Maintenance Therapy for Multiple Myeloma Patients

October 19, 2021

MODERATOR
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Multiple Myeloma Research Foundation
Norwalk, Connecticut

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Maintenance Therapy for Multiple Myeloma Patients
Webinar – October 19, 2021

Speakers

Suzanne Lentzsch, MD, PhD
Columbia University
New York, New York

Saad Z. Usmani, MD, MBA
Memorial Sloan Kettering Cancer Center
New York, New York
(as of 11/1/21)

Michael Mankowich
Patient Advocate

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Maintenance Therapy: Principles, Efficacy, and Use in Myeloma Patients

Suzanne Lentzsch, MD, PhD

Treatment of Multiple Myeloma

Transplant-eligible patients

- Initial therapy
- Consolidation
- Maintenance
- Treatment of relapsed disease

Transplant-ineligible patients

- Initial therapy
- Consolidation/maintenance/continued therapy
- Treatment of relapsed disease

Supportive care
**What is maintenance therapy?**

A prolonged, and often low-dose, treatment given to myeloma patients after their initial therapy (or transplant)

To prevent disease progression for as long as possible while maintaining favorable quality of life

To eliminate minimal residual disease (MRD) or maintain the absence of MRD, reduce the risk of relapse, and prolong survival

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**Successful Maintenance Therapy Must...**

1. Be convenient
2. Be safe and well-tolerated long term
3. Not prevent the use, or reduce the efficacy, of other future treatments
**Overview of Phase 3 Maintenance Studies**

<table>
<thead>
<tr>
<th>After ASCT</th>
<th>After induction therapy</th>
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<tbody>
<tr>
<td>• 7 Thalomid trials</td>
<td>• 5 Thalomid trials</td>
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<tr>
<td>• 2 Velcade trials</td>
<td>• 2 Velcade + Thalomid (VT) trials</td>
</tr>
<tr>
<td>• 1 Velcade + Thalomid (VT) trial</td>
<td>• 3 Revlimid trials</td>
</tr>
<tr>
<td>• 3 Revlimid trials</td>
<td></td>
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<tr>
<td>• 1 Ninlaro trial</td>
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**Conclusions**

- Most trials demonstrate a benefit in time when the myeloma remains quiet (defined as progression-free survival [PFS])
- No convincing evidence that relapses after receiving maintenance treatment are more aggressive

**Maintenance Therapy in Myeloma**

<table>
<thead>
<tr>
<th>What we know</th>
<th>What we don’t know</th>
</tr>
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<tbody>
<tr>
<td>• PFS advantage</td>
<td>• Whether all patients benefit from maintenance</td>
</tr>
<tr>
<td>• Overall survival (OS) improvements?</td>
<td>• Which agent to use and duration of therapy</td>
</tr>
<tr>
<td>• Side effects of treatment</td>
<td>• Response to higher doses of Revlimid at relapse</td>
</tr>
<tr>
<td>– Low blood counts</td>
<td>• Evolution of resistant clones</td>
</tr>
<tr>
<td>– Can cause other cancers to develop</td>
<td>• Whether maintenance can be stopped if patients achieve a complete response or MRD negativity</td>
</tr>
<tr>
<td>– Quality of life</td>
<td></td>
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<tr>
<td>• Cost</td>
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</table>

Revlimid as Maintenance Therapy

- **Reduction in myeloma progression (3 large studies)**
- **Improved survival (1 of 3 studies; meta-analysis)**
- **Increased risk of second cancers when used after melphalan**

Approved for use as maintenance treatment after autologous stem cell transplantation (ASCT)

*Low risk when used in the context of an autologous stem cell transplant

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Revlimid Maintenance: Overall Survival

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival.

![Overall Survival Graph](image)

N = 1,209

Treatments Following ASCT to Prolong Survival: Maintenance, Second Transplant, or Consolidation

STAMINA Trial (BMT-CTN0702)

- **Consolidation**
  - ASCT
  - MEL 200 mg/m²

- **Maintenance**
  - REV × 3 yrs

**Auto/Auto group**
- MEL 200 mg/m²
- REV × 3 yrs

**Auto/RVD group**
- RVD × 4
- REV × 3 yrs

**Auto/Rev group**
- No consolidation
- REV × 3 yrs

- There was no difference in PFS or OS between the three groups
- Discontinuation of Revlimid maintenance at 3 years is not recommended because of the increased risk of disease progression

MEL, melphalan; RVD, Revlimid-Velcade-dex; REV, Revlimid

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Revlimid Maintenance Continued or Stopped

![Graph showing probability of continued vs. stopped maintenance](image-url)

- Discontinuation of Revlimid @ 3 years did not impact overall second primary malignancies (SPM) rates @ 6 years

Minimal Residual Disease Testing

- **Diagnostic**
  - Tumor burden
  - Flow cytometry
  - Next-generation DNA sequencing

**Minimal residual disease**

**Tumor burden**

MRD Results During Revlimid Maintenance

**IFM/DFCI 2009 Trial**

- Initial therapy: RVD: 3 cycles
- Stem cell collection: Cytoxan
- Early ASCT
- ASCT
- ASCT at relapse
- ASCT at relapse
- Consolidation: RVD: 2 cycles
- Continue RVD: 5 cycles
- Maintenance: Revlimid 12 months
- Maintenance: Revlimid 12 months

**Graph**

- Patients (%)
- Months of Follow-Up


- Undetectable MRD* (MRD-)
- Detectable MRD* (MRD+)

*Next-generation sequencing. MRD was assessed at the start and at the end of maintenance therapy.
Key Points

- The body of evidence from phase 3 trials indicates that maintenance (or “continuous”) therapy improves PFS and likely OS.
- The optimal duration is uncertain; however, the data we have suggests that it should be given until progression.
- Given that myeloma is different in every patient, some patients likely do not need maintenance, whereas others may do well with a shorter course of maintenance.
- MRD testing helps to predict clinical risk of progression.

Maintenance Therapy: Benefits and Risks, Potential Alternatives to Revlimid

Saad Z. Usmani, MD, MBA, FACP
Maintenance Therapy
Benefits and Risks

The anti-myeloma benefits of continuous therapy must be balanced with the side effects of prolonged treatment.

A major concern with the use of maintenance therapy is the development of side effects that limit long-term use and potentially compromise the ability to receive optimal treatment in the future.

Continuous Therapy Concerns

• Effects on immune system
• Effects on blood production/bone marrow
• Potential effects on drug resistance\(^1,2\)
• Side effects\(^3\)
  – *Early* → fatigue, GI side effects, reduction in blood cell production, peripheral neuropathy, blood clots, diarrhea, others
  – *Late* → secondary primary cancer, decreased marrow reserve

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Management of Common Side Effects With Revlimid Maintenance

**Fatigue**
- Dose at night
- Dose reduction
- Regular thyroid function testing

**Diarrhea**
- Antidiarrheal agents (loperamide)
- Bile salt binders/low-fat diet (for example, colesev lam, cholestyramine)

**Rash**
- If minor, topical steroids
- Non-sedating antihistamines (Claritin)
- Hold and reduce dose

**Thrombosis**
- Prophylaxis with aspirin (100 mg); full-dose anticoagulation if patient is immobile or has history of blood clots

**Muscle spasms**
- Hydration
- Diazepam or clonazepam in severe cases

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Impact of Revlimid Maintenance Dose Reduction on Outcomes

A retrospective analysis of real-world data from the Canadian Myeloma Research Group national database

- Compared outcomes of 1,256 patients receiving either Revlimid maintenance or no maintenance following ASCT
- Most patients required a dose reduction or medication discontinuation at some point during maintenance treatment
- However, only 20% of patients discontinued maintenance therapy prior to relapse

Real-world experience suggests Revlimid maintenance is well tolerated and validates findings of large phase 3 randomized controlled trials illustrating clear advantage for Revlimid maintenance on PFS.

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Revlimid Plus Proteasome Inhibitors as Maintenance

Different strategies for high-risk patients

<table>
<thead>
<tr>
<th>RVd</th>
<th>RVd-Empliciti</th>
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<tbody>
<tr>
<td>Median PFS, months</td>
<td>33.64</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

Median PFS, months | 76.52 | 40.25 |
Median OS, months | Not reached | 78.16 |

High risk: gene expression profiling high risk, t(14;16), t(14;20), del(17p), or amp1q21, primary plasma cell leukemia and elevated serum LDH (≥2× ULN)

LDH, lactate dehydrogenase; ULN, upper limit of normal
Potential Alternatives to Revlimid Maintenance

What do we offer patients who are unable to tolerate Revlimid for an extended time?

Ninlaro as Maintenance Therapy*

TOURMALINE-MM3 Study

- Newly diagnosed myeloma patients eligible for ASCT
- Patients who achieved a partial response or better to induction therapy
- ASCT
- Ninlaro
- Placebo
- 395 patients
- 261 patients
- 2 years

More patients lived longer without disease progression on Ninlaro maintenance therapy compared to those who received no maintenance therapy.

Ninlaro maintenance helped to deepen responses of patients.

Only 7% of patients on Ninlaro maintenance discontinued treatment.

These results suggest that Ninlaro may represent a new treatment option for maintenance therapy for patients after stem cell transplant.

*Not yet FDA-approved as maintenance therapy.

Ninlaro as Maintenance Therapy*: Ongoing Clinical Trial Investigating Different Durations of Maintenance

GEM2012MENOS65 Trial
Newly diagnosed myeloma patients (following ASCT)

Revlimid-Ninlaro-dex Maintenance

MRD evaluation† at 2 years

MRD - End of Treatment

MRD + Revlimid-dex up to 3 years

*Not yet FDA-approved as maintenance therapy. †By next-generation flow cytometry

ClinicalTrials.gov Identifier: NCT02406144

Kyprolis-Revlimid as Maintenance Therapy*

Risk Groups Based on Presence of Chromosomal Abnormalities†

High risk: one or more; Double-hit: 2 or more; Standard risk: none

All risk subgroups benefited with respect to longer time until disease progression from:
- Treatment with KRd followed by ASCT
- Maintenance therapy with the Kyprolis-Revlimid combination

Patients with amplification of the long arm of chromosome 1 (amp1q) did not reap the same benefits as the other risk groups

*Not yet FDA-approved as maintenance therapy.
KRd, Kyprolis-Revlimid-dex; KCd, Kyprolis-Cytoxan-dex; KR, Kyprolis-Revlimid; R, Revlimid
Mina R et al. Presented at the 18th International Myeloma Workshop; September 8–11, 2021. Abstract OAB-004.
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Webinar – October 19, 2021

Kyprolis as Maintenance Therapy*

CARDAMON Trial
Newly diagnosed myeloma patients eligible for ASCT

- KCd
- Induction
- K
- Transplant or consolidation
- ASCT
- Maintenance

Patients who were MRD negative six months following maintenance therapy lived longer without disease progression than patients who were MRD positive

More patients converted to MRD negativity following ASCT than following KCd consolidation therapy (39.1% vs 16.1%)

23.5% of MRD-positive patients converted to MRD negative during maintenance therapy

More patients withdrew from maintenance therapy who had previously received an ASCT than consolidation with KCd (9.1% vs 1%)

The timing of achievement of MRD negativity had no impact on favorable outcome

*Not yet FDA-approved as maintenance therapy.

KCd, Kyprolis-Cytoxan-dex; K, Kyprolis


Darzalex as Maintenance Therapy*

CASSIOPEIA Trial, Part 2
Newly diagnosed, transplant-eligible myeloma patients (18–65 years old)

- Darzalex-VTd
- Induction
- Transplant
- ASCT
- Consolidation
- Darzalex-VTd
- Patients with ≥PR
- 442 patients

- Darzalex
- Maintenance
- Observation

- VTd
- ASCT
- VTd
- 444 patients

More patients receiving Darzalex maintenance than observation achieved MRD negativity (58.6% vs 47.1%)

Patients receiving Darzalex maintenance lived longer without disease progression than observation (Not reached vs 46.7 months)

More patients who had not been previously exposed to Darzalex experienced infusion reactions with Darzalex maintenance compared with those who had previously been exposed (54.5% vs 2.2%)

More patients receiving Darzalex maintenance than observation developed a second primary malignancy (5.5% vs 2.7%)

Benefits of Darzalex maintenance more pronounced in patients who had not received Darzalex as part of induction therapy

VTd, Velcade-Thalomid-dex

**Darzalex as Maintenance Therapy***

**GRIFFIN Trial**

- Newly diagnosed myeloma patients
- 104 patients

<table>
<thead>
<tr>
<th>Induction</th>
<th>Transplant</th>
<th>Consolidation</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>Darzalex-VRd</td>
<td>ASCT</td>
<td>Darzalex-VRd</td>
<td>Darzalex-Revlimid</td>
</tr>
<tr>
<td>VRd</td>
<td>ASCT</td>
<td>VRd</td>
<td>Revlimid</td>
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- 26.7 months of follow up

*Not yet FDA-approved as maintenance therapy.

VRd, Velcade-Revlimid-dexamethasone


sCR rate favored Dara-VRd vs RVd (42.4% vs 32%) at the end of post-ASCT consolidation

After maintenance therapy with either Dara-Revlimid or Revlimid, responses continued to deepen and remained higher for the Dara-RVd group

Following 1 year of maintenance therapy, sCR rate still favored Dara-VRd (63.6% vs 47.4%)

MRD negativity rates also favored Dara-VRd (26.9% vs 12.6%)

**Darzalex as Maintenance Therapy:**

**Ongoing Clinical Trial Investigating the Conversion Rate to MRD Negativity**

**AURIGA Study**

- Newly diagnosed myeloma patients who achieved a VGPR or better after ASCT and are MRD positive and have never been treated with an anti-CD38 antibody (eg, Darzalex, Sarclisa)
- 103 patients

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<tr>
<th>Treatment administered until progressive disease, unacceptable side effects, or end of study treatment</th>
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MRD to be measured† at 6, 12, 18, 24, and 36 months

Primary end point: MRD conversion rate from baseline to 12 months after maintenance treatment

*Not yet FDA-approved as maintenance therapy. †By next-generation sequencing

VGPR, very good partial response

ClinicalTrials.gov Identifier: NCT03901963
Key Points

Minimizing side effects and maximizing quality of life are essential to the success of maintenance therapy.

Most patients should receive maintenance who are thought to be Revlimid responsive and able to tolerate the side effects.

Proteasome inhibitor/immunomodulatory drug maintenance can be employed for high-risk multiple myeloma.

For patients who are unable to tolerate Revlimid there are other agents such as Ninlaro, Kyprolis, and Darzalex that are effective, but they are not yet FDA-approved for use as maintenance. Several clinical trials are under way.

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Our Chief Medical Officer, Haeun Cho, addresses important questions for multiple myeloma patients.


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## Upcoming Patient Education Events

### Save the Date

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<tr>
<th>Topic</th>
<th>Date and Time</th>
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<tr>
<td>Facebook Live Session: FAQs on MM</td>
<td>Monday, October 25 1:00 PM – 2:00 PM</td>
<td>Craig E. Cole, MD</td>
</tr>
<tr>
<td>Precursor Conditions in the Black Community</td>
<td></td>
<td>Amy Pierre, RN, MSN, ANP-BC</td>
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<tr>
<td>Expert Session – Newly Diagnosed Multiple Myeloma</td>
<td>Wednesday, November 10 1:00 PM – 3:00 PM</td>
<td>Noa Biran, MD</td>
</tr>
<tr>
<td>Precision Medicine: Updates for Multiple Myeloma Patients</td>
<td>Tuesday, November 23 1:00 PM – 2:00 PM</td>
<td>C. Ola Landgren, MD, PhD</td>
</tr>
<tr>
<td>Multiple Myeloma Highlights From the 2021 American Society of Hematology Meeting</td>
<td>Tuesday, December 21 3:00 PM – 4:00 PM</td>
<td>Hearn Jay Cho, MD, PhD, Faith E. Davies, MBBC</td>
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<td></td>
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<td>Irene Ghobrial, MD, Joshua Richter, MD</td>
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For more information or to register, please visit [themmrf.org/resources/education-program](http://themmrf.org/resources/education-program)
Thank you!