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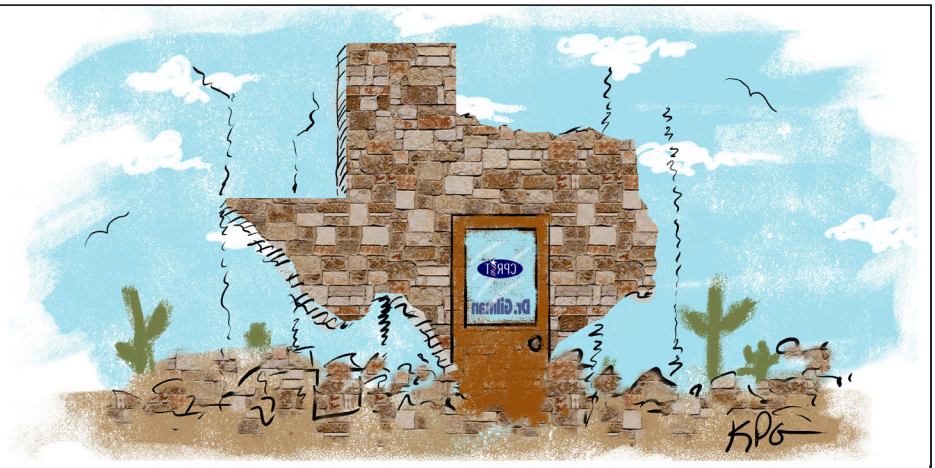

Slamming the Door

Part V: Gilman's Resignation Gambit

By Paul Goldberg

Gilman's letter of resignation, dated May 8, 2012, concludes with a hard slam:

"The purpose of this letter is to indicate my intention to resign from CPRIT, effective (with your permission) on October 12, 2012. At that time I will have worked for CPRIT for over three years—I believe longer than originally anticipated.

"During that time we have launched strong programs because funding decisions have been based on high-level competitions, where the judges have been some of the best cancer researchers and physicians in the country—free of conflicts of interest and all coming from outside of Texas.

(Continued to page 2)

Capitol Hill Briefing Focuses on Moonshot's Provision to Integrate FDA Cancer Portfolio

By Matthew Bin Han Ong

When the White House proposed a $1 billion startup fund for the National Cancer Moonshot, a largely unexpected directive to reform FDA raised many questions among oncology insiders.

The agency will create a virtual Oncology Center of Excellence, the

(Continued to page 6)

In Brief

Laurie Glimcher Named CEO of Dana-Farber

LAURIE GLIMCHER was named president and CEO of the **Dana-Farber Cancer Institute**.

Glimcher is currently the Stephen and Suzanne Weiss Dean of the Medical College at Weill Cornell Medicine, and is also professor of medicine

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Slamming the Door, Part V: Gilman's Resignation Gambit

(Continued from page 1)

"It was exciting to launch this program, to design effective requests for applications, and to oversee the peer review process.

"The program is now essentially at a steady state.

"Research activities that are yielding exciting results should be continued, and new applications should continue to be received—but some programs will perhaps need to be constrained or curtailed because of the desire to fund competitive renewals and expand commercialization activities. I doubt it will be possible to launch new initiatives at this point.

"The job of Chief Scientific Officer has become routine. You no longer require a full-time person.

"Your most critical concern will be to keep the external peer review system intact—retaining as many of the current committee chairs as possible. Your ability to do so will be critically dependent on the attitudes of CPRIT leadership, especially including the Oversight Committee.

"I have chosen the resignation date of October 12 for a few specific reasons:

• The next Scientific Review Council meeting that is scheduled to approve a slate of recommended research grants is October 5. I will stay until then to be certain that those who are preparing applications to be submitted by May 31 will still encounter a functional peer review system.

• Major decisions about research funding will be made by the Oversight Committee in July. I will attend that meeting to champion the research slate and to make it clear to the Committee that negative decisions about it would have a fatal impact on CPRIT's peer review system.

"Negative actions would in addition be extremely harmful to the research community's view of science in Texas, and thus on the ability to recruit scientists to the state (or, for that matter, the ability to attract capital for commercialization efforts).

"The MIRA grants to be presented to the Oversight Committee in July should have been funded in March; further delay simply must not happen. Also, July will see a large number of recommended recruitment applications. [MIRAs are Multi-Investigator Research Applications, the largest and most complex grants funded by CPRIT.]

"The relevant institutions are already engaged in attempts to secure commitments from these excellent candidates; some have already succeeded.

• If additional incubator grants are to be approved at the July meeting of the Oversight Committee, I will be there to hope that the rules governing review and

funding of incubators have been revised to prevent further award of vast funds for research programs ostensibly within incubators that were not described

and therefore could not have been reviewed.

• A delay of my resignation until October provides you with an extended opportunity to find someone new to fill my position.

• I ask for one additional week after the October 5 meeting of the Scientific Review Council to complete my affairs, dispose of professional books and papers, vacate my office, etc. I will be ending my career during its 42nd year."

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Gilman's message was clear: he would take no bullshit. The CPRIT politicos had until Oct. 5, 2012, to fix this mess. After that, Gilman et al. would go more public than they already had.

The letter from the scientific council was even tougher than Gilman's letter of resignation.

A seasoned academic fighter, Gilman was leaving it to outsiders make his strongest points, which in this case were about the possible failure to fund the MIRAs, accusations of bias, and the MD Anderson incubator.

It was clear that, with the sanctity of peer review on the table, the council members didn't need to be prompted.

Their letter, dated May 14, 2012, follows:

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"We received the letter (on May 11) from [members of the politically-appointed CPRIT Oversight Committee] James Mansour, Joseph Bailes, and [CPRIT Chief Executive Officer] William Gimson proclaiming their faith in the peer review system established under the initiative of Al Gilman for CPRIT: 'complete trust in the gold standard process that CPRIT has established.'

"Further, 'we know that the Oversight Committee wholly supports, and will continue to support, this process and will expect the Institute to maintain the high level of integrity and excellence that has been established.'

"However, these statements seem inconsistent with recent actions taken by CPRIT management or its Oversight Committee, and these actions are the reasons for Al Gilman's resignation. The following is a response to these statements set in the context of the related events as we understand them.

"1. The seven Multi-Investigator Research Applications that the Review Committee recommended for funding (out of the 40 that were reviewed) were never brought to the Oversight Committee for approval and funding at its March meeting. As related by Gilman, Mr. Gimson stated that the reason was that he feared they would not be approved because of opposition from certain Oversight Committee members over the fact that a substantial fraction of the funding would go to UT Southwestern. By this action, members of the Oversight Committee essentially accused Al of somehow biasing the system. Such an accusation of bias implies further that we and the members of our review committees participated in the scheme, a point that we vigorously deny. We judge the review system managed by Al Gilman and led by us to not have been biased in any way relative to any institute or individual. At every point in this process, we have attempted to select the best cancer research and cancer scientists in the service of the citizens of Texas.

"2. At the same meeting of the Oversight Committee in March 2012, a $20M award for one year's effort was approved for an incubator at Rice University and for research at The Institute for Applied Cancer Science (IACS) at MD Anderson. Approximately $18M of that award is slated for the IACS at MD Anderson. The IACS proposal was 6.5 pages long. It was submitted just a few weeks before the Oversight Committee meeting, and it contained essentially no scientific detail. The stated intent of the IACS is to discover anti-cancer drugs. From the proposal, it appears to have been developed to:

• Expand current target biology and small molecule discovery efforts

• Fund counter-screens against related protein family members

• Expand pipeline to include biologics

• Invest in efforts to develop novel chemistry platforms to address traditionally undruggable protein targets

"Although the brief document was strikingly lacking in specific research plans, we would characterize these activities as research. Apparently, the absence of a specific research plan was taken by CPRIT leadership as the justification for bypassing any review by CPRIT's panel of reviewers.

"As we understand it, CPRIT leadership determined that incubator proposals were to be considered under the category of commercialization, not research.

"However, no product candidates are mentioned in the IACS proposal, nor is a company involved. After concluding that this proposal should be considered under the rules governing incubators, CPRIT followed the letter of their own law, in that incubator proposals were not to be reviewed for scientific content.

"We are surprised and disappointed by the failure of proposals of this sort to receive scientific (research) peer review. The $20M one-year award is by far the biggest that CPRIT has ever made.

"As members of the body that has been authorized to pass judgment on the merits of scientific proposals made to CPRIT, we will be viewed to have approved this award, and the failure to include us in the process calls into question our roles and the integrity of the review program in general.

"More importantly, this bypass is inherently unfair to every scientist in Texas who participates in the CPRIT program. Over this past two years, we have reviewed

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Slamming the Door: How Al Gliman Taught Texas a Lesson in Science is a series that re-examines the concurrent controversies at the Cancer Prevention and Research Institute of Texas and MD Anderson Cancer Center.

This examination is possible in part because of new insight provided by Alfred Gilman, the Nobel laureate who served as the first scientific director of the state institution that distributes $300 million a year. Gilman died on Dec. 23, 2015.

Read the full series on The Cancer Letter website.

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proposals from many Institutions in Texas that include one or more of the four scientific objectives listed above. These scientists have played by the rules that we understood were established by CPRIT's Oversight Committee and publically stated in the announcements of the program.

"As the Oversight Committee is aware, in order to reduce possible conflict of interest, all members of the research peer-review teams are not from Texas and that we and the reviewers are excluded from discussions in which a real (or perceived) conflict of interest might arise because of a relationship with a Texas institution or investigator.

"Moreover Gilman, when present at the meetings, is there as an observer and to answer procedural questions. During the review process, Gilman does not offer an opinion on the scientific merit of a proposal, investigator, or institution. In fact, Gilman's reputation for integrity and high standards of scientific leadership is what attracted us to serve as chairs and panelists in the peer review process for CPRIT.

"We firmly believe that the integrity of the CPRIT review process and its proper implementation are essential for advancing cancer research and cancer care in Texas.

"We would appreciate it if you would please forward this letter to the other members of CPRIT's Oversight Committee and let us know when you have done so. It is essential that all members of this group are informed about the issues that face CPRIT.

"We are distributing copies of this letter to all members of CPRIT's research peer review committees.

"Sincerely yours,

Phillip A. Sharp [Koch Institute for Integrative Cancer Research Massachusetts Institute of Technology]

Clara Bloomfield [Ohio State University Comprehensive Cancer Center]

Sanjiv Gambhir [Stanford Cancer Institute]

Tyler Jacks [MIT Koch Institute for Integrative Cancer Research]

William George Kaelin, Jr. [Dana-Farber Cancer Institute]

Richard Kolodner [University of California San Diego]

Charles J. Sherr [St. Jude Children's Research Hospital and Howard Hughes Medical Institute]

Everett Vokes [The University of Chicago]"

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"I built something I am proud of, and now it's being taken apart," Gilman

said to me much later, when it appeared that the game seemed lost. "I can't work for people who are pushing their own interests at the expense of the interests of cancer patients."

He was disappointed but not surprised.

"A wise and experienced friend said to me: 'This is always the way it works when you put a large amount of public money on the table. The vultures and the hyenas lie low for two or three years to see how the system really works. And then they come in for their feast.'"

We will return to this statement a few times.

If the Gilman letter was akin to a stop sign, the letter from the scientific council was equivalent to flashing lights of a police cruiser in a rear-view mirror. Who could possibly ignore something like that?

In late May 2012, I wasn't sure how the Texas politicians would handle Gilman's departure.

Would they look for another world-class scientist to replace him? Would they be able to find someone who would have the credibility and skills to hold CPRIT's peer review system together?

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In those days, anyone could log on to the MD Anderson faculty blog to see what the insiders were saying.

Faculty and staff members used pseudonyms, but no great deductive leaps were required to see that the pseudonymous "Moonshot Marvin" was none other than MD Anderson's former apologist Len Zwelling.

On May 21, 2012, Moonshot Marvin posted the following:

"I think everyone involved needs to consider a round of damage control by telling the truth about the money, the suspension of the CPRIT scientific review procedures in this case, the obvious conflict of interest at MD Anderson and...our state's credibility. We seem to be living up to what New Yorkers think of us anyway.

"Quick responses involving great transparency and the elimination of the conflict of interest immediately would go a long way to save the reputation of CPRIT and MD Anderson and the role of both in generating the most important product of any scientific endeavor. The truth!

"So here are a few other questions for the principals:

• How did MD Anderson and the UT System allow this conflict of interest/nepotism arrangement to

be established?

• Who sanctioned it and what are the safeguards in the system to allow oversight and manage the conflict at the very top of MD Anderson?

• We know the President's conflict-of-interest disclosures are reviewed at the UT System level, but surely his wife's are reviewed like all the rest of the Anderson faculty by its conflict of interest committee. Is this so?

• With money so difficult to acquire to support research, how could so much of it go to one project, especially one purported to be ill-defined as yet?

• How was it possible to bypass the scientific system established by a highly-respected Nobel laureate who was so instrumental in establishing the credibility of CPR IT with the rest of the scientific world?

• Who allowed any of this to happen?

• Where was the oversight by the leadership of the health components of the UT System and the UT Board of Regents?

"I think the leadership of MD Anderson should try to get control of this story by simply telling the absolute truth, preferably through an interview of Dr. DePinho by Mr. Berger.

"CPRIT's Executive Director also has some explaining to do. The leadership of the UT System health care programs as well as the Board of Regents need to weigh in, too.

"How about it? Is there really any other way to get this behind us and all of us back to work?"

Comments by Moonshot Marvin notwithstanding, a subsequent audit by the UT System found no impropriety in the handling of the application.

In one of our on-record conversations, DePinho said he didn't "attempt to influence a specific award decision by CPRIT or any funding agency, period."

"I will, however, continue to be the most dedicated advocate for great science and drug development that's occurring at MD Anderson, and that is my job," he said. "I will continue to advocate the need to repair the broken ecosystem of drug development through greater joint efforts between academic entities and industries—it's vital for patients."

When I called him a few weeks after the CPRIT scandal became visible, DePinho declined to discuss the role the venture capitalist and CPRIT Oversight Committee member Charles Tate may have played in formulating the incubator proposal.

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In an interview in January 2016, MD Anderson Executive Chief of Staff Dan Fontaine said the idea of combining IACS with the Rice incubator came from several directions at once.

"I'm not sure we ever really accurately portrayed the reason for having the [IACS] joined with Rice's application for incubator infrastructure. And perhaps it's the benefit of hindsight, the [IACS] was important for having to add to that because it created a pipeline of both scientists and potential products that would have fed that incubator in a very successful way.

As it turned out, to follow up on your question, I think that Rice has gone on with their incubator project. To be perfectly honest with you, I have not stayed that keyed into it. But certainly the [IACS] has proceeded on its pathway with a great deal of success.

"So I think the concept over time of the [IACS] and the idea that there needed to be a bridging link between discoveries and developing products has actually been proven out as being a very worthwhile investment on MD Anderson's part because we've certainly invested in, and I think will continue to reap the benefits from the [IACS].

"Stepping back in time, as Ron arrived at MD Anderson, one of the things that I think he made pretty clear during his recruitment process is that he really believed that there needed to be something built so that we had a better chance of developing new drugs for cancer patients but didn't have the same failure rate," Fontaine said to me.

"And I think his theory at the time, based upon the work that he had done at the Belfer Institute [at Dana-Farber Cancer Institute], was that there needed to be a deeper level of chemistry, biology—those sorts of things in-house, with an academic component—which would then hopefully validate some of these inventions and move them along towards products.

"And he wasn't just talking about internally at MD Anderson, he was being invited to make presentations on his thoughts in that regard in numerous forms around Houston and Texas. One that I know took place, and I'm not quite sure as to the timing, was at the Houston Technology Center. But remember that when he officially started in November of 2011, but when he first started coming down prior to his official first day in the late summer of 2011, he had numerous appointments with people around the state—both in the technology world and the biotech world, but also with folks who were on our Board of Visitors.

"In talking about one of the things that he wanted to build, being this thing called the Institute of Applied

Cancer Science, was something that he was spending a great deal of time talking to people about. Because of that, I'm not quite sure which person was first, but I think there were people that were tied into the Houston Technology Center, people that were tied into biotech and the Venture Center, people that were tied into other areas that were knowledgeable about CPRIT, who said that sounds like something that might work well with a CPRIT grant.

"But since, I think, the RFA had been out for a while at that point in time—I'm not quite sure who made that introduction to Rice—but I think somewhere in those multiple discussions about it, this is probably one of those things that as you think about CPRIT funding for.

"The discussion about Rice having something that they were submitting might have come up. It may very well have been a conversation between Ron and someone at Rice, or it may have been a conversation between someone that knew what Rice was doing and had heard about the IACS presentation."

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I first called Gilman after he submitted his letter of resignation.

Gilman took my call.

I assured him that I would be fine with our conversations staying on background. He preferred that, because he wanted to make sure that CPRIT would be able to maintain its scientific integrity.

For starters, he wanted to make sure that the MIRAs would get funded, and he wanted assurances that the peer review system he built would remain intact.

He wanted the Texas politicos to understand that if they play nice, he would leave quietly, without slamming the door. Conversely, if they don't give him what he wanted for CPRIT, the door would slam. Publicly.

The Nobel laureate was prepared to turn whistleblower.

Then Gilman casually let it drop that the MD Anderson proposal was never reviewed by the provost—Ray DuBois.

This was astonishing, because the role of the provost is to promote the academic mission of an institution. The rule of thumb in academic medicine is that the provost gets to sign off on any grant application that contains a budget.

The idea that the provost wouldn't be consulted on something this was all the more astonishing, because the application asked for funds for expanding the capacity to conduct phase I trials, opening the potential for ethical problems to spill over into the clinic.

I asked Gilman whether he was absolutely certain. He was. Had DuBois signed off on the application, it would have been submitted through the CPRIT portal, which Gilman watched.

"Have you called DuBois?" I asked.

"I called and asked what the fuck," said Gilman. "He said he never saw it."

I realized that there would be no way for DuBois to stay at MD Anderson much longer. After all, he had been a contender for the president's job. You'd think an alpha male like DePinho wouldn't want him around.

I didn't know DuBois well, but he was almost always described in the same way by almost everyone: a nice guy, polite, respectful, collegial, clean, honorable, plays by the rules.

Unfortunately, the only move open to me for my first foray into Texas oncopolitics was to put unsuspecting DuBois on the spot.

Would he tell the truth?

Next week: Part VI - DuBois Responds

Hill Briefing Focuses on FDA Cancer Portfolio Integration

(Continued from page 1)

administration proposals and budget documents state.

Alas, nobody can claim to understand what "virtual" means in this context, and how the $75 million in proposed fiscal 2017 mandatory funds would be used to "leverage the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, and devices." (The Cancer Letter, Feb. 12.)

Some perplexed insiders suggest that virtual could translate as "we don't know exactly what we want right at this moment," in Washington-speak.

"First of all, there's nothing wrong, and FDA is doing a great job with what they have," said Ellen Sigal, chair and founder of Friends of Cancer Research, the advocacy group that convened a panel discussion to explore a way forward for the regulatory agency.

"People at Center for Devices and Radiological Health, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research are all doing a great job. But, the question is, can it be better?" said Sigal at the Capitol Hill briefing Feb. 24. "Patients get diseases, they don't get a biologic; they don't get a device. It all works together. Is there a more efficient

way that is better? Because the goal is to get patients better treatments. This is what it's about.

"It isn't about institutional structures; it's not about anyone doing a bad job. Is there an efficient, better way to serve the patient towards the goal of really integrating these centers of people in their particular fields working together?"

Panel members—representing industry, FDA, academic oncology and patient advocacy—agreed that the time has come to reassess the way medical products are regulated at FDA.

The panel included:

• Steve Galson, senior vice president of global regulatory affairs and safety at Amgen Inc., former director of CDER, and former acting Surgeon General.

• Mark McClellan, director of the Duke-Robert J. Margolis Center for Health Policy at Duke University, and former FDA and CMS commissioner.

• George Demetri, director of the Ludwig Center at Harvard Medical School.

• Otis Brawley, chief medical officer of the American Cancer Society.

FDA Structure Needs to Change

"The modern world of drug development actually doesn't fit the existing structure of FDA's drug-device-biologics organization structure, that has been—and continues to be—remarkably successful in making the U.S. and the FDA the gold standard globally," Galson said.

"Working with a global pharmaceutical company, I see this even more than I did when I was at FDA," he said. "Products typically receive multi-center reviews—many, many products—and I've been working closely with the agency on these since I've been there. FDA has recognized these product changes, so I don't mean to imply any criticism of the agency not being aware of all this.

"FDA's evaluated and made what I call 'tweaking' types of organizational changes, made sure that synergistic collaborations were in place. But there's recognition at FDA and by external collaborators that there's really a need for further assessment of this. In this world, with exciting products coming at an increasing pace, is this really the right structure?

"It's time to look at this again."

FDA's handling of biologics is a good example of how the agency can improve, Brawley said.

"Science is evolving because things are changing, definitions of cancer are changing. We're using molecular diagnostics along with drugs. It makes sense that the FDA might become a little more efficient in it's ability to review by a slight reorganization," Brawley said.

"I in no way want to criticize what the FDA has done in the last 15 years. My experience on the Oncologic Drug Advisory Committee is that the system is actually working very well. The system can work better, but the system is working very well," Brawley said. "Biologics integration was incredibly important, and I think that we could move further with even more integration.

"It's important, whenever you have an organization—the FDA is no different from any other—that every few years you look back and you examine and you say, 'What can we tweak, what can we change, what can we make more efficient?' That, in my mind, is effective.

"And in many respects, that's what we're doing right now."

Sigal said everyone at FDA—including the newly confirmed commissioner, Robert Califf—is in agreement that the agency needs to come up with a disease-oriented approach to development of medical products.

"This concept, basically, has everyone in agreement, clearly, from FDA, from Dr. Califf to Dr. [Janet] Woodcock, [director of CDER]. There's no question that conceptually people agree," Sigal said. "It's in the moonshot. We're very happy about that. It may be in some legislative language, but what does it mean?

"Clearly, FDA ultimately has the last word on it. They have to look at it and figure it out—but a large community is impacted by what they do, and that means the developer community, the patient community, the academic community—everyone.

"So some external input into this is really crucial."

It's unclear how structural changes at FDA would be implemented—Congress generally doesn't intervene in intra-agency matters, which means it could all be up to Califf and FDA leadership.

"Does it have to be legislative? I don't know. I assume there may be some statute issues, because of the way they're regulated at CDRH, but we don't want Congress telling us how to be or how to organize," Sigal said. "There may be some issues that have to be done, but I think it's absolutely critical to have external input, patient input, and expert thought from professional societies and others, so when the decisions are made, people understand it."

Restructuring FDA would likely require moving desks, which means that there would have to be discussion about whether the oncology center will be virtual or brick-and-mortar, Sigal said.

"This center, this integration, has to be real. It can't

be 'Let's all be friends and talk.' At some point, it has to have some teeth," Sigal said. "To do it, it has to be thoughtful, and it has to be done in a way that is real. It should not be disruptive. It should have the resources it needs. It can't be as if we're going to be talking to one another as we are talking to one another now. We need to go one step further.

"I also will say that it will need resources. This can't be done without resources. We have to attract people, we have to keep people; there will be the ability to figure out whether it needs bricks and mortar. Probably not, but will some people have to move over? Probably yes, but it's a decision that should be done quickly but thoughtfully with a lot of input from people. But ultimately, it's a decision made by the FDA, but not alone.

"We're only talking about clinical. We're not talking about manufacturing, legal, or all the complicated things. We're just talking about the integration in a way that's more meaningful, that will get to the right result for patients. And that's what this is about, and it is our core belief that this can be done. It should be done thoughtfully, it shouldn't be disruptive, it should be done with resources, and it should also recognize that the agency is doing a very good job, but can we do better? My answer is, 'Yes.'"

Should Oncology Go First?

Is cancer the right place to begin a discussion about integration at FDA? Or should this effort be coordinated across disease types?

Sigal said oncology is the place to start, because it has strong leadership.

"I do want to suggest that when we did approach FDA with this—some trepidation but with conviction—the leadership really thought that cardiovascular, maybe infectious disease, could really work in other diseases," Sigal said. "Because people get disease and the diagnostics and biologics, they're all working together with the drugs, so I think the issue is to be thoughtful: Is the leadership there? Are the resources there? How do you do it with the issues of the statute?

"We happen to have extraordinary leadership with Rick Pazdur [director of the FDA Office Hematology and Oncology Drug Products] and what he's done with any cancer. There are just huge opportunities, so maybe that can go first, but there certainly are other diseases. We'll leave that to the other experts. At the moment, we're suggesting that cancer can be the first place."

McClellan said combination immunotherapies might be an area where promising progress can be made and where broader integration can be achieved.

"I really think it depends," McClellan said. "I think we need to do a bit more work building on the Friends proposal. It's always legislative and statutory considerations about what FDA can and can't do, and I'm familiar enough with FDA law to know that I need good lawyers to make sure that we're handling that appropriately.

"But most important, from the scientific and medical product development standpoint, where are the biggest real challenges? Let's get real about moving from the concepts of complex medicine into the practicalities of a regulatory agency with limited resources.

"I think it would be very helpful to focus on some key areas where the challenges that you all have been talking about on the panel really seem to be greatest, clearest, most pressing. Steve mentioned combination immunotherapies—my sense of one area where there actually might be a number of applications, not just in cancer, but in a combination of products more generally, especially companion diagnostic products.

"This is an area that FDA has been thinking about. There's some cross-center structures to help coordinate action, but given the rapid growth in the development of targeted treatments and how well it fits with issues like the whole focus of the Cancer Moonshot and the president's Precision Medicine Initiative—on furthering the use of targeted therapies fits within the Breakthrough Designation—that may be a really good place to start, and start asking the questions of 'What's the best way forward in the short term, and maybe the longer term?'

"I like some of the models like these cross center councils that have some significant involvement from the commissioner's office, or that different centers believe that there is something to be gained from working a bit more formally together short of a restructuring, short of a fundamental restructuring. Maybe something like that is stuff that can be explored in the short term while these bigger issues are getting addressed."

There are tremendous opportunities in cancer, especially since oncology is well developed as a system, Demetri said.

"Not that cancer is so different—I like the idea—I don't want to have an internecine medical warfare between cancer and every other disease that afflicts humankind," Demetri said. "I actually think cancer is just a good proof-of-concept place to start exploring the concepts, and where we might reorganize the FDA for the good of everybody, because we already have protocols and treatments that are based on a standard pharmacy, on a cellular pharmacy with the

kind of engineered cellular agents that are causing so much excitement in our field, with novel diagnostics, and everything that hits each and every one of those different branches of the FDA right now.

"So bringing them together in a way that works and testing that out in cancer, first, might make a lot of sense, also because we have a history of making advances in cancer, from prevention to cures, through our comprehensive cancer type of way of doing research. This was a novel way of structuring research back in the 60s, of having basic scientists and clinical scientists work together under the umbrella of comprehensive cancer centers. We did that as a country because we felt that cancer lent itself to that kind of a solution.

"I actually think we're now seeing our neuroscientists say, 'Yeah, that makes sense.' We should develop neuroscience centers and cardiovascular centers. That model has worked. And frankly we see the London Cancer Center—that's being replicated around the world because it's effective. So I think we have many reasons to think this kind of organization would be good for the FDA."

McClellan disagreed.

"I do want to highlight the need, when you're thinking about organizational issues at FDA especially, to keep in mind that the resources are limited," McClellan said. "There is a tremendous amount of expertise in cancer at the agency, but looking at the scheme of things, it's really not that many people, compared to the vast and increasingly complex science and expertise involved and so forth. You really want those resources to go as far as possible.

"Not to defend the status quo, but there are some good efficiency reasons for having the same expert regulatory staff dealing with products across a number of areas. I think that's where this point of really looking at where this bang-for-the-buck is going to be, in terms of a more integrated structure, is very important.

"I've heard that, especially in drug and diagnostic combinations, despite the FDA efforts, there really are some challenges in getting the same answer, based on the coordinated sum total of clinical expertise in this increasingly important and complex area. That might be a place to start, as opposed to radiation therapy or surgical activities.

"I hope we can look more closely at managing the benefits and risk and doing it as efficiently as possible. And then maybe, after we take that on, and Friends takes on these issues around cancer at FDA, we can move to efficiency of cancer product development and the academic medical role."

The melding of elements in oncology is moving very rapidly in academic medicine and in the cancer centers, Brawley said.

"If I can, I'll back up what George just said," Brawley said.

"But as we look forward, all these new drugs that we have that end in 'ib' and 'ab,' virtually every one of them has a molecular marker associated with it. I do the test on the cancer, does it have a molecular marker, then I figure out which 'ib' or which 'ab' I prescribe to the patient. And that's true for a number of drugs. Indeed, when we talked about biologics, we are now starting to talk about CAR. We talk about designer antibodies, used to treat cancers.

"More and more, we need to have the regulators who do the diagnostics and markers working and collaborating with the regulators who do the treatment, because, in my world and in George's world, they are becoming the same very quickly. This is the new biology, this is the new 21st century definition of cancer."

McClellan: Don't Just Tear Everything Up

FDA shouldn't start to move people and desks without "serious, thoughtful consideration," McClellan said.

"When you think about managing this organization, you've got an enormous range of activities and an increasingly diverse and complex products to regulate with staff that are accordingly stretched in meeting all of these demands," McClellan said. "On the one hand, you want to have very effective, knowledgeable review. On the other hand, it needs to be predictable so that companies, product developers going through the process know what to expect."

FDA's current infrastructure was developed in response to the needs of an era when products fit into distinct, independent regulatory pathways—a system that no longer applies to many products on the market now, said McClellan.

"Historically, that's meant this division by types of products—that's the way the legislation is set up—historically, it's been for products that don't cross boundaries. That's a pretty efficient way to have limited staff predictability go across a range of different development areas," McClellan said. "But as FDA's found over the years, there are more and more products that don't fit neatly into that kind of arrangement. On one hand, you want to keep encouraging the kinds of activities that, say, CDRH has undertaken over past year with their strategic plan to make device regulation more efficient and predictable. There are initiatives at

CDER and CBER, all of which have made a difference, and which have been backed by legislation, like the 2012 Breakthrough Therapy Designation that Friends and our group was involved in. But no question, these challenges are getting bigger."

Informal coordination may work for some products, McClellan said, but a systematic relationship is needed for others.

"When FDA tries to recognize and respond to these issues, there are a lot of different levels of response. And for many of these products there can be some kind of informal coordination across the staff of different offices or different centers in the FDA, and that helps," McClellan said. "But for many of these product areas, it's better have more of a systematic kind of relationship in such areas as combination products, for example, there is kind of a more formal coordination process in place intended to give the same kinds of answer at the same time for products that need to be developed together.

"Where that's not sufficient, FDA has taken further steps and set up more commissioner-level initiatives. These would have support, leadership from the office of the commissioner to really help provide more structure and formal process for helping to make sure that the different parts in the agency do work together where they need to.

"So I think there are a range of options that have been used and can have more significant effects around structure and organization in the agency and it's very important to manage those with statutory and legislative authority issues and with the scientific issues that drive the most efficient way to handle these kinds of cross-cutting topics.

"My sense from that experience is that the best place to start in these issues is trying to get a sense of the priority list of problems: what are the biggest particular areas around, say, combination or complex product development in the areas of cancer or neurologic conditions or the like where it seems the benefits of new structure most likely outweigh the risks and try to start there and help that guide you in what further steps should be undertaken."

Demetri: The Devil is in the Details

The challenge in helping FDA become more disease-specific lies in the creation of a system that will be relevant, for instance, to the complexities of cancer, Demetri said.

"We live in an ecosystem where the science has never been better. And the science has shown us the complexity of what we're dealing with—cancer is not one disease, cancer is thousands of different diseases," Demetri said. "With thousands of different diseases, you have a risk profile, that goes from something that people can live with forever such as certain carcinoma-type diagnoses that are eminently curable to the most life-threatening acute leukemias that can kill people in six weeks but are also curable to a great extent with the use of modern technology.

"So I think that's the complexity of this, and since we're here to talk about organizational issues, I think that's the big deal. How can you get the kind of expertise to match, as Steve said, the right drug to the right patient, at the right time, in the right disease, with the right risk, at the right cost (eventually), so that the public benefits and so that the scientists are not left to their own devices, developing things that can't be applied effectively, and so that the regulators can have the tools at their disposal to use the kind of tools that they have to reliably, appropriately protect the public health and really guide the practice of modern medicine. I think that's what's really important.

"Separate from drug development, don't forget pharmacovigilance and effectiveness—we have a responsibility to say if we developed a drug, 'Is it really working outside of the rarified atmosphere of the clinical trials that we test things in?' The ability to really link that together in a different kind of a structure seems like a noble goal. I think, organizationally, it's possible."

Moving FDA toward a disease-oriented system is aligned with Vice President Joe Biden's goals of breaking down silos in oncology bioinformatics, Demetri said.

"I think the idea that is aligned with the Moonshot Initiative that's real, is this data sharing as well," Demetri. "Academics, traditionally, hoard data. We are trying very hard to break that culture and share data. We have to change our academic credit systems and we have to do an awful lot to do that.

"But in the same way, I am worried about different groups in the FDA. When I've talked to different, wonderful people at the FDA or CDER, or CBER, or in the diagnostics division, I do worry that they may be playing with different decks of cards. That's the concern I have, and where there could be an easy way of merging that, or at least having some sort of organization so we are all playing with the same deck of cards.

"In the same way, this is the perfect time because things like the AACR Project GENIE is getting places like Dana-Farber, Memorial Sloan Kettering and

international institutions to share data together on things as simple as genomics—and they're not simple, but they sound easy and it's just a couple of syllables. Genomics is tough, but so is linking genomics to clinical outcomes.

"So if our academic places are having trouble with all the computational biology help we have in all the high-powered help of the Broad [Institute] and Harvard and everything, think of how we could then share that with the agency. I think different structures need to be elaborated so that we can actually serve the country and the patients we serve the best possible way."

Harvard's consortia for oncology provide a good analogy for how FDA can bring together its separate divisions to work on specific diseases, Demetri said.

"At our cancer center, I'm one of the associate directors for clinical science at the Dana-Farber Harvard Cancer Center, we're a consortium cancer center because there is no 'Harvard Hospital,' Demetri said. There are many big famous teaching hospitals like the Brigham & Women's, the Dana-Farber, the Beth Israel, the Mass General, and others, all of which do cancer, so our consortium brought us together and said 'How can working together, in a structure that makes sense, help us do our work?' and in many ways I use this analogy for where I see a thoughtful way of helping the FDA.

"How can we not break something apart, but how can we bring things together in a rational organization so that we're not duplicating resources and wasting them? So that we actually have the right expertise at the right time to put the right regulatory framework on top, so that we can predict the outcomes and really help everybody along the line—the scientist, the development people, the clinical trialists, the regulators, everybody could benefit from this.

"I think the devil is going to be in the details about how to do this, and I really appreciate Mark's comments about that, because I have great respect for our colleagues at the FDA. They have always been very rational, very helpful to me as a clinical investigator, as somebody who goes to them with good data. We can share the good data, or as somebody who comes to them with not-so-good data, we can share the data and discuss what's the next step.

"That kind of back-and-forth collaboration is what, as practicing physician as well as a clinical investigator, we'd like to see and help with at the FDA as we think about how we can build this structure in a way that makes the most sense. I do feel bad for them because the resources are so darn limited and I think that's the other important thing. We want to do this in an effective way and have this be efficient for our colleagues there as well. They serve a vital public purpose."

Sarah Pavlovna Goldberg contributed to this story.

In Brief

Glimcher Named President And CEO of Dana-Farber

(Continued from page 1)

and provost for medical affairs at Cornell University.

"Dr. Glimcher is in many ways an ideal choice for Dana-Farber," said Josh Bekenstein, chairman of the Dana-Farber Board of Trustees. "She is a distinguished immunologist, widely renowned for her work in one of the most promising areas of cancer research. She has had extraordinary success as the leader of a major academic medical institution. Most importantly, she has a deep understanding of the latest developments in cancer research and care, and a clear vision of how Dana-Farber can most powerfully affect the fight against cancer."

Glimcher will also serve as a professor of medicine at Harvard Medical School, as well as president of Dana-Farber/Partners Cancer Care, principal investigator of Dana-Farber/Harvard Cancer Center, and trustee of Dana-Farber/Boston Children's Hospital Cancer Care.

Current President Edward Benz, Jr. has agreed to remain in the position until her arrival at the institute.

"It is an enormous honor and privilege to be chosen as the next leader of the Dana-Farber Cancer Institute," said Glimcher. "The opportunity to advance Dana-Farber's groundbreaking research and to improve the care available to patients with cancer is truly special to me, and I am thrilled to be returning home to Boston. Cancer research and care have reached a transformative moment in science, and I look forward to working with all of Dana-Farber's clinicians and scientists to find innovative therapies in the coming years."

Prior to joining Weill Cornell Medicine, Glimcher was the Irene Heinz Given Professor of Immunology at the Harvard School of Public Health, and Professor of Medicine at Harvard Medical School, where she headed one the immunology program.

She is widely considered to be one of the world leaders in understanding cellular differentiation pathways in lymphocytes and has made seminal

discoveries of key transcription factors that drive lineage commitment and activation in the immune system. Most recently she has discovered a critical signaling pathway in both tumor cells and in host immune responses, translating her basic discoveries in the control of immune cell differentiation into a new approach to cancer immunotherapy.

She has contributed more than 350 scholarly articles and papers to the medical literature. In addition, she is a fellow of the American Academy of Arts and Sciences, a member of the Institute of Medicine of the National Academy of Sciences and a member of the National Academy of Sciences. She is the former president of the American Association of Immunologists.

ROBERT CALIFF was appointed commissioner of the **FDA**, following a successful confirmation vote in the Senate. Califf has served as deputy commissioner for medical products and tobacco since January 2015.

Califf was nominated for the post by President Barack Obama in September 2015. Since then, his confirmation has been opposed and blocked by a handful of senators expressing concerns over the regulatory agency's policies on opioid painkilling medications. Before moving to FDA, Califf, a cardiologist, was a professor of medicine at Duke University.

"Prescription drug and heroin addiction is a crisis the likes of which we have never seen in America," said Sen. Edward Markey (D-Mass.) in a statement after the vote. Markey had previously placed a hold on Califf's nomination, stalling its progress in the Senate. "A decade from now, we will all be asked what did we do to help end this epidemic. That's why I voted no on Dr. Califf's nomination and why I will continue to stand up and fight for the solutions to end this scourge."

Markey previously called for "immediate reforms to the agency's approval process for opioid painkillers, which are fueling a prescription drug and heroin overdose crisis that led to 47,000 deaths, including more than 1,300 in Massachusetts, in 2014."

The final vote was 89 to 4, with Sens. Kelly Ayotte (R-N.H.), Richard Blumenthal (D-Conn.), and Joe Manchin (D-W.V.) voting alongside Markey. Democratic presidential candidate Sen. Bernie Sanders (Vt.), who had also placed a hold on Califf's confirmation, was not present for the vote, as were Republican candidates Marco Rubio (Fla.) and Ted Cruz (Texas). Sanders voiced concerns over Califf's ties to the pharmaceutical industry.

"We need someone who will work to substantially lower drug prices, implement rules to safely import brand-name drugs from Canada and hold companies accountable who defraud our government," Sanders said previously in a statement.

Earlier this month, in response to the opposition in the Senate, Califf and FDA leaders presented a plan to reassess the agency's approach to prescription opioids, including changes to immediate-release opioid labeling; updating its Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations; expanding access to abuse-deterrent formulations of opioid products; improving access to naloxone and medication-assisted treatment options for patients with opioid use disorders. (The Cancer Letter, Feb. 5.)

MANDI PRATT-CHAPMAN was named the associate center director for patient centered initiatives and health equity at the **GW Cancer Center.**

Pratt-Chapman will serve on the senior leadership team for the center, helping to create a patient support services program, which will build on programs that she developed during the past several years as director of the GW Cancer Institute. She will also work on community engagement and supporting access to clinical trials.

Pratt-Chapman joined the George Washington University's cancer efforts in 2008 and became the director of the GW Cancer Institute in 2013. She served as the co-founding director of the National Cancer Survivorship Resource Center, in partnership with the American Cancer Society. She also serves as an adjunct instructor in the Department of Clinical Research and Leadership.

She has served as chair of the Association of Community Cancer Centers guideline revision process and chair of the patient navigation certification process for the Academy of Oncology Nurse and Patient Navigators.

STEVE LIMENTANI was named vice president and medical director of Mission Cancer Services as well as chief research officer of **Mission Health.**

Limentani is a clinical professor at the University of North Carolina.

In 1995, Limentani moved to Carolinas Healthcare System and became medical director for clinical trials. One of the highlights of his tenure was helping to grow the research department from a staff of two to the current size of more than 100, with more than 200 actively accruing clinical trials.

He has conducted research and published in many

areas, including multiple myeloma, lung cancer and breast cancer, and has served on the Board of Directors for NSABP and is currently a member of the NRG breast cancer working group.

At Mission Health, Limentani will help develop programs that reach rural portions of Western North Carolina. Limentani will also help develop Mission's research program.

ROBERT KORNGOLD was awarded a Lifetime Achievement Award from the **American Society for Blood and Marrow Transplantation**.

Korngold is chief of the division of research at the John Theurer Cancer Center and chairman of the department of research at Hackensack University Medical Center.

The award, presented at the society's 2016 BMT Tandem Meetings in Honolulu, recognized his decades-long career and pioneering research in the field of blood and marrow stem cell transplantation.

Nearly 40 years ago, he demonstrated in mouse models that mature T cells in donor bone marrow were responsible for causing graft-versus-host disease directed to minor histocompatibility antigens in transplanted recipients. Korngold's study had a profound impact on the future course of clinical treatment for patients undergoing transplantation from matched sibling or unrelated matched donors.

Korngold's research has focused on the immunological mechanisms of GVHD and refining the hematopoietic stem cell transplantation process to avoid disease and allow for enhanced anti-leukemia immune reactivity.

He has served as a member of several NIH subcommittees and peer review panels, including the Cancer Immunopathology and Immunotherapy Study Section. He has also served as editor-in-chief of the journal Biology of Blood and Marrow Transplantation since 2001, and authored 140 research articles, reviews and book chapters.

THE BREAST CANCER RESEARCH FOUNDATION expanded its research program with a new collaborative breast cancer funding model, the BCRF Investigator-Initiated Drug Research Program.

The received a three-year, $15 million grant from Pfizer to support this effort, as well as access to Pfizer's portfolio of products.

"It will encourage more creative, academic-driven research and give more patients access to clinical trials. We believe this unique approach has the potential to greatly accelerate and impact research progress, and ultimately, lead to more breakthrough discoveries," said Larry Norton, BCRF's scientific director and medical director of the Evelyn H. Lauder Breast Center at Memorial Sloan Kettering Cancer Center.

Clifford Hudis, chairman of the BCRF Scientific Advisory Board and vice president for government relations and Memorial Sloan Kettering chief advocacy officer, said, "This will allow us to test every possible application for targeted therapies, or combinations of agents against different molecular targets that will hopefully translate into more effective and more meaningful therapies for people with all types of breast cancer, as well as other cancers."

BHARAT AGGARWAL, a former researcher at MD Anderson Cancer Center, has had seven papers retracted from Biochemical Pharmacology, according to Retraction Watch. The papers, of which he is the only common author, have been cited over 500 times.

According to an MD Anderson statement to Retraction Watch, Aggarwal retired from the institution Dec. 31, 2015.

The papers are:

• "Curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway and up-regulates cyclin-dependent kinase inhibitors p21 and p27 in multiple human tumor cell lines" (2007).

• "Thymoquinone poly(lactide-co-glycolide) nanoparticles exhibit enhanced anti-proliferative, anti-inflammatory, and chemosensitization potential" (2010).

• "Curcumin potentiates the antitumor effects of gemcitabine in an orthotopic model of human bladder cancer through suppression of proliferative and angiogenic biomarkers" (2010).

• "Suppression of pro-inflammatory and proliferative pathways by diferuloylmethane (curcumin) and its analogues dibenzoylmethane, dibenzoylpropane, and dibenzylideneacetone: Role of Michael acceptors and Michael donors" (2011).

• "Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo" (2010).

• "Cyclodextrin-complexed curcumin exhibits anti-inflammatory and antiproliferative activities superior to those of curcumin through higher cellular uptake" (2010).

• "Triptolide, histone acetyltransferase inhibitor, suppresses growth and chemosensitizes leukemic

cells through inhibition of gene expression regulated by TNF-TNFR1-TRADD-TRAF2-NIK-TAK1-IKK pathway" (2011).

THE COMMISSION ON CANCER of the American College of Surgeons granted a second installment of 2015 Outstanding Achievement Awards to 27 accredited cancer programs. Award criteria were based on accreditation surveys conducted during the second half of 2015.

The award recognizes cancer programs that achieve excellence meeting the CoC Standards.

The awardees are:

Fairbanks Memorial Hospital, Fairbanks, Alaska; Princeton Baptist Medical Center, Birmingham, Ala.; Washington Hospital Healthcare System, Fremont, Calif.; Northridge Hospital Medical Center, Northridge, Calif.; Feather River Hospital, Paradise, Calif.; Danbury Hospital, Danbury, Conn.; Johnson Memorial Hospital, Stafford Springs, Conn.; Martin Health System, Stuart, Fla.; Midtown Medical Center John B. Amos Cancer Center, Columbus, Ga.; Elmhurst Memorial Hospital, Elmhurst, Ill.; Ingalls Memorial Hospital, Harvey, Ill.; King's Daughters' Health, Madison, Ind.; University of Louisville Hospital, Louisville, Ky.; Owensboro Health Regional Hospital, Owensboro, Ky.; Pikeville Medical Center, Pikeville, Ky.; Lafayette General Medical Center, Lafayette, La.; Beth Israel Deaconess Hospital - Plymouth, Plymouth, Mass.; St. Dominic-Jackson Memorial Hospital, Jackson, Miss.; Forsyth Regional Cancer Center, Winston-Salem, N.C.; The Valley Hospital, Ridgewood, N.J.; Oregon Health & Science University, Portland, Ore.; Abington Memorial Hospital, Abington, Penn.; Reading Hospital, Reading, Penn.; Roger Williams Medical Center, Providence, R.I.; Texas Health Harris Methodist Hospital Forth Worth, Fort Worth, Texas; Baylor Medical Center at Grapevine, Grapevine, Texas; and Riverside Regional Medical Center, Newport News, Va.

KIDS V CANCER was named as one of **Fast Company's** Top 10 Most Innovative Companies of 2016 in Not-For-Profit, placing fourth. Fast Company praised Kids v Cancer for accelerating the discovery of pediatric cancer treatments.

Other organizations in this category include Black Lives Matter, 92nd St Y, Humans Of New York and UNICEF. Last year, Kids v Cancer received the 2015 Peter F. Drucker Award for Nonprofit Innovation.

Through the Creating Hope Act, Kids v Cancer has mobilized almost $1 billion for research and development of drugs. With the valuation of a Creating Hope Act pediatric priority review voucher reaching $350 million, biotech and pharmaceutical companies are now focusing on business plans built around pediatric rare disease drug development.

INDIANA UNIVERSITY Melvin and Bren Simon Cancer Center received a $100,000 women's cancer research grant from the **Kay Yow Cancer Fund.**

Since 2009, the Kay Yow Cancer Fund has supported a women's cancer research grant at an institution based in the host city of the annual NCAA Women's Final Four. This year's grant was awarded to the IU Simon Cancer Center in the host city of Indianapolis.

The Kay Yow Cancer Fund works in collaboration with The V Foundation Scientific Advisory Committee to identify and review grant proposals supporting women's cancer research. To date, the Kay Yow Cancer Fund has allocated more than $5.28 million.

Drugs and Targets

FDA Approves Gazyva In Follicular Lymphoma

FDA approved Gazyva (obinutuzumab) plus bendamustine chemotherapy followed by Gazyva alone as a new treatment for people with follicular lymphoma who did not respond to a Rituxan (rituximab)-containing regimen, or whose follicular lymphoma returned after such treatment.

The approval is based on results from the phase III GADOLIN study, which showed that, in people with follicular lymphoma whose disease progressed during or within six months of prior Rituxan-based therapy, Gazyva plus bendamustine followed by Gazyva alone demonstrated a 52 percent reduction in the risk of disease worsening or death (HR=0.48, 95% CI 0.34-0.68, $p<0.0001$), compared to bendamustine alone, as assessed by an independent review committee.

In addition, best overall response for those receiving the Gazyva regimen was 78.7 percent (15.5 percent CR, 63.2 percent PR) compared to 74.7 percent for those receiving bendamustine alone (18.7 percent CR, 56 percent PR), as assessed by IRC.

The median duration of response was not reached for those receiving the Gazyva regimen and was 11.6 months for those receiving bendamustine alone.

The Gazyva regimen reduced the risk of death by

38 percent compared to bendamustine alone based on a post-hoc analysis with 24.1 months of median observation time (HR=0.62, 95 percent CI 0.39-0.98). The median OS has not yet been reached in either study arm.

Gazyva is sponsored by Genentech. The supplemental Biologics License Application based on these data was granted Priority Review by FDA.

"People with follicular lymphoma whose disease returns or worsens despite treatment with a Rituxan-containing regimen need more options because the disease becomes more difficult to treat each time it comes back," said Sandra Horning, Genentech's chief medical officer and head of Global Product Development. "Gazyva plus bendamustine provides a new treatment option that can be used after relapse to significantly reduce the risk of progression or death."

The safety of Gazyva was evaluated based on 392 people in the GADOLIN study with indolent NHL of whom 81 percent had follicular lymphoma. The most common Grade 3-4 side effects of the Gazyva regimen were low white blood cell counts, infusion reactions and low platelet counts.

According to Genentech, marketing applications for Gazyva based on the GADOLIN study results have also been submitted to other regulatory authorities, including the European Medicines Agency, for approval consideration.

Gazyva, in combination with chlorambucil, is also approved by the FDA for patients with previously untreated chronic lymphocytic leukemia.

FDA approved Afinitor (everolimus), sponsored by Novartis, for the treatment of adult patients with progressive, well-differentiated non-functional, neuroendocrine tumors of gastrointestinal or lung origin with unresectable, locally advanced or metastatic disease.

The approval was based on demonstration of improvement in progression-free survival in a multicenter, randomized, placebo-controlled trial of everolimus 10 mg orally once daily plus best supportive care compared to placebo plus BSC.

The trial enrolled 302 patients with unresectable, locally advanced or metastatic, well differentiated, non-functional neuroendocrine tumors of gastrointestinal or lung origin. All patients were required to have evidence of disease progression within six months prior to randomization.

The major efficacy outcome measure was progression-free survival based on independent radiological assessment per RECIST. Median PFS were 11 months and 3.9 months in the everolimus and placebo arms, respectively [HR 0.48 (95% CI: 0.35, 0.67), p <0.001, stratified log rank test].

Overall response rates were 2 percent in the everolimus arm and 1 percent in the placebo arm. At the planned interim analysis, there was no statistically significant difference in overall survival between arms.

Safety data were evaluated in 300 patients who received at least one dose of investigational drug. The median exposure duration to everolimus was 9.3 months; 64 percent of patients were treated for greater than or equal to 6 months and 39 percent were treated for greater than or equal to12 months.

Everolimus was discontinued for adverse reactions in 29 percent of patients and dose reduction or delay was required in 70 percent of everolimus-treated patients. Serious adverse reactions occurred in 42 percent of everolimus-treated patients and included three fatal events (cardiac failure, respiratory failure, and septic shock).

The most common adverse reactions were stomatitis, infections, diarrhea, peripheral edema, fatigue and rash. The most common laboratory abnormalities were anemia, hypercholesterolemia, lymphopenia, elevated aspartate transaminase and fasting hyperglycemia.

FDA granted Breakthrough Therapy designation to PKC412 (midostaurin), an investigational treatment for adults with newly-diagnosed AML who are FLT3 mutation-positive, as detected by an FDA-approved test, and who are eligible to receive standard induction and consolidation chemotherapy.

The designation is primarily based upon results from the phase III RATIFY clinical trial. This study was conducted in partnership with the Alliance for Clinical Trials in Oncology and presented during a plenary session at the 57th American Society of Hematology Annual Meeting.

Patients who received PKC412 and standard induction and consolidation chemotherapy experienced a significant improvement in overall survival (HR = 0.77, p = 0.0074) compared to those who received standard induction and consolidation chemotherapy alone. The median OS for patients in the PKC412 treatment group was 74.7 months (95% CI: 31.7, not attained), versus 25.6 months (95% CI: 18.6, 42.9) for patients in the placebo group.

PKC412 is also being investigated for the treatment of aggressive systemic mastocytosis/mast cell leukemia.