5 Minute JournalClub

POST-ASH Issue 1, 2014

Follow-Up of IFM 2005-02: Lenalidomide Maintenance After Stem Cell Transplantation for Multiple Myeloma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on up-front and maintenance therapeutic options in the treatment of multiple myeloma (MM) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the efficacy and safety of lenalidomide in combination with low-dose dexamethasone (Rd) as an up-front therapeutic option for elderly patients with newly diagnosed MM, and consider this information for the treatment of patients.
- Compare and contrast the benefits and risks of bortezomib/melphalan/prednisone (VMP) and Rd for elderly patients with newly diagnosed MM when administered in a sequential versus an alternating manner.
- Assess the efficacy and safety of therapeutic regimens containing an alkylating agent versus those that do not for elderly, transplant-ineligible patients with newly diagnosed MM.
- Analyze the extended and updated results from the Phase III HOVON-65/GMMG-HD4 trial of bortezomib during induction and maintenance therapy for newly diagnosed MM, including outcomes of patients with renal failure.
- Evaluate the updated patient survival outcomes from the IFM 2005-02 study and the role of lenalidomide maintenance therapy after first-line autologous stem cell transplantation in MM.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: January 2014
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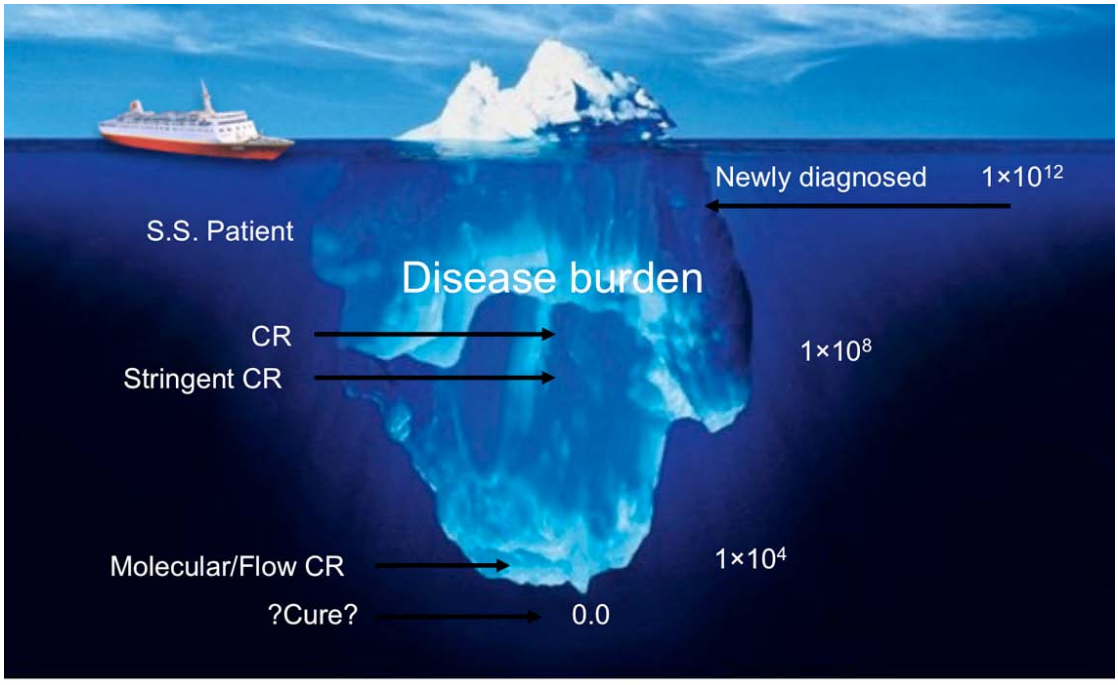
To go directly to slides and commentary for this issue, **click here**.

Sagar Lonial, MD

The revolution in myeloma therapy engendered by the development of proteasome inhibitors and immune modulatory drugs has not only changed the natural history of the disease but also has led some investigators to adopt a "more is better" treatment goal whereby efforts are made at diagnosis to maximally drive down the tumor burden and keep it suppressed for as long as possible. Dr Sagar Lonial is among the champions of this concept, and last week I chatted with him to further clarify his vision of this paradigm and better understand how it applies to evolving clinical research, especially new data emerging at ASH.

The fundamental idea behind this strategy is perhaps not that much different than what has been hypothesized for many cancers in the past. As depicted by the innovative "iceberg" graphic (see below) that Sagar has been using in many of his recent presentations, the goal is either a diffuse large B-cell lymphoma-like cure or a much longer duration of freedom from disease progression.



Getting to Minimal Residual Disease (MRD). Lonial, S. Reprinted with permission.

Assays to assess MRD are critical to this type of clinical research, and interestingly, Dr Lonial believes that the approach may be far less relevant in the relapsed/refractory setting, where many more mutant tumor clones have developed. The concept of prolonged disease suppression with some type of maintenance is also part of this strategy, and like a number of investigators Sagar often uses a variation of RVD maintenance, particularly in patients with higher-risk tumors.

Many oncologists — myself included — carry a hard-learned skepticism of the "more is better" paradigm from prior research in other tumors, including metastatic breast cancer, where a classic ECOG trial run by Dr George Sledge demonstrated the same survival with combination chemotherapy versus sequential single agents, and an important and vocal segment of myeloma investigators — particularly Dr S Vincent Rajkumar and his Mayo Clinic colleagues — have supported less intensive and better tolerated treatment choices in patients at standard risk. Both groups are committed to cure as a goal, but there is disagreement about what this all means to current practice, and even Sagar believes that with the available therapies a very small fraction of patients might be cured, even functionally, and he is particularly focused on patients with MRD negativity by new flow cytometry techniques along with PET scan normalization.

At the last ASCO meeting, Dr Lonial co-chaired the oral myeloma session and discussed several major up-front trials within the context of the iceberg model. We found his take on the issue to be quite provocative and as such attempted to recreate the format for the first issue of our annual post-ASH roundup. Here is his bottom line on the most noteworthy related oral papers from New Orleans mixed with Dr Lonial's perspectives:

1. FIRST trial (Phase III): MPT versus 18 months of lenalidomide/low-dose dexamethasone versus continuous Rd until disease progression in transplant-ineligible patients

Perhaps the most visible myeloma story out of ASH was this **largely European trial** that was afforded plenary status because in many parts of the world (unlike the US) where MPT is now utilized, this study will likely establish a new standard treatment as these data demonstrate superior PFS and OS in favor of continuous Rd versus MPT. However, perhaps even more relevant was the 38% statistically significant improvement in time to progression (32.5 versus 21.9 months) for continuous Rd as opposed to 18 months, though it may be too early to evaluate OS. This long-term treatment strategy is in keeping with (and may ultimately provide support for) Dr Lonial's notion to proactively attempt to delay disease progression.

2. Other trials of up-front management

Not surprisingly, **Dr Antonio Palumbo** was again on stage at ASH presenting yet another Phase III trial of up-front treatment, this time evaluating Rd versus MPR versus

cyclophosphamide/prednisone/lenalidomide (CyPR) in elderly patients not eligible for transplant. Building off the FIRST trial, all 3 arms of this effort yielded comparable disease-related outcomes in terms of PFS and overall response rates. Of note, patients receiving melphalan experienced more treatment-related toxicity than those receiving cyclophosphamide, and Dr Lonial sees this as one more reason that in myeloma the end may be near for melphalan.

Another important up-front trial — **HOVON-65/GMMG-HD4** — reported more follow-up at ASH. This study, which had previously demonstrated an advantage to bortezomib with doxorubicin/dex induction therapy followed by bortezomib maintenance versus vincristine with doxorubicin/dex followed by thalidomide maintenance, continues to yield a PFS and OS benefit for the bortezomib-based regimen, and the update provides further support for the use of this proteasome inhibitor in patients with renal failure and adverse risk factors. The study used a bortezomib maintenance schedule of 1 dose every other week for 2 years, but Dr Lonial notes that subcutaneous maintenance bortezomib may be even more patient friendly, and oral proteasome inhibitors such as ixazomib and oprozomib might further facilitate this strategy.

Finally, a paper by **Mateos et al** investigated the novel induction strategy of alternating Rd with VMP in elderly patients. Although Dr Mateos and her colleagues conclude that the alternating scheme is superior in efficacy versus the sequential approach, it is difficult to compare this regimen to the 3- and 4-drug combinations currently used in practice. In keeping with his intent to achieve rapid and deep responses even in older patients (with tolerable regimens), Dr Lonial favors the combination approach.

3. More data on lenalidomide maintenance

Of the 3 major Phase III trials of len maintenance, two — CALGB-100104 and the Italian MM-015 study — have demonstrated a survival benefit, and this led to a major shift in US practice. However, the **third study** from the French IFM group (IFM 2005-02), which was updated at ASH, continues to show a substantial PFS benefit without improvement in OS. In discussing this data set, Dr Lonial noted that part of this discrepancy may be related to the IFM 2005-02 trial's design, in which all patients received 2 months of post-transplant lenalidomide consolidation, including those randomly assigned to "no maintenance." Another critical difference is that the IFM stopped len maintenance treatment at 2 years as opposed to indefinite therapy until disease progression/toxicity in the other 2 studies.

Also at ASH we saw findings from a **meta-analysis** of lenalidomide maintenance, demonstrating a PFS and OS benefit. However, Dr Lonial found it difficult to dissect out the relevance of this data set because it included patients who did and did not receive a transplant. The study did, however, provide some additional insight about the incidence of second primary cancers, which to this point appears to be mainly a modest risk of hematologic neoplasms, including AML and MDS.

Although the “more is better” investigators have focused on current regimens with approved agents, it is likely that completely different classes of drugs will be required to melt away substantially more of the iceberg, and in another myeloma issue in this series we will attempt to pick out the agents farthest along in this desperate race, including monoclonal antibodies and filanesib — a fascinating kinesin spindle protein inhibitor reported at ASH by Dr Lonial’s group to cause responses (as a single agent and with low-dose dex) in patients refractory to conventional agents. Next on this series, an ASH CML update including the current status of ponatinib.

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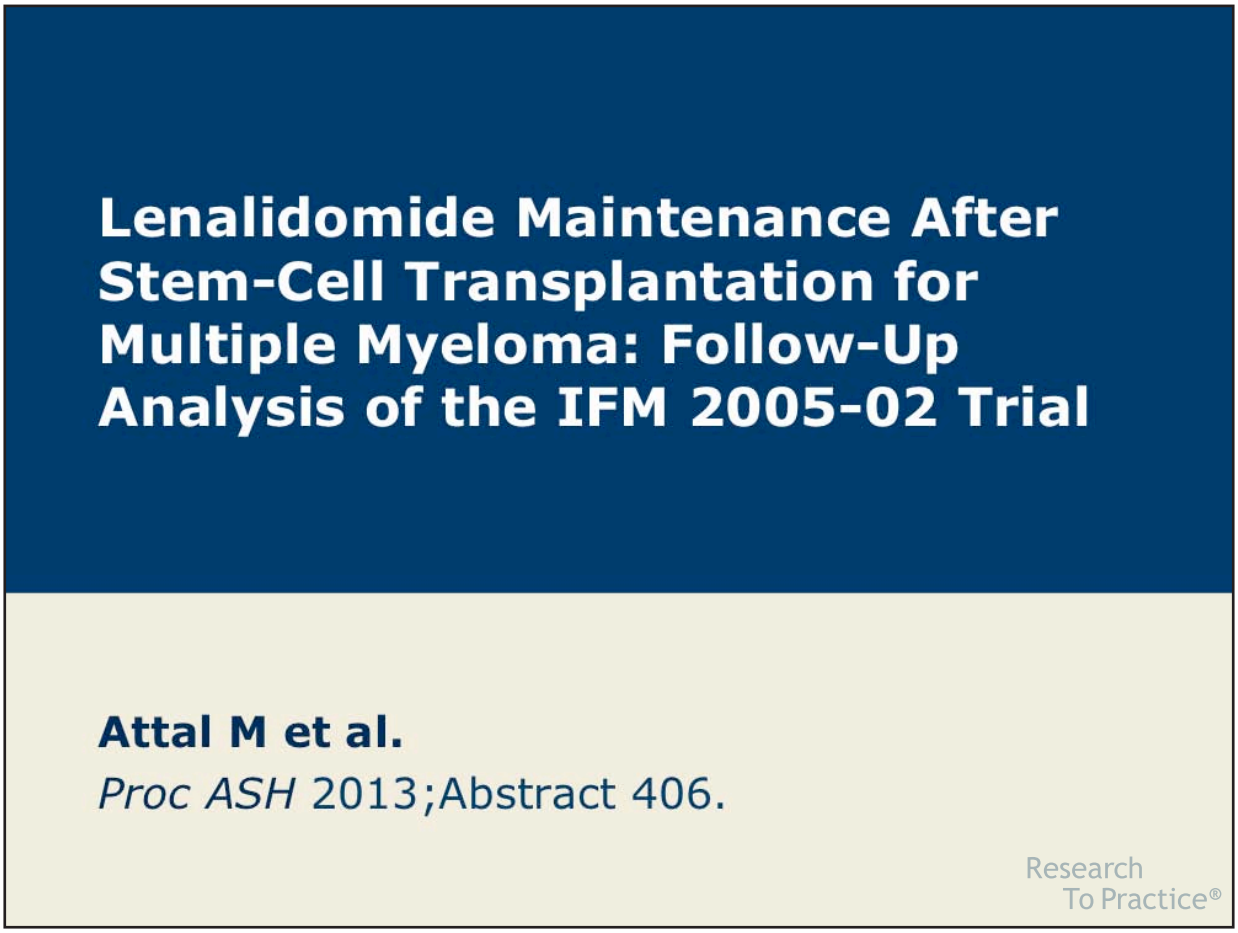
Follow-Up of IFM 2005-02: Lenalidomide Maintenance After Stem Cell Transplantation for Multiple Myeloma

Presentation discussed in this issue

Attal M et al. **Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: Follow-up analysis of the IFM 2005-02 trial.** *Proc ASH* 2013;**Abstract 406**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Sagar Lonial, MD (1/22/14)



Background

- The IFM protocol for this study was designed to develop the role of lenalidomide (Len) as maintenance therapy after transplantation for patients with multiple myeloma (MM).
- Previously, results from the IFM 2005-02 trial, after a follow-up period of 45 months, demonstrated that Len maintenance (*NEJM* 2012;366(19):1782):
  - Significantly improved progression-free survival (PFS) without significant impact on overall survival (OS)
  - Increased rates of Grade 3/4 neutropenia, infections, deep vein thrombosis and second primary malignancies (SPMs)
- **Study objective:** To determine the efficacy and safety of Len maintenance therapy after first-line autologous stem cell transplantation (ASCT) for patients with MM after a longer follow-up period.

Attal M et al. *Proc ASH* 2013;Abstract 406.

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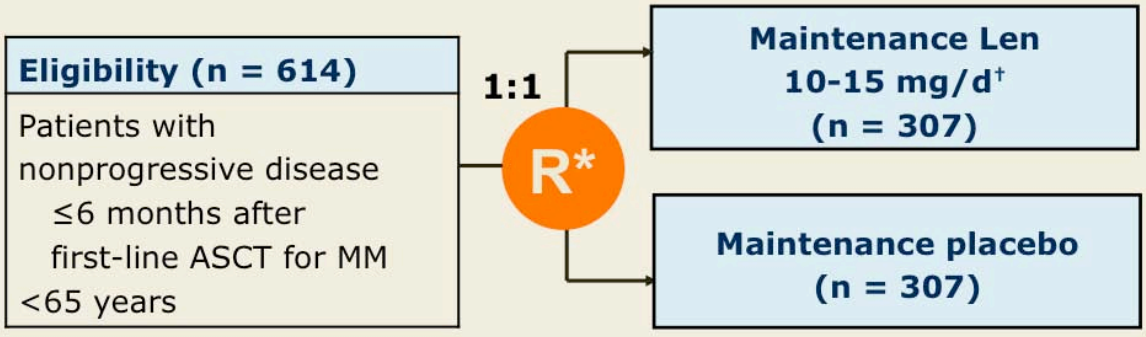
Phase III IFM 2005-02 Trial Design



* All patients initially received consolidation therapy with Len (25 mg/d) on days 1-21 every 28 days for 2 months.

† 10 mg per day for the first 3 months, increased to 15 mg if tolerated

- Recruitment took place from July 2006 through August 2008.
- In January 2011 the Data and Safety Monitoring Board (DSMB) recommended the discontinuation of Len due to increased incidence of SPMs.
- **Primary endpoint:** PFS
- No patient on the placebo arm received Len before progression.

Attal M et al. *Proc ASH* 2013;Abstract 406; *N Engl J Med* 2012;366(19):1782-91.

Survival Results from Randomization

PFS	Len (n = 307)	Placebo (n = 307)	*p*-value
Median PFS	46 mo	24 mo	<0.001
5-year PFS	42%	18%	<0.0001
OS	**Len**	**Placebo**	***p*-value**
Median OS	82 mo	81 mo	0.80

- The median duration of Len maintenance therapy was 2 years.
- As of November 2013, the median follow-up was 77 months from diagnosis and 67 months from randomization.
- Discrepancy between PFS and OS remained:
  - Poor outcome after disease progression for patients on the Len maintenance group was a likely hypothesis.
  - In order to confirm this hypothesis, additional analyses were performed.

Attal M et al. *Proc ASH* 2013;Abstract 406.

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Second PFS

	Placebo (n = 241)	Len (n = 165)	*p*-value
Median second PFS	24 mo	13 mo	<0.001

Attal M et al. *Proc ASH* 2013;Abstract 406.

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Second PFS According to Treatment at First Progression

	Total (n = 614)	Placebo (n = 307)	Len (n = 307)
Patients experiencing first progression (n)	406	241	165
Patients requiring treatment for first progression (n)	369	215	154

IMiD-based regimen	**Total (n = 181)**	**Placebo (n = 134)**	**Len (n = 49)**	***p*-value**
Median second PFS	—	19 mo	8 mo	0.003
Bortezomib-based regimen	**(n = 94)**	**(n = 31)**	**(n = 63)**	
Median second PFS	—	8 mo	9 mo	0.28
No new agents	**(n = 92)**	**(n = 50)**	**(n = 42)**	
Median second PFS	—	30 mo	18 mo	0.06

Attal M et al. *Proc ASH* 2013;Abstract 406.

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OS After First Progression

	Len (n = 165)	Placebo (n = 241)	*p*-value
Median OS	29 mo	48 mo	<0.001

Attal M et al. *Proc ASH* 2013;Abstract 406.

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Incidence of SPMs

	Len	Placebo	Total
Hematologic	**18**	**7**	**25**
AML/MDS	7	4	11
ALL	1	1	2
Lymphoma	6	1	7
Hodgkin lymphoma	4	1	5
Solid tumor	**13**	**11**	**24**
Esophageal/hypopharynx	2	0	2
Colon and rectal	4	1	5
Prostate	3	3	6
Lung cancer	0	1	1
Bladder/renal	1	2	3
Breast	2	1	3
Melanoma	1	3	4
Noninvasive skin cancer	**9**	**5**	**14**
Total (patients can have >1 SPM)	**37 (13%)**	**21 (7%)**	**58**

Attal M et al. *Proc ASH* 2013;Abstract 406.

Author Conclusions

- This new analysis confirms that Len is an effective treatment to prolong PFS (median 46 mo vs 24 mo, $p < 0.001$) after ASCT for patients with MM:
  - Reduced second PFS (median 24 mo vs 13 mo, $p < 0.001$), possibly due to clonal selection or secondary resistance (suggested by the IMiD and No new agent groups)
- PFS benefit is not currently associated with an improved OS because of a shorter survival after the first disease progression (median 29 mo vs 48 mo, $p < 0.001$).
- The risk of SPMs increased (13% vs 7%) for patients receiving Len maintenance.
- The risk of severe neutropenia also increased (51% vs 18%) for patients receiving Len (data not shown).

Attal M et al. *Proc ASH* 2013;Abstract 406.

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Investigator Commentary: Follow-Up Analysis of the IFM 2005-02 Trial of Len Maintenance After ASCT for Patients with MM

Of note, the initial analysis of the results from this IFM trial failed to show an OS benefit even though the PFS benefit was the same as in the US CALGB trial (*NEJM* 2012;366(19):1770). Some big differences between these 2 studies are that the IFM trial included 2 cycles of Len as consolidation and early trial termination resulted in patients receiving Len maintenance for a median of 2 years. The CALGB trial did not have a consolidation step and Len maintenance was administered longer, until disease progression.

After a median follow-up of 77 months, this trial continues to show an improvement in PFS but no OS benefit. We continue to see a warning about the development of SPMs for patients receiving Len maintenance. If you compare these results to the data from 2 trials that showed OS benefit — the US trial and the Phase III trial of early transplant versus no transplant with a second randomization to Len or no maintenance (*Proc ASCO* 2013;Abstract 8509) — 2 issues are evident with the use of Len maintenance. Side effects occur, and a higher risk of SPMs exists with Len maintenance, although that's a relatively low risk compared to the risk of MM relapse. If you limit therapy to 2 years, you're opening yourself up to all the risks and toxicities of therapy without necessarily allowing your patient to realize the survival benefit reported for patients who receive treatment until progression.

Interview with Sagar Lonial, MD, January 22, 2014