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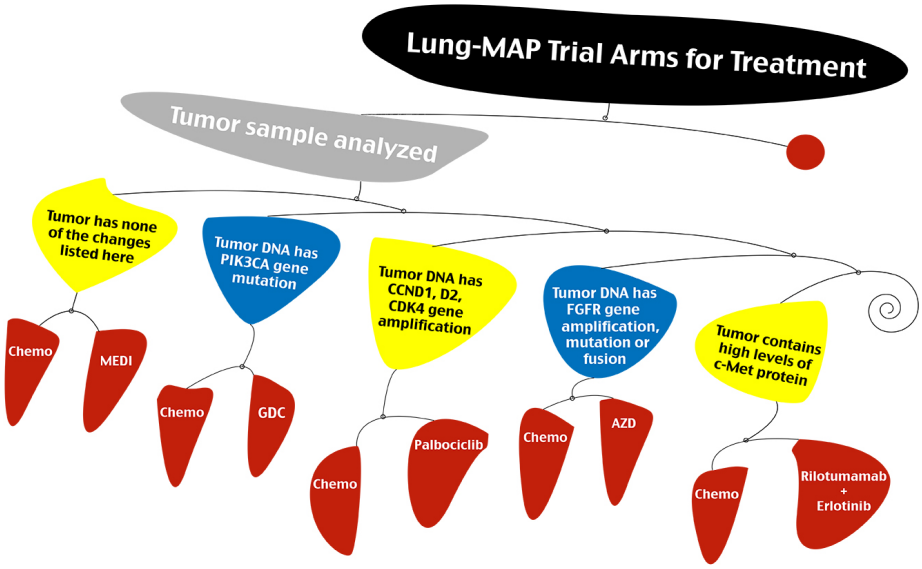

Partnership Points to New Path Forward For Drug Approval and Clinical Research

By Paul Goldberg

SWOG earlier this week started to accrue patients to Lung-MAP, a clinical trial for second-line treatment of non-small cell lung cancer.

The trial, also called Lung Cancer Master Protocol or SWOG S1400, uses the patients' tumor characteristics to select one of five targeted therapies, comparing them with active control in each arm.

Lung-MAP is funded by a public-private partnership, which combines NCI's limited funds with those of commercial sponsors, pointing to a new way of pooling resources to conduct faster, more efficient registration trials.

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Conversation with The Cancer Letter

What $34,000 per Patient Buys in Lung-MAP

The Cancer Letter asked David Wholley, director of research partnerships for the Foundation for the National Institutes of Health, to explain the novel scientific and administrative structure of Lung-MAP.

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In Brief

Patricia LoRusso Named Associate Director Of Innovative Medicine at Yale Cancer Center

PATRICIA LORUSSO was named associate director of innovative medicine at **Yale Cancer Center**. She will take the job in August, and will also serve as a professor of medicine.

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Lung-MAP Brings Industry Funds To NCTN Clinical Trials Groups

(Continued from page 1)

• For patients, Lung-MAP is an opportunity to be directed to therapies chosen from a wider-than-usual menu. Instead of undergoing multiple diagnostic tests to determine eligibility for different studies, patients are tested once, based on a "master protocol," and assigned to one of five different arms. The control arms are docetaxel or erlotinib, both FDA-approved therapies for second-line treatment of squamous cell non-small cell lung cancer.

• For drug companies, Lung-MAP is an opportunity to earn approval based on a game plan developed and executed with the participation of FDA. (The agency is also represented on the trial's governing board.) Five agents have been selected for the master protocol: MedImmune's MED14736, AstraZeneca's AZD4547, Amgen's Rilotumumab, Pfizer's Palbociclib, and a beta sparing PI3 kinase pathway inhibitor from Genentech. These agents could be approved concurrently with the biomarker assays. If any of these compounds fail to meet the endpoints, others will take their place in the ongoing trial. Also, patients treated in the phase II portion of the trial could be counted toward phase III. For rare populations of patients (5-20 percent by biomarker) this is one of the few ways such a trial can be done.

• For the clinical research groups that make up the new NCI National Clinical Trials Network, Lung-MAP and trials like it could represent a lifeline at a time when the institute is cutting support for the groups' infrastructure and setting limits to accrual.

The institute has committed money, about $24 million, to Lung-MAP. (With infrastructure costs, the NCI contribution is $43 million.) Altogether, the trial may cost as much as $169 million.

As it stands, with plans to screen 1,250 patients a year and enroll 1,000, Lung-MAP represents about 6 percent of NCTN's total projected enrollment. At least two more similar public-private trials—in colon and breast cancers—are in planning stages, sources said.

With pharma contributions, Lung-MAP offers a more generous per-case payment than standard NCI trials. On top of that, the trial provides money for the accruing institutions to screen patients. Moreover, the trial's administrators would pay for genotyping every patient considered for accrual. Genotyping isn't always covered by insurance.

"This trial is a good illustration of why it is essential to increase the NCI investment in the NCI National Clinical Trials Network and avoid plans to cap accrual."

— ASCO's Richard Schilsky

The amount of money spent per patient may seem staggering: $34,000, with about $9,000 coming from NCI.

"With this trial, we set out with the goal of creating a new innovative model for how future clinical trials could be conducted," said Ellen Sigal, chair of Friends of Cancer Research, a Washington, D.C. group. "Lung-MAP is a true collaborative effort that utilizes the existing infrastructure of the cooperative groups and presents significant opportunity to bolster them moving forward. What we have accomplished here has created substantial cultural and behavioral changes across the board that will truly benefit patients."

Sigal's group brought all the players together to make the project happen.

"It's a nice win-win for everyone," said David Wholley, director of research partnerships for the Foundation for the National Institutes of Health. "The cooperative groups welcome the supplemental funds that they can devote to the infrastructure and recruitment costs for the trial. And the companies—at $25,000 a patient—to do phase II and phase III testing, that's a pretty good deal for them. I think the financial model—the economic model—is a pretty

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nice model for collaboration between government and the private sector."

A conversation with Wholley appears on page 1 of The Cancer Letter.

The American Society of Clinical Oncology, which has been a stalwart defender of publicly-funded clinical trials, praised Lung-MAP, but expressed concerns about NCI's recent efforts to cut the budgets of the statistical centers and administrative offices of three of the four adult clinical trials groups (The Cancer Letter, May 16).

"The Lung Cancer Master Protocol is an exciting public-private collaboration that makes ideal use of the clinical trials infrastructure that NCI helps support," said Richard Schilsky, ASCO's chief medical officer.

"The trial takes a highly innovative approach to coordinate the screening and enrollment of lung cancer patients across multiple investigational treatment options. The collaboration illustrates the importance of having a standing network of research sites in the academic and community practice setting and an organized way to screen for small subsets and maximize patients' opportunity to enroll in clinical trials. We should expect more of these opportunities with the increasing use of molecularly based agents.

"This trial is a good illustration of why it is essential to increase the NCI investment in the NCI National Clinical Trials Network and avoid plans to cap accrual," Schilsky said to The Cancer Letter.

Budget cuts are just one part of the problem for NCTN groups. The funding levels for the groups are determined by accruals, and with accrual capped system-wide, several groups say that initiating new trials—even transformational trials that generate revenues—is a challenge.

Monica Bertagnolli, chair of Alliance for Clinical Trials in Oncology, said the private-public trials like Lung-MAP are good science and make financial sense to the groups, but the caps make it challenging to continue conducting other ongoing trials.

"We are still struggling with all of our [budget] cuts, but we certainly want to do this kind of work and are very happy to have this other support into the system," said Bertagnolli, chief of the Division of Surgical Oncology at Brigham and Women's Hospital and professor of surgery at Harvard Medical School. "I think the bottom line is: We are going to be able to do these trials, but we are not going to be able to do much else.

"There is stuff that has priority, and that's what's going to happen," Bertagnolli said. We are not going to do as many trials as we are used to doing."

How the Money Flows

Lung-MAP investigators expect to screen about 1,250 patients per year over five years—6,250 patients altogether—for inclusion in the study.

For each patient screened, the sites will receive $500 per patient plus $100 for tissue submission from NCI. This will be supplemented with a $479 tissue submission payment from non-federal sources.

For each patient enrolled, the sites would receive another $4,790. Of that sum, NCI would contribute the amount determined by its standard scale.

If the patient is enrolled through an institution that holds the new Lead Academic Participating Site designation, the NCI contribution would be about $4,000. If the patient enrolls through a non-LAPS site, NCI's contribution will be about $2,250.

The Foundation for the National Institutes of Health would then use money contributed by drug sponsors to erase the difference between LAPS and other institutions. Thus, total payment for screening and enrolling a patient in Lung-MAP is $5,869.

Foundation Medicine will use its FoundationOne assay to screen over 200 cancer-related genes for genomic alterations, and will receive payment from the FNIH. Also, one of the assays that will require immunochemistry (c-met) will be subcontracted from Foundation Medicine.

"Squamous cell carcinoma of the lung is a deadly cancer killer, and like many common solid tumors, analysis of no one or even several genes provides a sufficiently comprehensive characterization of the actionable alterations present in a population of patients to ensure a high screen hit rate when evaluating patients for a targeted therapy approach," Vincent Miller, chief medical officer of Foundation Medicine, said in a statement.

"Rather, multiple genes often altered by one or more classes of DNA changes and often co-occurring are unpredictably altered in any given patient. The comprehensive, broad based nature of FoundationOne testing allowed us to be uniquely suited to provide reliable results across an unprecedented broad swath of predictive biomarkers in a clinically relevant turnaround time to attract multiple interested pharma partners with distinct therapeutic targets."

The FoundationOne assay is usually billed at over $5,000.

SWOG will be able to charge its standard 26 percent in indirect costs for its portion of administering the clinical component of the study.

Registration Trial Design

Lung-MAP is designed to provide a fast, efficient path to full approval, said Roy Herbst, co-chair of the trial's steering committee and co-chair of its executive operations group. The idea is to get drugs to patients throughout the community, going seamlessly from a phase II portion to phase III, with all patients counting toward registration.

At the end of phase II, after 55 progression events, the trial's data monitoring committee will look for improvement in progression-free survival. It has to be either two-fold (HR= 0.5; Plan A) or 2.5 fold (HR=0.4; Plan B) in the biomarker-positive population.

"Some companies requested a stricter cutoff than others, and we were flexible; hence the two alternative plans," said Herbst, who is also the developmental therapeutics co-chair of the SWOG lung cancer committee and chief of medical oncology at Yale Cancer Center. "They wanted to ensure that there is little chance of their arm going forward unless there was clear activity predicting future success in phase III."

After choosing between the two cutoff thresholds (which is done at the outset), the companies and investigators have no say in the way the trial is conducted. "It's all done in the cooperative group system, as a standard randomized phase III study," Herbst said to The Cancer Letter. "Decisions are all in the hands of the Data Monitoring Committee.

"If it goes to phase III, the investigators, of course, won't know any details about the phase II result. It's all done in a blinded way to insure the integrity of the phase III trial. All the patients in phase II will hopefully count toward the phase III number.

"We assume, unfortunately, a couple of the arms aren't going to make it all the way to phase III, but that's the nature of clinical research. For overall survival, the trial is powered to observe a 50 percent improvement.

"But I am hoping that one or two of them will make it. Or all of them if we are lucky!"

Herbst said that it's noteworthy that NCI has agreed to a PFS endpoint in both phases of the trial. "It's a major step forward," he said. "We always want to have survival trials, but this is a second-line study, and many patients will go on to third-line or more drugs afterwards. We didn't want to confound our endpoint with post-trial therapies. That said, the trial is still powered for an overall survival analysis."

The lead study chairs for the trial are Vassiliki Papadimitrakopoulou, professor in the Department of Thoracic/Head and Neck Medical Oncology at MD Anderson Cancer Center; David Gandara, director of the Thoracic Oncology Program at UC Davis and chair of the SWOG Lung Committee; and Herbst.

Mary Redman, of the SWOG Statistical Center in Seattle, directs the biostatistics work.

Fred Hirsch, of the University of Colorado, and Philip Mack, of UC Davis, are study co-chairs for translational medicine. Lawrence Schwartz, of Columbia University, who serves as chair of the SWOG Imaging Committee, is study chair for imaging.

Lung-MAP is opening NCTN-wide, with all four of the adult NCTN network groups participating. The Alliance study chair is Everett Vokes, of the University of Chicago; ECOG-ACRIN's study chair is Suresh Ramalingam, of Emory University; and the NRG study chair is Jeff Bradley, of Washington University.

"I think the bottom line is: We are going to be able to do these trials, but we are not going to be able to do much else."

—Alliance's Monica Bertagnolli

Herbst stated that the team has worked very hard to bring all the groups in the NCTN into the fold.

"This trial will likely cost $160 million, and only a small portion of that comes from NCI," said Herbst. "The pharma companies simply don't have the infrastructure for this type of multi-arm umbrella study. They often employ CROs to put together trials, but you don't always know whom you get this way. The NCTN brings top academic groups, cooperative groups, and CCOP investigators to the table.

"They are all ready to go, but they benefit in Lung MAP from access to drugs and increased resources."

History of Lung-MAP

The concept of a lung cancer master protocol was first proposed informally by Richard Pazdur, director of the FDA Office of Hematology and Oncology Products, insiders say.

The idea emerged publicly in a Friends/Brookings white paper (chaired by Herbst) and a February 2012 meeting involving the NCI Thoracic Malignancy Steering Committee, FDA (chaired by Fred Hirsch), the European Medicines Agency, and several pharmaceutical

companies (The Cancer Letter, Dec. 3, 2013). We decided to merge the two efforts, said Herbst.

Late last year, at the 2013 Friends/Brookings meeting, David Gandara, chairman of the SWOG lung cancer committee and director of the thoracic oncology program at the University of California, Davis, described the trial's history:

"The topic [of the 2012 meeting] was: how do we incorporate new biomarkers into clinical development and new therapies for lung cancer? 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. 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. 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."

Next-Generation NCI Trials in Development

"Lung-MAP represents the first of several planned large, genomically-driven treatment trials that will be conducted by NCI's newly formed NCTN," said Jeff Abrams, associate director of NCI Cancer Therapy Evaluation Program. "The restructuring and consolidation of NCI's large trial treatment program, resulting in the formation of the NCTN, is quite timely, as it now can offer an ideal platform for bringing the benefits of more precise molecular diagnostics to cancer patients in communities large and small."

Lung-MAP is one of several new initiatives that NCI plans to launch in 2014 (The Cancer Letter, Feb. 21).

Earlier this year, NCI launched a pilot study to assess whether assigning cancer patients treatment based on the genetic characteristics of their disease can improve outcomes for patients with advanced metastatic solid tumors.

The Molecular Profiling based Assignment of Cancer Therapeutics trial, or M-PACT, was initially launched at NCI. The trial will eventually be opened to researchers in the institute's Early Therapeutics Clinical Trials Network. The plan is to report results by 2017.

The other studies are:

• ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial, which will test an ALK inhibitor and an EGFR inhibitor in patients with selected mutations who have early stage, resectable lung cancer. The 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.

• NCI-MATCH, or Molecular Analysis for Therapy Choice, will sequence tumors in 3,000 patients with advanced cancer whose disease has progressed on standard therapy to determine if 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.

Conversation with The Cancer Letter

Wholley: Lung-MAP is Win-Win For Patients, Science, Industry

(Continued from page 1)

Wholley spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

Paul Goldberg: *Can we start with the financial map of this trial?*

David Wholley: For the first five drugs that are going into the trial, NCI is putting in about $24 million, and companies are putting in about $55 million. This would cover the costs for all of the drugs to complete testing through phase III.

But that's probably not the most useful way to think about how the trial is financed, because the number of patients varies per drug, not all the drugs will complete testing through phase III of course, and at least one of the drugs has additional tests that the company wants to have performed, costs that are outside the base protocol.

The best way to think about this really is that over five years, the infrastructure is designed to screen about 6,250 patients with the goal that 5,000 of them would actually go on trial. It's going to do that at a cost of about $34,000 a patient who is enrolled, which includes the costs to screen patients.

The total cost to screen and treat all of these patients over the five years runs about $169 million. Out of the $34,000 per patient cost, NCI is paying about $9,000 a patient, and another $25,000 is being borne by the companies.

PG: *NCI is paying [enrolling institutions] about $2,000 for CTEP trials, and it can go up to $4,000. So that's pretty good.*

DW: It's a nice win-win for everyone. The cooperative groups welcome the supplemental funds that they can devote to the infrastructure and recruitment costs for the trial. And the companies—at $25,000 a patient—to do phase II and phase III testing, that's a pretty good deal for them. I think the financial arrangements—the economic model—offers a pretty effective model for collaboration between government and the private sector.

It produces economic efficiencies that benefit everybody.

[Note: SWOG, the group that leads the study, will be paying $5,269 per patient accrued to the study, sources said. Institutions will be paid $600 for each of the patients screened for inclusion. Genomic testing on patients by Foundation Medicine would be paid separately A standard NCI sponsored study pays $2,000 to $4,000 per patient. See story on p. 1]

PG: *This may be happening with other indications—colon and breast. Can you talk about that?*

DW: I know that there was an open meeting that Ellen Sigal and Friends of Cancer Research sponsored recently looking at a similar trial design in colon cancer. And that out of that meeting that there are some challenges that they are still working on. I do not know which indication is mostly likely to be next, if any.

PG: *What was your role in putting this trial together?*

DW: FNIH manages the partnership. We ran the run the weekly leadership calls that helped put the trial together, and the Trial Oversight Committee that is guiding the conduct of the trial. We raised the funds from the companies. We managed the contracting and budgeting process. And we brought in a regulatory contract research organization, CCSA, which had helped us out on the I-SPY 2 trial, to help SWOG sort out some of the regulatory issues with this trial.

So, project management, financing, governance, and managing the relationship with NCI and the companies and FDA.

But if there is a hero here, it's Ellen Sigal [chair of Friends of Cancer Research]. She was relentless, and this does not get done without somebody who is actually the champion. And she was it. It would not have happened without her.

PG: *I wonder whether this trial—and its potential—is tantamount to saying that cooperative groups are now more important than ever. Is that what it says?*

DW: I am not the right person to answer that. I do think that Lung-MAP provides a good model for providing supplemental funding to the cooperative groups, so they can do these kinds of trials.

I also know that we designed this trial at a time when the reorganization of cooperative groups was going on. And I give SWOG a lot of credit for putting the kind of attention and effort into this trial that they did, because they had a lot of other things on their plate.

PG: *They also did better than the other groups, perhaps also because of this. But let's get back to the lung cancer trial. So, essentially, what this will do is*

potentially lead to registration trials for all these drugs?

DW: Yes. Every single one of the drugs has the potential to graduate into a phase III registration trial. The way it works is, each drug is tested in a phase II context, and at the end of

Phase II, the company gets to look at the data for their drug and decide if they want to take to Phase III--assuming it hasn't failed for futility or safety reasons. If FDA agrees the drug is appropriate to continue, it can progress to Phase III in the same infrastructure.

PG: *This is interesting, because this is what FDA has been talking about for a very long time. We are going back to ten years ago, more really. This is going back to the AIDS model, where you run a randomized phase II to get an accelerated approval for viral load, and then move to survival and get full approval based on that. And this is doing exactly that, right? Except now it's a multi-drug test.*

DW: The FDA was very involved in the design in the design of Lung-MAP.

PG: *You started by telling me about the first phase for which you have money, and the second phase…*

DW: Actually, it's the first tranche of drugs. For the figures I cited you, were if all five drugs go through phase III, that's what it would cost.

And that's why I don't think those numbers are particularly germane, because we know that probably not all the drugs will go through to phase III.

Some may stop at phase II; some may stop earlier. There is an independent drug selection committee that is meeting constantly, looking at new agents, so we have something ready to go if we have to drop one of the drugs that are in the trial.

So drugs will go in and out of the trial, and some will go all the way to phase III, and some won't. That's why I thought the cost-per-patient number was probably more meaningful than trying to focus on who is paying for what for the first five drugs. Though the ratios [of public to private sector contribution] will be about the same.

PG: *So when we end up with a completely different trial by the time its over, right? Because all of these may fall off the map, and you will end up with an entirely different set of drugs, but in principle, you could also end up with a comparative analysis of all of them right?*

DW: The idea is not to do a head-to-head comparison; all of the drugs are aimed at different targets. The idea is to provide a common infrastructure in which you can efficiently and effectively test multiple drugs at once, using a common platform to screen patients at the front end.

A big part of the problem that the trial is trying to solve is recruitment. Now that we have "precision medicine," and targeted therapies in cancer, it becomes really difficult to recruit patients for an individual clinical trial if an agent is only going to be effective in 5 percent to 20 percent of the population.

So the idea is if you have one trial structure where you can test four drugs aimed at different targets simultaneously, plus a non-match arm, you can help address the recruitment issue. That's one of the main things the trial is designed to do.

PG: *Is the money in hand, or is it committed?*

DW: It's committed in the sense that the companies are all under contract to provide funds. There are payment schedules for each of them; there is a certain amount they have committed upfront so we can launch the trial, and a certain amount dependent on accrual. Both we and SWOG worked hard to design this so that revenues come in time to meet expenses—a pay as you go kind of thing.

PG: *As far as the governance, how much control does NCI have and how much control do the pharmaceutical companies have, or does, how does the structure in a kind of parliamentary way?*

DW: The companies have no more control—if that's the word you want to use—than they would in any other NCI-sponsored trial.

They are not directly involved in the governance of the trial. They do have a seat at the table in terms of hearing about how the trial is going and giving us a feedback on its design. They do that through the FNIH.

But trial oversight is carried out by a committee that includes FDA and NCI—Jeff Abrams, who runs CTEP, sits on it. It includes SWOG, it includes the investigators, and then it has three industry representatives, but they are clean of any conflicts. They are have good drug development experience, but they are not currently affiliated with any of the companies.

So we have got that kind of expertise at the table, but we don't have any specific company getting any information or making any judgments about competitors' drugs.

PG: *Is there anything we've missed?*

DW: It's taken us probably a year to get where we are from when the idea was first broached. And I think that was pretty fast. The companies have been great, and SWOG has worked hard; it took a lot of Sunday night conference calls to get the trial launched. It was a tremendous amount of work.

But people were incredibly motivated to make it happen.

90-Ton Cyclotron Delivered To University of Maryland, Touching Off D.C.-Area Proton Radiation Competition

By Tessa Vellek

BALTIMORE—Constructed in Germany, shipped to the port of Baltimore, and driven through downtown during the night, the 90-ton cyclotron arrived at the University of Maryland's Proton Treatment Center.

A suitably massive crane slowly lowered the plastic-wrapped machine at a rate of 12 inches per hour through the roof to its concrete resting place, completing its work at 3:30 p.m., June 13. Engineers and construction workers swarmed the cyclotron to check whether all parts were appropriately bolted and secured before giving the lines any slack.

"The facility is a monster—it's more concrete than you've ever seen in one place," said Kevin Cullen, director of the University of Maryland Marlene and Stewart Greenebaum Cancer Center. Indeed, over 4,000 truckloads of concrete were brought in for construction of the building that is nearly the size of two football fields.

The $200 million Maryland Proton Treatment Center is also one of three major proton beam facilities being built near the nation's capital. The District of Columbia State Health Planning and Development Agency recently issued certificates of need for a three-room center at Sibley Memorial Hospital of John Hopkins University, as well as a one-room center at MedStar Georgetown University Hospital. (Since the University of Maryland proton beam facility is across the street from the cancer center, the university didn't need to apply for a certificate of need.)

Is there a legitimate need for all that capacity?

Cullen says no. "I'm disappointed that the district government approved two additional proton facilities in D.C. We offered both MedStar and John Hopkins to use this facility for free and have their doctors share the use of this facility for free," Cullen said to The Cancer Letter. "But they both wanted to build their own despite the fact that sharing would save around $160 million. So we're facing a situation where there will be much more capacity than the entire Washington-Baltimore area will use.

"I think to some degree, it's an unnecessary arms race. Everyone wants to say they have the latest and greatest technology," he said. "But this is the perfect case where medical schools and cancer centers should work together. That would be the best thing for patients and it would keep down costs."

The University of Maryland center, for example, will open five treatment rooms to treat 1,900 cancer patients each year, beginning in 2015. The facility was constructed by Advanced Particle Therapy, a private investor.

Cullen and MedStar officials opposed Sibley's pediatric proton radiation facility (The Cancer Letter, Oct. 25, 2013). Cullen testified at hearings where CON was discussed and MedStar submitted a 49-page letter to the SHPDA March 17.

"Sibley Memorial Hospital/John Hopkins University Health System's extravagance needs to be placed in perspective," MedStar said in the letter. "Sibley has overstated the size and geographic expectations for its service area; it has ignored the impact existing and more service providers will have on the area's pediatric oncology service volume."

Sibley defended its application.

"The SHPDA recognizes that the Sibley Pediatric Radiation Oncology Service is composed of a clinical service component with physician and nursing staff dedicated 100 percent of time to pediatrics, and clinical trials and research access component with investigators dedicated 100 percent of time to pediatrics," Clifford Barnes wrote in a letter to the SHPDA March 18.

"These two components with 100 percent dedication to pediatrics are not available at any other institution and are the reason patients, families, and referring physicians who seek the best pediatric care will choose this service at Sibley."

D.C. officials approved the Sibley application April 30.

"The Applicant has demonstrated that pediatric patients needing radiation therapy do not have local access to the specialized oncology services," agency director Amha Selassie wrote in the approval report.

Proton beam treatments can cost more than twice as much as photon radiation to deliver, without proven clinical superiority in terms of safety or efficacy. "Proton therapy represents another tool in our toolbox," said William Regine, Isadore and Fannie Schneider Foxman Chair and Professor of Radiation Oncology at the University of Maryland.

"Most projections are that 20 to 30 percent of cancer patients getting radiation will benefit from proton radiation therapy, which will increase the dose of radiation to the tumor but decrease toxicity."

"There is general agreement that many children

will benefit from proton therapy because their bodies are growing and you can spare radiation to normal growing tissue," Cullen said to The Cancer Letter. "For adults, there is likely to be benefit for some spinal tumors and other central nervous system tumors, but there hasn't been evidence so far that proton therapy has been beneficial for most solid tumors."

Regine said there are between 120 and 160 ongoing clinical trials to test proton therapy's comparative effectiveness. Yet about 85 percent of patients who receive proton therapy have prostate cancer, not pediatric brain tumors.

Part of the University of Maryland's plan for their new proton radiation center is to enroll all proton radiation patients in research protocols to evaluate clinical and cost-benefit effectiveness, said Regine.

To avoid overuse of proton radiation, the University of Maryland is establishing a protocol for identifying patients who would be candidates for proton beam treatment versus those who would benefit equally from photon radiation, Regine said.

340B Drug Discount Program
HRSA Defends Orphan Drug Rule

By Tessa Vellek

The Health Resources and Services Administration said it stands by its interpretation of the Affordable Care Act orphan drug exclusion, despite a recent court ruling that challenged its authority to engage in legislative rulemaking.

The ruling may have implications on another HRSA legislative rule, the "mega-rule," which would clarify many of the fundamental definitions in the controversial 340B Drug Discount Program (The Cancer Letter, June 13).

Federal Judge Rudolph Contreras of the U.S. District Court of the District of Columbia vacated HRSA's attempt to expand the 340B drug discount program to include some uses of orphan drugs May 23.

HRSA released a statement on its website June 18, reaffirming its original interpretation, regardless of the court ruling.

"The Court did not invalidate HRSA's interpretation of the statute," the statement reads. "HHS/HRSA continues to stand by the interpretation described in its published final rule, which allows the 340B covered entities affected by the orphan drug exclusion to purchase orphan drugs at 340B prices when orphan drugs are used for any indication other than treating the rare disease or condition for which the drug received an orphan designation."

In addition, HRSA urged hospitals that take part in the 340B program to follow their posted guidelines for using discounts to purchase orphan drugs for non-orphan indications.

"HRSA…posted the Orphan Drug Designation List and the Orphan Selection File in order to assist the 340B stakeholders with complying with HRSA's policy before the new quarter start July 1," the agency said in a statement to The Cancer Letter.

"In terms of enforcement, covered entities and manufacturers should attempt to work out any issues in good faith. Manufacturers that do not comply with the statute may be subject to termination of their Pharmaceutical Agreement (PPA) and required to refund covered entities if those entities are overcharged.

"HRSA is assessing the impact of the recent U.S. District Court ruling on the proposed 340B Program omnibus rule. HRSA will convey information about next steps as soon as we know a path forward."

PhRMA, the industry group that challenged the HRSA orphan drug rule in court, refuses to comment directly on HRSA's decision to proceed with its previous interpretation.

"PhRMA cannot comment on matters concerning the ongoing litigation," the industry group said. "However, as indicated in our filing with the Court, we think the law is clear that HRSA may not issue interpretive rules implementing the orphan drug exclusion, as HRSA itself acknowledged in proceeding through rulemaking last year."

Safety Net Hospitals for Pharmaceutical Access, a Washington coalition, praised HRSA's decision to continue with its earlier interpretation of the orphan drug program.

"SNHPA is very pleased that the Health Resources and Services Administration is holding fast on its well-reasoned and legally valid interpretation on the use of orphan drugs in the 340B program. HRSA's policy will go far in helping rural and cancer hospitals better serve their vulnerable populations. These savings are absolutely vital to helping providers stay open and supply much-needed services."

Ted Okon, executive director of Community Oncology Alliance, said he hopes HRSA's different interpretation of the court ruling will give way to the mega-rule, which is expected to define who should qualify for 340B discounts.

"It's clear that HHS will not take the court ruling lying down," Okon said to The Cancer Letter. "It's a very interesting play, because they are interpreting a court ruling differently. I hope that now, with that, they will come out with the mega-rule."

In Brief

LoRusso Moves to Yale Center

(Continued from page 1)

Prior to her appointment at Yale, she served in numerous leadership roles at Wayne State University's Barbara Karmanos Cancer Institute, most recently as director of the Phase I Clinical Trials Program and of the Eisenberg Center for Experimental Therapeutics.

LoRusso has served as co-chair of the NCI Cancer Therapy Evaluation Program Investigational Drug Steering Committee. She also served on the scientific committee of the American Association for Cancer Research, and the education and scientific committees of the American Society of Clinical Oncology.

She is a former editor of Investigational New Drugs, is currently on the editorial board for Clinical Cancer Research, and is a reviewer for several journals.

She has garnered numerous awards, including the 1999 Heroes of Breast Cancer Award; 2004 Bennett J. Cohen Educational Leadership Award for Medical Research, 2008 NCI Michaele C. Christian Oncology Development Lectureship and Award; the 2014 Targeted Anticancer Therapies Honorary Award; and will receive the 2014 Michigan State University Distinguished Alumni Award.

CORINNE AUGELLI-SZAFRAN was named director of chemistry at **Southern Research Institute**.

She will be responsible for managing the institute's chemical research initiatives in oncology, infectious diseases and neuroscience.

Most recently, Augelli-Szafran was the director of the Laboratory for Experimental Alzheimer Drugs at Harvard Medical School and Brigham and Women's Hospital in Boston. In that position, she built a fully functional medicinal chemistry and drug discovery laboratory from the ground up which focused on the development of gamma-secretase Notch-sparing inhibitors for the therapeutic indication of Alzheimer's disease.

Augelli-Szafran also held a number of leadership roles at Parke-Davis Pharmaceutical Research and Pfizer Global Research and Development, as co-chair and project leader investigating central nervous system therapeutics with a major emphasis in neurodegeneration mainly in Alzheimer disease therapeutics, but also in the areas of cardiovascular, atherosclerosis, psychotherapeutics and inflammation/pain.

SANDEEP REDDY was named chief medical officer of **Caris Life Sciences**.

Reddy will lead the company's research efforts through the Caris Research Institute and will guide strategy for deployment of precision medicine tools in the clinical setting. He most recently served as senior medical director for Caris.

As head of clinical research activities, Reddy will be the principal investigator for the Caris Registry, a multi-center, observational outcomes database of consenting patients whose tumors underwent multi-technology profiling by Caris Molecular Intelligence.

HIROMITSU OTA received the 2014 Ching Jer Chern Memorial Award from **The Wistar Institute**.

The award is given annually to the Wistar postdoctoral fellow who has published the best scientific paper during the year. Ota works in the laboratory of Kazuko Nishikura.

Ota came to Wistar in 2009, after earning his Ph.D. in biology from Kyushu University, in Japan. His paper, "ADAR1 Forms a Complex with Dicer to Promote MicroRNA Processing and RNA-Induced Gene Silencing" appeared in the April 25, 2013 issue of Cell. Collaborating with Ota were Kazuko Nishikura and Masayuki Sakurai of The Wistar Institute, and Ravi Gupta, a former Wistar postdoctoral fellow.

Ota's research focuses on a newly-identified function of ADAR1 and sheds light on how ADAR1 proteins when combined with Dicer proteins regulate gene expression through enhancement of the production of microRNA, small non-coding RNA which function in post-transcriptional regulation of gene expression. According to the Wistar team, the RNA-editing protein ADAR1, once thought to have a minor role in gene regulation, can alter the expression of numerous human genes.

YESHIVA UNIVERSITY and **Montefiore Health System** agreed to have Montefiore assume greater responsibility for the day-to-day operations and financial management of **Albert Einstein College of Medicine**, with Yeshiva remaining the degree-granting institution.

Through the agreement, it is anticipated that there will be one unified faculty, retaining academic appointments from Yeshiva while being employed by Montefiore, as they continue to teach and mentor Einstein's students and Montefiore residents. Einstein faculty members will continue to collaborate with all areas of Montefiore and their faculty counterparts

in Yeshiva's other schools. Einstein will continue to operate consistently with Yeshiva's historic mission.

The Yeshiva Board of Trustees and Montefiore's Board Leadership endorse the decision to move forward with developing a final agreement, which will be subject to regulatory approval.

DANA-FARBER CANCER INSTITUTE and **Trovagene Inc**. entered into a clinical collaboration to investigate the utility of quantitative urine-based mutation detection and the ability to monitor tumor mutation burden and treatment response over time in metastatic melanoma patients.

Under the agreement, urine samples will be collected from patients with locally advanced or metastatic melanoma known to harbor driver oncogene mutations. A Dana-Farber oncology team, led by Jason Luke, will conduct clinical studies designed to monitor oncogene mutations in study subjects based on urinary cell-free DNA as an analytical specimen.

Studies will be designed to collect data regarding the clinical status of patients, treatment effect, and long-term outcomes of therapy using Trovagene's non-invasive molecular diagnostic technology.

ELI LILLY AND COMPANY and **Qiagen N.V.** announced a plan to co-develop universal and modular assay panels for the simultaneous analysis of DNA and RNA biomarkers targeting multiple cellular pathways involved in common cancer types.

The agreement includes the development of tests that will be based on Qiagen's multi-modal, multi-analyte Modaplex analysis platform, which can process multiple sample types and biomarkers in a single test.

The collaboration is the fourth project in the two companies' partnership. Qiagen's therascreenA KRAS RGQ PCR Kit was approved in 2012 by the FDA as a companion diagnostic to detect KRAS gene mutations in metastatic colorectal cancer patients. The test indicates which patients would benefit from a tailored oncology therapy marketed by Lilly and Bristol-Myers Squibb.

In 2011, QIAGEN and Lilly partnered to develop a companion diagnostic that evaluates a gene mutation which plays a role in some blood cancers. In 2013, QIAGEN announced a third project, building on a master collaboration agreement, to create a companion diagnostic to guide use of an undisclosed Lilly oncology compound.

BAYER PHARMA AG and **arGEN-X** announced a collaboration to develop therapeutic antibodies.

With this collaboration, arGEN-X will apply its SIMPLE Antibody technology to multiple targets submitted by Bayer. The parties will work together to validate human antibody leads in disease-relevant models, with Bayer being responsible for further preclinical and clinical development and commercialization of therapeutic antibody products.

Bayer will pay arGEN-X an upfront technology access fee, research support and technical success-based milestones. Bayer will also pay clinical, regulatory and product sales-based milestones as antibody programs progress through clinical development and registration.