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Revlimid In Limbo: Market Slams Celgene, Physicians And Payers Take Wait And See Approach

Absent proof of an overall survival benefit, new data suggesting a link between longer-term use of **Celgene Corp.**'s blockbuster *Revlimid* and secondary malignancies in multiple myeloma may encourage a cautious approach to maintenance treatment, threatening a major expansion for the drug.

Presentations of results from three major randomized controlled trials for longer-term use of Revlimid (lenalidomide) in newly diagnosed patients at the 2010 American Society of Hematology meeting bore good news and bad for Celgene. Two studies – CALGB 100104 and IFM-2005 02 – examined the drug following stem cell transplant and the third – MM-015 – was done in patients who had not undergone transplant.

Revlimid is currently approved for second-line use, but is being positioned for filings in the first-line and maintenance settings and is already widely used in newly diagnosed patients.

The studies confirmed a more than doubling of progression-free survival with extended use of Revlimid (*see chart*). But in all three studies, there was a slightly higher rate of secondary malignancies, including reports of acute myeloid leukemia and myelodysplastic syndromes, or "pre-leukemia," compared to placebo. The rates of secondary malignancies in the trials ranged from 3% to 6.5%. That compares to placebo rates of 1% in two studies and 2.6% in the third.

Follow-up in the studies was relatively short, from three to five years. In response to about 10 calls and e-mails from concerned patients after the release of the data at the ASH meeting, the Multiple Myeloma Research Foundation put the figures into context on its Facebook fan page.

All of the patients in the studies presented at ASH had received the alkylating agent melphalan at some point. Based on reports in the literature, the overall lifetime risk of developing secondary cancers for patients with myeloma and other primary blood cancers is up to 17% following administration of alkylating agents like melphalan and vincristine, so the incidence of about 5% in the studies at the three-to-five-year point "is not surprising," the MMRF statement notes.

It will be important to monitor these rates over time to see if the Revlimid rates surpass the population incidence, according to the MMRF. Also, the incidence in the placebo arm of 1% to 2.6% is lower than what would be expected and needs further analysis. Patients were not actually followed after progression for severe adverse events, which could help explain the lower incidence of secondary malignancies for patients on placebo.

Asked to comment on the results, insurance company WellPoint said the finding of secondary malignancies is not that surprising, given what is known about the myeloma population and cancer treatments generally. Unfortunately, secondary malignancies are common side effects with cancer treatments, WellPoint VP-Clinical Health Policy Laurie Amirpoor commented. Revlimid is highly effective and targeted, but like any cancer drug it has toxicities,

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Furthermore, the Revlimid label actually already notes risk of cancer for patients with MDS. According to the prescribing information, in other studies there were reports of benign, malignant and unspecified neoplasms, regardless of relationship to study drug treatment, in patients with MDS. These include acute leukemia, acute myeloid leukemia, bronchoalveolar carcinoma, lung cancer, lymphoma and metastatic prostate cancer.

In WellPoint's view, the data at ASH do not provide evidence that Revlimid is associated with more secondary malignancies and Amirpoor said that there is no need to change coverage policies. If the drug were to be shown later on to increase risk for secondary malignancies, risks and benefits would need to be weighed by oncologists and their patients, she said. It's possible that the dose could be minimized to cut down on the risk.

More Data Ahead

It could be some time before the results are fully understood. During a J.P. Morgan investors' call on Dec. 7, CALGB investigator Craig Hofmeister of Ohio State University, one of the largest CALGB study sites, said there is now a need to go back and review all of the data in light of the secondary malignancy findings. It's possible that the results from the CALGB study will be significantly revised from what was presented at ASH, he said during the call. Publication in a peer-reviewed journal will be delayed by at least five months, he added.

More details about the kinds of cancers seen in the studies are also needed. For example, as Bernstein analyst Geoff Porges said in a Dec. 6 note, it's important to know how many of the malignancies are highly treatable.

"In addition, if these tumors are identified early in the maintenance period, they may be more attributable to pre-existing conditions or prior treatment than to maintenance Revlimid," he noted.

Data Cast Gloom Over Maintenance Forecasts

Nevertheless, the results pose a threat for future earnings to the hugely successful Revlimid, which is Celgene's main growth driver. Though Revlimid is approved only for relapsed patients, as the far less toxic successor to Celgene's *Thalomid* (thalidomide), it is commonly used and accepted in first-line treatment. Sales amounted to $1.7 billion in 2009, up from $1.3 billion the previous year and $773 million in 2007. Consensus estimates from analysts project sales of $2.4 billion for 2010.

The duration of first-line treatment varies and hard figures are not available. ISI Group analyst Mark Schoenebaum estimates that maintenance, or treatment until relapse, accounts for little of current sales. Duration of treatment in first-line treatment in non-transplant patients is about 13 months, which could rise to 25 months if maintenance were to take off, Schoenebaum estimated. In the post-transplant setting, Revlimid use is currently minimal.

But the ISI Group had projected that by 2015, out of Revlimid's forecast sales of $6 billion, $1 billion would come from first-line maintenance and $1 billion from post-transplant maintenance. Those are the figures put at risk by the new data presented at the ASH meeting.

Celgene's stock price took a beating in a clear indication of the market's verdict about the data, falling from $60 on Dec. 3 on the way into ASH to $55 on the day studies were presented. The decline suggests that the market had essentially cut the maintenance opportunity in half, noted Schoenebaum in a slide presentation on Dec. 6. Stock later began to creep up as some investors took advantage of the weakness in price, trading at about $57 on Dec. 9.

Most analysts saw the price reduction as an over-reaction and advised purchasing on weakness. In an interview, Bernstein's Porges said there were unfounded questions about whether the product had become a victim of its own success.

"This was a storm in a teacup, mostly generated by trigger-happy Wall Streeters, afraid of a hit to their portfolios as we approach year-end," Porges said. "It's shoot first, ask questions later."

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Celgene accentuated the positive outcomes of the trials. In press releases, there was no mention of secondary malignancies, but rather a heavy focus on the dramatic improvements in progression-free survival. The company hammered the PFS message home during an investor meeting held at the ASH conference.

As for the rates of secondary malignancies, execs noted that these were within the expected background rate for the population. Celgene also affirmed plans to file Revlimid in first-line myeloma in Europe by the end of the year, giving some analysts confidence that the cancer signal was not going to present an obstacle to approval.

During the investor meeting, the company also stressed its diversification, noting that this year it had 68 oral presentations for more than six diseases and six drugs. The company is positioning Revlimid in a range of other blood cancers and said it is exploring accelerated approval prospects for a follow-on to Revlimid called pomalidomide ("Beyond Revlimid: Celgene's 2015 Plan Targets New Business Areas," April 19, 2010, "The Pink Sheet," April 19, 2010).

Expert: Data For Harm *And* Benefit Lacking

But for clinicians the data from ASH serve as a reminder of the need for caution when it comes to maintenance treatment, in the view of Shaji Kumar, Mayo Clinic-Rochester, a member of the steering committee for the MMRF.

In an interview, Kumar first noted that results should be interpreted with caution, because the drug is highly effective and has changed the outlook for patients with multiple myeloma. The Mayo Clinic has treated patients with Revlimid for from four to five years with no reports of secondary malignancies.

"There is a long track record for this drug in newly diagnosed patients," Kumar said.

Evidence about secondary malignancies is "very weak" at this point, he said, with very small case reports in the trials, relatively short-term follow up, and further analysis pending.

Also, if the risk did turn out to be real, it's possible that the issue could be limited to use in patients who have taken Revlimid and who have also been exposed to melphalan. If that were so, Revlimid could be used with more caution in this patient population.

That being said, Kumar added that the results overall at ASH support a more conservative approach to maintenance treatment until more is known about the risks *and* benefits.

Kumar views the lack of overall survival data as the main issue to consider when it comes to advising maintenance treatment. In two of the three studies, patients were permitted to cross over from placebo, which could have confounded results. But crossover was not allowed in the third trial, and still no survival benefit was shown.

This raises the question of whether it might be more prudent to give Revlimid at relapse instead of as a maintenance treatment, in Kumar's view. That way, patients can be spared side effects, including fatigue and myelosuppression. Cost is also a factor as the treatment is expensive, at $6,000 to $7,000 per patient per month.

"We don't have long-term data to show benefit and we don't have definitive evidence that maintenance increases the risk of secondary cancers. The takeaway message is that it is too early to say anything about benefit or harm," Kumar concluded.

There are some variations in care at the Mayo Clinic, but generally maintenance treatment is advised for those at higher risk, based on genetic factors, but not for standard-risk patients. High-risk patients make up about 15% to 20% of the myeloma population.

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Those at higher risk typically live for two to three years, so options are limited and the risk of toxicity may be worthwhile, Kumar said. In contrast, those at standard risk have average survival exceeding eight years.

Opinions Vary, And Long-Term Use Is Uncharted Territory

Still, there are differences of opinion with plenty of room for interpretation of the ASH data in coming months. In an e-mailed statement, The Regence Group, an affiliation of four not-for-profit Blue Cross/Blue Shield plans, based in Portland, Ore., commented that it was "not yet ready to embrace Revlimid for maintenance therapy."

The lack of full data for studies makes it difficult to assess the value of the treatment, Regence explained. There are also concerns with using progression-free survival as an outcome measure because PFS in certain types of cancers doesn't necessarily correlate with improved overall survival.

"The early reporting of trial results for Revlimid in this use continue to drive the challenges that health plans have in discerning a true benefit that outweighs risks (i.e. secondary malignancies observed) with long-term maintenance use," according to the statement from The Regence Group.

The MMRF's Ann Quinn Young, VP of communications, notes that the field is in uncharted territory when it comes to long-term myeloma treatment. Thanks to the introduction of Thalomid, Revlimid and **Takeda/Millennium**'s *Velcade* (bortezomib), patients are living longer, and there is hope that myeloma could one day become a manageable disease instead of a death sentence ("Market Snapshot: Myeloma Drugs Promise To Live Up To Hype," "The Pink Sheet," Feb. 15, 2010).

But little is known about the potential for development of resistance and toxicity with long-term exposure. The MMRF suggests a personalized approach may be needed, taking into account a patient's risk factors, genetic and otherwise, and quality of life.

In its statement to fans on Facebook, the MMRF advised that long-term differences are not known, but that Revlimid does decrease the risk of myeloma progression compared to placebo.

"The MMRF urges patients not to make any changes to their treatment regimens without speaking to your doctor, and if you are a candidate for maintenance therapy, to discuss the options, including these emerging data on safety and effectiveness with your doctor before making any decisions."

By Emily Hayes

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