

The Rise (and Fall?) of Avastin for the Treatment of Advanced

In a 12-to-1 decision, the July recommendation made by the Oncologic Drugs Advisory Committee (ODAC) to the U.S. Food and Drug Administration (FDA) to revoke Genentech's accelerated approval indication for advanced metastatic breast cancer (MBC) with Avastin (bevacizumab) has kicked up an enormous amount of dust within industry, as well as political and advocacy groups. From death panel accusations to lofty praise for nixing the high-cost drug, every perspective has found cause to agree or disagree with the ODAC decision. The immediate ramifications are clear: if the FDA follows ODAC's recommendation, Avastin will remain on the market for colorectal and lung cancers, but its breast cancer indication will be removed, and any future prescriptions for this treatment setting will be off-label. But there is a sense from all sides that this review is about much more than a single drug.

What new picture will emerge when all the frenzied dust settles? Will this recommendation signify a new era of tightened FDA scrutiny influenced by drug cost? Are we at the edge of healthcare rationing? Or is the ODAC decision simply a solid example of the system working efficiently? ODAC's review sheds light not only on the FDA's intense and careful process, but also on the many considerations that can and can't come under its purview.

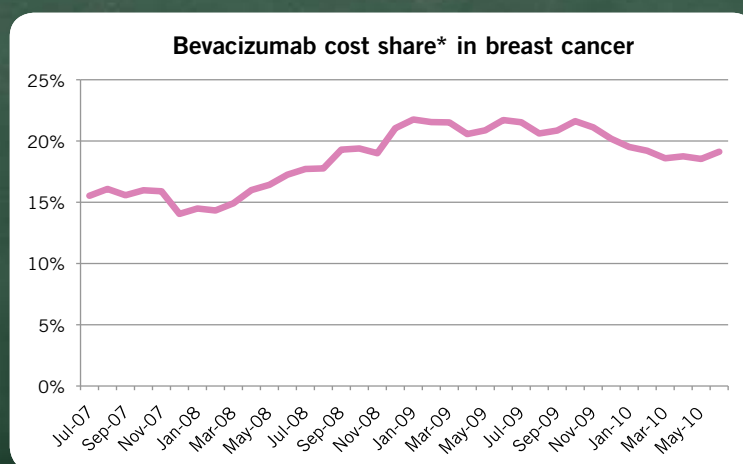
In light of Avastin's minimal benefit in the breast cancer setting, established and confirmed by the ODAC review, questions have been raised about what price tag can reasonably be attached to small increments in patient survival time. The FDA has had shots fired at it from both sides of this debate. On the one hand, critics say a drug should not be approved or dis-approved because it costs too much. On the other hand, another line of reasoning is that if a drug exists that works—or could work—patients should have access to it and pricing should not be considered when accounting for months of survival.

But for all the upset regarding ODAC's recommendation, the FDA is mandated to only examine the safety and efficacy of a product. By law, neither the agency nor its advisory panels can include cost in its considerations of new drugs, unlike its British counterpart, NICE, which declined approval of Avastin—marketed by Roche outside of the U.S. for this setting—with cost as part of the reason. (The U.K. agency also declined approval of Avastin for the treatment of colorectal, lung, and kidney cancers.)

According to Gregory Curt, MD, U.S. Medical Science Lead with AstraZeneca and a nonvoting industry representative on the ODAC panel that reviewed Avastin, ODAC based its recommendation solely on “the risks and the benefits” ratio.

What about those risks and benefits?

Approved in '04 for colorectal cancer in the U.S. and in '05 by the EMEA, Avastin is one of the largest selling drugs in the world, a position owing as much to its effectiveness in treating malignant diseases, widespread use in



*Cost share represents the total dollars spent in a given month in the care of breast cancer (all stages) as a portion of the total dollars spent on chemotherapy drugs for breast cancer. Oral and injectable chemotherapies are included in the calculation, but supportive care agents are not. Source: IntrinsiQ

Editor's Note: In spite of the volume of media coverage regarding the FDA's decision on Avastin in metastatic breast cancer, we decided it was worth adding our research especially because of the multiple perspectives presented. As of the time we went to press the FDA had not released their decision, due on or before September 17th.

Metastatic Breast Cancer

by Jessica Wapner

multiple indications, and price tag. Global sales for Avastin in '09 totaled approximately \$5.9 billion.

For its breast cancer indication, Avastin costs about \$88,000 per patient and earns an estimated \$855 million annually. According to Ed Kissel, VP Quantitative Analysis at IntrinsiQ, Avastin achieved 1% drug share in breast

cer use before ODAC's decision not to recommend its use in this setting, although we have heard from physicians about the possibility of such a move."

When it comes to the Avastin clinical data, ODAC asserted that the benefits indicated in the ECOG 2100 study—which served as the basis for the drug's approv-

Onc 101: MBC Treatment Options

- Avastin?
- Herceptin
- Xeloda
- Abraxane
- Taxotere
- Tykerb
- Taxol
- Gemzar
- ???

cancer by July '05. By October '06 Avastin use in breast cancer had achieved 6% share and was continuing to grow. In March '07, Avastin was approved in first-line MBC in the EU followed by an FDA approval in this setting in February '08. Since November '08 Avastin market share in MBC has been hovering around 9% occasionally reaching 10% (Feb-March '09, Oct-Nov '09).

Overall, IntrinsiQ data has consistently shown the uptake in bevacizumab use in breast cancer prior to approvals and ASCO events. According to Kissel, "We had not seen significant share declines in Avastin breast can-

al in breast cancer—did not bear out in two follow-up studies: AVADO and RIBBON-1. In ECOG 2100, patients treated with Avastin plus paclitaxel experienced a progression-free survival (PFS) that was a median of 5.5 months longer than that seen with patients who did not receive Avastin. However, in the follow-up AVADO study, presented at ASCO 2008, the extension in PFS was a median of 0.9 months for patients receiving Taxotere plus Avastin versus Taxotere plus placebo. While AVADO did meet its primary endpoint of improved progression-free survival, cont. on pg 14 >>

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there was no improvement in overall survival. This naturally leads to the endpoint argument over the clinical meaningfulness of PFS vs OS. Subsequently, more confirmatory data soon came out from the follow-up RIBBON-1 study.

Highlights of that trial, presented at ASCO 2009, showed that patients receiving taxane/anthracycline chemotherapy plus Avastin had a median PFS that was 1.2 months longer than those receiving chemotherapy alone, a difference that was statistically significant ($P < .0001$; hazard ratio, 0.64). In RIBBON-1's other cohort, patients treated with capecitabine plus Avastin had a median 2.9 months longer PFS compared with those treated with capecitabine alone, also statistically significant ($P < .0001$; hazard ratio, 0.69). But overall survival (OS) data were less impressive. In fact, the median OS among patients treated with Avastin plus chemotherapy was sometimes shorter than that for patients given chemotherapy alone. Neither trial showed statistically significant improvements in OS (Table 1).

Still, as Mikkael Sekeres, MD, Associate Professor of Medicine at the Cleveland Clinic Taussig Cancer Institute and a voting ODAC member, explains, "the committee would have given Avastin the green light if it had showed a quality of life benefit," but he continued, "Genentech, was not able to demonstrate an advantage in terms of so-called patient-reported outcomes."



Mikkael Sekeres, MD

the real significance of progression-free survival?" asks Sekeres.

Yet, the decision to axe a drug for this indication on the basis of population data is called into question. Considering that advanced MBC is a terminal disease, many patient advocates and clinicians argue that no potential therapeutic stone should be left unturned for these patients. It was pointed out at the ODAC meeting that some patients in the trials experienced a PFS or OS that was longer than the median. In one emotional testimony, a breast cancer patient spoke about how her treatment with Avastin had enabled her to see the birth of her grandchildren.

Sekeres, who has extensive training in epidemiology and pharmacoepidemiology, reiterated that ODAC's review of Avastin was confined solely to the data for the

In the two follow-up studies, patients experienced severe toxicities, including bleeding/hemorrhage, hypertension, and febrile neutropenia. Genentech's argument that the drug was not associated with a disadvantage in quality of life did not convince the panel. "If [a company] can't demonstrate a survival advantage and can't demonstrate a patient-reported outcome advantage, what's

Study	Treatment Regimen(s)	HR* for PFS	Difference in Median PFS	HR* for OS	Difference in Median OS
E2100	Paclitaxel +/- bevacizumab, 15 mg/kg	0.48	+5.5 mos	0.87	+1.7 mos
AVADO	Docetaxel +/- bevacizumab, 7.5 mg/kg	0.70	+0.8 mos	1.103	-1.1 mos
	Docetaxel +/- bevacizumab, 15 mg/kg	0.62	+0.9 mos	1.003	-1.7 mos
RIBBON	Taxane/Anthracycline +/- bevacizumab, 15 mg/kg	0.64	+1.2 mos	1.1 <i>1.24 (taxane subgroup)</i>	No improvement
	Capecitabine +/- bevacizumab, 15 mg/kg	0.69	+2.9 mos	0.88	+2.9 mos

Table 1. Summary of Progression Free Survival (PFS) and Overall Survival (OS); *HR=Hazard Ratio. Source: ODAC Meeting, July 20, 2010

entire study population. For any drug, he said, “[We] have to consider the benefit and safety to the public as a whole.” With the Avastin studies, he commented that, “for every one person...who had a great response, [there was] one person who suffered extreme toxicity from the [Avastin] combination.”

Persistent Cost and Insurance Concerns

The dilemma with the Avastin data illustrates the impossible task of weighing risk and benefit, and the impossibility of eliminating cost concerns from the picture. “One person out of a hundred may get a really good response, but is that enough to justify an extremely



Meryl Weinreb

expensive medication?” poses Meryl Weinreb, retired marketing executive for a major pharmaceutical company and who is also a two-time breast cancer survivor and a member of the board for the Susan G. Komen for the Cure Philadelphia Affiliate. But as Gary Owens, former Vice President of Medical Management and Policy at Independence Blue Cross, who now runs his own healthcare consulting firm, points out, there is no system in the U.S. for considering cost in new drug approval reviews. “Healthcare is a precious resource, and I don’t know that we can spend every dollar on everything. But [the U.S. is] not there yet. The FDA is still working on safety and efficacy [only].”

For the insurance companies, the waters get even murkier. Avastin is currently being used to treat many women with advanced MBC, and an FDA reversal of the drug’s indication could mean the end of that therapy (the final decision has not been made when this article went to press). Of course, the drug can still be prescribed off-label, but in these cases, insurance coverage will be tricky. Some states mandate that insurers follow official treatment guidelines, such as those issued by the National Comprehensive Cancer Network—which is also currently reviewing its recommendations for the treatment of advanced MBC. But in states without such a mandate, insurers will follow FDA approval and are likely to deny coverage for Avastin in this setting. “I think a lot of plans were reluctantly covering Avastin for breast cancer to begin with



Gary Owens

because they felt the data were somewhat sparse,” says Owens. “Now they are probably going to have a good reason to back off of that coverage.”

Additional studies of Avastin—say, with subgroups of advanced MBC patients who appear to gain the most benefit from the treatment—could provide the data necessary to garner coverage, but that will undoubtedly be a hard sell. With so few months to live, most patients will unlikely want to spend their remaining time arguing with their insurance company.

Owens and Weinreb both point out that ODAC’s review of Avastin isn’t precedent setting. As two examples, Vioxx and Mylotarg had FDA approvals that were revoked when follow-up data did not bear out the initial benefit. However, Weinreb questions the high level of expectation that the public and government regulators seem to have for new medications. “There is no such thing as a [completely] safe drug,” she says. “You have to make an informed decision that the risk of taking a drug is outweighed by the benefit. There is no one hundred percent guarantee.” In her estimation, aspirin would not be approved today if it were coming onto market, because it would be considered far too dangerous. “I understand why [the FDA] has become more conservative, but I also think that we are demanding unreasonable levels, sometimes, of perfect safety,” she concluded.

Where does all this leave us?

Whether or not the regulatory review of Avastin for the treatment of advanced MBC signals the start of a new era of heightened scrutiny, the ODAC ruling and the noise surrounding it does make one thing clear: That when it comes to drug reviews and approvals, nothing is simple. The process is one that is full of complications, where the needs of a patient population are sometimes at odds with the policies guiding the final determination. Still, nobody wants a cancer diagnosis, and as Weinreb succinctly puts it, “The FDA is between a rock and a hard place.” **JW**