

“The Pink Sheet”

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

February 15, 2010

Volume 72 Number 7 Page 31

Market Snapshot: Multiple Myeloma Drugs Promise To Live Up To Hype

Spurred by the introduction of new and highly effective drugs that have vastly improved survival rates, the fast-moving myeloma market is becoming a very attractive sector in oncology.

Among other factors propelling the market forward full-steam ahead are compelling trial data supporting longer-term treatment, extensive off-label use of drugs, and favorable reimbursement in the U.S.

Riveting revenue growth for the leading branded drugs in the space has been turning heads. Celgene recently announced sales for its immunomodulator *Revlimid* (lenalidomide), which mostly derive from multiple myeloma, were up to \$1.7 billion in 2009, from \$1.3 billion in 2008 and \$773 million in 2007 (“The Pink Sheet” DAILY, Jan. 10, 2010). The company foresees another 25 percent increase for 2010.

Multiple myeloma, a disease affecting plasma cells in the bone marrow, is newly diagnosed in about 20,000 patients in the U.S. every year. The Multiple Myeloma Research Foundation estimates that anywhere from 15 percent to 44 percent of these patients have the “smoldering” form of the disease, meaning they are asymptomatic, and typically receive no treatment.

The vast majority of smoldering cases will progress to full-blown disease, however. Those who have symptoms and/or organ damage receive a combination of treatments, including autologous stem cell transplant, chemotherapy agents, steroids and alkylators. Eventually, the drugs stop working, and MM becomes a death sentence.

Three drugs that have become available in the last decade, however, have had a striking impact on the course of the disease: Celgene’s *Thalomid* (thalidomide) and its follow-on Revlimid, and Millennium/Takeda’s injectable proteasome inhibitor *Velcade* (bortezomib), which is marketed outside the U.S. by Johnson & Johnson.

The introduction of Thalomid for multiple myeloma in 1999 represents a treatment turning point. According to a recent, large retrospective study from the Mayo Clinic of newly diagnosed multiple myeloma patients, no change in overall survival was reported during a 24-year period from 1971 to 1994. Survival improved modestly between 1995 to 2000, but the big shift began with a statistically significant benefit in overall survival emerging from 2001 to 2006 (*Blood* 2008 111:2516-2520). According to the study, survival for newly diagnosed myeloma patients nearly doubled in the last decade to four years from 2.5 years, thanks to the use of new drugs.

MM is now looking like a disease that one day could become manageable, said Susan Kelley, Chief Medical Officer at the MMRF. In oncology, in general, patients are getting treated for longer periods of time and practitioners aim to control disease with drugs to prevent recurrence.

“What we are trying to do, in some areas more successfully than others, is convert cancer to a chronic disease,” Kelley said. “It’s only when you get some decent drugs that you can use either in combination or sequentially that have reasonable safety and toxicity profiles that you can do that.”

“Virtually everyone with myeloma will end up getting more drugs in various combinations,” Kelley said.

While the improvements in survival are highly encouraging, relapse is common and there is high demand for new treatments to build on this success, Kelley said. In other words, the success of the available drugs is opening doors for drugs in development.

Sizing Up The Multiple Myeloma Market

Velcade was approved in mid-2008 for frontline use following second-line approval in 2003.

Revlimid has been approved since 2006 for use with the corticosteroid dexamethasone in relapsed multiple myeloma patients treated with at least one therapy, but off-label use as a first-line treatment has been growing steadily and was an important contributor to total sales ("The Pink Sheet" DAILY, Jan. 28, 2010).

The value of the total market today – including new and older drugs – is somewhat hard to gauge because of the extensive use of older generics but the sales figures for the leading new drugs provide a good reference point about its worth and potential.

A course of Velcade injections costs about \$30,000. Worldwide, revenues rose from \$799 million in 2007 to \$1.14 billion in 2008 and \$1.4 billion in 2009.

Celgene's \$1.7 billion in sales for 2009 partly reflect a higher price tag relative to other treatments. The oral Revlimid costs about \$6,000 per month and with treatment duration typically lasting 10 to 11 months, a typical course amounts to from \$60,000 and \$66,000.

As Revlimid came into wider use, Thalomid revenue pretty much flattened, dropping from \$447 million in 2007 to \$437 million in 2009.

Onyx Pharmaceuticals, which is developing a follow-on to Velcade called carfilzomib, estimates the multiple myeloma market as a whole is worth \$4 billion in 2010, based on performance for the leading drugs, market research reports and internal company research. Onyx further estimates the relapsed/refractory sector of the market accounts for about \$1 billion of the total.

At the J.P. Morgan Healthcare conference in January, Onyx Pharmaceuticals President and CEO Anthony Coles explained why his company was working in multiple myeloma.

"If you wind the clock back to 2003 prior to the approval of Velcade, this was an approximately \$0.5 billion marketplace. So you can see that there is an important commercial opportunity and significant unmet need in this marketplace," Coles said.

Survey: Velcade's Market Share Is On The Rise

The rapidly evolving science leaves room for market share shifts. Based on the number of patients treated, Velcade's first-line share gains have significantly outpaced Revlimid's over the past year, according to a physician survey recently published by Bernstein Research.

"Velcade now has a 52 percent patient share and Revlimid has a 40 percent share, which compares to a year ago when the drugs' first-line shares were neck and neck at just below 40 percent," reported analyst Geoffrey Porges in a Feb. 8 note.

Velcade also has maintained a significant lead in the second-line setting, with a 56 percent share, but that reflects a six-point drop from last year. In contrast, Revlimid was eight points up in second-line treatment with a 42 percent share.

A filing for Revlimid as a first-line treatment is expected in the second half of 2010, and will be supported by a Phase III study known as MM-015.

"Obviously we don't have a label – we don't promote first-line," said Celgene President and Chief Operating Officer Robert Hugin during a first-quarter earnings call. "Clearly physicians understand the data or they wouldn't be prescribing it the way they are in first-line myeloma."

An emerging cocktail that combines Revlimid, Velcade and dexamethasone is quickly gaining ground with opinion leaders as first-line therapy for newly diagnosed myeloma patients, noted Jeffrey Wolf, at a Jan. 23 meeting held by the Leukemia and Lymphoma Society for patients on emerging therapies.

At the last ASH meeting researchers at the Dana-Farber Cancer Institute, led by Paul Richardson, released a positive update on a Phase I/II escalation study using this trio, following release of initial results in 2008 (“The Pink Sheet,” Dec. 1, 2008).

This trend could give another boost to sales.

Frontline Regimens Are Rapidly Evolving

Market growth is also subject to the rapidly evolving treatment protocol trends. More than 10 combinations of treatments are used for frontline therapy and protocols are subject to change every few months as new data are released.

“Three or four times a week I get calls from [community] doctors asking ‘What is your flavor of the week? What is the best therapy for myeloma?’” said Wolf, director of the Myeloma Institute at the UCSF Helen Diller Family Comprehensive Cancer Center.

Recent data – including studies presented at the 2009 American Society of Hematology in December – suggest that “maintenance therapy” after an initial induction frontline regimen can further improve survival. The data are so compelling that the National Comprehensive Cancer Network this month revised its myeloma clinical practice guidelines to include a recommendation for using Revlimid as a monotherapy for maintenance after induction therapy.

One thing is for sure. Increasingly, an induction or first-line therapy including either Revlimid or Velcade is becoming the standard of care, according to Anne Quinn Young, MMRF’s vice president of communications.

In mid-2009, the NCCN upgraded recommendations for induction regimens including Velcade and Revlimid. A ‘Category 1’ recommendation signifies high-level evidence and uniform NCCN consensus. Category 2A means a lower level of evidence but uniform consensus and Category 2B refers to a lower level of evidence with lower-level consensus and no major disagreements.

In patients who are eligible for transplant, the bortezomib/dexamethasone and lenalidomide/dexamethasone combinations were upgraded to Category 1 from 2B, while thalidomide/dexamethasone was downgraded to 2B from 2A.

Every patient diagnosed today will need both Velcade and Revlimid at some point, said Quinn Young. But some big questions remain about the optimal first-line regimen for those who are newly diagnosed and about optimal sequencing.

“Even with a thousand-plus abstracts from ASH, those questions are still not answered,” said Quinn Young.

MM-015 Results Raise Questions About Revlimid

One of the biggest issues in MM right now is Revlimid’s value as the core of an induction regimen. This came under question at the ASH 2009 meeting, in light of results from the MM-015 study. Good results from this study are needed to support a first-line indication and equivalent or poor results could dampen Revlimid’s growth trajectory.

The MM-015 trial compared three arms: melphalan/prednisone/Revlimid; MP alone, and MPR with subsequent Revlimid maintenance. Revlimid as a maintenance therapy following induction was clearly shown to improve progression free survival in the study. But as an induction therapy, MPR did not show much benefit over MP alone.

Deutsche Bank's Mark Schoenebaum observed in a Dec. 7 note that no clear explanation was provided for this disparity. It's possible that it reflects the immaturity of the data or perhaps the starting dose for Revlimid was too low. Many analysts who follow Celgene argued Revlimid was not at all damaged by that particular finding.

However, Millennium/Takeda counters that in today's cost-conscious, reform-minded climate and given Revlimid's high expense, payers might view the situation differently. The Revlimid-based induction regimen did not show a benefit over the "good, old MP" protocol, said Christophe Bianchi, the company's executive vice president of commercial operations. Furthermore, Bianchi argues that the fact that Revlimid showed benefit as a maintenance treatment is not very meaningful considering that it was compared to placebo.

"If you are going to charge \$6,000 a month for a drug, you had better beat a placebo," he said. Compared to other drugs, "Velcade is a bargain," he added.

Maintenance Therapy Becoming Widely Accepted

Both Millennium/Takeda and Revlimid are pursuing the maintenance market. But the IV delivery method of Velcade, not to mention the troubling neuropathy side effects, represents a disadvantage compared to Revlimid. Recently, however, researchers reported positive results for follow-up with a pared-down, more manageable regimen of four Velcade injections given every three months.

In a trial presented at ASH '09, researchers from the Spanish Myeloma Group showed that the rate of complete remissions nearly doubled from 23 percent after induction to 42 percent after Velcade-based maintenance treatment.

"Velcade is so powerful that it did a pretty good job. even though it was not given week in and week out," Bianchi said.

Meanwhile, Revlimid appears destined to catch on as a maintenance treatment. Based on data from MM-015 and other studies, the NCCN in February updated its clinical guidelines to recommend Revlimid monotherapy as a maintenance treatment. Interferon, Thalomid and steroids are also recommended for maintenance.

"Although we had expected the NCCN to ultimately make this recommendation, the change comes six to 12 months earlier than we had anticipated," wrote Deutsche Bank's Schoenebaum in a Feb. 9 note.

"We believe this high-profile guideline shift could increase physician awareness as well as motivation to use Revlimid for longer periods of time. Our checks indicate that U.S. reimbursement is already widely available for most patients."

– Emily Hayes (e.hayes@elsevier.com)

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