5 Minute JournalClub

Key ASCO Presentations
Issue 4, 2010

Lenalidomide Maintenance After Autologous Transplantation for Myeloma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Counsel appropriately selected patients with MM about the efficacy and safety of lenalidomide maintenance therapy following autologous transplant.

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5 MinuteJournalClub

Key ASCO Presentations
Issue 4, 2010

To go directly to the slides and commentary, **click here**.

Chatting with myeloma investigators nowadays often yields extensive recounting of seemingly limitless clinical trials featuring weird acronyms and incredibly complicated results. What is also eminently apparent from these conversations is just how remarkably the face of this disease has changed with the recent introduction of two major classes of novel agents, the IMiDs® — thalidomide and lenalidomide — and the proteasome inhibitors, specifically bortezomib.

The dozens of cool papers presented at the recent ASCO meeting further affirmed the profound effects of these agents when used individually, in combination or in sequence, and here are our top picks for findings relevant to oncology practice:

1. **Triple therapy continues to impress**
   In a follow-up to a recently published paper in *Blood*, Dana-Farber's Paul Richardson once again wowed the masses as he presented unprecedented efficacy findings (100 percent response rate, 74 percent with VGPR or more) and acceptable toxicity with induction RVD (lenalidomide, bortezomib, dexamethasone). A new, huge trial will address post-transplant consolidation with this combination and also whether transplant can be delayed or avoided. In any event, our surveys of practicing oncologists and investigators show a rapid shift toward three-drug combos like RVD for patients eligible for transplant. In another impressive data set on a triple regimen, French investigators reported similar high response rates to vTD (bortezomib, thalidomide, dexamethasone), which utilized attenuated doses of both bortezomib and thalidomide that dramatically lowered the rate of peripheral neuropathy.

2. **Lenalidomide maintenance after autologous stem cell transplant is effective**
   No question this was one of the most important findings presented in any tumor type at ASCO as both the **CALGB and the French IFM** group demonstrated an impressive 50 percent reduction in disease progression among patients receiving this well-tolerated agent as maintenance therapy following transplant. Many clinical trials in both the transplant and nontransplant settings are now scrambling to add "L maintenance" to their control arms.

3. **Zoledronic acid (ZDA) may slow disease progression and extend survival**
   This MRC trial from the UK is in a sense the myeloma version of the Austrian breast cancer study presented during the ASCO plenary session two years ago. Monthly ZDA resulted in an impressive five months-plus improvement in survival compared to clodronate. Investigators are not yet jumping on the idea of treating patients without bone disease, but this might be coming in the future.

Next up on 5-Minute Journal Club: A smorgasbord of ASCO papers on breast cancer, including some interesting new data on sentinel node biopsy.

Neil Love, MD
Research To Practice
Miami, Florida

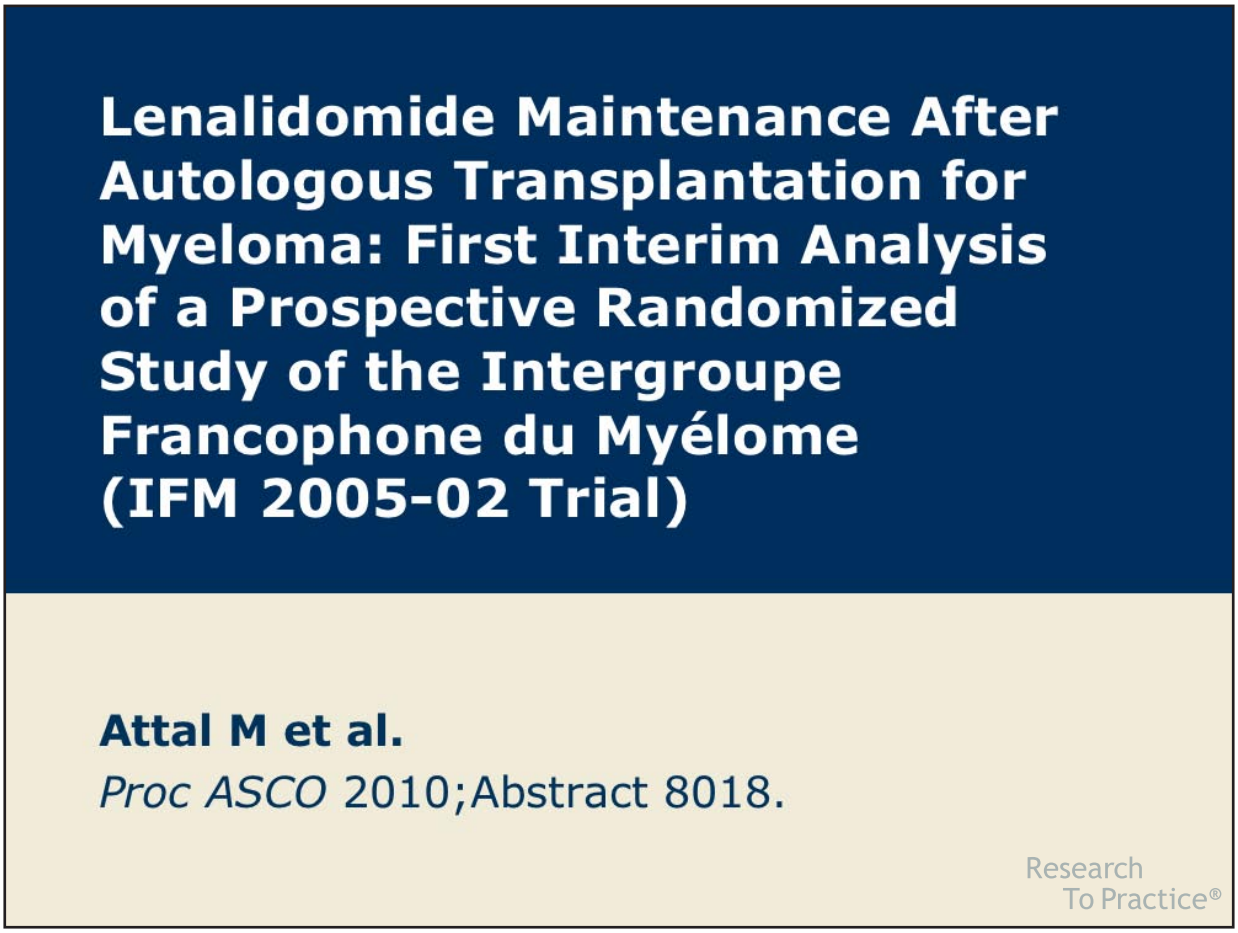
Lenalidomide Maintenance After Autologous Transplantation for Myeloma

Presentations discussed in this issue

McCarthy PL et al. **Phase III I ntergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for Multiple Myeloma: CALGB 100104.** *Proc ASCO* 2010;**Abstract 8017**.

Attal M et al. **Lenalidomide maintenance after autologous transplantation for myeloma.** *Proc ASCO* 2010;**Abstract 8018**.

Slides from presentations at ASCO 2010 and transcribed comments from recent interviews with Michele Cavo, MD (7/1/10), Sagar Lonial, MD (6/21/10), Robert Z Orlowski, MD, PhD (6/18/10) and Ravi Vij, MD (7/1/10)



Background and Rationale

- High-dose therapy with autologous stem cell transplantation (ASCT) is standard treatment for eligible patients with multiple myeloma (MM).
- Residual disease responsible for relapse is always present.
- Maintenance thalidomide has shown improved survival (*Blood* 2006;108:3289, *J Clin Oncol* 2009;27:1788).
- Clinical use of maintenance thalidomide is limited because of peripheral neuropathy with prolonged administration.
- Lenalidomide is
  - A thalidomide analogue.
  - Devoid of neurological complications.
  - Likely to be both effective and safe with prolonged administration.

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

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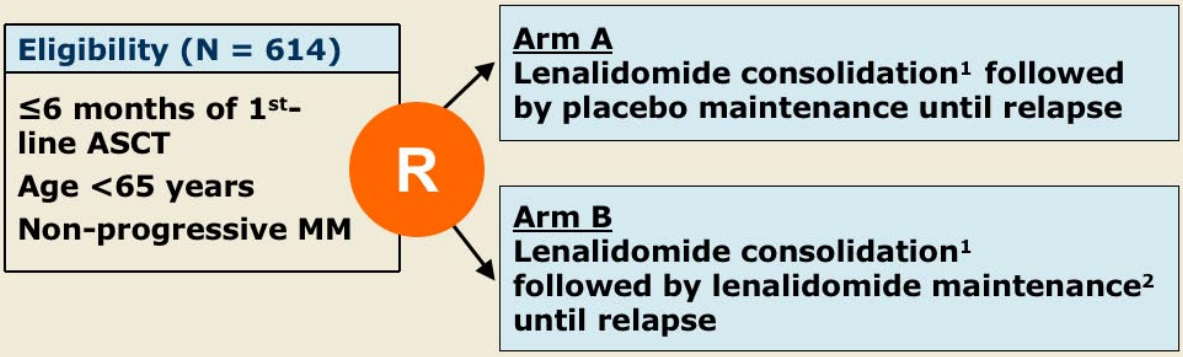
IFM 2005-02 Study Design



Randomization stratified according to β2 microglobulin, del 13 and VGPR

[1] Lenalidomide 25 mg/day, days 1-21 every 28 days x 2 months
[2] Lenalidomide 10-15 mg/day until relapse
VGPR = very good partial response

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

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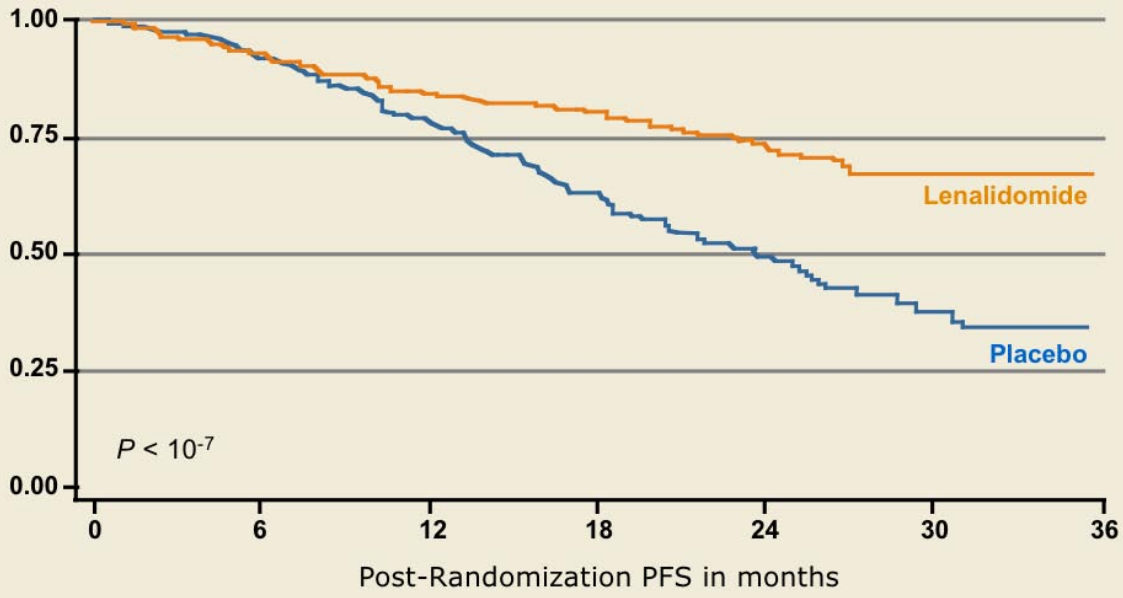
IFM 2005-02: Progression-Free Survival (PFS)



With permission from Attal M et al. *Proc ASCO* 2010;Abstract 8018.

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IFM 2005-02: Efficacy Evaluation

	Placebo Maintenance (n = 307)	Lenalidomide Maintenance (n = 307)	*p*-value	Hazard Ratio
Complete Response (Immunofixation Negative)	22%	25%	0.4	—
≥VGPR	70%	77%	0.08	—
Progression or Death	143 (47%)	77 (25%)	—	—
Median PFS	24 months	Not Reached	$<10^{-7}$	—
3-Year Post-Randomization PFS	34%	68%	$<10^{-7}$	0.46
3-Year Post-Randomization OS	80%	88%	Not Reported	0.88

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

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Conclusions

- Significant improvement in PFS with maintenance lenalidomide in:
  - Overall study population.
  - Pre-specified strata by β2-microglobulin, VGPR as well as del 13 (data not shown).
- Longer follow-up will be needed to find impact of lenalidomide maintenance on overall survival.
- No unexpected adverse events, and no increased incidence of DVT or peripheral neuropathy with lenalidomide maintenance (data not shown).

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

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Investigator comment on the use of lenalidomide maintenance therapy in myeloma

As I see it, the paradigm for treating myeloma has expanded from a view of an induction therapy and eventually of a consolidation therapy to the concept of a maintenance therapy. At ASCO, two highly important studies were reported from two independent groups, one a Phase III study in the US and the other a Phase III study in Europe, and both these trials clearly demonstrated the role of lenalidomide as maintenance therapy for younger patients with myeloma after autologous stem cell transplantation.

At this time we have no data concerning overall survival, but we do have data concerning decreased risk of relapse and prolonged progression-free survival. Although this approach is available at this time in the setting of younger, transplant-eligible patients with myeloma, the concept of a maintenance therapy and the value of maintenance therapy have also been reported and demonstrated for elderly, nontransplant-eligible patients.

Interview with Michele Cavo, MD, July 1, 2010

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Phase III Intergroup Study of Lenalidomide versus Placebo Maintenance Therapy Following Single Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM): CALGB 100104

McCarthy PL et al.

Proc ASCO 2010;Abstract 8017.

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Background and Rationale

- High-dose therapy with autologous stem cell transplantation (ASCT) is standard treatment for eligible patients with myeloma.
- Disease relapse/progression is a primary cause of treatment failure after ASCT.
- Maintenance therapy may prevent or delay disease progression and improve response and survival.

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

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CALGB-100104 Study Design

Registration (N = 568)

Stage 1-3 Multiple Myeloma
≥2 Cycles of Induction Therapy
Attained Stable Disease or Better
Age <70 Years
≥2 x 10^6 CD34 Cells/kg

↓

ASCT

↓

Restaging at Days 90-100 Post-ASCT
Those with CR, PR or SD Randomized

Placebo (n = 208) ← **R** → **Lenalidomide[1] (n = 210)**

[1] Lenalidomide 10 mg/day with increase or decrease to 5-15 mg
CR = complete response; PR = partial response; SD = stable disease

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

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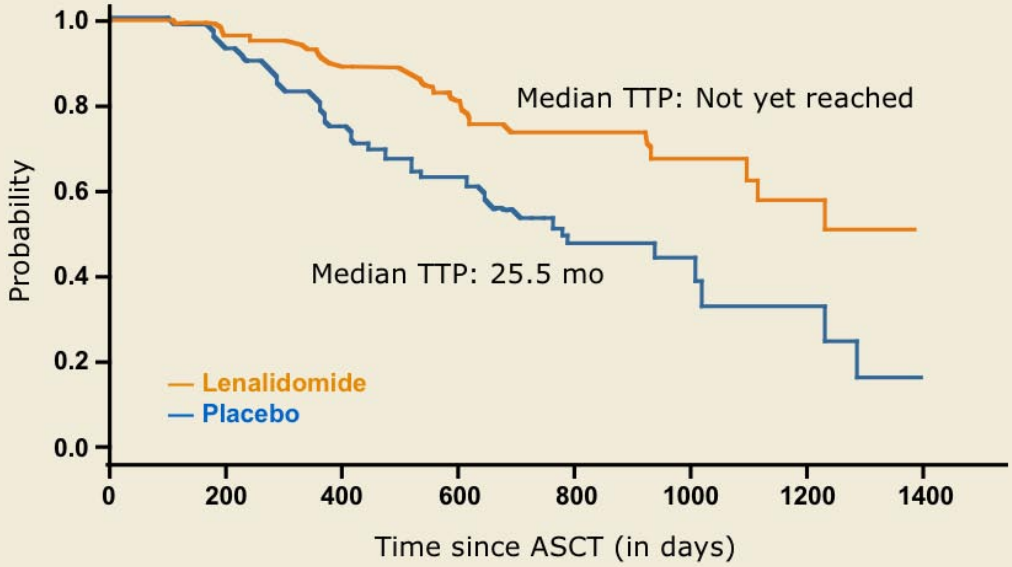
CALGB-100104: Time to Progression (TTP)

Median follow-up since ASCT is 12 months



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CALGB-100104: Efficacy Evaluation

	Placebo Maintenance (n = 208)	Lenalidomide Maintenance (n = 210)	*p*-value	Hazard Ratio
Progression or Death	58 (27.9%)	29 (13.8%)	<0.0001	0.42
Median Time to Progression	25.5 months	Not Reached	<0.0001	—
Death Events	17 (8.2%)	11 (5.2%)	<0.2	—

Median follow-up since ASCT is 12 months

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

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Grade 3-5 Adverse Events During Maintenance (n = 368)

Grade 3-5 Adverse Event	Placebo (n = 174)	Lenalidomide (n = 194)	*p*-value
Anemia	1%	6%	0.0028
Thrombocytopenia	3%	12%	0.01
Neutropenia	7%	42%	<0.0001
Febrile Neutropenia	2%	6%	0.48
Infections	2%	7%	0.03

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

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Conclusions

- Lenalidomide maintenance results in improvement in TTP in:
  - Overall study population.
  - Pre-specified strata of β2 microglobulin as well as prior exposure to lenalidomide or thalidomide (data not shown).
- Lack of survival benefit:
  - Median follow-up was one year.
  - Longer follow-up will be needed.
- Lenalidomide maintenance resulted in some hematologic toxicity, though this was not severe.

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

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Investigator comment on the results of the CALGB-100104 study of lenalidomide maintenance therapy for myeloma

I've been recommending lenalidomide maintenance to all of my patients in the post-transplant setting. The risks are cytopenia and the potential that when their disease does relapse it may be lenalidomide resistant and that, therefore, they may have lost one treatment option in that setting. We still don't have the overall survival data from the two lenalidomide studies, which I believe will be important. If we improve progression-free survival (PFS) but don't improve overall survival, then the importance of those studies will be somewhat decreased.

Subset analyses were also done that showed that lenalidomide worked well whether patients had elevated or normal levels of beta-2 microglobulin, whether or not they were exposed to thalidomide and even whether or not they had received lenalidomide as part of their induction regimen.

The one issue that is not addressed by this study is whether, when patients do experience disease progression on lenalidomide, they no longer have disease that responds to full-dose lenalidomide. If that's the case, the benefit in terms of PFS may be lost with one less option to use in the relapsed setting.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

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Investigator comment on the use of lenalidomide maintenance therapy in myeloma

In the CALGB study patients are being allowed to cross over from observation to the arm with lenalidomide maintenance, so a survival advantage may not be demonstrated. However, in the French study, patients are being followed on their assigned arms. So perhaps in a few years we will have survival data.

People are taking different approaches to this. Some will administer maintenance therapy to everybody after transplant, and some administer it to patients who've had less than a very good PR. Others will administer it to anybody who has not experienced a complete remission. And still others are talking about administering it to patients in complete remission only if they have high-risk features.

Certainly, few people will be using maintenance thalidomide anymore, and many will be adopting lenalidomide maintenance.

Interview with Ravi Vij, MD, July 1, 2010

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Investigator comment on the use of lenalidomide maintenance therapy in myeloma

In our own group we're having extensive discussions about how we're going to come up with a standardized recommendation for patients in the post-transplant setting. In the US we are quick to act on abstract data. I think what makes me feel more confident about this is that it was corroborated with two independent studies, so the data are robust.

The real question, "does there have to be a survival benefit for this to have meaningful impact?" is a tough one to answer. We may be able to show a survival benefit, but we may not. And if we don't, does that mean we should throw out maintenance lenalidomide? I don't believe so. The PFS data are fairly convincing.

Interview with Sagar Lonial, MD, June 21, 2010

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