



*POST-ASH* Issue 6, 2015

**Phase III QUIREDEX Trial of Lenalidomide (Len) and Dexamethasone (Dex) and Phase II Trial of Carfilzomib and Len/Dex in High-Risk Smoldering MM**

## 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 novel agents and salvage therapeutic options for the treatment of relapsed or refractory multiple myeloma (MM) and Waldenström macroglobulinemia (WM), high-risk smoldering MM (SMM) and the front-line management of AL amyloidosis 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

- Evaluate the final efficacy and safety results from the Phase I/II 1703 study of elotuzumab in combination with lenalidomide and dexamethasone for patients with relapsed/refractory MM.
- Appraise recent clinical research findings on the effectiveness of the monoclonal anti-CD38 antibodies SAR650984 and daratumumab in combination with lenalidomide and dexamethasone in relapsed/refractory MM.
- Investigate the efficacy and safety of ibrutinib as a single agent or in combination with dexamethasone in relapsed or relapsed/refractory MM.
- Compare and contrast the benefits and risks of lenalidomide and low-dose dexamethasone with or without carfilzomib for patients with high-risk SMM.
- Analyze the role of front-line cyclophosphamide in combination with bortezomib and dexamethasone (CyBORd) in AL amyloidosis.
- Assess the safety and efficacy of the proteasome inhibitor oprozomib as a single agent in the treatment of WM.

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**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Ola Landgren, MD, PhD  
Chief, Myeloma Service  
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Contracted Research: Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary.

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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: May 2015

Expiration date: May 2016

To go directly to slides and commentary for this issue, [click here](#).

One of my favorite days of the year occurs every April when the American Society of Clinical Oncology (ASCO) releases their iPlanner for the upcoming annual meeting that provides a first glimpse at the titles of all the oral abstracts that will be presented during the conference. This year my review quickly established that in the world of solid tumors there would be many highlights, including the long-awaited MARIANNE report evaluating pertuzumab and T-DM1 in HER2-positive breast cancer and a ton of impressive checkpoint inhibitor papers in lung cancer (squamous and nonsquamous), melanoma and a number of other diseases.



**Sagar Lonial, MD**

In terms of hematologic cancers, ASCO is always good for a few headline grabbers, and in reviewing the papers, my attention was immediately drawn to the first abstract in the multiple myeloma (MM) oral session — the Phase III ELOQUENT-2 trial in relapsed/refractory (RR) disease. The study, one of the most anticipated in MM in many years, randomized patients to lenalidomide (len)/dexamethasone (dex) alone or combined with the novel monoclonal antibody elotuzumab (elo).

This was definitely not the first time I became aware ahead of time that an important new data set was about to be presented, and as usual I was desperately curious to find out the results. About a week later I had my chance when the principal investigator, Dr Sagar Lonial, participated in a symposium we were doing as part of our always rewarding annual visit to the Oncology Nursing Society Congress. However, as usual my hopes were crushed by a strict embargo, and Sagar was a complete stone-wall Buddha sphinx, rebuffing all my attempts to squeeze the information out of him and leaving me totally clueless whether the study proved what earlier smaller trials suggested, namely that a special synergy exists between this antibody, which has no single-agent activity, and len.

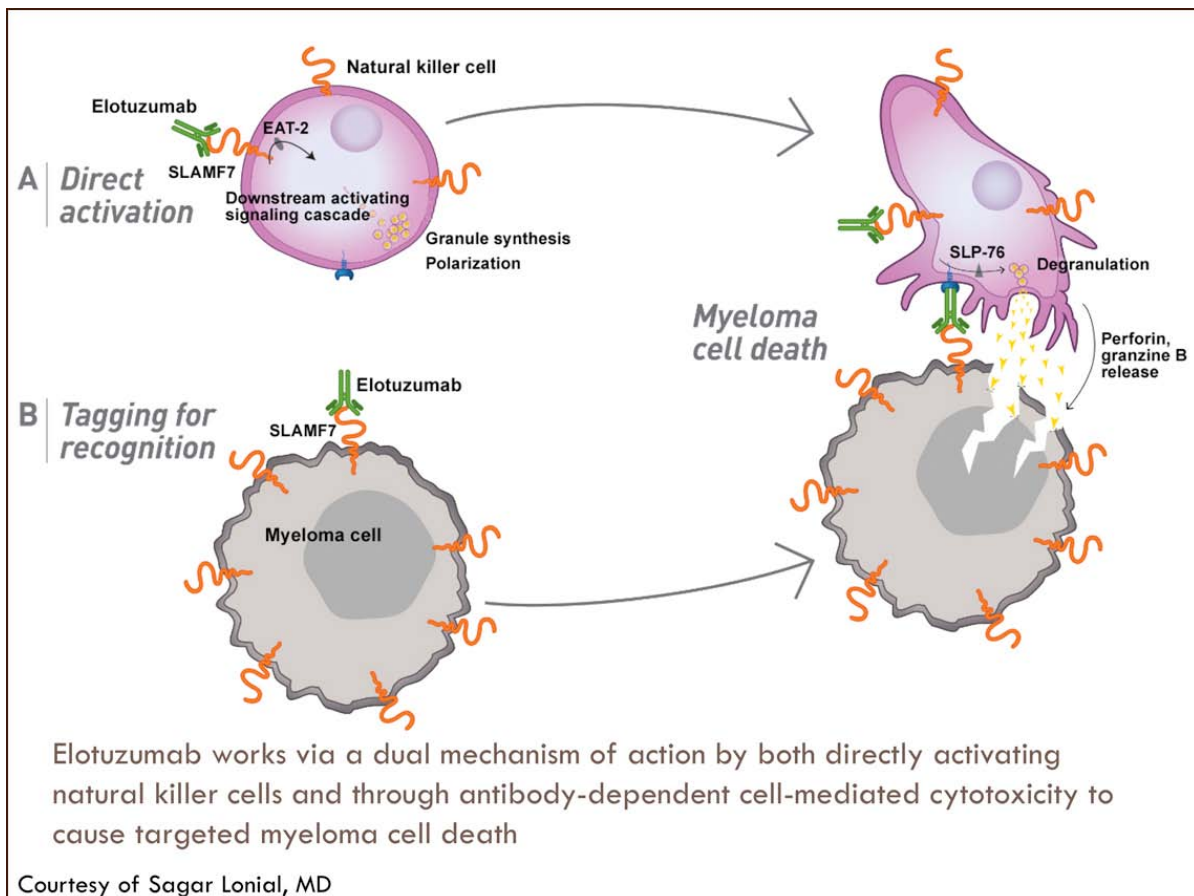
Fast forward to a week ago, when ASCO released online all but the late-breaking abstracts. My first click was to ELOQUENT-2, and to my delight, elo/len/dex resulted in a 30% reduction in the risk of disease progression and also a mortality benefit. While we most definitely need to see the data and hear Sagar and the rest of the myeloma community's take, if first impressions are any indication it could be that finally a cancer of cells that produce antibodies is soon going to have one as part of its treatment.

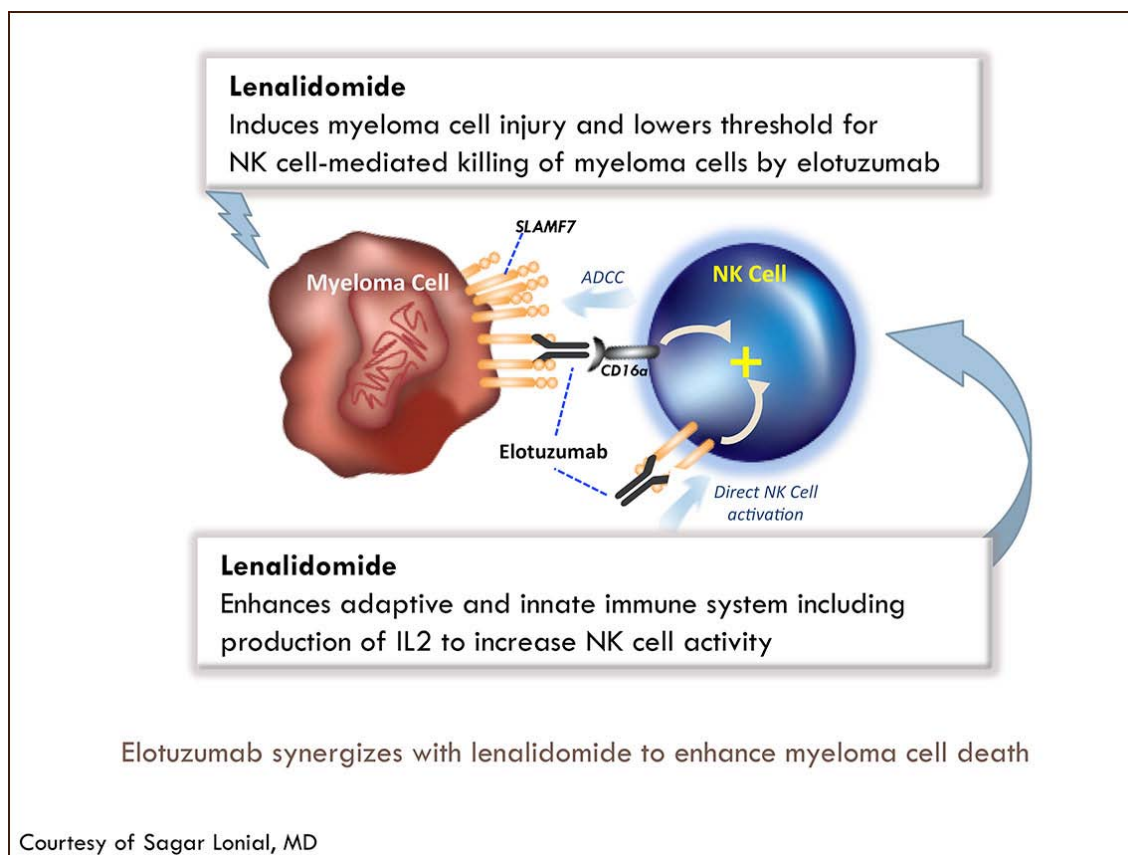
However, until the fun begins in Chicago, there is still much work to be done, and this issue of our American Society of Hematology (ASH) review series highlights a number of new directions in the treatment of MM, including antibodies, and several other related (at least in terms of who manages them) diseases, including Waldenström macroglobulinemia and AL amyloidosis.

## Monoclonal antibodies in MM

### • Elo/len/dex

After years of asking investigators to explain how immunomodulating drugs work (and still not completely understanding the answer), I suspect that elo may be even more of a challenge. Signaling lymphocytic activation molecule F7 (SLAMF7) is a glycoprotein that is highly expressed on MM and natural killer (NK) cells but not on normal tissue. As a monoclonal antibody targeted against SLAMF7, elo is thought to directly activate and engage NK cells and selectively target SLAMF7-expressing MM cells for destruction.





As we learn more about the biologic basis of the apparently important synergy of len and elo, ongoing trials are evaluating this approach clinically. At ASH we saw Paul Richardson's [report of 73 patients](#) with RR MM who were treated with this regimen in the Phase II portion of the 1703 study, revealing similar encouraging outcomes as a prior single-arm study (response rate: 84%) with good tolerability. The bottom line now is that on Tuesday, June 2nd at 9:45 AM in the McCormick Place Convention Center, we will find out just how much it helps patients.

### ● **Anti-CD38 antibodies with len/dex**

While elo may be first with Phase III data, among MM investigators there is perhaps even more excitement about anti-CD38 agents, particularly daratumumab (dara) and the as yet nameless SAR650984 (sar). For quite some time now on our CME programs we have been hearing about the single-agent activity of these compounds, and I can recall a number of cases with impressive responses after disease progression on multiple therapies. However, the future of MM treatment seems to be combinations, which are firmly entrenched in the induction setting and gaining traction in RR disease. Thus it is no surprise to see strategies like [the 2 featured here](#) of combining these antibodies with len/dex and producing very good outcomes (77% very good partial response or greater with dara/len/dex; 64.5% overall response rate with sar/len/dex). Many investigators, including Dr Lonial, believe that depth of response is critical in MM, and the hope has been that bringing in new classes of effective agents might push the disease into a more prolonged remission, also raising the possibility of cure as a treatment goal. Much more to come.

## **Ibrutinib in MM**

Ibrutinib has been a revelation in terms of efficacy and activity across many variants of non-Hodgkin lymphoma, and when laboratory evidence emerged regarding the activation of Bruton tyrosine kinase in MM cells, there was optimism that this drug might play an important role in the management of this disease. Unfortunately, at ASH we saw data from [a Phase II trial](#) evaluating ibrutinib as a single agent or in combination with dex for patients with RR MM that demonstrated modest, somewhat underwhelming activity (clinical benefit rate of 8% with single-agent ibrutinib and 25% with the combination of ibrutinib/dex). Although further research is ongoing, few are optimistic that ibrutinib in MM will be anything close to what it is in chronic lymphocytic leukemia and mantle-cell lymphoma.

## **High-risk smoldering MM (SMM)**

Although the standard therapy for these patients continues to be observation, a variety of predictive factors identify a subgroup with at least a 75% risk of disease progression at 5 years. As such, there continues to be significant interest in whether early intervention could help improve outcomes for these patients. In this regard, in San Francisco we saw more follow-up from the [landmark Spanish Phase III QUIREDEX trial](#) that had previously demonstrated an important benefit with the use of len/low-dose dex. With a median follow-up of 64 months, these findings continue to be positive, revealing that progression to symptomatic disease occurred in 25% of patients who received treatment versus 85% in the control group (overall survival rate at 7 years: 94% versus 64% with a hazard ratio of 4.6 and  $p = 0.001$ ).

The NCI group formerly led by Ola Landgren, MD, PhD decided to take things even further and evaluate a triplet regimen, in this case carfilzomib/len/dex, followed by len maintenance in patients with high-risk SMM. Among the 12 patients who received treatment in this manner, 10 became MRD-negative after 8 cycles as determined by next-generation sequencing, which, by way of indirect comparison, appears to be an even greater benefit than the approach taken by the Spanish.

Importantly, a number of ongoing studies are pursuing these encouraging leads, including a major ECOG trial chaired by Dr Lonial in an attempt to confirm the Spanish len/dex data, and it could very well be that one day soon treating high-risk SMM will become part of practice.

## **Cyclophosphamide/bortezomib/dex (CyBorD) in AL amyloidosis (ALA)**

Based on the results from a number of smaller trials, CyBorD has become one of the most commonly used up-front regimens for the treatment of this disease. To further confirm the benefits of this approach, 2 major ALA centers in London, England and Pavia, Italy prospectively collected findings from 230 cases of patients with newly diagnosed disease who received this regimen. The result is the [largest data set ever reported](#) with up-front CyBorD in the disease, from which a number of important observations can be made. Notably, of 30 patients with Stage I ALA (no cardiac

involvement), 80% responded (56% complete response/very good partial response) and there were no deaths with a median of 25 months of follow-up. Median survival of all patients was 72 months.

However, it appears that cardiac stage was the main determinant of survival, and patients with advanced heart disease (defined as those with N-terminal pronatriuretic peptide type B >8,500 ng/L) had poor outcomes, although 37% did achieve a response and seemed to fare better overall. The key takeaway from this data set is that due to the high clonal response and excellent outcome in early-stage ALA, CyBorD remains a preferred induction option and further research is needed to determine whether autologous stem cell transplant should be initiated as part of up-front treatment.

### **Novel agents in Waldenström macroglobulinemia (WM)**

On January 29, 2015, ibrutinib became the first ever agent approved by the FDA for the management of WM. This significant milestone, along with emerging data indicating the activity of a number of other established and novel therapeutics, has breathed new life and interest into the treatment of this rare disease. At ASH we saw several examples of work attempting to move the field forward, including a Phase I/II trial evaluating [single-agent len](#) in 17 patients with RR WM. Thirty-six percent of these individuals responded to therapy, and with a median follow-up of 36 months, 35% of patients had a progression-free survival greater than 24 months.

Similarly, we also saw data from a Phase Ib/II trial evaluating the oral proteasome inhibitor oprozomib, which, like its intravenous cousin carfilzomib, appears to have significant efficacy in this disease. Notably, responses were observed in 5 of 7 patients refractory to bortezomib, and treatment was reasonably well tolerated, although some of the gastrointestinal toxicity that has plagued this agent was observed. To potentially eliminate this troubling side effect there is great interest in evaluating an extended-release formulation of the agent in both MM and WM.

Next, on the final issue of our ASH series, we check out papers on non-Hodgkin lymphoma, including the evaluation of anti-CD20 maintenance treatment in mantle-cell lymphoma.

Neil Love, MD

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Miami, Florida

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# Phase III QUIREDEX Trial of Lenalidomide (Len) and Dexamethasone (Dex) and Phase II Trial of Carfilzomib and Len/Dex in High-Risk Smoldering MM

## Presentations discussed in this issue

Mateos MV et al. **Long term follow-up on the treatment of high risk smoldering myeloma with lenalidomide plus low dose dex (Rd) (phase III Spanish trial): Persistent benefit in overall survival.** *Proc ASH 2014*; **Abstract 3465.**

Landgren O et al. **Carfilzomib, lenalidomide, and dexamethasone in high-risk smoldering multiple myeloma: Final results from the NCI phase 2 pilot study.** *Proc ASH 2014*; **Abstract 4746.**

**Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Ola Landgren, MD, PhD (2/9/15)**

**Long Term Follow-up on the Treatment of High Risk Smoldering Myeloma with Lenalidomide plus Low Dose Dex (Rd) (Phase III Spanish Trial): Persistent Benefit in Overall Survival<sup>1</sup>**

**Carfilzomib, Lenalidomide, and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Final Results from the NCI Phase 2 Pilot Study<sup>2</sup>**

**<sup>1</sup> Mateos MV et al.**  
*Proc ASH 2014*; Abstract 3465.

**<sup>2</sup> Landgren O et al.**  
*Proc ASH 2014*; Abstract 4746.

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# Long Term Follow-up on the Treatment of High Risk Smoldering Myeloma with Lenalidomide plus Low Dose Dex (Rd) (Phase III Spanish Trial): Persistent Benefit in Overall Survival

**Mateos MV et al.**

*Proc ASH 2014;Abstract 3465.*

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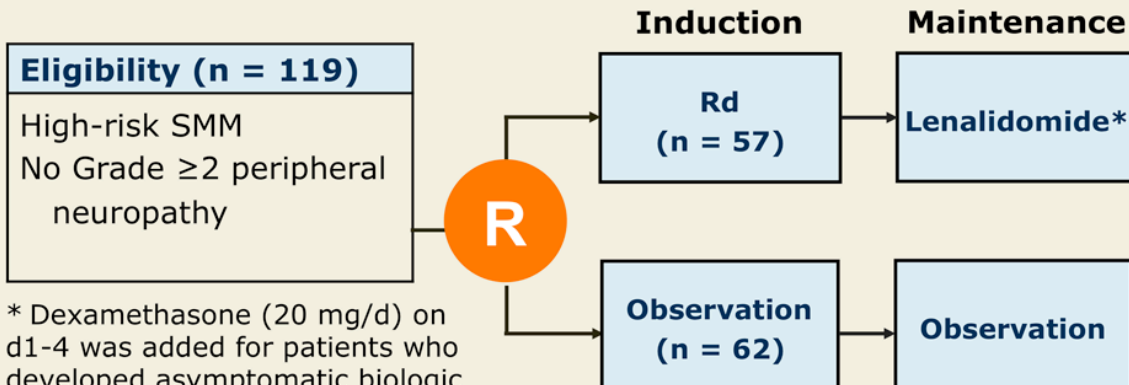
## Background

- The current standard approach for smoldering multiple myeloma (SMM) is watchful waiting until disease progression.
- Several small randomized studies have explored the value of early treatment with either conventional agents (melphalan/prednisone) or thalidomide or bisphosphonates, but these studies showed no significant benefit.
  - Notably, these trials did not focus on high-risk SMM.
- The Phase III trial by the Spanish Myeloma Group comparing lenalidomide/low-dose dexamethasone (Rd) to observation in high-risk SMM (*NEJM* 2013;369:438) demonstrated that:
  - After a median follow-up of 40 months, Rd was superior in time to progression (TTP) to active disease and overall survival (OS).
- **Study objective:** To report updated efficacy and safety results from the Phase III trial of Rd for patients with high-risk SMM after a median follow-up of 5 years.

Mateos MV et al. *Proc ASH 2014;Abstract 3465.*

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# Phase III QUIREDEX Trial Design



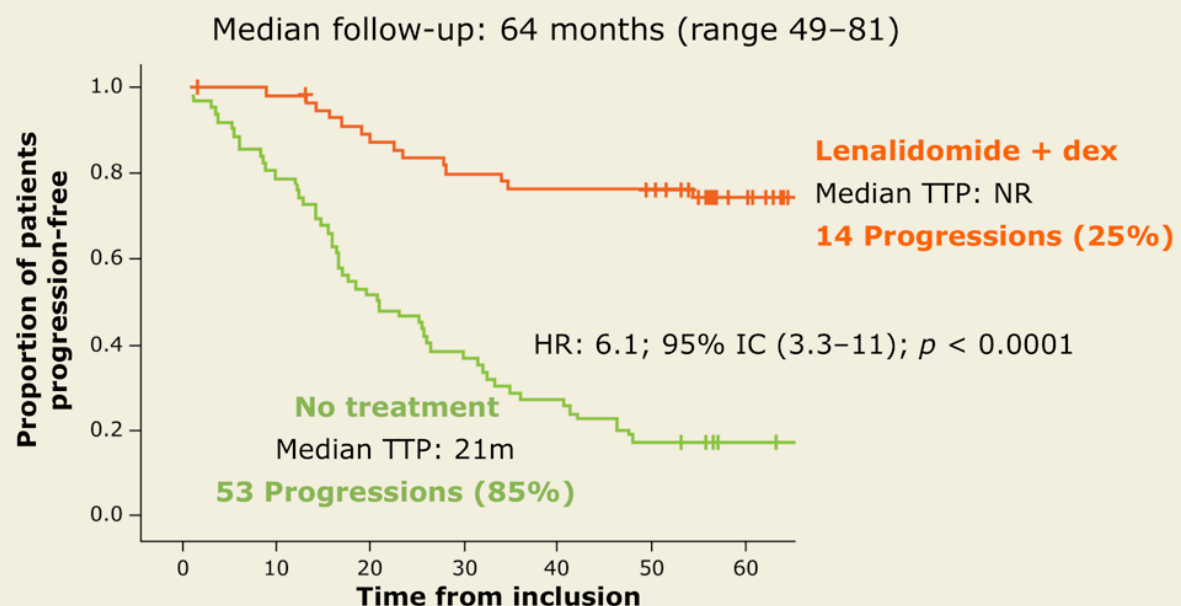
\* Dexamethasone (20 mg/d) on d1-4 was added for patients who developed asymptomatic biologic progression during maintenance.

- Induction: Lenalidomide 25 mg/d on d1-21 and dexamethasone 20 mg/d on d1-4 and d12-15 every 4 weeks for 9 cycles
- Maintenance: Lenalidomide 10 mg/d on d1-21 for up to 2 years (initially until disease progression before protocol amendment in Aug 2011)
- **Primary endpoint:** TTP to symptomatic disease

Mateos MV et al. *Proc ASH* 2014; Abstract 3465; Mateos MV et al. *N Engl J Med* 2013; 369(5):438-47.

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## TTP to Active Disease (N = 118)

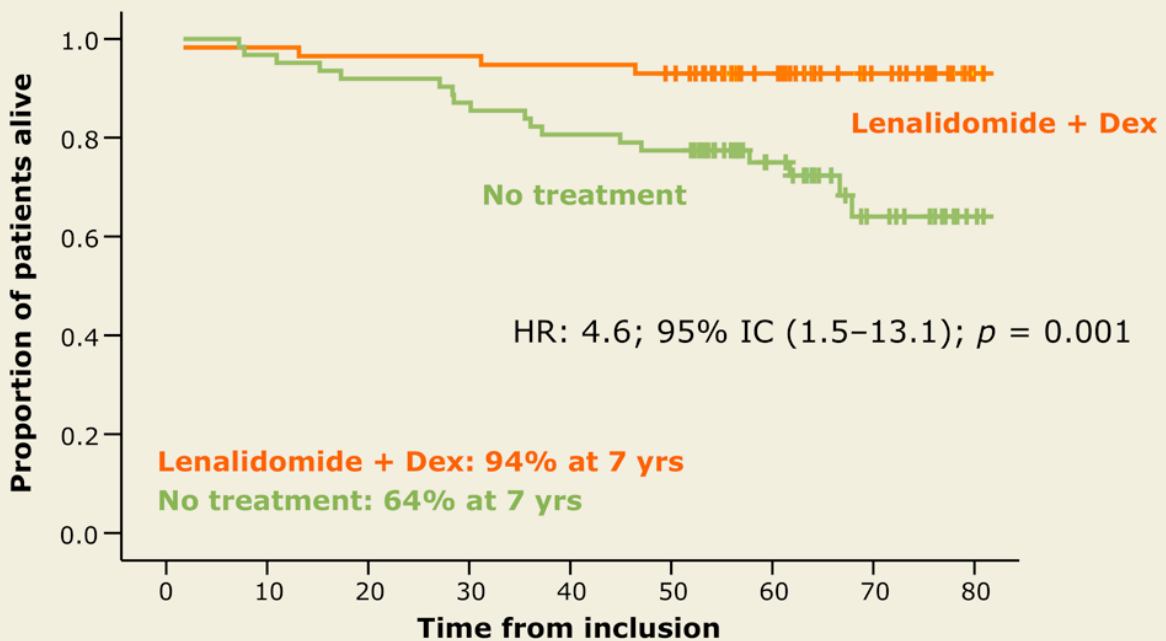


- **Median follow-up = 64 months (range, 49–81)**

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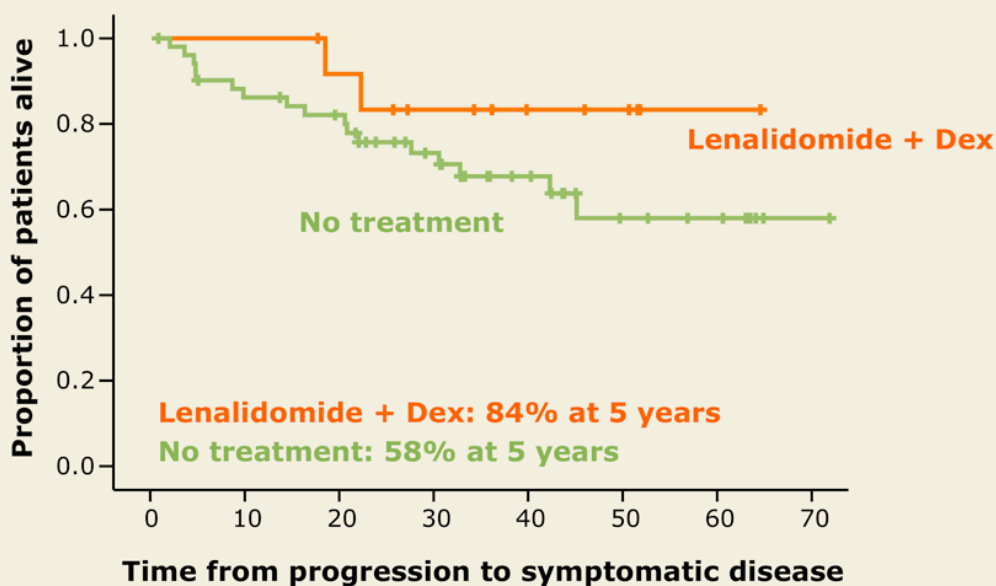
## OS from Study Entry (N = 118)



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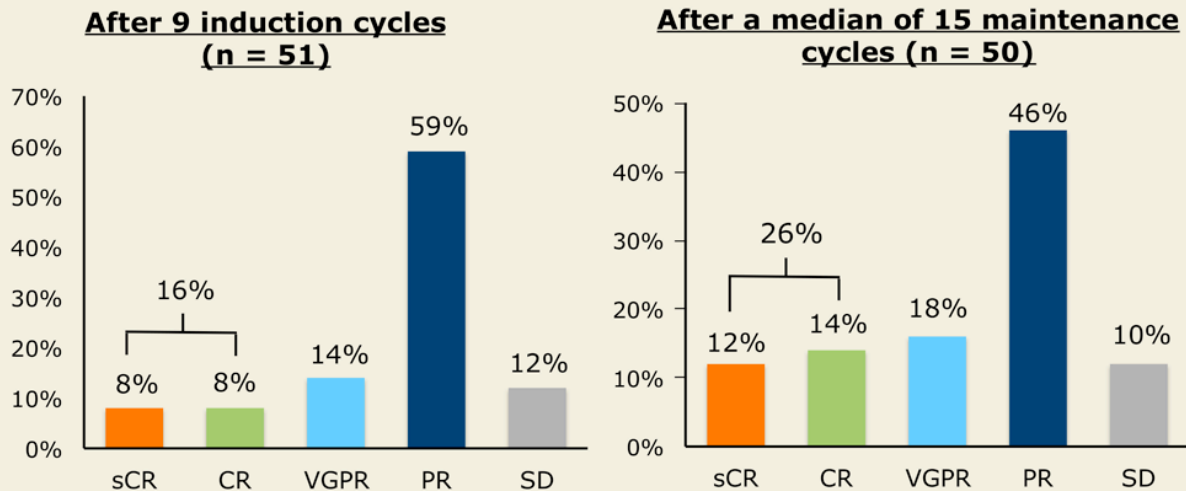
## OS from Progression to Symptomatic Disease (N = 65)



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# Response Rates



- **In the ITT population (n = 57):** ORR = 80%; stringent complete response (sCR) = 7%; complete response (CR) = 7%; very good partial response (VGPR) = 11%; partial response (PR) = 65%; stable disease (SD) = 21%

With permission from Mateos MV et al. *Proc ASH 2014*;Abstract 3465.

# Select Adverse Events

Event	Induction		Maintenance	
	Grade 1	Grade 2	Grade 1	Grade 2
Infection	35%	11%	21%	11%
Rash	23%	11%	NR	NR
Anemia	20%	7%	11%	3%
Diarrhea	17%	7%	NR	NR
Tremor	13%	4%	2%	NR
Thrombocytopenia	11%	2%	0%	9%
Asthenia	11%	9%	NR	2%
Neutropenia	6%	14%	3%	9%
Paresthesia	2%	4%	NR	2%

- Number of second primary malignancies: 4 (lenalidomide arm) vs 1 (observation arm)

Mateos MV et al. *Proc ASH 2014*;Abstract 3465.

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## Author Conclusions

- After long-term follow-up, early treatment of high-risk SMM with Rd continued to show benefits:
  - Significant reduction in the risk of progression to active disease
  - Significant reduction in the risk of death
- The long postrelapse survival observed among patients who received early treatment with Rd and subsequently experienced progression to symptomatic disease indicates that this strategy does not induce the development of more resistant cancer cell clones.

Mateos MV et al. *Proc ASH* 2014;Abstract 3465.

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### **Investigator Commentary: Updated Efficacy and Safety Results from the Phase III QUIREDEX Trial of Rd in High-Risk SMM**

The initial results from this study were published in 2013 (Mateos MV et al. *NEJM* 2013;369(5):438). After an initial follow-up of 40 months, progression-free survival (PFS) and OS were significantly improved in the treatment arm compared to the observation group. In the updated analysis the median follow-up was 64 months. The investigators showed that progression to symptomatic disease occurred in 25% of the patients who received Rd versus 85% of those on the observation arm. These results are significantly different. Also, no evidence indicated that patients who received Rd had an inferior response to treatment.

Second primary cancer occurred in 4 patients on the Rd arm and 1 in the observation group. Of note, 4 patients versus 1 does not provide information on how many patients were at risk. If patients do not survive, there will be fewer potential events. In essence, these numbers are similar. The bottom line is that with long-term follow-up, Rd as an early treatment for patients with high-risk SMM continues to show significant improvement in both PFS and OS. Importantly, there is no evidence that Rd induces more resistant disease clones later.

***Interview with Ola Landgren, MD, PhD, February 9, 2015***

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# Carfilzomib, Lenalidomide, and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Final Results from the NCI Phase 2 Pilot Study

**Landgren O et al.**

*Proc ASH 2014;Abstract 4746.*

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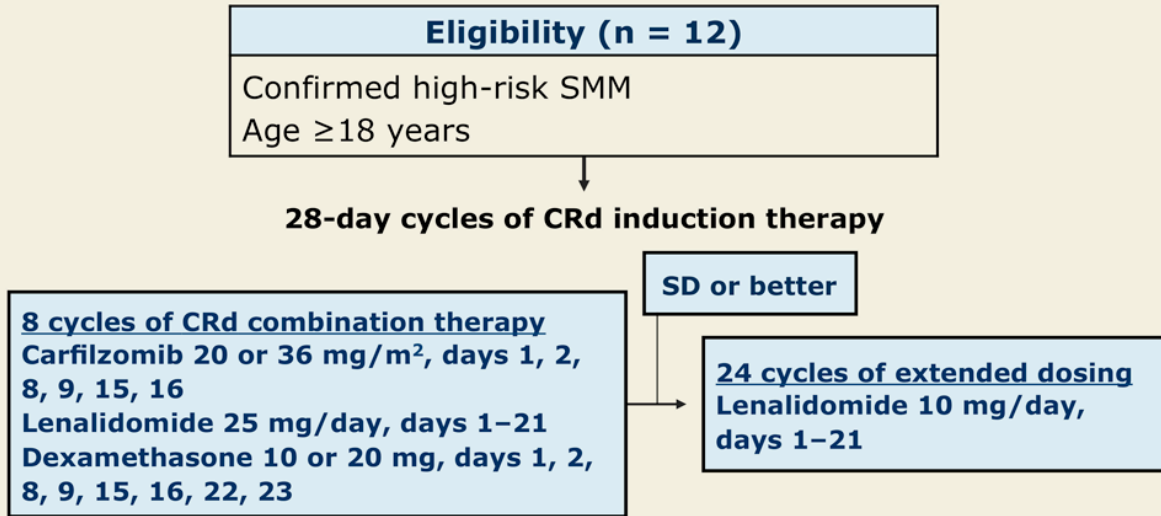
## Background

- The standard approach for smoldering multiple myeloma (SMM) has been to clinically follow the patient and initiate therapy when the disease becomes symptomatic.
- Recently a subgroup of patients with SMM at high risk for disease progression was identified (*Blood* 2007;110:2586; *Blood* 2008;111:785):
  - This subgroup has a 5-year risk of progression of about 75% and a median time to progression of 2 years.
- The addition of the selective proteasome inhibitor carfilzomib to lenalidomide and dexamethasone is highly effective in newly diagnosed MM (*Blood* 2012;120:1801).
- **Study objective:** To report the final results of a Phase II study evaluating whether early treatment with carfilzomib/lenalidomide/dexamethasone (CRd) will result in deeper and more durable responses among patients with high-risk SMM.

Landgren O et al. *Proc ASH 2014;Abstract 4746.*

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# Phase II Pilot Trial Design



SD = stable disease

- **Primary endpoint:** ≥Very good partial response (VGPR) after 8 cycles of CRd
- **Secondary endpoints** include progression-free survival and safety

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

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## Best Response and Mean Monoclonal Protein Levels by Cycle

- Evaluable patients: Cycles 1-6 (n = 12); cycles 7-8 (n = 11)
- Patients who completed 8 cycles of CRd (n = 11):
  - All patients (100%) achieved near complete response (nCR) or better after 8 cycles of CRd
- The study met its prespecified endpoint of ≥5 of 12 patients achieving VGPR or better after 8 cycles of therapy
- Extended dosing (maintenance) with lenalidomide improved the depth of response in 4 of 11 (36%) patients
  - The level of response achieved during induction therapy with CRd was maintained in the remaining 7 patients
    - Stringent complete response (sCR): n = 6
    - Complete response (CR): n = 1
- The mean monoclonal protein level decreased significantly from baseline to completion of cycle 1 and continued to decrease with the increasing number of completed cycles

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

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## Minimal Residual Disease (MRD) Status

- After 8 cycles or achievement of a CR, 10 (83%) and 11 (92%) patients tested negative for MRD by next-generation sequencing (NGS) and flow cytometry criteria, respectively.
- After 1 year of extended dosing with lenalidomide, 3 patients underwent additional MRD analysis: 2 remained negative for MRD by flow cytometry; 1 tested positive by flow cytometry despite remaining negative by NGS.

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

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## Select Adverse Events

<b>N = 12</b>	<b>All events</b>	<b>Grade 3 or 4</b>
Lymphopenia	100%	42%
Leukopenia	92%	8%
Thrombocytopenia	92%	25%
Electrolyte disturbances	92%	17%
Elevated liver function tests	92%	17%
Rash/pruritus	75%	25%
Anemia	67%	17%
Diarrhea	67%	17%
Neutropenia	42%	17%
Increased serum creatinine	17%	17%

- No deaths occurred during therapy

Landgren O et al. *Proc ASH* 2014;Abstract 4746.

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## Author Conclusions

- Early treatment with CRd followed by extended dosing with lenalidomide was associated with rapid, deep and durable responses among patients with high-risk SMM.
  - Patients who achieved  $\geq$ VGPR after 2 cycles of CRd: 50%
  - Patients who achieved  $\geq$ nCR after 8 cycles of CRd: 100%
  - No patient experienced disease progression on study
- MRD negativity was observed in at least 10/12 (83%) patients using both flow cytometry and NGS criteria.
  - This high rate of MRD-negativity may translate into improved patient outcomes as time-to-event data continue to mature.
- Overall, the CRd regimen was safe and tolerable with manageable toxicities.
- These data support the need for larger studies for patients with high-risk SMM.

Landgren O et al. *Proc ASH 2014*;Abstract 4746.

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### **Investigator Commentary: Final Efficacy and Safety Results of the Phase II Trial of CRd for Patients with High-Risk SMM**

The Phase III QUIREDEX trial intellectually sets the stage for 3-drug combinations in high-risk SMM, and the pilot Phase II trial of CRd for 12 patients addresses that issue. All 11 patients (100%) who completed 8 cycles of therapy achieved nCR or better after receiving 8 cycles of CRd. Of the 12 treated patients, 11 were MRD-negative by multicolor flow cytometry and 10 patients were MRD-negative by NGS. One of the 2 patients who were MRD positive by NGS was the patient who was positive by flow cytometry, but an additional patient was also positive by NGS.

Although we have to be cautious comparing across studies, results with the 2- versus 3-drug combinations in the population of patients with high-risk SMM are fascinating if one compares the 100% achievement of nCR or better with CRd head to head with the results obtained in the Spanish QUIREDEX study, in which 16% of patients who received Rd achieved a CR or sCR after 9 cycles of therapy.

***Interview with Ola Landgren, MD, PhD, February 9, 2015***

continued

## **Investigator Commentary: Final Efficacy and Safety Results of the Phase II Trial of CRd for Patients with High-Risk SMM (continued)**

If data from these 2 trials are then compared to data from the Phase III ASPIRE trial (Stewart AK et al. *NEJM* 2015;372(2):142), showing the depth of response for patients with relapsed MM and how the results differ for 2- versus 3-drug regimens using the same drug combinations (Rd versus CRd) and showing PFS and OS benefits, the comparison becomes even more fascinating. If the same rule applied to the setting of high-risk SMM, that would be a huge readout, but this is a small study and we do not yet have the long-term follow-up results. At this time I don't treat high-risk SMM outside of a protocol setting. I try to open several new trials and offer patients careful monitoring. If such data continue to emerge, we may start offering therapy outside the trial setting.

***Interview with Ola Landgren, MD, PhD, February 9, 2015***

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