THE CANCER LETTER

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Vol. 39 No. 35
Sept. 20, 2013

Turmoil in Texas

Patient Harm—Including One Death—Cited As Faculty Challenges MD Anderson Leadership

By Paul Goldberg

More than half of MD Anderson clinical faculty said the administration's demands to increase the workload have eroded patient safety at the institution.

Preparing for a meeting with the UT System Chancellor Francisco Cigarroa, the MD Anderson Faculty Senate conducted a survey to gauge the faculty's assessment of the quality of care—particularly patient safety.

The result: 56.4 percent of the 546 clinical faculty members who answered the question dealing with patient safety said that aggressive financial quotas set by the MD Anderson President Ronald DePinho's administration have made patients less safe.

(Continued to page 2)

Drug Approval

Pertuzumab Signals FDA's Resolve In Granting Accelerated Approvals

By Paul Goldberg

The recommendation by the FDA Oncologic Drugs Advisory Committee to grant an accelerated approval to the Genentech agent Perjeta (pertuzumab) for neoadjuvant treatment of breast cancer makes three important statements about the agency's criteria for approval of cancer drugs:

• The committee vote—13:0 with one abstention—establishes a pathway for approval of neoadjuvant therapies in breast cancer.

• Since pertuzumab is on the way to becoming the first agent to be approved for a neoadjuvant indication, the gates may have opened for neoadjuvant therapies for other cancers.

• Having established its authority—and having affirmed its political will—to remove indications that fail to earn full approval in confirmatory trials, FDA is saying that it is now willing to take big risks on accelerated approvals.

(Continued to page 6)

Capitol Hill

HHS, NIH Prepare for Government Shutdown

By Will Craft

The House of Representatives Sept. 20 voted 230-189 to defund the Affordable Care Act and keep the government open through Dec. 15 at $986 billion—about $1.2 billion below sequester-level funding.

By combining the continuing resolution with the measure to defund the ACA, the House Republicans are presenting Senate Democrats with an ultimatum—one that the Senate is unwilling to accept.

(Continued to page 12)

Patient Safety Not Affected, MD Anderson Officials Say

(Continued from page 1)

In other highlights of the clinical faculty survey, 66.2 percent said that MD Anderson's clinical reputation has been "diminished," and 64 percent said they had either interviewed for other jobs or considered doing so.

MD Anderson officials said in a statement to The Cancer Letter that their "patients are and have been receiving safe, quality care," and that "if there was an error or even the possibility of an error, MD Anderson has reporting mechanisms to call out the incident."

Questions about the quality of care weren't asked in previous surveys conducted by the MD Anderson Faculty Senate (The Cancer Letter, Sept. 6). The results of the most recent survey are posted on The Cancer Letter website.

MD Anderson holds the No. 1 rating by U.S. News & World Report, albeit in part due to an error in data submitted to Centers for Medicare and Medicaid Services (The Cancer Letter, July 19). Both reputation and patient safety are considered by U.S. News in ranking cancer hospitals.

The latest survey invited MD Anderson faculty members to offer "final comments" and recommendations. Many of these comments—there are about 100 pages altogether, sources said—focused on the quality of care and patient safety. Only clinicians were polled.

One clinician wrote:

"I have had two major clinical mistakes in the past year due to over burdened clinical demands on complicated patients. One of these incidents clearly resulted in a patient death."

The survey was taken anonymously.

"It is extraordinary for a clinician at an outstanding institution to publicly voice concern that a patient death may have been attributable to avoidable mistakes resulting from overburdened staff," said Arthur Caplan, head of the Division of Medical Ethics at NYU Langone Medical Center.

"To note a link between a death and culpable error is not only rare but bespeaks a concern about a slippage in the quality of care that a premier cancer institution must not tolerate," Caplan said. "It also raises obvious questions about where resources are being allocating within the institution if a key clinician feels compelled to warn about their concern over patient safety being compromised.

"At many levels, worry about safety is as serious an ethical concern as can be evidenced in any health care setting."

Sheldon Krimsky, the Lenore Stern Professor of Humanities & Social Sciences and an adjunct professor of public health and community medicine at Tufts University, said: "The old adage, 'what goes around comes around' is a fitting description of what has befallen MD Anderson.

"A new director arrives with egregious financial conflicts of interest, spends money on furnishings befitting a Fortune 500 company executive, promotes his personal financial interests in the media, and adopts a management strategy that is designed to turn a great public medical center into a Walmart-style health care provider," said Krimsky.

"The management principles of a 19th century industrial assembly line are not what a 21st century research and clinical health center needs."

Medical malpractice lawyers say that the faculty's statements of concern may expose MD Anderson and the UT System to claims.

"The burden is on the patient's representative to establish that the cause of the patient's death was 'caused by' the failure of the defendants to meet the ordinary and customary standard of care in the medical community," said an attorney who reviewed the faculty survey, but spoke on condition that he wouldn't be identified by name.

"One of the allegations of negligence would be that the change in medical care, driven by financial rather than medical considerations, 'caused' the death because

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Paul Goldberg
Associate Editor: Conor Hale
Reporter: Matthew Bin Han Ong
Intern: Will Craft

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd.

In your opinion, has the demand for increase in clinical productivity negatively impacted patient safety?

	Response Percent	Response Count
Yes	**56.4%**	**308**
No	17.8%	97
Not sure	25.8%	141

'but-for' the change the error would not have occurred," the attorney said. "The fact that the defendant's own employees have already stated as much is strong evidence of this causation.

"An additional allegation of negligence would also likely be that once the defendants were put on notice of this heightened risk they took no steps to address, eliminate, or reduce the risk. It is one thing to have a paid expert from outside offer that opinion, but it is particularly damning when your own people say it."

Asked to comment, MD Anderson officials responded with a statement signed by Thomas Burke, executive vice president and physician in chief; Alma Rodriguez, vice president for medical affairs; Charles Levenback, associate chief quality officer for medical affairs; Barbara Summers, vice president and chief nursing officer; and John Bingham, vice president for performance improvement and chief quality officer.

The text of the statement follows:

There is nothing more important to The University of Texas MD Anderson Cancer Center than our patients' safety.

Our commitment to safety is as true today as it has been for all of MD Anderson's 70-year history. It is the bedrock of our mission and the mindset of each of our 20,000 employees, whether they work in a clinic or inpatient unit or in an administrative office. This commitment is reflected in our outstanding and consistent patient safety record that has not declined in any way over the past five years.

We deeply regret our patients and their families may have been upset by recent reports that call this commitment into question.

In response to external pressures in health care, we acknowledge that our clinics and people have been asked to do all they can to be more efficient and effective, while never compromising quality.

However, as evidenced by our data and reporting systems, our patients are and have been receiving safe, quality care. If there was an error or even the possibility of an error, MD Anderson has reporting mechanisms to call out the incident. We encourage and compel such reporting.

Ultimately, we believe that every outstanding professional on our health care teams exercises the highest level of personal and professional responsibility when it comes to patient care.

And, our industry-recognized data indicate that, as an institution:

• The Joint Commission has certified our safe practices every three years since 1951.

• Our nurses have met the rigorous standards of the American Nurses Credentialing Center and have received Magnet designation in 2001, 2006 and 2010.

• Our surgical faculty and staff have participated in a National Surgical Quality Improvement Program since 2011, which shows our surgical safety record to be extremely strong.

• In 2011, our radiation oncology practice was accredited by the American College of Radiology and the American Society for Therapeutic Radiology and Oncology.

• We follow the standards set by the Institute for Safe Medication Practices and have developed programs to continually educate our physicians, nurses and pharmacists in cancer medicine prescription and administration.

• Our stem cell and cellular therapy teams recently earned their fifth accreditation since 2000 by the Foundation of Accreditation and Cellular Therapy.

• We have been recognized by the University HealthCare Consortium as one of the top three academic medical institutions (out of 75) to reduce hospital-acquired conditions through adherence to safe practices.

• Every clinical department has a faculty quality

Compared to 2010 do you feel that our clinical reputation at the current time has been:

	Response Percent	Response Count
Enhanced	4.6%	25
Stayed the same	29.2%	157
Diminished	**66.2%**	**356**

Have you interviewed for or considered other job opportunities in the past 12 months?

Considered	**37.4%**	**204**
Considered and interviewed	26.6%	145
Not considered	29.9%	163
I've considered retirement	6.2%	34

officer who continuously monitors and reports on clinical metrics.

• Over the past eight years, 1,000 people have been trained in Clinical Safety and Effectiveness.

We remain continuously proud of the men and women who care for our patients and their demonstrable record of unwavering commitment to provide the safest patient care possible.

Meeting With Chancellor

In recent weeks, MD Anderson faculty members have been more willing to openly challenge the administration.

At a meeting with the UT System chancellor on the MD Anderson campus Sept. 18, statements by two surgeons received applause from the faculty. The Houston Chronicle reporter Eric Berger covered the meeting. The Cancer Letter obtained a recording.

"People really come here for excellence," said Gary Clayman, chair of head and neck surgery at MD Anderson. "They come here to see individuals. They come here for the best. Not just to get treated."

Clayman, who joined MD Anderson in 1989, said he has seen a change in ethos at the cancer center. "I actually try to go around and smile and say hi to people, because there are a lot of people looking down, a lot of people not making eye contact.

"And it's not just faculty. I think it's very pervasive throughout the institution. It's uncomfortable.

"I never really thought about leaving this institution. But I have seriously considered it over this past year, not because of very tangible issues, but because of very intangible issues."

Frederick Lang, director of clinical research in the department of neurosurgery, said the new emphasis on financial performance is harming the institution.

"I've been here since 1995, and I think that the last two years the major shift has been an emphasis by our leaders away from excellence and toward budget only," Lang said.

"There is a new email each month, I think, and the first line of that is always how we haven't made budget, and the key thing that Dr. Clayman points out is we really don't know why that budget is what it is.

"As a naive clinician, I see us making lots of money. We are positive every [month]. They say, 'Oh, you can't include philanthropy in that.' That seems silly. Most organizations include that. If you include philanthropy, I think we are making even more money.

"So what the emphasis now is the patient is viewed as an ATM machine by the administration. He or she is not viewed as a patient we are trying to take care of. My perception is the administration doesn't care whether we do a good job or no.

"They just want to make more money.

"My feeling is that up to now the emphasis of MD Anderson is excellence. And excellence, in my mind, is if you do well, money will follow. If your goal is to

make money, you will fall.

"And we've lost that perspective. We now want to make money, and that's the only thing that matters. Until we get to the perspective—the top people—that all we want to do here is be excellent, and if we are excellent, then we don't have to worry, but that's not the perspective anymore."

Kenneth Shine, the UT System's former executive vice chancellor for health affairs who chaired the search committee that hired DePinho, said that "Dr. DePinho made a serious mistake, which he has acknowledged" when, as a guest on a television show, he touted the stock of a company he had co-founded (The Cancer Letter, Sept. 13).

"The question is, how much of a pound of flesh do you extract because of that significant error?" Shine said.

Shine cautioned the faculty members not to believe everything they read.

"The Houston Chronicle wants to publish papers, and The Cancer Letter is used to trying to be provocative or rake mud or whatever and that's the role that the media plays," Shine said. "My only point that I would make to you is I don't think it's helpful to have this put in the newspaper."

Negative coverage causes poor morale, Shine said. "Because that often means you could do the wrong thing and I'm very sensitive about morale," he said. "What happens is the more bad media you get, the more detrimental that is to morale."

At the meeting, Cigarroa said he came to "listen and learn," and Shine's successor Raymond Greenberg, the official to whom DePinho now reports, didn't say much at all.

Asked by a faculty member to comment on the rumor that DePinho had a golden parachute that was worth between $25 million to $50 million, Shine said this was not the case. The terms of DePinho's hiring are a matter of public record, he said.

DePinho didn't attend the meeting.

MD Anderson's Clinical Faculty Speaks

A selection of comments from clinical faculty members follows:

I have witnessed this first hand. Repeat blood draws in radiology, soft calls on CT scans necessitating additional studies (imagine being a patient have experiencing the anxiety of having to do an additional study to see if there was a recurrence). I think the additional radiographic studies are being done to increase revenue: this is disgusting. Patient care on the wards is significantly worse. And, how many patients can a physician and her/his team see before mistakes are made. People's lives depend on us being sharp; that is now a thing of the past, as we are now just here to generate revenue. Why do you think so many senior people are leaving? Wake up Austin! You are watching MDACC turn into a second rate center while you remain indecisive.

This is not a biotech company; this is not an IT company. This is a hospital where patients stare at death in the face. This is a hospital where patients come from thousands of miles. They come with hope. We cannot let them down.

RECOMMENDATIONS: Bring in people who have actually treated cancer patients to manage this institution. Change the leadership and management at the highest level.

The big boss gets away with everything, yet I get hounded to death by conflict of interest committee for a $100 dollar honorarium to speak to a professional society.

I also get hounded about speaking at a national conference where they cover my plane and hotel, but nothing else and am asked to provide THEIR funding sources for a conference put on a by a nationally recognized university. Yet, the top brass is cashing it in.

Patient care is deteriorating due to the failure of leadership to expand clinical operations. As an example, we only have 3 Da Vinci Robots and so patients are forced into having open surgery due to lack of robotic access. MSKCC has 10 robots in their operating room. We are falling behind and

with the current leadership, have little likelihood of catching up.

The leadership is more concerned with hiring high priced scientists, rather then provide the essential equipment needed to offer patients optimal care.

There are serious efficiency problems that have not been appropriately addressed by the leadership. The leadership seems to be in another planet, or perhaps a moon. It is really not a joke.

Our services are overcrowded. Hospital bed availability is generally low. Time to obtaining CT, MRI, endoscopy has increased. Inpatient services are being strained.

Increasingly we have young faculty members who don't seem as committed to patient care and don't have the necessary expertise or experience. This has been a progressively dominant trend in the last 5 to 10 years due to the rapid growth of the institution without a parallel attention to quality.

The infrastructure that supports the physicians is being eroded by plans to reduce staff, while the load is increasing. There is no overarching plan for information systems to help support the increased patient numbers. Some of our best physicians are leaving because of the leadership and we will spend years replacing them.

---

1. The demand for clinical team operation and expectation are not realistic and not reasonable;

2. The entire MD clinical team is working very hard, with at least more than 100% overload of service work compared to nearly all of the academic centers in the nation;

3. However, incentive and encouragement to clinical physicians are poorly treated or significantly tortured by current administration leader.

4. The current administration leader treats the clinical team and physicians similarly as basic scientists, but fails to recognize the MD Anderson revenue is generated essentially all by clinical teamwork, but by researchers. Incentive and encouragement to the clinical physicians should be different. This has been well recognized by former president Dr. Mendelsohn, MD, who is well respected by most of our MD physicians.

5. We greatly appreciate the system and model from Dr. Mendelsohn, who has shown his respect to our clinical MD physicians. During his tenure as president at MD Anderson, we have not had any single year break of merit award and incentives, even in the most difficult economy collapsed seasons in the US.

6. The current deterioration of MD Anderson reflects the lack of good understanding in areas of operation, finance, respect, perspectives, etc. from current administration leader, who is only interested in his own research aims, nature publications from his own team, personal incomes from pharms, etc.

7. Finally, we need to emphasize that the MD Anderson is world known for its reputation in clinical service, quality, high caliber of MD physicians, advanced support of molecular/genetic/genomic related trials, not because of basic research. To change the strategic plan from clinical focused operation to basic research oriented system is completely a stupid mistake, reflecting unqualified skills and knowledge of current administration leader.

Drug Approvals

ODAC's Perjeta Recommendation Based on Totality of Evidence

(Continued from page 1)

At the ODAC meeting Sept. 12, FDA officials and the agency's clinical advisors said that they were willing to approve pertuzumab based on the totality of evidence.

Indeed, the extent of evidence supporting the Perjeta application is unusual for a new drug:

• The sponsor provided data from a trial in a metastatic disease setting, which showed a statistically significant and robust clinical effect on overall survival.

• A fully-accrued adjuvant therapy trial.

• A well-studied mechanism of action of Perjeta in the HER2 pathway, with evidence that a sister drug, Herceptin (trastuzumab), can improve disease-free survival.

• Also, the sponsor had submitted a database reflecting extensive exposure of thousands of patients to the drug in a variety of breast cancer settings.

Realistically, can this amount of evidence be expected to accompany future applications for neoadjuvant indications?

The answers will have to wait, as it is not publicly known whether there are any other applications for neoadjuvant indications before the agency.

Specifically, the agency is betting that pathological complete response, an endpoint that has not been validated, would translate into prolongation of event-free survival and overall survival.

In one of the meeting's more dramatic moments, Richard Pazdur, director of the FDA Office of Hematology and Oncology Products, extracted a pledge from Sandra Horning, a Genentech senior vice president and global head for clinical hematology and oncology, that the company would voluntarily renounce the neoadjuvant indication if the confirmatory clinical trial failed to show benefit.

Genentech, a unit of the Roche Group, fought hard—and in vain—to retain the breast cancer indication for Avastin (bevacizumab), but the agency insisted that failure to demonstrate patient benefit must lead to revocation of an accelerated approval.

Though legislation that established accelerated approval allows for stripping the indications, until the Avastin dispute, no sponsor had ever fought back. To remove the indication, FDA was forced to construct administrative procedures for removing accelerated approvals.

Now, with precedent set and administrative procedures for removal of accelerated approvals in place, the agency appears to be more game to take a risk. And, having lost one of Avastin's indications, Genentech now stands to benefit from the drug's legacy.

The Gamble

Pertuzumab is a monoclonal antibody that targets the extracellular domain of the human epidermal growth factor receptor 2 protein.

The agent was approved in June 2012 for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

The company is seeking to market pertuzumab for "neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide or carboplatin."

The supplemental Biologics License Application is based on results from NEOSPHERE and TRYPHAENA, phase II studies of Perjeta in high-risk, HER2-positive early stage breast cancer, as well as on longer-term safety data from the phase III CLEOPATRA study of Perjeta in HER2-positive metastatic breast cancer.

The NEOSPHERE study (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) is a randomized, multicenter, international phase II study that was conducted in 417 people with newly diagnosed HER2-positive, locally advanced, inflammatory or early stage breast cancer with tumors greater than two centimeters.

Participants were randomized to four study arms and received four cycles (12 weeks) of neoadjuvant treatment. The primary endpoint was pCR. Secondary endpoints included clinical response, time to clinical response, safety profile, disease-free survival, breast-conserving surgery rate and biomarker assessment.

Treatment with Perjeta, Herceptin and docetaxel chemotherapy significantly improved the rate of total pCR by 17.8 percentage points compared to Herceptin and docetaxel alone (39.3 percent vs. 21.5 percent, p=0.0063). pCR demonstrated by arm included:

• pCR of 21.5 percent for Herceptin and docetaxel

• pCR of 39.3 percent for Perjeta, Herceptin and docetaxel

• pCR of 11.2 percent for Perjeta and Herceptin

• pCR of 17.7 percent for Perjeta and docetaxel

The TRYPHAENA study (ToleRabilitY of Pertuzumab, Herceptin and AnthracyclinEs in NeoAdjuvant breast cancer) is a randomized, multicenter phase II study conducted in 225 people with HER2-positive, locally advanced, inflammatory or early stage breast cancer with tumors greater than two centimeters.

TRYPHAENA participants were randomized to one of three neoadjuvant Perjeta regimens. The primary endpoint was cardiac safety. Secondary endpoints included pCR, clinical response, breast-conserving surgery rate, DFS, progression-free survival, overall survival and biomarker assessment.

The study was not powered to compare the three study arms. The rates of total pCR in the three arms were as follows:

• pCR of 56.2 percent for Perjeta, Herceptin and anthracycline-based chemotherapy, followed by Perjeta, Herceptin and docetaxel.

• pCR of 54.7 percent for anthracycline-based chemotherapy, followed by Perjeta, Herceptin and docetaxel.

• pCR of 63.6 percent for the anthracycline-free arm (Perjeta, Herceptin, docetaxel and carboplatin chemotherapy).

ODAC member Tito Fojo questioned reliability of pCR as a surrogate endpoint.

"There are so many variables here with what the pCR rate is going to be, you only need to look at the sponsors catalog at all of the pCR rates, they are all over the place," said Fojo, director of the NCI Medical Oncology Fellowship Program. "So you just wish that there was something a little more reliable than this to hang your hat on. And the other thing is that this study had a higher percentage of hormone-negative than was in your meta-analysis that the FDA has done.

"We know HR-negative patients have a higher pCR rate, so that's always going to push your pCR rate a little bit higher, if you want a higher pCR, enroll more HR-negative patients and for a lower one enroll more HR-positive patients, so there's a lot of variables here that we have to consider."

Endpoint/Study Population	H + T	Ptz + H + T	Ptz + H	Ptz + T
Overall ITT	**N=107**	**N=107**	**N=107**	**N=96**
pCR[1], n (%) [95% CI][2]	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes corr. for CMH test)[3]		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)
Hormonal receptor-positive subgroup	**N=50**	**N=50**	**N=51[4]**	**N=46**
pCR[1], n (%) [95% CI] 2	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormonal receptor-negative subgroup	**N=57**	**N=57**	**N=55[4]**	**N=50**
pCR[1], n (%) [95% CI][2]	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13(26.0%) [14.6, 40.3]

T=docetaxel, Ptz=pertuzumab, H=trastuzumab, CI=Confidence Interval

[1] ypT0/isypN0, [2] 95% CI for one sample binomial using Pearson-Clopper method. [3] p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment

[4] One patient had unknown hormonal receptor status. The patient did not achieve a pCR.

Summary of efficacy from the phase II NEOSPHERE trial. *Source: FDA*

FDA "Not Unfavorable"

"At the risk of being castigated for using a double negative, I will say that the briefing documents are not unfavorable towards the applicant," noted ODAC Chair Mikkael Sekeres.

Indeed, before the application went to ODAC, the agency published a draft guidance for development of drugs for the neoadjuvant indication in breast cancer.

Genentech's application proposes making the drug available while the company conducts the confirmatory trial, called APHINITY, which compares a Perjeta, Herceptin and chemotherapy combination to a combination of Herceptin and chemotherapy in patients with HER2-positive early-stage breast cancer.

The study has completed enrollment of approximately 4,800 people, and the primary endpoint is invasive disease-free survival. Data are expected in 2016.

Patients will be followed for 10 years, and the study's secondary objectives include second non-BCs, DFS, OS, recurrence-free interval, distant recurrence-free interval, cardiac safety, overall safety, and health-related quality of life.

At the meeting, Pazdur employed prosecutorial questioning tactics to establish that if Perjeta doesn't

pan out, Genentech would not fight to keep it on the market:

PAZDUR: I think our outlying presentation of the accelerated approval pathway clearly delineated that there is a mechanism for removal of in this case an indication, not the removal of the drug from the market, if the confirmatory study was negative.

There are two issues that you bring up in accelerated approval: sponsors not doing the confirmatory trials, and then whether the trials are negative. That trial is already done here basically, so I assume that Genentech would be planning on submitting that at the appropriate time when the requisite number of events has occurred.

I think a much more cogent question to ask Genentech at this time, and perhaps Dr. Horning would like to answer it, is if that trial is negative—we only have one adjuvant trial that's ongoing here, and it would take years to launch another adjuvant trial—are there other adjuvant trials, and what is the corporate philosophy of Genentech if this trial is negative in removing that indication? Dr. Horning?

SEKERES: It seems we were here about two years ago answering the same questions for another Genentech drug. You and me both, Dr. Pazdur, you and me both.

HORNING: Give me all the easy ones. Well, the APHINITY trial, as you have heard, is fully enrolled and that is our main study that we proposed as a conversion plan for this application.

With regard to other large ongoing studies at this time, we are not sponsoring other large adjuvant studies.

With this application for Perjeta and for future applications, we would of course be speaking with the agency in working in a very collaborative manner all across the spectrum from the standpoint of the original conception of the study, the endpoints, and following right through to the endpoints, so I think it would be a discussion for the future as to the outcome of the APHINITY study.

As you can imagine with this FDA draft guidance, we and others have looked to this innovation from the FDA and we do applaud the efforts to bring promising new agents to patients with high-risk early breast cancer at an earlier point in time. And we do think that this particular application does contain strong data, but it is somewhat unique in that we have the mechanism of action and that has been shown in multiple studies of dual HER2 blockade we have the overall survival benefit in the CLEOPATRA study and we have what we believe to be a favorable benefit risk in our neoadjuvant setting.

PAZDUR: Well, you didn't answer the question.

The question is, and you can just answer it yes or no, if the adjuvant trial is negative and does not demonstrate any difference between the two arms with the addition of pertuzumab to the Herceptin containing combination, would Genentech voluntarily withdraw this application for this indication?

HORNING: If the APHINITY study is negative…

PAZDUR: And there are no other trials.

HORNING: Of course, we are hopeful that that is not going to be the case.

PAZDUR: We all are, we all are.

HORNING: Then we would certainly speak to the agency about withdrawing the neoadjuvant indication.

PAZDUR: So you are unwilling to make a commitment at this time.

HORNING: Honestly, negative or positive might be a very simplistic way to look at the overall outcome.

So I do think that if the trial is clearly negative that we would be willing to withdraw the indication. I do think we should leave some room for evaluating the context of the trial and we know that context is always important and can be very rich in these very large trials, but to answer your question specifically, yes we would be willing to withdraw this if the APHINITY study were negative.

PAZDUR: Thank you.

SEKERES: Thank you Drs. Pazdur and Horning. Just to be clear, this represents a remarkable opportunity to bring a drug that has been effective in the metastatic HER2-positive setting to the very upfront setting very quickly and probably quicker than most drugs do.

Short-Term Bet

The fact that the approval would be contingent on a single trial that would produce data within three years made committee members more willing to vote for the accelerated approval.

Said Sekeres: "This is a historic moment as we have voted to support the first approval of a drug for the neoadjuvant treatment of breast cancer: pertuzumab. In so doing, we are supporting the rapid movement of a highly active drug for metastatic breast cancer to the

first-line setting, with the hope that women with earlier stages of breast cancer will live longer and better. We do this with some words of advice to Genentech.

"All eyes will be on the confirmatory APHINITY trial and on you to verify this initial signal of efficacy and to confirm the bandwidth of safety that we have seen so far. If these are not confirmed, we urge you to avoid a repeat performance of Avastin and voluntarily remove this drug from the market."

Other ODAC members similarly focused on the totality of evidence supporting the application:

James Leibmann, assistant professor of medicine at the University of Massachusetts: "Probably the main reason I voted yes is because the adjuvant trial is completed. I think if the adjuvant trial was going to be something done that we might get news about 10 years from now, I would definitely have voted no. In this setting in accelerated approval, it would be nice if there was an established patient registry of patients who are treated on this indication and can be followed."

Deborah Armstrong, associate professor of oncology at Johns Hopkins University: "I think that this is almost the ideal situation—we have potential for having a benefit but not proven in this setting in a drug that has a fairly substantial benefits in the metastatic setting, and a completed adjuvant trial where the accelerated approval won't affect accrual to an adjuvant trial. I do have concerns as well. I also share the concerns, because we have some hints of increased cardiac toxicity, and having had a 34-year-old patient die in the adjuvant setting receiving cardiotoxic drugs including Herceptin—you only have to have that happen once to be very sensitized to this.

"And I would strongly encourage a very close examination of the cardiotoxicity in the patients who receive longer-term Perjeta in the adjuvant trial and in the post-marketing neoadjuvant study that was proposed. I also share the concerns that Dr. Liebmann had alluded to during our discussions about sort of opening the floodgates.

"We struggle now with what to do with a patient's small node-negative, HER2-positive tumor that we wouldn't normally give chemotherapy to, except that it's HER2-positive, and are we now going to be struggling with people with smaller tumors than we would be giving neoadjuvant therapy to because we want to give them the benefit of this.

"I think those of us who have to make these decisions are going to have to be very careful about what kinds of decisions we make, and whether we actually are doing it based on science or based on emotion. And I do think we have the potential to be opening floodgates and treating people with this therapy that is perhaps not appropriate at this point in time."

Louis Diehl, professor of medicine at Duke University Medical Center: "The totality of the data convinced me, but I would like to make the following comment, or a guess more directly, second Dr. Sekeres comment that I look forward to the day several years from now that this has improved survival. But if we don't see that that day then I think we all have the courage to stand up and say that it didn't work—that we did the very best we could today but it didn't work—and to not have a fight over withdrawing it."

David Steensma, associate professor of medicine at Harvard Medical School: "I thought that is was worth taking that step and worth making this therapy available to women in this high-risk setting earlier than perhaps has been done with other agents in the past, knowing that we are going to have additional data and if the APHINITY trial comes and it looks like a strongly positive signal, I think we'll all feel good about what we did today.

"If it's negative, I share all the comments and the sentiments that have been made, perhaps my quote is not as newspaper-ready as Mikkael's but let's not have a drop-down, dog-rolling-over kind of fight as with Avastin. Again the totality of the evidence was convincing to me."

Michael Menefee, assistant professor at the Mayo Clinic: "I thought, looking at the data as presented, answering the question accurately was yes, there was clearly potential benefit for this patient population with this drug. I thought the risk associated with it was low.

"I do share the concern that any of the others have regarding any of the potentials for toxicity, and it is my hope that the FDA is very clear in the ultimate labeling that it provides so that practitioners have clear guidelines on how to use this drug best and most safely.

"Because, as it was mentioned many times in the discussion, these kind of drugs, once they become available, they're subject to be used in a lot of ways

that are unintended, and I think we need to minimize that risk as much as possible. I'm sure it will provide some limitations if the labeling is done properly, but that was generally my thought process."

Bernard Cole, professor in the Department of Mathematics and Statistics at the University of Vermont: "I always struggle with these kind of questions as a statistician particularly when they're phrased in terms of risks and benefits, I don't treat patients so I don't carry the burden of trying to make an assessment of risk and benefit on an individual patient basis, but in a public health basis is how see I reconcile my vote, looking at the totality of the data, and so from that public health perspective I think it's important that the accelerated approval process be available, and I'm pleased that it is.

"I do agree with this being an historical moment I found that the totality of the data that multiple studies showing anticancer activity was compelling to me. I shared concerns that were well-articulated around the table about the quality of, well not the quality, but the possibility that there was a chance finding, particularly in the NEOSPHERE study, being small, but I think the advantages outweigh the limitations and particularly important consideration was the strong accrual to the APHINITY study. It's really very well designed, so that tipped the scale for me to vote yes."

Brent Logan, professor of biostatistics at the Medical College of Wisconsin: "I think in general, certainly a single, small randomized trial with an effect on the pCR rate, particularly one with flaws like we've been discussing—unblinded review, non-U.S. population—would not really be sufficient I think in this setting.

"There would be uncertainties about clinical benefit, there would be uncertainties about clinical profiles, but that's not what we have here. We have a supplementary, supportive trial in particular showing efficacy in metastatic breast cancer setting, and we also have kind of a consistent toxicity profile across all the trials, and so I think this a reasonable role for the accelerated approval process.

"Particularly, I'm happy that there is an almost completed large, randomized adjuvant trial, which really lends credence to this process."

Gary Lyman, professor of medicine of the Duke University School of Medicine: "I felt the potential for providing meaningful clinical benefit exceeded the potential harms in this case, but it's done with two cautions: one is that if it wasn't for the robust overall clinical development of this drug that Genentech's undertaken, I think we could be coming to different conclusions based on the one trial and so I would hope that the agency would look at this as sort of an N of 1, as a specific example that's going to test this concept, but is not opening up to much less rigorous trials.

"I would also echo Dr. Sekeres and Dr. Diehl, that both to the company and to the agency, to look very closely at the results of the adjuvant trial and if need be, to modify or remove the indication if the data don't support the evidence that we think it will."

Conor Hale contributed to this story.

Capitol Hill

HHS Could Furlough 57 Percent Of Employees Beginning Oct. 1

(Continued from page 1)

"In case there is any shred of doubt in the minds of our House counterparts, I want to be absolutely crystal clear. Any bill that defunds Obamacare is dead. Dead,'' Senate Majority Leader Harry Reid (D-Nev.) said in a news conference Sept. 19.

This represents the latest in over 40 attempts that House Republicans have made to curb the president's healthcare legislation, which is scheduled to take effect Oct.1.

Sen. Ted Cruz (R-Texas) said in a Sept. 19 press conference that he would do whatever it takes to defund the ACA—and did not rule out the possibility of a filibuster.

Senate Democrats lack the 60 votes required to end the potential Republican filibuster, but they do have the simple majority needed to strip the defunding language from the bill and send it back to the House.

If the current version of the resolution, titled H.J. Res. 59, appears before the president, it will be shot down.

"The administration strongly opposes House passage of H.J. Res. 59, making continuing appropriations for fiscal year 2014 and for other purposes, because it advances a narrow ideological agenda that threatens our economy and the interests of the middle class," said a Sept. 19 statement from the Office of Management and Budget.

"The resolution would defund the Affordable Care Act, denying millions of hard-working middle class families the security of affordable health coverage.

"If the president were presented with H.J. Res. 59, he would veto the bill."

House Leaders Bow to Tea Party

Previously, Speaker John Boehner (R-Ohio) and House Majority Leader Eric Cantor (R-Va.) voiced support for a resolution that would have averted a shutdown and allowed the funding of the ACA.

Such a move would likely have drawn support from Democrats in both the House and the Senate.

However, Boehner and Cantor faced fierce opposition from a group of Tea Party Republicans and agreed to conflate both measures rather than fight their own party.

Boehner announced the Sept. 20 vote on the CR just two days prior.

"We're going to continue to do everything we can to repeal the president's failed health care law," Boehner said at a press conference Sept. 18. "This week, the House will pass a continuing resolution that locks the sequester savings in, and defunds Obamacare."

Many analysts see this as the House leadership's desire to appease a fringe minority of the party, whose opposition to the Affordable Care Act is fueling a deadlock with the White House and the Senate.

With the passing of the bill, the "battle," as Boehner called it, is headed to the Senate, where the bill will face heavy opposition.

If no resolution is passed, and no budget compromise reached, the government will shut down on the first day of the 2014 fiscal year, Oct. 1.

NIH's Contingency Plan

The Office of Management and Budget released a memo earlier this week ordering agencies to update their shutdown contingency plans.

"There is enough time for Congress to prevent a lapse in appropriations, and the administration is willing to work with Congress to enact a short-term continuing resolution to fund critical government operations and allow Congress the time to complete the full year 2014 appropriations," the memo reads. "However, prudent management requires that agencies be prepared for the possibility of a lapse. To that end, this guidance reminds agencies of their responsibilities to plan for agency operations under such a contingency."

These contingency plans outline which government employees will be allowed to report to work for the completion of essential services.

Most government employees will be furloughed without pay—only essential personnel will be allowed to work, with pay coming retroactively after the shutdown. Historically, all employees have been retroactively paid for lost time, but the government is only required by law to pay essential personnel.

Fifty-seven percent of all HHS employees will be furloughed— excluding the FDA, which will retain full staffing, according to an OMB document.

The NIH Clinical Center will retain 2,564 staff members in order to continue providing medical services and maintaining research protocols for current patients.

No new patients will be admitted through the duration of the furlough, and no new clinical trials will be started. Also, NIH is prohibited from making any

new extramural research grants.

With a number of experiments at risk of being harmed or destroyed, 982 staff members will be kept on to protect ongoing experiments and research. Further, 652 staff members will report to work in order to maintain care for the over one million animals held at 24 different NIH facilities.

During normal operation, the NIH would have over 8,000 faculty and staff to fulfill these duties.

In Brief

Lengyel Named Ob/Gyn Chair At University of Chicago

ERNST LENGYEL was named chair of the Department of Obstetrics and Gynecology at the **University of Chicago**.

In 2004, Lengyel joined the university as an associate professor of obstetrics and gynecology. He succeeds Arthur Haney, who has served as chair of the Department of Obstetrics and Gynecology since April 2003. Haney will remain an active member of the faculty.

Lengyel studies the biology of how ovarian cancer metastasizes and the use of novel drugs for its treatment. His laboratory was the first to culture metastatic ovarian cancer cells in a three-dimensional environment, similar to how these cells would grow in the body, and the first to use high-throughput drug screening in this model.

He was a recipient of the prestigious Burroughs Wellcome Fund Clinical Scientist Award in Translational Research and serves on the editorial board of the journal Gynecologic Oncology. Lengyel combines his research with an active clinical and surgical practice, focusing on treating ovarian cancer and organ-preserving treatment of cervical cancer.

UNC LINEBERGER Comprehensive Cancer Center appointed two associate professors of medicine to clinical research leadership positions.

E. Claire Dees will serve as medical director of the Clinical Protocol Office. **Peter Voorhees** will serve as chair of the Protocol Review Committee.

Dees currently co-leads the center's clinical research program and leads the Early Phase Clinical Research Unit. She is also a medical oncologist with the University of North Carolina Breast Center.

Voorhees, a medical oncologist, directs the UNC Myeloma Program. He joined the UNC faculty in 2004 and has previously served as the co-chair of the Protocol Review Committee.

The Clinical Protocol Office provides centralized management and oversight of clinical trials including protocol registration, regulatory affairs, patient management, and compliance committee work. The Protocol Review Committee is a multidisciplinary standing committee charged with the peer review of local and national research protocols involving cancer patients or a focus on cancer to ensure the scientific quality and patient safety of proposed studies.

CHARLES BUTLER was named chair of plastic surgery at **MD Anderson Cancer Center**, effective Oct. 16.

Butler joined MD Anderson in 1999 as assistant professor in plastic surgery, became an associate professor in 2003 and a professor in 2008. His work includes a focus on torso reconstruction, as well as basic science research in regenerative medicine and tissue engineering. He has been a visiting professor at 22 institutions worldwide, and is the current vice president of the American Society of Plastic Surgeons.

Butler will replace Geoffrey Robb, who has served as chair since 1998. Robb will continue as a professor of plastic surgery. Butler has been director of the department's Graduate Medical Education Program and Microsurgery Fellowship Program for eight years. He also served as director of the Plastic Surgery Clinic from 2002 to 2006.

SALLY COWAL was named the senior vice president for global health of the **American Cancer Society**.

Cowal will lead the society's international efforts of advocacy for effective tobacco control measures; improvement of access to cancer screening, treatment and pain relief; and collaborations with other cancer control organizations, advocates and governments.

Cowal served as ambassador to the Republic of Trinidad and Tobago, appointed by former Presidents George H.W. Bush and Bill Clinton. Cowal has also served as deputy assistant secretary of state, minister counselor for public affairs at the U.S. embassy in Mexico, and counselor for political affairs at the U.S. Mission to the United Nations.

She helped to found the Joint United Nations Program on HIV/AIDS in Switzerland, and served as its director for external relations to raise awareness. She is also serves as the founder, president and CEO of the Cuba Policy Foundation, a nonprofit organization that

studies the benefits of expanding trade and people-to-people contact with Cuba.

She most recently served as senior vice president at Population Service International, a nonprofit organization focused on combating chronic diseases, including cancer, in 65 developing countries.

THE AMERICAN ASSOCIATION FOR CANCER RESEARCH published its annual cancer progress report, highlighting higher survival rates and discoveries, and cautioning the federal government against cutting research funding.

Over the past few decades, cancer survivability has increased: in 1971, 1 in 69 people diagnosed became cancer survivors—in 2012, that number had been raised to 1 in 23 people.

According to the AACR, the rate of discovery in cancer research will continue at its current pace only if the federal government continues to fund research at or above current levels. Without significant investments in research, the increased economic burden from cancer will cost both lives and money, said the report.

Cancer treatment costs 20 percent more than any other disease. In 2008, the disease cost the U.S. economy $201.5 billion—with $77.4 billion spent on medical costs, and $124 billion lost due to forgone wages, disability, and premature loss of life, an NIH report said.

Although the NIH budget was increased every year from 1970 to 2010, the NIH budget has risen much slower than biomedical inflation, which, combined with the recent sequester, means that the NIH has effectively lost 20 percent of its funding power, said the AACR.

THE CANCER RESEARCH INSTITUTE named 21 new members to its scientific advisory council.

The council created funding and research priorities for the distribution of its $14.6 million in grants and fellowships last fiscal year. The council is made up of 68 immunologists and tumor immunologists, and is led by James Allison, professor and chair of MD Anderson Cancer Center's Department of Immunology.

A list of the new members follows:

- Nina Bhardwaj, Mount Sinai School of Medicine
- Jonathan Cebon, Ludwig Institute for Cancer Research, Australia
- Vincenzo Cerundolo, University of Oxford
- Lisa Coussens, Oregon Health & Science University
- Charles Drake, Johns Hopkins Medicine
- Richard Flavell, Yale University School of Medicine
- Thomas Gajewski, The University of Chicago
- Patrick Hwu, MD Anderson Cancer Center
- Elizabeth Jaffee, Johns Hopkins Medicine
- Carl June, University of Pennsylvania
- Michael Karin, University of California, San Diego
- Cornelis Melief, Leiden University Medical Center, The Netherlands
- Kunle Odunsi, Roswell Park Cancer Institute
- Stanley Riddell, Fred Hutchinson Cancer Center
- Shimon Sakaguchi, Osaka University, Japan
- Ton Schumacher, The Netherlands Cancer Institute, Amsterdam
- Craig Slingluff Jr., University of Virginia
- Mark Smyth, Queensland Institute of Medical Research, Australia
- Emil Unanue, Washington University School of Medicine
- Robert Vonderheide, University of Pennsylvania
- Cassian Yee, MD Anderson Cancer Center

FDA News

FDA Approves Generic Version Of Capecitabine for Metastatic Colorectal and Breast Cancer

FDA approved Xeloda (capecitabine), a generic chemotherapy pill for metastatic colorectal cancer and metastatic breast cancer.

Its producer, Teva Pharmaceuticals USA, will market the generic capecitabine in 150 and 500 milligram strengths.

In clinical trials for Xeloda, the most commonly observed adverse reactions included: diarrhea; vomiting; nausea; pain, redness, swelling, or sores in the mouth; hand-and-foot syndrome; and fever or infection.