



News Analysis

The Years With Harold

By Paul Goldberg

The National Cancer Institute Harold Varmus will leave on March 31 is leaner, cleaner, and more focused than it was on July 12, 2010, the day he became its 14th director.

Chalk it up to irony, but the first phase of the Nobel laureate's stewardship at the circa-\$5 billion-a-year institution can be classified as janitorial work—clearing out the pet projects of his predecessors.

The Andrew Von Eschenbach-era dysfunctional bioinformatics and biorepository projects got the defenestration they deserved. The institute's outsized PR operation got edited down with deft ax work.

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FDA's Activism Changes the Landscape In Treatment, Trials of Squamous NSCLC

By Paul Goldberg

Citing a dramatic improvement in overall survival in second-line squamous non-small cell lung cancer, FDA rapidly approved the Bristol-Myers Squibb drug Opdivo (nivolumab).

The action, announced March 4, demonstrates the extraordinary activist stance FDA can take when it sees an advantage in overall survival.

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In Brief

Bailey Named Director of UW Cancer Center

HOWARD BAILEY was named director of the **University of Wisconsin Carbone Cancer Center**, effective April 1. Bailey has served as interim director since September 2013.

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Varmus Didn't Anticipate Starvation Diet at NCI

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The proud tradition of shielding the directors' pet projects from peer review by having them funded through NCI's contractor came to an end.

Varmus has signature projects, to be sure, but they were presented for review and chopping, like everything else. Even the contractor-operated Frederick National Laboratory for Cancer Research now has an advisory committee that holds open meetings.

When he came to NCI, Varmus let it be known that he preferred to be addressed as Harold (The Cancer Letter, [July 16, 2010](#)).

"My first name is not Doctor," he announced. "It's Harold, and I like to be called Harold."

Harold didn't use speechwriters. He avoided slides. His email address was publicly known—Harold.Varmus@NIH.gov—and he responded to the emails he received.

Covering NCI, one learned quickly that Harold, who alternatively could have been at his lab or riding a bike through the rolling hills of upstate New York, came to run NCI because of his love for the scientific process and heated, open debate.

For most of his nearly five years at the institute, Harold faced indignities that included the government shutdown, the first-ever appropriations cut, and sequestration. Throughout, he railed against moronic

federal rules that kept him from recruiting top people and traveling to scientific conferences.

While the volume of programmatic dreck Harold discarded squarely earns him the designation of an outstanding NCI director, the programs he built aren't entirely ripe for evaluation.

We don't know whether the clinical trials infrastructure will need to be expanded or tweaked.

We don't know whether [his big bet](#) on the RAS gene will pay off.

We don't know whether his move away from reliance on priority scores in review of grants applications will remain viable after he leaves the institute.

We don't know whether the rethinking of the funding formula for cancer center core grants would keep its momentum after this month.

We don't know whether NCI really needs the massive intramural program it has.

In his final months, Harold seemed to be open to discussion of expanding funding for cancer centers. Will his successor—Douglas Lowy—continue this discussion?

Note something that *didn't* happen during the Varmus years at NCI: there were no scandals, no allegations of conflicts of interest—none of that crap. Harold wasn't there to get rich, famous or adored.

The saddest what-if that repeatedly popped into this reporter's mind was what if Harold had been the NCI director at a time when the institute had money to burn? Did Harold get the opportunity to implement his vision, or did it get squelched by the weight of budgetary pressures?

Harold didn't sign up for the starvation diet.

He was one of the co-authors of the Obama campaign cancer plan, which included doubling federal expenditure on cancer research over the following five years and increasing accrual to clinical trials to 10 percent of all cancer patients (The Cancer Letter, [Nov. 7, 2008](#)).

However, by early 2011, NCI and the rest of the government was staring at what Harold dubbed the "budgetary disaster" (The Cancer Letter, [Jan. 13, 2011](#)).

In July 2011, a year after he got to NCI, Harold did a Q&A with this reporter (The Cancer Letter, [July 22, 2011](#), [July 29, 2011](#)).

"I knew that it would be a tough time," he said. "I didn't think that we would be on the chopping block. I was surprised to see the budget dip below previous years' levels. I thought we would continue to see an erosion of our buying power by sub-inflationary increases or totally flat budgets. The one-percent decrease, to me, was fairly important symbolically. And I think it's not unreasonable

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to expect that this year we will have another reduction.”

Harold recognized a silver lining in the deepening budgetary disaster.

“We are dealing with difficult times,” he said in the Q&A. “Difficult times are interesting in ways that I think can be useful. I’d rather have life be fiscally easier, but, frankly, when budgets are rising, it’s very hard to shut anything down. So that’s an issue. People understand, when things are tight, that you are going to take money out of some programs and put them into other things, because you can justifiably say, ‘We’ve got to always do new things. Otherwise, we are not going to make optimal progress.’”

At meetings of NCI advisory committees, Harold spoke in precise, direct sentences, delivering lengthy briefings from his own handwritten notes.

Covering Harold required a lot of ink. There was meaning in those taut sentences, and many of them warranted underlining with a sharp No. 2 pencil.

Harold could be personable. This reporter will never forget a brief conversation about relative merits of titanium, steel and carbon as materials used in building road bike frames. Harold’s unwillingness (or inability) to suffer fools was legendary, and one didn’t have to be a fool to get a tongue-lashing.

Harold had no patience for patient advocacy groups that lobby for higher expenditures on specific diseases.

“I wonder whether we are at the point where we ought to rethink the idea that we have organ-specific disease groups,” Harold said at an advisory committee meeting last September (The Cancer Letter, [Sept. 12, 2014](#)). “Maybe they should be pathway-based, or gene-profile-based, or, when we take on the match program, then all hell breaks loose, because every patient is a potential entry into a match-type clinical trial. I just wonder whether these boundaries are now increasingly artificial... Maybe we need a UN of disease groups.”

For nearly five years, Harold was a good story and good theater. You knew that he would say exactly what was on his mind, proudly not giving a rip about being impolitic.

It was thus a surprise that Harold dropped the F-bomb at a webcast meeting of an advisory committee on only one occasion (The Cancer Letter, [Sept. 12, 2014](#)). At meetings of NCI advisory committees, you could watch him express a strong opinion, elicit response and slowly come around to a different point of view.

When you sat in a conference room, hanging onto the meaning of Harold’s every word, you knew that you were a part of an extraordinary performance and that you will never experience anything like it again.

NCI Director Harold Varmus To Step Down March 31

By Matthew Bin Han Ong

NCI Director Harold Varmus announced that he will be stepping down at the end of this month.

Douglas Lowy, the current deputy director, will serve as acting director for NCI beginning April 1. Lowy, a long-time NCI intramural researcher, received the National Medal of Technology and Innovation from President Barack Obama in 2014 for his research that led to the development of the human papillomavirus vaccine.

In a letter to colleagues March 4, Varmus, 75, reflected on his five years at the institute, saying that he is leaving with a “mixture of regret and anticipation.”

Varmus was appointed by President Obama May 18, 2010, and started work July 12, 2010. He previously served as director of the NIH under President Bill Clinton from 1993 to 1999, and as president of Memorial Sloan Kettering Cancer Center from 2000 to 2010.

“The nearly five years in which I have served as NCI Director have not been easy ones for managing this large enterprise—one that offers so much hope for so many,” Varmus wrote. “We have endured losses in real as well as adjusted dollars; survived the threats and reality of government shutdowns; and have not yet recovered all the funds that sequestration has taken away.

“This experience has been especially vivid to those of us who have lived in better times, when NIH was the beneficiary of strong budgetary growth. As Mae West famously said, ‘I’ve been rich and I’ve been poor, and rich is better.’”

Varmus will join Weill Cornell Medical College’s faculty as the Lewis Thomas University Professor of Medicine, and team up with the New York Genome Center as a senior associate core member to promote the use of cancer genomics.

“When I return to New York City full time on April 1st, I will establish a modestly sized research laboratory in the Meyer Cancer Center at the Weill-Cornell Medical College and serve as a senior advisor to the Dean,” Varmus wrote. “In addition, I plan to assist the recently founded New York Genome Center as it develops its research and service functions and helps regional institutions introduce genomics into cancer care.”

Varmus’s laboratory, which will be housed in the Belfer Research Building, will continue to focus on lung adenocarcinoma and the cancer-driving mutations found in that disease. Those mutations affect cell signaling,

cell growth and processing of RNA.

Varmus will also serve as a senior advisor to Laurie Glimcher, the Stephen and Suzanne Weiss Dean of Weill Cornell and provost for medical affairs for Cornell University, and will have an appointment in the Weill Cornell Graduate School of Medical Sciences.

During his tenure at NCI, Varmus instituted the Provocative Questions initiative, created NCI's new Center for Global Health, revitalized the cooperative clinical trials system, launched an initiative to find drugs that target the cell signaling pathway controlled by the RAS oncogene, led the cancer component of the Precision Medicine Initiative, and contributed many other important ideas to biomedical research.

Varmus is the recipient of the 1989 Nobel Prize in Physiology or Medicine, the 2001 National Medal of Science, and the 2001 Vannevar Bush Award. He was also elected to the U.S. National Academy of Sciences in 1984 and in the Institute of Medicine in 1991.

NIH was fortunate to have one of the world's best minds in cancer research, said NIH Director Francis Collins.

"Who better than Harold Varmus, who won the Nobel prize for discovering oncogenes, to lead the charge as we leap forward in our knowledge about the disease? And it's not just about cancer," Collins said in an email. "Few people in history have had as much influence and impact as Harold in shaping the course of modern biomedical science. Harold, indisputably, is a true giant, and we have been lucky to have him here not once, but twice, to help lead this great agency.

"I ask you to join me in congratulating Harold on a job extraordinarily well done, and wishing him the best for the next chapter of his distinguished scientific career."

Varmus established valuable initiatives that will help transform cancer research for the 21st century and improve cancer care on a global level, said Richard Schilsky, chief medical officer of the American Society of Clinical Oncology.

"He accomplished these tasks during a period when the NCI faced unprecedented financial instability," Schilsky said.

"As NCI director, Dr. Varmus drew on his deep knowledge of cancer biology and the nation's biomedical research enterprise to focus the efforts of the cancer community on identifying and tackling the most vexing problems in cancer research and care. ASCO is grateful for his service to the cancer community and the country."

Varmus demonstrated exemplary leadership and vision in cancer research, prevention and treatment,

said Chris Hansen, president of the American Cancer Society Cancer Action Network.

"Dr. Varmus achieved major accomplishments during nearly five years at the helm of NCI, despite the enormously challenging budget environment," Hansen said. "He initiated the creation of two new centers within NCI, one focusing on global health and another on cancer genomics, that address critical areas in the fight against cancer. He significantly improved the efficiency and breadth of the National Clinical Trials Network and the Community Oncology Research Program to ensure that NCI's clinical trials programs reflect new approaches to cancer treatment. He also spearheaded the innovative Provocative Questions Initiative to identify potentially promising approaches to cancer research.

"On behalf of millions of people in this country and around the world who have battled cancer or supported a loved one in their fight, ACS CAN thanks Dr. Varmus for his unshakable commitment to public service and his unwavering leadership of the National Cancer Institute."

Varmus guided NCI with a steady and sure hand in an era of exceptional fiscal challenges, said Louis Weiner, director of the Georgetown Lombardi Comprehensive Cancer Center.

"His focus on promoting the NCI's scientific mission has led to a set of initiatives that position the national cancer effort for ongoing success," said Weiner, chair of the Board of Scientific Counselors for Clinical Sciences and Epidemiology for NCI.

The full text of Varmus's letter follows:

To NCI staff, grantees, and advisors:

I am writing to let you know that I sent a letter today to President Obama, informing him that I plan to leave the Directorship of the National Cancer Institute at the end of this month.

I take this step with a mixture of regret and anticipation. Regret, because I will miss this job and my working relationships with so many dedicated and talented people. Anticipation, because I look forward to new opportunities to pursue scientific work in the city, New York, that I continue to call home.

The nearly five years in which I have served as NCI Director have not been easy ones for managing this large enterprise—one that offers so much hope for so many. We have endured losses in real as well as adjusted dollars; survived the threats and reality of government shutdowns; and have not yet recovered all the funds that sequestration has taken away. This experience has been especially vivid to those of us who have lived in better times, when NIH was the beneficiary of strong

budgetary growth. As Mae West famously said, “I’ve been rich and I’ve been poor, and rich is better.”

While penury is never a good thing, I have sought its silver linings. My efforts to cope with budgetary limits have been guided by Lord Rutherford’s appeal to his British laboratory group during a period of fiscal restraint a century ago: “...we’ve run out of money, it is time to start thinking.” Rather than simply hold on to survive our financial crisis without significant change, I have tried—with essential help from my senior colleagues—to reshape some of our many parts and functions. In this way, I have tried to take advantage of some amazing new opportunities to improve the understanding, prevention, diagnosis, and treatment of cancers, despite fiscal duress.

This is not the place for a detailed account of what we have achieved over the past five years. But a brief list of some satisfying accomplishments serves as a reminder that good things can be done despite the financial shortfalls that have kept us from doing more:

- The NCI has established two new Centers: one for Global Health, to organize and expand a long tradition of studying cancer in many other countries; and another, for Cancer Genomics, to realize the promise of understanding and controlling cancer as a disorder of the genome.

- Our clinical trials programs (now called the National Clinical Trials Network and the NCI Community Oncology Research Program) have been reconfigured to achieve greater efficiencies, adapt to the advent of targeted drugs and immunotherapies, and enhance the contributions of community cancer centers.

- Research under a large NCI contract program in Frederick, Maryland, has been redefined as the Frederick National Laboratory for Cancer Research (FNLCR), with more external advice, a large new initiative to study tumors driven by mutant RAS genes, and greater clarity about FNLCR’s role as a supporter of biomedical research.

- In efforts to provide greater stability for investigators in these difficult times, we have established a new seven year Outstanding Investigator Award; are discussing new awards to accelerate graduate and post-doctoral training; and are planning to provide individual support for so-called “staff scientists” at extramural institutions.

- To strengthen the NCI-designated cancer centers, we are awarding more supplements to the centers’ budgets to encourage work in high priority areas; helping centers to share resources; and working with the center directors to develop more equitable funding plans.

- The NCI has attempted to improve the grant-making process in various ways at a time when success rates for applicants have reached all-time lows:

- We have engaged our scientists to identify inadequately studied but important questions about cancer—so-called Provocative Questions—and have provided funds for many well-regarded applications to address them.

- We have pioneered the use of a descriptive account of an applicant’s past accomplishments, moving away from mere listings of publications, to allow a fairer appraisal of past contributions to science.

- Our program leaders now make more nuanced decisions about funding many individual grants, considering a wide range of highly rated applications, not simply those with scores above an arbitrary pay-line.

- And we have maintained NCI’s numbers of research project grants, despite the limits on our budget, while continuing to emphasize the importance of balancing unsolicited applications to do basic cancer research against an increasing call for targeted programs to deliver practical applications.

Of course, it is still too early to judge the long-term consequences of most of these actions. But we do know that many good things have happened in cancer research over the past five years as a result of existing investments:

- Our understanding of cancer biology has matured dramatically with the near-completion of The Cancer Genome Atlas and with results from other programs that depend on genomics and basic science, including work with model systems.

- Many new targeted therapies have been tested in clinical trials, and several have been approved for general use.

- Remarkable clinical successes against several kinds of cancers have been reported with immunological tools—natural and synthetic antibodies, checkpoint inhibitors, and chimeric T cell receptors.

- More widespread use of a highly effective vaccine against human papilloma viruses (HPV) and the several cancers they cause has been encouraged by further studies and by an important report from the President’s Cancer Panel.

- Radiographic screening for lung cancers in heavy smokers—validated by a large-scale trial just after I arrived at the NCI—has now been endorsed for wide-spread use and for reimbursement by Medicare and other insurers.

- New computational methods, such as cloud computing and improved inter-operability, are advancing

the dream of integrating vast amounts of molecular data on many cancers into the daily care of such cancers.

Some of these advances are now essential features of the President's recently announced Precision Medicine initiative that will focus initially on cancer.

Such accomplishments have been possible only because the NCI has been able to recruit and retain exceptional people during my years here; I am grateful to all of you. I am also grateful to the many selfless individuals who have made our advisory groups stronger than ever and to the cancer research advocates who regularly remind me—as well as Congress and the public—about the importance of our work to human welfare.

So what is next?

In my remaining few weeks in this position, I will continue to do the NCI Director's job with customary energy, despite my inevitable status as a "lame duck." I will also schedule a Town Hall meeting to review some of the things that have happened during my tenure here—revisiting the ambitions I announced when I accepted the job and answering questions.

As I just learned today, the White House has approved the appointment of my chief deputy and close friend, Doug Lowy, to serve as Acting Director of the NCI, beginning on April 1st. This gives me enormous pleasure, because Doug—along with Jim Doroshow, the NCI's Deputy Director for Clinical and Translational Research—made many of NCI's recent accomplishments possible; is a distinguished scientist, who was recently honored by the President with a National Medal for Technology and Innovation for his work on human papilloma virus vaccines; and is a remarkably congenial person to work with. The NCI will be in excellent hands.

Finally, when I return to New York City full time on April 1st, I will establish a modestly sized research laboratory in the Meyer Cancer Center at the Weill-Cornell Medical College and serve as a senior advisor to the Dean. In addition, I plan to assist the recently founded New York Genome Center as it develops its research and service functions and helps regional institutions introduce genomics into cancer care.

While I look forward to these new adventures and to leading a life concentrated in one place, I know I will miss many of the people, authorities, and ideas that make the NCI Directorship such a stimulating and rewarding position.

With deep respect and gratitude to the entire NCI community,

Harold Varmus

Pazdur Calls For Re-Evaluation Of Trials in Squamous NSCLC

(Continued from page 1)

In this case, FDA received the data and sprung into action before the results were unblinded to the sponsor, said Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research.

"With regard to the impetus for this rapid action, we began working immediately on this review and submission strategy after being informed of the survival results. This was prior to BMS having been informed of the results since they were still blinded," Pazdur said to The Cancer Letter.

The agent, which inhibits the PD-1 cellular pathway, was approved after demonstrating a survival advantage over docetaxel. The drug is approved in the second and third-line indications. This is the second indication for Opdivo, which was previously approved for unresectable or metastatic melanoma in patients who no longer respond to other drugs.

The agency's handling of Opdivo is consistent with its increasingly activist role in the conduct of clinical trials in oncology. The agency has a seat at the table in the running of the Lung-MAP trial ([The Cancer Letter, June 20, 2014](#)).

"Patients and physicians need to be informed about these findings and this was the impetus for the rapid inclusion of the survival data in product labeling," Pazdur said to The Cancer Letter. "With regards to clinical trials, the oncology community has repeatedly stated that trials should offer patients the best treatment available. Therefore, there needs to be a pause and a re-evaluation of on-going and planned trials in squamous NSCLC."

Lung-MAP, which is also called Lung Cancer Master Protocol, or SWOG S1400, uses the patients' tumor characteristics to select one of five targeted therapies, comparing them with docetaxel as control in each arm.

Charles Blanke, chair of SWOG, agreed that changes in Lung-MAP need to be considered.

"Changes in potential standard of care can certainly upend clinical trials," Blanke said to The Cancer Letter. "Lung-MAP is lucky to have a team of scientific experts who meet regularly and who will be able to make any necessary changes in timely fashion."

Roy Herbst, co-chair of the Lung-MAP oversight committee and chief of medical oncology at Yale Cancer Center, said the trial will certainly change.

“That’s clinical medicine—you have to adapt,” Herbst said to The Cancer Letter. “I am thrilled for patients. In fact, the recognition of the promise of immunotherapy is why the Lung MAP drug selection committee chose a similar drug to be part of the inaugural launch of the trial.

“Given the flexibility of the Lung-MAP study and in recognition of the recent approval, our Lung-Map study team and investigators is already working to assess what modifications are necessary to ensure further research and patient access to these beneficial new agents,” Herbst said.

Opdivo’s efficacy to treat squamous NSCLC was established in a randomized trial, [called Check-Mate 017](#).

That trial enrolled 272 participants, of whom 135 received Opdivo and 137 received docetaxel. The trial was designed to measure overall survival in the second-line indication. On average, participants who received Opdivo lived 3.2 months longer than those who received docetaxel.

The company also had a single-arm trial, [Check-Mate 063](#), which the agency accepted as confirmatory. That single-arm trial of 117 participants who had progressed after receiving a platinum-based therapy and at least one additional systemic regimen. The third-line study was designed to measure objective response rate, or the percentage of participants who experienced partial shrinkage or complete disappearance of the tumor. Results showed 15 percent of participants experienced objective response, of whom 59 percent had response durations of six months or longer.

BMS is expected to price the drug at about \$12,500 a month, or \$150,000 for a year. The price is the same in the melanoma indication.

In an in-depth interview, FDA’s Pazdur described the handling of the Opdivo application and the drug’s significance in the treatment and ongoing clinical trials. Pazdur spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

Paul Goldberg: *Does the approval of the nivolumab application in squamous NSCLC set a record for the speed of approvals? The PDUFA date is in June.*

Richard Pazdur: We have approved many drugs in oncology prior to their PDUFA due date. This is one of the more rapid reviews.

The important aspect of this approval is the submission of the randomized trial data for the Check-Mate-017 study. We became aware of the results of this randomized trial demonstrating a survival advantage in second-line squamous NSCLC on Dec. 19, 2014.

FDA had asked for the pre-specified interim analysis results of this study as a condition for accepting a single arm trial for third-line treatment of squamous NSCLC (CheckMate 063) as the final component of the rolling marketing application. The report was from an independent statistical contractor that supported the external Data Monitoring Committee.

Based on these results, FDA communicated with a single contact person in BMS to notify him that the final component of the NSCLC BLA could be submitted. The report remained blinded to all others in BMS. On Jan. 10, 2015, the independent DMC met and noted that the 017 study had demonstrated superior survival for the nivolumab arm and recommended that patients randomized to docetaxel (the control arm) be allowed to cross-over and receive nivolumab.

Upon seeing the magnitude of the survival effect from the 017 trial, FDA believed that it was important to bring the data—both the 017 and 063 trials—into the review process and incorporate these findings into the product label as well as broaden the indication to include both a second-line and third-line treatment of squamous NSCLC. Therefore, within a two-month span, the randomized trial results were disclosed to FDA, reviewed by FDA, and approved by FDA. This is the important sequence of events for this rapid approval.

The information from the randomized trial submitted to FDA was the data submitted to the DMC, including survival and demographic data and clinical protocol. The safety data for the randomized trial does not appear in the product label. We believe that the safety data from the prior approval in melanoma, in addition to new safety data from the single arm trial, provides a sufficient basis to inform prescribers and adequately justify a favorable benefit-risk analysis considering the magnitude of the survival effect.

A conventional submission of all of the data from the randomized trial would have required BMS to prepare a large standard dossier that would have delayed the submission by probably six months or more. BMS is required to submit a more comprehensive report of this trial, including the safety data from the randomized trial, and it will be reviewed as a supplement. Patients with squamous NSCLC who have few therapeutic options and a poor prognosis will now have access to a drug with a demonstrated survival advantage months earlier than if we required a conventional submission of the randomized trial.

PG: *What’s the significance of the improvement by the drug? Could the single-arm trial have been enough? Did the impetus for this rapid action come from the agency or the sponsor?*

RP: Our goal is to provide the best therapies to these patients as quickly as possible without comprising review quality. An FDA approval for an indication provides the best access to patients. There are several unique factors about this application. First, there is a large unmet medical need for patients with squamous NSCLC, especially those who have progressive disease on already approved therapies. Second, we are dealing with an improvement in overall survival—a gold standard for clinical benefit—over a standard treatment (docetaxel). Overall survival is an objective endpoint, not influenced by potential bias that can be observed with progression-free survival. The magnitude of improvement in overall survival observed also increased our confidence that the therapy provide meaningful benefit to patients.

Could the single arm data have been enough? While the single arm study (063) had a modest response rate of 15 percent, many of the responding patients appeared to have long response durations. Whether or not this magnitude of response rate and response durations would support an accelerated approval would require close examination of the data and significant discussion. For this reason, we were interested in the preliminary results of the randomized trial. If the randomized trial failed to disclose any advantage, we would question the clinical significance of the response rate data.

The patient population of the patients entered into the single arm trial supported a third-line indication—all patients had progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen. In contrast, those entered into the randomized trial were second-line patients who experienced disease progression during or after one prior platinum-based chemotherapy regimen. The incorporation of the survival data from the randomized trial allowed a more general treatment indication—“metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy”—that would include both second- and third-line indications.

With regard to the impetus for this rapid action, we began working immediately on this review and submission strategy after being informed of the survival results (Dec. 17). This was prior to BMS having been informed of the results since they were still blinded.

PG: *Was the current approval in lung cancer a regular approval or an accelerated approval?*

RP: Regular (traditional) approval. Overall

survival of a clinically meaningful magnitude with a favorable benefit/risk evaluation has been demonstrated. Hence, clinical benefit for this indication has been established. If we had only the results of the single arm trial and were basing an approval on response rates, then an accelerated approval would have been considered.

PG: *Does this approval have any broader significance?*

RP: Yes. Prior approvals for PD-1 inhibitors have been accelerated approvals. This is the first of the class to demonstrate clinical benefit, the ultimate goal of drug development. Hence, the demonstration of the improvement in overall survival validates the emerging importance of PD-1 and PD-L-1 drugs and the contributions of numerous preclinical and clinical investigators, and patients to the development of this drug class.

PG: *Is there a lesson to be derived from what randomized trials can show?*

RP: FDA has often pointed to the limitations of single arm trials since response rates are the only endpoint that can be reliably evaluated. Randomized trials provide information with regard to other endpoints, including overall survival, progression-free survival, and patient reported outcomes. Randomized trials also provided greater clarity to adverse event reporting. Most of the sponsors of PD-1 drugs have comprehensive drug development programs and are not limiting their registration plans to single arm trials, but have considerable investments in randomized trials in many indications.

In addition, the modest effect on response rate (15 percent), compared to the magnitude of improvement in overall survival noted in the randomized trial should caution drug developers that the treatment effects of this class of drug may not be entirely captured by the “response rate surrogate.” Hence, early decisions merely examining response rates may underestimate the true value of these drugs.

PG: *Does the full approval of nivolumab close the door for accelerated approval of other PD-1 drugs in lung cancer?*

RP: No. FDA grants accelerated approval on the basis of a surrogate endpoint reasonable likely to predict clinical benefit provided that the drug is an improvement over available therapy. If a registration plan provided convincing evidence that a drug had a substantially higher response rate compared to nivolumab or higher activity in a subgroup of patients (e.g., patients with PDL-1 positive biomarker) then

FDA would be open to discussion of that registration strategy based on a single arm or randomized trial.

PG: *Do you see any problems with the development of PD-1 or PD-L1 inhibitors?*

RP: One of my concerns is the lack of uniformity in developing biomarkers to determine PD-1/PDL-1 “positive” tumors. This work is evolving, but it appears many sponsor are going in many directions with different technologies and different “cut-off” points. These diverse approaches may potentially lead to confusion. Our colleagues in CDRH will be having a public workshop to discuss these emerging issues.

For the nivolumab squamous NSCLC application, the randomized trial (017) enrolled patients regardless of their PD-L1 status. Therefore, the extrapolation of the clinical findings from the trial to patients is not dependent upon any biomarker.

Another issue is appropriate characterization of immune-related adverse reactions, such as immune-related pneumonitis, hepatitis, and nephritis. Data collection on certain features of these reactions and their subsequent medical management has not been optimal and will require further characterization and study.

PG: *Is nivolumab the new standard of care? What does it mean for the Lung MAP trial or other trials which use docetaxel as the comparator?*

RP: FDA does not set the “standard of care.” Standard of care is established by medical practice. CheckMate017 did demonstrate a convincing and substantial improvement in overall survival for the entire second-line population of squamous NSCLC. Patients and physicians need to be informed about these findings and this was the impetus for the rapid inclusion of the survival data in product labeling. With regards to clinical trials, the oncology community has repeatedly stated that trials should offer patients the best treatment available. Therefore, there needs to be a pause and a re-evaluation of on-going and planned trials in squamous NSCLC.

PG: *Any closing comments?*

RP: Yes. A thank you to the review staff—Dickran Kazandjian, Sean Khozin, Lijun Zhang, Shenghui Tang—the team leader, Gideon Blumenthal, and the Division Director, Pat Keegan, and our project manager, Meredith Libeg, for providing the insight and flexibility in getting the submission in and reviewed. Many hours were spent outside the regular work schedule and many personal plans needed to be changed to accomplish this task.

From the Kilimanjaro Summit

By Charles D. Blanke

After months of training, hundreds of hours spent in a high-altitude sleep tent, and almost a week spent ascending the mountain, our climbing group was destined to have only 12 minutes at Mt. Kilimanjaro’s summit. However, that was enough to pay tribute to the 200,000 heroes who have participated in more than a half-century of SWOG cancer clinical trials.

We brought those volunteers to the “roof of Africa” last month to recognize their contributions to finding effective cancer treatments. We put their 200,000 sets of initials onto a banner that we unfurled at Uhuru Peak (19,382 feet), in the middle of a major lightning storm. Along the way, we garnered some good press for the value of publicly funded cancer clinical trials, and of what we stand to lose because of declining federal support of those trials, while at the same time raising more than \$110,000 to help offset that decline, a portion of which was shared with our sister network groups the Alliance and the Children’s Oncology Group, and with ASCO’s Conquer Cancer Foundation.

Our climbing group of nine flew to Tanzania and spent our first days in Africa in the town of Moshi, the standard embarkation point for climbs. In trekking around Moshi, you are struck immediately by the vibrantly colored clothing, the dust, and the friendly noise. You soon learn not to rely on traffic skills from your native land, as you will NEVER get right of way from a moving vehicle. And what a variety of vehicles there were. In fact, the order of transport frequency was: human, human powered, scooter, motorcycle, multi-passenger van or truck, and then normal car (but never with fewer than two people in them). Other random observations: A lot of commerce also involved human-powered devices (e.g., sewing machines powered by foot pedals); differing from the U.S., you almost never saw an animal in the street (pet or stray); and you can buy steak-flavored potato chips. As predicted, it was roasty hot—apparently 102 degrees the day we arrived.

Careful packing brought my duffel (to be carried during the day by a porter) to 19.75 kg, with 20 kg being the maximum allowable. A two-and-a-half-hour drive brought me, the team, our guides and our duffels to our entrance to Kilimanjaro National Park—Lonodorosi Gate—where we encountered the world’s skinniest cows and friendliest monkeys, the latter of which looked like tree-climbing skunks (I was later told they were black and white colobus monkeys).

My plan had been to post every day from the mountain to the climb's Facebook page via my phone. Unfortunately, in spite of what we had been told, cell service petered out after the first day for our American phones, and what few messages I could send were conveyed over a local phone one of our porters was kind enough to let me use. In leaving behind cell service, we also left the rain forest and started into what I considered to be "high desert." The plant life was phenomenal, with beautiful flowers everywhere, but no animals to be seen, except for the birds. We did see and hear some pretty savage-sounding fowl.

After nights at Shira Camp 1 (a huge dusty plateau with a view of the bottom of Kilimanjaro) and Shira Camp 2, we hiked up to Lava Tower at 15,000 feet, which we made our base camp for two nights, arriving on a gorgeous day with the clouds swirling dramatically around us. The move into the upper part of the mountain brought symptoms of mild altitude sickness to many in the party, though it wasn't clear to me whether my own headache at that point was due to the altitude or to caffeine withdrawal, as I had already run through the party's entire supply of coffee in the first two days. What was clear was the unbelievable beauty of the night sky on the mountain, as we were surrounded by more stars than you could ever imagine.

From Lava Tower Camp we made a day hike up to Arrow Glacier at 16,000 feet (climb high, sleep low), right up against the upper portion of Kili, with beautiful views of the crater ridge and Lava Tower itself. The landscape around us looked like the surface of the moon, but buried in snow and with clouds hovering around our knees. We hiked back down to Lava Tower Camp in time for lunch, just as a huge hail storm hit. Another storm came through that night—an amazing thunderstorm with significant and unexpected snowfall. This almost ended the climb, but we decided to push through to spend the night at Arrow Glacier Camp and, depending on the weather, aim to reach the summit one day early, skipping our overnight stay in the crater.

I can't say I honestly minded that we would NOT be sleeping in the poorly-oxygenated crater at 18,800 feet the next night. Sleeping even at an altitude of 16,000 feet was definitely interesting—when I was asleep, I was sound asleep, but I would periodically wake up gasping for breath.

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Very similar to what I had experienced during training in the high altitude sleep tent, when it was set above 17,000 feet. In any case, climbing to Arrow Glacier this time was very different than the same climb the day before—snow covered the route, and we needed completely different clothes, plus our glacier glasses. Our party remained pretty excited, though there was some nervousness about planning to do the hardest part on Kilimanjaro in bad weather. Given the weather, we came within a hair of calling off the summit attempt altogether. In the end, one party member decided not to make the attempt, as he felt he might slow everyone down. A very generous decision.

We awoke at 3 a.m. on summit day and had a light climbers' breakfast. The first two hours climbing were by headlamp, letting us basically see only the snow and the feet of the person in front of us. When it got light, we could not believe how high we already were! The next several hours were tough. Everyone says a Kili climb is the hardest thing they have ever done, and I now understand why.

It was quite steep, cold, and of course we had about half the oxygen we wanted. Several times the cliff was too steep to directly ascend, so we traversed and ascended at the same time. This part was hairy, as the slope to our side would not have allowed an arrest in the case of a fall. Thus, we had several hours of placing poles and stepping but not weighting until we were sure the steps were solid, and repeating, times 2000 feet. Several sections had 5- to 15-foot rock climbs, which made our route unique. While the simple hiking and traversing were physically demanding tasks, these scrambles just about killed everyone in terms of exertion (a laugh, because it would have been fourth class climbing at best in a rock gym).

We stopped at the crater at 18,000+ feet, leading to sudden, acute mountain sickness in most of the party. There were beautiful small glaciers, though they were much smaller than expected. We then ascended another thousand feet, climbing that was similar to the morning's effort but in deeper snow, and then we hit the summit ridge.

Fifteen more minutes of walking, and we were at Uhuru Peak! Sadly a monster storm moved in immediately, with thunder, giant hail, and high winds. We realized we were on the highest point on the continent, in a lightning storm, with no trees, so we decided to get down as soon as possible. We stayed at the peak for about 12 minutes; just long enough for a group hug, a brief ceremony to spread some of the ashes of a patient of my climbing colleague Dr. Brett

Sheppard, and a summit shot with the SWOG patient and volunteer banner.

We started our descent, spent the night in Barafu Camp at 15,260 feet and were quite surprised to wake up to deep snow. In fact, several of the tents collapsed, though no one was harmed (a couple were trapped though). We packed up and descended another 5,000 feet, with the snow ending about 600 feet below our start. Amazingly we soon started to see plant life again, and before we could blink, we were back in a humid rain forest, replete with gorgeous flora and quite a few bugs!

After a final night on the mountain with about fifty rain bursts, we had dry weather for the remaining 3,000 feet down, which felt like descending a million stairs, but in a lovely rainforest.

Climbing the mountain was truly a life-changing experience. I hope we also changed some of complacency out there regarding cuts to clinical trials funding. The fundraising effort continues at least through the end of March, but I am pleased with the amount brought in to date. I was honored to carry the banner and to have an opportunity to discuss the project and oncology research with so many survivors and families of patients with cancer. I again want to thank all the supporters of the climb and donors, as well as everyone who liked our Facebook page!

And most of all, I wish to express profound gratitude to the 200,000 heroes who have been the heart of all SWOG has done during more than half a century of cancer research.

The author is the chair of SWOG and professor of medicine at the Knight Cancer Institute of the Oregon Health and Science University.

FDA Approves Zarxio, Its First Biosimilar Drug

By Matthew Bin Han Ong

FDA approved Zarxio, making Sandoz's granulocyte-colony stimulating factor the first biosimilar product to enter the U.S. market.

The agency announced its decision March 6. Biosimilars are approved based on a demonstration that they are similar to already-approved "reference" agents.

The biosimilar must show it has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowed.

Sandoz's Zarxio (filgrastim-sndz) is biosimilar to Amgen's Neupogen (filgrastim), which was originally licensed in 1991.

The introduction of biosimilar products will not bring about the same 80 to 90 percent price drops, largely due to limited competition, compared to the introduction of generic versions of small-molecule drugs, according to Rena Conti, an economist at the University of Chicago, whose work focuses on drug pricing (*The Cancer Letter*, [Feb. 6](#)).

Zarxio is approved for the same indications as Neupogen, including: patients with cancer receiving myelosuppressive chemotherapy; patients with cancer undergoing bone marrow transplantation; patients undergoing autologous peripheral blood progenitor cell collection and therapy; acute myeloid leukemia, while receiving induction or consolidation chemotherapy; and severe chronic neutropenia.

"Biosimilars will provide access to important therapies for patients who need them," FDA Commissioner Margaret Hamburg said in a statement. "Patients and the health care community can be confident that biosimilar products approved by the

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FDA meet the agency's rigorous safety, efficacy and quality standards."

The approval was made possible by the Biologics Price Competition and Innovation Act of 2009, which was passed as part of the Affordable Care Act and signed into law in March 2010.

The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product, called the "reference product."

This abbreviated licensure pathway under section 351(k) of the Public Health Service Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

A biosimilar product can only be approved by FDA if it has the same mechanisms of action, routes of administration, dosage forms and strengths as the reference product, and only for the indications and conditions of use that have been approved for the reference product. The facilities where biosimilars are manufactured must also meet FDA's standards.

The approval of Zarxio is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Zarxio is biosimilar to Neupogen.

Zarxio has been approved as biosimilar, not as an interchangeable product. Under the BPCI Act, a biological product that has been approved as an "interchangeable" may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

The most common expected side effects of Zarxio are aching in the bones or muscles and redness, swelling or itching at injection site. Serious side effects may include spleen rupture; serious allergic reactions that may cause rash, shortness of breath, wheezing and/or swelling around the mouth and eyes; fast pulse and sweating; and acute respiratory distress syndrome, a lung disease that can cause shortness of breath, difficulty breathing or increase the rate of breathing.

For this approval, FDA has designated a placeholder nonproprietary name for this product as "filgrastim-sndz."

The provision of a placeholder nonproprietary name for this product should not be viewed as reflective

of the agency's decision on a comprehensive naming policy for biosimilar and other biological products.

While FDA has not yet issued draft guidance on how current and future biological products should be named, the agency intends to do so in the near future.

Sandoz, a Novartis company, is based in Princeton, N.J. Neupogen is marketed by Amgen.

Obituary

Mark Green, 70, Center Director

Mark Green, former director of Hollings Cancer Center at the Medical University of South Carolina and the University of California, San Diego, Moores Cancer Center, died Feb. 23, at the age of 70.

Green was an important figure in the development of medical oncology and played a pivotal role in the history of both cancer centers.

Green received his MD from Harvard University and trained at Harvard's Beth Israel Hospital, the NCI and Stanford University. In 1976, he joined UCSD, where he held the Edwin and Evelyn Tasch Chair in Cancer Research and served as director of the UCSD Cancer Center. In 1986, he led the center to its first NCI designation.

In 1996, Green joined MUSC as the director of the Hollings Cancer Center and the Mary M. Gilbreth Professor of Oncology. Serving as director until 2000, he retired from the full-time faculty as professor emeritus in 2004.

A highly respected oncologist, he contributed to the understanding and treatment of solid tumors. His research focused on clinical trials of new therapies for cancers of the lung and pancreas. He was widely published, and his impactful research to improve cancer treatments made a difference in the lives of thousands of cancer patients worldwide.

"Dr. Mark Green was one of the most influential lung cancer medical oncologists in the past 50 years," commented Gerard Silvestri, the Hillenbrand Professor of Thoracic Oncology at MUSC. "He had a command of the oncologic literature that was second to none. He was one of the few doctors I have known who was not only able to quote chapter and verse about the latest cancer research, but he was also able to synthesize it for your particular patient—a marvelous combination and one that is rare in medicine."

Green served as chair of the NCI's Cancer and Leukemia Group B Respiratory Committee for over 20 years and as vice chairman of CALGB from 1995 to 2007. During his tenure as chair, he oversaw the development of innovative treatments used in 30

member universities and hundreds of medical centers. He was also a member of the American Board of Internal Medicine subspecialty Board of Medical Oncology from 1989 to 1999 and served as the subspecialty board chair from 1995 to 1999.

Most recently, Green was the chief medical officer of Xcenda and vice president of Xcenda's Oncology Insights consulting practice, a position he held since 2007.

To honor his contributions to Hollings Cancer Center and the field of thoracic oncology, the Mark R. Green, MD, Distinguished Endowed Visiting Professorship in Thoracic Oncology was established in 2011. Green has been the driving force behind this lectureship, including the most recent lecture in January of 2015, which hosted Joan Schiller, chief of the Division of Hematology and Oncology and deputy director of the Simmons Comprehensive Cancer Center at the University of Texas Southwestern Medical Center.

Schiller commented, "Dr. Green was always upbeat, energetic, and remarkably knowledgeable in every aspect of lung cancer care. In addition to knowing the literature like the back of his hand, he was always extremely interested in fostering the careers of young physicians. He will be missed."

In Brief

Howard Bailey Named Director Of UW Carbone Cancer Center

(Continued from page 1)

He is a professor of medicine at the UW School of Medicine and Public Health, and specializes in gynecologic and soft-tissue cancers and cancer prevention.

Bailey, who worked under and alongside Paul Carbone, for whom the cancer center is named, has been an active cancer clinician and researcher since joining the faculty of the University of Wisconsin-Madison in 1994.

He has led the development of three different state- and nationwide clinical research networks to expand access to research for patients. In 2011, he was appointed to the national committee which reviews all NCI-designated Cancer Centers and is currently the national chair of the American Society of Clinical Oncology's Cancer Prevention Committee.

An expert on drug and nutrient development for cancer prevention and treatment, he has directed or participated in more than 100 cancer clinical trials examining agents for preventing or treating malignancies.

MEREDITH MULLINS joined the **University of Arizona Cancer Center** as associate director of administration.

As associate director, Mullins is responsible for oversight of the development, implementation and programmatic evaluation of the center's research efforts. She will work with Director Andrew Kraft in unifying clinical development strategies across the UACC's Tucson and Phoenix campuses.

Mullins will also be responsible for the center's administrative units, including fiscal management, human resources, grants and contracts management, public affairs, development and facility management.

She was most recently vice president for administration at the Levine Cancer Institute of the Carolinas HealthCare System. She has administration experience at several cancer centers, including the Nevada Cancer Institute; the Barbara Ann Karmanos Cancer Institute; H. Lee Moffitt Cancer Center and Research Institute; Oregon Health Sciences University Knight Cancer Institute; and the Medical University of South Carolina.

SILVIA FORMENTI was appointed chair of the Department of Radiation Oncology at **Weill Cornell Medical College** and radiation oncologist-in-chief at **New York-Presbyterian/Weill Cornell Medical Center**, effective April 15.

Formenti, currently the chair of radiation oncology at New York University Langone Medical Center, has also been named the associate director of radiation oncology at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College.

Formenti also is currently associate director of the NYU Cancer Institute and co-leader of its Breast Cancer Research Program, as well as the Sandra and Edward H. Meyer Professor of Radiation Oncology at NYU Langone.

Formenti's work demonstrated the efficacy of combining radiotherapy with immunotherapy to control cancer cell growth in solid tumors. She has translated preclinical work into clinical trials in metastatic breast cancer, lung cancer and melanoma, and has used localized radiation as an adjuvant to immunotherapy of solid tumors and lymphomas.

Formenti will expand the existing radiation oncology program; faculty in the department will investigate precision medicine approaches to radiation oncology, focusing on combining radiotherapy with immunotherapy and other modifiers of the tumor microenvironment to design advanced treatments and therapies tailored to each patient's individual tumor.

PHILLIP SHARP was awarded the 2015 Othmer Gold Medal by the **Chemical Heritage Foundation**.

Sharp is an institute professor at the Massachusetts Institute of Technology and a faculty member of the Department of Biology and the Koch Institute for Integrative Cancer Research. He will receive the award at the foundation's Heritage Day, May 14.

"In 1977 Phil Sharp gave the scientific world a new view of the structure of genes," said Carsten Reinhardt, CHF president and CEO. "In addition to his Nobel Prize-winning research he has founded very successful biotechnology companies, including Biogen. One of his graduate students is also a Nobel laureate, and dozens of other Sharp lab alumni run labs and companies and hold prestigious positions in hospitals and universities around the world."

The 2015 Othmer Gold Medal will be the fourth award CHF has presented to Sharp. In 2002 he received the Biotechnology Heritage Award, and then in 2004 he delivered the annual Ulliyot Public Affairs Lecture. Sharp was awarded the Winthrop-Sears Medal at Heritage Day 2007.

Sharp joined the Center for Cancer Research (now the Koch Institute) in 1974 and served as its director for six years, from 1985 to 1991, before taking over as head of MIT's Department of Biology, a position he held for the next eight years. More recently, he was founding director of the McGovern Institute, a position he held from 2000 to 2004. Sharp is also a cofounder of Biogen (now Biogen Idec) and Alnylam Pharmaceuticals.

His research interests have centered on the molecular biology of gene expression relevant to cancer and the mechanisms of RNA splicing. His landmark work in 1977 provided the first indications of "discontinuous genes" in mammalian cells. The discovery fundamentally changed scientists' understanding of gene structure and earned Sharp the 1993 Nobel Prize in Physiology or Medicine.

ANDREW ROBBINS was appointed chief operating officer of **Array BioPharma Inc.**

Array also announced that **David Snitman**, chief operating officer, announced his intention to retire at the end of June 2015. Until that time, Snitman will serve as executive vice president of business development.

Robbins is currently senior vice president of commercial operations at Array. He will have responsibility for sales, marketing, manufacturing and business development activities.

INDIANA UNIVERSITY School of Medicine and **Lilly USA** have partnered to form a medical student rotation program focused on drug development. The four-week program is available to third- and fourth-year students.

Through real-world projects and workshops, the students become directly involved with various departments within Lilly, such as research, clinical trial development, medical affairs, regulatory, bioethics, and patient safety. Students also get the opportunity to meet and network with Lilly medical leaders.

"As a former medical educator, scientific investigator, and health system administrator, I recognize that there are few opportunities for medical students to learn about the scientific rigor and complexity involved in developing new medicines," said Ora Hirsch Pescovitz, Senior Vice President at Lilly.

"Future physicians will be dependent on new medicines for their patients and will benefit from learning about the discovery and approval process. I am thrilled that we can offer this unique educational experience," said Pescovitz, former executive associate dean of research affairs at IU School of Medicine and CEO of the University of Michigan Health System.

FRED HUTCHINSON Cancer Research Center expanded its relationship with **Cryoport Inc.** to provide cryogenic logistics support to additional labs in its Clinical Research Division.

Cryoport is working with researchers to support access of their crucial research to the scientific and patient communities, specifically supporting cord blood transplants and clinical research and trials for cell-based therapies.

MEMORIAL SLOAN KETTERING Cancer Center partnered with **PeraHealth** to help improve clinician communication and detect subtle, unexpected patient deterioration. MSK will use PeraHealth's suite of patient monitoring software across its entire health system, including its 21 ambulatory clinics.

Powered by the Rothman Index, a disease-agnostic universal score, PeraHealth solutions integrate within all major electronic health record systems. Rothman Index scores are automatically computed from a provider's existing EHR data and recomputed every time new data is entered into the EHR, requiring no manual data entry for nurses or other staff.

"Improving nurse-physician and nurse-nurse communication is key to prioritizing care services," said Elizabeth McCormick, MSK senior vice president

and chief nursing officer. “We believe the software will help fortify communications between our care teams to help them provide patients with the best care available.”

THE CENTERS FOR MEDICARE & MEDICAID SERVICES approved the **American College of Radiology Lung Cancer Screening Registry** as a method for providers to submit data, meet Medicare quality reporting requirements, and receive payment for CT lung cancer screening.

“The ACR Lung Cancer Screening Registry is ready to help providers quickly and efficiently meet Medicare reporting requirements and monitor and demonstrate the quality of CT lung cancer screening in their practice,” said Ella Kazerooni, chair of the American College of Radiology Lung Cancer Screening Committee and ACR Thoracic Imaging Panel. “The ACR registry will also compile quality information that can help improve and refine lung cancer screening care over time at the national level.”

Drugs and Targets

FDA Grants Breakthrough Therapy Designation to EBV-CTL

FDA granted Breakthrough Therapy Designation to EBV-CTL for the treatment of Epstein-Barr Virus following transplant of bone marrow stem cells.

EBV-CTLs are donor-derived, not genetically modified, cancer fighting T-cells. EBV-CTLs are designed to provide immunocompromised patients with T-cells that recognize, target and destroy EBV-infected lymphoma cells.

The program is sponsored by Atara Biotherapeutics Inc. In September 2014, Atara entered into an exclusive option agreement with Memorial Sloan Kettering Cancer Center to acquire the exclusive, worldwide license rights to three clinical product candidates focusing on targets involved in cancers and serious infections.

The Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a positive opinion to extend the marketing authorization for Vectibix (panitumumab) to include combination with FOLFIRI as first-line treatment in adult patients with wild-type RAS metastatic colorectal cancer.

The new indication is based upon the 20060314 study, which evaluated Vectibix plus FOLFIRI in the first-line setting. Vectibix is already approved in the

European Union for the treatment of adult patients with wild-type RAS mCRC.

The CHMP positive opinion will now be ratified by the European Commission who, should they affirm the CHMP opinion, will extend the centralized marketing authorization which is valid in the 28 countries that are members of the EU, as well as European Economic Area members, Iceland, Lichtenstein and Norway. Vectibix is sponsored by Amgen.

FDA launched a mobile application designed to speed public access to information about drug shortages. The app identifies current drug shortages, resolved shortages and discontinuations of drug products.

Users can search or browse by a drug’s generic name or active ingredient, and browse by therapeutic category. The app can also be used to report a suspected drug shortage or supply issue to the FDA.

The agency developed the drug shortages app to improve access to information about drug shortages, as part of the FDA’s efforts outlined in the Strategic Plan for Preventing and Mitigating Drug Shortages.

The app is available for free download for Apple and Android devices.

AbbVie announced a definitive agreement to acquire Pharmacyclics and its flagship asset Imbruvica for \$21 billion. Under the terms of the transaction, announced March 4, AbbVie will pay \$261.25 per share, comprised of a mix of cash and AbbVie equity.

Imbruvica is a Bruton’s tyrosine kinase inhibitor approved for use in four indications to treat three different types of blood cancers, including chronic lymphocytic leukemia, mantle cell lymphoma and Waldenstrom’s macroglobulinemia. Imbruvica received initial FDA approval in 2013, and is the only therapy to have received three Breakthrough Therapy designations by the FDA. It is currently approved in more than 40 countries.

According to AbbVie, greater opportunity exists with further Imbruvica indications, including solid tumors, the potential to leverage AbbVie’s immunology expertise for the development of Pharmacyclics’s immunology program, and advance AbbVie’s efforts in hematologic malignancies. AbbVie will acquire all of the outstanding shares of common stock of Pharmacyclics through a tender offer, followed by a second-step merger. Pharmacyclics’s stockholders will

be permitted to elect cash, AbbVie common stock, or a combination, subject to proration.

The aggregate consideration will consist of approximately 58 percent cash and 42 percent AbbVie common stock. The closing of the tender offer is subject to customary closing conditions, including regulatory approvals, and the tender of a majority of outstanding shares of Pharmacyclics's common stock, and is expected to close in mid-2015.

AbbVie will acquire all remaining shares of Pharmacyclics's common stock that are not tendered in the tender offer through a second-step merger, which will be completed immediately following the tender offer and without a vote of Pharmacyclics's stockholders. AbbVie expects to fund the transaction through a combination of existing cash, new debt and stock.

Bristol-Myers Squibb Co. and Bavarian Nordic formed an agreement providing Bristol-Myers Squibb an exclusive option to license and commercialize Prostavac, Bavarian Nordic's investigational phase III prostate-specific antigen targeting immunotherapy in development for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer, in a deal worth up to \$975 million.

Under terms of the agreement, Bavarian Nordic will receive an upfront payment of \$60 million. Bristol-Myers Squibb can exercise the option in its sole discretion within a designated time after data is available from the ongoing phase III trial. Bavarian Nordic would be entitled to a payment of \$80 million upon exercise of the option plus additional incremental payments starting at \$50 million, but with a potential to exceed \$230 million should the median overall survival benefit of Prostavac exceed the efficacy seen in phase II results.

Furthermore, Bavarian Nordic could receive regulatory milestone payments of \$110 million, up to \$495 million in sales milestones as well as tiered double-digit royalties on future sales of Prostavac. The parties have also agreed to enter into a supply contract, under which Bavarian Nordic will undertake the future commercial manufacturing of Prostavac.

An investigator-sponsored phase II study is currently in the planning stages to investigate the combination of Bristol-Myers Squibb's Yervoy (ipilimumab) and Prostavac.

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Amgen launched the Neulasta (pegfilgrastim) Delivery Kit in the U.S.

The kit includes a specially designed single-use prefilled syringe co-packaged with the new On-body Injector for Neulasta. The kit will enable the healthcare provider to initiate administration of Neulasta on the same day as cytotoxic chemotherapy, with delivery of the patient's full dose of Neulasta the day following chemotherapy administration, consistent with the Neulasta prescribing information.

Although Neulasta has been available for 12 years, some patients still do not receive Neulasta at least 24 hours after cytotoxic chemotherapy. Among patients receiving myelosuppressive chemotherapy, many return one day after treatment for the sole purpose of receiving a Neulasta injection; however, a portion of patients requiring Neulasta may not be able to return to their provider, which means they may not be in accordance with recommended dosing.

Array BioPharma Inc. announced the completion of both the binimetinib and encorafenib definitive agreements with Novartis.

Novartis terminated its global, exclusive license to binimetinib, with all rights reverting to Array, which also received global rights to encorafenib.

Array will receive an \$85 million upfront payment from Novartis and reimbursement for certain transaction-related expenses. Novartis will provide transitional regulatory, clinical development and manufacturing services as specified below and will assign or license to Array patent and other intellectual property rights it owns to the extent they relate to binimetinib and encorafenib.

All clinical trials involving binimetinib and encorafenib currently sponsored by Novartis or Array, including three pivotal trials, COLUMBUS (in BRAF-mutant melanoma), NEMO (in NRAS-mutant melanoma), and MILO (in low-grade serous ovarian cancer), will continue to be conducted.

There are no milestone payments or royalties payable between the parties under the encorafenib agreement. As part of the transactions, Array has agreed to obtain an experienced partner for global development and European commercialization of both binimetinib and encorafenib. If Array is unable to find a suitable partner in the prescribed time period, a trustee would have the right to sell such European rights. Array entered into a third party agreement necessary to complete the transactions. Net consideration Array agreed to pay amounts to \$25 million.