THE CANCER LETTER

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Drug Approval

AVEO's Tivozanib Sunk by Fundamental Flaw: Higher Overall Survival in the Control Arm

By Paul Goldberg and Matthew Bin Han Ong

As the FDA Oncologic Drugs Advisory Committee pounded on the application for the renal cancer drug tivozanib, observers of this gruesome spectacle could have been forgiven for wondering: Why is this application before the committee in the first place?

After all, the tivozanib application, which the agency threw to the committee May 2, had a flaw that even an uninitiated observer would recognize as fatal.

Survival in the experimental arm of the sole randomized trial supporting the application was *worse* than survival in the control arm.

(Continued to page 2)

Turmoil in Texas

AVEO, DePinho Joined at the Hip (Pocket)

By Paul Goldberg

In May of last year, on a television show for investors, MD Anderson Cancer Center President Ronald DePinho recommended the stock of AVEO Pharmaceuticals Inc., a company he co-founded.

Now, materials FDA released for a meeting of the Oncologic Drugs Advisory Committee earlier this week raise questions about how much DePinho knew about serious problems with the data on the pivotal trial of the drug tivozanib at the time when he offered his stock tip.

People who develop drugs know that FDA doesn't approve drugs that may shorten survival. Indeed, at a May 2 meeting, ODAC nixed tivozanib in a decisive 13:1 vote.

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In Brief

Pollock Named Director of Surgical Oncology At Ohio State Comprehensive Cancer Center

RAPHAEL POLLOCK was named professor and director of the Division of Surgical Oncology in Ohio State's Wexner Medical Center College of Medicine.

He also will serve as chief of Surgical Services of **Ohio State's Comprehensive Cancer Center–James Cancer Hospital and Solove Research Institute.**

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ODAC Votes 13:1 Against Approval Of Tivozanib, Citing Survival Data

(Continued from page 1)

The difference didn't reach statistical significance, but when it comes to toxicity—particularly survival—a negative signal kills a drug.

Yet, in a randomized open-label trial of tivozanib versus sorafenib, overall survival pointed to a detrimental effect: 28.8 months for the experimental agent, and 29.3 months for the control arm.

"This trial demonstrated a negative trend in the most important safety parameter—overall survival, with a hazard ratio of 1.25, implying a 25 percent increased risk of death on tivozanib," said FDA reviewer Jacinta Arrington. "Overall survival is the most important safety endpoint in any trial."

On the positive side, progression-free survival was improved with tivozanib (HR=0.80, p=0.04), and median progression-free survival was 11.9 months in the tivozanib and 9.1 months in the sorafenib.

Tivozanib, a tyrosine kinase inhibitor, is co-developed by AVEO Pharmaceuticals Inc. and Astellas Pharma Inc.

The sponsors said they could explain the survival deficit: subsequent treatment received by patients in the control arm made them live longer. However, the committee wasn't convinced, nixing the drug in a decisive 13:1 vote.

In addition to reaffirming the long-standing and non-controversial FDA approval standard, the vote deals a setback to Ronald DePinho, president of MD Anderson Cancer Center and co-founder of AVEO, who was involved in tivozanib's development (See related story on page 1).

Of course, FDA could have rejected the Tivozanib application quietly, without consulting ODAC, letting the entire drama play out backstage.

Companies don't have to disclose the content of refusal-to-file or not-approvable letters from the agency. This would mean that the public would never have learned about the agency's rationale for its action.

By staging a public event, FDA disarmed potential critics and reminded the oncology field that even if a drug is approved based on its ability to delay progression as a primary endpoint, the agency cares intensely about overall survival, even when it is a secondary endpoint, as was the case with tivozanib.

Do No Harm

Minutes before the ODAC's vote, Richard Pazdur, director of the agency's Office of Hematology and Oncology Products, publicly mulled over the array of regulatory and ethical considerations, which the tivozanib application forced the agency to confront.

How would you tell a patient about a therapy that may slow the disease at a cost of hastening death?

"We have discussed this application for months, and we've gone around and around and come back to the same conclusion of being confounded from a risk-benefit analysis," Pazdur said. "If I could summarize our biggest fear here—it can be summarized by the statement 'do no harm.'

"We are all aware that people want new options for the treatment of cancer. That's not only renal cell cancer, but that enthusiasm should not be just a wild enthusiasm without looking at the data.

"Our biggest issue is potential 25 percent increased risk of death. It's a very significant issue that sets a precedent as far as an oncology approval as we go forward.

"We have to take a look at why we would accept this uncertainty. This is what I have to hear from the committee: is there an overwhelming efficacy signal here that would say, 'Yes, just abandon the survival curves, we have a modest difference in progression-free survival—but almost a negative impact on overall survival, and a positive impact on progression-free survival.'

"Obviously, overall survival is a much more important clinical endpoint than progression-free survival.

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"Secondly, from a safety point of view, we see differences. We can't make a definite statement that this is a better drug. There are differences in toxicities between the TKIs and this drug we are comparing to. So we are having a very difficult time of why we should accept this potential uncertainty.

"Lastly, we can't say, 'Well, there are no other drugs for this disease.' There are multiple other drugs for this disease. So here again, to accept that risk is very tenuous for us to do.

"I am extremely disappointed in the sponsor's proposed labeling for this drug. There is no survival curve in the proposed labeling. There is no hazard ratio—there's difference in the means and the explanation in one or two sentences confounding by crossover.

"But if this drug is approved, one would have to have a very careful conversation with the patient about this potential negative impact on overall survival. And how would you do this?

"I've been playing this in my mind in several scenarios, and any logical patient that I could think of would say, 'Doc, if you are so uncertain about this most important endpoint, don't we have any other drug to use here?'

"And that's what brings me back to this whole confounding of this risk-benefit issue. We really need to hear from the committee: what would be the compelling evidence, given this uncertainty in overall survival that would warrant a favorable approval action?"

Crossing Over to the Uninterpretable

Tivozanib was studied in an open-label phase III trial where 517 patients with metastatic renal cell carcinoma were randomized to receive tivozanib or sorafenib. The study was carried out at 76 sites, most of them in Eastern Europe.

On progression, patients assigned to the sorafenib arm could receive tivozanib on a one-way crossover study.

Patients on the tivozanib arm could receive additional medications. However, second-line use of targeted therapies isn't considered the standard of care in many of the countries participating in the trial.

This crossover made the study uninterpretable, FDA said.

"This is a textbook example of why we recommend against crossover," said Lori Dodd, a statistician from the Biostatistics Research Branch of the National Institutes of Allergy and Infectious Diseases. "We don't know whether sorafenib worked well, and tivozanib didn't, or whether tivozanib worked well, or whether the survival signal is just noise.

"I would've advised strongly against crossover and if it was deemed absolutely necessary from an ethics perspective, then I would've recommended against allowing the one-way crossover.

"This saddens me, because we want to speed up the drug development process, but when a trial is poorly conducted, we get fuzzy answers. The crossover in this case was one-sided going from the sorafenib arm to the tivozanib arm, bringing up the question about the integrity of the progression-free survival result.

"It is possible that the impact of this crossover may have led to bias in the blinded independent central review for progression-free survival. And I haven't seen any data to suggest that there is bias or that there isn't bias.

"So one of the things that was discussed in the ODAC meeting in July of last year was the question about informative censoring when progressions that were assessed and determined by the site are not valued at the central review (The Cancer Letter, July 27, 2012).

"One would expect, in a crossover trial, that those undergoing crossover have additional imaging follow-up. So, we would expect that there is less informative censoring in the arm that undergoes crossover, and therefore, less bias in that arm's survival Kaplan-Meier curve, whereas in this case, in the tivozanib arm, perhaps there was more informative censoring.

"And the impact of this would be the stretch via the survival curve for the progression-free survival curve with tivozanib upwards and shift the Kaplan-Meier curve for PFS for the sorafenib via crossover down, and could potentially lead to an overestimate of the progression-free survival hazard ratio."

Dodd seemed obviously affected by testimony of patients, most of whom came to the open public hearing to urge the committee to approve the drug.

"I want to say thank you to the people who spoke during the public session. That was a very moving session and it clearly emphasized the need for high-quality data.

"And listening to all of you talk actually made me angry that we are sitting here today discussing this trial because of its severe limitations.

"It was a single trial. The crossover—which was an issue—it was unblinded, there were concerns about bias in the progression-free survival curves because of the dosing of sorafenib and the crossover.

"I wished that we were not in the gray zone here—I think if this trial had been conducted in a better way in terms of the designs, specifically, then we might not be here."

Even without a survival deficit, approval based on a single, unblinded trial requires robust, compelling data and internally consistent evidence of clinical benefit, said ODAC member Brent Logan, associate professor of biostatistics in the Division of Biostatistics at the Medical College of Wisconsin.

"What do we have here?" Logan said.

"We have modest evidence of an effect of radiologic endpoint of progression-free survival, marginally significant p-value of .04, which in the context of typical approvals, which require two studies to be significant, is not statistically convincing.

"We have potential concerns about a couple issues related to potential bias in the progression-free survival endpoint, effective dose reduction on sorafenib as well as potential informative censoring, as discussed by Dr. Dodd.

"We also have an inconsistent effect on overall survival. In general, I think as it has been alluded to in several points, we have a poor trial design for considering the impact on survival—and survival is a very important safety consideration.

"The use of crossover, in particular, the use of this one-sided crossover, makes the overall results very difficult to interpret.

"There have been a number of hypotheses that have been proposed for why there may be adverse impact, but these are all hypotheses. We just don't know which one is the source of this potential adverse impact on survival.

"So, all these things seem to indicate that the single, unblinded trial is perhaps not sufficient here."

Anatomy of a One-Way Crossover

FDA briefing documents state that the agency didn't sign off on the crossover design.

So how did the sponsors end up with a one-sided crossover?

ODAC Chair Mikkael Sekeres, associate professor of medicine at the Department of Hematologic Oncology and Blood Disorders at the Cleveland Clinic Taussig Cancer Institute, decided to get a detailed answer:

SEKERES: Can you explain to the committee your theories about how you designed your trial where only one arm was able to cross over to what you consider to be an active therapy?

BILL SLICHENMYER [AVEO chief medical officer]: At the time that the study was designed, the focus initially was on the primary endpoint of progression-free survival. A crossover was not built into the study as it was initially conceived and discussed with all authorities here, with the FDA and CHMP [Committee for Medicinal Products for Human Use].

It was only after moving ahead towards implementation of the study, talking with investigators at study sites, that they said that they really wanted the study to be designed in a way so that all of their patients could have access to tivozanib.

So it was in response to that then that we wrote a protocol for Study 902 to allow patients to receive the drug and cross over and move forward with the implementation at that time.

PAZDUR: I'm ready to follow up on that issue of crossover and the reasoning behind it, because usually in a randomized study, when you have a known effective therapy such as sorafenib, at the time of disease progression, you would cross patients over [from] the experimental arm to receive the standard therapy.

Because here you don't have proof that the experimental drug has any activity, we don't have a demonstration of the results of the trial.

So, were the investigators in equipoise when they were making that decision? I just find this whole issue that you have a one-way alignment, or a one-way crossover.

And here again, from an ethical point of view, if one was talking about crossover, one would want to ensure that patients that were on an experimental drug receive a standard of therapy, not the flip situation.

SEKERES: Yes, and that's exactly the direction I was going with this too. A majority of the patients deriving from Eastern and Central Europe, where the case is being made, actually some of your submission documents—they may not have access to the standard therapies that we do in North America or Western Europe.

And I wonder about the ethics of allowing the crossover only on one arm when frankly, people in other countries are desperate for subsequent therapy.

SLICHENMYER: I'll ask Dr. [Robert] Motzer [TIVO-1 principal investigator and an oncologist at Memorial Sloan-Kettering Cancer Center] to comment in a second, but I just want to reinforce that our focus in the design of the trial was on the primary endpoint progression-free survival, which had been the precedent for approval in RCC in the past, and that is not influenced by the crossover element, and so is relevant to the population.

Dr. Motzer, can you share your thoughts—you were involved in the thinking about the addition of the crossover. Your perspective, please.

MOTZER: At the time the study was designed,

Table 2: FDA Approvals in Renal Cell Carcinoma				
Product	Population	Comparator	PFS[1]	Overall Survival[1]
Sorafenib	1 prior therapy (cytokines)	Placebo	5.5 vs. 2.8 mo HR 0.44, p<0.01	17.8 vs. 15.2 mo HR 0.88 (95% CI; 0.74, 1.04)[2]
Sunitinib	Newly diagnosed	Ifn-α	10.8 vs. 5.1 mo HR 0.42, p<0.01	24.5 vs. 20.4 mo HR 0.82 (95% CI; 0.67, 1.00)[2]
Temsirolimus	Newly diagnosed Poor prognosis	Ifn-α	5.5 vs. 3.1 mo HR 0.66	10.9 vs. 7.3 mo HR 0.73 (95% CI; 0.58, 0.92) p=0.008
Everolimus	Prior sorafenib, sunitinib	Placebo	4.9 vs. 1.9 mo HR 0.33, p<0.01	14.8 vs. 14.4 mo HR 0.87 (95% CI; 0.65-1.15) [2, 3]
Bevacizumab + Ifn-α	Newly diagnosed	Ifn-α	10.2 vs. 5.4 mo HR 0.60, p<0.01	23 vs. 21 mo HR 0.86 (95% CI; 0.73-1.04)[2]
Pazopanib	Newly diagnosed or prior cytokine	Placebo	9.2 vs. 4.2 mo HR 0.46, p<0.001	22.9 vs. 20.5 mo HR 0.91 (95% CI: 0.71-1.16)[2]
Axitinib	Prior anti-angiogenic or cytokine	Sorafenib	6.7 vs. 4.7 mo HR 0.67, p<0.0001	20.1 vs. 19.2 mo HR 0.97 (95% CI; 0.80-1.17)[2]
Tivozanib	Newly diagnosed or prior cytokine	Sorafenib	11.9 vs. 9.1 mo HR 0.76, p=0.02	28.8 vs. 29.3 mo HR 1.25 (95% CI; 0.95-1.62)[2]

[1]HR < 1 favors the investigational drug [2]Not statistically significant [3]Cancer 2010 116:4256

How tivozanib compares with approved drugs for renal cell carcinoma. Source: FDA

there was available phase-II data, and from our standpoint, the phase-II data looked very good with regard to safety profile.

So there was a lot of enthusiasm around tivozanib from an investigator perspective.

With regard to people going on the study, we felt that, since there were multiple treatment options available at the time—pazopanib, sunitib, sorafenib—that one of the reasons the patients could choose to go a trial when there are multiple other options available, would be to have access to tivozanib.

So the investigators were somewhat concerned in an environment where there are multiple drugs that patients would not go on and stay on if they received sorafenib, if they were registered to sorafenib, that they might drop out and say that I don't really feel like going to this center, I'll go elsewhere.

So it's the dropout to sorafenib in a setting of multiple treatment options. We all felt, and continued to feel, that this is a very promising drug.

I think what we didn't anticipate was the lack of availability of other treatment options in some of the countries that accrued lots of patients. Because from the standpoint of the United States, many different treatment options were available.

SEKERES: You make good points here. You are obviously extremely well respected in this community and have helped some drugs to approval, Dr. Motzer, but I have to say, that last comment was disingenuous.

You all were aware of what drugs were and weren't approved in Eastern and Central Europe and whether or not patients would have the available options they are after.

So I think we are talking about two different points in terms of patients agreeing to go on in a study. Sure, it's great to be able to stay to somebody, 'Hey, eventually you'll get this drug that we think is really hot and active, even if you are randomized to the control arm of sorafenib.'

But what we are asking about is the ethics, when, in the submission materials, the point is made quite clearly, first of all, that other treatments are not really available in Eastern and Central Europe, and secondly, based on retrospective studies, that subsequent therapies with TKIs appear to improve survival.

So you are offering on one arm, subsequent therapies with the TKIs, and on another arm, knowingly allowing patients to get treated with just one TKI. And I guess I just don't understand what the thought was going into that.

SLICHENMYER: Maybe I can shed some additional light on that. It is true that we had awareness at the time the study began, which drugs were approved in each other the different countries.

What we didn't fully appreciate was the extent to which access was limited by lack of reimbursement by health care systems in some of these Eastern European and Central European countries.

And in retrospect, I think we at the company wish the study had a two-way crossover, but at the time, based on what we knew, the decision was to go ahead a just make tivozanib, our drug, available to all the patients. We thought that that was the right thing to do for the patients.

We did anticipate that it might have a bit of an effect on improving the overall survival outcome for the patients in the control arm. We did not anticipate that that would be a bad thing.

And I think it is also fair to say that we underestimated the benefit of the active control—we were looking back to historical precedent and the difference between a placebo control trial was done some years before in an active control study with crossover—it was a bigger impact that we had expected.

SEKERES: Well, mea culpa.

Turmoil in Texas

FDA First Expressed Concern About Survival Deficit in May 2012

(Continued from page 1)

The agency's briefing document states that it communicated its concerns about the negative survival data to the company in May 2012.

"A pre-NDA meeting was held in May 2012," the agency states in the briefing document. "Here, the FDA expressed concern about the adverse trend in overall survival in the single phase III trial and recommended that the sponsor conduct a second adequately powered randomized trial in a population comparable to that in the U.S."

The agency document didn't specify the exact date of the May 2012 meeting.

This timing is crucial because in an appearance on the CNBC program "Closing Bell with Maria Bartiromo" May 18, DePinho, who at the time served on the AVEO board of directors, extolled the virtues of the company's drug and its stock.

The company "has utilized, has exploited science-driven drug discovery, and it's about to announce, or has announced already publicly, and will present in detail at ASCO, a very effective drug that has a superior safety profile for renal cell cancer, a major unmet need," DePinho said on the television show. "So these are massive advances in our ability to really do something about a disease that has long been very refractory."

The appearance is available on the CNBC website, and a full transcript can be downloaded at http://www.cancerletter.com/categories/documents.

The Cancer Letter asked DePinho whether he knew about the negative survival trend at the time he appeared on the CNBC stock advice program. Also, DePinho was asked about his and his family's current holdings in AVEO.

"It is not appropriate, given my position, for me to comment on any decisions or activities related to commercial entities," DePinho said in an emailed statement forwarded by a spokesperson for MD Anderson. The spokesperson said that "equity interests in AVEO held by Dr. DePinho have been or will be placed in a blind trust or similar trust approved by UT System."

The question of what DePinho knew at the time he appeared on the CNBC program is relevant in part because the ODAC vote has sent the AVEO stock into a rapid meltdown, prompting suits by shareholders.

Usually, companies file formal requests for pre-NDA meetings several weeks or even months before such meetings are scheduled. Briefing documents with analysis of the data are prepared before the meetings.

At the time DePinho offered his investment advice, he and his family held 590,440 shares in AVEO, company filings show. DePinho stepped off the board shortly after the company filed the NDA for tivozanib. His wife Lynda Chin, also an AVEO co-founder, continues to serve on the company's scientific advisory board.

DePinho's current holdings in AVEO aren't publicly known.

"Since Ron is no longer on the board of directors of AVEO, and in addition, his holdings don't reach the threshold for reporting, his shares and those of his wife are no longer included in the proxy," a company spokesman said to The Cancer Letter before the ODAC meeting. Following the ODAC vote, AVEO said it wouldn't communicate with the press or the investors until the July 28 PDUFA deadline for the agency to make its decision.

At a June 2, 2012 presentation during the annual meeting of the American Society of Clinical Oncology, Robert Motzer, an attending physician on the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center and the principal investigator on the study, didn't disclose the survival data, saying that overall survival data would be reported at a later date.

The company publicly acknowledged FDA's

concern about the survival deficit in August 2012, as part of release of its quarterly results.

The press release AVEO issued at the time reads:

"Regulatory Update: The FDA has expressed concern regarding the OS trend in the TIVO-1 trial and has said that it will review these findings at the time of the NDA filing as well as during the review of the NDA. AVEO is conducting additional analyses to be included in the NDA submission that demonstrate that the OS data from TIVO-1 are consistent with improved clinical outcomes in RCC patients receiving more than one line of therapy; analyses that the company believes will directly address this issue. AVEO is continuing to work toward submitting the NDA by end of the third quarter; however, there is a chance that the additional OS analyses may cause the submission to move into the fourth quarter."

DePinho Viewed as Expert in Drug Commercialization

DePinho was anointed to lead MD Anderson in part because of his reputed expertise in commercialization of pharmaceutical compounds, and tivozanib represents the closest he has been to developing a commercial product.

DePinho didn't invent tivozanib. AVEO licensed the compound from Kiowa Hakko Kirin Pharma. Yet, over the past year, DePinho's actions and pronouncements, as well as unusual public scrutiny of his conflicts of interest made AVEO and its drug inseparable from his name.

Ability to forge connections with the industry was an important element of the sales pitch that convinced the UT System regents to hire DePinho and his wife and colleague, Chin. It appears that at least some key players in Texas also saw an opportunity to parlay DePinho's and Chin's drug development expertise into retooling of the Cancer Prevention and Research Institute of Texas, a $3 billion venture funded through tax money.

This story can be told because MD Anderson is a state institution and is subject to Texas open records law, which over the past year has made it possible to pull back the curtains of secrecy and obfuscation.

The theme of marriage of academia and industry can be traced in DePinho's correspondence with the search committee and Kenneth Shine, the UT System executive vice chancellor for health affairs.

In what amounts to an application essay, dated Feb. 28, 2011, DePinho wrote:

"I would welcome the opportunity to articulate my vision of how I would enable MD Anderson to mount a concerted effort that would enhance patient care through advanced molecular medicine, fortify its already strong programs in clinical science, including its impressive SPORE programs, establish productive relationships with biotechnology and pharmaceutical companies, enhance its basic science to improve its competitive position in securing peer-reviewed R01 and P01 support. In addition, there are a number of exciting opportunities for the development of new programs to enhance both the science and finances. Such opportunities would include the establishment of novel academic constructs to enhance drug discovery and development and translational medicine as well as forge productive revenue generating alliances with industry."

The UT System regents obviously bought into DePinho's vision of creating something of a hybrid of an academic institution and a novel pharmaceutical industry structure. DePinho's and Chin's relationship with AVEO figures specifically in the letter that offered DePinho the job that paid a $1.8 million salary during the first year. (Chin's compensation package was $813,000 at the time the offer was made.)

"Your knowledge and expertise with technology transfer and commercialization is valuable in your role as President," the UT System Vice Chancellor for Health Affairs Kenneth Shine wrote to DePinho in a letter dated June 15, 2011.

"You will continue with positions at Karyopharm and Metamark, which will involve no cash compensation and will be limited to founder shares. You will continue on the Board of Directors of AVEO from which you are likely to resign once an FDA decision is rendered on the approval of its first Phase III drug. Any cash you receive for this service will be donated to the MD Anderson Cancer Center graduate programs. Identification of your role with these companies will be part of any consent forms signed by clinical trials."

AVEO was built on the foundation of the Human Response Platform, which was developed by DePinho, Chin and Raju Kucherlapati, professor of medicine, Harvard Medical School, who remains on AVEO's board.

According to information on AVEO's website, the proprietary platform creates mouse models that inform the design and patient selection for oncology clinical trials, and ultimately lead to the development of new cancer therapies.

In Texas, DePinho's and Chin's first setback was precisely about hybridization of industry and academia.

Their effort to bypass CPRIT's acclaimed peer review and establish a $20 million incubator (of which an $18 million portion would be co-directed by Chin) prompted the resignation of CPRIT's Chief Scientific Officer Alfred Gilman, and, subsequently, disintegration of the peer review structure (The Cancer Letter, May 25, 2012).

DePinho acknowledged to The Cancer Letter that recommending the AVEO stock at his May 18, 2012, appearance on CNBC was inconsistent with his role as an employee of the state of Texas (The Cancer Letter, June 1, 2012).

His buy recommendation was unambiguous:

MARIA BARTIROMO: Are there companies out there, from an investment standpoint; for our audiences are obviously looking for money-making opportunities, trying to figure out how to capitalize on what's going on in this marriage of health care and technology and biotech. Are there companies out there that you think are most promising, and also what is going to come out of this ASCO meeting, you think?

DePINHO: Well, the companies in the biotech sector, you have to be very careful because you have to really understand which companies are driven by good management, that are driven by the kinds of scientific advances that I've mentioned, and there are a few of them out there. Historically of course Genentech was one of the prime examples of this, more recently a company…

BARTIROMO: They were the first to come out with that "targeted…"

DePINHO: Right. Targeted. So you think about Herceptin and so on, those are very important advances. And, in fact, some of the most effective drugs have come out of the idea of using science to shepherd the cancer drug development. A company that I was involved in founding—AVEO Pharmaceuticals, one of the more successful biotechs…

BARTIROMO: That's A-V-E-O…

DePINHO: That's correct… Has utilized, has exploited science-driven drug discovery, and it's about to announce, or has announced already publicly, and will present in detail at ASCO, a very effective drug that has a superior safety profile for renal cell cancer, a major unmet need. So these are massive advances in our ability to really do something about a disease that has long been very refractory.

AVEO Stock Continues to Fall

For three days preceding DePinho's appearance on CNBC, AVEO's stock price had been in a free-fall, trading at $11.28 per share just before DePinho went on camera.

The slide of per-share price, on a heavy trading volume, coincided with the announcement of top-line results from the company-sponsored clinical trial, which investors apparently interpreted as underwhelming.

However, following DePinho's appearance, the share price started to climb back up, trading at about $12.73 when the market closed on May 31, making the DePinho holdings worth about $7.5 million.

In addition to being inconsistent with his role as a state official, DePinho's stock advice turned out to be bad.

AVEO stock tanked to $8 in late July, after the company acknowledged that FDA has expressed concern regarding the overall survival trend in the company's pivotal trial, called TIVO-1. (The company said it had an explanation: the data were consistent with improved clinical outcomes in renal cell carcinoma in patients receiving more than one line of therapy.)

In months that followed, stock traded as low as $6.

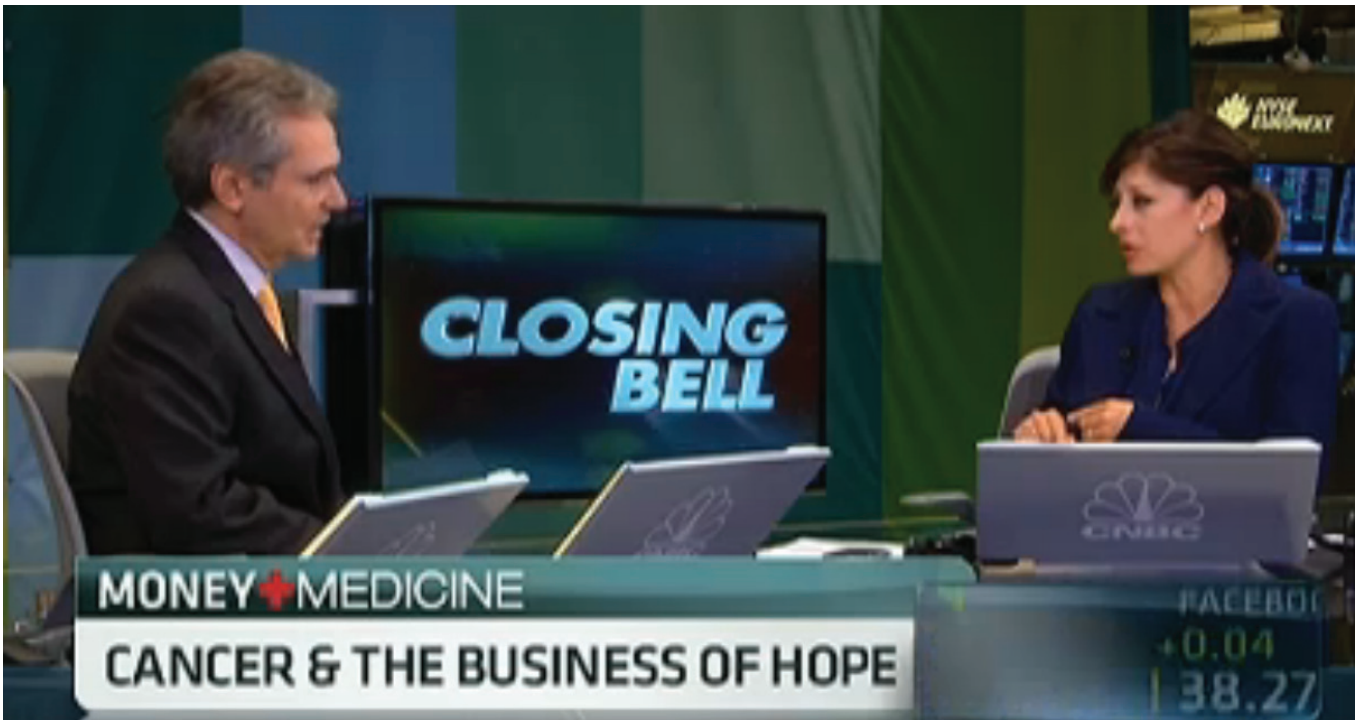
Meanwhile, AVEO continued to figure in the MD Anderson controversies.

DePinho reportedly sought a broad waiver from conflict of interest rules, which would cover 12 entities.

He received a waiver, which enabled him to stay on the AVEO board. His application and a recommendation of a six-member committee that advised Shine on the matter was requested by several news organizations, including The Cancer Letter, but was exempted from the open records law (The Cancer Letter. Oct 26, 2012).

The response, signed by Shine, refers to DePinho's special expertise in drug development being a benefit to the people of Texas:

"Among the major issues which I considered was your unique history and experience in developing new agents to help patients and to create companies



In an appearance on CNBC May 18, 2012, Ronald DePinho recommended the stock of AVEO Pharmaceuticals, which he co-founded. Now, an FDA document says it informed AVEO that month about serious problems with the application.

and procedures which would bring research results to the bedside. This is reflected in the large number of startup companies with which you have been associated as well as the other companies with whom you have worked.

"The Regents of the University of Texas believe that this experience is valuable to MDACC and to the University of Texas System. It was reflected in the employment offer letter which I sent to you, in which three of these companies were specifically identified. Maintaining some relationship with this expertise and these companies, is in my opinion warranted, provided it is combined with scrupulous attention to the issues of transparency, safety and integrity to which I have referred."

In an interview with The Cancer Letter, Shine said that Dr. DePinho can continue under this arrangement to serve on the board of AVEO, "but any money he receives from that goes to the graduate programs at MD Anderson. Which was, again, a stipulation that I made in the offer letter."

Meanwhile, DePinho's and MD Anderson's involvement with AVEO continued to generate toxic publicity in the Houston Chronicle.

Finally, last December, DePinho announced a surprising decision to step down from AVEO's board of directors, but Chin remained on the company's scientific advisory board. DePinho also resigned from the boards of Karyopharm and Metamark.

"It's been the plan all along for me," he said to The Houston Business Journal at the time. "When I became the sole finalist at MD Anderson for president I had planned to unwind my business links and I did so immediately with all of those that I could withdraw from."

DePinho said he remained on the AVEO board because the company would have been destabilized by a sudden departure.

It's not publicly known whether DePinho's resignation was indeed voluntary or whether he was urged to step down by the UT System, the MD Anderson ethics officials or the company itself.

During days immediately preceding ODAC, the value of AVEO stock continued to slide, dropping to $5.07 on April 30, the day the ODAC briefing documents were posted on the FDA website. Now, post-ODAC, the company is trading at just above around $2.50, which means that if the DePinho holdings in AVEO remained the same, they would be worth just under $1.5 million.

Investors who acted on DePinho's stock tip would have seen their holdings shrink by 80 percent.

Science Funding

Obama Pledges More Money For Research in NAS Speech

By Matthew Bin Han Ong

Addressing the National Academy of Sciences April 29, President Barack Obama said that, sequestration notwithstanding, "we can't afford to stand still for a year, or two years, or three years" in advancing science.

"We have got to seize every opportunity we have to stay ahead, and we can't let other countries win the race for ideas and technology of the future," Obama said at the academy's 150th annual meeting.

"Right now we are on the brink of amazing breakthroughs that have the chance, the potential to change life for the better, which is why we can't afford to gut these investments in science and technology," Obama said.

"Unfortunately that's what we're facing right now because of the across-the-board cuts that Congress put in place—the sequester—as it is known in Washington-speak, it's hitting our scientific research."

The White House 2014 budget proposal, released April 10, plans to reverse the sequestration cuts for NIH and NCI—and add a nearly two-percent raise on top of it (The Cancer Letter, April 12).

This would be good news for NIH, as it prepares to cut nearly $1.486 billion from its $30.7 billion budget sometime between now and the end of September. Cuts to NCI could be as high as $219 million.

The president also highlighted the $100 million initiative he proposed to Congress to map the human brain.

"What's true of all sciences is that in order to maintain our edge, we have got to protect our rigorous peer review system and ensure that we only fund proposals that promise the biggest bang for taxpayer dollars," Obama said. "I will keep working to make sure that our scientific research does not fall victim to political maneuvers or agendas that, in some ways, would impact on the integrity of the scientific process.

"That's what's going to maintain our standards of scientific excellence for years to come."

Obama, who also spoke at the 2009 NAS meeting, is the first president to address the academy twice.

The excerpted text of Obama's remarks follows:

What I want to communicate to all of you is that, as long as I'm president, we're going to continue to be committed to investing in the promising ideas that are generated from you and your institutions because they lead to innovative products, they help boost our economy, but also because that's who we are.

I'm committed to it because that's what makes us special and ultimately, what makes life worth living. And that's why we're pursuing grand challenges like making solar energy as cheap as coal, and building electric vehicles as affordable—as the ones that run on gas.

Earlier this month, I unveiled the brain initiative which will give scientists the tools that they need to get a dynamic picture of the brain in action and better understand how we think and learn and remember.

Today, all around the country, scientists like you are developing therapies to regenerate damaged organs, creating new devices to enable brain-controlled prosthetic limbs and sending sophisticated robots into space to search for signs of past life on Mars.

That sense of wonder and that sense of discovery, it has practical application but it also nurtures what I believe is best in us. And right now we're on the brink of amazing breakthroughs that have the chance, the potential to change life for the better, which is why we can't afford to gut these investments in science and technology.

Unfortunately that's what we're facing right now because of the across-the-board cuts that Congress put in place—the sequester—as it is known in Washington-speak, it's hitting our scientific research.

Instead on racing ahead on the next cutting-edge discovery, our scientists are left wondering if they'll get to start any new projects, any new research projects at all over the next few years, which means that we could lose a year, two years of scientific research, as a practical matter, because of misguided priorities here in this town.

With the pace of technological innovation today, we can't afford to stand still for a year, or two years, or three years, we have got to seize every opportunity we have to stay ahead, and we can't let other countries win the race for ideas and technology of the future.

And I say that, by the way, not out of just any nationalistic pride, although obviously, that's part of it, but it's also because nobody does it better than we do—when it's adequately funded, when it's adequately supported.

And what we produce here ends up having benefits worldwide. We should be reaching for a level of private and public research and development investment that we haven't seen since the height of the space race. That's my goal.

And it's not just resources.

One of the things that I've tried to do over these last four years and we'll continue to do over the next four years is to make sure that we are promoting the integrity of our scientific process that not just in the physical and life sciences but also in fields like psychology and anthropology and economics and political science—all of which are sciences because scholars develop and test hypotheses and subject them to peer review, but in all the sciences, we have got to make sure that we are supporting the idea that they're not subject to politics, that they are not skewed by an agenda.

That, as I said before, we make sure that we go where the evidence leads us, and that's why we have got to keep investing in these sciences.

And what's true of all sciences is that in order to maintain our edge, we have got to protect our rigorous peer review system and ensure that we only fund proposals that promise the biggest bang for taxpayer dollars.

And I will keep working to make sure that our scientific research does not fall victim to political maneuvers or agendas that, in some ways, would impact on the integrity of the scientific process. That's what's going to maintain our standards of scientific excellence for years to come.

That's why, by the way, one of the things that I have focused on as president is an all-hands-on-deck approach to the sciences as well as technology and engineering and math, and that's why we're spending a lot of time focused on the next generation.

With the help of John Holden and everybody who is working with my administration, we want to make sure that we are exciting young people around math and science and technology and computer science.

We don't want our kids just to be consumers of the amazing things that science generates—we want them to be producers as well. And we want to make sure that those who historically have not participated in the sciences as robustly—girls, members of minority groups here in this country, that they are encouraged as well.

We have got to make sure that we are training great calculus and biology teachers in encouraging students to keep up with their physics and chemistry classes—and that includes Malia and Sasha.

It means teaching proper research methods, and encouraging young people to challenge accepted knowledge. It means expanding and maintaining critical investments in biomedical research and helping innovators turn their discoveries into new businesses and products. And it means maintaining that spirit of discovery.

Last week, I got a chance to do one of my favorite things as president, and that is—we started these White House science fairs.

And these kids are remarkable. I mean, I know you guys were smart when you were their age, but I might give them the edge.

I mean, you had young people who were converting algae to sustainable biofuels—that was one of my favorites, because the young lady had—she kept her algae under her bed, she had a whole lab, which meant that she had really supportive parents. I pictured it bubbling out, down the stairs, creeping into the hallways.

You had young people who are purifying water with bicycle-power generated batteries, you had young people who had already devised faster and cheaper tests for cancer—15, 16 year olds.

They are all dreaming to grow up and be just like you. Maybe with a little less gray hair, but they share your passion. They share that excitement and what was interesting was, not only did they share that sense of wonder and discovery, but they also shared this fundamental optimism that if you figure this stuff out, people's lives would be better.

There were no inherent barriers to us solving the big problems that we face as long as we are diligent and focused and observant and curious. And we have got to make sure that we are supporting that next generation of dreamers and risk takers.

Because if we are, things will be good—they leave me with extraordinary optimism. They leave me hopeful; they put a smile on my face.

And I am absolutely convinced that if this academy and the successors who become members of this academy are there at the center and the heart of our public debate, that we will be able to continue to use the innovation that powers our economy and improves our health, protects our environment and security, that makes us the envy of the world.

So I want to thank you, on behalf of the American people, and I want to make sure that you know that you've got a strong supporter in the White House.

In Brief

Pollock Named Division Chief At Ohio State Cancer Center

(Continued from page 1)

Pollock, whose appointments are effective Sept. 1, comes to Ohio State after 31 years at MD Anderson Cancer Center, where he has held many leadership roles, most recently serving as head of the Division of Surgery.

Pollock's surgical practice and laboratory research focus on soft tissue sarcoma, and he is principal investigator for an $11.5 million Specialized Programs of Research Excellence grant from the NCI, the largest award ever to study sarcoma. He has published widely on sarcoma surgery and treatment, and his funded research includes sarcoma molecular biology and novel therapeutics.

A graduate of Oberlin College, the St. Louis University School of Medicine and the University of Texas Health Science Center at Houston, Pollock completed surgical residencies at Rush-Presbyterian-St. Luke's Medical Center and the University of Chicago Hospitals and Clinics, both in his hometown of Chicago.

As director of Surgical Oncology, Pollock will expand on the tremendous foundation built by William Farrar over the last two decades. A professor and surgical oncologist at Ohio State for the last 25 years, Farrar will continue to direct The Stefanie Spielman Comprehensive Breast Center and serve as medical director of credentialing at the OSUCCC–James.

SAUL WEINGART was appointed chief medical officer of **Tufts Medical Center**.

Weingart currently serves as vice president for quality improvement and patient safety at Dana-Farber Cancer Institute. He is also the current chair of the National Patient Safety Foundation's board of governors.

Weingart will succeed **Michael Wagner**, who was named chief executive officer of the Tufts Medical Center Physicians Organization last year, and has continued to fill the CMO role during the search for his successor.

While at Dana Farber, Weingart led a series of quality and safety initiatives. He implemented infection control enhancements, including universal influenza vaccinations for staff—improving compliance from 58 percent to 100 percent in four years.

He created and oversaw a research program focused on ambulatory medication safety, information technology and patient engagement, securing $1.7 million in grants to fund the program.

Prior to joining Dana-Farber, Weingart was director of patient safety in the Division of General Medicine and Primary Care at Beth Israel Deaconess Medical Center.

STEPHEN BONNER was named executive chairman of **Cancer Treatment Centers of America**, effective July 1, after serving as president and CEO since 1999. **Gerard van Grinsven** was named the new president and CEO.

Bonner will manage the company's financial

relationships, the charitable activities of The Gateway for Cancer Research and the operations of Cancer Nutrition Centers of America. All other corporate functions will report to van Grinsven.

For the past seven years, van Grinsven has served as president and CEO of the Henry Ford West Bloomfield Hospital in Detroit. Prior to his tenure at the Henry Ford, van Grinsven held several executive positions with the Ritz-Carlton, Peninsula, and Mandarin Oriental hotel companies.

Additionally, **GLEN WEISS** was named the director of clinical research for Cancer Treatment Centers of America, and will lead strategy and implementation of phase I and II clinical trial initiatives based out of its Western Regional Medical Center in Arizona.

Weiss served as the director of thoracic oncology and associate clinical investigator with the Virginia G. Piper Cancer Center at Scottsdale Healthcare. He is a clinical associate professor and co-head of the lung cancer unit of the Cancer and Cell Biology Division at the Translational Genomics Research Institute in Phoenix. He is also the chief medical officer of the Cancer Research and Biostatistics Clinical Trials Consortium.

WILFRIDO CASTANEDA-ZUNIGA, DAVID KUMPE and **KENNETH THOMSON** were each awarded the **Society of Interventional Radiology's Gold Medal** at the society's annual scientific meeting in New Orleans. This is the society's highest honor.

Castaneda-Zuniga, a past-president of SIR and of the Iberoamerican Society of Interventional Radiology and a member of the National Academy of Medicine in Mexico, currently serves as emeritus professor of radiology at Louisiana State University School of Medicine and professor of radiology at the University of Minnesota Medical School and the University of Texas School of Medicine at San Antonio.

Kumpe is professor of radiology, surgery, and neurosurgery at the University of Colorado. His contributions include some of the earliest descriptions of balloon angioplasty applications, numerous techniques of thrombolysis, the use of splenic embolization to control hypersplenism in children, and recently, dural sinus stenting for idiopathic intracranial hypertension.

Thomson is professor and program director of radiology and nuclear medicine at the Alford Hospital in Melbourne, Australia. He was instrumental in developing the use of carbon dioxide as an alternative contrast agent for angiography, studying percutaneous venous valves in humans, investigating irreversible electroporation for liver tumors and introducing endograft technology for aortic pathology.

THE MAYO CLINIC and **GenomeDx Biosciences** expanded an existing research agreement to license Mayo intellectual property.

The agreement also includes continued access to the clinical data concerning the clinic's cohort of prostate cancer samples to allow for longer-term follow up and evaluation of biomarkers.

The initial collaboration entered in 2009 led to the development of Decipher, a genomic test that forecasts risk of metastasis in men with prostate cancer.

In addition, GenomeDx announced five studies evaluating the ability of Decipher to predict metastatic prostate cancer will be featured at the annual meeting of the American Urological Association May 4-8.

MD ANDERSON CANCER CENTER signed an agreement with **Gene By Gene Ltd**. of Houston, taking it on as one of its affiliated clinical laboratories.

Under the agreement, scientists at Gene By Gene's Genomic Research Center will provide the clinical phase instruction, training and supervision required for students in the Molecular Genetic Technology Program, one of the undergraduate programs offered through MD Anderson's School of Health Professions.

ROBERT MILLER was appointed editor-in-chief of the **American Society of Clinical Oncology** patient information website, www.cancer.net. He will begin June 1, at the 2013 ASCO annual meeting.

Miller is an assistant professor of oncology at the Johns Hopkins University School of Medicine, and clinical associate of the Breast Cancer Program and Oncology Medical Information Officer at the Sidney Kimmel Comprehensive Cancer Center.

He will succeed Diane Blum, CEO of the Lymphoma Research Foundation. She has served as editor-in-chief for 10 years.

He has been an active ASCO member and volunteer since 1992. He currently serves on the Health Information Technology Workgroup, the Cancer Education Committee, and the editorial boards of Cancer.Net and the Journal of Oncology Practice. Previously, he was a member of the ASCO board of directors.