

*An interview with Silvana Martino, DO, Chair of the Food and Drug Administration's Oncologic Drug Advisory Committee*

## Fulfilling a duty to cancer patients

By Cori Vanchieri

**I**t is an exciting time in cancer drug development and Dr. Silvana Martino has had a front-row seat. As chair of the Food and Drug Administration's (FDA) Oncologic Drug Advisory Committee (ODAC), she has reviewed the data on new, targeted drugs such as erlotinib (Tarceva) and weighed in on hot-button issues such as surrogate endpoints for clinical trials. ODAC reviews only those drugs that the FDA requests advice on—usually the trickier drugs, where the decision whether to approve is less than obvious.

Dr. Martino is director of the breast cancer program at The Angeles Clinic and Research Institute in Santa Monica, CA. We spoke with her as she enters the final months of her ODAC tenure, which is scheduled to end in June.

### **Community Oncology: What big challenges does ODAC face in the coming years?**

I don't think ODAC's challenges will be terribly different from those it has faced to date. The FDA is caught in a bit of a trap, and that trap is a reflection of our culture: We want everything now. We want the drugs now and we want to know quickly and completely that they'll be safe when used for a long time. All of this can't happen at once, but these are the competing needs that society presents to the FDA. It's not new and it's not likely to change.

### **Accelerated approval was devised to respond quickly to the demand**

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**for new drugs, and post-marketing studies are meant to address those long-term impact questions. But in March, the FDA reported that two-thirds of post-approval drug studies promised by manufacturers have yet to start. Why is that?**

This is the biggest thing that ODAC struggles with. When you have very little information to demonstrate effectiveness, you want more data to feel more certain about the future. This assumes that the company providing you with the initial data has the same commitment, and that it has started the process of gathering a larger body of data.

The problem is, once a drug is on the market, the drug company has achieved its major goal. It's less critical for the company than for me to prove the drug's benefit. In addition, once the drug is approved and available, it becomes difficult for a physician to randomize a patient to receive that agent or not. The physician is more uncomfortable randomizing because you've already given them a drug that supposedly works. Patients certainly are not so willing to accept a randomization when you've already said this drug works. They want to know why they might not get it. In that environment it's more difficult to gather the information that you want.

Once a drug company has approval, it becomes less likely that they will complete a study. If they have been slow getting it under way, or are just planning or thinking about it, it becomes increasingly complex and difficult for them to do.

**So it's too difficult to do the post-marketing studies?**

Personally, speaking as an individual, I would prefer more data from the very beginning. I prefer making judgments with more information than I sometimes get. And that gets to the very concept of accelerated approval. Yes, it's true that the FDA has the ability to withdraw a drug if data are not forthcoming or if toxicities are revealed, but it's not very easy to do. I would never have chosen



**Dr. Silvana Martino**

the term "accelerated approval." It implies the drug is so wonderful we don't want to deny it to any human being. There are a lot of emotions attached. I would prefer "conditional approval," during which the company gets a certain number of years to demonstrate further benefit, or the drug comes off the market.

**How do ODAC members deal with the pressure they must feel**

## **to recommend approval of drugs because they know patients await better treatments?**

The pressure to approve, even when a drug is trivial, is what I personally have difficulty with. Drugs are being put on the market when their activity appears to be so limited, and I have to wonder if we should be settling for that. Even poor drugs require a tremendous amount of work and financial commitment from a drug company and come with huge

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financial costs to patients, insurers, and society. When we’re measuring time to disease progression in days, and measuring response rate in single digits—that bothers me. We should be looking for drugs that are more active, in all fields of medicine.

## **So what is needed to provide better, more active drugs?**

I actually think the future is very rich and very promising. As we understand the biology of cancer better, we will know better how to affect a cancer cell in specific ways and cause fewer toxicities. Herceptin [trastuzumab] for breast cancer falls into that category. It’s a very specific drug with a specific target. The future of medicine and the future of oncology will be based on understanding the behavior and needs of the cancer cell. Very different therapies will be our future—not more of the same. Hopefully, we’re not going to continue to be faced with chemotherapies that have a broad-based killing mechanism.

**The newer, targeted drugs have high price tags. Does it make sense to you that the FDA instructs ODAC members not to consider cost when reviewing a drug?**

Yes, it does, though I have struggled with this question myself. I think our duty is to ask what is best for the patient. If we keep that question in mind, then we should be judging the value of the drug based on its efficacy and toxicity, and not get emotionally or intellectually involved with, “So what does it cost?” Clearly, the question of cost is important. But it’s not a question for ODAC.

## **What were the most difficult reviews during your tenure?**

Many have been difficult, which is why the voting is not always unanimous. The very fact that a drug is being presented to us means the data have certain weaknesses. The drugs that are great or have no activity are not brought to ODAC; we see the “problem drugs.” Invariably, within the Committee, there are people in favor and those against, based in great part on their experience, their own ethics, and their views of their purpose on the Committee. Some believe they should put a drug out there as soon as possible and then simply allow the medical system to study the drug and decide whether it’s good, bad, or indifferent. If you take that approach, then you need much fewer data to feel a drug should be approved. Then there are people like myself, who are somewhat more conservative, who feel the only drugs to put on the market are those that have a certain reasonable level of activity. I am more stringent than some of my colleagues on the panel.

## **Is there a drug you wished you could’ve approved, but the data just weren’t there?**

This is true for every drug. You are always disappointed when the data are such that you don’t feel you can give it a yes vote. Most of us are practicing physicians and a few are statisticians and a lay member. We

are all people who have a very serious and personal interest in improving the lives of cancer patients. Most of the time, the issue is disappointment in the level of activity of a drug.

## **Your tenure on the ODAC is scheduled to end in June. What advice do you have for incoming members?**

Keep in mind what you’re there for: It’s the patients. If your mind is clear that you represent the patients—not the FDA, not the drug company, not the media—then the job is much easier to handle. It’s a tremendous amount of work and soul searching. But it is most worthwhile. You are making decisions for this country: How do we practice medicine? What drugs do we use? That’s a lot of responsibility. The FDA invites people to join ODAC, but anyone could submit their name for consideration. Community physicians who have the opportunity to serve should do so.

## **How were you selected for service on ODAC?**

I was asked to meet with members of the FDA and give a lecture, and subsequently I was invited to join ODAC.

## **Do you feel you brought a special perspective as a practicing community oncologist?**

I hope I brought something valuable to ODAC. I am a very practical and realistic person, someone not easily impressed by weak data. When presented with data on which I have to make a judgment, I have enough experience as a researcher and as a practicing oncologist to understand statistical tricks as well as what patients and their families go through.

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