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The Avastin Showdown:

Genentech: ODAC Lacks Expertise, Impartiality; FDA: Company's Proposal Unscientific

By Paul Goldberg

The battle over Avastin escalated last week as Genentech asserted that members of the FDA Oncologic Drugs Advisory Committee lacked qualifications and open-mindedness to evaluate the anti-angiogenesis agent.

"The ODAC panelists' lack of insight into Avastin's role in real-world clinical practice, and its apparent unwillingness to take into account the views of metastatic breast cancer patients and breast oncologists, limit the utility of the conclusions reached by the panel," the company said in a filing dated Aug. 4.

ODAC's stance on Avastin (bevacizumab) should have been no surprise to anyone. In three votes since 2007, the committee has recommended against approval of the drug in the metastatic breast cancer setting. The first vote was disregarded by the agency—it chose to give the drug an accelerated approval in 2008.

Yet, public criticism of the expertise and mindset of academic oncologists and statisticians who comprise ODAC is unusual. In disputes with FDA, companies often claim that the advisory committee lacked the expertise required to appreciate the nuances of an application. Such complaints are made with some regularity in private conversations with reporters and, sometimes, in letters to FDA officials.

However, as Avastin's breast cancer indication continues to bring the drug closer to losing its accelerated approval, Genentech is finding itself airing its complaints publically.

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In Brief:

Fadlo Khuri Named Editor-in-Chief of Cancer; NCCN Launches Outcomes Improvement Program

FADLO KHURI was appointed editor-in-chief of **Cancer**, a peer-reviewed journal of the American Cancer Society. His five-year term begins Sept. 1. Khuri will succeed Raphael Pollock, who served as Cancer's editor-in-chief for 11 years.

Khuri is professor and chair of Hematology and Medical Oncology at Emory University and deputy director for Emory's Winship Cancer Institute, where he holds the Roberto C. Goizueta Distinguished Chair in Cancer Research. He served as editor for the journal's lung section since 2005.

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The Cancer Letter is taking a publication break. We will return to publishing Friday, Sept. 9.

Genentech, CDER Trade Jabs Over Avastin Withdrawal

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The assertion that ODAC lacks expertise and impartiality was part of dueling filings submitted by Genentech and FDA, which summarized the two-day public hearing over the agency's decision to revoke the drug's metastatic breast cancer indication (The Cancer Letter, July 1).

The company also submitted a description of the clinical trial it wants to conduct, to confirm the benefits of using Avastin in conjunction with a weekly paclitaxel regimen.

In the hearing June 28-29, ODAC played a role akin to that of a jury. Following legal procedures that FDA designed specifically for the occasion—a first-ever hearing on the withdrawal of an accelerated approval—the staff of the FDA Center for Drug Evaluation and Research played a role reminiscent of a prosecutor. Karen Midthun, director of the FDA Center for Biologics Evaluation and Research, at least partially served in a judge-like role.

Though Midthun ran the two-day hearing, the ultimate decision would be up to FDA Commissioner Margaret Hamburg, and could be made "downtown" by the HHS Secretary or the White House (The Cancer Letter, May 27).There is no deadline for Hamburg to make her decision. Since the decision will be, at least in part, political, there is no reliable way to assess Genentech's chances of keeping the indication.

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The company's filing included a particularly strongly worded attack on ODAC, a committee that recommended three times against approval of the indication.

In focusing on the committee's most recent vote, Genentech said:

• ODAC members lacked expertise in breast cancer. "The final composition of the ODAC panel for the hearing included only six voting members, an unusually small size that required a special quorum waiver from the Commissioner," the document states.

"There were only two medical oncologists and no breast cancer specialists, as CDER's Director acknowledged after the hearing, the panelists had little expertise with solid tumors, and no panel member cited direct clinical experience with Avastin. This absence of a real-world understanding of Avastin's effect in first-line MBC, and the underlying disease of breast cancer itself, was evident throughout the hearing."

• The committee was closed-minded. "As their deliberations made clear, the ODAC panelists' conclusions rested on their pre-existing views, not a considered analysis of the data in light of the presentation of new data and new questions addressed at the hearing," the filing reads.

• Committee members applied the wrong regulatory standard. "Several ODAC members applied an incorrect efficacy standard, and the ODAC's lack of clinical experience with breast cancer and Avastin limited its ability to assess the medication's benefit-risk profile," the document states.

• The committee demonstrated "a longstanding ODAC aversion to [progression-free survival] as a clinical endpoint in first-line MBC, dating back to the December 2007 ODAC on Avastin's MBC indication. The refusal by key ODAC members to embrace FDA's judgment that PFS improvement demonstrates clinical benefit necessarily undermines their votes. Indeed, given CDER's admission that no HER2-negative first-line treatment has shown a quality of life or overall survival benefit—which reflects the challenges of demonstrating these measures in first-line MBC—ODAC's position risks barring any MBC approvals."

The Genentech document states that, unlike ODAC, the breast cancer panel of the National Comprehensive Cancer Network has the expertise to assess the drug. ODAC's and FDA's position notwithstanding, NCCN continues to list Avastin as a treatment for HER2-neu-negative breast cancer.

Shifting the Burden of Proof?

In its post-hearing filing, CDER argues that Genentech is attempting to shift the burden of proof for support of continuation of an accelerated approval from the sponsor to FDA.

The center's filing states:

Genentech argues that withdrawal of accelerated approval is not appropriate unless there is: (1) "no reasonable likelihood [that the drug has] clinical benefit;" and (2) "no possibility that additional study might further characterize any potential benefit."

In so arguing, Genentech has turned the withdrawal standard on its head, attempting to create a new standard that is inconsistent with the purposes of the accelerated approval program and that impermissibly imposes on CDER the burden of proving that Avastin can never be shown to be effective in treating MBC.

Avastin's MBC indication was approved under the statutory and regulatory provisions that permit accelerated approval based on adequate and well-controlled clinical trials establishing that the product has an effect on a clinical endpoint other than survival or irreversible morbidity.

It appears that Genentech derived its novel withdrawal standard by conflating a different approval provision—one that permits CDER to grant accelerated approval based on a drug's effect on a surrogate endpoint that is "reasonably likely to predict clinical benefit"—with the withdrawal standard.

But that provision refers only to the relationship between a surrogate endpoint and clinical benefit, and only as grounds for approval. As noted, the MBC indication was not approved based on Avastin's effect on a surrogate endpoint, and its withdrawal does not depend on whether CDER can prove the absence of "reasonable likelihood" of clinical benefit. To the contrary, when the accelerated approval program was created, the Agency was clear that the sponsor "has the responsibility for providing the needed evidence confirming clinical benefit."

This standard parallels the standard for regular approval of a drug.

Genentech's proposed legal standard impermissibly imposes a burden on CDER to show that there is "no possibility" that an additional trial "might" further characterize the potential benefit of a drug.

Requiring CDER to establish that there is no possibility of clinical benefit would be inconsistent with the Agency's approval standards, which place the burden of demonstrating safety and efficacy upon the sponsor, and would be virtually impossible as a practical matter. Another trial of any drug almost always will provide more information about that drug, and there is always the possibility that another trial might have a different result. These realities are not grounds to "evergreen" accelerated approval.

The Trial

Genentech wants to conduct a confirmatory trial of Avastin with a weekly regimen of paclitaxel, essentially repeating the E2100 trial that led to the drug's accelerated approval.

The difference is that the new trial would focus on a biomarker. No other company has conducted a confirmatory trial in the exact same indication as the study leading to an accelerated approval.

Also, if the company prevails, it would be the first to conduct a repeated round of confirmatory trials.

The confirmatory trial would be accompanied by a Risk Evaluation and Mitigation Strategy, and the Avastin label would include new, restrictive language.

Avastin received accelerated approval based on progression-free survival, demonstrated in a trial of the regimen in conjunction with weekly paclitaxel. The approval was granted based on progression-free survival.

However, two confirmatory trials failed to demonstrate the magnitude of PFS that ODAC and FDA would consider acceptable to justify retaining an accelerated approval.

FDA says that the result of E2100 was likely a "random high," a statistical fluke. There is no compelling data to substantiate the claim that the regimen with which Avastin is administered has any bearing on results.

Moreover, there is no data to substantiate the company's claim that the drug is of benefit to patients with more aggressive and treatment-resistant forms of breast cancer, including triple-negative disease.

Genentech proposes a trial that would allow withdrawal if interim study results indicate that the trial likely will not confirm the magnitude of Avastin's clinical benefit as evidenced by E2100 trial data.

The Genentech filing includes the following description of the proposed study:

The confirmatory trial will target a study population of 480 patients with HER2-negative MBC who have not received prior chemotherapy for metastatic disease. Randomization will be stratified by plasma VEGF-A level, prior adjuvant therapy use, and hormonal receptor status.

Treatment regimens of the study are identical to E2100, with standard 3-weekly out of 4 weeks paclitaxel

and Avastin continued until progression and with no built-in crossover (as was the case in AVADO and RIBBON1).

The study has two co-primary objectives: PFS in all patients, and PFS in patients with high plasma VEGF-A. Overall survival, 1-year survival, and response rate would be secondary endpoints. The study size would target 326 PFS events, which provide 85% and 99% power to detect a hazard ratio of 0.67 or 0.5 respectively.

The primary objective of the study is to confirm the magnitude of benefit seen in E2100 when Avastin is combined with weekly paclitaxel. A secondary key objective of the study is to validate a method of selecting patients who may derive a more substantial clinical benefit with Avastin using plasma VEGF-A.

Recent data from AVADO, as presented by the investigators at the December 2010 San Antonio Breast Cancer Symposium, suggest that plasma VEGF-A may be a potential predictive marker for Avastin activity.

Patients in AVADO with high levels of VEGF-A had a PFS hazard ratio of 0.49 (standard dose), whereas patients with low levels of VEGF-A had PFS hazard ratio of 0.86. This finding suggests that patients with high levels of VEGF-A may be more likely to derive a more substantial benefit from Avastin.

Genentech met with CDER this February to review the study's design. At this Type B meeting, CDER confirmed that PFS results showing the same magnitude of median PFS difference as in E2100, without a detriment to OS, would support full approval with paclitaxel.

At the hearing, Genentech addressed CDER's concerns about study feasibility:

• Enrollment Timing: Genentech expects enrollment to start in the first quarter of 2012.

• Prompt Action on Study Results: Genentech will perform a prespecified interim PFS analysis. This early analysis could trigger an early voluntary withdrawal of accelerated approval if the futility boundary is crossed. Genentech discussed this analysis being conducted roughly three-and-a-half years after the study's start, although its post-hearing third-party feasibility assessment indicates that this analysis could occur at 2.6 years.

• Patient Enrollment: The study will include sites in the United States, but Genentech expects (based on its prior Avastin study experience and a country-specific survey Genentech has already conducted) the study to be enrolled largely outside of the United States.

U.S. enrollment will be driven by interest in the biomarker component and by those patients and physicians who are near equipoise on the Avastin data. Enrollment in the roughly 50 participant countries outside the U.S. will be driven by the fact that Avastin reimbursement and funding is limited in many countries outside the United States.

• Broad Experience: Genentech has substantial experience in recruiting global trials and has successfully enrolled 10 Phase III Avastin breast cancer trials with 15,574 patients.

REMS and Restrictions on the Label

Genentech's filing includes a proposed labeling change and the proposed REMS language.

The changes proposed by the company follow:

"Avastin is indicated in combination with weekly paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment.

"The effectiveness of Avastin in MBC is based on an improvement in progression free survival in a single study.

"Two additional studies with different chemotherapy combinations did not confirm the same magnitude of benefit. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.

"Avastin is not indicated 1) in combination with other chemotherapies for patients who have not received chemotherapy for MBC, or 2) for patients who have received prior chemotherapy for MBC."

The filing also includes a proposed REMS and a mock-up of a dear-doctor letter that discusses the adverse events associated with the drug.

The Genentech filing states that CDER "did not respond to the core basis for this restricted labeling proposal: the lack of treatment options and uniquely severe, and undisputed, unmet need for patients with TNBC or hormone receptor-positive disease characterized by aggressive features, e.g., by visceral metastases, high tumor burden, or rapidly progressive disease."

The company asks FDA to exercise "regulatory discretion" in the case.

This should be done for the following reasons, the company said:

• Avastin addresses a significant unmet medical need and is a valuable treatment option for MBC.

Only one other non-hormonal treatment is specifically approved for first-line treatment encompassing HER2-negative disease—Gemzar—and the Gemzar data are weaker than those seen in E2100. Patients with aggressive forms of MBC face even poorer prognoses, have fewer treatment options, and represent a greater unmet medical need.

• The post-approval trials continue to demonstrate that Avastin provides clinical benefit in first-line MBC, with each meeting its agreed-upon primary endpoint. The smaller median PFS effect seen in these trials, when Avastin was combined with chemotherapies other than paclitaxel, can reasonably be attributed to a difference based on the chemotherapy partner.

• Avastin's safety profile is well-characterized, accurately described in the approved prescribing information, and not uniquely toxic compared to other therapies. The confirmatory studies have not identified any new safety signals.

• Genentech completed the post-approval studies with rigor and diligence.

• The confirmatory studies were selected without the knowledge that CDER would require replication of the magnitude of median PFS benefit in E2100, based on CDER's guidance that the magnitude of benefit may vary with chemotherapy regimen, and with CDER's knowledge that the agreed upon confirmatory trials—first AVADO and later RIBBON1—would not show the same magnitude of median PFS benefit as seen in E2100. This history explains the unique unforeseen circumstances present here that justify a new confirmatory trial with paclitaxel.

The only basis that CDER raises for withdrawal on these facts is the concern that the benefit seen in the confirmatory trials was smaller than in E2100. Withdrawal is not appropriate where there is demonstrated benefit, no new safety signals, a reasonable alternate explanation for the lesser effect on median PFS (that the choice of chemotherapy partner affects the level of benefit), and a means of testing that explanation through a further trial.

The only open question is whether the magnitude of benefit observed in E2100 will be confirmed in a new study of Avastin with paclitaxel. Given the rigor of review of the E2100 data, the meaningful probability that the chemotherapy partner has an impact on the magnitude of benefit, and the feasibility of a new study with paclitaxel, accelerated approval should be maintained pending completion of the study.

Withdrawal on these facts would fundamentally undermine the goals of the accelerated approval program by prematurely and unnecessarily depriving patients and physicians of a treatment choice where the safety profile is unchanged and well-characterized, the confirmatory trials were positive, and a viable study could more definitively confirm clinical benefit.

FDA Filing

The agency's filing lists the following arguments against accepting the company's plan:

• Genentech's Proposed New Trial Will Not Be Completed Until at Least 2016 and May Fail.

At the hearing, Genentech stated that it does not plan to begin accruing patients for its proposed new trial of Avastin for MBC until the first quarter of 2012. The trial is not projected to be complete until at least 2016, and it may not be feasible at all.

The trial contemplates a "futility boundary" after which the firm says withdrawal would be appropriate if the treatment effect is not confirmed; however, the interim analysis to identify the futility boundary will not be reached until three and a half years after the trial begins, i.e., until the end of 2015, shortly before the trial is scheduled to be complete.

To permit Avastin to remain approved for MBC for five more years in the face of the data from five adequate and well-controlled trials supporting withdrawal is not in the interest of public health.

Moreover, the study may take longer than Genentech projects, in part because it may be difficult to recruit subjects in the U.S., because they may be reluctant to agree to participate in a trial in which they might be randomized to not receive an approved treatment. And as explained below, if conducted, the trial may, like the post-approval trials to date, fail to verify the magnitude of PFS treatment effect seen in E2100.

• Available Data Do Not Support the Existence of a Subgroup of Women for Whom Avastin's Benefit-Risk Analysis is Favorable.

Genentech also argues that Avastin's MBC indication should not be withdrawn because there is a subset of women for whom Avastin provides a clinical benefit, but this hypothesis is not supported by the data.

As noted previously, CDER has reviewed five adequate and well-controlled trials of Avastin in MBC, which included seven independently powered comparison arms and more than 3,500 patients.

Yet the data from these trials do not support Genentech's hypothesis that there is a subgroup of women for whom Avastin works particularly well and for whom the drug's benefits would outweigh its risks.

Genentech's expert Dr. [Joyce] O'Shaughnessy [of Texas Oncology-Baylor Charles A Sammons Cancer

Center] suggested multiple times at the hearing that "triple negative" patients who have hormone receptor negative disease might be one such subgroup.

However, the only data she presented to support this speculation were from the E2100 trial; these findings were not confirmed in subsequent trials. CDER analyzed the E2100, AVADO, and RIBBON1 trials, looking at each independently powered cohort within each trial and separating the triple negative patients from other patients who were HER2-negative and ER or PR-positive. CDER found there were no differences in terms of treatment effects between triple negative patients and others with respect to either overall survival or PFS.

Dr. O'Shaughnessy also suggested that patients with "rapidly progressive symptomatic or heavily tumor-burdened metastatic breast cancer" are a subgroup that receives clinical benefit with Avastin. However, there is no way to know whether women with more symptomatic disease will benefit more than others, because baseline information about symptoms was not collected in the clinical trials. In fact, based on Eastern Cooperative Oncology Group ("ECOG") performance status, one would conclude that all patients in the three trials were either asymptomatic or minimally symptomatic at the time they entered the trials. Thus, as CDER's Dr. [Patricia] Keegan [director of the CDER Division of Biologic Oncology Products] noted, there are "no data on whether or not symptomatic patients would benefit or to what degree they would benefit because they were not studied." In addition, Genentech's proposed additional trial is not designed to test whether this subset of patients would respond well to Avastin in the manner hoped for by Genentech.

Another theory advanced by Genentech is that the subgroup of MBC patients with high plasma levels of certain forms of Vascular Endothelial Growth Factor (VEGF), particularly VEGF-A, "may be more likely" to benefit from Avastin. The company proposes to explore this hypothesis in the "biomarker component" of its proposed study. CDER does not dismiss this hypothesis or the merits of studying it. However, the underlying science is very preliminary, and largely based on exploratory, retrospective analyses with mixed results. A scientific theory about whether it is possible to identify a subgroup of MBC patients that may benefit from Avastin based on a biomarker is not a reason to maintain approval in light of the known and certain risks of harm for all.

There are simply no available data to support Genentech's theory that there is a subgroup of women for whom Avastin's benefit-risk analysis may be favorable.

• Genentech's Chemotherapy Partner Hypothesis is Not Supported.

Genentech also argues that the magnitude of the treatment effect seen with Avastin in combination with chemotherapy will be influenced by the specific chemotherapy partner used. According to Genentech, to confirm the benefit seen in E2100, the company should be permitted to conduct a trial in which Avastin is again paired with paclitaxel.

If there were merit to Genentech's chemotherapy partner hypothesis, one would expect to see evidence of drug interactions or antagonism between Avastin and other chemotherapy drugs. There is none.

Moreover, Genentech has submitted no data suggesting a synergistic relationship between Avastin and paclitaxel that would lend credence to the idea that Avastin in combination with paclitaxel might work better than the additive effects of paclitaxel or Avastin alone. And Genentech has submitted no data suggesting an antagonistic relationship between Avastin and the other chemotherapy partners paired with Avastin in the AVADO, RIBBON1, and RIBBON2 trials that might have accounted for the much smaller PFS difference seen in those trials. As Dr. Keegan explained at the hearing, "[c]lassic pharmacokinetic study designs have been developed to test such hypotheses, but these tests have not been done, or if performed, have not been submitted to CDER."

To the contrary, existing pharmacokinetic data demonstrate that "there are no interactions between Avastin and any of the chemotherapeutic agents administered with Avastin in the AVADO and the RIBBON 1 studies." In the absence of a scientifically supported basis for chemotherapy-specific interactions, the more likely explanation for the failure of the clinical trials to verify the results of the E2100 trial is that the magnitude of the PFS treatment effect observed in E2100 is an outlier.

Additionally, CDER reviewed a report published online in The Lancet in March 2011 on the CIRG-TRIO-010 trial—a three-arm, randomized, placebo and active-controlled phase 2 trial—which Genentech

referenced in its Jan. 16, 2011 submission and which CDER referred to as "Study 10" at the hearing.

Study 10 contained one arm in which paclitaxel was administered alone and one arm in which paclitaxel and Avastin were administered together. The authors of the article provided the results of a comparison between those two arms and concluded that there was no statistically significant increase in median PFS in the Avastin-containing arm compared to paclitaxel alone. Although PFS difference was not a primary endpoint in this trial, Study 10's results certainly do not suggest that another new trial, in which Avastin is yet again paired with paclitaxel, would succeed in demonstrating clinical benefit.

Finally, Genentech's proposed trial is not designed to test its "chemotherapy-specific partner" hypothesis.

In light of the foregoing, allowing Avastin's MBC indication to remain approved until at least 2016, when Genentech's proposed trial may be completed, is neither responsible nor in the public interest.

• A "Middle-Ground" Approach is Inappropriate Here and Would Run Counter to the Intent and Purpose of the Accelerated Approval Program.

Genentech has stated that there is a desirable "middle ground" between withdrawing the MBC indication for Avastin and maintaining that approval. For example, Genentech has proposed to modify the labeling to state that the MBC indication is only for use with paclitaxel (and not other chemotherapy agents) and to reflect the current data regarding Avastin use for MBC. Genentech has also stated that it would adopt a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide and a special communication plan to help physicians and patients make informed treatment decisions.

There is no realistic middle ground here. FDA can require a company to develop and implement a REMS to manage serious risks associated with a drug when the agency determines that such a strategy is "necessary to ensure that the benefits of the drug outweigh the risks of the drug."

The data here do not demonstrate that Avastin provides a clinical benefit for MBC patients. If a drug does not provide a benefit, no amount of communication, training, or distribution restrictions will make that drug safe and effective. Simply stated, there is no REMS that can achieve the goal of ensuring the benefits of Avastin outweigh its risks for MBC.

Permitting Avastin's MBC indication to remain approved with labeling changes and/or a REMS is inappropriate where, as here, the totality of the evidence shows that Avastin for MBC is not safe and effective. Prescription labeling is designed to give prescribers and their patients information about the risks and safe use of a demonstrably effective product; if a drug has not been shown to be effective, any risk is unacceptable. This is all the more true where, as here, the known adverse events associated with Avastin use are serious.

In this matter, Genentech is asking that the drug remain approved for the MBC indication, despite its failure to establish that Avastin for MBC is safe and effective. But doing so will provide false hope: leading patients and physicians to believe that Avastin can be safely and effectively used for MBC.

The full documents are posted at **http://www.cancerletter.com/categories/documents**.

In Brief:

Khuri Named Editor of Cancer; NCCN Starts Outcomes Database

(Continued from page 1)

"It is a great privilege for me to serve as editor-in-chief of Cancer, succeeding my long-time friend and colleague, Dr. Raphael Pollock, who has done an outstanding job as editor-in-chief," Khuri said in a statement. "I received my first peer-reviewed grant from the American Cancer Society and published my first senior authored paper in Cancer. Given my long-standing relationship with both this exceptional journal and the ACS, this is a particularly meaningful honor for me."

Khuri's clinical interests include thoracic and head and neck oncology. His research interests include development of molecular, prognostic, therapeutic, and chemopreventive approaches to improve the standard of care for patients with tobacco-related cancers. His laboratory is investigating the mechanism of action of signal transduction inhibitors in lung and aerodigestive track cancers.

"The Search Committee reviewed many exceptional candidates and is very pleased to have been able to select Dr. Khuri," said Otis Brawley, chief medical officer of the American Cancer Society. "As an accomplished molecular oncologist who has conducted seminal research on oncolytic viral therapy, and having led major chemoprevention efforts in lung and head and neck cancer, Dr. Khuri brings an expertise that will benefit our journal and the entire oncology community."

Khuri is a grant reviewer for the American Cancer Society, NCI, the American Association for

Cancer Research, and the American Society of Clinical Oncology. He is a permanent member of NCI's Thoracic Malignancies Steering Committee and of NCI's Clinical Oncology Study Section. Khuri also serves on the ACS's Council for Extramural Funding.

"We are excited to have Dr. Khuri on board," said Esmeralda Buchanan, journals director at ACS. "He has some great ideas around increasing Cancer's visibility and obtaining only the very best papers in the field. It is an exciting time for us."

Khuri published more than 200 peer-reviewed articles and received numerous awards, including the Nagi Sahyoun Award from the Middle East Medical Assembly and the Waun Ki Hong Award from MD Anderson Cancer Center.

"I will work hand-in-hand with Cancer's outstanding editorial staff, section editors, and editorial board to further accelerate the substantial progress of my predecessor," Khuri said. "We will work hard to enhance [Cancer's] already stellar and hard-earned reputation by seeking to publish only the very best work in the field."

RICHARD DRAKE was appointed director of the Proteomics Center at the **Medical University of South Carolina Hollings Cancer Center**.

Drake is a professor in MUSC's Department of Cell and Molecular Pharmacology and Experimental Therapeutics, and an endowed chair of South Carolina's SmartState Program.

CARLOS ARTEAGA will become the new associate director for clinical research at Vanderbilt-Ingraham Cancer Center.

He is currently professor of medicine and cancer biology, director of the Breast Cancer Program, and director of the cancer center's Specialzed Program of Research Excellence in breast cancer.

The previous associate director, R. Daniel Beauchamp, will move up and become deputy director of the cancer center.

Artegea's work helped develop several oncogene-targeted drugs, such as trastuzumab (Herceptin), cetuximab (Erbitux) and erlotinib (Tarceva), as well as other combinations currently in development.

ISIDORE RIGOUTSOS and his research team at the **Computational Medicine Center of Thomas Jefferson University** were awarded a $1 million medical research grant from the W.M. Keck Foundation.

Rigoutsos, a computational biologist and member of Jefferson's Kimmel Cancer Center, founded the Computational Medicine Center in 2010, where he now serves as director. His team includes researchers and physicians from the Thomas Jefferson University and Hospital, the Children's Hospital of Philadelphia, the University of North Carolina at Chapel Hill, and MD Anderson Cancer Research Center.

The research team will use the grant to study a particular group of DNA motifs called pyknons. Rigoutsos originally discovered pyknons in 2005 using computational analyses, and since then, evidence has suggested that these pyknon motifs mark transcribed, non-coding RNA sequences with potential functional relevance in human disease.

Rigoutsos said that he will study pyknons using samples from a diverse collection of human tissues: prostate, colon and pancreatic cancer, chronic lymphocytic leukemia, type-1 diabetes, hyper- and hypo-reactivity in platelets, multiple sclerosis, and systemic sclerosis.

His team's goal to investigate the presence of pyknon-marked non-coding RNAs in these cells affected by these diseases, and to determine the rules governing the biogenesis, processing, and mechanisms of regulatory action of these transcripts. The planned research activity will involve a combination of computational analyses and modern experimental techniques.

"This is very exciting. The grant comes on the heels of six years of research," Rigoutsos said in a statement. "It will help us get to the bottom of this story: an unexplored territory that we strongly suspect has something important to reveal about human disease. There is disconnected evidence, and we want to assemble all the pieces."

THE NATIONAL Comprehensive Cancer Network will launch the **Opportunities for Improvement Initiative**, a continuing medical education program that will use data from the NCCN Oncology Outcomes Database to measure the impact of NCCN clinical guideline concordance on patient outcomes. The initiative is supported by a three-year, $2 million educational grant from Pfizer.

The goal of the program is to develop and implement

an outcomes-based performance improvement initiative that utilizes practice data from NCCN member institutions.

NCCN will design provider-specific action plans for improvement, and quantify and evaluate the impact of educational interventions on changes in practice and patient outcomes.

Ten NCCN member institutions are participating in the program, and quality improvement coordinators at each center were appointed to act as liaisons between practicing breast cancer providers and data analysts at NCCN.

During the first phase of the program, NCCN will provide participating institutions with center-specific reports detailing their concordance rates for each of the selected guideline measures to be studied.

The report will detail the center's concordance rate, the aggregate peer concordance rate, and identify whether the center's concordance is significantly below the rate at their peer centers.

Based on these reports, each center is responsible for identifying reasons for non-concordance and then developing and initiating interventions to address those reasons. Practices to improve quality will be shared across participating centers. After these interventions, concordance to the NCCN Guidelines will be reassessed to evaluate the impact of each center's interventions.

In a latter phase of the program, NCCN plans to host an educational summit to share the results from the quality improvement initiative with the oncology community. The summit proceedings will be published in Journal of the National Comprehensive Cancer Network.

Participating NCCN member institutions include: City of Hope Comprehensive Cancer Center, Dana Farber/Brigham and Women's Cancer Center, Duke Cancer Institute, Fox Chase Cancer Center, Massachusetts General Hospital Cancer Center, the Ohio State University Comprehensive Cancer Center, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Roswell Park Cancer Institute, University of Michigan Comprehensive Cancer Center, and MD Anderson Cancer Center.

NILANJAN CHATTERJEE received the President's Award from the **Committee of Presidents of Statistical Societies**. Chatterjee is chief of the Biostatistics Branch at NCI's Division of Cancer Epidemiology and Genomics.

The award is given annually to statisticians under the age of 41 who have made outstanding contributions to the field of statistics. Chatterjee is the first recipient from outside academia since the award was established in 1981.

The award is jointly sponsored by the American Statistical Association; Institute of Mathematical Statistics; the International Biometrics Society; and the Statistical Society of Canada.

KAISER PERMANENTE's Research Program on Genes, Environment, and Health has genotyped DNA and analyzed telomere length in more than 100,000 participants.

"By funding this project, the National Institutes of Health has significantly accelerated research into conditions such as cardiovascular disease, diabetes, cancers, mental health disorders, and age-related diseases such as Alzheimer's disease," said Cathy Schaefer, executive director of the program, said.

The genetic information generated by the project will also include data about drug metabolism and drug response.

The project completed its first phase, which was to extract and genotype DNA from 100,000 participants with an average age of 65, and measure the length of participant telomeres. Telomere length may reflect the degree of aging in a person's cells and may be a marker for age-related conditions.

Results of the genotyping and telomere length analysis will be linked to a broad spectrum of California environmental data and to health-related information, supplied by participant health surveys and the Kaiser Permanente electronic health record, researchers said.

The genotyping project was funded by a two-year, $24.8 million NIH grant awarded to the Kaiser Permanente RPGEH and UCSF. The grant's sources include the National Institute on Aging, the National Institute of Mental Health, and the Office of the Director.

Extracted DNA was transferred to UCSF's Institute for Human Genetics, which worked with Affymetrix Inc. to create arrays for genotyping 675,000 to 900,000 markers (comprised of single nucleotide and insertion-deletion polymorphisms) across all samples.

Over the next year data from the genotyping project will be processed and cataloged by RPGEH and UCSF scientists so that it can be made available to researchers in late 2012.

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ASCO Releases Policy Paper On Reducing Cancer Disparities

The American Society of Clinical Oncology released a policy statement outlining how specific provisions of the Patient Protection and Affordable Care Act have the potential to reduce racial and economic disparities in cancer prevention, diagnosis and treatment.

ASCO recommends that the provisions are carried out effectively, and urges additional steps to address insurance reform, quality of care, prevention, research, and diversity in the health care workforce.

ASCO's statement was published in the Journal of Clinical Oncology.

It identifies specific measures to help eliminate cancer care disparities including:

• Adopting patient-centered quality improvement initiatives;

• Attracting more minority physicians and improving the training of the oncology workforce to meet the needs of racially and ethnically diverse patients with cancer;

• Improving data collection on cancer disparities and determine what must be done to make meaningful medical evaluations;

• Ensuring access to cancer specialists for all patients who seek treatment at federally qualified community health centers;

• Allowing for cancer-centered services to be at the direction of oncology professionals in community health centers and medical homes where many seek medical care.

"The Affordable Care Act provides a foundation for meaningful progress in eliminating disparities in health care," said ASCO President Michael Link. "However, many of its provisions are vague and open for interpretation. In addition, significant progress requires added measures that are not in the new law."

By increasing Medicaid eligibility, the Affordable Care Act has the potential to reduce the number of uninsured by 59 percent. However, 23 million individuals are estimated to be uninsured by 2019.

According to ASCO, evidence shows that with low reimbursement, cancer patients on Medicaid fare no better than patients who have no health insurance.

To ensure that Medicaid patients have consistent access to quality cancer care, ASCO asks policy makers to: provide Medicaid patients diagnosed with cancer with immediate, presumptive eligibility for Medicare; and reimburse doctors who treat cancer patients on Medicaid at Medicare rates.

In addition, ASCO and other medical societies are calling on Congress to ensure that Medicare to fix a flawed payment formula known as the Sustainable Growth Rate, to ensure that patients have continued access to quality cancer care.

Although the reform legislation mandates that insurers cover certain cancer screenings, it does not expressly require insurers to cover follow-up tests if an abnormality is found.

For example, if a polyp is found during a colonoscopy, insurers are not required by law to cover follow-up diagnostic examinations and biopsies.

ASCO is calling for Congress to require insurers to cover appropriate follow-up testing without patient deductibles or copays.

CDC Report Confronts Smoking Depicted in Television and Film

CDC's Morbidity and Mortality Weekly Report demonstrated new data showing substantial drops in on-screen smoking in films rated G, PG or PG-13. The reduction, however, was inconsistent across the industry and varied among studios.

NCI, the Institute of Medicine and other authorities state that there is a causal relationship between smoking in movies and youth uptake of smoking. Nearly 80 percent of adult smokers begin before age 18, and research suggests that on-screen smoking is a major factor in youth smoking.

According to the report, the three major studios with published policies on smoking in youth-rated films (Comcast/Universal, Disney, and Time Warner/ Warner Bros.) reduced depictions by 96 percent between 2005 and 2010, compared to 42 percent in the rest of the industry. Youth-rated movies accounted for approximately 40 percent of the smoking depictions portrayed to U.S. theater audiences in 2010, down from nearly 55 percent in 2005.

In 2010, the Department of Health and Human Services' plan to reduce tobacco use included limiting youth exposure to on-screen smoking.

"Each day in the United States, about 3,400 young people between the ages of 12 and 17 smoke their first cigarette, and an estimated 850 youth become daily cigarette smokers," said Ursula Bauer, director of CDC's National Center for Chronic Disease Prevention and Health Promotion. "Completely eliminating smoking from new youth-rated movies could help prevent America's young people from starting down the road of tobacco addiction, disease, and premature death."

According to the report, "expanding the R-rating to include movies with smoking could further reduce exposures of young persons to on-screen tobacco incidents, making smoking initiation less likely."

The American Academy of Pediatrics, the American Medical Association, the World Health Organization, and others endorse the following policies, developed by the national Smoke-Free Movies campaign:

1. Rating "R" any new movie with smoking, with the exception of movies that depict the health consequences of smoking or actual historic figures who actually smoked;

2. Inserting strong, evidence-based anti-smoking public service announcements before movies with smoking, in all distribution and exhibition channels;

3. Requiring producers to certify that no consideration of any kind was received for tobacco depictions in a film;

4. Ending the depiction of tobacco brands on screen.

"Without a uniform R-rating for smoking, it will be difficult to make further progress to finally end smoking depictions in films rated for youth that entice them to begin deadly life-long addictions," Stanton Glantz, professor of Medicine at UC San Francisco and director of the Smoke-Free Movies Project, said in a statement

The report also noted that in 2010, 15 states spent $288 million to subsidize films that portrayed smoking—more money than they budgeted for their tobacco control programs in 2011 ($280 million). The report suggests that these subsidy programs should make future film projects with tobacco content ineligible for taxpayer support.

Obituaries:

Cancer Biologist Reuben Lotan, Of MD Anderson, Dies at 65

Cancer researcher Reuben Lotan died Aug. 2, following a stroke. Lotan served as a tenured professor at MD Anderson Cancer Center for 26 years. He retired in 2010.

As a scientist, Lotan was an accomplished cancer biologist who made seminal contributions in cancer prevention and therapy. He was a pioneer in the field of retinoid biology. He is the author of over 200 research publications and review articles in that area, which served as the foundation that supported clinical use of those compounds in prevention and treatment of various neoplasms.

"Reuben fully deserved his impeccable global reputation in the cancer research community," said Waun Ki Hong, head of the Division of Cancer Medicine at MD Anderson, and Lotan's long-time friend and collaborator. "His impact on the fields of retinoid biology and chemoprevention will outlive us all."

Lotan is survived by his wife of over 40 years, Dafna, his three sons, Ori, Yair and Dan, and seven grandchildren.

He was 65.

Former NIH Director Healy, 67

Former NIH Director Bernadine Healy died Aug. 6 from recurring brain cancer, at her home in Ohio. She had been living with brain cancer for 13 years.

Healy became the first woman to head the NIH in 1991. A cardiologist, she previously served as president of the American Heart Association. Later she became dean of the medical school at The Ohio State University.

While at NIH she helped launch the Women's Health Initiative, a 10-year, $500-million study focused on diseases affecting mid-life women.

She was 67.

Former Sen. Mark Hatfield, 89

Former Sen. Mark Hatfield died the evening of Aug. 7, in Portland, Ore.

A Republican, Hatfield represented the state of Oregon for 30 years, from 1967 to 1997. During that time he spent six years as the chairman of the Senate Appropriations Committee on two occasions.

He was known as an ardent supporter of medical and health research. The NIH Mark O. Hatfield Clinical Research Center in Bethesda, Md., was named in his honor in 2005.

"Senator Hatfield demonstrated a passionate belief that health and research for the health of all Americans are national priorities," said John Edward Porter, former Illinois Congressman and chair of Research!America.

"He was a 'giant' of the Congress who believed deeply in bipartisanship and working with all Members of the Congress to make good things happen for the country. As chair of the Senate Appropriations Committee, Senator Hatfield fought for strong growth in appropriation for the National Institutes of Health. During his chairmanship funding for the NIH increased an average of nearly 10 percent a year."

He was 89.