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Drug Development:

Trials in a Small Indication Tell Big Story About Pitfalls of Delaying Progression

By Paul Goldberg

Just like patients have excellent reasons to dread maladies doctors call "interesting," pharma companies would rather avoid presenting interesting applications for drug approval.

Usually, FDA's oncology office approves slam-dunk cases without consulting outside experts. An advisory committee gets called upon only when the science and methodology edge into confounding territory.

On April 12, the FDA Oncologic Drugs Advisory Committee got a bucketful of interesting questions as it considered two oral drugs for nearly identical supplemental indications:

• Afinitor (everolimus), a Novartis drug for advanced neuroendocrine

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Guest Editorial:

As Journals Retract His Biomarker Research, Anil Potti Turns to "Online Reputation Managers"

By Taylor Doherty

The author is the news editor of The Chronicle, an independent student-run newspaper at Duke University. He is a junior at Duke.

Google search results can ruin a reputation these days. Anil Potti, formerly of Duke University, knows that.

Potti, the cancer researcher who falsely claimed to be a Rhodes Scholar, and whose papers are being retracted from premier medical journals, recently hired a company to push unfavorable online content about him off the front page of search engines.

The firm Online Reputation Manager specializes in such efforts. Potti paid the company to create websites, social media accounts and press releases, all built to crowd out unwanted negative attention by accentuating the positive.

These reputation management efforts became evident when a Google Alert for "Anil Potti" began to identify new results daily, containing generic and positive information about Duke's former academic star. Some top search results still detailed Potti's missteps, but a number of the newly-created sites were quickly prioritized by search engines over unfavorable articles.

AnilPotti.com, one of at least five websites registered between Jan. 14 and 17 containing the researcher's name, said that "Dr. Anil Potti is an oncologist and an advocate for personalized cancer treatments," and featured stock photos of smiling doctors congregating around laptops.

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ODAC Recommends Approval For Afinitor, Sutent for pNET

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tumors of pancreatic origin.

• Sutent (sunitinib malate), a Pfizer drug for unresectable pancreatic neuroendocrine tumors.

The committee overwhelmingly voted in favor of approving both, but only after struggling with fundamental methodological and procedural peculiarities that surfaced in these trials.

pNET is a miniscule indication. The disease occurs in two to four people per million annually.

However, questions raised at the committee meeting transcended pNET and the drugs in question. Rather, they were about potential pitfalls of relying on metrics of delaying progression as a basis for approving drugs. By addressing these questions, the committee was clarifying approval standards that could affect drug applications for years, if not decades, to come.

Though intensity of debate might have suggested split decisions, ODAC voted unanimously 10-0 to recommend approval for Afinitor, and 8-2 to recommend approval for Sutent.

As committee members explained their rationale for voting the way they did, several acknowledged that their ultimate decisions were close calls, influenced by the fact that both drugs were indicated for rare diseases with no compelling treatment options. Presumably, this could mean that the outcome could be different for larger indications.

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"I voted yes, maybe just barely," said ODAC temporary voting member Tito Fojo, program director for medical oncology at NCI, explaining his vote on Afinitor. "There are patients who have a real need for an intervention with this drug. Hopefully, the sponsor as well as academia will work very hard to identify the small fraction of patients who benefit."

Explaining his rationale for voting to approve Sutent later that day, Fojo said, "I voted yes after much deliberation, and the glass is actually about a quarter full at best. But for a rare disease, it's okay to be a quarter full."

The strange event in the Afinitor application involved the differences in assessment of response. The Sutent trial was unusual because it was stopped early, resulting in a higher degree of uncertainty regarding the balance of benefit and risk.

In the beginning, Novartis sought two indications for Afinitor, conducting a randomized study in each.

The second trial of Afinitor ran in neuroendocrine tumors of gastrointestinal or lung origin, also known as carcinoid tumors.

In a protocol-specified analysis in the carcinoid indication, investigator review determined that the trial should be stopped because the drug had crossed the threshold of demonstrating efficacy. However, central review came to the opposite conclusion: the trial should be stopped because there is no chance that it would ever demonstrate efficacy.

Novartis ended up with two diametrically opposed conclusions based on the same scans. This was an unprecedented in the history of the FDA oncology office, the agency's medical reviewer said at the ODAC meeting.

Days before the meeting, after release of the briefing documents, Novartis notified the agency that it wouldn't seek the carcinoid tumor indication. Prior to that, the company amended the protocol on the pNET indication.

In the Afinitor application, PFS was based primarily on investigator determination, and PFS determined by central review became a secondary endpoint. As a result of making that change in the pNET protocol, the company's Special Protocol Assessment agreement with the agency became invalid.

The pNET indication remained viable because the PFS metrics went in the same direction.

In the case of Sutent, the company had no SPA agreement with the agency.

Pfizer's pNET registration trial was designed to enroll 340 patients. The first interim analysis was to be

conducted at 130 PFS events, to assess safety.

Originally, the experiment was monitored by an internal "pharmaco-vigilance group" comprised of Pfizer employees who were independent of the study team.

However in 2008, while the trial was in progress, the company followed a guidance published by FDA and changed its standard procedures for monitoring trials. It formed an independent data monitoring committee comprised entirely of outside experts, none of whom were Pfizer employees.

Such groups are charged solely with protecting the interests of patient, as opposed to the interests of sponsors.

The independent committee took a succession of looks, spaced at six-month intervals. The earlier reviews were conducted primarily for safety purposes, but looked at parameters of efficacy as well, in order to get a better sense of the overall risk/benefit basis for recommending that the study continue or be terminated. Following the second DMC meeting, the group requested to reconvene in three months, rather than six.

When the group met for the third time, it encountered a result that it viewed as stunning. It found what looked like an overwhelming benefit-to-risk relationship in favor of Sutent and recommended that the trial be stopped—and that the control group cross over to the treatment arm.

The board made this recommendation after assessing 73 PFS events and reviewing safety and efficacy data on 154 patients. The board found that there were 15 deaths on placebo and only five on Sutent.

There were 24 PFS events on Sutent and 49 events on placebo. The hazard ratio for PFS was 0.397 (95% CI: 0.243-0.0.649). There were 28 serious adverse events on placebo and 20 such events on Sutent.

The recommendation to approve Afinitor was based on the RADIANT trial (RAD001 In Advanced Neuroendocrine Tumors), the largest conducted in patients with advanced NET.

RADIANT-3 is a phase III, prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter study. The trial examined the efficacy and safety of Afinitor plus best supportive care versus placebo plus BSC in 410 patients with advanced-, low- or intermediate-grade pancreatic NET. Patients who met the study entry criteria were randomized 1:1 to receive either Afinitor 10 mg once-daily orally (n=207) or daily placebo (n=203), both in conjunction with BSC.

The primary endpoint of RADIANT-3 is progression-free survival. Secondary endpoints include safety, objective response rate (confirmed according to RECIST), duration of response and overall survival.

Results from the trial showed that Afinitor more than doubled median PFS from 4.6 to 11.0 months when compared with placebo and reduced the risk of cancer progression by 65 percent (hazard ratio=0.35 [95% CI, 0.27 to 0.45]; $p<0.001$) in patients with advanced pancreatic NET.

Trials of the Future

An argument can be made that both trials for the pNET indication were of the sort that will be conducted increasingly in the future.

In these cases, the populations were small, and the trials were randomized and placebo-controlled—and were the largest ever conducted in these populations.

Both development programs aimed to measure progression-free survival, a metric visible only in randomized trials. Both trials used crossover design, which allowed patients receiving placebo to cross over to receive the drug once their disease progressed. Since crossover obscures survival, neither agent could set survival—the metric that trumped all other metrics in the FDA of old—as the primary endpoint.

The two drugs have different mechanisms of action, and both are being used for a variety of small indications.

Afinitor is an mTOR inhibitor. It's approved in the U.S. for advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. The drug also has FDA approval for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis who require therapeutic intervention, but are not candidates for curative surgical resection. In the European Union, it's approved for patients with advanced RCC whose disease has progressed on or after treatment with vascular endothelial growth factor-targeted therapy.

Sutent is a kinase inhibitor. It's indicated in the U.S. for advanced renal cell carcinoma and gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. In Europe, it's approved for unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with disease progression in adults.

In the U.S., everolimus is available under the trade name Zortress for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. In the E.U., everolimus is available under the trade name Certican for the prevention of organ rejection in heart and kidney transplant recipients.

The agent is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Though the drugs are different, pairing them for the same meeting helped ODAC focus on commonalities and produced clear messages for the two sponsors as well as others involved in drug development.

For example, the committee discussed the heterogeneity of the pNET population in the context of Afinitor, during the morning session.

Though the same discussion would have applied to Sutent, there was no need to repeat it during the afternoon session.

The two cases can be viewed jointly in ways that raise profound questions about the role—and potential pitfalls—of reliance on metrics of delay in progression:

• Afinitor's trial in carcinoid tumors shows that assessments of PFS can be so soft and so dependent on who is looking at the scans that conclusions can produce recommendations to halt trials for diametrically opposed reasons.

• Well-known side effects of both of these drugs can in effect unblind the studies, introducing bias on the part of investigators.

The most frequent adverse events associated with Afinitor include stomatitis, oral mucositis and ulcers, anemia, hyperglycemia, rash, diarrhea, fatigue, infections, nausea, peripheral edema, lung or breathing problems and decreased appetite.

Side effects associated with Sutent include hepatotoxicity, decreases in left ventricular ejection fraction to below the lower limit of normal, as well as diarrhea, fatigue, asthenia, nausea, mucositis/stomatitis, anorexia, vomiting, neutropenia, hypertension, dyspepsia, abdominal pain, constipation, rash, hand-foot syndrome, skin discoloration, hair color changes, altered taste and bleeding.

The Sutent example and the Afinitor carconoid trial raise questions about reliance on PFS data as a basis for stopping trials. Of course, this isn't exactly what transpired in the case of Sutent. That trial was stopped based on an imbalance deaths, toxicity and PFS.

However, the case raises questions about what the next data monitoring committee should do when statistically significant differences in PFS emerge early. This may sound like a hypothetical situation, or a situation limited to the context of Afinitor or Sutent. It isn't.

Something similar occurred in the trial E2100 that led to an accelerated approval of the Genentech drug Avastin (bevacizumab) for metastatic breast cancer.

In a decision memorandum that lays out the FDA rationale for proceeding to withdraw Avastin's breast cancer indication, Richard Pazdur, director of the FDA Office of Oncology Drug Products wrote:

"The evaluation of PFS in E2100 was based on an interim analysis. E2100 was stopped early when 65% (357/546 of the planned events had occurred). Stopping a trial early for efficacy based on an event-driven, pre-planned analysis with pre-specified allocation of type I error ensures that a valid statistically significant result has been obtained. However, the estimate of the treatment effect based on an interim analysis is more variable than at the study completion and may represent a 'random high' estimate of the true effect size of Avastin in that trial. In contrast, nearly all the planned events were observed in the AVADO and RIBBON1 trials and the trials were not stopped early. Although all three trials demonstrate a statistically significant result for PFS, it is possible that the magnitude of effect observed in the E2100 based on the interim analysis represents a random high and that the true effect is more consistent with the smaller effect seen in the other trials."

The memorandum is posted at: http://www.cancerletter.com/categories/documents.

The Sutent situation isn't identical to Avastin. The Pfizer drug study was stopped not only due to a difference in PFS, but also due to a higher number of deaths and SAEs in the placebo arm.

These potential pitfalls of reliance on PFS have to be accepted as characteristics of the regulatory paradigm Pazdur created.

Soon after coming to FDA in 1999, Pazdur started to create a theoretical framework that would make it possible to approve drugs based on metrics of delay in progression. This could allow the agency to get away from granting accelerated approvals based on tumor shrinkage observed in large single-arm phase II trials.

Pazdur wanted to explore the idea of granting accelerated and full approvals based on the same trials, a practice common in approval of HIV drugs.

According to his initial schema, drugs could get accelerated approval based on delay in progression demonstrated in large phase III trials.

As the agent hits the market based on a protocol-specified interim analysis, the trials would continue to determine whether the metric used as a basis for accelerated approval produces a survival benefit.

This approach worked with some solid tumor drugs. However, oncology is very different from HIV.

As discussions of metrics went on, FDA started to recognize that a delay in progression as a benefit in

its own right that could support full approval for some indications.

After that shift occurred, ODAC has been asked repeatedly to determine how much PFS improvement is sufficient to justify approval.

A Benefit of the Doubt for Rare Indication

If the agency decides to follow ODAC's advice, Sutent and Afinitor could be used in a broad indication that spans a variety of diseases lumped together as pNET. Some of these diseases are indolent, others aggressive.

ODAC Chair Wyndham Wilson voted for approval of both drugs.

"This is a drug that does have serious side effects," Wilson, chief of the Lymphoma Therapeutics Section of the NCI Center for Cancer Research, said in discussion of Afinitor.

"It's a drug that has effectiveness as well," Wilson said. "And I think this is a drug where the risk-benefit is going to be greatest in people who need therapy. I really am convinced of that when I look at the subgroup analysis, because all the hazard ratios are more favorable in patients who have worse performance status, who are older. It seems to benefit those at higher risk. If there is some way to label this, so we would be enhancing the risk-benefit for patients."

Later that day, Wilson lamented the early termination of the Sutent trial.

"This is a very unfortunate example of where a trial was stopped early in good faith," he said. "It's made our jobs and physicians' jobs more difficult. But in the end of the day, despite the small sample size, I would have to convince myself that these numbers were half of what the lower bounds of the FDA's hazard ratio guidelines are."

Wilson said he voted for the drug because pNET is a "rare disease in which there are very few options."

"I think that it is always useful to get another study done, and so I would say that's a good idea for the sponsor. But I have to say that I wouldn't have voted yes if I didn't feel that, under these settings, this drug shouldn't be made unavailable.

Biostatistician Brent Logan voted for approval of Afinitor, but against approval of Sutent.

"There appears to be a fairly sizable magnitude of benefit—progression-free survival—in a number of different analyses, given the potential for bias," said Logan, associate professor of biostatistics at the Medical College of Wisconsin. "There were concerns, and I share those concerns, over delineation of patients who really need the drug, given that many patients have indolent disease."

Later that day, Logan was unwilling to give the same benefit of the doubt to Sutent.

"The fact the study was stopped early with a very small sample size and small number of events just raised too many questions for me to judge the magnitude of the treatment benefit—and the ability to really get an assessment of the survival, and those kind of things," he said.

Mikkael Sekeres, associate professor of medicine at Cleveland Clinic Taussig Cancer Institute, similarly voted for Afinitor and against Sutent.

"My caution is to avoid using this drug in patients with carrcinoid tumors, in whom no benefit has been demonstrated and in whom the drug may actually do harm," he said of Afinitor.

Casting a vote against Sutent, Sekeres said he wanted to see more data.

"This drug has modest activity, but I don't know of the content or durability of that activity," he said. "Since so many [ODAC] members have voted and called for more studies, I'd rather call for more studies prior to approval than after."

After the votes were cast, Pazdur asked ODAC members to suggest additional studies for Sutent.

"Many of you commented on the need for further studies of this drug—obviously if the drug was approved, a placebo-controlled trial would probably be impossible and imprudent to do—so could people comment on the studies they would like to see on this drug?" Pazdur said.

David Kelsen, chief of Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, suggested streptozocin, a drug often used to treat these tumors.

"I was thinking about how streptozocin [a drug used to treat pNET] has been dragged through the mud over and over again," Kelsen said. "Everybody thinks 1980 toxicities apply in 2010. They don't. We have great anti-emetics—I use a ton of streptozocin. It's a very well tolerated drug.

"That's what I would randomize against: streptozocin."

Conor Hale contributed to this story.

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Decision to Stop Sutent Trial Early Protected Patients, Chariman Says

Immediately following the ODAC meeting, The Cancer Letter editor Paul Goldberg discussed the outcome with Mace Rothenberg, senior vice president, clinical development and medical affairs at Pfizer Inc., and Robert Maki, chair of the independent data monitoring committee that recommended stopping the Sutent trial. Maki is a pediatric oncologist and medical director of the Sarcoma Cancer Program at Mt. Sinai Medical Center's Tisch Cancer Institute.

Novartis officials declined The Cancer Letter's request for an interview.

TCL: *These are interesting cases, both of them, which is a bad thing, perhaps.*

ROTHENBERG: I think it's the other way around. A lot went right. We now have two more drugs to treat a rare, difficult disease that didn't have very many options. The discussions were robust, very thoughtful, and they brought out some important points. But the bottom line is, as you can see from the vote, the majority of the members of ODAC felt that there was a favorable benefit-risk ratio for the use of sunitinib in patients with pancreatic NET.

TCL: *How will these drugs shake out against each other?*

ROTHENBERG: I think only time will tell. There is no head-to-head data. We heard some discussion regarding the kinds of trials that investigators may be interested in doing, and we are certainly willing to entertain any possible options that will allow us to develop better treatment options for these patients.

TCL: *Is there a lesson to be learned about data safety monitoring boards?*

ROTHENBERG: I'll let Bob answer this question. But when I think about what the independent data monitoring committee provided to this trial is an independent unbiased view of how the trial is going with a focus on patient safety. It's impossible to put into a DMC charter every possible scenario no matter how much you try. You can put in limits for efficacy. But very rarely are there limits or guidelines regarding how to evaluate multiple elements of risk and benefit, especially when they are all lining up in the same direction. I think that's what happened here. I will turn over to Bob to elaborate on that.

MAKI: It was a real challenge. And it was brought out really well by ODAC, the struggles they have when the data are not pristine and the strongest they can be. At the same time, the IDMC is constructed to watch out for patient safety on a micro level instead of a macro level.

We struggled with this decision, because we knew it could impact the ultimate endpoint of a study, which would potentially cause problems for the greater population of people with pancreatic NET.

But at the end of the day, seeing the greater number of deaths, seeing the separation of the survival curves, as opposed to the primary endpoint, that led the IDMC to the decision to recommend stopping the study and let the chips fall where they would. It was a struggle for ODAC with those data as a result, but we are happy that, as Mace mentioned, there are now two drugs available to this population of patients that don't have great options.

TCL: *How do you think this will this shake out?*

MAKI: The survival data, at least initially, there was a difference between placebo and treatment. There is significant activity of the drug. But the risk-benefit ratio is definitely in favor of treatment, and I think that's why we saw the vote go the way that it did today.

TCL: *From the point of view of patient protection, is there a lesson there? What's the larger lesson to be learned? Of course, the patients in the trial are important, but there is also a larger population of patients who would benefit from more robust answers to questions about this drug.*

MAKI: This is right on a cusp. Some data will be more clear, and some would be less clear. And when the data are less clear, that's when the trial continues. And this just crossed that threshold to us. But it allowed us a very important function to minimize the number of deaths that occur on-study as a result of not getting the appropriate therapy. That's what we are charged with. But that also has to be balanced against the fact that if the data are not strong enough, then the entire community is at a loss. That's what the struggle was throughout the study.

TCL: *Would you do this again?*

MAKI: I would. Given similar circumstances, I would do the same thing. I think the IDMC was comfortable with the decision they made, given the data that they had.

European Committee Broadens Avastin's Use in Breast Cancer

The European Committee for Medicinal Products for Human Use changed its stance on the combination of Avastin (bevacizumab) and Xeloda (capecitabine) for first-line treatment of metastatic breast cancer.

CHMP issued a positive opinion for an extension to the Avastin breast cancer label to include the use

of Avastin in women for whom treatment with other chemotherapy, including taxanes and anthracyclines, is inappropriate, the drug's sponsor, Roche, announced on April 15.

In Europe, Avastin is approved in combination with paclitaxel chemotherapy for metastatic breast cancer. In the U.S., FDA seeks to remove the drug's breast cancer indication.

The Avastin submission by Roche was based on results from the phase III RIBBON 1 study, which demonstrated a significant increase in progression-free survival for the Avastin-capecitabine combination, compared to those who received capecitabine alone.

The RIBBON 1 study showed that Avastin in combination with capecitabine could give these women an additional first-line therapy choice. Final approval from the European Commission is expected later this year, the company said.

"We are pleased the CHMP has determined that Avastin in combination with capecitabine provides a meaningful clinical benefit in metastatic breast cancer, affording physicians and patients more choice in selecting an appropriate treatment option," Hal Barron, chief medical officer and head of global product development, said in a statement. "Avastin is the only anti-angiogenic therapy approved to treat HER2-negative metastatic breast cancer in Europe and the capecitabine data from the RIBBON 1 study, which was the basis of this positive opinion, add to the clinical evidence supporting the use of Avastin as a treatment for this disease."

RIBBON 1 showed that Avastin in combination with capecitabine resulted in:

• A 45 percent increase in the likelihood of women being alive without disease progression compared to those who received capecitabine alone (hazard ratio=0.69; p=0.0002).

• A median PFS of 8.6 months compared to 5.7 months in those women that received capecitabine alone.

• 35.4 percent of women experienced a major shrinkage of their tumor, compared to 23.6 percent of those receiving capecitabine alone (p= 0.0097).

The latest opinion partially reconsiders the opinion CHMP issued last December. The EMA at the time confirmed that Avastin in combination with paclitaxel was shown to extend PFS.

At that time, CHMP recommended the removal of the combination of Avastin with docetaxel and recommended against a label extension with capecitabine.

On July 20, 2010, the ODAC reviewed the results of the AVADO and RIBBON 1 trials and voted 12-1 to recommend against the use of Avastin in combination with chemotherapy for first-line treatment of metastatic breast cancer and recommended the withdrawal of the accelerated approval of the first-line breast cancer indication.

An FDA hearing on removing Avastin's breast cancer indication is scheduled for June 28-29. Roche seeks to keep an accelerated approval while it conducts a confirmatory trial of the Avastin-paclitaxel combination.

Guest Editorial:

Potti Launches Multiple Websites To Displace Negative Stories

(continued from page 1)

The obvious clue that a reputation management company was behind the effort was the fact that an online database showed that AnilPotti.com was registered to the email address accounts@onlinereputationmanager.com. In an industry where clients are best served behind the scenes, the visible link between Potti and the company was a misstep.

Another site, DrAnilPotti.com, focuses on the places where Potti has lived: India, North Dakota and North Carolina. Another, PottiAnil.com, details the doctor's work with different types of cancer and cites Potti's publications in major journals, neglecting to note the numerous retractions.

The site contains inspirational sayings by Eleanor Roosevelt, Winston Churchill, William Faulkner, Jimmy Valvano—and Anil Potti.

"Dr. Anil Potti believes in treating the entire person—not just the disease," the site reads. "His motto (one that he learned from one of his patients) which has helped him during his own personal battles and one that he always tries to pass on to his patients is 'Hope beats despair everyday [sic.] of the week and twice on Sundays.'"

Press releases published in recent months tout awards the scientist won years ago (in one case, as a resident in North Dakota) and note that Potti enjoys spending time with his family.

Social media accounts, on sites such as LinkedIn, Twitter and Facebook, were filled with links to the newly created sites about Potti—another telltale sign that they were run by a reputation management firm. The practice, called backlinking, helps promote the pages on Google by taking advantage of search algorithms.

After seeing all this activity, I called the firm. Ronald Smith, manager of business development,

told me that Online Reputation Manager is willing to work with clients as long as they are not attempting to hide criminal activity that has not been reported to the authorities. Smith declined to comment on Potti's case specifically, but said that the company accepts about 90 percent of the individuals who seek the firm's assistance. The company takes on between 40 and 45 new projects a month, he added.

"Offline, a lawyer is hired to help them out, fight their case—I think we're the online lawyers," he said. "So it's quite ethical, on our part, and I think quite right to help them out at a certain charge."

Online Reputation Manager typically charges clients by the number of key phrases, or search terms, that drive the most traffic to what the company calls "offensive listings." One key phrase—"Anil Potti," for example—costs $500 a month for four months, after which the customer can purchase a maintenance plan for $400 a month. The specialists focus on the top page of search results, which far more searchers view than subsequent pages.

Potti hasn't returned my calls or emails, so I asked Smith to let the doctor know that I was interested in asking him about his efforts to improve his image. Smith agreed to be my conduit. Alas, this failed to produce a conversation with Potti.

Jerome Kassirer, former editor-in-chief of The New England Journal of Medicine, one of the publications that retracted a Potti paper, said it appears that Potti is trying to manipulate his image, which he characterized as a "shady" activity.

Hiring an online reputation management firm may not be illegal, though, so he said Potti "can probably do just about anything he wants without any substantial sanction," Kassirer said.

Where Potti crossed the line, according to Kassirer, was by making it more difficult to find retraction notices that Potti himself approved, such as in the Journal of Clinical Oncology, Nature Medicine, The Lancet Oncology and NEJM—"an enormous number of important retractions," Kassirer noted.

When should doctors acknowledge past transgressions?

"Only when the issues are serious," Kassirer said. "A resignation and retraction seems to me to be serious. So, sure, you might not publicize everything that you've done, the negative things, but if you've done some substantial and important negative things such as publishing a paper that had to be retracted, or you were required to resign from an important institution, then it seems to me that to not acknowledge that is inappropriate.

"It sounds like he has...crossed the line by not giving the whole story," he said. "It seems to me inappropriate and unprofessional."

Roy Poses, president of the Foundation for Integrity and Responsibility in Medicine and a professor at Brown University, said Potti promoting himself online is a part of larger trend of the commercialization of medicine.

Poses, a blogger, said he is troubled by the growth of advertising in the industry, which he noted would have been "unthinkable" 30 years ago. The culture of advertising—making your product look as good as possible without commiting fraud—is troubling for the healthcare industry, he noted.

Poses said it is difficult to scientifically isolate the effect of advertising on the industry from other major changes that have contributed to the commercialization. But, he said, healthcare evolving into a highly commercialized field is probably one of the strongest reasons why the United States has the world's most expensive healthcare rates per capita—along with major problems of access, a large number of uninsured patients and a quality of care that is "certainly not better" than many other countries.

"I think [advertising is] not good for healthcare, because patients aren't in a position to pick physicians, hospitals [and] medical treatments the way they pick automobiles. Things are too complicated, they're too technical, they're too uncertain and there's too much emotion caught up in decision, so exposing patients to advertising's psychological manipulations is just likely to make things worse."

Sheldon Krimsky, an expert on medical conflicts of interest and a professor at Tufts University, said that efforts to influence search engine results aren't necessarily unethical. However, undercutting or voiding charges made against him by journals or other authoritative bodies can easily cross the line.

"If he says anything that has been disputed by an authoritative body, it would be unethical for him to promote himself in that way," said Krimsky.

Appropriations:

Congress Passes Spending Bill; Cuts $210 Million from NIH

By Conor Hale

The House, Senate and the president have finally crossed the 2011 budget off their list of funding debates—just in time to begin deliberating over the 2012 budget and raising the national debt ceiling.

On April 14, Congress passed a resolution that would fund the government through Sept. 30, after weeks of debate, brinksmanship and deadline extensions. One main issue holding up passage was federal funding for Planned Parenthood.

The House passed the bill 260-167; the Senate voted in favor 81 to 19.

The bill, H.R. 1473, cuts the NIH budget by $210 million. This cut would be spread out proportionally, based on total funding, between all NIH institutes, centers and the office of the director. The measure allocates $50 million for NIH buildings and facilities for the remainder of this fiscal year.

The bill also calls for an audit of NIH's grants and research funding, to be performed by the Government Accountability Office and submitted to Congress within the next 60 days.

The study would focus on funding allocated by the Recovery and Reinvestment Act—the stimulus bill—and would include a list of NIH grants made for "comparative effectiveness research," and descriptions of each.

Professional Societies:

AACR Attendance Down 5 Percent; ACS Awards $51.4 Million in Grants

THE AMERICAN ASSOCIATION FOR CANCER RESEARCH registered more than 16,000 people from all over the world for its 102nd Annual Meeting 2011 in Orlando, April 2-6. This number is down 5 percent from last year.

According to the AACR, 75 percent of the nearly 550 Japanese registrants were able to attend the annual meeting. All invited speakers from Japan were able to attend. The AACR is communicating with its members in Japan and will provide them with timely and pertinent information about research presented during the annual meeting, they said.

The AACR said it would work with its partner organizations in Japan to determine how it can best be of assistance to its friends and colleagues affected by the recent tragedies.

THE AMERICAN CANCER SOCIETY awarded 132 national research and training grants to 85 different institutions, totaling $51,473,000.

This second grant cycle begins July 1. There are 118 new grants and 14 renewals.

Grant applications were chosen by several discipline-specific peer review committees, each comprised of 12 to 25 scientific advisors or expert reviewers. The Council for Extramural Grants, a committee of senior scientists, recommended funding based on the relative merit of the applications, the amount of available funds, and the society's objectives.

The council also approved 82 research grant applications that could not be funded due to budgetary constraints. They will be granted if additional funds become available. More information about the ACS Research Program can be found at http://www.cancer.org/research.

Across several categories, the recipients include:

Cancer Causes

• **Anny Shai**, from the University of California-San Francisco, will study connections between two oncogenes and tumor angiogenesis in lung cancer cells, with the goal of providing information valuable in designing targeted therapeutics.

• **Erik Kline**, of Emory University, will focus on the molecular steps that lead tumor cells to metastasize, with the goal of identifying subsets of lung cancer patients with a mutation that can be targeted for anti-metastatic drug therapies.

• **Sheila Stewart**, from Washington University in St. Louis, will investigate the relationship between cancer cell mutations and non-mutational changes in the stroma. She will analyze how stroma contributes to tumor development and tumor progression.

• **Jeremy Nance**, of the New York University School of Medicine, will study how epithelial cells make connections with one another and keep one another from dividing uncontrollably and from invading other areas, as a basis for new approaches in treatment.

Cancer Treatment

• **Arden Morris**, of the University of Michigan, will investigate how trust, communication, and the patient-provider relationship influence the use of chemotherapy among a diverse, population-based sample of 1,000 recently diagnosed colorectal cancer patients in the Detroit and Atlanta cancer registries.

• **Edith Crumb**, at the University of Louisville Kent School of Social Work, will explore the psychosocial needs of siblings of pediatric cancer patients and children who have lost a sibling to cancer, and developing interventions to meet those needs.

Detection and Prevention

• **Jesse Nodora**, of the University of Arizona, will use patient navigation and health literacy education to facilitate follow-up care and increase the number of women with timely diagnosis and initiation of treatment for cervical dysplasia or cervical cancer in a medically underserved community health center population.

Preclinical and Translational Research

• **Jin Xu**, working in the laboratory of American Cancer Society Research Professor Kevin Shannon at UCSF, is working to understand why changes in the N-RAS gene can cause leukemia, while other members of the RAS gene family cannot. Leukemia mutations in the RAS gene family preferentially occur in the N-RAS member.

• **Daniel Costa**, at Beth Israel Deaconess, is analyzing lung cancer patient tumors that develop drug resistance to identify mutations that arise during therapy. The characterization of such mutations will guide second generation drug development.

• **Ramanuj Dasgupta** at the NYU School of Medicine and **Naoaki Fujii** at St. Jude Children's Research Hospital are developing inhibitors as drug candidates by focusing on different parts of the WNT pathway, aberrations in which are associated with a wide range of tumor types, including liver, colon, breast, pancreas, bone, lung, and skin. It is estimated that more than 80 percent of colon cancers are driven by mutations in this pathway.

• **Mark Chiang**, at the University of Michigan, is focused on inhibitors of two genes, NOTCH and TLX1 both of which are found at much higher levels in acute lymphocytic leukemia. They will test novel drug combinations in a unique mouse model in which they can readily turn on and off some of the genes which allow ALL to develop.

Clinical Cancer Research and Immunology

• **Gang Chen**, of the University of Kentucky, will study how arsenic induces cell transformation leading to cancer.

• **Patrick Brown**, of Johns Hopkins University, will test whether new drugs lead to more effective treatments for children with leukemia caused by mutations in the MLL gene.

• **Fiona Simpkins**, of the University of Miami, is studying how to reverse the resistance to drugs targeting estrogen-resistant cancers and use combination therapies to prevent anti-estrogen resistance or treat anti-estrogen resistance ovarian cancer.

Cancer Survivorship

• **Jessica Keim**, at the University of Virginia, will study the experience of young women cancer survivors by analyzing their online postings and connections. She will use this information to understand how they describe their overall experience with cancer, understand barriers that exist in accessing the healthcare system, and the physical, emotional, and psychological impacts of the disease during treatment and beyond into extended survivorship.

• **Emily Tonorezos**, at Memorial Sloan-Kettering Cancer Center, will receive a career development award that will help her investigate diet and insulin resistance in survivors of childhood cancer.

• **Elizabeth Kvale**, of the University of Alabama at Birmingham, will evaluate an intervention designed to empower cancer survivors to manage their survivorship.

THE UNIVERSITY OF MICHIGAN A. Alfred Taubman Medical Research Insitute has announced its new round of Taubman Scholars, who will receive grants to conduct "high risk, high reward" research. In addition, four Emerging Scholars were appointed, who are early in their careers but show great promise in medical research.

The 15 Taubman Scholars will receive three-year grants of $150,000 per year. The Emerging Scholars will receive $50,000 a year for three years. In addition, four of the original scholars have been named Senior Taubman Scholars, and will continue their research with grants of $50,000 per year for the next three years.

The Taubman scholars will receive unrestricted funding from the institute's endowment. The Emerging Scholars are funded by gifts from members of the institute's leadership advisory board and their families. The donors are Edith Briskin, Frances and Kenneth Eisenberg and the Marvin and Betty Danto Family Foundation.

The new Taubman Scholars include:

• **Arul Chinnaiyan**, the S.P. Hicks endowed professor of pathology, professor of urology, director of the U-M Center for Translational Pathology, and Howard Hughes Medical Institute investigator. Chinnaiyan was the first to discover gene fusions in a common solid tumor—the joining together of two separate genes

thought to be an important mechanism in prostate and other cancers. His lab is exploring whether gene fusions can serve as a biomarker for the characterization of the cancer, allowing clinicians to know how aggressive a case of prostate cancer is likely to be and how best to treat it.

• **Theodore Lawrence**, Isadore Lampe professor and chair of department of radiation oncology. Lawrence is studying how to combine radiation most effectively with molecularly targeted drugs to provide the best treatment for patients with liver and pancreatic cancer.

• **Kenneth Pienta**, professor of internal medicine and urology; director of experimental therapeutics at the Michigan Center for Translational Pathology; and principal investigator in the Specialized Program of Research Excellence in Prostate Cancer. Pienta's research focuses on how prostate cancer cells metastasize to bone.

The Emerging Scholars include:

• **Ronald Buckanovich**, assistant professor of internal medicine, obstetrics and gynecology. Buckanovich is studying novel diagnostic tests and therapeutic agents for women's cancer, including breast and ovarian. His laboratory is developing immune-based therapies that can specifically kill the blood vessels of tumors and has identified two drugs that directly target cancer stem cells.

• **Erika Newman**, assistant professor of pediatric surgery. Newman is exploring the role of DNA repair in the development of the often fatal childhood cancer neuroblastoma. She is studying the effect of faulty DNA repair in the embryonic development of the neural system, which may provide insight into the origins of neuroblastoma and allow a more targeted approach to effective treatment.

The Senior Taubman Scholars include:

• **Valerie Castle**, Ravitz professor and chair of the Department of Pediatric and Communicable Diseases, and pediatrician-in-chief and director of the Institute's Neuroblastoma Research Program. Castle is conducting a clinical trial of new drug that may reduce the chemotherapy resistance of neuroblastoma. In addition, by comparing embryonic stem cell lines differentiated into neural crest stem cells with neuroblastoma cancer cells established in her laboratory, she hopes to gain insights into the origins of the disease.

• **Max Wicha**, founding director of U-M's Comprehensive Cancer Center, distinguished professor of oncology and internal medicine. Wicha leads a team that is conducting the world's first three human clinical trials targeting cancer stem cells, aimed at stunting the growth of these cells, which he believes drives the growth of tumors or makes them less resistant to other therapies.