THE CANCER LETTER

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

Vol. 39 No. 43
Nov. 15, 2013

FREE ISSUE

Clinical Trials

"Master Protocol" To Rely on Biomarkers In Testing Multiple Lung Cancer Agents

By Matthew Bin Han Ong

A new kind of clinical trial that will assign patients to therapy based on molecular characteristics of their disease is being launched by a coalition of government agencies, pharmaceutical companies, and a non-government organization.

The effort, called the lung cancer "Master Protocol," is a phase II and phase III trial that would test five drugs, assigning patients to therapy based on tumor biomarkers.

The master protocol in advanced squamous cell lung cancer (S1400) is one of at least three next-generation trials now in the works at NCI and its clinical trials cooperative groups.

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NCI News

Varmus: "We Are Shrinking Everything" To Keep Grant Numbers Level During Cuts

As NCI digs out after the two-week shutdown of the federal government, its leadership has to contend with the prospect of another shutdown weeks away, which may kick in after the current continuing resolution expires Jan. 15, 2014.

Meanwhile, the institute's budget remains unclear. Will funding come through a continuing resolution and remain stagnant throughout the next fiscal year? Can new money materialize? Or will sequestration take another bite?

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Watch Varmus's remarks to the NCI Board of Scientific Advisors on The Cancer Letter website.

Drug Approvals

FDA Grants Accelerated Approval to Imbruvica

FDA granted an accelerated approval to Imbruvica (ibrutinib) for mantle cell lymphoma patients who have received at least one prior therapy.

Imbruvica was approved four months after submission of its New Drug Application. The agent is sponsored by Pharmacyclics Inc.

The drug received the Breakthrough Therapy designation due to the overall response rate and duration of response seen in the phase II study, PCYC-1104, and the serious and life-threatening nature of MCL.

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Master Protocol Will be Joined By NCI's MATCH and Alchemist

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The protocol grew out of discussions between members of the cooperative groups, the NCI Thoracic Malignancy Steering Committee, and a panel put together by Friends of Cancer Research, a Washington, D.C., group.

The trial will be coordinated by the Southwest Oncology Group, in partnership with all the adult cooperative groups in North America, and is expected to open for accrual at all sites that participate in NCI's new National Clinical Trials Network by spring 2014.

According to sources at the NCI, the trial will be funded by a combination of institute support for cooperative group trials as well as a major contribution by the Foundation for the NIH, and by industry collaborators who have drugs in this trial.

"To my knowledge, there is nothing like this that has ever been attempted before," said David Gandara, chairman of the SWOG lung cancer committee, and director of the thoracic oncology program at the University of California, Davis. "The governance and organizational structure includes the Friends of Cancer Research, Foundation of the NIH, NCI, FDA, and Foundation Medicine, who will provide the genomic screening, and pharma, who will provide the drugs and funding for this.

"Every one of these groups is directly engaged in this master protocol, and each one will lead one of the arms of the study," Gandara said, during a D.C. conference co-sponsored by FOCR and the Brookings Institution Nov. 7. "We now have the National Clinical Trials Network going into effect early next year, and these groups are a part of that."

The master protocol would screen about 1,250 refractory squamous cell lung cancer patients annually, testing multiple lung cancer agents simultaneously, and thereby speeding up the drug development process and reducing costs.

Five agents have been selected for the master protocol: MedImmune's MED14736, AztraZeneca's AZD4547, Amgen's Rilotumumab, Pfizer's Palbociclib, and a PI3 kinase pathway inhibitor from Genentech. Agreements and company partnerships are being negotiated.

It's unclear at this point how much the master protocol trial would cost. According to the trial's organizers, this private-public partnership is estimated to cost less than what drug companies currently pay per patient for a clinical study.

The primary investigator for the trial is Vassiliki Papadimitrakopoulou, a professor at MD Anderson and a SWOG group member.

"This is a phase II-III biomarker driven master protocol for squamous cell lung cancer in the second-line setting, and this is a team effort at the intergroup level with leaders from all the cooperative groups actively participating and leading arms of this study," Papadimitrakopoulou said. "We've taken this challenge, but we want to take it the right way, so no patients should be wasted in this clinical trial.

"All the patients that are potentially screened could be potentially eligible for this, because not only do we offer a wide range of targets, but also because we have an arm for the patients whose targets are not being represented in the protocol.

"This allows for homogeneity in our population and consistency in the eligibility. This is, we hope, a better way to complete the registration and a faster way to safe and effective drugs for patients."

Hamburg: Trial to Produce Richer Data

Progress in developing new therapies for lung cancer is quite slow, and patients often become resistant to some of the newer targeted therapies, said Roy Herbst, co-chair of the protocol's executive operations group, translational medicine chair of the SWOG lung cancer committee, and chief of medical oncology at Yale Cancer Center.

"Squamous cell lung cancer is a particular area

THE CANCER LETTER

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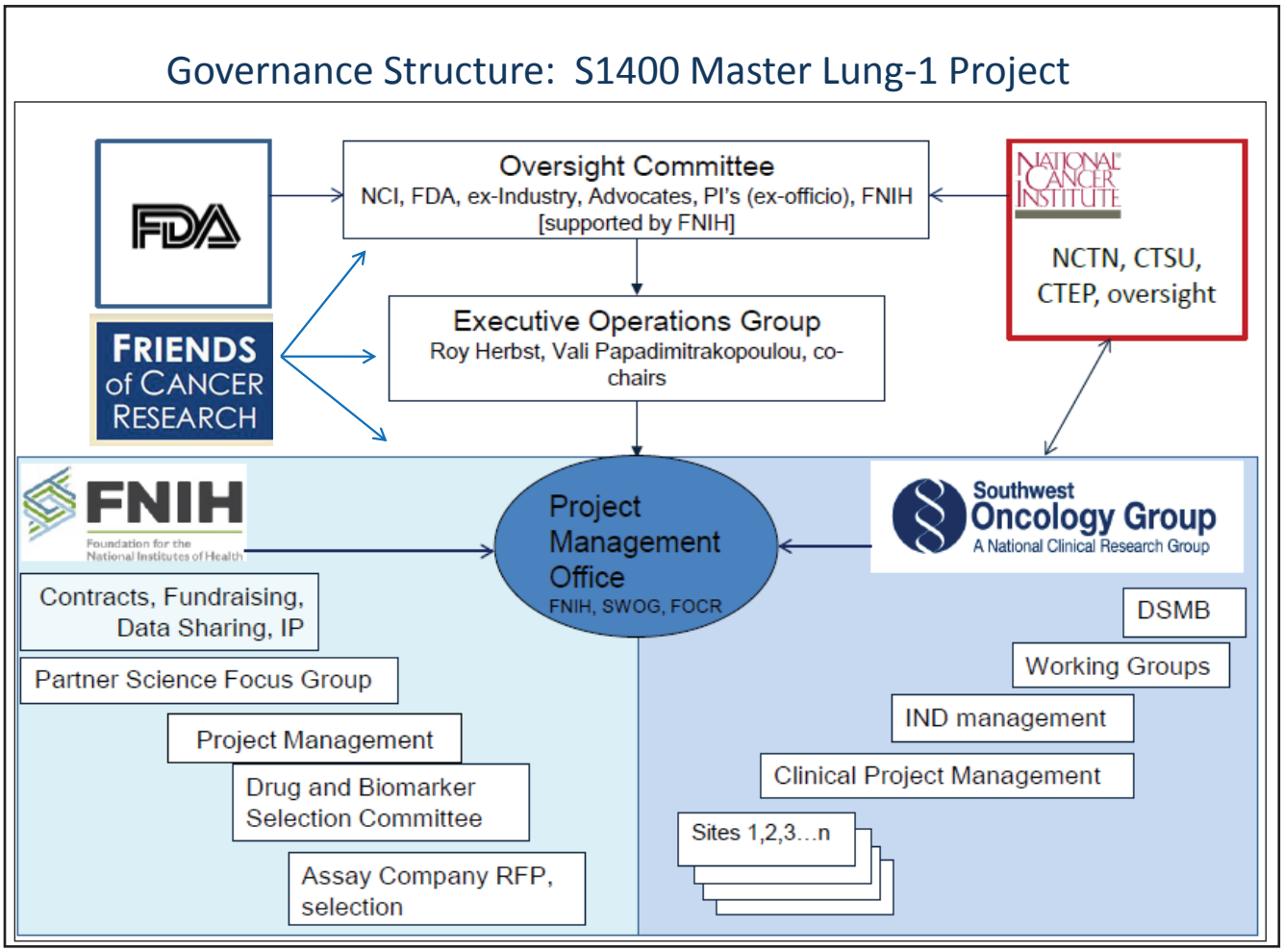
Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.



Slides presented by Roy Herbst of SWOG and Yale Cancer Center at a recent conference unveiling the master protocol. The slides are available at The Cancer Letter website.

where there hasn't been much progress with new FDA approved agents in the last few years," Herbst said. "Many patients have genetic profiling and some even next generation sequencing but we estimate that very few actually then get a drug that can actually help them. Or often patients receive a drug, perhaps off label (often called n of 1) but that's equally frustrating because there is currently no national database to follow up on the outcome of these treatments. So how do we come together and do better?"

The current clinical trials methods need to be modified for this new generation of agents, Herbst said.

"For example, if you're looking for a target that's comprises only 5 percent of the lung cancer population, you're unlikely to find enough patients at one center," Herbst said. "You're might not even find them at 10 centers.

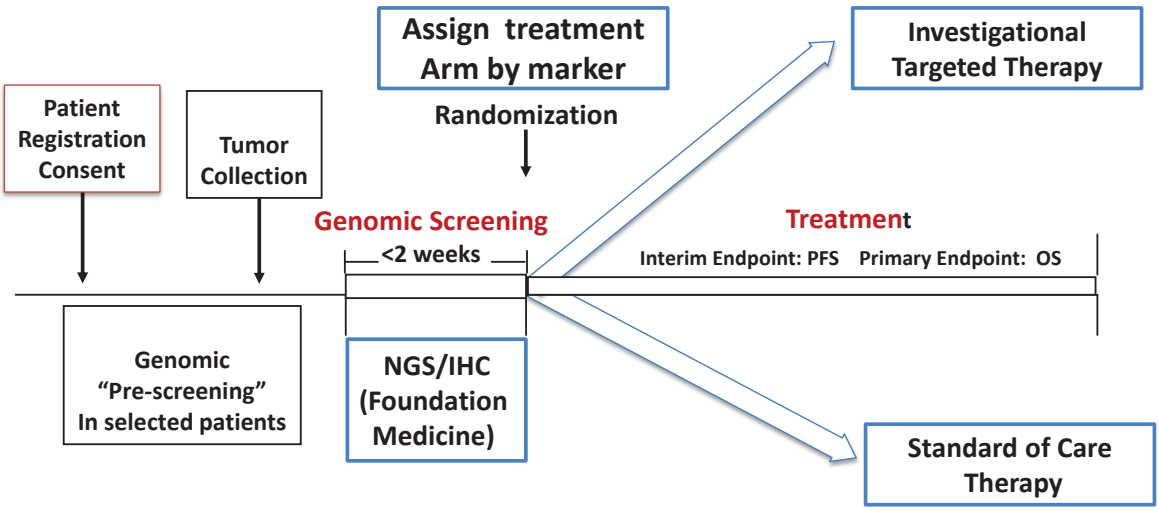
"Our goal is to help patients, and we developed a phase III trial where we can take drugs based on molecular profile and bring them to testing for clinical benefit.

"Then more agents can become available for patients throughout the country, including both academic and importantly, community sites."

FDA Commissioner Margaret Hamburg said the approach would produce "a rich amount of data [that] will be collected more quickly and at lower cost. By combining the resources of drug companies to test several therapies specifically targeted to individuals with particular genetic traits and makeup, and to do so in potentially hundreds of clinics throughout the U.S.

"The development of this protocol vastly increases the chance that we will find more and better treatments and does so in a creative and more cost-effective way.

"But the promise of this protocol is not confined to the development of specific lung cancer therapies," Hamburg said. "Its significance also derives from the model it establishes for other clinical research as well as for future collaborations between FDA, industry and academic researchers."



- **Organizers: FOCR,NCI-TMSC, FDA, FNIH**
- **Participants: Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)**
- **Screening: 500-1,000 patients/year**
- **With 4-6 arms open simultaneously, "hit" rate ~70% in matching a patient with a drug/biomarker arm.**

Next-Generation NCI Trials in Development

The master protocol in advanced squamous cell lung cancer is one of several new initiatives that NCI plans to launch in 2014.

"The others include a study of 'exceptional responders' to drugs that seemingly have not worked well for most patients in a given disease but for which a small number (usually less than 10 percent) have a major durable response," according to sources at the NCI. "Another study is called 'Alchemist' and this study will test an ALK inhibitor and an EGFR inhibitor in patients with selected mutations who have early stage, resectable lung cancer.

"To have ample patients with these uncommon mutations, this trial will screen over 7,000 patients nationwide over the next five years. Those who don't have the select mutations will be followed and their genomes studied

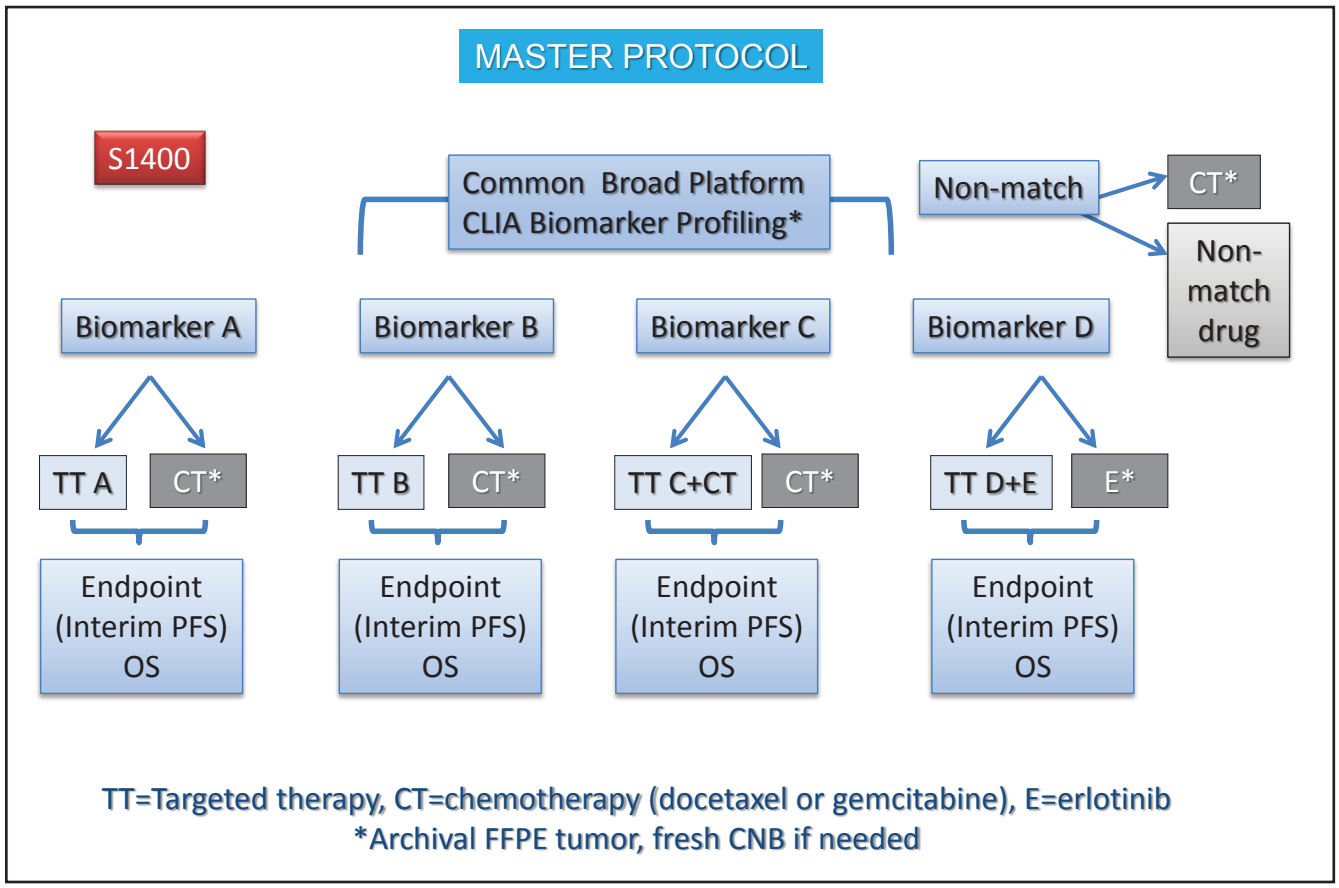
"The final study, NCI 'MATCH,' will sequence tumors in 3,000 patients with advanced cancer whose disease has progressed on standard therapy to determine in they have a select molecular change for which a targeted agent might be beneficial. NCI will work with a large number of company partners to have as many agents available to cover the majority of actionable mutations."

Fulfilling An Unmet Need

The idea for the lung cancer master protocol first emerged from a Friends/Brookings white paper and a concurrent February 2012 meeting involving the NCI Thoracic Malignancy Steering Committee, FDA, the European Medicines Agency, and several pharmaceutical companies.

Patients need a better clinical trial structure, because it takes 7.5 years on average for drugs to reach approval status and many fail along the way, Gandara said.

"The topic [of the meeting] was: how do we incorporate new biomarkers into clinical development and new therapies for lung cancer?" Gandara said. "Among the topics that we discussed was the fact that



unselected patients in randomized trials in lung cancer—the track record for those studies is very poor.

"Secondly, the need to develop biomarkers very early on in the context of drug development. Out of the last 22 randomized clinical trials for non-small cell lung cancer, only two trials were positive for overall survival. Only one of these incorporated a biomarker although all of these therapies were presumed to be targeted.

"The product of this meeting was the creation of the 'master protocol' task force in the thoracic malignancies steering committee to develop a series of master protocols for drug development and lung cancer."

"Not only did we conclude that this needs to be sped up, but that we could also consider phases of development of a companion diagnostic, and that it should be in sync, step-by-step, with the development of the drug," Gandara said. "So, at the end of the day, the FDA would approve a new drug and a companion diagnostic identifying those patients most likely to benefit from the drug.

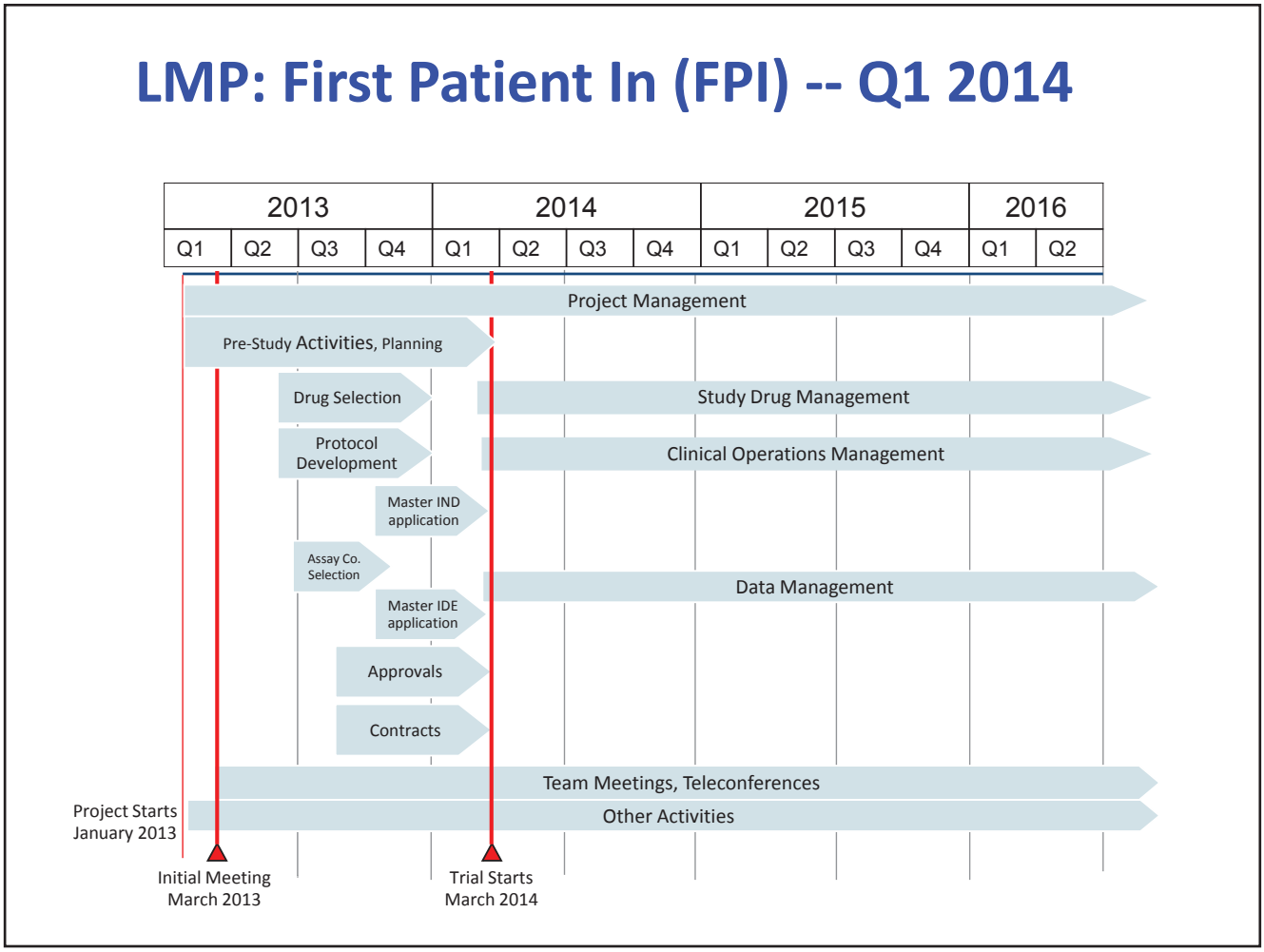
"We also discussed the fact that these changes, if they were implemented, need to be taken into context with the current understanding that non-small cell lung cancer is not one disease, or even a few histologic subtypes, but a multitude of genomic subsets. So the issues to be addressed by the master protocol are: 'How do we develop drugs for uncommon or rare genotypes?'

"Pharma by itself has great difficulty in doing a registration trial for a targeted drug for the population that is a fraction of 1 percent of patients," Gandara said. "How do we incorporate broad-based screenings such as next-generation sequencing? How do we, in a clinical sense, have an acceptable turnaround time of less than two weeks to get the information to the investigators, to the patients, so that they can be randomized? And how do we expedite the entire drug approval process?

"There were parallel efforts between the thoracic steering committee, one of those early-stage trials in development is called Alchemist, and we focus, with the Friends of Cancer Research and this public-private partnership on advanced-stage squamous cell lung cancer, to be coordinated through the Southwest Oncology Group.

"So this represents, perhaps, the greatest unmet need—advanced-stage squamous cell lung cancer—almost all the new targeted therapies have really been in adenocarcinoma, but we now know there are molecular targets which are druggable in squamous cell lung cancer and we have drugs for these targets," Gandara said.

Herbst said the trial's organizers wanted to work



with NCI and the cooperative groups.

"We decided to do it through SWOG," he said. "I think that's great, because what better time to do a trial through the cooperative groups following the IOM report recommending how to revise the clinical trials infrastructure. When you do a trial within SWOG now, it's not only with SWOG, it's with all the North American cooperative groups because it's part of the NCTN."

This trial, along with other parallel NCI initiatives, will benefit cancer patients nationwide, said Jeff Abrams, director of clinical research at the Division of Cancer Treatment and Diagnosis at NCI.

"These precision medicine initiatives will begin to deliver therapy for cancer nationwide via research trials in a way that truly individualizes treatment according to our desire to learn how best to predict what drug is indicated for which molecular change in any tumor type," Abrams said.

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NCI News

Varmus: Clearer Rules Needed To Guide NCI Through Shutdowns

(Continued from page 1)

The institute needs to have clear rules for operating under shutdowns, NCI Director Harold Varmus said at the Nov. 7 meeting of the Board of Scientific Advisors.

A video of Varmus's opening remarks appears on The Cancer Letter website.

"We need some clearer guidance on what is permitted to be done under the law, without making up all kinds of guidelines that might make the shutdown look terrible, but also makes it actually terrible—and, in my view, ends up costing us money," said Varmus, a survivor of two government shutdowns.

"We need to protect our trainees, especially those who might be arriving here on Jan. 1, and have not gotten their lives worked out, and we need to deal with a problem that may not concern most of you, but we worry about it, and that is how we deal with the matter

of furloughing and paying back contractors who are not directly NIH employees, but nevertheless work side-by-side with those employees and should be treated in a way that is fair, considering the differences in employment status, and other things," Varmus said.

The lack of clarity about the budget is affecting NCI's ability to move forward with programs new and old.

At the Nov. 6 meeting of the NCI Clinical Trials and Translational Research Advisory Committee, James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis, was in no position to offer many details about the status of revamping of the institute's clinical trials cooperative groups.

"The review of the NCTN occurred in July. The results were presented by Dr. [Meg] Mooney [chief of the Clinical Investigations Branch of the Cancer Therapy Evaluation Program] to the senior leadership committee of the NCI and were accepted.

"All I can tell you for sure is that there will be five groups that will be supported: one pediatric and four adult groups," Doroshow said. "There will be one Canadian group that will be supported. There will be an organizational infrastructure to support imaging and radiation therapy that will go forward. Exactly how many institutional grants we are able to support as well as the number and size of the translational research grants that we are able to support absolutely depend on what happens over the next couple of months in Congress. So we have a plan, but we can't execute that plan or anything related to it.

"I hope we will be able to get the money and make the allocations early in 2014, but we will see. "We will announce very shortly after NCI gets a budget. How much is allocated for RFAs and grants and various other pieces so we can put together on the division-by-division level what the support levels would be. After we get a budget, it will be a couple of weeks until we finally get granular enough to know."

The text of Varmus's remarks to BSA follows:

Comparative Shutdowns

One of the things the shutdown does is it makes you glad to go to work, when you actually can go to work.

I'm one of the few people who has had the privilege of sitting in two leadership positions at the NIH during two profound shutdowns: one in 1995, which actually lasted longer than the recent one. I was then the NIH director, but the two shutdowns felt very different, with the longer one, in 1995, seeming a whole lot less onerous than the recent one, and it's worth asking why.

That shutdown occurred on Dec. 15 and ended on Jan. 6. Some of us called that Christmas vacation, and indeed it felt like that. There was a different precipitating issue: at that time the fight was over the budget. That's what it's supposed to be about—fighting over an appropriations bill. It made sense. This time, we were fighting about a piece of legislation that was extraneous to the budget battle, and it presented a real threat to the way we conduct our democracy.

Last time, in the 1995 shutdown, the major warring parties, Speaker Gingrich and President Clinton, were actually sitting in a room talking most of the time. This time, there was silence on both sides. It wasn't clear whether we would ever have an endgame.

There were different sets of guidance issued, this time extremely draconian pieces of advice—like don't use your government issued email or don't use your government computer, even to look at a scientific article if you are sitting at home furloughed.

These struck me as complete absurdities.

Last time, the message was quite simple: you may not be officially at work and we can't guarantee you'll be paid, but keep the important things, the critical things, that would cost us money going. We can't spend money, because that would be a violation of the Anti-Deficiency Act, and that all makes sense.

But this time was quite different, and there were consequences that I'll come back to. Now, given all these differences, I think we have to remember that there was a cosmic significance to the president holding the line here.

Some people say this whole thing didn't have to happen—and on the one hand, perhaps it didn't have to happen because of those who precipitated it—but it did have to happen, and to continue from the administration's side, because to fold over the issue of whether we are going to allow Congress to hold the country hostage, because they wanted to reverse legislation that had already been voted on over 40 times, reviewed by the Supreme Court, and endorsed by the public, both in polls and in the 2012 election, struck me as completely inconsistent with the better parts of our democracy.

So I applaud the president for the strong stand he took in not negotiating under terms that would have been similar to a hostage situation. During the shutdown, for those of you who were not on campus, I don't think anyone in this area was happy.

It was hard to be at home and wanting to be at work. It was hard to be on campus without the usual intensity, the usual companionship, and the *esprit de corps*. For all of us, the lack of communication and uncertainty of when this shutdown was going to end added to the difficulty.

It was only 15-16 days, depending how you count them. It was not a good time. I'm very grateful to my colleagues who are NCI employees for a great deal of flexibility—and special kudos for those of you who did have to come to work and do the things on an empty, inconvenient campus: from providing essential care to our patients at the clinical center, to keeping our animals healthy, to keeping existing research investments going.

Because it may be a violation of the Anti-Deficiency Act to try to buy reagents—it's also, in my view, a violation of our fiscal responsibility to let experiments die and have to be redone at expense later on.

We need some clearer guidance on what is permitted to be done under the law, without making up all kinds of guidelines that might make the shutdown look terrible, but also makes it actually terrible—and, in my view, ends up costing us money.

I think it was important to keep a low level of research going; not everybody agrees with that. I was especially grateful to some of the leaders of the intramural research program who had to thread the needle here, and try to understand that the rules that were coming from high up in the administration, and to reconcile those with what is a sensible thing to do.

Our postdocs, many of whom came from abroad—some of them arriving on Oct. 1—to do government work, were not sure what the hell was going on in this so-called advanced economy. And without a salary and without a place to live, they had quite a lot on their minds—and to have their goals of trying to make progress against cancer on the NIH campus thwarted by political events they couldn't possibly understand was a little frustrating.

So we are trying to think ahead about that. I'll come back to the issue of how we make use of lessons learned from this debacle on the one hand, but in a sense a triumph on the other, because it did turn out alright.

On Restarting

The shutdown is one thing; the startup is another. There was a lot of anxiety about the startup. Many of you received a memo from me—not something I was encouraged to do by higher-ups, but I sent you a memo to warn you that, while the extramural community was somewhat spared during the actual shutdown, there would be demands placed on you later.

It was clear already as we got into the second week of the shutdown that we would be canceling site visits and study sections. That was true both in Paulette's office [Paulette Gray is the director of the Division of Extramural Activities] at NCI and within the larger NIH community, especially through [the NIH] Center for Scientific Review.

There would be a need to reschedule meetings fairly promptly, and we were to ask for a lot of flexibility from you.

In addition, we knew the startup would involve getting payroll systems starting up again. All the managerial things that had been shut down had to get up to speed. And although I know it wasn't easy, it did seem a little easier than I thought. The payroll system worked—it not only worked, it incorporated pay for the first several days in the previous pay period in the first part of the shutdown, that wasn't going to be covered by the first payroll period.

So we got all that done, we got all the NIH employees got their fully expected pay. Many other systems got rolling quite quickly, such as our budget system and grant making system, and I'm grateful to John Czajkowski [NCI deputy director for management] and his colleagues who worked hard to make these things happen with systems that seem inherently more robust, compared to other systems that give us trouble.

I am grateful to Paulette and her colleagues, and to many of you in this room and not in this room for helping us to get site visits and study sections rescheduled.

Indeed, everything that was postponed has been rescheduled in a reasonably timely way. There will be no significant delays in getting grants reviewed, processed, discussed, and awarded—as you might have hoped. And I'm grateful for all that.

Threat of Another Shutdown

Now, as you all know, the shutdown ended with a continuing resolution that lasts three months. It ends Jan. 15. I'm not going to review all the political machinations that are currently underway, including the high-level budget discussions to try to reach a consensus on how to move forward in the fiscal year after Jan. 15.

I would have thought there couldn't be a shutdown. It would be a bad political move. It was called a bad move up to Oct. 1 too, and yet it happened. I'm not going to make predictions this time because the predictions I made last time were all wrong.

But it is possible we'll have a shutdown, so we are thinking through the lessons learned.

Namely, we need a better means to communicate within the intramural program, and between NIH central and with our tens of thousands of investigators and others.

We need some clearer guidance on what is permitted to be done under the law, without making up all kinds of guidelines that might make the shutdown look terrible, but also makes it actually terrible—and, in my view, ends up costing us money.

We are shrinking everything. It's a little bit like climate change. Things change all around you; it's not all that perceptible.

A percent here, a percent there, and pretty soon it is real money.

We need to protect our trainees, especially those who might be arriving here on Jan. 1, and have not gotten their lives worked out, and we need to deal with a problem that may not concern most of you, but we worry about it, and that is how we deal with the matter of furloughing and paying back contractors who are not directly NIH employees, but nevertheless work side-by-side with those employees and should be treated in a way that is fair, considering the differences in employment status, and other things.

I think at this point, there were not a lot of casualties from the shutdown.

The extra work of rescheduling site visits and study sections I've mentioned already. We had a very important roundtable to discuss the future work of the Center for Cancer Genomics. You heard Lou Staudt [head, molecular biology of Lymphoid Malignancies Section and Deputy Branch Chief at the Center for Cancer Research] at the last meeting discussing that ambitious program. A roundtable that had been scheduled for early October has now been, I believe, rescheduled for Dec. 3. That was a delay that I wasn't happy about.

We discussed in June and received an enthusiastic endorsement for our plans to go forward with an outstanding investigator award. There's been no progress with those awards because of all these interfering activities.

Let me say a few things about what has come out of the resolution, and what Congress is doing. As you know, the continuing resolution we are working on until Jan. 15 is at fiscal year 2013 levels.

So it's the same amount of money as projected in that period, but the allocation to us was larger than first continuing resolution we received last year.

Last year, we got about 28 percent of what we expected to get for the year for the first six months, based on previous spending patterns. This time, we have 29 percent of the year's allocation for the next three months. That means that we can be a little more liberal in the way we give out money for non-competing and even our competing applicants until Jan. 15.

What will happen then? Well, setting aside the stalemate issue, assuming something happens, I think there are at least three general propositions, and many in between. We could end up with a year-long continuing resolution at FY13 levels.

We could see an additional decline in our budget, because the original rules of the sequestration process would have dictated another 2 percent be reduced, and that of course would create problems. We're trying to think through what we would do if that happened.

And then there's also the possibility that we'll end up with the withdrawal of the sequestration directive, or the award of some flexibility to the appropriators—so they can favor favored agencies in giving out money, and not do an across-the-board, mindless reduction. If that happened, that could lead to increases.

Whether we'll actually get the level that the president recommended for the NIH for this year—which would be about 1.5 percent above FY12 levels—that would be a great moment, because it would feel like a great increase. But if it's possible to end up with something above last year's level, we'll have to see.

Meeting Approval

In the interim, there is some good administrative news—not a whole lot, but some—and these were issues that you cared about last time.

One is that there's been some relaxation from OMB about the approval of meetings. So now meetings like this, FACA advisory committee meetings, don't need to be approved each time we want to have them. That seems like a very small thing in the history of mankind, but it's some relief, and we don't need that kind of approval for study sections.

Again: an absurdity, when relieved, makes us feel good—but it's absurd to begin with.

We also have learned that we've been given back the ability to make some bonuses. These are relatively small amounts of money, but being able to serve an appropriate function as a manager by being able to award extra work and good work is very important to us. Having that ability back is certainly a good thing. There are said to be some other good things coming, so we're holding our breath, but we're happy about that.

We are, of course, in the process of awarding grants now.

As is common in situations like this, we're paying our non-competing awards, Type 5s, at the 90 percent level.

We expect to restore some of the additional money, but when it will get to the 100 percent of the money is not clear. That will depend on the final determination of the FY14 budget, but, at least for the moment, we're giving out the expected full-year award for type 5s and we're making our other awards as we did in the first part of FY13.

It's now possible to say a few things about what happened in FY13: when, as you recall, we had roughly a 6 percent decline in our budget, when you add together the roughly 5.1 percent reduction from sequestration, plus some taps from the department that were essential to help fund the insurance exchanges.

I want to give you a little synopsis.

There's a chart, and we'll get all this data up on our website where we show the retrospective look at prior years, but first the highlight:

You'll recall that we planned our budget for FY13 once we knew what it was with the proviso or the goal of making more or less the same number of competing awards as we made the previous year in FY12.

We've almost exactly achieved that. There are some who think it serves a political purpose to be able to say 200 people who would have gotten their grant didn't get their grant, and that sequestration is monstrous.

I chose, and I think most people around our table agree with this, to make cuts in other parts of the portfolio, to be sure that we were maintaining the grant award numbers, because people's careers end when they don't get grants.

I think this was the wise thing to do. But it shouldn't be understood that there's no pain when you do that. We are shrinking everything. It's a little bit like climate change. Things change all around you; it's not all that perceptible. A percent here, a percent there, and pretty soon it is real money.

We have to remember that, while our grant numbers overall look pretty good, that everybody is getting less for everything. We already know that over the past decade, NIH budgets have not kept up with either the computed inflation rate. Even the Biomedical Research and Development Price Index is below the estimates, most of us who run labs know, to be the increasing cost of research.

This enterprise is built on some assumptions that worked well in the early days, and don't work so well anymore.

I think all of us should be paying some attention to what these changes mean.

The kits, machines, high-throughput stuff, and more animal models have driven the cost of research up in a way that can't be captured by simple inflationary indices. We know that we are starving everybody, in requiring co-funding by institutions and advocacy groups and lots of other folks, and eventually the belt-tightening all around us doesn't work. Then Florida is drowned and more glaciers melt, and we have got to keep an eye on that.

But minimizing the pain in the short run to me seems to be the reasonable thing, while, at the same time, I think we should all be thinking about what is actually happening with the non-sustainable industry that we are a part of.

This enterprise is built on some assumptions that worked well in the early days, and don't work so well anymore. I think all of us should be paying some attention to what these changes mean.

Let me just say a couple of things in greater detail about last year's grant numbers. There were some small declines in the numbers of R01s issued, both Type 1 and Type 2. And that, in part, reflects some declines in the

number of applications. The success rates didn't really change, but we are particularly concerned by a very modest, but it seems to be persistent, decline of early-stage investigators and new investigators applying for R01s. So we need to keep an eye on that.

There was a moderate increase in the number of R21s, exploratory two-year grants, including increases in the applications. The success rates remain lower, especially for new investigators. They are R21s but they are an appealing way to apply for funding—whether the perception is that it's easier to get a smaller grant; that's wrong. The success rate is lower. How good those applications are is another issue. It's a little harder to evaluate.

There were a few more P01s with better success rates, whether that reflects that this round we had a lot of really good P01 groups coming in for review, or whether it reflects the perception that is generally shared around our leadership table: that in bang-for-the-buck, P01s are really pretty good.

Anyway, we'll get those numbers up on the website and let you all know so you can look at them in more detail.

Changing the Biosketch

We talked last time about the biosketch changes that the NCI is endorsing, and I feel very strongly about getting a biosketch that depends on an account by the applicant of that person's five most contributions to science—as opposed to placing a lot of weight on a bibliography that's read by looking at the positions of the author in a pile of authors and seeing where the paper was published.

And I think most people agree with this. Nevertheless, this seems to be a process-oriented government department, and we're going through a pilot phase. Paulette has used the new biosketch for a couple of RFAs and we're going to be asking some informal questions of the reviewers who have used the system, and hopefully we can get some answers.

What I'd like to do is see the whole NIH adopt this biosketch proposal, which is very similar to some of our institutions on the outside and is used by the Howard Hughes Medical Institute.

There continues to be a lot of interest in the problem of replicating data from work supported by the NIH, and we discussed this in some detail last time.

If you haven't seen it already, I urge you to have a look at an article that appeared in The Economist recently with an editorial. There's not a lot new there, but it's got a pretty good summary of what's going on. An elite population of readers is looking at this issue, and we've already received questions from Sen. [Richard] Shelby (R-Ala.) at the hearings.

Having this idea more generally known in the politically astute community is going to result in you all encountering questions about what the hell is going out there, and what is going on at the NIH, and why do you guys want more money.

Some of you may be aware that there is a group that has positioned itself to attempt to reproduce work done by NIH scientists, and they have chosen 50 papers published in the last three years that have had many citations—and many of these to try to undergo replication of the work.

I see at least one, two—quite a few people around this table, and some who should be around this table, like Dr. Andrea Califano [professor of systems biology, chief of the Division of Biomedical Informatics, and associate director of bioinformatics at Columbia University Herbert Irving Comprehensive Cancer Center]—who have such papers, and have been approached by the replicators.

They have proposed, how, I don't know, to replicate work that took several years and cost literally hundreds of thousands of dollars over a short term with relatively small amounts of money, and without the necessary skills.

So, NIH is not intending to issue an RFA for replicating work. We would like to improve the way work is done in the first place, and there is a lot of discussion about how that could be done—both by trying to examine the underlying conditions that impel people to publish prematurely and without adequate attention to detail.

A lot of that has to do with the culture of science. We're very proud that, here at the NCI, the work that [NCI Biostatistician] Lisa McShane and her colleagues have done to establish checklists. Just a few weeks ago, that group published a paper—actually in two places, in Nature and the BMC [Medicine] journal—that provided guidelines to carrying out so-called omics studies.

You'll recall that, just after I arrived here, we had an unfortunate episode. At one of our leading universities, studies that led to the design of clinical trials were based on work in the omics domain that were not sound.

We asked the Institute of Medicine to do a report on high-throughput studies that have clinical relevance. That report was influential, and for the work that Lisa and her colleagues have done, I congratulate them for

pushing forward here and getting a lot of attention focused on building checklists that can be used to improve the likelihood of replicatibility.

We've been discussing for the past few meetings our response to the so-called Recalcitrant Cancer Act. A brief update, since Jim Doroshow has had to sit in for me at the institute directors' meeting, which occurs Thursday mornings.

He normally reports on this, but the report on pancreatic ductal adenocarcinoma research is nearly done. A workshop was held earlier this summer on small-cell lung cancer. There were some interesting conclusions from that meeting, and a report is in progress.

I've mentioned in the past the interest in several members of the NIH leadership have in working more closely with the Centers for Medicare and Medicaid Services. Those discussions have been reactivated and allowed me to go back to a point that I tried to make two or three years ago: that CMS needs to pay close attention to helical CT scanning for lung cancer.

Of course, now with the U.S. Preventive Services Task Force draft report, it's now clear that there will be a need for reimbursement policy to provide the rules for coverage by Medicare and Medicaid of this test, and the insurance companies will be following along with their deliberations.

There is now an active group of staff from NCI and leading staff from CMS talking about some of the issues that were raised there. It's not just a matter of saying we're going to follow the National Lung Screening Trial and the results of that trial. It's a matter of saying what coverage is appropriate for the follow-up tests. There is a very high percentage of false positives in these tests, even in the trial, which used only healthy smokers. There were a lot, 25 percent, of people had to have something else done besides than the low-density helical CT scan. And when you put in the smokers who were not well—you're going to have a lot more bronchitis and false positives.

How do you incentivize the improvements in the methodology, what do you do about the coverage of other aspects, and what do you do about the people who don't quite fit the criteria? There are going to be a lot of significant issues.

There's also some developing interest in the issue of developing diagnostics that depend on genomics and other molecular technologies in diagnosis of cancer, which, of course, leads frequently to hopefully a more correct, precise choice of therapies. And we're finally going to have some discussion with CMS about that as well.

Just a few things about meetings and events, for those of you who want to be oriented to these things. You heard last time about the President's Cancer Panel's report on human papilloma virus vaccinations. We hope that report will be done sometime within the next few weeks and presented publically.

Bill Gates is another victim of the shutdown, because his Barmes [Global Health] lecture had been scheduled for early October and has now been rescheduled for Dec. 2, when he and some of his colleagues will be on campus to interact with the institute directors.

A few of us happened to have an off-site discussion with him in early October, and one of the things that he expressed an interest in developing was a wider range of interactions with the NIH, with an increased level of interest in the things that the NCI does.

So we are looking forward to some more substantial interactions with the Gates Foundation, especially on matters of common interest, like infectious cancers, cancers that affect young people and disrupt maternal-infant relationships, and so forth.

There was a very good International Cancer Genome Consortium meeting in Toronto on Oct. 1. Some of us, happily, were there, and there was much discussion about something I mentioned last time—this plan for a global alliance to try and get information about the genetic basis of cancer and the way it's treated into a digestible, interoperable form.

The alliance is now issuing a monthly newsletter, and the last newsletter said there would be a meeting of planned members of the alliance that intend to join the alliance in March. Hopefully we'll have more information on what the alliance will actually be able to do.

I've talked here in the past about this consortium of leaders of international funding agencies for cancer that Harpal Kumar [chief executive of Cancer Research UK] and I have been organizing for the past couple of years, and I think I've distributed a report that we published in Science Translational Medicine last year about the goals of this international group.

We are going to be meeting again—this time happily organized by others; by Fabien Calvo [Deputy General Director of the National Cancer Institute, France], in particular—in Paris Jan. 13-14.

Also, at the risk of apparent immodesty, I'd ask that a recent profile of me and our objectives at the NCI be distributed. I don't see it on the tabletop. I asked that it be put at everybody's place; we'll get it for you

during the day. Some of you have seen this.

Frankly, it was a piece that pleased me. But I think it does highlight many of the things that many of us here at the NCI are aspiring to do even in these difficult times. I think it's probably useful for all of you to see it, if you haven't.

I think it does portray the message I'm trying to make: that we're unhappy about limited budgets—that there's a lot to do, but we've got a fair amount of resources to do it with, and we can't spend all our time whining. We've got to be doing some things that are important for world health.

Drug Approvals

Accelerated Approval Granted To Imbruvica MCL Therapy

(Continued from page 1)

With approval, it becomes the second Breakthrough Therapy to get on the market.

On Nov. 1, the agency approved the Genentech agent Gazyva (obinutuzumab) for previously untreated chronic lymphocytic leukemia. Altogether, 32 agents have been granted the Breakthrough Therapy designation since the designation was established in July 2012.

The Imbruvica approval was based on the results of a multi-center, international, single-arm trial of 111 patients with previously treated mantle cell lymphoma.

Tumor response was assessed according to the revised International Working Group for non-Hodgkin lymphoma criteria.

The efficacy results demonstrated a 65.8 percent overall response rate (95% CI: 56.2, 74.5); 17 percent of patients achieved a complete response and 49 percent of patients achieved a partial response. The median duration of response was 17.5 months (95% CI: 15.8, not reached).

Safety was evaluated in the same 111 patients.

The most common Grade 3 or 4 non-hematological adverse reactions were: pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections. Five percent of patients had Grade 3 or higher bleeding events, such as subdural hematoma, gastrointestinal bleeding, and hematuria.

Treatment-emergent Grade 3 or 4 cytopenias were reported in 41 percent of patients. The Warnings and Precautions listed in the Prescribing Information include hemorrhage, infections, myelosuppression, renal toxicity, second primary malignancies and embryo-fetal toxicity.

Ten patients discontinued treatment due to adverse reactions in the trial. Adverse reactions leading to dose reduction occurred in 14 percent of patients.

As a condition of the accelerated approval, FDA required that the sponsor submit 24-month follow-up data for all patients in the single-arm trial and submit the results of a randomized controlled trial comparing Imbruvica in combination with bendamustine plus rituximab to bendamustine plus rituximab in patients with newly diagnosed MCL.

Prescribing information is available on the FDA website.

The company said FDA is reviewing Imbruvica on an expedited basis for relapsed chronic lymphatic leukemia.

Imbruvica inhibits the function of Bruton's tyrosine kinase, a signaling molecule of the B-cell receptor signaling complex that plays an important role in the survival of malignant B cells.

"This is a meaningful day for previously treated mantle cell lymphoma patients, who are in need of new treatment options," said Michael Wang, of the Department of Lymphoma/Myeloma at MD Anderson Cancer Center, lead investigator for the registration trial PCYC-1104.

Imbruvica is commercially available immediately.

"After observing early signs of efficacy and tolerability of Imbruvica four years ago, we single-mindedly focused our attention on fully developing this medicine," Bob Duggan, CEO and Chairman of the Board of Pharmacyclics, said in a statement.

"We continue to explore Imbruvica's potential to treat cancer patients in need. Presently we are in the midst of investigating this medicine in numerous additional B-cell malignancies with 37 clinical studies ongoing."

A breakthrough therapy is a drug:

• Intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and

• Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

When a drug is designated as breakthrough therapy, FDA expedites the development and review of such drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt.