THE CANCER LETTER

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SPECIAL ISSUE

"Market Resistance"

Zaltrap Price Cut In Half Effective Immediately As Sanofi Responds to Criticism From Oncologists

By Paul Goldberg

Responding to criticism from oncologists, the French pharmaceutical company Sanofi said that it would cut in half the price of its colorectal cancer drug Zaltrap (ziv-aflibercept).

Critics said Zaltrap's price—about $11,000 a month—was more than double that of a competing therapy, Genentech's Avastin (bevacizumab), which is also used in the second-line colon cancer indication.

Sanofi's decision to re-price the drug a bit more than two months after its launch points to new forces emerging in the marketplace for oncology drugs, as cancer centers and major practices used their institutions' drug formularies and the media as a means of wielding power in the drug marketplace.

To its credit, Sanofi quickly accepted the scientific evidence—and new political reality—and contacted its critics and key opinion leaders earlier this week to let them know that the price of Zaltrap would now be aligned with that of a commonly used dose of Avastin.

In a statement, the company cited "market resistance" as the reason for the price cut.

"We know how important it is for patients who could potentially benefit from Zaltrap to have access to this treatment," the company said. "We believe that Zaltrap is priced competitively as used in real-world situations. However,

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In Brief

David Carbone to Lead New Center Of Thoracic Oncology at Ohio State

DAVID CARBONE will be developing and leading a new thoracic oncology center at **The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute**.

He comes to Ohio State from Vanderbilt University, where he was a professor of medicine and cancer biology and directed the experimental therapeutics program, and then the thoracic and head and neck cancer program, at the Vanderbilt-Ingram Cancer Center. In addition, he led the

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Zaltrap's New Price Matches Lower Dose of Avastin

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we recognize that there was some market resistance to the perceived relative price of Zaltrap in the U.S.—especially in light of low awareness of Zaltrap in the U.S. market.

"As such, we are taking immediate action across the U.S. oncology community to reduce the net cost of Zaltrap."

Though the company statement doesn't mention the magnitude of the cut, knowledgeable sources said the drug's price was being cut by 50 percent. Zaltrap is approved only in the U.S.

The anatomy of the "market resistance" to the price of Zaltrap is probably destined for textbooks, because the drug's critics have brought sunlight to the rarely examined process of setting the price of a cancer drug.

This price-moderating force is particularly important in the U.S., where the federal government is precluded from considering a drug's price at the time of the approval decision and severely limited in regulating the price in providing coverage under the Medicare program.

The arithmetic of the pricing of Zaltrap is as simple as it gets.

The drug's price was originally pegged to the 10 mg/kg every two weeks dose of Avastin. However, this dose is almost never used, top academic oncologists say. Data show that a lower dose of 5 mg/kg, which has been shown to produce equivalent results in colorectal cancer. Both doses are listed on the Avastin label,

Thus, by pegging the price of Zaltrap to the higher dose of Avastin, Sanofi ended up charging twice the going price for a similar treatment. By resetting the price to the lower, the company made its drug competitive.

The events that led to the re-pricing of Zaltrap are extraordinary both in their precipitating factors and their aftermath.

Last month, three doctors from Memorial Sloan-Kettering Cancer Center wrote an editorial for The New York Times, explaining their decision to exclude Zaltrap from the cancer center's formulary.

In the past, premier institutions didn't register public objections to pricing of cancer drugs, especially in high-profile venues like The New York Times. Of course, individual doctors have objected to pricing and overutilization of drugs, but this was different—this was MSKCC using its formulary as a weapon, and explaining the gutsy move to the public.

The American Society of Clinical Oncology chimed in with a letter to the editor of the Times, praising the cancer center for focusing attention on the cost of drugs.

Though cautiously worded, the letter left no doubt that Memorial's action represented the new mainstream in oncology.

Following up, The Cancer Letter invited the Sanofi officials to explain their rationale for setting the price.

Their explanation further demonstrated that Zaltrap's price was pegged to the dose of Avastin that was twice as high as commonly used dose (The Cancer Letter, Nov. 2). No subscription is required for downloading that issue of the newsletter.

The Cancer Letter story also demonstrated that premier experts in gastrointestinal oncology regarded Zaltrap's price as a "mistake" on the part of the sponsors, Sanofi and partner Regeneron Pharmaceuticals Inc.

At the time, Sanofi officials stood by using the 10 mg/kg dose of Avastin as a legitimate comparator.

"It works out that you've got about 55 percent of the market use 5 mg/kg in a second-line setting," said Charles Hugh-Jones, vice president for medical affairs North America for Sanofi Oncology. "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."

Another Sanofi official, Paul Hawthorne, vice president and head of the Oncology Business Unit at Sanofi US said the price reflected the drug's value, but appeared to be open to reconsideration.

"I'm not going to say at this point that we are

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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."

Correcting the Miscalculations

Whether Sanofi had miscalculated the dose, the political climate, or both, the company responded rapidly and honorably.

Earlier this week, Sanofi executives notified the Memorial doctors who had written the piece in the Times as well as doctors who had been quoted in The Cancer Letter that Zaltrap's price is being cut in half.

"US Oncology welcomes the price rollback, and since we consider cost, efficacy and toxicity to payers and patients, we will seriously reconsider the placement of this treatment on our pathways because of the cost reduction," said Roy Beveridge, chief medical officer of US Oncology Network, a unit of McKesson Specialty Care Solutions, a national health care provider with 1,000 oncologists.

Unlike MSKCC and US Oncology, Ohio State included Zaltrap in its formulary, but until the price drop, physician-in-chief Richard Goldberg said he could see no rationale for using the drug outside clinical trials.

"In my opinion, Sanofi has done the right thing for both patients and payers in adjusting their pricing strategy to reflect the prevailing use in clinical practice of the main alternative agent, bevacizumab, that oncologists currently use with chemotherapy in the setting of second line treatment of metastatic colorectal cancer," said Goldberg, the Klotz Family Chair in Cancer Research, 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.

"More patients will likely get to benefit from the agent because of Sanofi's new approach."

Peter Bach, director of the MSKCC Center for Health Policy and Outcomes and one of the authors of the Times piece, said he was uncertain how federal regulations on reimbursement would come into play now that Sanofi was dropping their sales price.

CMS reimbursement rates will only fall to the new price over many months, unless the manufacturer takes some active step with the agency.

Bach, a former senior advisor to the Centers for Medicare and Medicaid Services, said he was not even sure what the needed step would be, but they would probably involve changing the published price as well as redoing the calculation of the average sales price.

"They would have to go in to CMS and see what could be done," Bach said.

The problem is short-term. For a few months after the drug comes on the market, it is covered based on the "average wholesale price," essentially the amount set by the sponsor. The reimbursement rate at this time is based on this published price.

Meanwhile, data are collected to calculate the "average sales price," or ASP. Since there is no other case of a company cutting the price in half during this period, it's unclear how this should be handled.

If the company discounts the drug's price without adjusting the Medicare reimbursement rate, this would create a windfall for prescribing physicians. Also, the patients' copayments would continue to be calculated based on the old price.

"The problem is really complicated from a regulatory standpoint," Bach said. "I honestly don't know how to solve it. Reducing the price alone will not reduce costs to patients but create a windfall for doctors, a problem that will take several quarters to get straightened out, unless they find a way of getting Medicare and insurers to immediately match reimbursement to the new price, as would have happened had they launched at the lower price.

"Our focus was and is on the financial impact that the higher priced drug would have on our patients."

Impact of Lower Price

Zaltrap and Avastin have never been compared head-to-head.

Now, it's not clear how the price pegged to the lower dose of Avastin used in colorectal cancer (which also happens to be the lowest dose of Avastin used in oncology) would affect the plans the company may have for expanding the indication.

Studies listed in the clinicaltrials.gov database show that the sponsors are investigating Zaltrap in ovarian, lung, thyroid, renal, brain and pancreatic cancers as well as melanoma, multiple myeloma, leukemia, myelodysplastic syndrome, and non-Hodgkin's lymphoma.

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

Avastin's approved indications include first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.

Both drugs inhibit VEGF. The sponsors say that Zaltrap has a 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.

In cross-study comparisons it appears that both drugs 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 NCCN guidelines state that the drugs are basically equivalent, pointing out that there is no basis for switching a patient from FOLFIRI-Avastin to FOLFORI-Zaltrap or vice versa upon disease progression.

The guidelines are posted at http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

MD Anderson

Memo Lays Out Management Of Ronald DePinho's Conflicts

The University of Texas System released a decision memorandum that sets up the framework for managing the conflicts of interest on the part of MD Anderson President Ronald DePinho and his wife Lynda Chin, a senior scientist at the institution.

The memo accompanies a letter notifying DePinho that Kenneth Shine, the executive vice chancellor for health affairs, had granted a limited waiver that allows him to maintain ties with several commercial entities (The Cancer Letter, Oct. 26).

The document, obtained by The Cancer Letter under the Texas Public Information Act, lays out the framework for management of DePinho and Chin's conflicts.

The text of the document follows:

As you know, I recently convened The UT System Special Committee for Conflicts of Interest Review, which is composed of experts in the field at UT System's other five health institutions, to assist me in reviewing your disclosures and in formulating appropriate management and monitoring strategies related to certain financial interests held by you and your spouse, Dr. Lynda Chin.

The management of your financial interests necessarily involves the management of the financial interests of Dr. Chin since her financial interests may inure to your benefit and thus are covered by MD Anderson's conflict of interest policy.

Accordingly, this letter addresses the management of the financial interests of both of you. I will be transmitting my decisions to Dr. Chin in a separate letter.

It is critically important to the patients, to the integrity of research conducted at MD Anderson, to our clinical enterprise, and to MD Anderson's reputation that we carefully manage any potential conflicts of interest due to your financial interest and your position as President of MD Anderson.

I am also mindful of the fact that your experience and knowledge in bringing cancer therapies and drugs to the market so that more patients will ultimately benefit is an asset that is recognized by The UT System Board of Regents. An integral part of your experience and knowledge involves your relationships with several companies that began before your appointment at MDACC.

I appreciate your transparency in making those

interests known to me, and also appreciate the fact that you have terminated your financial relationships with a number of companies. For those companies in which you or Dr. Chin may have a continuing financial relationship, and after carefully considering the recommendations of the Special Committee, I have made decisions regarding the management and monitoring of those interests.

My decisions are more fully described in the document attached to this letter, but some of the major points may be summarized as follows:

• All stock and stock options held in AVEO, Karyopharm, and Meta mark as of Oct. 12, 2012, must be placed in a blind trust, and no additional stock or stock options in those companies may be acquired. More specifically, the stock and stock options held in Karyopharm as of Oct. 12, 2012, may include such assets earned for services rendered prior to Oct. 12, 2012. Such stock and stock options must be specifically outlined and itemized, including when they were earned and for what services, in your concurrent conflict of interest management plan for Karyopharm.

• Pursuant to your offer letter, you may continue to serve on the Board of Directors of AVEO and Karyopharm. Any cash compensation that you might have received from AVEO for that service must be donated to the MDACC graduate programs. You may not accept compensation of any kind for your service on the Karyopharm Board of Directors, including cash, stock, or stock options.

• Dr. Chin must resign from the Board of Directors of Metamark by or before Jan. 11, 2013.

• All stock and stock options held in Epizyme and Agios as of Oct. 12, 2012, must be placed in a blind trust, and must be divested not later than Aug. 31, 2013.

• Any service by either you or Dr. Chin on the Scientific Advisory Board of AVEO, Karyopharm, Metamark, or Agios or as a consultant, as detailed in the document attached to this letter, must be performed without compensation of any kind, including cash, stock or stock options.

• Although nonprofit organizations such the Dana Farber Cancer Institute and the Sidney Kimmel Foundation are not typically the subject of conflict of interest management procedures, in the interest of full transparency, I have outlined management and monitoring strategies that you and Dr. Chin must follow in regard to your relationships with these organizations.

• You and Dr. Chin must strictly adhere to the management strategies related to patient consent, company transactions, research, supervisory relationships, and public disclosure as more fully detailed in the document attached to this letter.

It is my expectation that the MD Anderson Conflict of Interest Office will immediately begin the process of drafting management and monitoring plans that comport with my decisions. Of course, the Institutional Review Board will have an opportunity to review any research involving an IRB Protocol, and their review will provide an additional safeguard to protect patients and research integrity. Additionally, the policy waivers granted to you that are related to AVEO, Karyopharm, and Metamark are subject to review in three years by The UT System Special Committee for Conflicts of Interest Review.

I note that a management or monitoring plan is not needed with respect to Eden because the company is not currently conducting or proposing to conduct any research at MD Anderson. Additionally, a management or monitoring plan is not needed with respect to Merck, Sanofi-Aventis, Boehringer lngelheim, Enzon, GlaxoSmithKline, and Elan because neither you nor Dr. Chin currently have any financial relationships with those companies that trigger the application of MD Anderson's conflict of interest policy. Prospective waivers are not appropriate, and thus there is no need for action with respect to those companies.

Please review the attached document carefully and let me or Barry Burgdorf know as soon as possible if you have any questions.

In Brief

Carbone to Lead New Center At Ohio State University

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Thoracic Oncology Program at Vanderbilt.

Carbone studies the molecular genetics of lung tumors, which includes understanding the specific cells and genetic markers in each patient's lung cancer and developing treatments and drugs that target specific tumor cells.

He has authored more than 200 peer-reviewed publications, book chapters and review articles and has served on several NCI grant review panels. He also serves as chairs of the Scientific Advisory Boards for the Addario Medical Research Institute; the Lung Cancer Foundation of America and Lungevity.

MURRAY KORC received the Vay Liang and Frisca Go **Award for Lifetime Achievement** from the American Pancreatic Association.

Korc, professor of medicine, biochemistry and molecular biology, and the Myles Brand Professor of Cancer Research at Indiana University Melvin and Bren Simon Cancer Center, focuses on developing strategies for early pancreatic cancer detection and improved prevention. His work centers on aberrant growth-factor signaling in pancreatic cancer and genetic mouse models of pancreatic cancer, with the goal of designing novel therapeutic strategies.

He has published more than 270 peer-reviewed manuscripts, and he is internationally recognized for his contributions to the understanding of the role of the EGF receptor and transforming growth factor-beta in pancreatic cancer, work recognized by an NIH MERIT award.

FEYRUZ RASSOOL and **STEPHEN BAYLIN** were awarded the inaugural **Laura Ziskin Prize** in translational cancer research.

Baylin is deputy director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Rassool is an associate professor of radiation oncology at the University of Maryland School of Medicine.

The one-year grant of $250,000 will be shared between the husband and wife cancer research duo, at different institutions, to collaborate on developing therapies that can reverse estrogen-targeted treatment resistance in estrogen receptor-positive breast cancer and identify strategies to block mechanisms or restore sensitivity to hormonal therapies.

Rassool's work focuses on development of drugs that will block a genetic pathway that facilitates the survival of large numbers of cancer cells. Baylin is studying the epigenetic mechanisms that cancer cells use to modify the function of normal genes and pathways in a way that contributes to the abnormal growth in cancer.

Ziskin was co-founder of Stand Up to Cancer, the initiative founded in 2008 by nine women from the entertainment industry to accelerate research. Ziskin died of metastatic breast cancer that was ER+ and had the luminal A gene expression profile usually associated with a response to estrogen-targeted therapies.

MINESH MEHTA joined the faculty of the **University of Maryland School of Medicine** and will serve as the medical director of the Maryland Proton Treatment Center, which is currently under construction.

He will also treat patients at the University of Maryland Marlene and Stewart Greenebaum Cancer Center and serve as associate director of clinical research in the Department of Radiation Oncology.

Mehta was a professor and co-director of the Radiation Oncology Residency Training Program at Northwestern University.

The Maryland Proton Treatment Center, a 110,000-square-foot facility in the University of Maryland BioPark in west Baltimore, is expected to open in 2015.

GEORGIA WIESNER joined the Vanderbilt Department of Medicine's Division of Genetic Medicine and Vanderbilt-Ingram Cancer Center as professor of medicine and director of the newly-created Clinical and Translational Hereditary Cancer Program.

Wiesner was an associate professor of genetics and medicine and medical director of the Genetic Counseling Training Program at Case Western Reserve University. She was also the medical director of the cancer genetics program and a past director of the Center for Human Genetics at University Hospitals Case Medical Center. She has served as a past president of the American Board of Medical Genetics.

Wiesner said she came to VICC because of the cancer center's existing focus on genetic medicine and the infrastructure already in place at Vanderbilt to help patients who are at risk for hereditary forms of cancer. She also plans to work with other VICC leaders to develop a research program to follow patients who don't have an identified genetic marker for cancer but still appear to have an elevated risk for disease development.

YERVOY (ipilimumab), an immunotherapy and the first medicine approved for unresectable or metastatic melanoma in more than a decade, received the **Prix Galien USA 2012 Award for Best Biotechnology Product**.

The award, which is selected by a scientific committee that includes several Nobel laureates, is considered the most prestigious prize in biopharmaceutical research and development.

"Immuno-oncology, or the science of harnessing

the immune system to fight cancer, represents a new paradigm in the treatment of cancer and this requires a willingness to think differently about the discovery, development and commercialization of these novel agents," said Elliott Sigal, executive vice president, chief scientific officer, and president of research and development at Bristol-Myers Squibb.

The mechanism of action of Yervoy's effect in patients with melanoma is indirect, possibly through T-cell-mediated anti-tumor immune responses. Yervoy is the only metastatic melanoma therapy proven in a phase III study to deliver a durable long-term survival benefit at two years for 24 percent of previously-treated patients. In the study, median overall survival was 10 months (95% CI: 8.0-13.8) for Yervoy and 6 months (95% CI: 5.5-8.7) for the gp100 control arm.

Overall, the types of adverse events attributed to Yervoy are generally mechanism-based. Yervoy can result in severe and fatal immune-related adverse reactions due to T-cell activation and proliferation. Adverse events associated with Yervoy were managed with protocol-specific guidelines, including the administration of systemic corticosteroids, dose interruption/discontinuation and/or other immunosuppressants.

Yervoy was also selected this year as a finalist for the Prix Galien prize in Germany under the category of specialized care.

THE ASSOCIATION OF COMMUNITY CANCER CENTERS has published new **Patient Advocacy and Financial Services guidelines** as part of its Cancer Program Guidelines.

These services include explaining insurance benefits and coverage eligibility to patients and their families; assessing and explaining treatment costs; and conducting financial screening of patients and families and assisting them with appropriate patient assistance and support service applications.

According to a recent survey conducted for the American Cancer Society Cancer Action Network, "Four in 10 (41 percent) of people with a cancer diagnosis have had difficulty paying for healthcare costs in the past couple of years. Half (52 percent) of people under 65 with a history of cancer have had difficulty affording medical costs, and as a result 28 percent have used up all or most of their personal savings, 27 percent have been contacted by a collection agency, and 21 percent have incurred thousands of dollars in medical debt."

The addition of guidelines on patient advocacy and financial services reflects the increasing need for these services. The guidelines cover the organization of a patient advocacy or financial assistance program, as well as the duties and responsibilities of patient advocates and financial specialists, including examination of insurance coverage and eligibility, determination of treatment-related costs for which the patient will be responsible, and screening and referral processes for support and financial assistance resources.

They can be found at http://www.accc-cancer.org/guidelines.