THE CANCER LETTER

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SPECIAL ISSUE

Drug Shortages Prompt Doctors, Societies To Consider Non-Profit Pharma Company

By Paul Goldberg

The market hasn't been working very well in producing enough generic drugs lately.

The government hasn't done much to correct the problem, either.

This year alone, as many as 180 different generic drugs have been affected by shortages.

In oncology, drugs in short supply include cytarabine, daunorubicin, doxorubicin, leucovorin, 5-FU, cisplatin and paclitaxel.

To solve the problem, several players in oncology are considering novel ways to produce generic drugs, as well as drugs that have no chance to become blockbusters, or for that matter, even modest sellers.

One group of prominent oncologists is circulating a proposal—and trying

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The Duke Scandal:

Duke Researchers Retract Paper From Blood; Dozens of Retractions of Potti's Work Expected

By Conor Hale

The journal Blood published a retraction by a group of scientists including former Duke University researcher Anil Potti—continuing a cascade of retractions of the group's work over the past several months.

Additional retractions of papers published by Potti during his time at Duke are in the works, university officials said.

The 2006 paper—which claimed that gene-expression patterns could predict the possibility of thrombotic events—was retracted by the authors Aug. 19. The retraction states that the authors "have been unable to reproduce the results that were performed independently by the first author, Anil Potti, regarding validation of predictive models for thrombotic phenotypes."

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Clinical Trial Participants Sue Duke University, Potti, Nevins and Others For Causing Harm

By Lucas Thomas

Patients participating in Duke University clinical trials of a discredited genomic technology filed two separate lawsuits against the university, its top officials and cancer researchers earlier this week.

The two lawsuits filed Sept. 7 in the Durham County Superior Court claim that Duke and its researchers had "knowingly engaged in a plan to generate billions of dollars in revenue; and that rather than actively protecting

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Citizens Oncology Foundation Seeks $2 Million Investment

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to obtain funding—to create a non-profit pharmaceutical company that would produce generic drugs.

The group, called Citizens Oncology Foundation, has approached professional societies and advocacy groups in an effort to raise $2 million, hoping to supply at least one cancer drug affected by the shortages. The proposed non-profit would need as much as $20 million to become self-sustaining, organizers say.

The mission of the foundation is broader than addressing the shortages of generic drugs. Its goals also include developing drugs that fail to generate interest from pharmaceutical companies—either because intellectual property protection is too weak, or because the potential markets are too small.

COF is trying to obtain financing at a time when shortages of older, inexpensive drugs are threatening the foundations of oncology practice—drugs that are used in both standard care and clinical trials. Several other entities have been considering forming non-profits that would produce cancer drugs, The Cancer Letter has learned. Also, NCI officials have said that they are weighing the options of acquiring and distributing finished drugs or bulk drug supplies, which are unaffected by shortages.

FDA is trying to figure out what to do as well.

On Sept. 26, the agency will hold a public workshop on drug shortages. The gathering would "provide information for, and to gain additional insight from, professional societies, patient advocates, industry, consumer groups, health care professionals, researchers, and other interested persons about the causes and impact of drug shortages, and possible strategies for preventing or mitigating drug shortages."

COF would likely be a "virtual drug company," its founders say. It would have no manufacturing facilities. Instead, the company would license or establish Abbreviated New Drug Applications and contract with manufacturers to make drugs. Also, the company may seek to import drugs produced outside the U.S.

The foundation is seeking initial funding from professional societies, charities and advocacy groups, including the Leukemia and Lymphoma Society and the American Society of Clinical Oncology.

"We have been in discussions," said George Dahlman, LLS senior vice president for public policy. "It's not much more than discussion at this point. We are trying to figure out how this could be done and what would be involved."

The LLS had been considering starting a similar enterprise before they were approached by COF, Dahlman said. "The fact that they were starting to think about it and we were starting to think about it is a happy coincidence."

Now, the LLS is waiting to see whether ASCO would get involved.

"We really want to have ASCO leadership involved with this," Dahlman said. "We don't know what form this would take, but I guess their board is supposed to discuss that in a couple of weeks."

ASCO President Michael Link said the society is reviewing a variety of approached to resolving the problem of drug shortages.

"The cancer drug shortage problem is one of the most distressing developments we've seen in oncology," Link, the Lydia J. Lee Professor of Pediatrics at Stanford University School of Medicine, said in a statement.

"ASCO is exploring every viable idea to solve the problem, and at this stage we are listening to concepts involving a non-profit drug company model and any other potential solutions. We are also pursuing all possible legislative and regulatory fixes with Congress, FDA, other medical societies, and patient groups in an effort to permanently solve the problem."

The foundation has not been formally registered. Its directors are:

• George Tidmarsh, who also serves as the CEO, is a pediatric oncologist who has worked in the pharmaceutical industry for over two decades, most

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Editor & Publisher: Paul Goldberg
Copy Editor: Conor Hale
Intern: Lucas Thomas

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recently as chief scientific officer and head of research and development at Spectrum Pharmaceuticals Inc., a company that has benefited from the shortages of the old generic drug leucolorin by selling the far more expensive branded drug Levoleucovorin (The Cancer Letter, Jan. 16, 2009).

• Laurence Baker, chair of SWOG, a clinical trials cooperative group, and

• Gabriel Hortobagyi, chair of the Department of Breast Oncology at MD Anderson Cancer Center.

Mark Ratain, chairman of the COF scientific advisory board, has been contemplating forming a non-profit drug company for several years.

The non-profit drug development model has the potential to solve problems that are deeper than the shortage of generic drugs, said Ratain, the Leon O. Jacobson Professor of Medicine and director of the Center for Personalized Therapeutics at the University of Chicago Comprehensive Cancer Center.

"The generic drug shortage could conceivably be solved through legislation and better regulation," Ratain said. "Those are the barriers: restrictive restrictive regulation and the legislation that impeded free-market pricing of generic drugs.

"I would also like to solve the other challenge, which is bringing forward useful drugs for smaller and smaller populations. At some point, we will have pricing controls, and at some point pricing constraints will make it extremely difficult to finance the development of novel drugs for small-marker indications, not to mention developing competitors to some of the expensive, branded drugs that would be equally effective and much less expensive."

In an interview with The Cancer Letter, Tidmarsh said he decided to join the non-profit after meeting with his mentor Link, who first learned about the non-profit in a conversation with Ratain and became involved in the project before being elected president of ASCO.

Link was not available to speak with a reporter by deadline.

The idea of forming a non-profit was in the air, Tidmarsh said. "It was just a bunch of people having the same idea, and we all ended up in the same place at the same time."

The non-profit's business plan includes a lengthy discussion of the causes of drug shortages. Excerpts of the document are posted at http://www.cancerletter.com/categories/documents.

The text of the executive summary of the COF business plan follows:

Citizens Oncology Foundation (COF) is a not-for-profit oncology entity founded to fix critical healthcare problems in oncology that are not being addressed by the biotechnology and pharmaceutical industries. Currently, the primary unmet need results from the widespread shortage of generic oncology drugs. Secondarily, industry ignores the development of potentially safe and effective new drugs due to insufficient intellectual property protection or market size. These two needs of the oncology community will be address by COF in that order of priority.

The drug shortage resulted from many deficiencies in the current for-profit system working together to cause a growing list of over 100 drugs to be unavailable for important medical indications. Oncology has been among the most severely impacted due to the lack of substitute therapies and the fact that many or most of these drugs provide the patient with life-prolonging or life-saving treatment. The current industry deficiencies include lack of financial incentive, manufacturing quality problems and limited manufacturing capacity. COF intends to provide short, medium and long-term solutions to fix or circumvent these barriers and provide an available, consistent, cost-effective supply of these oncology drugs.

Mission

1. Provide patients and oncologists uninterrupted access to critical oncology medications either in short supply or threatened to be in short supply. Offer oncologists information and tools to manage the drug shortage.

2. Develop innovative oncology drugs that are of low interest to traditional biotechnology or pharmaceutical companies because of intellectual property and/or market size concerns.

Start-up Keys to Success

The keys to success for COF are as follows:

1. Obtain initial capitalization.

2. Establish key partnerships with [professional societies or advocacy groups.]

3. Identify the fastest solution to the generic shortage problem for a list of 6 top drugs.

4. Identify longer-term solutions to provide an available consistent supply of these drugs.

5. Identify key problems, with solutions, in the regulatory and pricing environment contributing to the

shortage problem.

6. Attempt to utilize existing distribution system and GPO (Group Purchasing Organization) infrastructure currently in place.

7. Recruiting top-notch management with the skill set to implement the solutions.

8. Develop programs in partnership with ASCO to help oncologists manage the drug shortage.

9. Develop a plan for sustainable funding of the mission.

Implementation of Solutions

COF will explore every legally available route to provide quality drugs to the oncology community to alleviate the shortage. These avenues include:

1. Obtain existing Abbreviated New Drug Applications (ANDAs) allowing us to manufacture, sell and distribute in the US.

2. Establish our own ANDAs allowing us to manufacture, sell and distribute in the US for those drugs for which we cannot obtain an existing ANDA.

3. Import and distribute final drug product from FDA-approved, ex-US sources. We have already made progress on our goals. On August 25, 2011 we met with FDA and gained clarity on our key questions. We have identified and contacted target companies for purchase of an ANDA.

In addition, we have identified potential ex-US sources of final drug product for several of our priority drugs.

Financial Requirements

We are seeking to raise $2M in order to succeed in supplying at least one shortage drug to oncologists. We expect that we will need $10-20M to get to a self-sustaining revenue flow.

The Duke Scandal:

Duke Identifies 40 Potti Papers Of Which 2/3 Will Be Pulled

(Continued from page 1)

In recent months, Potti papers have been retracted by The New England Journal of Medicine, Nature Medicine, The Lancet Oncology, and The Journal of Clinical Oncology.

Separately, patients who had been enrolled in clinical trials that tested the technology developed by the Duke genomic scientists filed two separate lawsuits, claiming that they had been harmed.

In those trials, patients were assigned to chemotherapy treatments based on genomic predictors developed by Potti and his mentor Joseph Nevins, also of Duke. Patients claim that the clinical trials were fraudulent and that they went through unnecessary and improper chemotherapy as a result.

The suits against the researchers, Duke University, the Duke University Health System and their officers, were filed in the Durham County Superior Court on Sept. 7. See the full story on page 1.

The lawsuits were filed at a time when Duke officials continue to investigate Potti's research and—sometimes under pressure—admitting institutional failures to manage conflicts of interest in clinical research, as well as failures to obtain required regulatory approvals.

On Aug. 22, the Institute of Medicine held a meeting to discuss the use of genomics-based markers in clinical trials, the basis of Nevins and Potti's work.

Robert Califf, director of the Duke Translational Medicine Institute and vice chancellor for clinical research, said that the university has nearly completed an internal investigation of Potti's published research.

"There were about 40 [manuscripts] that had original data that were generated at Duke," Califf said. "We had an institutional need to understand the veracity of the manuscripts that had the institution's name on it."

Those 40 manuscripts included 162 co-authors. The university mailed letters to each co-author announcing their intent to review the manuscripts, informing them of the criteria for paper authorship, and asking each co-author if they stood by their work.

"About a third of the manuscripts are being fully retracted," Califf said. "About a third are having a portion retracted with other components remaining intact, and about a third seem to be ok."

"In those retractions and partial retractions, there is a clear correlation between the need to withdraw the

data and the extent to which the data originated from Dr. Potti," Califf said. "It looks like they're fundamentally not reproducible."

No timeframe was given for these retractions.

Inherent Conflicts of Interest Established

Members of the working group of the IOM committee also focused on conflicts on interest that affected the work of the Nevins and Potti group.

According to IOM member Thomas Fleming, professor of statistics and biostatistics at the University of Washington, the informed consent forms for the Lung Metagene Study—CALGB30506—did not acknowledge that study chair David Harpole, currently vice chief of the division of surgical services at Duke University Health System, had applied for a patent on the LMS predictor for lung cancer occurrence only four months earlier.

"Nor was there an acknowledgement of related financial interest of co-chair Anil Potti in that informed consent," Fleming said. "It's our understanding that Dr. Potti was either the PI of the trials at various times, or otherwise at least significantly involved in leadership, where these trials were evaluating genomic signatures for which he held or had applied for a patent, or for which he might have had financial interest in companies that were providing services directly related to the genomic predictors that were under investigation in the trials.

"If so, these issues seem to be creating significant conflicts of interest. What were the measures that were employed to address these, and also were these potential conflicts of interest fully disclosed—and in a timely fashion disclosed—to all relevant parties that would need to know this, including any federal agencies that were involved in funding these trials or related research projects?"

The university usually manages such conflicts, acknowledged Ross McKinney, chair of the conflict of interest committee.

"We generally notify the IRB any time there's a management plan that could affect human research subjects, so that they could include language to the effect that an individual, or Duke, has a conflict," McKinney said. "We notify the IRB; we notify the feds. We notify the feds more often than any other institution about potential conflicts."

McKinney said financial gains from royalties on genetic predictors would make up one percent of the distribution revenue—or one third of the total revenue. At the time, when personalized genetic cancer diagnostics was a field in its infancy, it was very difficult to guess what economic benefit there would be, and how that would fit into the thresholds built into an institution's policy, he said.

"Different institutions have chosen different standards," McKinney said. "Our current standard is that as soon as you begin discussions around licensure or with the IRB, either one, then we're going to be managing the conflict.

"But that's a discussion that continues to be ongoing, because people don't really have clear standards. I don't think that the new federal regulations that will be coming out will help us in regards to the development of new intellectual property and at what point we'd begin to manage that risk."

William Barry, an assistant professor of biostatistics and bioinformatics at Duke, told the committee that he had previously been one of 17 people party to a licensure agreement regarding the links between gene predictors and tumors while collaborating as a biostatistician for Potti and Nevins.

Those conflicts did not occur until the winter of 2009, Barry said.

"That was when I was approached by Dr. Nevins with the Invention Disclosure Form, as the mechanism by which you could disclose the intellectual property interest, and I was offered a percent interest in terms of the research that had been done to define the prospective algorithms in which to apply genomic technologies," he said.

"That was the only contact I had—being able to request and sign a disclosure form," said Barry. "I was not aware of the arrangements that went past that point."

Barry said how members of CancerGuide Diagnostics, a company in which Duke University and the genomic researchers held equity positions, approached him to work as a biostatistics consultant to develop a server and software to run those prospective algorithms.

Barry said he consulted his department chair, and then the dean of the school of medicine, and ultimately the conflict of interest committee, on the best plan to manage the relationship.

"I was given the go-ahead, that as long as you were transparent and going through the right channels that faculty could and couldn't do, that I was encouraged to pursue these relationships," Barry said. "It wasn't until later, when continued issues about the science were being raised, that everyone did get some advice from a mentoring standpoint on whether a biostatistician should have IP interest in the research he's working on. At the time there wasn't that perspective."

IDE's Not Sought or Obtained by Duke

The committee also focused on the decision by Duke researchers not to obtain an Investigational Drug Exception from FDA. Such licenses are generally required, and in this case, not only were the predictors guiding therapy, but invasive biopsy procedures were also used in the clinical trials.

"When you develop a predictor to define or guide selection, that defines an experimental regimen, whose efficacy and safety inherently could be considerably different from that of a caregiver's independent decision making about which agent to choose," said Fleming. "It becomes an experimental regimen that has a different efficacy and safety from the standard of care that wouldn't engage that predictor."

"To that point, there was never any question that this was a research question," responded John Falleta, senior chair of the Duke IRB. "This was research, this was not simply standard of care activities. We were not at all misled by the notion that because these were generally reviewed across the community as comparable therapies therefore this was no longer research. This was a very important research question, and we understood that."

FLEMING: "If you were reviewing this today, would you indicate that an IDE would be necessary?"

FALETTA: "Absolutely. And now we have guidance that we didn't have in 2009 that's very clear, we have Final Guidance Number One, we have had many communications with our colleagues at FDA about this."

"FDA has made very clear several things.

"Number one, the use of an invasive biopsy makes a device more than minimal risk.

"Number two, FDA has made perfectly clear that any new techonology is subject to an IDE, unless FDA says no. It's the newness and the innovation nature of it that has taken away any cloud of uncertainty. And we are grateful for that."

Gilbert Omenn, chair of the IOM committee and director of the University of Michigan Center for Computational Medicine and Bioinformatics, raised questions about the decision by the Duke IRB to allow Potti's mentor and business partner Nevins play a role in investigating the flaws in research of the genomics research group.

The problems were uncovered by two biostatisticians at MD Anderson Cancer Center, Keith Baggerly and Kevin Coombes.

"You mentioned missed signals many times today," Omenn said. "There are other situations when people do stupid or illegal things. Sometimes they get confronted and it all ends right there. It's not like it never happens. And it's awkward. I'm trying to understand this whole conversation of the central role of the IRB.

"The question is first, did you feel it was appropriate for the IRB to be in charge of this kind of investigation?

"Do you think now as the supervisor of the IRB, it's appropriate to turn the whole thing over to Dr. Nevins? That's to say to decide what data will be given to the external reviewers.

"To decide how to present it, and to persuade them what he did in all cases was correct close enough to correct to be sufficient. That whoever decided to suspend the trials had made a mistake and they should resume. Those are big questions to drop on the IRB. What's your retrospective on this, at least."

FALETTA: "I was somewhat peripheral to this whole process because I was out of the country when this whole thing began. While I kept my finger on the pulse during the time, I wasn't attending meetings, I wasn't participating in the discussions that Sally [Kornbluth, vice dean for research at Duke] described, so I can't comment firsthand on any of that.

"To the point of turning things over to Nevins, I don't think that was done. I do understand the point at which you might conclude that, but the actions by John [Harrelson] to share that information with him was done in good faith, and done as a courtesy, rather than done as a abrogation of responsibility the resumption of the trials was a complex process that had to do number one with information back from FDA, response to that information in keeping with our previous experience with the federal trial.

"Lack of information back, lack of response from the FDA to what we thought was the response to them in December, which was a serious attempt to respond and clarify and modify the trial to accommodate the concerns that FDA had.

"And hearing nothing. We felt that it was appropriate to go ahead and proceed.

"In retrospect, we now know that the obligation is on us to pick up the phone and call. And that didn't happen. Email yes, but not call and call and call. We would do things differently."

In commenting on the IOM meeting, MD Anderson biostatistician Keith Baggerly, who is not a part of the committee, said:

"This couldn't have been an easy meeting for the Duke presenters. But at the end of the day, I was left with the impression that the group's leaders did indeed now "get it" with respect to the severity of what happened, and that they were actively trying to deal with the

problems identified in a straightforward fashion. Some things did break down unacceptably, but this fact is acknowledged. These problems are hard, and many are decidedly not unique to Duke.

"I continue to be frustrated by Duke's statements that in 2009-2010, and in particular throughout the period covering the external review, that they saw our (and the NCI's) objections as a normal matter of 'scientific dispute,' and their assertion that the data management and data integrity issues were not recognized. In part, this is because (as I've noted before) we'd tried to make it clear that there were data integrity issues involved, and I don't know what else we could have done to draw attention to the fact."

Baggerly's notes and recordings of the IOM meeting can be found here: http://bit.ly/qWWLnX

Two Cancer Patient Lawsuits Claim Fraudulent, Harmful Care

(Continued from page 1)

the safety and rights of patients in proper clinical trials, they chose a path of conduct that was evasive, deceptive, misleading and fraudulent by falsely representing that the delivery of chemotherapy agents to human subjects was based on valid science, when in fact they either knew or should have known that it was not."

In addition to claiming that patients had been harmed, the two suits focus on two companies owned by Duke and the researchers involved in developing the genomic technology and testing it in the clinic. The companies in question were CancerGuide Diagnostics and Private Diagnostic Clinic, PLLC.

The suits were filed by different lawyers, but contain identically worded claims that patients "under false pretenses, in a fraudulent clinical trial" were exposed to unnecessary chemotherapy.

One suit was filed on behalf of seven participants in the lung cancer trial against the following defendants: Duke University, Duke University Health Systems, Private Diagnostic Clinic, CancerGuide Diagnostics, Joseph Nevins, Anil Potti, Michael Cuffe, Sally Kornbluth, and John Harrelson.

Another, filed by a breast cancer patient, Joyce Shoffner, names the same defendants as well as Paul Marcom, the principal investigator in the breast cancer trial funded by the Department of Defense.

Duke spokesperson Sarah Avery declined to comment on the suits.

"We have no comment on active litigation." CancerGuide Diagnostics and Private Diagnostic Clinic both provide healthcare through facilities owned and/or operated by Duke University and Duke University Health System, the lawsuits state.

In November 2006, Duke genomic researchers Joseph Nevins and Anil Potti, and two other Duke employees—Geoffrey Ginsburg and Judd Staples—founded CancerGuide Diagnostics under the former name Oncogenomics Inc "to capitalize on any financial gain resulting from the alleged cancer breakthrough research," according to the court documents. In the same month, Nevins and the Duke Institute for Genome Sciences and Policy submitted a pre-IDE approval to the FDA for the clinical trials.

The following January, FDA sent Nevins a memorandum in response to the request, stating that the university's submission "contained insufficient information and data." Included in the memo were suggestions and analytical comments from the FDA.

Simultaneously, Keith Baggerly and Kevin Coombes, two biostatisticians at MD Anderson Cancer Center, expressed concern about the legitimacy of Duke's research—claims that directly reached Nevins and Potti.

However the lawsuit claims that nobody in the Duke camp made any attempt to alter the trials' protocols; and no final IDE approval was ever sought or granted before the clinical trials began.

Also included in the lawsuit are allegations of a Duke "cover up."

After the research that formed the baseline for the clinical trials was called into question by NCI, Duke pledged a "genuine investigation and independent review of the Duke research and methodology."

The university appointed Nancy Andrews, dean of the School of Medicine, and Victor Dzau, chancellor for health affairs and CEO of Duke University Health System, to oversee the internal review. Court documents point out that Andrews is married to Bernard Mathey-Prevot, "a Duke researcher whose career is closely tied with Nevins and Potti as a result of past collaboration with Nevins, and recent national journal publication with Nevins and Potti."

The group ignored outside science; and those assigned by Andrews' investigation to analyze the research of Nevins and Potti had no expertise in reviewing laboratory protocols or handling data, the suits state.

The review panel was ordered by Duke to not perform an extensive investigation into the matter and Andrews' appointees buried potentially damaging information for the sake of shielding "the work of the Duke team of investigators including Nevins, Potti, and Mathey-Prevot, from adverse judgment and professional condemnation, and also in an effort to protect the highly valuable proprietary interests of Duke and/or DUHS, its patents, corporations and venture capitalists," according to the lawsuit.

The names of the biostatisticians who eventually recommended that the trials continue were never made publicly available.

Even when the trials were suspended in October 2009, Duke chose to continue treating patients who were already participants.

Duke has retracted five major papers on which Potti figures as an author, and additional retractions are on the way, officials say. Potti has resigned from the university and is practicing medicine at the Coastal Cancer Center in Myrtle Beach, S.C.

The full text of the lawsuits are posted at www.cancerletter.com/categories/documents.

FDA Approvals:

FDA Approves Two Pairs

Of New Drugs and Diagnostic Tests

FDA approved **Zelboraf** (vemurafenib) for the treatment of BRAF V600E mutation-positive, inoperable or metastatic melanoma. FDA also simultaneously approved the cobas 4800 BRAF V600 Mutation Test, a companion diagnostic to identify patients eligible for Zelboraf treatment.

This is one of two drug/diagnostic pair approvals that the agency has granted since it released a draft guidance on companion diagnostic tests in July of this year. The guidance is currently available for public comment.

Zelboraf is the first personalized medicine to show improved survival in people with this mutation-positive melanoma. It inhibits some mutated forms of the BRAF protein found in about half of all cases.

Approval was based on two clinical studies (BRIM3 and BRIM2) in patients identified with the cobas BRAF Mutation Test.

BRIM3 was a global, randomized, open-label, phase III study that compared Zelboraf to dacarbazine chemotherapy in 675 patients with previously untreated mutation-positive melanoma. The primary endpoints of BRIM3 were overall survival and progression-free survival.

The risk of death was reduced by 56 percent for patients receiving Zelboraf compared to those who received chemotherapy (HR=0.44, $p<0.0001$). At the time of analysis, median overall survival of patients receiving Zelboraf had not been reached and was 7.9 months for those receiving chemotherapy.

People who received Zelboraf also had a 74 percent reduced risk of the disease getting worse compared to those who received chemotherapy (HR=0.26, $p<0.0001$). Median PFS was 5.3 months for those who received Zelboraf compared to 1.6 months for those who received chemotherapy.

The confirmed investigator-assessed response rate in people who received Zelboraf was 48.4 percent (1 percent complete responses and 47.4 percent partial responses) compared to 5.5 percent (partial responses) for those who received chemotherapy ($p<0.0001$).

BRIM2 was a single-arm, open-label phase II study that enrolled 132 patients. In this study, Zelboraf shrank tumors in 52 percent of trial participants.

Zelboraf may cause cutaneous squamous cell carcinoma, that usually does not spread.

Possible serious side effects of Zelboraf include severe allergic reactions; severe skin reactions; QT prolongation; abnormal liver function tests; eye problems; or new melanoma lesions.

FDA granted an accelerated approval for Pfizer's **Xalkori** (crizotinib) to treat certain patients with late-stage, non-small cell lung cancers who express the abnormal anaplastic lymphoma kinase gene.

FDA also granted a simultaneous approval for a companion diagnostic test that will help determine if a patient has the ALK gene, the Abbott Vysis ALK Break Apart FISH Probe test.

This ALK gene abnormality causes cancer development and growth. About 1 percent to 7 percent of those with NSCLC have the ALK gene abnormality. Patients with this form of lung cancer are typically non-smokers.

Xalkori works by blocking kinases, including the protein produced by the abnormal ALK gene. Xalkori is a pill taken twice a day as a single-agent treatment.

Xalkori's accelerated approval was based on two multi-center, single-arm studies, enrolling a total of 255 patients with late-stage ALK-positive NSCLC. A sample of a patient's lung cancer tissue was collected

and tested for the ALK gene abnormality prior to study enrollment. The studies were designed to measure objective response rate. Most patients in the studies had received prior chemotherapy.

In one study, the objective response rate was 50 percent with a median response duration of 42 weeks. In the other, the objective response rate was 61 percent with a median response duration of 48 weeks.

The FDA based its approval of the companion diagnostic test on data from one of the studies.

The most common side effects reported in patients receiving Xalkori included vision disorders, nausea, diarrhea, vomiting, swelling, and constipation. Vision disorders included visual impairment, flashes of light, blurred vision, floaters, double vision, sensitivity to light, and visual field defects. Xalkori use has also been associated with pneumonitis, which can be life-threatening. Patients with treatment-related pneumonitis should permanently stop treatment with Xalkori. The drug should not be used in pregnant women.

FDA granted an accelerated approval for **Adcetris** (brentuximab vedotin) to treat Hodgkin's lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. The approval was granted based on two single-arm trials, one covering each indication.

Adcetris is the first new treatment for Hodgkin's since 1977 and the first specifically indicated to treat ALCL. Adcetris is marketed by Seattle Genetics of Bothell, Wash.

Adcetris is an antibody-drug conjugate—the antibody directs the drug to a target on CD30 lymphoma cells. Adcetris is to be used after autologous stem cell transplant or after two prior chemotherapy treatments for those who cannot receive a transplant. In ALCL, Adcetris may be used in patients whose disease has progressed after one prior chemotherapy treatment.

"Early clinical data suggest that patients who received Adcetris for Hodgkin lymphoma and systemic anaplastic lymphoma experienced a significant response to the therapy," said Richard Pazdur, director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

The effectiveness of Adcetris in patients with Hodgkin's was evaluated in one single-arm trial involving 102 patients. The study's primary endpoint was objective response rate, and 73 percent of patients achieved either a complete or partial response to the treatment. On average, these patients responded to the therapy for 6.7 months.

The effectiveness of Adcetris in patients with systemic ALCL was evaluated in a separate single-arm trial that included 58 patients. This study's primary endpoint was also objective response rate, and 86 percent of patients experienced either a complete or partial response and responded on average for 12.6 months.

The most common side effects experienced with Adcetris were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory infection, diarrhea, fever, cough, vomiting, and low blood platelet levels. Pregnant women should be aware that Adcetris might cause harm to their unborn baby.

Obituaries:

Fritz Bach, 77, Developed Techniques to Match Donors

Fritz Bach, a researcher and physician who pioneered the techniques to match compatible donors for bone-marrow transplants, died August 19.

Bach was an assistant professor of genetics at the University of Wisconsin in 1965 when he developed a test that could identify matched patients for organ transplantation. He called it the Mixed Leukocyte Culture test.

In the past, certain leukemias and other related diseases were regarded as fatal. Today, if patients can receive a matched bone marrow transplant, survival rates can be as high as 60 percent.

Bach was born in Vienna, Austria on April 5, 1934. After the country was invaded by Germany, he and his brother escaped to England through the Kindertransport, a rescue mission that helped move over 10,000 predominately Jewish children. They were eventually reunited with their parents in England in 1939, and later relocated to the United States in 1948.

Bach attended Harvard Medical School and served a post-doctoral fellowship at New York University before coming to the University of Wisconsin in 1965.

Bach left Wisconsin in 1980 for the University of Minnesota. In 1990, he returned to Harvard Medical School as a faculty member and researcher, and remained there until his retirement in 2010.

He wrote more than 800 articles for publications including Science, Nature, and the New England Journal of Medicine.

Bach was married twice and is survived by six children and four grandchildren. He was 77.

William Wolff, 94, Helped Invent the Modern Colonoscopy

William Wolff, who helped develop the colonoscopy as it is practiced today, died on Aug. 20.

Working with Hiromi Shinya at Beth Israel Medical Center in New York in the 1960s, they developed a device that could remove a polyp immediately during a colonoscopy, eliminating the need for a second procedure.

The soft, flexible colonoscope solved a longstanding problem: it could negotiate the sharp first turn of the large intestine, allowing it to examine the full five feet of the organ. Previous procedures could penetrate only about 10 inches before being blocked.

The procedure, if done early, can eliminate more than 60 percent of large-intestine growths. More than 1.6 million colonoscopies are performed every year in the U.S.

Wolff served as an Army medical officer during World War II in Europe. Afterwards, he became a surgeon at veterans' hospitals in New York and Butler, Pa., specializing in thoracic surgery.

While at the Pennsylvania hospital, Wolff revived a man who had apparently died while being prepared for a lung operation. He had no pulse or heart sounds for six minutes. Wolff opened his abdomen and massaged his heart until it beat. It was one of the first times a clinically dead person was resuscitated.

Wolff was married twice, and is survived by his five sons, four daughters and 16 grandchildren. He was 94.

In Brief:

Gilbertson Named Director at St. Jude; Lowe To Chair Geoffrey Beene Center

RICHARD GILBERTSON was named director and executive vice president of **St. Jude Children's Hospital's Comprehensive Cancer Center.**

"During the past decade, Dr. Gilbertson has emerged as perhaps the world's top physician-scientist working on childhood brain tumors," said St. Jude Director and CEO William Evans. "He is a highly collaborative and insatiably driven investigator."

Gilbertson will oversee pediatric cancer researchzand collaborate with other NCI Comprehensive Cancer Centers nationwide.

SCOTT LOWE was appointed chair of the **Geoffrey Beene Cancer Research Center at Memorial Sloan-Kettering Cancer Center.** He has also been appointed a member of Memorial Sloan-Kettering's Cancer Biology and Genetics Program.

"Scott is a world leader in efforts to understand the cellular mechanisms that suppress tumor formation and control responses to chemotherapeutic drugs," according to Thomas Kelly, director of the institute.

Much of Lowe's work has focused on the tumor suppressor gene p53, found in about half of all cancers. His work has shown how changes in p53 can lead to the development of tumors and how disruption of p53 can affect a tumor's response to therapy. He has developed strategies for identifying many new tumor suppressor genes.

THE AMERICAN COLLEGE OF RADIOLOGY plans to open the first-ever professional academy for radiology in 2012—the **Radiology Leadership Institute.**

"The ACR recognized the growing need for specialized leadership development in the increasingly dynamic healthcare environment," said Cynthia Sherry, chair of the ACR Commission on Leadership and Practice Development.

"RLI will satisfy that need with a robust curriculum relevant and targeted to all levels of radiology experience, whether in private practice or academia, including management fundamentals for residents, fellows, and practicing physicians." Sherry will also serve as the institute's medical director.

"ACR is committed to build RLI into the premier institution that will equip radiologists, radiation oncologists and medical physicists with the leadership skills they will need to shape the future of our profession," said John Patti, chair of the college's board of chancellors.

THE AMERICAN CANCER SOCIETY received a $2 million grant from **The Walmart Foundation** to fund community health advisors in underserved communities.

The grant will provide Jackson, Miss.; Minneapolis, Minn.; and Portsmouth, Va., with $300,000 to expand access to breast cancer screening for African-American women. Additionally, 30 other towns across the country will receive $30,000 to fund existing community health advisor programs.