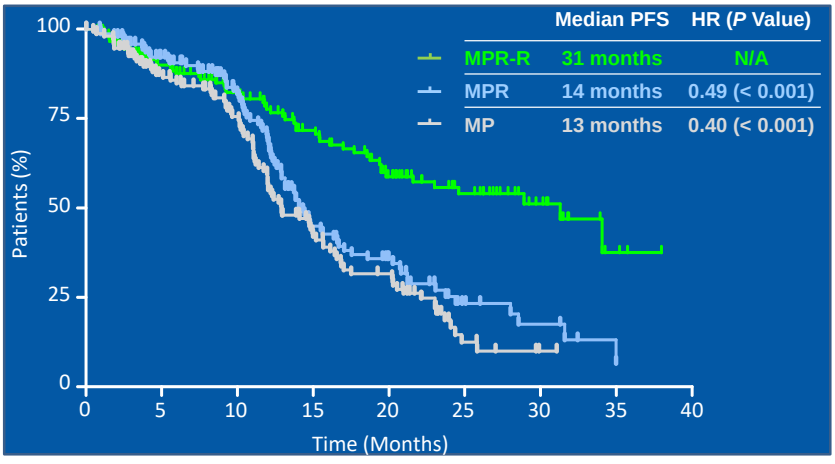


Palumbo A, et al. *N Engl J Med*. 2012;366:1759-1769.

These are response rates that were observed in this trial. As you can see, the highest level of overall response rate at 77% was achieved among those patients who received melphalan and prednisone along with lenalidomide, followed by lenalidomide maintenance.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

MM-015: Progression-free Survival

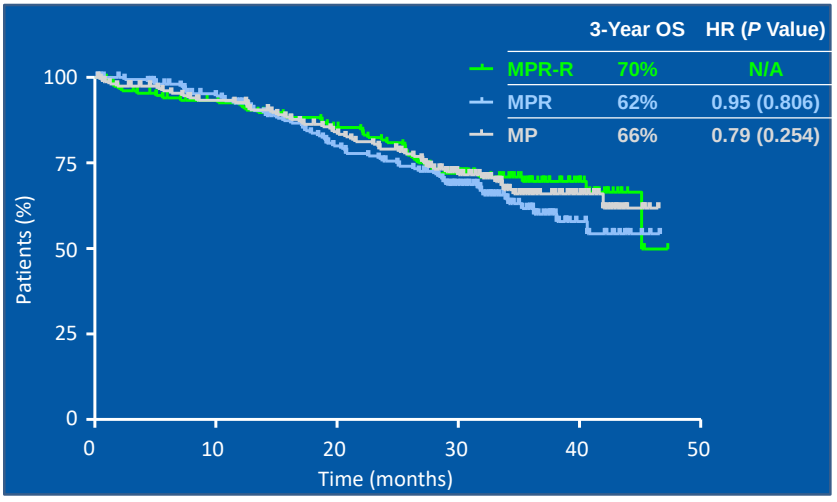


Palumbo A, et al. *N Engl J Med*. 2012;366:1759-1769.

Progression-free survival is shown here. As you can see, it favors the inclusion of lenalidomide maintenance as a part of the patient's overall treatment regimen.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

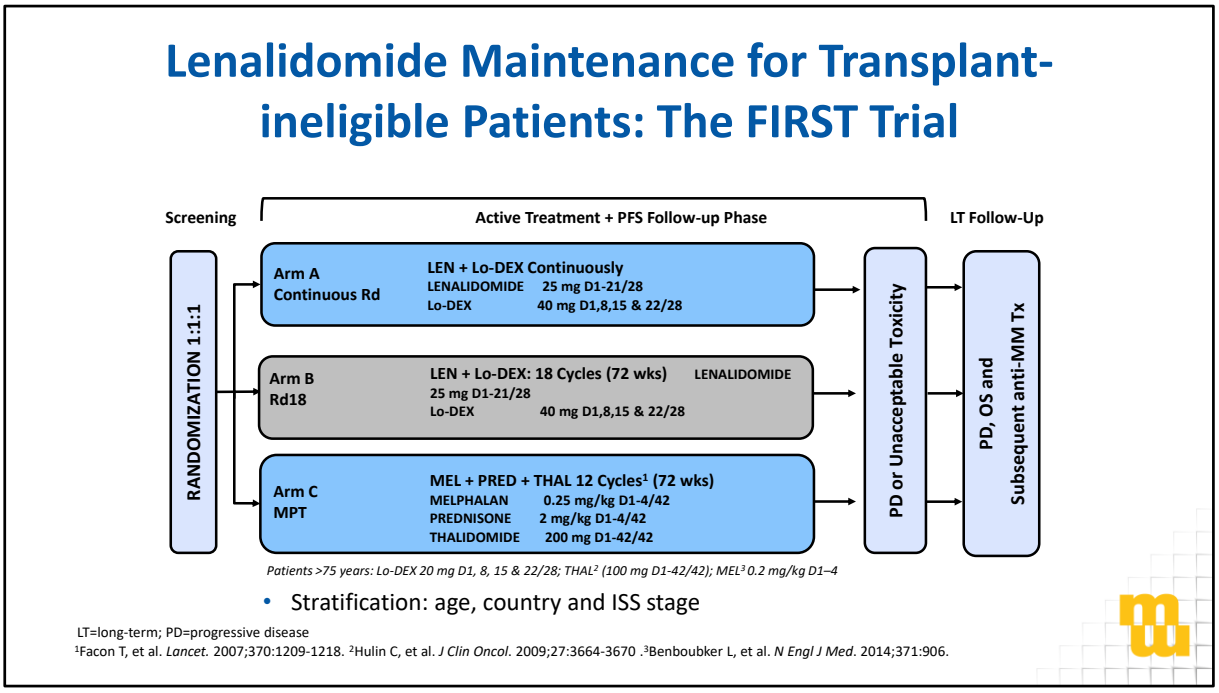
MM-015: Overall Survival



Palumbo A, et al. *N Engl J Med*. 2012;366:1759-1769.

There was no impact on overall survival with the addition of lenalidomide maintenance.

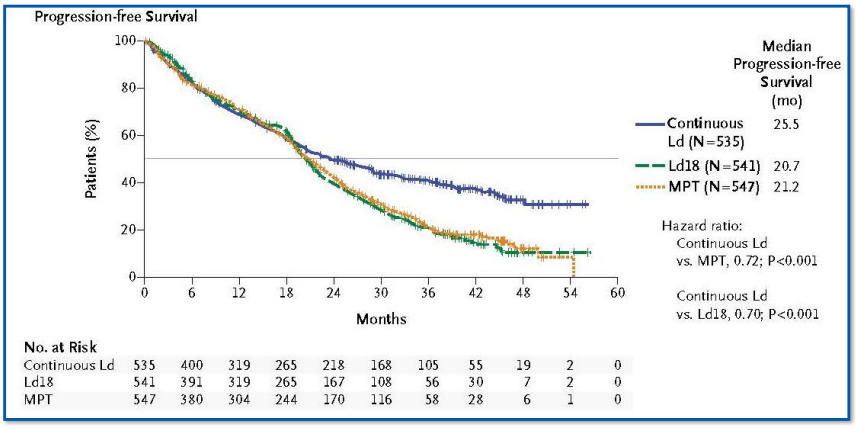
Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



The FIRST trial was another pivotal trial evaluating the role of lenalidomide maintenance in transplant-ineligible patients. In this study, patients were randomized 1:1:1 to receive either lenalidomide plus low-dose dexamethasone continuously; lenalidomide plus low-dose dexamethasone for 18 cycles; or melphalan and prednisone plus thalidomide for a total of 12 six-week cycles. There was stratification on the basis of age, country, and ISS stage.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Progression-free Survival

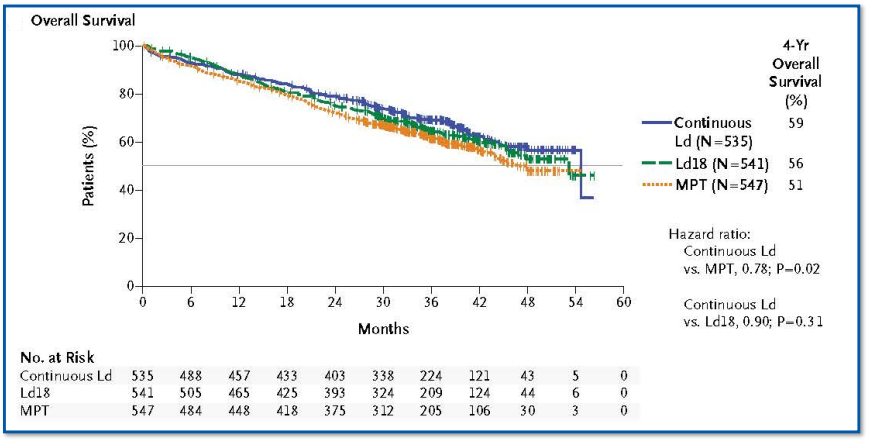


Benboubker L, et al. *N Engl J Med*. 2014;371:906.

These are the progression-free survival curves. Once again, progression-free survival was superior with the incorporation of lenalidomide maintenance as part of the overall treatment approach.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Overall Survival



Benboubker L, et al. *N Engl J Med*. 2014;371:906.

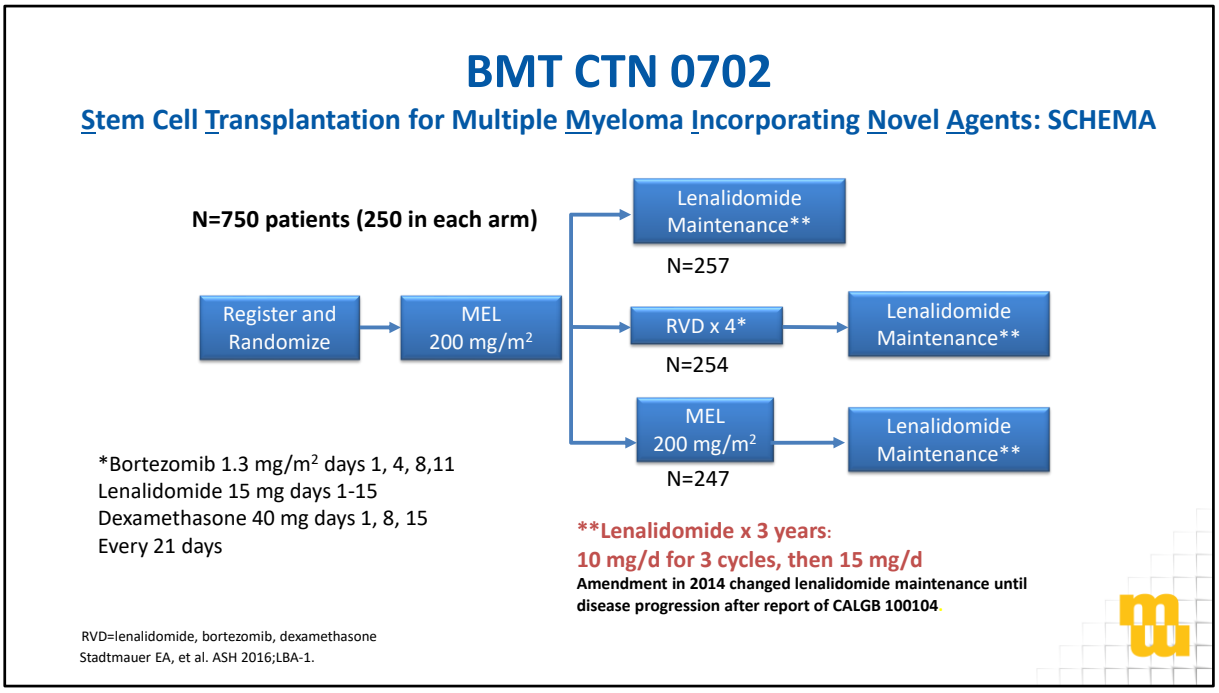
There was no benefit conferred with the inclusion of lenalidomide maintenance on overall survival, however.

Primary Results from the Randomized Prospective Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – STaMINA Trial) NCT#01109004

Autologous Hematopoietic Cell Transplant (AHCT), with and without Consolidation (with Bortezomib, Lenalidomide (Len) and Dexamethasone) and Len Maintenance versus Tandem AHCT and Len Maintenance for Up-Front Treatment of Patients with Multiple Myeloma

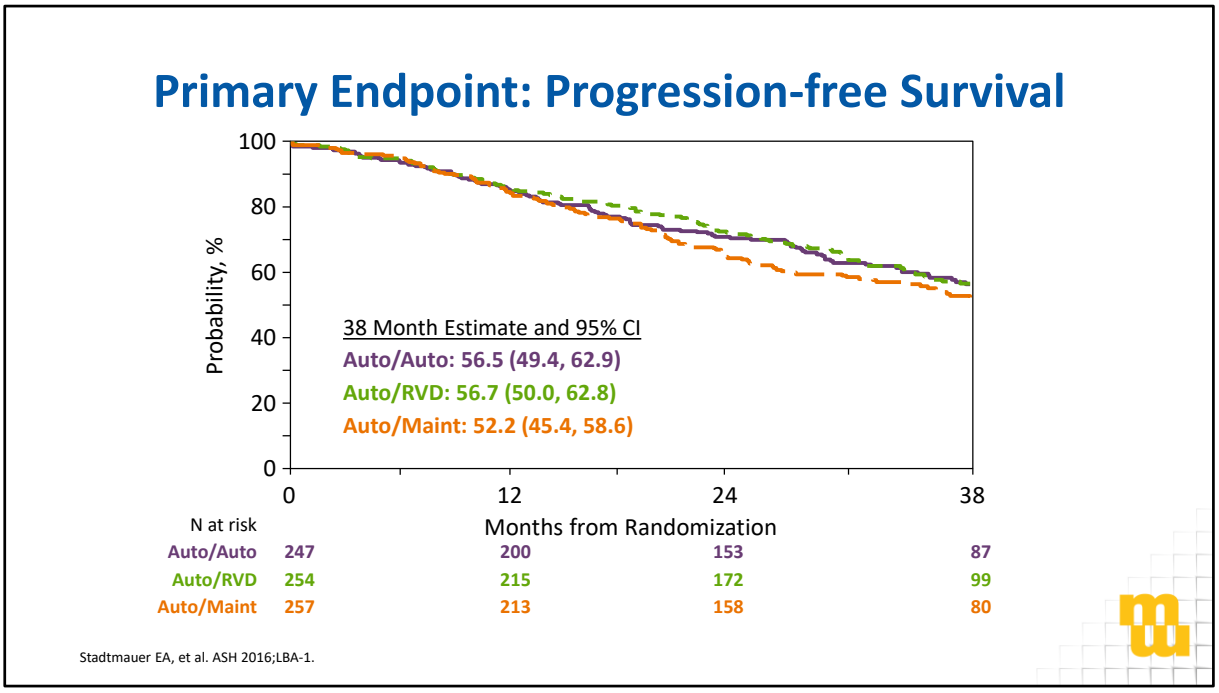
With regard to the topic of post-transplant consolidation therapy, which has been an area of great clinical interest, important insights were gleaned from the CTN 0702 or STaMINA trial, which was reported on at the 2016 American Society of Hematology Meeting by Dr. Stadtmauer and his colleagues.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



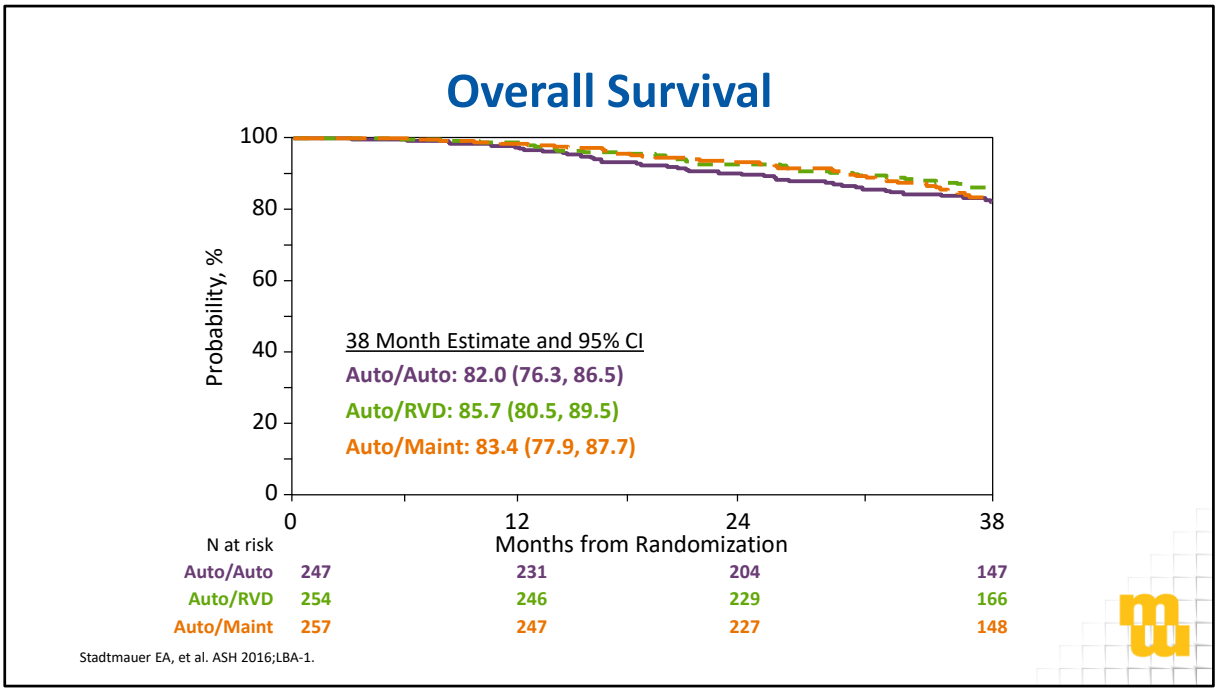
In this trial, 750 patients who had undergone autologous stem cell transplantation were randomized 1:1:1 to receive single-agent lenalidomide maintenance; post-transplant consolidation therapy with lenalidomide, bortezomib and dexamethasone for four cycles followed by maintenance therapy with lenalidomide; or tandem autologous stem cell transplantation followed by lenalidomide maintenance.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



The primary endpoint of the study was progression-free survival. As you can see here, there was no difference in progression-free survival across the three arms of the study.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach



Moreover, there was no difference in overall survival across the three arms of the study.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Patient Cases

- 70-year-old gentleman presents with fatigue and is found to be anemic with renal impairment
  - Diagnosed with ISS III IgG lambda myeloma
  - Receives 5 cycles of cyclophosphamide, bortezomib, and dexamethasone; achieves very good partial response prior to autologous stem cell transplantation (ASCT)
- 76-year-old woman presents with shoulder and sternal pain and is found to have a sternal mass and numerous lytic bone lesions
  - Diagnosed with ISS II IgA kappa myeloma; FISH showing additional copies of 1q, trisomy 9, monosomy 13, and del17p
  - Receives 8 cycles of lenalidomide, bortezomib, and dexamethasone; achieves very good partial response
- 43-year-old gentleman presents with back pain and is found to have diffuse lytic bone lesions along with anemia, hypercalcemia, and renal impairment
  - Diagnosed with ISS II kappa light chain myeloma; noted on FISH to have both del13q and del17p
  - Receives 6 cycles of lenalidomide, bortezomib, and dexamethasone followed by ASCT

Let us return now to the patient cases that we had discussed earlier on in our presentation. The first was a 70-year-old gentleman who had presented with fatigue and was ultimately diagnosed with ISS stage III lambda multiple myeloma. He had a very good response to induction therapy with cyclophosphamide, bortezomib and dexamethasone, and ultimately underwent autologous stem cell transplantation. We discussed treatment options. Noting the fact that he had achieved a good response, and that there was very strong data from multiple phase III clinical trials supporting the use of posttransplant lenalidomide therapy, we opted to pursue lenalidomide maintenance in his case. He is now approximately three years removed from autologous stem cell transplantation. We have had to dose-reduce lenalidomide and manage a bit of lenalidomide-associated diarrhea, but otherwise he has tolerated the drug well and continues to do well, from an overall clinical standpoint.

The second case, as you will recall, is that of a 76-year-old woman who had presented with shoulder and sternal pain and found to have numerous lytic bone lesions, as well as a sternal mass. She had high-risk disease by virtue of a complex karyotype that included additional copies of 1q, as well as deletion 17p. She had a very good partial response to eight cycles of lenalidomide, bortezomib, and dexamethasone. At the age of 76 years old, she was not an ideal candidate for autologous stem cell transplantation. We discussed options in her case, and ultimately made the decision to proceed with two-drug maintenance therapy utilizing both lenalidomide and bortezomib, because of the high-risk nature of her disease. It is also important to emphasize that, as part of her initial therapy, she tolerated both bortezomib and lenalidomide quite well, had very little peripheral neuropathy related to bortezomib, and withstood lenalidomide with regard to blood counts, diarrhea, and other issues. She has continued to tolerate lenalidomide plus bortezomib maintenance well. She is now approximately three years into her course and has not shown evidence of disease progression at this point.

Finally, we discussed the case of a 43-year-old gentleman who has high-risk multiple myeloma. He had a number of important clinical manifestations related to his myeloma, as you will recall, and also had both deletion 17p and deletion 13q on FISH analysis. He was treated with a standard regimen of lenalidomide, bortezomib and dexamethasone and had a good response. He then went on to autologous stem cell transplantation and emerged with a complete response. I discussed options with him, reviewing results of important clinical trials in the field, including both the IFM as well as the CALGB trial. It was noted at that time that there was an increased risk of second primary cancers. To this particular patient, being a younger patient, he was quite concerned about the possibility of developing another tumor. We thus discussed alternative approaches to maintenance therapy. We ultimately decided to utilize the approach that had been taken in the HOVON trial, administering bortezomib every other week as maintenance therapy. He is now approximately 3-1/2 years from his autologous transplantation and doing well. He is tolerating bortezomib with minimal side effects, if any, and remains in a good response with regard to his disease.

Role of Maintenance and Consolidation Therapy in Multiple Myeloma: A Patient-centered Approach

Conclusions

- Multiple randomized trials have shown a PFS benefit with lenalidomide maintenance in ASCT eligible and ineligible patients, and an overall survival benefit was observed in the CALG100104 study
- Lenalidomide maintenance is typically well-tolerated, with decreased blood counts and diarrhea being common side effects requiring appropriate supportive care
- Second primary malignancies have been associated with lenalidomide maintenance in the transplant and non-transplant setting in patients who have received melphalan
- The risk of death due to second primary malignancies is substantially less than risk of MM-related death
- Bortezomib is a safe, well-tolerated option for maintenance therapy in patients who cannot or choose not to receive lenalidomide
- Post-transplant consolidation therapy with either a second autologous transplant or lenalidomide, bortezomib, and dex prior to lenalidomide maintenance does not appear to confer benefit in terms of PFS or OS relative to lenalidomide maintenance alone

In terms of conclusions, I would say that as mentioned during the course of this presentation, multiple randomized clinical trials have shown a progression-free survival benefit associated with the use of lenalidomide maintenance in both transplant-eligible and transplant-ineligible patients with multiple myeloma. An overall survival benefit was observed in the CALGB 100-104 study. Lenalidomide maintenance is typically well tolerated, with decreased blood counts and diarrhea being relatively common side effects, both of which can be managed with appropriate dose reductions, at times schedule changes, and appropriate supportive care. Second primary malignancies have been associated with lenalidomide maintenance in the transplant and non-transplant setting in patients who have received melphalan. The risk of death due to second primary cancers, however, is substantially less than the risk of multiple myeloma-related death. It is my practice generally, at the time we would initiate post-transplant maintenance therapy (approximately two to three months after transplant) to discuss the relative merits of maintenance therapy with lenalidomide including potential side effects like secondary malignancies. Together with the patient and family members we make a decision about which approach to follow. As mentioned before, bortezomib is a safe and well-tolerated option as maintenance therapy for patients who, for whatever reason, prefer not to receive – or cannot receive – lenalidomide as maintenance therapy. With regard to post-transplant consolidation therapy with either: a second autologous transplant; or lenalidomide, bortezomib and dexamethasone prior to lenalidomide maintenance; these approaches in a large randomized phase III trial did not confer benefit in terms of progression-free or overall survival relative to lenalidomide maintenance therapy alone. In my view, this further establishes lenalidomide maintenance as the standard of care. However, it is recognized that certain populations of individuals with multiple myeloma who are particularly high risk (for example, those with complex karyotype, 17p deletion, or very aggressive clinical characteristics) may benefit from use of a two- or even three-drug maintenance approach.

Future Directions

- Insight regarding the optimal duration of maintenance therapy will come from the ongoing IFM/DFCI 2009 study
- Studies of ixazomib, the first FDA-approved oral proteasome inhibitor, as a maintenance approach are ongoing
  - Due to oral administration, this agent has significant potential as monotherapy and in combination regimens
- Studies are evaluating the safety and efficacy of monoclonal antibodies elotuzumab and daratumumab in the maintenance setting, particularly in combination with lenalidomide

In terms of future directions, I will leave you with these final key takeaway points. Insight regarding the optimal duration of maintenance therapy will come from the ongoing IFM/DFCI 2009 study; recognizing that in the IFM component of the study, patients received lenalidomide maintenance for a fixed period of time, whereas those in the American portion of the study are receiving lenalidomide maintenance until time of disease progression. It is also of note that studies of ixazomib, the first FDA-approved oral proteasome inhibitor, are ongoing. As this is an oral agent, it has significant potential as a monotherapy or in combination regimens for post-transplant consolidation and maintenance therapy. Ixazomib also has significant potential in transplant-ineligible patients as maintenance therapy. Studies are also now evaluating the safety and efficacy of monoclonal antibodies elotuzumab and daratumumab in the maintenance setting, particularly in combination with lenalidomide. Thanks very much for viewing this activity.