THE CANCER LETTER

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Unwanted Distinction

MSKCC Bars Zaltrap From Formulary, Triggering Debate Over Drug Pricing

By Paul Goldberg

The colon cancer drug Zaltrap, jointly marketed by Sanofi and Regeneron Pharmaceuticals Inc., is getting the attention no company wants.

It has triggered a discussion about the pricing of cancer drugs. Not the cost—an issue that is explosive enough—but something far deeper: the decisions that go into setting the drug's price.

The debate was triggered by an editorial in The New York Times, in which three physicians from Memorial Sloan-Kettering Cancer Center explained why their institution decided not to include Zaltrap into its formulary.

"The reasons are simple: The drug, Zaltrap, has proved to be no better than a similar medicine we already have for advanced colorectal cancer, while its price—at $11,063 on average for a month of treatment—is more than twice as high," the MSKCC doctors wrote Oct. 14.

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Conversation with The Cancer Letter

Sanofi: Zaltrap Price Reflects Competing Drugs In Second-Line Metastatic Colon Cancer

Sanofi officials said that, criticism notwithstanding, their drug Zaltrap was priced responsibly and is consistent with other drugs used to treat second-line metastatic colorectal cancer.

Recently, officials at Memorial Sloan-Kettering Cancer Center excluded Zaltrap (ziv-aflibercept) from their formulary because it's priced twice as high as a comparable agent, Genentech's Avastin (bevacizumab), but Sanofi officials disputed this analysis.

Zaltrap's price is reasonable, if compared with the higher of two doses of Avastin, as mentioned on that drug's label, the drug company's officials said, citing industry studies.

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In Brief

Schilsky Named ASCO Chief Medical Officer

RICHARD SCHILSKY was named chief medical officer of the **American Society of Clinical Oncology**. He will take the newly created position Feb. 28, 2013.

Schilsky, chief of hematology/oncology in the Department of Medicine and deputy director of the University of Chicago Comprehensive Cancer

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Critics Say Zaltrap Priced Twice As High As Avastin For mCRC

(Continued from page 1)

In drug company parlance, the trio would be called key opinion leaders—KOLs for short—the sort of folks you don't want to trash your product, especially in the Times. They are: Peter Bach, director of the Center for Health Policy and Outcomes, Leonard Saltz, chief of the Gastrointestinal Oncology Service and chairman of the Pharmacy and Therapeutics Committee, and Robert Wittes, physician-in-chief.

In an interview with The Cancer Letter, Sanofi officials acknowledged the need to focus on the prices of cancer drugs, but contended that Zaltrap (ziv-aflibercept) was reasonably priced.

"It's an important debate, and we should be having it in terms of the total cost of therapy," said Paul Hawthorne, vice president and head of the Oncology Business Unit at Sanofi US. "But we have to have that debate in a systematic way, with all the facts on the table, and do so with a full appreciation of the value that this particular product can bring to patients."

Hawthorne and colleague Charles Hugh-Jones, vice president for medical affairs North America at Sanofi Oncology, said the drug was priced appropriately.

"It's at risk of becoming the poster child, and I think that's not necessarily justified," Hugh-Jones said. "It's got a different mechanism of action, it had a priority review [at FDA], and if you go through in in the most systematic way, you are showing that, based on its use in the marketplace, [Avastin and Zaltrap] are actually very similarly priced—or even cheaper if you base it on the [Avastin] approval dosage of the second-line setting."

A Q&A with the Sanofi officials appears on page 1.

Sanofi officials say they priced the drug based on the value it brings to the marketplace, making the traditionally repeated industry argument that drug pricing should allow the sponsor recoup investment and continue to invest. Also, they acknowledge looking at the prices of other drugs used to treat second-line metastatic colorectal cancer.

And that is precisely what led Sanofi and Regeneron to make a pricing error, critics say.

Zaltrap's main competing drug, Genentech's Avastin (bevacizumab) is approved in two doses: 5 mg/kg every two weeks or 10 mg/kg every two weeks. In most cases, the drug is used in the 5 mg/kg dose.

If you peg a competing drug to the 10 mg/kg dose, which Sanofi has done, you end up with double the price tag of Avastin.

"I think it was a mistake," Saltz said to The Cancer Letter. "To my knowledge, it's just not used [in the 10 mg/kg dose]. I've never used [Avastin] at 10, and I have one of the busier colorectal practices anywhere. We don't use it that way at Memorial Sloan-Kettering. If you look at NCCN guidelines, all of the NCCN guidelines are listed at 5."

In an interview with The Cancer Letter, Sanofi officials acknowledge that they used the 10 mg/kg dose of Avastin as a comparator, but they say that this assumption was based on outside marketing research confirmed by the company's internal studies.

"It works out that you've got about 55 percent of the market use 5 mg/kg in a second-line setting," Sanofi's Hugh-Jones said. "Forty-five percent use variants of 10 mg/kg, whether it's 10 or 15 every three weeks, but essentially it's about a 55-45 split."

Avastin's label lists the 10 mg/kg dose alongside the 5 mg/kg dose, with the larger dose being based on the Eastern Cooperative Oncology Group study, E3200, which enrolled patients who had not received Avastin in the first line, and gave them Avastin in the second line.

However, other studies found no difference between the two doses of Avastin.

"I don't know anyone who uses the 10 mg/kg dose of Avastin," agreed Richard Goldberg, the Klotz Family Chair in Cancer Research, physician-in-chief, associate director of outreach, and a professor of medicine at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard Solove Research Institute.

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TABLE 17 PREFERRED DOSE OF AVASTIN, FIRST AND SECOND LINES, METASTATIC COLON CANCER, UNITED STATES, 2011

Avastin Schedule	First-Line	Second-Line
5 mg/kg every 2 weeks	42.5%	34.6%
10 mg/kg every 2 weeks	36.8%	38.5%
7.5 mg/kg every 3 weeks	13.8%	19.5%
15 mg/kg every 3 weeks	6.9%	6.8%

Note: The data are presented as a percentage only of those mCRC patients who receive Avastin as part of first- or second-line chemotherapy.

Source: Survey of 70 physicians who treat a total of 5,418 colon cancer patients monthly, surveyed in August 2011; 63 physicians completed data for first-line, and 51 physicians completed data for second-line.
Kantar Health, 2011

This summary of Avastin utilization data guided Sanofi's pricing decisions regarding Zaltrap.

"The only justification I can think of is you can make more money with the 10 mg/kg dose, but I think that most doctors are trying to manage health care dollars effectively."

Goldberg said the drug is included in the Ohio State formulary, but will be used only in clinical trials, one of which will open next week. The trial will compare the FOLFOX regimen with FOLFOX and Zaltrap in first-line therapy.

"I would not use it outside of the clinical trial at this point, because it's more expensive and it has less of a track record," Goldberg said. "Bevaciszumab has a mild toxicity ratio, and I have lots of experience with it."

One practice that uses the 10 mg/kg dose of Avastin is Florida Cancer Specialists. After reading the Times story, William Harwin, president and managing partner at the practice that employs 130 doctors at 50 sites located mostly on the Gulf Coast, said 10 mg/kg has been the group's preferred dose of the Genentech drug.

"As best I can tell, that's the standard, short of a clinical trial," said Harwin, a general oncologist. "That was the dose used in the original clinical trials. We just don't go about in oncology arbitrarily lowering doses. We don't take Rituxan and cut it in half and hope for the best." The prospect of using the drug would be particularly compelling with the FOLFIRI regimen, especially in patients who had received Avastin with the FOLFOX regimen, he said.

Harwin said he finds it ironic that Zaltrap, a drug he describes as a niche product, has come to epitomize the problem of the high price of cancer drugs. "Nothing negative about Genentech, but they also have the most expensive drugs in the market," said Harwin.

Skeptics have a difficult time accepting the notion that 45 percent of Avastin used in second-line metastatic colorectal cancer is used in the 10 mg/kg dose.

"We looked at every data source we could find, and it is apparent that the standard in the U.S. is 5 mg/kg every two weeks in second line," said Memorial's Bach. "Not only the NCCN guidelines say this, but the second-line registry of Avastin use which covers both academic and community centers—the BRITE registry—has fewer than one percent using 10 mg/kg, and 98 percent are using some version of 5 mg/kg every two weeks.

"And the relevant comparator trial for Zaltrap is the TML trial, and that also used 5 mg/kg every two weeks or the equivalent," Bach said. "We even pulled a sample of ongoing studies off clinicaltrials.gov, and all we found were 5 mg/kg or the like when the doses were specified. So only the company that is asking for the higher price seems to have some data suggesting the higher dose of Avastin is used.

"But the really interesting thing here is not a mistake by the company over what dose of Avastin is used in routine practice, it's the outright admission that they set their price based on the price of other cancer drugs, not on some abstract notion of 'value' or 'innovation,'" Bach said. "Of course, it has been plainly obvious, if you look either at prices over time or understand how the regulatory environment enables companies to set whatever price they think the market will tolerate, that, in fact, price-setting was disassociated from value.

"I cannot remember another large pharmaceutical company deviating from the talking points that are routinely used to justify exorbitant prices so markedly," Bach said.

Sanofi may have an additional problem: few U.S. sites were used in the Zaltrap pivotal trial, which means that few U.S. physicians have had experience with the drug.

Also, since the Zaltrap clinical trial didn't raise any methodological questions and pointed to a 1.4-month survival advantage, FDA approved the drug without consulting the Oncologic Drugs Advisory Committee last August.

"Since American physicians didn't have the opportunity for wide participation in the [Zaltrap trial], we will be learning one patient at a time how best to use them after approval—absent the experience of key U.S. research leaders or ODAC's insight," Ohio State's Goldberg wrote in a guest editorial in The Cancer Letter at the time of the dug's approval (The Cancer Letter, Aug. 10). Now, it appears that this lack of experience could mean that Zaltrap hasn't developed a political constituency among oncologists.

Avastin, a VEGF inhibitor, is approved for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.

Zaltrap is approved for use in combination the FOLFIRI regimen for patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.

Zaltrap has a slightly different mechanism of action than Avastin. It consists of VEGF-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1.

However, the mechanisms of action for both drugs were defined in preclinical models, and clinical effects of inhibition of VEGF are unknown.

Though the drugs were never compared head-to-head, in cross-study comparisons it appears that both have a 1.4-month survival advantage when added to other regimens.

Sanofi's VELOUR study, which led to Zaltrap's approval in the U.S., was a multinational, randomized, double-blind trial comparing FOLFIRI in combination with either Zaltrap or placebo in patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

The Zaltrap arm had an improved median survival of 13.5 months, compared to 12.06 months for FOLFIRI and placebo, an 18 percent relative risk reduction.

On the Avastin side, the TML study, presented at the 2012 annual meeting of the American Society of Clinical Oncology, found that continuing Avastin without interruption after tumor progression improves survival by 1.4 months, compared to chemotherapy alone after progression.

The phase III trial, led by Dirk Arnold, of the University Cancer Center in Hamburg, enrolled 820 patients whose metastatic colorectal cancer progressed while on a regimen of bevacizumab and standard first-line oxaliplatin (Eloxatin) or irinotecan (Camptosar)-based chemotherapy. For second-line therapy, patients were switched to the other of the two chemotherapy regimens with randomization to take it alone or with continued bevacizumab.

Overall survival after progression improved with bevacizumab to a median of 11.2 months, compared with 9.8 on chemotherapy alone.

"The TML study showed a 1.4-month advantage to continuing bevacizumab beyond progression in a randomized study," Goldberg said. "And you can argue that five months of bevacizumab at a cost of $70,000 for a 1.4-month average increase of median survival is lots of expense for little bang. There is little sizzle here, and because there is little sizzle, I am going to use the drug with the less severe toxicity profile that I am more familiar with rather than trying to learn something new about a drug that has some daunting toxicity issues that I haven't ever used before."

The TML study used the Avastin dose of 2.5 mg/kg every week or equivalent, which is viewed as similar to 5 mg/kg every two weeks.

Initially, Saltz saw no difference between the two drugs.

As chair of Memorial's GI Oncology Service and the Pharmacy and Therapeutics Committee, he was in the process of preparing the submission documents for Zaltrap to the formulary when he learned one crucial detail: Zaltrap's price.

"Originally, on the basis of the available data, I saw it the same way that NCCN sees it," said Saltz, who is a member of the NCCN colorectal cancer guidelines committee. "Basically, what we said at NCCN is that these are similar drugs that got extremely similar results

in similar studies and we see it as acceptable to use either."

The NCCN guidelines are posted at http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. In addition to stating that the drugs are basically equivalent, the NCCN guidelines point out that there is no basis for switching a patient from FOLFIRI-Avastin to FOLFORI-Zaltrap or vice versa upon disease progression.

After learning about the price difference from Memorial's pharmacy staff, Saltz saw the problem in a different light: "I thought about it, I discussed it with a number of my colleagues, and I basically said in an email to all the doctors who treat all of these patients at Memorial, 'Here is what I have just learned about the price. Given this, I can't envision a circumstance where I would be using this drug. Can you?'

"And no one could."

Saltz and colleagues Bach and Wittes saw an opportunity to make a political point: someone needs to make certain that drugs are priced in a way that makes sense. After all, FDA doesn't consider the price and the Affordable Care Act prohibits Medicare from changing coverage based on cost comparisons.

"But if no one else will act, leading cancer centers and other research hospitals should," the MSKCC doctors wrote. "The future of our health care system, and of cancer care, depends on our using our limited resources."

It's not clear whether other hospitals are following Memorial's lead and excluding the drug from their formularies, or whether the drug would be judged as equivalent to the 10 mg/kg dose of Avastin and prescribed freely.

One major player that could help determine Zaltrap's future is US Oncology Network, a unit of McKesson Specialty Care Solutions, a national health care provider with 1,000 oncologists.

Roy Beveridge, US Oncology's chief medical officer, declined to disclose whether Zaltrap is included in the company's Level I Pathways, which guide clinical practice, stating that such information is generally not made public.

"US Oncology has always taken into consideration costs in terms of its value-based Level I Pathways," Beveridge said. "I think that discussions around costs of treatment are very valuable and very needed. And we applaud these discussions of cost, because we believe it is part of a whole dynamic around the choice of treatments for our patients."

ASCO joined the debate as well, when the professional society's president, Sandra Swain, wrote a letter to the Times.

"I feel very strongly that, as oncologists, we have an absolute responsibility to ensure that our patients receive high-quality, high-value care consistent with strong evidence of efficacy. We have to be willing to take on the issue of healthcare costs to make sure our patients are provided with the best we have to offer, while avoiding costly tests, procedures, and treatments that have marginal benefit," Swain said to The Cancer Letter.

"As a participant in the American Board of Internal Medicine Foundation's Choosing Wisely campaign, ASCO recently issued a Top Five List of common, costly procedures in oncology that are not supported by evidence and that should be questioned. According to ASCO, these test and treatment options should be very carefully considered by the physician and patient to determine if their use is appropriate in the individual case."

Sanofi officials say they are willing to take part in the debate, but ask that all the facts be considered.

"You have to look at the entire second line setting as well; you can't only look at Avastin, because, first of all, we are not interchangeable with Avastin," Hawthorne said. "We are not the same drug as Avastin; we're very different.

"You look at the drug marketplace, you look at how things are being used, and you look at the number of different agents that are available in second line, including Erbitux and Vectibix.

"You look at the value that you're bringing into the marketplace and you look to set a responsible price. Which I think is what we looked to do when we launched Zaltrap."

Would the company consider revising the price?

"I'm not going to say at this point that we are making any changes," Hawthorne said. "I think that we've got an appropriate price here that best reflects the value for Zaltrap, so I can't really comment on what we may do in the future. That would be really inappropriate for me to say at this time."

Conversation with The Cancer Letter

Sanofi Officials Say Zaltrap Price Is Reasonable and Responsible

(Continued from page 1)

The Cancer Letter's editor, Paul Goldberg, discussed the decisions that went into the pricing of Zaltrap with Paul Hawthorne, vice president and head of the Oncology Business Unit at Sanofi US, and Charles Hugh-Jones, vice president for medical affairs North America for Sanofi Oncology.

PG: *How did you set the price for Zaltrap? Was it based on a value pricing approach or based on comparable drugs, like Avastin?*

PH: I think it would be worth taking a step back here for a little bit, looking at some of the stories that have come out on Zaltrap and some of the analyses.

Let me answer your question directly: You have to look at the entire second-line setting as well; you can't only look at Avastin, because, first of all, we are not interchangeable with Avastin. We are not the same drug as Avastin. We are very different—we'll talk about that in a second.

But you look at a lot of things. You look at the current marketplace, you look at how things are being used, you look at the number of different agents that are available in second line, including Erbitux and Vectibix, you look at the value that you are bringing into the marketplace, and you look to set a responsible price, which I think is what we looked to do when we launched Zaltrap.

I think there are a couple of things that are worth noting: first, that it's an entirely different mechanism of action than Avastin. I think it's important that this product was approved under a priority review, and Charles can speak a little more to that from a medical perspective.

When you look clearly and specifically at Avastin and how it was used in its clinical trials leading to FDA approval, I think that's important, because we are looking at evidence-based here and when you look at how Avastin was used in its trials that led to its second-line indication, and how Zaltrap was used in our trials that led to a second-line indication as well, you see different doses being used.

And I think when you compare them, you are going to find that, in those trials that led to approval, we are actually less expensive than Avastin, but that's not our message. Then we went further and looked at how Avastin is used in the marketplace today.

PG: *Yes, can we look at that?*

PH: It's blended.

In the story that came out in The New York Times, it was all based on the 5 mg/kg dose—but you've got centers that use exclusively 10 mg/kg as well. So there is a blended usage out in the marketplace. When you look at the blended use and how we were used in trials leading to approval as well, you'll find that we are priced comparably to Avastin and we are in line with a lot of the second-line agents that are available for use in metastatic colorectal cancer.

CH-J: If you look at the dose for the trial with which Avastin got approval in the second-line setting, that was the E3200 study, then we are indeed cheaper than Avastin, but the reality is that in the marketplace there are several different dosages used, 5 mg/kg, 10 mg/kg, both every two weeks—then there are varying other dosages, like 7.5 every three weeks.

It works out that you've got about 55 percent of the market using 5 mg/kg in a second-line setting.

PG: *And 45 percent use other doses? Is that correct?*

CH-J: Forty-five percent use variants of 10 mg/kg, whether it's 10 or 15 every three weeks, but essentially it's about a 55-45 split between.

PG: *In the U.S.?*

CH-J: In the U.S., yes. And that's based on external market research. We've done our own internal market research but it's based on externally validated market research that we can provide you with.

PG: *I can't find a single doctor whom I know who uses 10 for colorectal cancer.*

CH-J: We are basing it on Kantar Health CancerMPact. Obviously, there's a large collection of information on cancer impact, and certainly the surveys they've done show a blend between 10 mg/kg and 5 mg/kg.

What's interesting about the Avastin label is that there is no specific dosing in the Avastin label by line of therapy.

What you see is that it's 10 mg/kg based on the FOLFOX regimen, it's 5 mg/kg based on IFL, and it doesn't give any indication as to whether that's first- or second-line setting.

What we see in the marketplace is this blended use.

PG: *So you basically disagree with the Memorial Sloan-Kettering doctors' analysis, about it being as beneficial as Avastin, and Avastin is half the price. I guess now would be a good time to ask: what would be the reason for people to use Zaltrap? I'm asking this neutrally.*

CH-J: Let me chime in from a clinical point of

view. I think that, first, it's a great drug. It's got, as Paul said, a very different mechanism of action. Ours is a fusion protein and it targets all VEGF-A isoforms as well as the VEGF-B and placental growth factor. And that's different, obviously, from bevacizumab which is a recombinant monoclonal antibody that targets just VEGF-A. We target all VEGF-A as well as VEGF-B and PlGF.

And what we've seen in the clinical trial—which was VELOUR, the pivotal trial—we saw a significant survival benefit in these particular patients. And that's important for patients who don't have options.

How many? There are 150,000 people being diagnosed with colorectal cancer every year. We know that only a small proportion get a response from existing therapies. There was an interesting synopsis from the U.K. that came out last week looking at biomarkers for Avastin, and demonstrating that one particular biomarker that discounts 50 percent of people that benefit from Avastin.

So what I'm thinking is, the takeaway message is that this really is a critical unmet need, and you need various options for patients—which is one of the reasons why the FDA approved it under their priority review process.

To quote them, it's obviously a process for patients who have an unmet need or there wasn't any existing available therapy. And that's an important point to take away from this environment with colorectal cancer.

PG: *Have any other centers that you know of excluded Zaltrap from the formularies?*

PH: It's still early as you know; institutions can still use Zaltrap while its formulary position is being reviewed.

We are expecting that in the first six months we'll begin to see some decisions on formulary status. We've already seen some acceptance of formulary positions for Zaltrap, but I think it's too early to tell at this point what the reaction in the marketplace will be.

We've seen very strong uptake from Zaltrap. We are encouraged by the physician responses on Zaltrap at this point. And we talk about the fact that Zaltrap and Avastin are not the same. They are not interchangeable. They haven't been studied in a similar way.

There is a different mechanism of action—that message comes through, especially when you start to look at the data in the VELOUR trial. You start to look at the response rates, and you look at the overall survival curves and you look at the sustainability of the response, and so we've been able to get very positive receptivity to Zaltrap at this point.

And one of the big challenges that we have is just to ensure that people understand that there are multiple doses that are being used within the marketplace today, and when we look at utilization in the marketplace we see that blend of doses and we see that the receptivity to Zaltrap has been very positive.

PG: *Do you have the numbers? Do you have any data on that, on how it's been received in the marketplace? And by the way how long has it been around?*

PH: It was launched in August—it's been around since the third week of August. And I can comment on our sales, because they're public at this point: our third quarter earnings disclosed that we have €7 million ($9.0 million) in sales as of Sept. 30, so that's about one month of sales for Zaltrap, which I think is reflective of a very positive marketplace response.

PG: *So 45 percent of medical centers use the 10 mg/kg. Are most of them non-academic or how does that work?*

PH: If you look at William Harwin's message, he responded to one of the blogs in the OBR in the last week—Bill is the president of Florida Cancer Specialists, one of the largest community practices in the U.S.—he commented that the authors of the Times piece did not account for how the doses are used in the U.S.

PG: *It's just that I don't know anybody that does use the 10 mg/kg dose, that's the problem. I called a whole bunch of people. And, of course, that's a skewed sample, because they are in academic centers. Maybe community practices use something else.*

PH: When we looked at the published data and we looked at our own internal data, they did align. We do see a blended use in the market.

PG: *Were U.S. doctors involved in the Zaltrap pivotal trial?*

CH-J: Absolutely. We had 52 centers accruing patients in the U.S. into VELOUR, and it was an interesting mixture of both academic centers—Thomas Jefferson, the University of Florida, and we had community centers as well, which I think gave us a representative sample of the type of practice in the U.S. And they accrued 138 patients to the trial.

PG: *So about 10 percent came from the U.S.?*

CH-J: About 10 percent. It was multinational, so we had centers around the world.

PG: *So whom would I call, any key opinion leaders in the U.S. who have had experience with Zaltrap and disagree with Memorial's analysis?*

CH-J: I think there are certainly key opinion leaders who have had experience with the drug. Whether

they, in the midst of their clinical practice on a day-to-day basis, would have been doing the analysis like MSK, in terms of running the numbers, I don't know.

I think there are plenty of physicians, both in the trial, and from the feedback that we are getting from physicians using it every day—to our medical teams and to our commercial teams as well—who are getting a good experience with the drug.

They are getting to understand the drug, and they are starting to see it as a useful option for patients. Certainly, there is the example of Dr. Harwin, who has had the time to run the numbers and has disagreed.

PG: *If he is saying this, and I hear Len Saltz say that using the 10 mg/kg dose was a mistake, and you are saying it was not a mistake, that it was based on data in your marketing surveys, that's fascinating.*

CH-J: You have to remember, the only data with which Avastin has a second-line approval is based on the 10 mg/kg, so everything else beyond that in a second-line setting is inference, and isn't supported by a large randomized clinical trial, which is what Zaltrap did have.

Additional data is being generated all the time, but certainly the way that we see the drug being used at the moment, there is definitely a blend in that order of magnitude, between 10 and 5. We don't have an indication of first-line, nor would we attempt to try to imply that there is. It was done in a different setting with IFL—and that was a different trial, a different patient population, and so on.

PG: *I understand most of the use in second line in the U.S. occurs, because they treat with Avastin and fail in the first line. And then they move on to Avastin in second line as well, probably some of them with the same dose; right?*

PH: At this point, for those Avastin failures are out of a lot of options as well, that's also when you look at the Zaltrap approval the priority review and the response that we're seeing in the marketplace. I think it's reflective of the need for another option for patients.

PG: *Are you seeing that people are using a first-line regimen containing Avastin; second line again containing an Avastin regimen; and then, when it fails, they go to Zaltrap? Or has there not been enough time?*

CH-J: What's interesting here is that we know that patients are failing on chemotherapy plus Avastin in the first-line setting—and I think that what's critical is that these physicians have an option to give patients a drug with a different mechanism of action that has good substantial data in the second-line setting, and gives those physicians a chance to try additional therapies with patients.

We don't know which patients respond to different therapies at the moment—it's an active area of biomarker research for us.

What we do know is, based on market research, is that 25 percent of patients go all the way through Avastin maintenance second line, but about 30 percent just get first-line and maintenance and then don't go on to get second-line Avastin.

Some patients also get first-line, no maintenance, and then second-line. And some patients just get first-line. So there is a lot of real uncertainty among physicians about the benefits of continuing with Avastin once you've already failed on it, and I think this is where Zaltrap provides a really important option for the patients.

I think the message from that is that it's not as clear cut as maybe folks are saying. Maybe at some of the academic centers, in terms of utilization in the U.S.

PG: *What is the regulatory status outside of the US and do you expect these issues to come up elsewhere?*

PH: We are not global, we are the U.S., but what we can say is that Zaltrap is currently under EMA review. We expect to get feedback in early 2013. But beyond that, we are not in a position to really comment, since this is an issue outside of our areas of responsibility.

PG: *Do you believe that this is the right price? Or that using 10 mg/kg was the thing to do in terms of either the science or the marketing issues, and is changing the U.S. price an option at this point?*

PH: I think that, yes, we believe it was the right price. We believe it's a responsible price.

When you look at our comparisons in how we've priced this product, and we go back to the fact that if you look at the evidence, and you look at the data, and you look at how the products being used in the U.S., we believe we priced this in a responsible manner.

We believe we priced this in second-line setting when looking across all the products that are used, as well as in a second-line setting. We believe that we have a responsible price, and so at this point, no, I don't believe that this price is incorrect.

We priced it in a way that was reflective of how the product is being utilized in the marketplace, in terms of how the competition is being utilized. We believe that this is a different molecule entirely, and there's no head-to-head, as we talked about, at this point.

But clearly Zaltrap works differently than

Avastin, and Charles has walked you through a little bit of that difference already. The fact that we got a priority review from FDA also speaks to the importance of this approval for Zaltrap, and to the receptivity we are seeing from the market already. I think it's also reflective of good early uptake.

One thing we haven't talked about, which may be worth looking at, is what Genentech said about how their products are used in second-line colorectal cancer treatment. If you look at the Pink Sheet—at the end of, I think, September—you see how Genentech is commenting on the use of their agents in first and second line. I think you'll see further support that there are differences in dosing; in how they see the second-line versus the first-line dose.

CH-J: I've got a copy in front of me here. The monthly wholesale acquisition cost of Avastin is $5,000 a month for first-line treatment in advanced colon cancer. And $10,000 in the second-line therapy, variable with pricing and variable with future differences in dosing. And that's from Roche.

PG: *How does this compare with the price of other drugs used in second line?*

PH: I think they are very comparable. If you look at Erbitux, for a two-week treatment cost, the [wholesale acquisition cost] is a little over $5,000. If you look at vectobix it's close to $4,400. So I think that Zaltrap is right in line with some of these second-line agents in price.

PG: *I have never seen this kind of discussion or this kind of controversy about the price of drugs. Does this surprise you?*

PH: I think the price of care in general is an important area of discussion. I think it's important to have the debate. And when we have the debate I think it's important to have all the appropriate facts and do it in a balanced way.

We can't comment on the total cost of care for oncology, but we can talk about how we are bringing innovative and novel agents to market that satisfy an unmet need, and how we are pricing those products accordingly.

Does the debate surprise me? No.

I think the way that the analysis was done was a bit one-sided, if you will—just doing the analysis on 5 mg when there's quite a lot of 10 mg use in the marketplace, as well.

CH-J: I would agree with that, and I think that the bigger concept of healthcare cost as an overall topic is a really valid one in the U.S. at the moment; one that we need to have at a national level.

But I think that an analysis of this sort—you need to work through all the evidence, which we believe we have, and in the end we have come up with a responsible pricing based on what we're seeing in the market.

PG: *You are talking about price points versus value, or are you talking about what the market would bear?*

PH: Well, I think what you also have to look at is that we are continuing to study Zaltrap. So if you look at our portfolio at large, close to 95 percent of our pipeline has biomarker work associated with it.

The indication in the approval that we have is important, but I think it's important that we continue to study Zaltrap, to better characterize where the patient can gain the best benefit from Zaltrap. The work doesn't end; the work continues. And we are committed to that.

CH-J: I think that what's exciting for Zaltrap is not just about the immediate first indication.

We know hundreds of examples of cancer drugs that have opened up in different areas, and we are looking at combinations with other anti-angiogenic products that we have in the pipeline.

We are looking at three or four other things put in combination, studying how they work together. We've got a pretty strong biomarker program at the moment, finding which patients do best.

So it's part of an ongoing process.

PG: *This could be my thick skull, but I'm not sure I understood the answer to the first question, which was how was the price set, based on the inputs that you have in the drug, how much you have invested based on how much you want to spend on studying it? Or was it just based on the comparables?*

PH: I think it's a variety of those areas. We certainly look at what usage in the marketplace looks like. What products are out there and how they're priced—certainly we have to be cognizant of that and because we want to make sure we're pricing in a certain way—but we also look at the investment that we have.

We look at the future investment that we are bringing to the product as well. We bring into consideration all of those factors when we set the price, and we try and do so in a responsible way. And we believe not only that the price we have today—but with all the patients' access to resources that we have, and assistance programs that we have—our goal is to make this product available for patients and insure

broad access. And so that's all part of our strategy in bringing a product and pricing it within a marketplace.

PG: *Is there any chance that you'll be tweaking the price now?*

PH: I'm not going to say at this point that we are making any changes. I think that we've got an appropriate price here that best reflects the value for Zaltrap, so I can't really comment on what we may do in the future. That would be really inappropriate for me to say at this time.

PG: *It's just really interesting to see a drug that's not really a huge drug become the poster child of a much larger problem.*

PH: Well, as we said earlier, it's an important debate and we should be having it in terms of the total cost of therapy.

But we have to have that debate in a systematic way with all the facts on the table and do so with a full appreciation of the value that this particular product can bring to patients. So the real challenge is, how do you make sure that you have appropriate usage for Zaltrap? You get the experience out there so that patients and doctors can ultimately have those conversations themselves, in terms of what's the best approach for patient care.

That's where we'd like to see a lot of debate happen—is have access for these products and ultimately allow physicians and patients to make the decisions.

CH-J: What's important here is that, as you say, it's at risk of becoming the poster child, and I think that's not necessarily justified. It's got a different mechanism of action, it had a priority review, and if you go through it in the most systematic way, you are showing that, based on its use in the marketplace, the drugs are actually very similarly priced—or even cheaper if you base it on the approval dosage of the second-line setting.

So I think it's important just to get that message across. While healthcare costs are a critical issue, it is something that needs be done in an appropriate way.

I think it's not necessarily the right drug to be the poster child of that, because I don't think we necessarily agree with the analysis that was done at Memorial Sloan-Kettering.

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In Brief

Richard Schilsky To Take New Job As ASCO's Chief Medical Officer

(Continued from page 1)

Center, is a former ASCO president and Fellow of the American Society of Clinical Oncology.

Schilsky specializes in drug development and treatment of gastrointestinal cancers.

The chief medical officer position was created by the board of directors to provide additional senior leadership and support to ASCO's programs, public policy and communications efforts, as well as fundraising for ASCO's Conquer Cancer Foundation. Schilsky will report to CEO Allen Lichter.

"I've been an ASCO member for 32 years and I admire the organization tremendously," said Schilsky. "It's made an enormous difference in my work and in the care of my patients and it has provided countless opportunities for my younger colleagues and trainees."

Schilsky spent most of his career at the University of Chicago. He joined the faculty in 1984, subsequently rising to professor of medicine and serving in many roles including associate dean for clinical research in the Biological Sciences Division and as the director of the university's cancer research center.

From 1995 to 2010, Schilsky served as chair of the Cancer and Leukemia Group B. He has served as a member and chair of the NCI Board of Scientific Advisors, the NCI Clinical and Translational Research Committee, and as a member and chair of the Oncologic Drugs Advisory Committee of the FDA.

Schilsky has served on the editorial boards of cancer journals, including the Journal of Clinical Oncology and most recently was an associate editor of JNCI and senior associate editor of Molecular Oncology.

Early in his career Schilsky worked in the Clinical Pharmacology Branch of the Division of Cancer Treatment at the NCI, and was an assistant professor in the Department of Internal Medicine, Division of Hematology and Oncology at the University of Missouri-Columbia School of Medicine, and was the head of the hematology/medical oncology unit at the Harry S. Truman Veterans' Administration Hospital in Columbia, Mo.

Schilsky's letter to his colleagues at the University of Chicago follows:

Dear Colleagues,

Thanks to those of you who attended my State of the Section address today. For those not able to attend, I am writing to share the news that I have informed Dr. [Everett] Vokes [chairman of the University of Chicago Department of Medicine] of my desire to step down as Section Chief in order to pursue a new opportunity. I have accepted a position as Chief Medical Officer of the American Society of Clinical Oncology to begin next year. I plan to retire from the University of Chicago faculty at the end of this year and then take a bit of time off before beginning work at ASCO at the end of February.

Dr. Vokes will inform you of his plans for leadership transition in the near future. I have been a faculty member at the University of Chicago since 1984 and have a relationship with this great institution that extends over more than 40 years, since I entered medical school here in 1971. It has been a great joy to work here and to serve the institution in many roles during my time on the faculty. And it has been my privilege to serve as your Section Chief for the last 3 years. I think we have achieved some great things together. The Section is on sound footing and poised for continued growth. This has been made possible by you and the work you do every day on behalf of our patients and in your dedication to our research and education missions. I wish each of you continued success in the years ahead.

Best regards,

Rich

JOHN DURANT, founding director of the UAB Comprehensive Cancer Center, died Oct. 28.

Following 14 years as the director of the UAB CCC, Durant was named president and CEO of the Fox Chase Cancer Center in Philadelphia, serving from 1983-1988. In 1988, he returned to UAB as senior vice-president for health affairs, and in 1995, he became the first executive vice-president for the American Society for Clinical Oncology.

Durant made a major impact on each of these organizations as well as in his work in medical oncology and the use of combination chemotherapy.

MICHELLE LE BEAU was named the new president of the **Association of American Cancer Institutes**.

Le Beau, director of the University of Chicago Comprehensive Cancer Center, took the position Nov. 1.

She succeeds William Dalton, longtime head of the Moffitt Cancer Center. Dalton stepped down in August as Moffitt's president, chief executive and center director to focus on leading the center's new Personalized Medicine Institute. Dalton will continue to serve as chief executive officer of M2Gen, Moffitt's biotechnology subsidiary.

Le Beau was elected as AACI's vice president and president-elect in October 2011.

AACI presented its Distinguished Scientist Award and its Special Recognition Award during its annual meeting with the **Cancer Center Administrators Forum** Oct. 14-16 in Chicago.

Margaret Spitz was presented the Distinguished Scientist Award. She was professor and founding chair of the Department of Epidemiology during a 27-year career at The University of Texas MD Anderson Cancer Center. She joined the Dan L. Duncan Cancer Center at Baylor College of Medicine in 2009 to provide strategic direction for its population sciences program. Following the award presentation, Spitz delivered a special keynote talk on integrative epidemiology.

AACI presented a Special Recognition Award to **Alan Rabson**, deputy director of NCI. His award honors his more than five decades as a pathologist, cancer researcher, administrator and clinical advisor, as well as his work in virology and authorship of more than 100 scientific journal articles. Rabson's son, Arnold Rabson, accepted the award on his father's behalf.

AACI's executive director, Barbara Duffy Stewart, also announced the winners of AACI's Translational Cancer Research Fellowship, representing four institutions: University of California, Los Angeles; The University of Chicago; University of Michigan and Stanford University. The one-year, $50,000 non-renewable grants are funded by Amgen, Astellas, Lilly USA, and Novartis.

Additionally, the association's Distinguished Public Service Award was presented to **Sen. Jerry Moran** (R-Kan.) and **Rep. Debbie Wasserman Schultz** (D-Fla.).

KATHY MILLER and **HARIKRISHNA NAKSHATRI** were named co-leaders of the breast cancer research program at the **Indiana University Melvin and Bren Simon Cancer Center**.

Miller is associate professor of medicine and Sheila D. Ward Scholar at the Indiana University School of Medicine. Currently, Miller is leading a

clinical trial to reduce breast cancer recurrence in women with recently diagnosed breast cancer. The nationwide study will determine if anti-angiogenic treatment, in combination with standard breast cancer drugs, will reduce recurrence of the disease, particularly among high-risk women with early-stage disease.

She received the Young Investigator Award from the Eastern Cooperative Oncology Group for scientific contributions in 2007. Miller succeeds George Sledge, who was a co-leader of the program.

Nakshatri, the Marian J. Morrison Professor in Breast Cancer Research, professor of surgery and of biochemistry and molecular biology at the university's school of medicine, was first named interim co-leader of the program in 2011. Nakshatri isolates and studies breast cancer stem cells as potential targets for treatment. His research focuses on the theory that the stem cell is within the tumor mass but most likely escapes treatment because of its enhanced ability to survive.

Nakshatri also is working to determine if the type of stem cell present in a tumor predetermines where the cancer will metastasize. Nakshatri and his colleagues also study why certain breast cancers do not respond to commonly used anti-estrogen therapies.

ELIZABETH LaBORDE was named chief development officer of the **Conquer Cancer Foundation** of the American Society of Clinical Oncology. LaBorde will oversee the foundation's fundraising operations.

Prior to joining the Conquer Cancer Foundation, she served as vice president of development for Make-A-Wish America, and senior vice president of development and chief operating officer of the Children's Memorial Foundation, the philanthropic arm of the of Ann and Robert H. Lurie Children's Hospital of Chicago.

LaBorde is a member of the Association of Fundraising Professionals, Association for Healthcare Philanthropy, Association of Advancement Professionals, and Association of Donor Relations Professionals.

SANOFI and **MASSACHUSETTS GENERAL HOSPITAL** announced a two-year agreement to collaborate on clinical and pre-clinical translational research.

The Global Oncology Division of Sanofi, based in Cambridge, Mass., will work with with **Daniel Haber**, **Keith Flaherty**, and **Jeffrey Engelman** at the MGH Cancer Center to share scientific expertise, research and development capabilities and resources to execute joint projects. The collaboration will initially involve two early development molecules, both of which are viewed as promising approaches to developing new treatments for various types of advanced tumors.

The agreement has the option to extend for a longer term at the discretion of both partners. Financial details of the collaboration were not disclosed.

CITY OF HOPE received a $1 million gift to establish the Dr. Norman & Melinda Payson Professorship in Medicine, which will support the office of the institution's chief medical officer, **Alexandra Levine**.

Norman Payson is a member of City of Hope's board of directors and chair of the City of Hope Medical Foundation board. He and his wife have supported numerous City of Hope programs through their private foundation. Payson is CEO of Apria Healthcare Group, which focuses on home health services and equipment.

In 1995, President Bill Clinton appointed Levine to the Presidential Advisory Council on HIV/AIDS; she also chaired the council's research committee. As City of Hope's chief medical officer, Levine oversees all clinical and hospital care programs, including quality, patient safety, clinical research, clinical information management and professional education.

Funding Opportunity

National Lung Cancer Partnership Offering $200k For Clinical Research

The National Lung Cancer Partnership and Uniting Against Lung Cancer announced a new funding opportunity intended to accelerate lung cancer research into clinical application. They are offering a single award of $200,000. Pre-applications are due November 12, with full applications subsequently invited.

This award is intended to support clinical translational research that will promote significant improvements over current approaches in lung cancer prevention, detection or therapy.

Applicants are expected to demonstrate an ability to produce significant progress for lung cancer patients in the near term. Applicants must present a strategic plan and timeline for clinical implementation within

five years of the two-year award period.

At the time of application, the principal investigator must hold position at or above the level of assistant professor at not-for-profit sponsoring institutions in the U.S.

A full description of the award can be found here. Letters of Intent can be submitted here. For questions, please contact Holli Kawadler, senior director of scientific programs at Uniting Against Lung Cancer.

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FDA Approvals

Synribo Receives Accelerated Approval For Adult CML Patients

FDA approved Synribo for Injection to treat adult patients with chronic or accelerated phase chronic myeloid leukemia. The indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival.

Synribo (omacetaxine mepesuccinate) received an accelerated approval based on an analysis of combined data subsets from two phase II, open-label, multicenter studies. The pooled analysis included patients who had received two or more approved tyrosine kinase inhibitors and, at a minimum, had evidence of resistance or intolerance to dasatinib and/or nilotinib.

In the studies, 47 percent of chronic phase patients and 63 percent of accelerated phase patients had failed treatment with imatinib, dasatinib, and nilotinib. The majority of patients had also received other treatments including hydroxyurea, interferon, and cytarabine.

For chronic patients, 18 percent (14/76) achieved a major cytogenetic response with a mean time to onset of 3.5 months. The median duration of response for these patients was 12.5 months.

For accelerated phase patients, 14 percent (5/35) achieved a major hematologic response with a mean time to onset of 2.3 months. The median duration of response for these patients was 4.7 months.

Most common adverse reactions in chronic and accelerated phase patients: thrombocytopenia, anemia, neutropenia, diarrhea, nausea, fatigue, asthenia, injection site reaction, pyrexia, infection, and lymphopenia

The mechanism of action of Synribo is not fully understood but includes inhibition of protein synthesis. It acts independently of direct Bcr-Abl binding to reduce protein levels of both the Bcr-Abl oncoprotein and Mcl-1 which inhibits apoptosis, in vitro. Synribo also showed activity in mouse models of wild-type and T315I mutated Bcr-Abl CML. It is the first protein synthesis inhibitor for the treatment of CML.

Synribo is sponsored by Teva Pharmaceutical Industries Ltd.