

Nancy Simonian, M.D.

Chief Medical Officer, Clinical, Medical and Regulatory Affairs for Millennium



Nancy Simonian, MD

Nancy Simonian, M.D. is Chief Medical Officer, Clinical, Medical and Regulatory Affairs for Millennium. She is responsible for clinical, regulatory, pharmacovigilance and development project management. Prior to joining Millennium, Dr. Simonian was a vice president of clinical research at Biogen where she was responsible for the clinical development of AVONEX® (Interferon beta-1a) and Tysabri® (natalizumab) in multiple sclerosis and other inflammatory conditions and clinical oncology programs.

She graduated from Princeton University in 1988 and received her M.D. from the University of Pennsylvania Medical School. She completed her internship in medicine and residency and fellowship at Massachusetts General Hospital (MGH) in neurology. She is an assistant clinical professor of neurology at MGH and at Harvard Medical School and is board certified in neurology.

Oncology Business Review interviews Dr. Simonian regarding new data recently presented at the International Myeloma Workshop

OBR: *Can you provide us with some background on the current position of VELCADE in the multiple myeloma (MM) treatment algorithm? Where/when did VELCADE enter the multiple myeloma market versus where is it today?*

NS: In May 2003, VELCADE® (bortezomib) for Injection was approved by the FDA as treatment for relapsed and refractory multiple myeloma patients who had already received two or more prior therapies. This approval was based on Phase II data, making VELCADE one of the fastest developed and approved oncology products in history and the first therapy approved for MM in more than 30 years.

In 2005, Millennium received full approval by the FDA for VELCADE based on Phase III data from the APEX trial. As a result, Millennium received label expansion, including the treat-

ment of MM patients who received only one prior therapy. VELCADE as a single-agent therapy not only shows a proven survival benefit for patients in the relapsed setting, but also is the only single-agent MM therapy with survival in its FDA-approved label.

After its initial approval, VELCADE quickly became the market leader in the relapsed setting and continues to be the dominant therapy. In addition, VELCADE has experienced unsolicited growth in the front-line setting even though Millennium only promotes VELCADE for its approved indication. Given the strong clinical data seen to date and ongoing registration trials, Millennium believes that VELCADE will be a leader in the front-line setting. These strong data are already influencing treatment decisions as evidenced by unsolicited growth. In December 2006,



VELCADE was the first drug approved for the treatment of patients with mantle cell lymphoma (MCL), who have received at least one prior therapy. MCL is a relatively uncommon and aggressive form of non-Hodgkin's lymphoma (NHL) for which there was previously no standard of care. VELCADE also is in development for other indications, including NHL and solid tumors, with more than 300 clinical trials ongoing and planned. VELCADE is currently approved in more than 80 countries.

OBR: *At the recent International Myeloma Workshop (IMW) on June 28th in Kos, Greece, results from four clinical studies using VELCADE-based therapies were presented. Can you give us a quick overview and tell us which study you found the most compelling?*

NS: The clinical trials featured at IMW show consistently high complete remission and survival rates in the front-line MM setting. These are among the highest ever seen in this treatment setting. A summary of the data follows:

- 1) The combination of VELCADE, melphalan and prednisone (VMP) showed a complete remission / complete response (CR) rate of 43 percent, the strongest rate ever reported for an MP regimen. At more than three years (38 months), 85 percent of patients were still alive. This is the highest three-year survival rate reported in this disease setting.
- 2) The combination of VELCADE, adriamycin and dexamethasone (VcAD or PAD) showed a CR rate of 29 percent prior to stem cell transplant (SCT), which further improved to 57 percent following SCT. At one year, 100 percent of patients were alive, and 95 percent at two years. This is the highest reported two-year survival rate in the front-line treatment setting.

3) VELCADE, DOXIL[®] (pegylated liposomal doxorubicin) and dexamethasone (VDD) showed a CR rate of 43 percent prior to SCT and 65 percent after SCT. At approximately 1.5 years, all patients were alive.

4) VELCADE, lenalidomide and dexamethasone (VRD) showed an overall response rate of 100 percent and a CR rate of 20 percent.

5) An update of the large Phase III Intergroupe Francophone du Myelome (IFM) study showed a CR rate of 20 percent with VELCADE and dexamethasone vs. 7 percent with VAD as induction therapy prior to SCT. This translated to a higher proportion of patients with \geq VGPR (75 percent vs. 46 percent) who did not require a second transplant.

A summary of these data are presented in the Table 1 (following page).

OBR: *You have to be encouraged by the results of the VELCADE, DOXIL, dexamethasone combination in newly diagnosed patients. With your collaboration with J&J and what appears to be promising results with this combination, do you plan to begin a Phase III with this combination and go for the front-line indication?*

NS: As discussed in the prior question, the data from the VELCADE, DOXIL and dexamethasone trial are indeed very strong. We will continue to study this regimen and others in trials moving forward.

These data build on the impressive results of the VELCADE-DOXIL combination in the relapsed setting, which was approved by the FDA in May 2007. The FDA recognized this therapy for having the strongest response rate and longest time to progression of greater than nine months, as evidenced in the approved label. **cont. on pg 48 >>>**

| Therapy | VELCADE, melphalan, prednisone ¹ | VELCADE, adriamycin, dexamethasone ² | VELCADE DOXIL, dexamethasone ² |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Complete response (CR) rate ³ | 43% | 29% pre-transplant 57% post-transplant ⁴ | 57% post-transplant 65% post-transplant ⁴ |
| 1-yr survival rate | 93% 91% (16 months) | 100% | 100% (16 months) |
| Longer-term survival rate | 85% 3-yr ratesurvival rate | 95% 2-yr rate | Not yet reached |
| Notes | <ul style="list-style-type: none"> • Highest CR for MP combination • Strongest recorded 3 - yr survival rate | <ul style="list-style-type: none"> • Strongest recorded 2 -yr survival rate | |

Table 1. Notes: ¹Trial conducted in elderly, non-transplant-eligible patients; ²Trial conducted in transplant eligible patients; ³Includes immunofixation positive and negative responses; ⁴Complete response further improved after transplant.

OBR: *Although it was a small study, the VELCADE-Revlimid combination had an 87 percent response rate in newly diagnosed, untreated patients. What is the significance of this study and do you have plans for expanded clinical trials of this combination in the front-line setting?*

NS: Cancer is treated by combination therapies, and we are researching a variety of combinations in the front-line setting to maximize long-term survival of patients. This study is just one of many studies that include VELCADE as the foundation therapy for combination treatments. In evaluating the novel and most active agents (VELCADE and lenalidomide-dexamethasone), we are evaluating if it is the right combination to prolong survival. We will continue investigating the potential development of this and other combinations in future trials.

OBR: *What other events can we look forward to with VELCADE? Especially with ASH coming up in December?*

NS: Millennium has been working on its own pipeline for only seven years. During this

short period of time, we have made impressive accomplishments including:

VELCADE, which represented the fastest development and approval of an oncology product in history

Seven new, novel molecules that advanced from discovery to development in only three years

- Progress in novel areas with the Company being the first to establish proof of concept with an Aurora A kinase
- Discover novel target NAE and progress a novel molecule to this target in preclinical trials
- Show biologic activity with a CCR2 antagonist
- Advance an IKK β inhibitor to clinical trials

OBR: *Overall, Millennium continues to demonstrate a high level of innovation and productivity in all its research and development activities.*

NS: For more information please visit Millennium's Web site at: www.millennium.com.