The Role of Maintenance Therapy for the Treatment of Multiple Myeloma

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Welcome to *Managing Myeloma*, I'm Dr. Sarah Holstein. Today I will review the role of maintenance therapy for the treatment of multiple myeloma. In this presentation I will describe the importance of maintenance therapy in the treatment of multiple myeloma, I will compare and contrast the efficacy and safety of new and emerging agents for the treatment of multiple myeloma in the maintenance setting, and I will review how to incorporate evidence-based recommendations when determining the appropriate maintenance treatments for patients.

Speaker Disclosure

Consultant with the following company:

- Celgene Corporation

These are my disclosures.

The Role of Maintenance Therapy for the Treatment of Multiple Myeloma

Autologous Stem Cell Transplant (ASCT)

- Remains a standard of care for patients eligible for high-dose therapy (melphalan)
- Nearly all patients will relapse post-ASCT
  - Can the incorporation of post-ASCT therapy improve outcomes?

As a bit of background, autologous stem cell transplant remains a standard of care for patients who are eligible for high-dose therapy, mainly high-dose melphalan therapy. In this country we routinely consider patients who are up to the age of 75 as transplant candidates, but really there is no strict age cutoff. We know that despite the benefit of transplant in terms of consolidating the response that one achieved from induction and deepening a response, many patients, if not nearly all patients, will relapse post-transplant. Therefore, the question has been asked for quite some time now as to whether or not we can incorporate post-transplant treatment that can improve outcomes for our patients.

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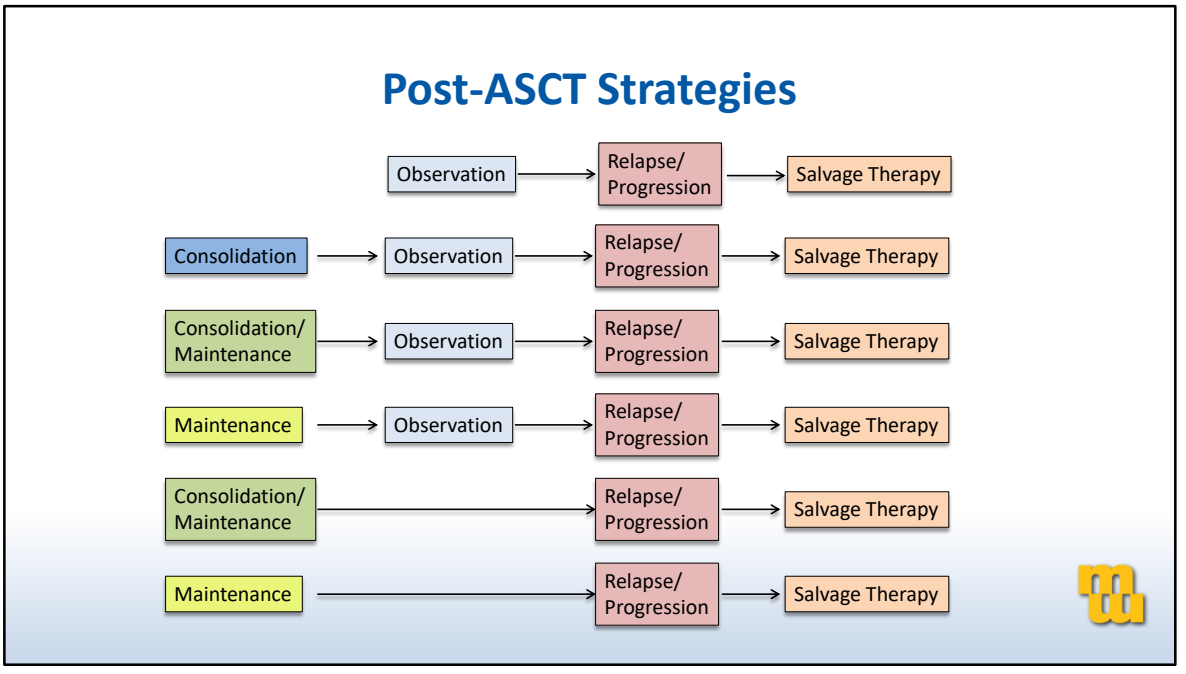

There are a number of post-transplant strategies that have been attempted over the years. Historically what one would do would be to simply observe the patient after they completed their transplant. At some point the patient would relapse or progress and then they would be offered salvage therapy. An alternative strategy involves the use of fixed-duration therapy. This might be consolidation therapy (where perhaps multiple agents are used for a briefer period of time), or consolidation followed by maintenance therapy, or just maintenance therapy (perhaps with one or two drugs). The idea here would be that these treatments would be for a fixed duration of time and then patients would be observed again until time of relapse or progression, at which point they would be offered salvage therapy. More recently the concept of continuous therapy has been introduced. Here, we are looking at either consolidation or maintenance or just maintenance alone, but the differing point here is that treatment would be continued until time of progression, and then at time of progression patients would receive a different salvage therapy. What I'll be talking about today is the maintenance strategy, in one context in a fixed duration, but for most of the time I'll be talking about maintenance continued until progression.

Treatment Goals for Maintenance Therapy

- Improve progression-free survival (PFS) and overall survival (OS)
  - Does improved PFS result in improved OS?
- Factors to consider:
  - Timing
  - Duration
  - Intensity
  - Toxicity
  - Response to subsequent therapies

What are the goals of maintenance therapy? We certainly want to improve progression-free survival (PFS) and we would also like this to translate into overall survival (OS), but the question has been – with several other randomized studies – as to whether or not the improved PFS that was observed actually does translate into improved overall survival. There are a number of factors to consider when talking about maintenance therapy with a patient. Some of these include what the patient can tolerate and for how long they can tolerate it. When can maintenance therapy start after transplant, and how intense should the therapy be? Should it just be one agent at a lower dose, should it be multiple agents at lower doses? What are the toxicities associated with this treatment and how will this affect the patient's ability to tolerate the treatment long term? Another important point is whether or not what we give the patient as a maintenance therapy affects their response to subsequent therapies offered in the salvage setting.

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Thalidomide Maintenance after ASCT

Table 2. Thalidomide maintenance after autologous HSCT

Study	N	Initial dose, mg	Maintenance vs no maintenance: EFS or PFS	Maintenance vs no maintenance: OS	Benefit EFS/OS
Attal et al[45]	597	400	3 y EFS 52% vs 37% ($P < .009$)	4 y OS 87% vs 75% ($P < .04$)	+/+
Barlogie et al[46]	668	400	5 y EFS 64% vs 43% ($P < .001$)	8 y OS 57% vs 44% ($P = .09$)	+/trend+
Lokhorst et al[47]	556	50	Median EFS 43 vs 22 mo ($P < .001$)	Median OS 73 vs 60 mo ($P = .77$)	+/trend−
Morgan et al[48]	820*	50	Median PFS (HSCT) 30 vs 23 mo ($P = .003$)	3 y OS 75% vs 80% ($P = .26$)	+/ND
Spencer et al[49]	243	200‡	3 y PFS 42% vs 23% ($P < .001$)	3 y OS 86% vs 75% ($P = .004$)	+/+
Krishnan et al[50]	436†	200‡	3 y PFS 49% vs 43% ($P = .08$)	3 y OS 80% vs 81% ($P = .817$)	ND/ND
Maiolino et al[51]	108	200‡	2 y PFS 64% vs 30% ($P = .002$)	2 y OS 85% vs 70% ($P = .27$)	+/ND
Stewart et al[52]	332	200‡	4 y PFS 32% vs 14% ($P < .0001$)	4 y OS 68% vs 60 ($P = .18$)	+/ND

EFS indicates event-free survival; and ND, no difference.
*This cohort was part of a 1910-patient study examining transplantation and nontransplantation therapies.
†This cohort was part of a 710-patient study examining allogeneic and autologous HSCT.
‡Glucocorticoids were given with thalidomide.
Adapted from McCarthy et al.[42]

McCarthy PL, Hahn T. *Hematology Am Soc Hematol Educ Program*. 2013;2013:496-503.

This is really more from a historical perspective, but I briefly want to discuss the use of thalidomide maintenance after transplant. There have been eight studies that have been performed and this table summarizes those studies. There's a red line separating this table into two halves; the top half represents those studies which just looked at thalidomide as a single agent in the post-transplant maintenance setting; the bottom half represents those studies that incorporated glucocorticoids into the thalidomide maintenance strategy. You can see that a variety of different doses were utilized, anywhere from 50 to 400 mg. When one looks at the primary outcome of these studies which was generally event-free survival (EFS) or progression-free survival, in general there was either a trend or a statistically significant benefit in favor of thalidomide maintenance. However, this EFS or PFS benefit did not generally translate into an overall survival benefit. It is likely that this overall survival benefit was not observed with thalidomide because of the toxicities which made it so that most patients only stayed on treatment for around one year.

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HOVON 65/GMMG-HD4: Thalidomide vs Bortezomib Maintenance

- Induction: VAD (vincristine, doxorubicin, dexamethasone) (n=413) vs PAD (bortezomib/PS-341, doxorubicin, dexamethasone) (n=414)
- Single or tandem ASCT
- Maintenance:
  - VAD arm: thalidomide 50 mg/d x 2 years (n=270)
  - PAD arm: bortezomib 1.3 mg/m^2 every 2 weeks x 2 years (n=230)

J Clin Oncol. 2012;30(29):3654.

I also wanted to touch on the HOVON study as this is frequently discussed in the context of bortezomib as a maintenance strategy. I should point out, however, that this study not only looked at the role of bortezomib in maintenance but also looked at the role of incorporating bortezomib in the upfront setting. This was a randomized study in which patients were randomized to two induction strategies. One was the standard of care regimen at that time of VAD (vincristine, doxorubicin and dexamethasone) versus the newer regimen of PAD (bortezomib/PS-341, doxorubicin and dexamethasone). This was about an 800-patient study. Some patients in the study underwent single transplant, others underwent tandem transplant, and then for the maintenance part there was not another randomization. Instead, those patients who were on the VAD arm went on to receive thalidomide maintenance, while those patients who were on the PAD arm went on to receive bortezomib maintenance. The bortezomib was dosed every-other-week for two years. The thalidomide was given daily for two years.

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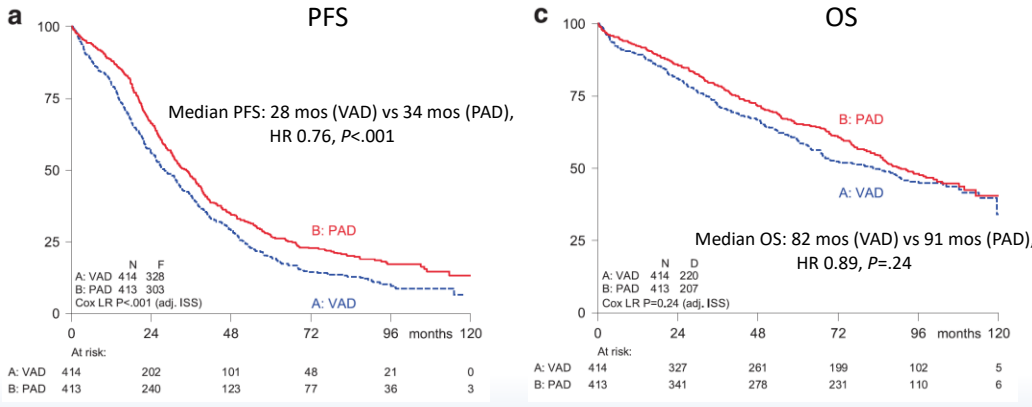
Bortezomib Induction/Maintenance Improves PFS



- Bortezomib improved PFS/OS for patients with Cr >2 at presentation and for patients with del(17p) but not for patients with t(4;14) or gain(1q21)

Goldschmidt H, et al. *Leukemia.* 2018;32:383-390.

Recently there has been a report of long-term follow up for this HOVON study, and the Kaplan-Meier curves for both PFS and OS are shown here. On the left is the PFS data. What we can see is that the red curve represents the PAD regimen and the blue curve represents the VAD regimen. There is a separation of the two curves and in fact the study was statistically significant with respect to its primary endpoint, such that the median PFS was 28 months for VAD and 34 months for PAD, with a hazard ratio of 0.76. However, when we turn our attention to the overall survival curves we see that there the PFS benefit did not translate into a statistically significant overall survival benefit. Here, the median OS for VAD was 82 months versus 91 months for PAD; the hazard ratio was 0.89 with a non-statistically significant *P*-value. However, a subset analysis did indicate that bortezomib – and again remember that this is bortezomib in the context of both induction and maintenance – improves progression-free and overall survival for patients who presented with renal failure or for patients with deletion (17p). However, it should be noted that when they looked at other high-risk cytogenetic features such as translocation (4;14) or gain of 1q21, the survival benefit was not observed. Despite this, the study is often cited as a rationale for why patients with high-risk cytogenetics should receive bortezomib maintenance.

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Lenalidomide Maintenance

Table 2. Summary of randomized trials assessing lenalidomide maintenance after ASCT.

Study	*N*	Induction therapy	Dosing schedule	Duration of maintenance	EFS or PFS (maintenance *versus* no)	OS (maintenance *versus* no)
CALGB 100104[58,59]	460	⩽2 regimens; 94% received a regimen containing Thal, Len, or Bor	10 mg continuous, increase up to 15 mg	Until progression	Median TTP: 57 *versus* 29 months ($p < 0.0001$)	Median OS: 114 *versus* 84 months ($p = 0.0004$)
IFM 2005-02[60]	614	46% received vincristine, doxorubicin, Dex and 46% received Bor and Dex 21% received tandem transplant	All patients received 2 cycles of consolidation (25 mg/day, 21 out of 28 days) Maintenance: 10 mg continuous, increase up to 15 mg	Stopped due to concerns regarding second primary malignancies at a median time of 2 years (range 1–3 years)	Median PFS: 41 *versus* 23 months ($p < 0.001$) 4-year PFS: 43% *versus* 22% ($p < 0.001$)	Median follow up 45 months: 74% *versus* 76% ($p = 0.7$) 4 year OS: 73% *versus* 75% ($p = 0.7$)
RV-MM-209[61]	402	4 cycles Len/Dex followed by either transplant or MPR	10 mg (3 weeks on, 1 week off)	Until progression	Median PFS*: 42 *versus* 22 months ($p < 0.001$)	3-year OS*: 88% *versus* 79% ($p = 0.14$)
Myeloma XI[57]	1247§	CTD *versus* RCD followed by CVD if suboptimal response	10 mg (3 weeks on, 1 week off)	Until progression	Median PFS: 60 *versus* 30 months ($p < 0.0001$)	3-year OS: 88% *versus* 80% ($p = 0.013$)

*Combining ASCT and chemotherapy groups.
§Transplant eligible only (total number in the study was 1970).
Bor, bortezomib; CTD, cyclophosphamide, thalidomide, dexamethasone; CVD, cyclophosphamide, bortezomib, dexamethasone; Dex, dexamethasone; Len, lenalidomide; MEL200, melphalan 200 mg/m^2; MPR, melphalan, prednisone, lenalidomide; PFS, progression-free survival; OS, overall survival; RCD, lenalidomide, cyclophosphamide, dexamethasone; Thal, thalidomide.

Holstein SA, et al. *Ther Adv Hematol*. 2018;9:175-190.

I'd like to turn our attention now to lenalidomide maintenance where we have a significantly higher level of evidence for this maintenance strategy. This table summarizes four randomized phase 3 studies that have been performed. The first one was the CALGB 100104 study that was performed in the United States, performed about the same time as the IFM study that was done in France, and then we have a study done in Europe and then the Myeloma XI study which is the most recently reported study out of the UK. In general, these studies all used the same dosing of lenalidomide, staring at 10 mg; however, there were some subtle differences. For the IFM study all patients received two cycles of consolidation with full-strength lenalidomide. For the latter two studies a three-week on, one-week off regimen was used, whereas for the first two studies, lenalidomide was given continuously. There are differences with the studies with respect to what types of induction regimens patients received. In three out of four of the studies, lenalidomide was continued until progression; however the IFM study was stopped because of concerns of second primary malignancies which we'll discuss in greater detail in just a minute.

For all of these studies the primary endpoint was event-free survival or progression-free survival, and all four of these studies strongly favored lenalidomide for that primary endpoint. If you look at the CALGB 100104 data, the median time to progression, which was really progression-free survival, was 57 months for lenalidomide versus 29 months for placebo. Looking at the most recent study, the Myeloma XI study, we see strikingly similar results such that the median PFS was 60 months for lenalidomide versus 30 months for observation. None of these studies was powered to look at overall survival; however, despite this there as an overall survival benefit observed with CALGB 100104. Although the data are premature, thus far there has also been an overall survival benefit observed with Myeloma XI. To better evaluate whether or not there is an overall survival benefit with lenalidomide, a recent meta-analysis was performed.

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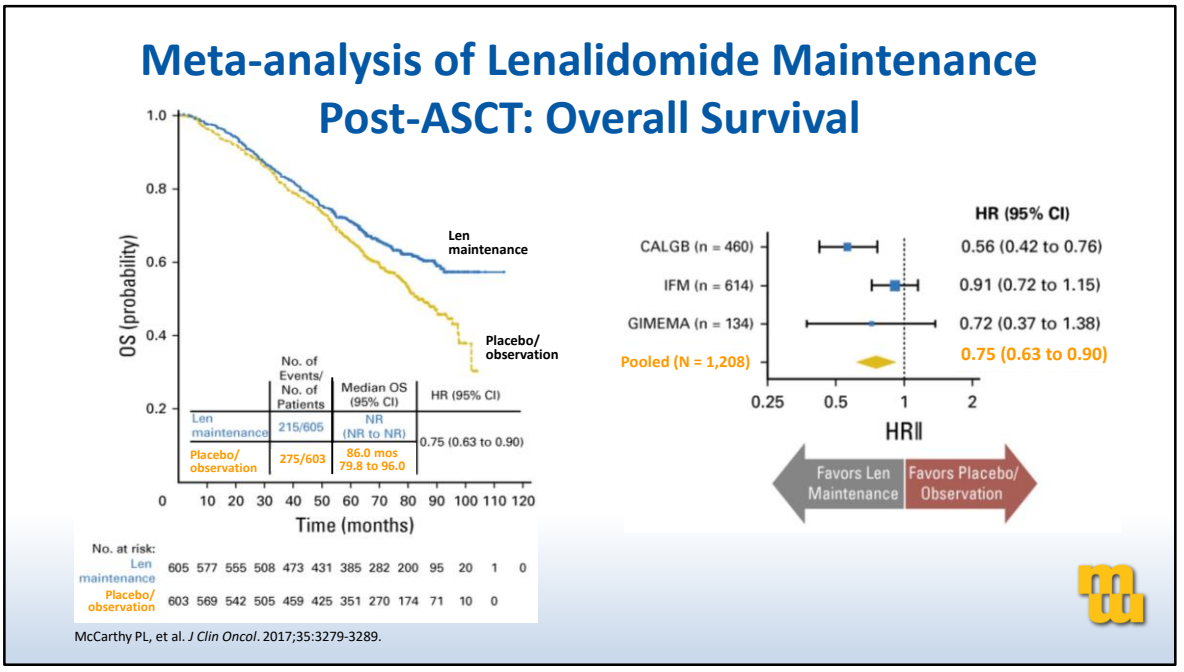

McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279-3289.

This meta-analysis incorporated the first three studies that I discussed from the previous slide, the CALGB study, the IFM, as well as the GIMEMA. This study incorporated over 1200 patients' worth of data. What I'm showing in specific is the overall survival data. On the left are the Kaplan-Meier curve is for overall survival with blue representing lenalidomide and yellow representing the placebo or observation patients. With longer follow-up there has been separation between the two curves. At time of cut off of this analysis the median OS had not yet been reached for lenalidomide but was 86 months for placebo. There was a statistically significant hazard ratio of 0.75 in favor of lenalidomide maintenance. If we look over on the right-hand side, here we're looking at the individual hazard ratios for the three studies. You can see that the CALGB study was strongly significant in favor of lenalidomide maintenance; but again, incorporating all three studies and looking at 1200 patients in aggregate, the overall hazard ratio is 0.75 in favor of lenalidomide maintenance.

Presented in abstract form at this most recent ASH was the Myeloma XI study. The authors presented some information regarding a meta-analysis that they have performed in which they have incorporated not only these three studies but now their study. When they did that, they also showed that there was a statistically significant benefit for all four studies in aggregate in favor of lenalidomide maintenance for overall survival.

Lenalidomide Maintenance and Cytogenetic Risk Groups

- Myeloma XI study
- Cytogenetic risk groups:
  - High risk = presence of any one of t(4;14), t(14;16), t(14;20), del(17p), gain(1q)
  - Ultra-high risk = presence of more than abnormality
  - Standard risk = absence any of the abnormalities
  - Maintenance associated with improved OS regardless of risk group
    - Standard risk: HR 0.35
    - High risk: HR 0.58
    - Ultra high risk: HR 0.38

Jackson G, et al. *Blood*. 2017;130(Suppl 1):436.

We've discussed lenalidomide maintenance in the context of an overall patient population but there are a few subgroups that I'd like to focus on. The first subgroups would be those involving different cytogenetic risk groups. Unfortunately, we really don't have cytogenetic data from the older studies, however we do have good cytogenetic data from the Myeloma XI study and this was recently presented in abstract form.

In this study they performed cytogenetic testing and divided patients into several categories based on whether or not they had any high-risk features. These high-risk features included the presence of t(4;14), t(14;16), t(14;20), del(17p) or gain of 1q. If a patient had one of those high-risk features then they were classified as high-risk, if they had more than one abnormality then they were classified as ultra-high-risk, and if they did not have any of those abnormalities then they were classified as standard risk. What this analysis had shown thus far is that maintenance with lenalidomide is associated with improved overall survival regardless of the cytogenetic risk group. When we look at the different hazard ratios we see that all of them are in favor of lenalidomide. For standard risk, the hazard ratio is 0.35, for high-risk 0.58, and for ultra-high-risk 0.38.

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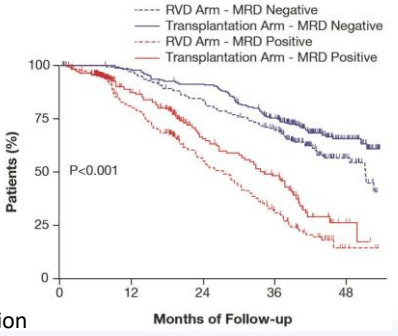
Lenalidomide Maintenance and Minimal Residual Disease (MRD) Status

- Myeloma XI[1]:
  - Lenalidomide maintenance until progression
  - PFS advantage demonstrated in both MRD-negative and MRD-positive
  - Conversion to MRD-negativity during maintenance observed in 30% of MRD-positive patients compared to 4% of patients randomized to no further therapy
- IFM 2009[2]:
  - Lenalidomide maintenance for one year following ASCT vs RVD consolidation
  - Progression events begin to occur following discontinuation of maintenance in MRD negative patients



RVD=lenalidomide-bortezomib-dexamethasone

[1]Owen RG, et al. *Blood.* 2017;130 (Suppl 1):904.; [2]Attal M, et al. *N Engl J Med.* 2017;376:1311-1320.

The second question that's often raised with respect to maintenance and lenalidomide maintenance is whether or not patients need this if they have achieved a good response after transplant. Historically a good response was classified as a complete response (CR) and the data from CALGB 100104 did demonstrate that patients benefited from maintenance regardless of whether or not they were in a CR. However, more recently we have to come to understand that achieving a CR is not enough and instead, that achieving minimal residual disease (MRD) negativity is associated with improved survival outcomes. Now the question has become: is maintenance necessary for those patients who have achieved MRD negativity?

To try to answer this question I'll again turn your attention to the Myeloma XI study. In this study they have performed MRD testing on a subgroup of their patients. What they have shown, at least in abstract form thus far, is that there is a PFS advantage in both MRD negative and MRD positive patients. In addition, lenalidomide maintenance is associated with an increased rate of conversion from MRD positivity to MRD negativity; such that those who received maintenance converted over to MRD negativity 30% of the time, as opposed to only 4% of patients who were observed after transplant. This data really suggests that patients, even if they're in an MRD-negative state after transplant still benefit from lenalidomide maintenance.

Some additional data regarding lenalidomide maintenance and MRD status can be obtained from the IFM 2009 study. This study did not specifically address the role of maintenance, but as you'll see in a minute I think it does provide us with some important information. This study randomized patients after receiving RVD induction therapy to either transplant or to consolidation with additional RVD. Eventually both arms went on to receive one year of lenalidomide maintenance. In this study they did look at MRD, and what is shown on the right are some curves looking at the various arms: those patients who got RVD versus transplant as consolidation, and then various MRD statuses. MRD negative patients are shown in blue and MRD positive patients are shown in red. We're looking at progression events on this curve.

The first thing that we note is that the patients who were in blue, that is, those who achieved MRD negativity, had a superior progression-free survival than those patients who did not achieve MRD negativity or who were MRD positive, shown in red. This is very consistent with multiple other studies demonstrating the benefit of being MRD negative after transplant. However, what is interesting is to look at the top two curves, the blue curves, and look at when the progression events start to occur. If you do that you'll see that the progression starts to occur around the time that that one year of lenalidomide maintenance is discontinued. I think what these data suggests is that even if patients are MRD negative, one year of lenalidomide maintenance is not sufficient. Whether or not these patients need to be on lenalidomide maintenance until progression is not yet known, but certainly at this point one-year of therapy should not be considered as standard of care.

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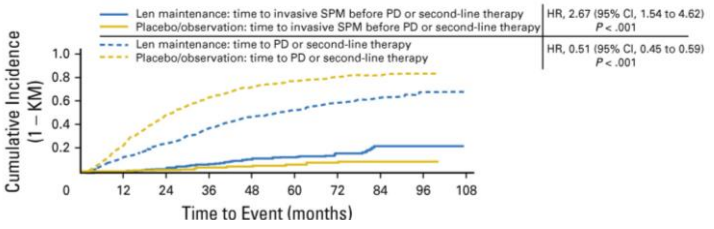
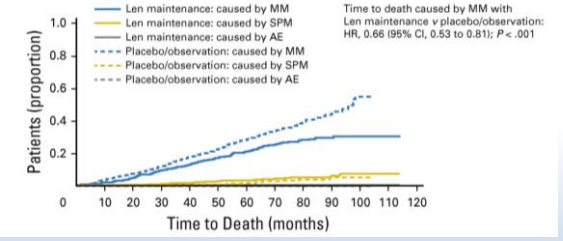
Lenalidomide Maintenance and Second Primary Malignancy (SPM) Risk





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

Now I'd like to discuss the second primary malignancy (SPM) risk. I alluded to this earlier on when I said that the IFM study stopped treatment with lenalidomide because of an increased risk of SPMs. The CALGB study also early on noted an increased risk of SPMs, however their study continued. Instead of discussing the studies individually, I'd like to discuss the data that resulted from the recent meta-analysis that we discussed earlier. Here again we're combining over 1200 patients' worth of data. What the top curves are looking at are the risks, the cumulated incidence risk over time of either, on those bottom two lines, the risk of getting a second primary malignancy or, in the top two hashed lines, the risk of progressing with myeloma or requiring second-line therapy for myeloma. We first draw our attention to the bottom two lines, the blue versus the gold: the blue represents those patients who were receiving lenalidomide maintenance who went on to be diagnosed with an invasive SPM. You can see that there is an increased risk with lenalidomide compared to the placebo or observation patients, and in fact the hazard ratio is 2.67. However, you see that the absolute risk is quite small compared to the absolute risk of progressing from myeloma. Here again, I'll draw your attention back to the top two hashed curves where yellow represents those placebo patients who progressed over time and blue represents the lenalidomide patients. Here, the hazard ratio is strongly in favor of lenalidomide maintenance with a hazard ratio of 0.51.

It's also important to note that not every patient who is diagnosed with an invasive SPM will actually die from this SPM. To really address the death rates, the second analysis on the bottom graph is shown. Here, what we're looking at are either the risk over time of dying from the second primary malignancy (the two bottom gold curves), or the risk of dying over time of myeloma, shown in blue. If we first just look at the bottom two gold curves, we do see a slightly higher risk for those patients dying of an SPM if they were on lenalidomide maintenance: that's the solid gold line as opposed to the dashed yellow line. However, the magnitude of this risk is quite small compared to the magnitude of the risk of a patient dying from myeloma. Again here, we see that there is a strong benefit for lenalidomide maintenance in decreasing the risk of dying from myeloma. In aggregate, the data for SPMs do suggest that there is a signal for an increased risk of SPMs with lenalidomide maintenance. However, the magnitude of that risk is smaller than the magnitude of the benefit achieved in terms of decreasing the risk of progressing and also dying from myeloma.

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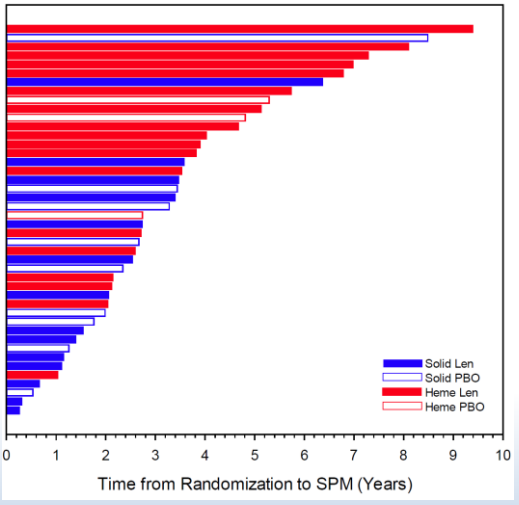
CALGB 100104: Time from Randomization to SPM



Holstein SA, et al. *Lancet Haematol*. 2017;4:e431-e442.

There's one more point I'd like to make about SPMs in the context of lenalidomide maintenance and this comes from data from the CALGB 100104 updated analysis. Here we're looking at how long it takes for each patient who was eventually diagnosed with an SPM to be diagnosed with their SPM after randomization. In this swimmer's plot each individual line represents a patient. The red color represents hematological SPMs, the blue color represents solid tumor SPMs. You can see that over the first couple of years is when primarily the majority of the solid tumor SPMs are diagnosed. However, when you look at the solid red bars, and those are the patients who received lenalidomide maintenance and ultimately went on to being diagnosed with a hematological SPM, that this risk continues over time, such that we have patients being diagnosed over nine years out from their randomization to lenalidomide maintenance. Thus, I think it's always important to continue to be vigilant in terms of monitoring your patients who are on maintenance with respect to developing an SPM, particularly with respect to developing a hematological SPM. From this context I have a very low threshold for performing a bone marrow biopsy if I see any blood count changes that occur while patient is on lenalidomide maintenance.

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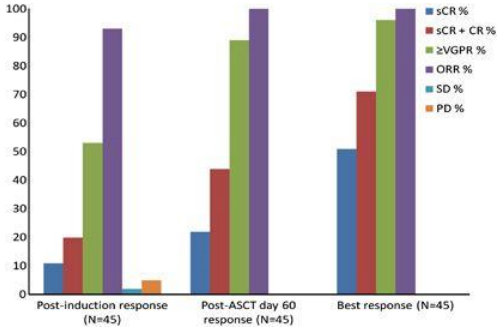
IMiD/PI Maintenance for High-risk Patients

- RVD maintenance[1]
  - 45 high-risk patients (including primary plasma cell leukemia)
  - Lenalidomide 10 mg days 1-21, weekly bortezomib and dexamethasone for up to 3 years followed by single-agent lenalidomide
  - Median PFS 32 months, 3-year OS 93%
- LenI maintenance[2]
  - Lenalidomide 10-15 mg continuous, ixazomib 3-4 mg days 1, 8, 15
  - 64 patients, 20 with high-risk disease
  - Median PFS for entire cohort not yet reached (median follow-up 38.2 months)
  - Median PFS for high risk not reported



[1]Nooka AK, et al. *Leukemia.* 2013;28:690-693. [2]Patel KK, et al. *Blood.* 2017;130 (Suppl 1):437.

Switching gears a little bit, I want to talk about some of the data supporting more aggressive strategies for high-risk patients. What I've shown you thus far is that there is some data supporting the use of bortezomib for the del(17p) population and there is also a data that single-agent lenalidomide maintenance can improve outcomes for high-risk and ultra-high-risk patients. Despite this, though, we know that patients who received single-agent maintenance therapy and who have high-risk disease continue to have increased rates of progression and decreased survival rates. Therefore, there have been a number of strategies that have been looked at. I'm just going to focus on two of them which involved combining IMiD and proteasome inhibitor (PI) maintenance.

The first study that is cited quite often is the RVD maintenance study which was published by Dr. Nooka, et al., back in 2013. This was a small study just looking at 45 high-risk patients. Of note, this did include some primary plasma cell leukemia patients who would not have been included in any of the other maintenance studies that we discussed. In the study, the authors used a modified RVD maintenance strategy and patients were treated up to three years, followed by single-agent lenalidomide if they had not yet progressed. The median PFS for this study was 32 months with a three-year overall survival of 93%. If you look at the graph on the right-hand side, this is looking at response rates over time. Although they are looking at post-induction and post-transplant responses, what I'd really like to draw your attention to would be the best response overall, and in particular the blue and red colors. The blue represents those patients who achieved a stringent CR, the red represents those who achieved a stringent CR or a CR. What you can see over time with maintenance is a deepening of response. This RVD maintenance strategy did improve response rates, particularly deep response

rates, over time.

More recently, a small study has been presented which has evaluated the combination of lenalidomide and ixazomib, the oral proteasome inhibitor. This study has thus far only been presented in abstract form. It's a small study involving 64 patients, 20 of whom were classified as having high-risk disease. Thus far, we do not yet know what the median PFS for the entire cohort is, at least at a median follow up of 38 months. In addition, the median PFS for the high-risk group has not yet been reported but certainly, based on the available data, this seemed like a feasible approach.

Considerations for Incorporating Other Agents into the Maintenance Setting

	Administration	Single agent anti-MM activity	Immune modulating activity	Side-effect profile
Proteasome inhibitors	+++ (ixazomib) ++ (bortezomib) + (carfilzomib)	+++	+	++
Anti-CD38	+ (IV)/++ (SQ)	+++	++	+++
Anti-CS1	+	+	++	+++
Checkpoint inhibitors	+	+	+++	+
HDAC6 inhibitors	+++	+	++	++

Finally, there are a number of other drugs out there that certainly we could think about incorporating into the maintenance setting, either as a single agent or potentially in combination with lenalidomide. Again, going back to the factors that are important to think about for maintenance: for administration, from a patient perspective, oral therapy is advantageous; we want a drug that has preferably single-agent myeloma activity; it's probably also important that the agent has some immune modulating activity. Then again, from a patient perspective it's also important that the side-effect profile is such that this therapy can be continued long-term.

What I've listed here are a variety of different classes of myeloma drugs. The proteasome inhibitors we have talked about. There is quite a bit of interest right now in the incorporation of anti-CD38 monoclonal antibodies into the maintenance setting and several studies are ongoing. There has also been some interest in incorporating anti-CS1 monoclonal antibody. I have put checkpoint inhibitors on here, although for right now this field is somewhat halted. I've also listed HDAC6 inhibitors as these are oral agents which also have single-agent myeloma activity and also have been reported to have some immune modulating activity.

The Role of Maintenance Therapy for the Treatment of Multiple Myeloma

Key Points

- Lenalidomide maintenance post-transplant is associated with improved PFS and OS (category 1 per NCCN guidelines)
  - Benefit is observed regardless of response status or cytogenetic risk group
  - Associated with an increased risk of SPMs
- Bortezomib maintenance may be considered for patients unable to tolerate lenalidomide but placebo-controlled randomized phase 3 studies have not been performed
- Consider IMiD/PI maintenance for patients with high-risk cytogenetic features
- Ongoing studies are evaluating the role of other novel agents in the post-transplant maintenance setting

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To conclude, I'd like to leave you with these key takeaway points. First, lenalidomide maintenance post-transplant is associated with improved progression-free and overall survival, and this is category 1 per NCCN Guidelines. I'd like to reiterate that this benefit is observed regardless of the response rate (that includes MRD negativity) or cytogenetic risk group (that includes patients who have achieved MRD negativity). However, the caveat here is that this maintenance strategy is associated with an increased risk of SPMs or second primary malignancies and so it is important to monitor patients carefully for the development of these SPMs. Remember, however, the relative magnitudes of risk. The relative risk of a patient being diagnosed with an SPM is significantly less than the relative benefit that patients achieve with respect to not progressing from their myeloma and not dying of their myeloma. Bortezomib maintenance may be considered for patients unable to tolerate lenalidomide, but remember that placebo-controlled randomized phase 3 studies have not been performed. I generally do consider a combination strategy of IMiD and PI maintenance therapy for patients with high-risk cytogenetic features, but at this time we do not have high-level data to support this strategy.

This is a very exciting time in myeloma because of all the new agents that are available. There are a number of ongoing studies that are evaluating the role of other novel agents in the post-transplant maintenance setting. Over the next several years I think we will have more data that will help us perhaps develop more patient-specific strategies and patient-tailored strategies to pick the optimal maintenance strategy for patients. Thank you for your attention.