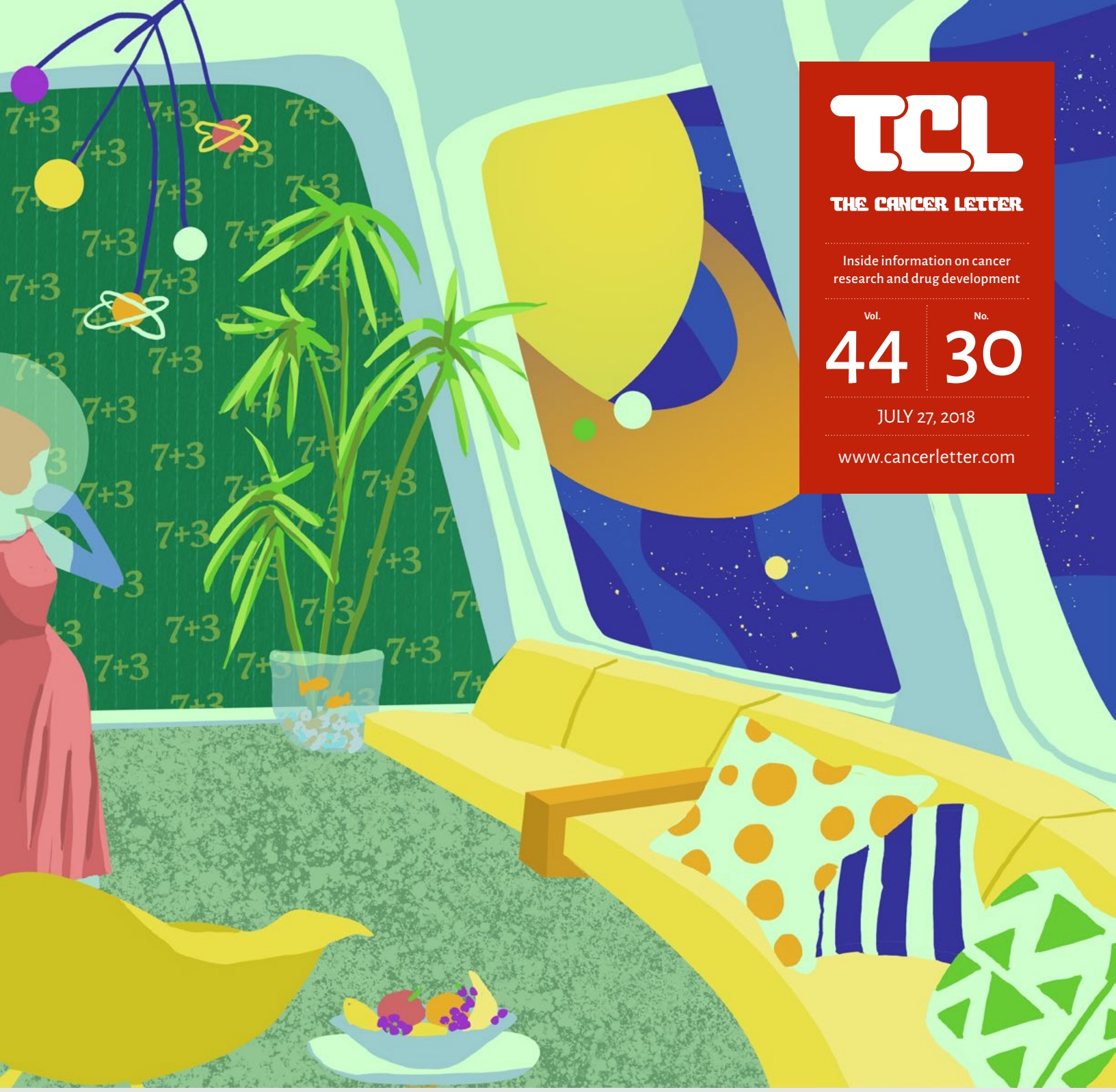

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NEW DRUGS AND NEW IDEAS ARE TRANSFORMING AML

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THE CLINICAL CANCER LETTER

NEW DRUGS AND NEW IDEAS ARE TRANSFORMING AML

By Paul Goldberg

An actuary might note that if you were in residency at the time when the 7+3 protocol of cytarabine and daunorubicin was first used to treat acute myelogenous leukemia, chances are you are considering retirement just about now.

Sadly, not very much has happened in AML through the bulk of your career.

This has been changing over the past year. AML is not alone. In recent years, large numbers of new drugs have gone through FDA. How are these drugs changing oncology? Most physicians can answer this question within their own subspecialty, but keeping track of changes in another field, even one that is closely related, is hard to do.

In this issue, The Cancer Letter presents a case study in AML that examines change as it occurs—focusing on the roles of FDA, The Leukemia & Lymphoma Society, industry, and academic oncologists have played in developing new therapies.

Since last April, FDA has approved five agents for the treatment of frontline and relapsed AML, with the most recent of these approvals announced last week.

More drugs are in the pipeline and more applications are in the hopper at FDA.

Also, a clinical trial called "Beat AML Master Trial," sponsored by LLS, is trying to live up to its name by using next-generation sequencing to match patients with treatments—and, possibly, to produce data that FDA would deem sufficiently convincing to support application for approval.

Insiders predict that soon, you will likely see that the entity that now goes under the name AML is made up of a cluster of distinct diseases that will have separate treatments.

"There are many. I don't have the exact number of clinical trials and targets, but there are probably at least 15 and probably more subtypes of AML. Some will be able to be treated the same way, but many will have different paths that ultimately lead to a targeted therapy," said John Byrd, one of the principals of Beat AML, Distinguished University Professor, the D. Warren Brown Professor of Leukemia Research at The Ohio State University, a member of the NCI Leukemia Steering Committee, chair of the Leukemia and Correlative Science Committee within the Alliance for Clinical Trials in Oncology.

"For some, targeted therapy may not be the path; it may be immunothera-

py," Byrd said. "But I think, really, what's going to limit us in our exploitation of the science of AML now is the ability to get sufficient patients on clinical trials to ultimately isolate these small groups of patients that respond really well to targeted therapy."

A conversation with Byrd appears on page 9.

Since changes in the field have just begun, it's too early to measure the impact these new therapies are having on what's defined as CML. But efficacy is there, and it's dramatic in some subsets of patients. In the case of Tibsovo, for example, complete remission plus complete remission with partial hematological recovery was at 32.8 percent.

Indeed, the agency has been at the table where key strategic decisions at AML are made, and it's thinking creatively. In the case of the most recent approval—Tibsovo (ivosidenib), sponsored by Agios Pharmaceuticals Inc.—FDA accepted data from a single-arm trial to give the agent a full approval.

The agency decided that reduction of transfusions of blood or platelets due to AML constituted a patient benefit. A year ago, the agency granted full approval of enasidenib (IDHIFA), co-sponsored by Agios and Celgene Corp., based on similar endpoints.

Tibsovo is approved for relapsed or refractory AML associated with the isocitrate-dehydrogenase-1 (IDH1) mutation, and IDHIFA is associated with an isocitrate dehydrogenase-2 (IDH2) mutation. Both drugs have to be used with FDA-approved tests.

"I think it speaks to where the FDA is, but I think it also speaks to the compelling data we've been able to demonstrate," David Schenkein, CEO of Agios, said to The Cancer Letter. "The primary endpoint for both our studies, which led to the two approvals was the percentage of patients who have a complete remission. And in this setting, one would expect the complete remission rate with chemotherapy to be about 10 percent.

"And so, we're seeing with Tibsovo a little over 33 percent complete remissions. So, that's the primary endpoint. But the secondary endpoint, because of the way the drug works, such a novel way of differentiating or repairing the leukemic cell, led to these transfusion benefits," Schenkein said.

"The FDA has historically always believed that a reduction in the need of transfusions is a direct measure of clinical benefit. So, the combination of the compelling results, a complete remission rate, together with the transfusion improvement data, and safety profile, is what led to the full approvals, which is unusual, based on a non-randomized trial."

A conversation with Schenkein appears on page 16.

Albert Deisseroth, a medical officer and associate director of the FDA Division of Hematology Products, said the pace of development of AML drugs reminds him of the recent revolution in the treatment of lung cancer.

"It's a victory of genetics and structural biology that enables chemists to develop drugs that could suppress signals in the leukemic cells that are driving them out of control," Deisseroth said to The Cancer Letter.

"This seems to be following a pattern that we witnessed in the area of lung cancer, where the discovery of genetic changes led to targeted therapy that has clearly transformed how we think of lung cancer and created opportunities for new types of therapy for patients with lung cancer," Deisseroth said. "I am seeing the same process and pattern emerging in the area of AML."

"It's a victory of genetics and structural biology that enables chemists to develop drugs that could suppress signals in the leukemic cells that are driving them out of control."

– Albert Deisseroth

AML is not a huge indication—about 20,000 new cases a year in the U.S. When you split this into 15 or more subsets, some of these subsets will be very small. Will there be enough of an incentive for drug companies to develop compounds for such populations?

"When I started my career, drug companies were interested in developing drugs for big, common diseases," said Ruben Mesa, a member of the LLS board and director of the Mays Cancer Center, the newly named home to the UT Health San Antonio MD Anderson Cancer Center. "We continue to have an evolving benefit that really started with imatinib, where even in small populations, if you have a targeted therapy and it's efficacious, the economics are viable for biotech companies to develop therapies. In the past, you'd have said a subset of relapsed/refractory AML with a particular definition is an orphan disease."

Pharmaceutical Participation

AML Subtype	Drug	Company
Tet2/WTI	CD33 + Aza	BI
IDH2 Mutation	Enasidenib	Celgene
MLL	Entospletinib (Syk inhibitor)	Gilead
CBF	Samalizumab (CD200 Ab) + induction	Alexion
P53 mutation	Entospletinib (Syk inhibitor) + Decitabine	Gilead
Complex Karotype	Entospletinib (Syk inhibitor) + Decitabine	Gilead
P53 mutation	Pevonedistat (Nedd8 inhibitor) + Aza	Takeda
Marker Negative	CD33 + Aza	BI
NPM1 w FLT3 WT	Entospletinib (Syk inhibitor)	Gilead
FLT3 mutation	Gilteritinib	Astellas
IDH1 Mutation	Ivosidenib + Aza	Agios

Source: Leukemia & Lymphoma Society

Here is the list of recently approved AML therapies:

- The first new AML therapy approved in decades is **midostaurin (Rydapt)**, on April 28, 2017. This marked the first significant advance for AML patients in 40 years. The drug, sponsored by Novartis, is approved in combination with chemotherapy for a subset of patients with a mutation called FLT3. Midostaurin is not part of LLS's Beat AML Master Trial; the study includes a different FLT3 inhibitor.
- Celgene and Agios's **enasidenib (IDHIFA)** was approved on Aug. 1, 2017, for AML patients with the IDH2 mutation, which impacts 12 percent of AML patients. This therapy is part of the Beat AML trial; the FDA approval was for relapsed and refractory AML patients; it is being studied as a first-line treatment in the trial.
- **CPX-351 (Vyxeos)**, sponsored by Jazz Pharmaceuticals, is a reformulation of two standard chemotherapies that optimizes the ratio and delivery of the drugs. It was approved Aug. 3, 2017 for patients with secondary AML, a high-risk subtype that has a very poor prognosis and occurs in 10-20 percent of AML patients. Vyxeos was originally developed by Celator Pharmaceuticals, which was acquired by Jazz in 2016.
- Pfizer's **gemtuzumab ozogamicin (Mylotarg)**, for treatment of adults with newly diagnosed AML both in combination with chemotherapy and on its own, and for the treatment of patients aged two years and older who have experienced a relapse or who have not responded to initial treatment. Mylotarg is approved for patients whose AML cells express a specific protein, CD33, commonly found on the surface of the cancer cells. The drug was approved on Sept. 1, 2017.
- **Ivosidenib (Tibsovo)**, sponsored by Agios Pharmaceuticals, was approved on July 20 for AML patients who have relapsed or do not respond to standard chemotherapy and have the IDH1 genetic marker, which is found in approximately six to 10 percent of the 20,000 people in the U.S. diagnosed with AML each year.

> We continue to have an evolving benefit that really started with imatinib, where even in small populations, if you have a targeted therapy and it's efficacious, the economics are viable for biotech companies to develop therapies.
>
> *– Ruben Mesa*

LLS holds the IND for the master protocol trial, which it operates through a separate entity, Beat AML LLC. The corporation employs a contract research organization, pays Foundation Medicine for sequencing, hires other contractors, and distributes money to the academic centers that accrue patients to the trial.

The trial will end up costing at least $55 million, which includes funding from pharmaceutical companies and private donors, said Amy Burd, vice president for research strategy at LLS. The trial is part of a broader series of ALS programs at LLS, which will commit a total of $125 million to this area of research.

Decisions that involve the trial are made by a group of four scientists: Burd, Byrd, Brian Druker, director of Knight Cancer Institute at Oregon Health & Science University and JELDWEN Chair of Leukemia Research, and Ross Levine, the Laurence Joseph Dineen Chair in Leukemia Research and director of the Center for Hematologic Malignancies at Memorial Sloan Kettering Cancer Center.

With just a dozen clinical trial sites, the trial is more manageable than an NCI-sponsored study that might have a hundred sites or more. This trial has smaller groups as well, but is full cooperative with the NCI effort, and hopefully will inform ideal agents to test in larger patient groups. Both byrd and Levine actively contribute to both the NCi and LLS effort.

"The difference here is that the decision-making is more nimble, probably, than the cooperative groups," Burd said to The Cancer Letter. That acknowledged, Burd recognizes that the study may have to expand to about 20 sites, and arms will have to be added for researchers to attempt to define combinations of novel drugs.

"Our real push at the moment would be to go to combination therapies," Burd said. "We certainly believe that it's going to take a combination of drugs to have the durable, curative responses that we are looking for. That's the next step for us."

The following cancer centers are enrolling patients in The Leukemia & Lymphoma Society's Beat AML study:

- The Ohio State University Comprehensive Cancer Center
- Memorial Sloan Kettering Cancer Center
- Oregon Health & Science University Knight Cancer Institute
- Harold C. Simmons Comprehensive Cancer Center at University of Texas Southwestern
- University of Chicago Comprehensive Cancer Center
- University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center
- Huntsman Cancer Institute, University of Utah
- Mayo Clinic Cancer Center (Rochester, MN)
- Mayo Clinic Cancer Center (Jacksonville, FL)
- Mayo Clinic Cancer Center (Phoenix, AZ)
- UCLA Health
- Winship Cancer Institute, Emory University

Since Beat AML consists of single-arm studies, there is no real stopping rule for the entire enterprise, and the number of arms that can be added is limit-

ed only by scientific curiosity and the sponsors' willingness to play.

"One of the principles we had across all the stakeholders was that no one was in this for the credit," Burd said. "We needed to put our egos aside and work together, and that would be the only way we could instill change."

Unlike many studies by cooperative groups, Beat AML is gearing to produce data that may support registration.

"We start out with a small number of patients to make early go/no-go decisions. If you achieve the CR rate that you expect, then we have a discussion with FDA to expand out the study to something that could be registrational without doing a randomized study," Burd said. "We are looking for really large signals. We are not looking for something that's incremental. But it's something where we have to weave in a synthetic control arm for the natural history of the disease to determine whether we can get to registration without doing a randomized trial."

The planning for Beat AML started in June 2014, when LLS noted that it was devoting about 26 percent of its research budget to the disease. "This prompted me and some of the other scientists at the department to take a pause and question what was really happening in the field and—more importantly—how we can better prioritize our dollars to have a real impact, especially considering that the standard of care at that point hadn't changed in 40 years," Burd said.

Burd put together a meeting of key researchers, including Levine, Druker and Byrd. "This was where the idea for the trial was born," she said.

"We then had a meeting with FDA in the fall of 2014, and continued to have these discussions on how the field was challenged and how we could improve the outcome for patients with AML and get drugs approved."

Next, LLS put together a larger gathering, about 30 people, at the 2014 annual meeting of the American Society of Hematology. That meeting sparked the eventual discussions that produced the concept for a trial that would drive innovation in AML. FDA, too, gave a nod to the idea.

At the 2015 annual meeting of the American Society of Clinical Oncology, the trial's designers met with representatives of 27 pharma and biotech firms, and soon thereafter filed an IND. In July 2016, the society received a safe-to-proceed letter from FDA and the study began in November 2016.

As the study was being designed, LLS and the academics involved consulted NCI and FDA. At the time, NCI was just starting to climb out of a long financial crunch.

Early on, a decision was made that if NCI were to start some version of an AML trial, LLS would abort its plans for Beat AML.

"Our goal was all about the patients, it's about finding the drugs and helping the patients," Burd said.

> One of the principles we had across all the stakeholders was that no one was in this for the credit. We needed to put our egos aside and work together, and that would be the only way we could instill change.
>
> *– Amy Burd*

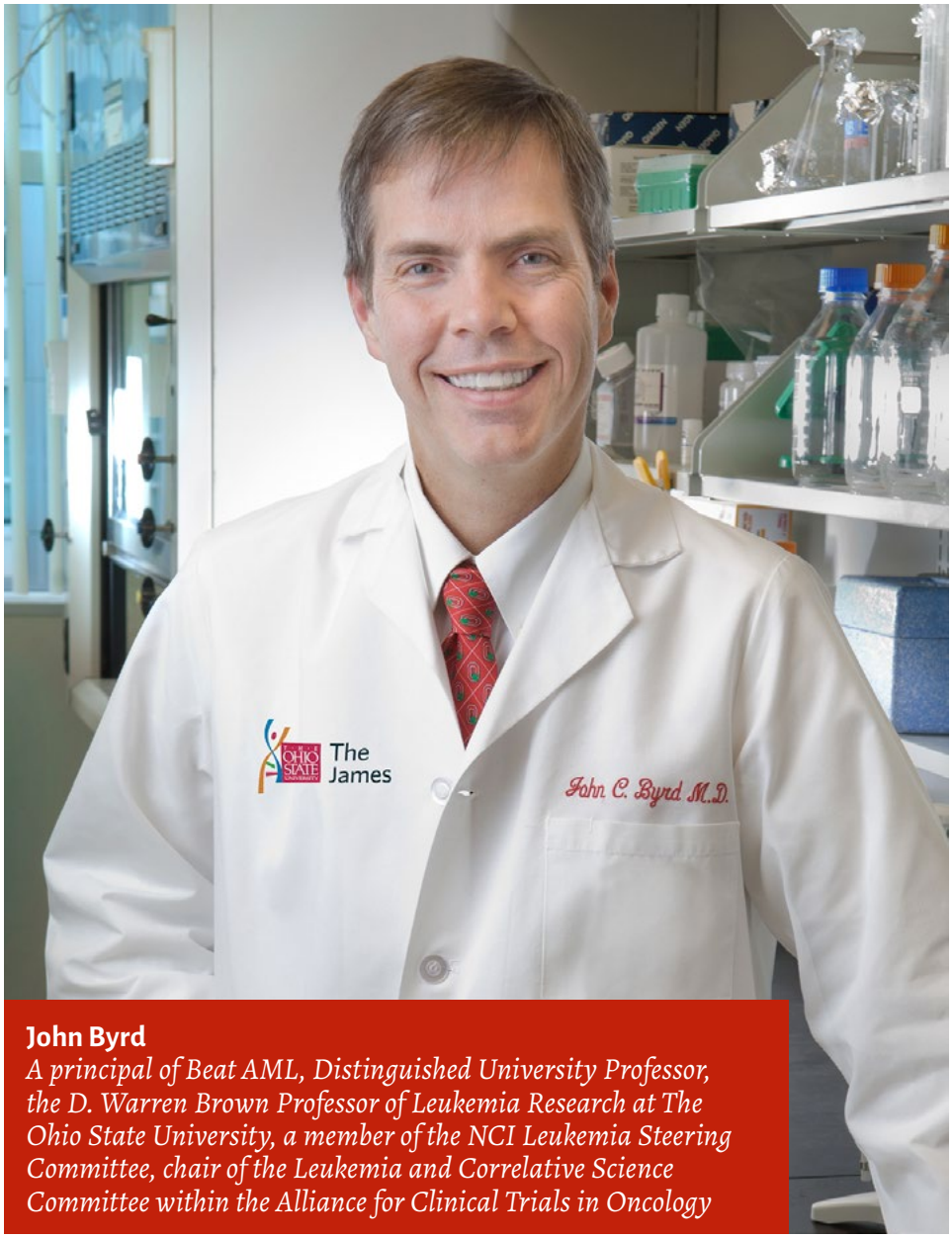
Q & A

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

CONVERSATION WITH THE CANCER LETTER

OSU's Byrd: "It's becoming necessary to consult with an expert, because it is complicated, and things are moving"

> A big part of the initial study was, can we actually assign genomic cytogenetic, biochemical therapy within seven days, because that's probably the time period you need to do it. We move much quicker to assigning therapy.



John Byrd
A principal of Beat AML, Distinguished University Professor, the D. Warren Brown Professor of Leukemia Research at The Ohio State University, a member of the NCI Leukemia Steering Committee, chair of the Leukemia and Correlative Science Committee within the Alliance for Clinical Trials in Oncology

As the landscape in acute myelogenous leukemia changes, consultations with top-tier experts have become a necessity, said John Byrd, the principal investigator of Beat AML, Distinguished University Professor, the D. Warren Brown Professor of Leukemia Research at The Ohio State University, a member of the NCI Leukemia Steering Committee, chair of the Leukemia and Correlative Science Committee within the Alliance for Clinical Trials in Oncology.

"Even as somebody who does this every day, physicians really have to be on their feet with emerging data that's coming forth," Byrd said. "But I think it's becoming more and more necessary, as treatment decisions are made, to consult with an expert who really deals in that disease, because it is complicated, and things are moving, particularly when you get beyond first-line therapy. It's a team effort.

"Local hospitals and hematologists in the community might treat this disease, particularly in the elderly, but it's probably best getting help from somebody that focuses in AML, say, on a daily basis."

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

Paul Goldberg: AML used to be a quiet little corner of medicine. What happened?

John Byrd: I know. It's amazing—after probably 40 years of the same therapy being used in this disease.

It's a pretty common theme—people in their 50s and 60s saying, "Well, I treat AML the same way that I did when I was a fellow."

We've seen all of the investment that Congress and the taxpayers and philanthropic groups, such as The Leukemia & Lymphoma Society, have invested in basic science research of leukemia, to understand its pathogenesis.

That has led to a disease that was treated at one time just with one therapy, 7+3 chemotherapy and transplant, to one where we have a burgeoning number of targeted therapies—and where we recognize it's probably not one disease, but 12 or 15 diseases.

We're talking about a lot of drugs in the pipeline, and a lot of drugs approved—three in the frontline, two in refractory. How many are in the pipeline?

JB: There are many. I don't have the exact number of clinical trials and targets, but as I said, Paul, there are probably at least 15 and probably more subtypes of AML.

Some will be able to be treated the same way, but many will have different paths that ultimately lead to a targeted therapy.

For some, targeted therapy may not be the path; it may be immunotherapy. But I think, really, what's going to limit us in our exploitation of the science of AML now is the ability to get sufficient patients on clinical trials to ultimately isolate these small groups of patients, such as the one with the IDH1 and IDH2 mutations that respond really well to targeted therapy.

Do physicians now know which drug to use when? Is that a problem yet?

JB: Yeah. It's very similar to CML. I also work in CML, and the AML field is becoming very similar in that the field is moving so quickly, and you have a whole set of physicians who trained before the genomic era.

And even as somebody who does this every day, physicians really have to be on their feet with emerging data that's coming forth. In general, I would say yes, because the U.S. breeds a very confident group of hematologists and oncologists that keep up with the field.

But I think it's becoming more and more necessary, as treatment decisions are made, to consult with an expert who really deals in that disease, because it is complicated, and things are moving, particularly when you get beyond first-line therapy. It's a team effort.

Local hospitals and hematologists in the community might treat this disease, particularly in the elderly, but it's probably best getting help from somebody that focuses in AML, say, on a daily basis.

So, one shouldn't go to a garden variety oncologist with AML; one should go to someone like you?

JB: Right. Or to a specialist who works predominately in leukemia.

What's the rationale and the ultimate goal of your trial, Beat AML? In terms of design, how is it distinct from, say, NCI-MATCH?

JB: The Beat AML study is distinct from MATCH in a couple of ways. It is an um-

brella study that encompasses untreated AML right now over the age of 60, although we're broadening to under the age of 60 to select genetic groups, and it builds upon several things that are different than MATCH.

AML is different than most solid tumors. With the majority of solid tumors you can wait a couple weeks to get your results back to decide on therapy. AML tends to move quicker.

A big part of the initial study was, can we actually assign genomic cytogenetic, biochemical therapy within seven days, because that's probably the time period you need to do it. We move much quicker to assigning therapy.

Say, we're really focusing on the hypothesis that AML starts with, a trunk lesion or a primary mutation, and so we're going after the dominant clone with our targeted therapy.

Another difference between our study and MATCH is that it encompasses all patients. We have our targeted arms, but then patients who are marker-negative, in other words, who don't have a genomic marker that we target, still include an arm for that group.

We call it the marker-negative group. It's not exactly marker-negative, but it has a marker that we don't have an agent for right now. Everybody that goes on our study knows that they are going to get access to a new and exciting approach.

The other thing that we are doing in our trial—and we are moving toward right now—is doing novel-novel combinations, because AML and most cancers are not going to be cured with one therapy. It's going to be a targeted approach.

We are moving to giving several targeted drugs together, to build upon synergy and really try to get away from chemotherapy when it's appropriate—when chemotherapy isn't curative.

How many arms does Beat AML have now?

JB: There are 11 treatment groups, and we have seven pharmaceutical sponsors. Since the study opened in November of 2016, and as of yesterday, I believe we're up to 332 patients enrolled.

The study has gone well thus far. It's a multi-center study, which with one presupposition, and the presup that has allowed to move along the quickest is that in our initial bylaws, the principles we put together, the Number One bylaw is: If you want to participate you can't care about credit.

It's been an effort of a lot of centers, of The Leukemia & Lymphoma Society, a lot of different organizations rolling up their sleeves, doing the work, and moving it along quickly.

It's run like a pharmaceutical company trial, not a cooperative group study, in the sense that we have monitoring. We have a CRO—all the data is being collected with the intent that if a study is positive, it can be filed as an NDA.

It's looking for big differences. We aren't looking for small differences, we're looking for big responses in these small groups, with the decision to move forward with therapy or not.

So, this could be, in principle, a whole series of registration trials, right? Eventually?

JB: That's correct.

But just to delineate that the most recent approval, the Agios [IDH1] drug; do you have it in one of the arms?

JB: Yes, we do.

But their registration study was not your study?

JB: No, that registration study was done in relapsed disease. And, Paul, as I said, our study only is looking at upfront disease, and in patients who have not had prior therapy.

We do have an arm where we're testing new combinations, where we need to look at the safety before moving forward to untreated patients, where they could be previously treated.

But really, as a team we believe that targeted therapy will probably have a modest effect—with very, very good drugs—in the relapsed setting.

Because in most cases of AML, by the time patients have relapsed, particularly when they've received chemotherapy, it's very likely that you have seven or eight diseases.

The clonal evolution as the disease moves on makes it, probably, many diseases within a patient, and targeted therapy there is not going to work.

But with the IDH1 and IDH2—they're moving towards frontline, does Beat AML play a role in that, or will it? Does it need to?

JB: Yes, Beat AML has a study with both the IDH1 and IDH2 inhibitor. The IDH2 inhibitor that Celgene is marketing was one of our first studies, and has accrued well.

And we have a trial with the [Agios] IDH1 inhibitor that was just approved in the upfront setting. Our study is different from a typical registration study. For instance, the study that recently got midostaurin approved had to enroll hundreds of patients and went over the span of eight years.

Our study is single-arm, and we are looking either at monotherapy or combinations of these targeted drugs. The big difference is, hopefully, the FDA and regulatory agencies where you see big differences in safety data, will consider these for upfront registration.

Why did you go with LLS sponsorship as opposed to NCI?

JB: The full scope of the Beat AML Master Trial will be at least $55 million, which includes funding from pharmaceutical companies and private donors.

And that's come from organizations like The Harry F. Mangurian Foundation, that have contributed dollars, from patient donors, from others, including the pharmaceutical companies and institutions that are participating.

This is run similar to the cost of a pharmaceutical company, but they very much are partners in trying to help underwrite a cost, but the cost is considerably more [than a cooperative group trial], because you're doing it for registration intent, which is somewhat different than the NCI studies.

So, that's sort of how the funding is handled.

While I'm a professor of Ohio State, I'm also the chief medical officer of the study, and I work with the Leukemia & Lymphoma Society.

The society is an honest broker. They can bring together the different companies, the FDA, the institutions, and really we're a patient-focused organization.

And while the NCI has supported a lot of the research, we interact with the NCI, and hopefully our study is going to inform some of the NCI studies. By doing it this way, the opportunity just arose to move this very quickly.

And that's an incredibly important part of drug development, as you know, Paul—to be able to move quickly. We're a very nimble team. We're using a lot of novel technologies, such as Protocol First, myClin, and other platforms that minimizes the need for detailed on-site monitoring. And by doing that, and being very nimble, as you would be with any patient-focused organization is going to be, we're able to do it at less cost and quicker.

That's fascinating. But a massive amount of planning must have gone into designing this thing. Who was at the table? How did you put it all together?

JB: It started in 2014, when The Leukemia & Lymphoma Society looked at what they were investing their research dollars in, and they saw that about a third or more of their research budget was going to AML, yet that was the only disease where in the past decade their research dollars had not led to something being approved.

They met with the FDA to talk about the concept of this, and there was discussion that the NCI was doing this at the same time. And they brought together experts in the fall of that year.

Brian Druker [director, Knight Cancer Institute at Oregon Health & Science University and JELD-WEN Chair of Leukemia Research], who led the development of Gleevec, was there. I was there as somebody that has been very involved in ibrutinib, and acalabrutinib, and Ross Levine had done a lot of the work with Jakafi in myeloproliferative disorders.

They had people that had done drug development successfully and other diseases, as well as AML.

There were two sessions including a session at ASH. After this ASH session—Brian Druker called me, and we came to the conclusion that, well, let's get a small group of us together—and we agreed.

I do drug development, and Brian is a big-thinker and a big leader, and also is a kinase person. And we decided to bring Ross Levine [Laurence Joseph Dineen Chair in Leukemia Research; director, MSK Center for Hematologic Malignancies] who did genomics, and we started having weekly telephone conferences, often on Sunday, because that's when our schedules would allow.

We put together this document that we talked about and presented it to The Leukemia & Lymphoma Society. Amy Burd [LLS vice president, research strategy] started getting on our calls. And it really sort of started off that way, and we worked through a document, a vision statement, and went and met with the FDA. And the FDA loved the concept of this type of a trial.

At that point, you asked about the NCI, they asked us, well … the NCI has been talking about that, and we all decided at that point that if we got to the end, and we were ready to start our study

and the NCI had a trial like this going, because they were talking about it, that we would stop ours, because we didn't want something to be redundant.

In the spring of that year, after meeting with the FDA, we identified a genomic sequencing organization that ended up being Foundation Medicine, and met at ASCO with about 40 companies, and presented the idea to the companies, and several of them were interested.

After that, we identified a CRO that would partner with us, and some of these model technologies that I was mentioning, such as Protocol First. And we moved forward to write the trial.

The IND opened in the late summer of 2016.

Because we're treating patients with AML in the untreated setting, we had to really nail down our diagnostic-- that delayed us a little bit. This trial actually opened in November of 2016.

It's phenomenal how it started. If you'd have asked me in November of 2016 if we'd be at this point on, say July 25, 2018, with well over 300 patients on study and things really cranking, I would have said, "I don't know."

But again, coming back to what we said, everything has moved in this trial quickly, because of that presup that if you want to be part of this trial, you can't care about credit.

The only people that can care about credit, we've decided, are the junior investigators that are leading the different arms of the trials, because they need to get publications for when the study's done for their promotion.

That's sort of a neat thing about this study as well: the studies are led by junior to mid-level investigators at the different sites. We're facilitating clinical investigations for these individuals. So, it's been a lot of fun.

What's really interesting is there are so many pieces of it that it's easy to lose sight of something gigantic, which is a new endpoint that the FDA is recognizing here for full approval. They've just approved two drugs based on single arm trials, and they gave full approval based on reducing the need for transfusions. Is it something that they designed in cooperation with you?

JB: I think the FDA has been a great partner in our trial. And for our trial we've had incredible dialog and input from them. But I think Brian Druker's my hero, but also, I would say Rick Pazdur [director of the FDA Oncology Center of Excellence] is one of my big heroes.

I think that the FDA has really adopted an approach with new medicines, that if it really makes a big difference for patients … And the transfusion endpoint—that is a big difference, and they look at everything.

Still, if you have a drug that causes a lot of side effects, the answer to that would probably be no.

This may sound disrespectful to statisticians, but I think drugs where you can really see clinical benefits where there's an acceptable safety, that you don't really need a statistician even to tell that you have a winner are what we are all looking for.

I'm sure that in our study, if we get to the point of talking to them about a registration, their comments would be, "Well, we want to see the data."

With Agios and other companies, they've shown that they're very open to new ideas for medicines that are going to help patients. It's refreshing to see that this approach is moving to AML.

We saw the same thing with ibrutinib, where they approved ibrutinib in CLL where just on a phase II study. By approving it on a single-arm before the phase III studies were done, probably thousands of patients are alive today that wouldn't have been alive.

Again, the medical officers in the FDA are physicians, and they're really looking at the data in an open way. It's very facilitatory to patients.

I don't know of another area in medicine where a single trial might actually inform the entire future development; has that ever happened before?

JB: Lung cancer is probably the other disease. But, as I said before, I think what's sort of unique as AML is not common; there are only 20,000 cases a year. I think that this study, Beat AML, is the first umbrella study run by a charitable organization, a patient-focused organization.

What will the world look like five years from now in AML?

JB: All of us hope there are a good number of young patients that are going to still be getting 7+3 chemotherapy maybe, with one of the new drugs—because that cures them.

In the patients over the age of 60 and a small subset of the younger patients, Paul, what I hope that five years from now, that we will have moved away from chemotherapy and be using targeted or non-chemotherapy drugs to get AML patients into remission.

> Hopefully, when chemotherapy is not essential to cure, we will be moving away from that to a more precision medicine-based treatment approach.

And then a neat part of our trial is that all of us acknowledge that allogeneic stem-cell transplant is still curative for these patients. So, when we have an older patient, there's nothing more gratifying than being able to get them into complete remission with their targeted therapy.

With an outpatient, in some cases, it's just a pill, and not being in the hospital for months at a time with toxicities from chemotherapy. And then, getting them onto transplant, if they're a candidate for that.

And a hot area that we're really excited about, too, is after patients get this, is if they have still a small degree of evidence of their disease after transplant, is continuing targeted therapy after transplant.

And so, that's where I see things going. Hopefully, when chemotherapy is not essential to cure, we will be moving away from that to a more precision medicine-based treatment approach.

Is there anything we've missed? Anything I didn't ask that I should have?

JB: No. I think we've covered things. The only thing I would say is that Dr. Lou DeGennaro who is the CEO of The Leukemia & Lymphoma Society, and their board, the leadership at the founding institutions (The Ohio State University, Memorial Sloan Kettering, Oregon Health Sciences University) and everybody, how they stuck out their neck to do this, and believe in this approach.

I think that really set us up for a chance that we'll get to impact AML in a different way. I know from the patients, the investigators, everybody that's been involved in that, we're just really appreciative of that.

Q & A

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

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CONVERSATION WITH THE CANCER LETTER

Agios's Schenkein: "It's not one disease. Just like lung cancer's not one disease"

David Schenkein
CEO, Agios Pharmaceuticals

> In this setting, one would expect the complete remission rate with chemotherapy to be about 10 percent. We're seeing with Tibsovo a little over 33 percent complete remissions.

Agios Pharmaceuticals Inc., the sponsor of two drugs that may change the outcomes for a subset of acute myelogenous leukemia patients, is focused on more than AML.

The company is pursuing research on isocitrate dehydrogenase mutations, which are present in multiple cancers, said David Schenkein, CEO of Agios.

"We started with AML, because it's easy to measure activity in the blood, and you get an answer much more quickly than you can in solid tumors," Schenkein said. "So, we're not an AML company. We're a precision medicine drug development company with a focus in metabolism. And that's how we got into AML."

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

Paul Goldberg: You have established your track record at Genentech. What was it that got you interested in AML?

David Schenkein: My first exposure to the industry side of drug development was actually running the oncology development group at Millennium, and we developed one of the first new drugs for multiple myeloma called Velcade back in 2003. It was approved.

And then I moved to Genentech early 2006. I think what I learned at Genentech is the power of precision medicine. I'm a hematologist, so I've been taking care of AML patients for over 30 years.

But when we started Agios, and even today, we didn't set out to make new drugs for AML. We set out to make important novel precision medicine drugs, and we would let the science take us to whatever cancer it made sense.

And again, Agios was started based on the concept of dysregulated metabolism. And so, when we discovered the IDH mutation's function, we saw that the mutation occurred in multiple cancers—AML and several solid tumors.

We are pursuing all of them. We started with AML, because it's easy to measure activity in the blood, and you get an answer much more quickly than you can in solid tumors.

So, we're not an AML company. We're a precision medicine drug development company with a focus in metabolism. And that's how we got into AML.

People in the field are talking about a revolution in AML. What I'm seeing is not so much a revolution as a strategic approach to the disease. I think it may be analogous to lung cancer, but not much else. Do you think the AML situation is unique in oncology right now?

DS: I don't think it's a question of unique. We went through close to 40 years in AML without any novel new ways of treating patients other than chemotherapy, where the other blood cancers, multiple myeloma, CLL, lymphoma have seen a variety of different and novel drugs, most of them precision targeted drugs, but some just totally novel ways of treating the disease.

It's a question of the biology getting to the point where we understand now that AML, like many other cancers, is a very heterogeneous disease. No two AMLs are alike. And understanding the molecular driver of the disease allows one to come up with medicines that are precisely targeting that driver.

The 20 percent of AML patients who carry the IDH mutation, either IDH2 or IDH1 are very different biologically than the patients who carry a FLT3 mutation or another different type of mutation.

I do think there is revolutionary change in that, like in other blood cancers, we're moving away from nonspecific cytotoxic chemotherapy to much safer and more effective precision medicines.

Now, we're just at the beginning. 2017 saw four drug approvals in AML, two of them targeted. One was our first one, IDHIFA, an IDH2 inhibitor, and the other was Rydapt, from Novartis, which is a FLT3 inhibitor.

Now, we have our IDH1 inhibitor, Tibsovo approved last week. So, it's beginning, and I think over the next five years, you are going to see change in the way we treat patients with AML.

Well, let's talk about FDA for a minute. What's their role in advancing this? Are they present at all the right meetings?

DS: They are. Rick Pazdur [director of the FDA Oncology Center of Excellence] and the oncology group—and that's the group I work with the most--have really been enlightened for a long time.

That group has been leading the charge on advancing medicines as quickly as possible that appear to be safe and effective. So, no roadblocks at all coming from the FDA.

And in AML, I think, the change that is happening that will really facilitate approvals in newly diagnosed AML pa-

tients is historically the FDA was really looking for overall survival for large phase III studies.

And as novel therapies become available, just like we've seen in other cancers, it really gets harder and harder from an ethical position to do studies where overall survival is the primary endpoint.

So, the FDA is beginning to show an openness to other endpoints such as event-free survival, and they talked about that at a recent session at the American Society of Hematology.

They are present at all the major meetings. They are at ASH, they are at ASCO. They are excited about what's happening in AML, and they're helping to facilitate it.

Well, actually, it's interesting that your company's two drugs are approved based on an unusual endpoint—decrease in transfusions. And that's regarded as a patient benefit, which actually gave you two full approvals based on single arm trials.

DS: Yeah.

I think that says quite a bit about the FDA's flexibility here.

DS: I think it speaks to where the FDA is, but I think it also speaks to the compelling data we've been able to demonstrate.

The primary endpoint for both our studies, which led to the two approvals was the percentage of patients who achieve a complete remission. In this setting, one would expect the complete remission rate with chemotherapy to be about 10 percent.

We're seeing with Tibsovo a little over 33 percent complete remissions. So, that's the primary endpoint. But the secondary endpoint, because of the way the drug works, such a novel way of differentiating or repairing the leukemic cell, led to these transfusion benefits.

The FDA has historically always believed that a reduction in the need of transfusions is a direct measure of clinical benefit. So, the combination of the compelling, a complete remission rate, together with the transfusion improvement data, and safety profile, is what led to the full approvals, which is unusual, based on a non-randomized trial.

So, we were very pleased about that.

I don't believe I've seen that before.

DS: It has happened, but it's unusual.

I've seen a decrease in transfusion as a primary endpoint once, and that was the ESAs [erythropoiesis stimulating agents], but that's the only times I've really seen it. I guess that's a sign that you and the agency are having fruitful discussions. Were they open to this idea?

DS: Absolutely. We've always considered the FDA a partner, not an adversary. And I think that's critically important when you're doing drug development, because they are here to make sure that we develop important, safe and effective medicines.

And for us, they've been a great partner from day one on these programs and all of our programs.

Does this idea come from them or from you; just sort of curious?

DS: Which idea?

To use the decrease in transfusions as a justification for full approval.

DS: It was a secondary endpoint in our clinical trial, so the FDA had all of that data. The decision to go down the route of full approval or accelerated approval—that's totally in the FDA's domain, and they, during the review process, began to indicate to us that they were leaning towards full approval.

And so, we were very excited by that. And we gave them all the information they needed.

But the secondary endpoint of the study, among others, was looking at transfusion burden in these patients, which is such an impact on these patients' lives. Because right now, patients with AML spend most of their time either in the hospital or in the outpatient clinic getting transfusions and chemotherapy.

And the fact that both of our medicines are pills that patients can take at home, and if their blood counts improve, which in most patients they do, they don't need to come to the clinic to get transfusions.

So, quality of life and benefit is pretty dramatically different.

Are you moving these drugs towards the front line?

DS: Absolutely. There's no question that we want both of these drugs to become the cornerstone of therapy for patients with IDH mutant AML, and then eventually other cancers.

> The decision to go down the route of full approval or accelerated approval—that's totally in the FDA's domain, and they, during the review process, began to indicate to us that they were leaning towards full approval.

So, we've already initiated one randomized phase III study in newly diagnosed patients. These are slightly older patients who are not young enough to get aggressive chemotherapy, but still fit enough to get standard of care. So, we're doing a randomized study there.

Later this year, we'll be starting a very large randomized study in the young patients who are getting aggressive chemotherapy now, and that would be with both IDH inhibitors.

Our goal in that study is to improve the cure rate, because for young patients, there is a 20 to 30 percent chance of cure, and that needs to move. It hasn't moved in 25 years, since I was a fellow in 1986. So we want to move it...

And then, the third population that we're studying, believe it or not, an important population, there's a significant number of patients in the U.S. and around the world with AML who are older and who don't get any treatment at all.

They're sent home with hospice. And given that our medicines are well tolerated, and they're a pill, and we've already shown in a small number of patients very impressive data, we're going to continue to pursue that population as well.

Well, you mentioned one of these trials is randomized. Why randomized?

DS: Yeah, two of them. We'll combine with standard of care therapy versus standard of care plus placebo.

Will you be doing any of this through the Beat AML trial; is that helpful to you?

DS: It is helpful. So the Leukemia and Lymphoma Society is running the Beat AML Trial, and we are participating. Both IDH inhibitors are in the Beat AML Trial. That's not a randomized trial, but it's an important trial in newly diagnosed patients. And so, both our drugs are participating in that trial. But in addition, we're doing the phase III randomized studies combining with standard of care or using placebo that would hopefully lead to worldwide labels in the newly diagnosed patient, which is our ultimate goal.

So this is more of a, kind of a supplementary trial for you?

DS: It is, but important. And LLS is a great organization, and we're excited to work with them.

If you were to blink right now and imagine what AML looks like in five years, what do you see?

DS: So, I'll give you the analogy. But if I were to really blink and say, "What could things look like in the next five years?"

In the young patient, we'd see a significant improvement in the cure rate. We know it's not going to be 100 percent. But a real pickup in the cure rate in the young patient.

And in the older patient, today, there's no potential for cure. So, if I'm going to dream, I'm going to dream that in that patient population, either with our drugs or other novel drugs, we'll begin to see the potential for cure and/

or long-term remission in these older patients.

And remember, in AML, the median age at diagnosis is 68. But most of the patients cannot today get cured with intense therapy. And if that could change, that would be amazing.

Now, if you remember, when I started working on multiple myeloma in 2001, the median survival in myeloma with melphalan and prednisone for any age was three years.

Today, with Velcade and Revlimid, and daratumumab, and other therapies that have been developed, overall survival in newly diagnosed myeloma is at least 10 to 12 years from the time of diagnosis, and there are some patients who are out much longer.

And that's what I'm hoping will happen with AML.

How many drugs do you think there is room for here? Because it's a fairly small indication.

DS: Given how dismal the current outcome is in AML, and that in the United States alone there are 20,000 new patients per year with AML, which is not all that different from some of the other blood cancers, there's a lot of room.

Because until we move the response and survival data up in a meaningful way, it's going to take a lot of different drugs, targeting different subsets. It's not one disease. Just like lung cancer's not one disease. So, we're going to need lots of novel targets, and we're going to have to combine them. One of the beauties of our two IDH inhibitors is how well tolerated they are, and they're pills. So we've already shown so far that combining them with other therapies has been very easy. And that's what the future will bring is to combine these new drugs together.

Well, that seems to be where Beat AML is going, right—combinations?

DS: Absolutely, but that's just the beginning. We're going do combination trials with our drugs as well. And there needs to be more, and more, and more--and there will be. So, there's plenty of room. We're nowhere near where we need to be in AML. We're just starting. Myeloma, CLL, the other blood cancers are a decade ahead of us.

Fascinating. Is there anything we've missed in our conversation?

DS: I think we've hit the main points. Again, as a hematologist, someone who's been taking care of AML patients for 30 years, it's just really exciting to see light at the end of the tunnel there, and the hope that we may actually see a meaningful difference in survival in these patients over the next 5 to 10 years.

Well, thank you so much.

FDA will organize new review divisions around disease types, Gottlieb testifies

By Jordan Williams and Matthew Bin Han Ong

To modernize drug development, FDA plans to add review divisions to its Center for Drug Evaluation and Research and organize those divisions around disease types, FDA Commission Scott Gottlieb said July 25 to members of Congress in a House Energy and Commerce Committee hearing.

Gottlieb was part of a panel of HHS officials that also included NIH Director Francis Collins and NCI Director Ned Sharpless. The hearing focused on the implementation of the 21st Century Cures Act. The measure, which was approved December 2016, seeks to accelerate drug development and modernize clinical trials (The Cancer Letter, Dec. 16, 2016).

"FDA recently announced a new drug development modernization plan that provides the structural framework necessary to advance many goals of the Cures Act—and more closely align the scientific prospect of complex and innovative new products with methods and approaches that can best unlock these opportunities," Gottlieb said at the Energy and Commerce hearing July 25.

Gottlieb's remarks are posted here.

On July 26, FDA announced two initiatives to improve its drug regulation programs—the Quality Metrics Feedback Program and the Quality Metrics Site Visit Program—in response to requests for continued dialogue on quality metrics, and to provide methods for industry to engage and inform the agency's use of these metrics in the future.

Earlier this year, the agency announced a proposal to modernize new drug development, citing the need to keep up with evolving technology and advances in medicine—the genomic revolution, the rise of targeted therapy, the availability of digital health data, the focus on patient involvement, complex drug-device combinations, globalization of drug development, and harmonization of international standards.

In a June 4 blog post, CDER Director Janet Woodcock listed the agency's priorities in the modernization process:

- Recruiting the best and brightest individuals from many disciplines,
- Enhancing our focus on multidisciplinary teams,
- Prioritizing operation excellence,
- Improving knowledge management,

- Emphasizing the importance of safety across a drug's lifecycle, and
- Incorporating the patient voice.

"These changes are intended to free up resources so that our scientists and physicians have more time to focus on drug development, particularly for unmet medical needs, and on the multiple collaborations needed to make sure candidate drugs are developed and assessed properly, with appropriate input from external scientists, expert physicians and patient communities," Woodcock wrote in the blog post.

"We're also proposing changes that will increase the number of offices that oversee our review divisions from five to nine—and we're envisioning 30 review divisions within those offices—up from our current 19. In addition to enabling greater efficiency, these envisioned changes will help us to better understand the diseases intended to be treated by the drugs we evaluate for approval—another way we aim to enhance our knowledge management."

At the Energy & Commerce hearing, Gottlieb said FDA's Oncology Center of Excellence is an example of the agency's efforts in meeting the Cures Act's mandate to leverage the combined skills of regulatory scientists and reviews with expertise in drugs, biologics, and devices.

"OCE's interdisciplinary work is yielding significant advances. For example, last May, FDA approved, for adult and pediatric patients, the first cancer treatment based on a tumor's biomarker rather than the tumor's site or cell type," Gottlieb said. "In November, using a coordinated, cross-agency approach, the Center for Devices and Radiological Health approved the first breakthrough-designated, next generation sequencing-based in-vitro diagnostic test to identify patients with any of five tumor types who may benefit from 15 different FDA-approved targeted cancer treatment options. (The Cancer Letter, Nov. 28, 2017, Feb. 2, 2018).

"OCE supported CDRH's review team in evaluating this innovative testing approach which provides patients and health care professionals with access to critical information in one test report, avoiding the need for duplicative biopsies."

As part of FDA's broader innovation initiative, the agency is encouraging the use of state-of-the-art innovations, such as adaptive trials, modeling, and simulations to allow an evaluation of a product's safety and effectiveness, Gottlieb said.

"CDER and FDA's Center for Biologics Evaluation and Research are currently deploying these tools to help predict clinical outcomes, inform trial design, support evidence of effectiveness, and evaluate potential adverse event mechanisms," Gottlieb said. "The centers are updating guidance to assist sponsors in incorporating modeling and simulation—and applying these tools, for instance, to optimize product dosing based on individual physiology and genetics. CDER is currently collaborating with scientists to develop natural history models in Parkinson's, Huntington's, Alzheimer's, and muscular dystrophy which may facilitate modeling of some aspects of product design and evaluation."

On July 18, two FDA pilot programs—Real-Time Oncology Review and Assessment Aid—resulted in the first approval for the Novartis drug Kisqali (ribociclib), thereby demonstrating that the agency is able to initiate regulatory review immediately after the clinical trials datasets are locked (The Cancer Letter, July 20).

On competition

In response to a question from E&C Chairman Rep. Greg Walen (R-OR) about the correlation between clinical trial reform and lower costs of medical products, Gottlieb said that specialty drugs that target unmet medical needs have longer monopoly periods.

"The data shows this when competition enters the market, prices come down. That competition isn't entering, and the prices aren't coming down. And, we have data to show this, we'll be publishing it soon, and I gave a snapshot of it today," Gottlieb said. "I think there's things we can do to try to facilitate more efficient routes to market for second-in-class drugs and third-in-class drugs while at the same time increasing our assurance to safety and effectiveness, not sacrificing it one bit. Those are the kind of development reforms that we're focused on."

> "We're also proposing changes that will increase the number of offices that oversee our review divisions from five to nine—and we're envisioning 30 review divisions within those offices—up from our current 19."
>
> *– Janet Woodcock*

Rep. Leonard Lance (R-NJ) asked Gottlieb whether Congress created perpetual monopolies for many rare diseases since the 1984 enactment of the Orphan Drug Act.

Rep. Michael Burgess (R-TX), chairman of the E&C subcommittee on health, said Gottlieb's proposed clinical trial reform is likely to have a significant impact.

> There's things we can do to try to facilitate more efficient routes to market for second-in-class drugs and third-in-class drugs while at the same time increasing our assurance to safety and effectiveness, not sacrificing it one bit. Those are the kind of development reforms that we're focused on.
>
> *– Scott Gottlieb*

"Medicines have been brought to market for only some rare diseases and there are many rare diseases as you both know where there are no medicines at all," Lance said. "For many of these diseases, however, there has been zero second-generation newly innovative medicines brought to market for patients."

Second-generation drugs are harder to bring to market, because they are harder to study, Gottlieb said.

"Typically, the subsequent drugs will have to be studied on top of the available therapy and you'll have to show improved efficacy with combination therapy as opposed to just monotherapy," Gottlieb said. "It's hard to run head-to-head comparative studies when already effective therapy is available. People don't want to forego an effective treatment especially, when you're dealing with a child with degenerate disease."

"I always felt while we were doing the roundtables for Cures, that that is likely where the big money was," Burgess said. "If we could reduce the time in trial, if a product was going to fail allow it to be identified and fail early so we don't spend a lot of time chasing something that was not going to pan out."

Competition and innovation for development of biosimilar agents has slowed down, said Rep. Frank Pallone (D-NJ) , ranking member of the Energy and Commerce committee.

"Last week, FDA announced the release of its biosimilar action plan which strives to encourage more innovation and competition in the biologics market, and I believe such action is critical and necessary if patients were to realize the full benefits of biosimilars," Pallone said. "Well, eight years have passed since the Biologics Competition and Innovation Act, only three biosimilars are marketed in the U.S. despite FDA having approved eleven of them."

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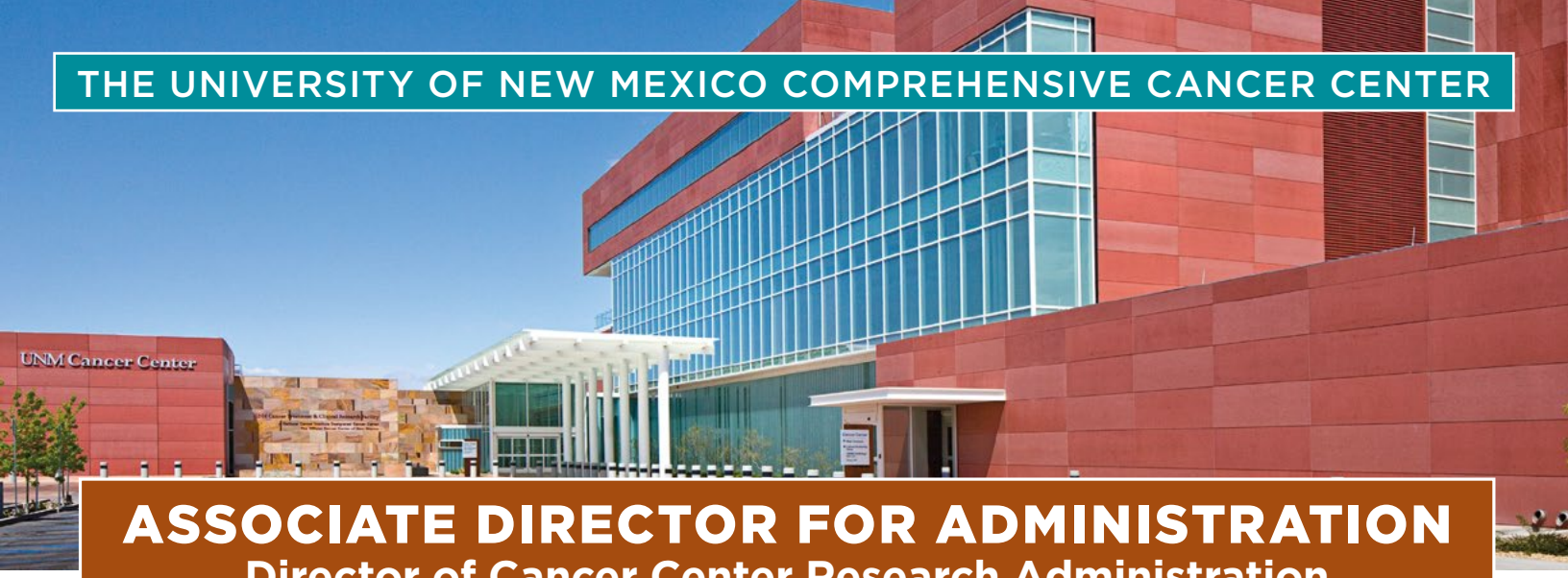

ASSOCIATE DIRECTOR FOR ADMINISTRATION

Director of Cancer Center Research Administration

The University of New Mexico NCI-Designated Comprehensive Cancer Center (UNMCCC) invites applications for the position of Associate Center Director for Administration who will also serve as Director of Cancer Center Research Administration. This senior staff position reports to directly to the UNMCCC Director & CEO and oversees the administration of all research facets of the UNMCCC relative to its NCI P30 Cancer Center Support Grant (CCSG) and other key programs and initiatives, including operations relative to strategic planning; program development and implementation; research grants and contracts, ensuring compliance with funding agency guidelines and reporting requirements; developing and implementing policies and procedures; and providing operational planning, budgeting, and assessment. In this role, the Associate Director provides advanced leadership, consultation, and expertise in research administration; management of activities and staff; and technical writing support for grants and contracts.

Located in Albuquerque, New Mexico, the UNMCCC is the Official Cancer Center of New Mexico and the only NCI-Designated Comprehensive Cancer Center within a 500-mile radius. The Center has 140 board-certified oncology physicians and surgeons, forming New Mexico's largest cancer team which provides care to over 60 percent of New Mexicans diagnosed with cancer. Over 50% of the patients treated at the Center are racial/ethnic minorities (predominantly Hispanic and American Indian) and a large fraction are rural and underserved. The Center's statewide clinical research and clinical trials network, funded in part by a NCI Community Oncology Research Program (NCORP) Minority/Underserved grant, is considered an "exemplary national model for cancer clinical trials and health care delivery research." The UNMCCC CCSG has 134 members engaged in four research programs: Cancer Control & Population Sciences; Cancer Genetics, Epigenetics & Genomics; Cancer Cell Biology & Signaling; and Cancer Therapeutics. Research centers at the UNMCCC include: Project ECHO; The Molecular Discovery and High Throughput Target Screening Center, one of the nation's Chemical Biology Consortia in The NCI NExT Program; and The New Mexico Center for the Spatiotemporal Modeling of Cell Signaling, one of 13 NIH-funded National Centers for Systems Biology. The UNMCCC is also a member of the ORIEN National Network of NCI Cancer Centers engaged in precision oncology, data sharing, and collaborative research. Through its affiliates (Los Alamos and Sandia National Laboratories, Lovelace Respiratory Research Institute), the UNMCCC integrates advanced computational, imaging, radioisotope, nanotechnology, and drug discovery capabilities into its rich scientific environment. Focused on discovering the causes and the cures for cancers disproportionately affecting the multiethnic peoples of the American Southwest, the UNMCCC has developed new diagnostics and treatments for leukemia, and cancers of the breast, lung, ovary, prostate, liver, pancreas, brain, and melanoma.

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Master's degree with at least 5 years experience or a Bachelor's degree with at least 7 years experience, directly related to the duties and responsibilities specified. Experience in NCI Cancer Center administration, or administration and leadership in similar NIH-funded research-intensive centers, is preferred.

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- Creates and implements research tracking and reporting strategies for major grant-funded projects.
- Establishes and implements short- and long-range goals, objectives, policies, and operating procedures; monitors and evaluates operational effectiveness and effects changes required for improvement.
- Oversees and coordinates the preparation of comprehensive research activity and operational reports; provides guidance on research operations and compliance.
- Oversees the supervision of personnel, including work allocation, training, promotion, enforcement of internal procedures and controls, and problem resolution; evaluates performance and makes recommendations for personnel actions; motivates employees to achieve peak productivity and performance.
- Provides comprehensive advice, consultation, and facilitation to researchers on all aspects of grant preparation and submission, and preparation and submission of RFI's and RFP's.
- Serves as a principal point of collaboration, leadership, and expertise to both internal and external constituencies on professional and operational matters pertaining to the mission, goals, objectives, and work scope of the program.
- Develops and manages annual budgets and performs periodic analyses.
- Prepares and administers government and sponsored research agreements and memoranda of understanding.
- Participates in drafting, editing, and writing of research documents, grant applications, and internal and external reports, with Center faculty and staff.

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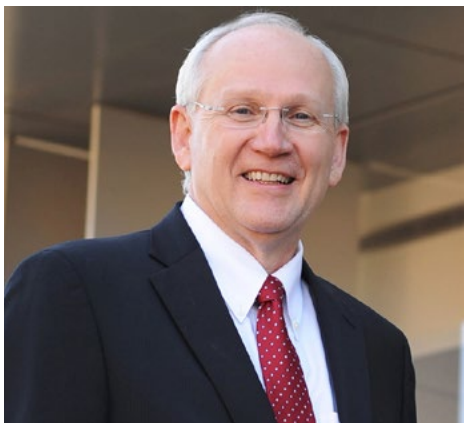
COMPREHENSIVE CANCER CENTER

IN BRIEF

DuBois, Pollak named editors of *Cancer Prevention Research*

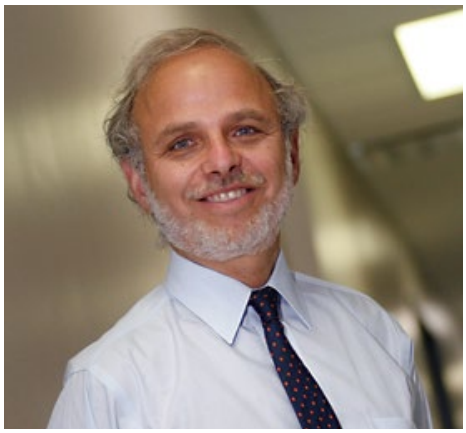
The American Association for Cancer Research named Raymond DuBois and Michael Pollak as editors-in-chief of *Cancer Prevention Research*.

Cancer Prevention Research publishes original preclinical, clinical, and translational research on the biology of premalignancy, risk factors and risk assessment, early detection research, and chemopreventive interventions, including the basic science behind these areas. The journal was launched in 2008 with Scott Lippman as the founding editor-in-chief.



DuBois is an expert in the molecular and genetic basis of colorectal cancer. His work in this area has led to a better understanding of the role of anti-inflammatory agents such as aspirin in the tumor microenvironment, and has subsequently resulted in various clinical trials, including treating precancerous polyps with celecoxib (Celebrex), an arthritis drug that selectively inhibits COX-2, an enzyme that facilitates inflammation.

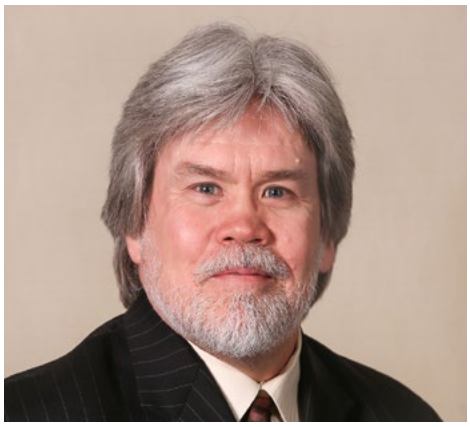
DuBois is past president of the AACR, chairman and president of the AACR Foundation, a fellow of the AACR Academy, and has served as a member of the AACR Board of Directors. In addition, he has served as an editorial board member of Clinical Cancer Research and as an associate editor of Cancer Research. He is also a recipient of the Dorothy P. Landon-AACR Cancer Research Prize and the AACR-Richard and Hinda Rosenthal Foundation Cancer Research Award.



Pollak has served on the editorial board of *Cancer Prevention Research* since its inception. He holds the Alexander Goldfarb research chair in cancer research at McGill University in Montreal and directs the Division of Cancer Prevention of the Department of Oncology. Pollak is a medical oncologist at the Jewish General Hospital in Montreal and is involved in clinical trials of novel agents related to growth factor targets.

He directs a multi-disciplinary research program at the Lady Davis Research Institute, which investigates insulin and insulin growth factor physiology in relation to cancer, and provides specialized ELISA assays for epidemiologic and pharmaceutical collaborators. He has received a number of prestigious honors and awards.

Walker named new COO of City of Hope



Jeff Walker, formerly a chief operating officer at Ohio State University, has been named COO of City of Hope.

Walker has more than two decades of experience in cancer center leadership and transformation. He joined City of Hope earlier this year as senior vice president in transformation development and has been leading the institution's efforts around operational design and planning for new strategic initiatives and ventures.

As COO, Walker will lead patient care operations for the Duarte, California, campus and all community practice locations as well as all research operations. He will oversee the management of the enterprise-wide physical plant, including an estimated $1.1 billion in new construction projects.

Prior to coming to City of Hope, Walker served as the chief operating officer for The Ohio State University Comprehen-

sive Cancer Center and the James Cancer Hospital, overseeing and integrating the administrative and operational structure to support the program's research and clinical missions. During his tenure, the new James Cancer Hospital was built and opened, becoming the third largest cancer hospital in the country.

Walker has also served as executive vice president for the Roswell Park Cancer Research Institute in New York and, prior to his roles at Ohio State and Roswell Park, he held administrative leadership positions at the University of Pittsburgh Cancer Institute during his 14 years at UPCI.

Walker serves as vice-chair of the Alliance of Dedicated Cancer Center executive committee, treasurer of the Association of American Cancer Institutes, and is a member of the executive and finance committees of the National Comprehensive Cancer Network and the Cancer Center Administrators Forum.

Manotti named senior vice president, chief development officer at MSKCC

Kenneth Manotti has been named senior vice president and Chief Development Officer at Memorial Sloan Kettering Cancer Center.

Manotti has more than 30 years of fundraising and leadership experience at major institutions, including the University of Pennsylvania, Columbia University, the American University in Cairo, and the University of Chicago. He was senior vice president of University Development and Alumni Relations at New York University.

Manotti's appointment concludes a national search for new leadership for MSK's fundraising program, which was led for the past 15 years by Richard Naum as senior vice president for Development and Anne McSweeney as Special Advisor to the President.

Under their direction, the Campaign for MSK surpassed its $3.5 billion goal, providing vital support for innovation and discovery research to transform cancer treatment in New York and around the globe.

At the University of Chicago, where Manotti served as vice president for Alumni Relations and Development from 2011 to 2017, he helped direct a successful $5 billion capital campaign, working collaboratively with university leadership, trustees, and advancement colleagues.

Before that, he served as vice president for Institutional Advancement at the AUC, where he led university-wide development, alumni affairs, and marketing and communications programs in the United States, the Middle East, and Europe. Prior to his work at the AUC, he was associate dean for External Affairs at the University of Pennsylvania's Wharton School of Business, where he directed the $550 million Wharton Campaign.

Agarwal named chief medical officer at Epizyme

Shefali Agarwal was named chief medical officer of Epizyme Inc. In this role, Agarwal will oversee all of the company's activities related to the global strategic development of tazemetostat, a potent, selective, orally available EZH2 inhibitor, as well as additional pipeline candidates.

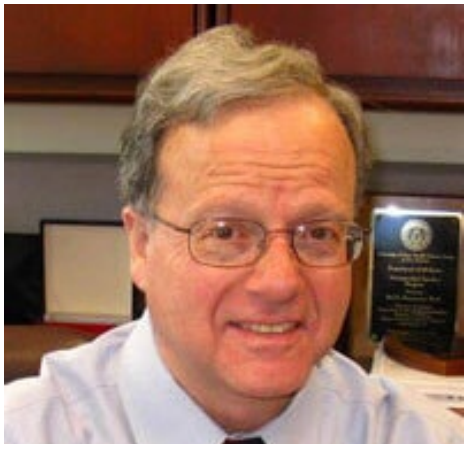
Over the span of her career, Agarwal has held leadership positions across medical research, clinical development, clinical operations, and medical affairs. She has led clinical and regulatory engagements for small molecules, biologics, liposomal and cell therapy products across the full spectrum of drug development, from pre-IND work to filing.

Agarwal most recently served as chief medical officer at SQZ Biotech, where she built and led the clinical development organization, which included clinical research operations and the regulatory function. She brings significant oncology experience to Epizyme, having held leadership positions at Curis and Tesaro.

At Curis, Agarwal oversaw the phase II study for its dual HDAC/PI3K inhibitor in diffuse large B-cell lymphoma, and the phase I study in solid tumors for its oral checkpoint inhibitor. At Tesaro, Agarwal led the NDA and EMA submissions for Zejula (niraparib) in ovarian cancer. She has also held positions of increasing responsibility at Covidien, AVEO Oncology, and Pfizer.

In addition to receiving her MBBS medical degree from Karnataka University's Mahadevappa Rampure Medical School in India. Agarwal earned a master's of public health from Johns Hopkins University, where she led clinical research in the Department of Anesthesiology and Critical Care Medicine. She also holds a master's of science in business from the University of Baltimore's Merrick School of Business.

IU's Broxmeyer receives NHLBI Outstanding Investigator Award



Indiana University Distinguished Professor Hal Broxmeyer received the National Heart, Lung, and Blood Institute Outstanding Investigator Award to continue his 35 years of research into umbilical cord blood transplantation.

Broxmeyer received a seven-year, $5.4 million grant to continue his research into how to maximize the use of adaptable blood-forming cells in cord blood for transplantation for certain types of cancer, metabolic and blood diseases.
Broxmeyer is a professor of microbiology and immunology, the Mary Margaret Walther Professor Emeritus, and chairman emeritus of the Department of Microbiology and Immunology at IU School of Medicine. He is also a co-leader of the hematopoiesis and malignant hematology research program at the Indiana University Melvin and Bren Simon Cancer Center.

The National Heart, Lung, and Blood Institute created the awards program in 2016 to provide leading researchers with more flexibility and financial security to conduct groundbreaking research or expand on previous discoveries.

Broxmeyer has focused on expanding the effectiveness of cord blood since 1983 when he and colleagues first proposed the concept of using umbilical cord blood as an alternative source of hematopoietic stem cells for transplant. In 1988, his lab processed the blood used in the first successful umbilical cord blood transplant in Paris and the cord blood used in subsequent transplants in Baltimore, Cincinnati and Minneapolis. The first treatment for a 5-year-old boy with the blood disorder Fanconi's anemia was a success, and five of the six subsequent cord blood transplants were successful.

Over the years, the Broxmeyer lab has worked on finding solutions to issues that limited the use of cord blood for transplant. One key problem that restricted its use for transplant in large children or adults was the limited number of stem cells collected from one umbilical cord.

However, his team published a remarkable finding in the journal Cell in 2015 that found that the numbers of stem cells in bone marrow and umbilical cord blood had been grossly underestimated because they are typically collected in ambient air that has an oxygen level of about 21 percent. By collecting blood in a more controlled environment with lower oxygen levels, they determined that many more useable stems cells could be harvested.

He also has been at the forefront of research that identified an enzyme, dipeptidyl peptidase-4, that can reduce blood cell production. Research on this enzyme to enhance blood cell production remains one of his interests.

Royce, Kircher selected for ASCO's 2018-2019 Health Policy Fellowship Program

Trevor Royce and Sheetal Kircher have been selected for the American Society of Clinical Oncology Health Policy Fellowship Program.

Now entering its third year, the fellowship program offers oncologists the opportunity to gain the knowledge base, skills, and experience necessary to shape regulatory and legislative policies that directly affect the practice environment and impact patients with cancer and their care teams. The next ASCO health policy fellowship runs from July 1 to July 1, 2019.

Royce is chief resident at the Harvard Radiation Oncology Program and immediate past vice-chair of the Association of Residents in Radiation Oncology Executive Committee.

During medical school at the University of North Carolina at Chapel Hill School of Medicine, he spent a year as a Doris Duke Clinical Research Fellow conducting health services research with a focus on prostate cancer.

Royce attended the University of Virginia, where he studied biomedical engineering. Before medical school, he pursued graduate school at Georgetown University and completed an internship in internal medicine at Brigham and Women's Hospital. During residency he obtained an MPH at the Harvard School of Public Health. He will join the faculty at UNC Chapel Hill this fall.

Kircher is a medical oncologist and assistant professor in the Department of

Medicine at Northwestern University. She obtained her medical degree from the Rush Medical College and completed her fellowship in medical oncology at Northwestern University. During her research fellowship at the Ann Arbor Veterans Affairs, focusing on health services, she also obtained a master's degree in Health and Health Outcomes from the University of Michigan.

Kircher's clinical focus is the treatment of gastrointestinal malignancies and her research interests are related to health care delivery throughout the cancer continuum, including long-term survivorship and the impact of cancer treatment costs on patients, health systems, and payers. She currently serves as the medical director of the Survivorship Institute of Northwestern, where she oversees programmatic aspects of delivering survivorship care.

As ASCO health policy fellows, Royce and Kircher will participate in the following activities:

- Active participation in policy development for high-impact issues in oncology,
- Small-group teaching sessions delivered by ASCO professional staff and qualified volunteers,
- Training in communication and leadership skills, as well as advocacy strategies, and
- A mentored research project that advances an ASCO policy initiative.

The application period for next year's Health Policy Fellowship opened July 1 and must be submitted online using ASCO's Grants Portal.

ASCO conducts and administers the fellowship with funding support from the Conquer Cancer Foundation Mission Endowment.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

UCLA's Yang receives $1.4M to develop cellular therapy using blood stem cells

Lili Yang, a researcher at the UCLA Jonsson Comprehensive Cancer Center and the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, has received a Quest Discovery Program award totaling approximately $1.4 million from the California Institute for Regenerative Medicine.

CIRM, a state stem cell agency, established the program to support the development of promising novel stem cell-based technologies that will be ready for translational studies within two years.

The award will fund Yang's efforts to develop a cellular therapy that could potentially be used to treat multiple cancers including solid tumors (melanoma, colon, lung, breast, and head and neck cancers) and blood cancers (such as leukemia, multiple myeloma, and myelodysplastic syndromes).

Yang's novel approach will genetically modify blood-forming stem cells—which produce every type of blood cell, including the immune cells that can fight disease—to create large supplies of invariant natural killer T cells, a powerful subset of immune cells that have the remarkable capacity to target a broad range of cancers.

To date, the clinical applications of iNKT cells have been greatly limited because they don't naturally exist in high numbers in the body; one drop of human blood contains around 10 million total blood cells but only around 10 iNKT cells; cancer patients typically have even less iNKT cells.

Using blood-forming stem cells from healthy donors, Yang's approach will first genetically modify the cells in two ways:

- One genetic modification will insert a receptor that will prompt the blood-forming stem cells to create only iNKT cells and not any other kind of T cell.
- The second genetic modification will remove specific molecules from the blood-forming stem cells, prompting the stem cells to create iNKT cells that won't cause rejection when transplanted into a patient. This means the cells could come from any donor but still be universally compatible with any patient.

The genetically modified blood-forming stem cells will then be put into an artificial thymic organoid in collaboration with Gay Crooks, a professor of pathology and laboratory medicine and of pediatrics and co-director of the UCLA Broad Stem Cell Research Center, whose lab developed the organoid.

This organoid mimics the natural functions of the thymus, which turns blood-forming stem cells into immune cells within the body. After 8 weeks, the blood-forming stem cells will produce iNKT cells that will be multiplied in the lab, tested for safety and then frozen.

Using this method, Yang and the research team estimate that about 1,000 to 10,000 doses of iNKT cells can be produced from a single blood stem cell donor.

The team plans to test the effectiveness of the iNKT cells in preclinical animal models of various types of human cancer. If the method proves successful, the team hopes to take the concept to clinical trials in the future and ultimately create a lasting supply of iNKT cells that are readily available to treat a large population of cancer patients.

Takeda's Alunbrig meets PFS primary endpoint

The global, randomized, phase III ALTA-1L trial met its primary endpoint at the first pre-specified interim analysis, with Alunbrig (brigatinib) demonstrating a statistically significant improvement in progression-free survival compared to crizotinib in adults with anaplastic lymphoma kinase-positive locally advanced or metastatic non-

small cell lung cancer who had not received a prior ALK inhibitor.

Takeda Pharmaceutical Company Limited sponsors this drug.

The trial was designed to assess the efficacy and safety of ALUNBRIG in comparison to crizotinib based on evaluation of the primary endpoint of PFS, or length of time from the start of treatment that a patient lives without the disease getting worse. Alunbrig is currently not approved as frontline therapy.

The safety profile associated with Alunbrig from the ALTA-1L (ALK in Lung Cancer Trial of AP26113 in 1st Line) trial was generally consistent with the existing prescribing information, with no new safety concerns.

The results from this interim analysis will be submitted for presentation at an upcoming medical meeting.

The phase III ALTA-1L (ALK in Lung Cancer Trial of AP26113 in 1st Line) trial of Alunbrig in adults is a global, ongoing, randomized, open-label, comparative, multicenter trial, which enrolled 275 patients with ALK+ locally advanced or metastatic NSCLC who have not received prior treatment with an ALK inhibitor.

Patients received either Alunbrig, 180 mg once daily with seven-day lead-in at 90 mg once daily, or crizotinib, 250 mg twice daily. Independent Review Committee-assessed progression-free survival was the primary endpoint.

Secondary endpoints included objective response rate per RECIST v1.1, intracranial ORR, intracranial PFS, overall survival, safety and tolerability. A total of approximately 198 PFS events are planned at the final analysis of the primary endpoint in order to demonstrate a minimum of six months PFS improvement over crizotinib.

The trial is designed with two pre-specified interim analyses for the primary endpoint—one at 50 percent of planned PFS events and one at 75 percent of planned PFS events.

Alunbrig is a targeted cancer medicine discovered by Ariad Pharmaceuticals Inc., which was acquired by Takeda in February 2017. In April 2017, Alunbrig received Accelerated Approval from the FDA for ALK+ metastatic NSCLC patients who have progressed on or are intolerant to crizotinib.

This indication is approved under Accelerated Approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Alunbrig received Breakthrough Therapy Designation from the FDA for the treatment of patients with ALK+ NSCLC whose tumors are resistant to crizotinib and was granted Orphan Drug Designation by the FDA for the treatment of ALK+ NSCLC, ROS1+ and EGFR+ NSCLC.

A Marketing Authorization Application for Alunbrig was submitted to the European Medicines Agency in Feb 2017.

The brigatinib clinical development program further reinforces Takeda's ongoing commitment to developing innovative therapies for people living with ALK+ NSCLC worldwide and the healthcare professionals who treat them.

The comprehensive program includes the following clinical trials:

- Phase I/II trial, which was designed to evaluate the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of Alunbrig.
- Pivotal phase II ALTA trial investigating the efficacy and safety of Alunbrig at two dosing regimens in patients with ALK+ locally advanced or metastatic NSCLC who had progressed on crizotinib
- Phase IIII ALTA-1L trial assessing the efficacy and safety of Alunbrig in comparison to crizotinib in patients with ALK+ locally advanced or metastatic NSCLC who have not received prior treatment with an ALK inhibitor
- Phase II single-arm, multicenter study in Japanese patients with ALK+ NSCLC, focusing on patients who have progressed on alectinib
- Phase II global study evaluating Alunbrig in patients with advanced ALK+ NSCLC who have progressed on alectinib or ceritinib

DRUGS & TARGETS

FDA approves magnetic device system for sentinel biopsies in breast cancer

FDA approved Magtrace and Sentimag Magnetic Localization System (Sentimag System), a magnetic device system for guiding lymph node biopsies

in patients with breast cancer undergoing mastectomy. It uses magnetic detection during sentinel lymph node biopsy procedures to identify specific lymph nodes, known as sentinel lymph nodes, for surgical removal.

FDA granted approval of the Sentimag System to Endomagnetics Inc.

Sentinel lymph nodes are the first lymph nodes to which cancer cells are most likely to spread from a primary tumor. For patients with breast cancer, testing the sentinel lymph nodes indicates whether the cancer has spread from the breast. A sentinel lymph node biopsy is used to identify, remove and examine lymph nodes to determine whether cancer cells are present.

The Sentimag System uses magnetic materials to guide the sentinel lymph node biopsy procedure. The system is comprised of a sensitive magnetic sensing probe and base unit designed to detect small amounts of Magtrace, the magnetic tracer drug that is injected into breast tissue.

The Magtrace particles travel to lymph nodes and become physically trapped in them, facilitating magnetic detection of the lymph nodes. Following the injection of Magtrace, the Sentimag probe is applied to the patients' skin in areas closest to the tumor site containing the lymph nodes. The sensing of the magnetic particles is indicated by changes in audio and visual alerts from the base unit, enabling the surgeon to move the hand-held probe around the area of the lymph nodes, and locate the sentinel lymph node or nodes (if there are more than one). The surgeon then makes a small incision and removes the node, which is checked by a pathologist for the presence of cancer cells.

A negative sentinel lymph node biopsy result suggests that cancer has not spread to nearby lymph nodes. A positive result may indicate that cancer is present in the sentinel lymph node and may be present in other nearby lymph nodes and, possibly, other organs. This information can help a doctor determine the stage of the cancer and develop an appropriate treatment plan.

The FDA evaluated data from a trial of 147 patients with breast cancer to compare the Sentimag System to the control method of injecting patients with blue dye and radioactive materials together and using a gamma probe to identify the sentinel lymph node.

Patients were administered both methods to compare lymph node detection rates. The lymph node detection rate for the Sentimag System was 94.3 percent while the control method detection rate was 93.5 percent. Overall, 98.0 percent of patients had the same detection rate with both the Sentimag System and the control method.

The most common adverse event reported include breast discoloration, which is reported to disappear after three months in patients who underwent mastectomy, cardiac disorder and potential allergic reaction to the magnetic materials.

The Sentimag System is contraindicated in any patient with hypersensitivity to iron oxide or dextran compounds It is also not recommended for patients with iron overload disease or with a metal implant in the axilla or in the chest.

Magtrace may travel to regions away from the injection site such as liver or spleen, if injected directly into the bloodstream. In such cases the presence of Magtrace may cause image artifacts during Magnetic Resonance Imaging. Magtrace residues have not been reported to produce artifacts affecting imaging in X-ray, positron emission tomography scans, computed tomography scans, PET/CT scans or ultrasound studies.

FDA reviewed the Sentimag System application using a coordinated, cross-agency approach. The clinical review was conducted by CDRH in consultation with the Center for Drug Evaluation and Research and with support from the Oncology Center of Excellence, while all other aspects of review and the final product approval determination was conducted by CDRH.

FDA accepts Celyad IND application for CYAD-101, a non-gene edited allogeneic CAR-T candidate

Celyad said FDA has accepted the company's Investigational New Drug application for CYAD-101, the first non-gene edited allogeneic clinical program. FDA has indicated that the Allo-SHRINK trial, evaluating the safety and clinical activity of CYAD-101 in patients with unresectable colorectal cancer in combination with standard chemotherapy, is allowed to proceed.

CYAD-101, Celyad's first allogeneic CAR-T cell product, encodes both the company's autologous CYAD-01 CAR-T and a novel peptide, TCR Inhibiting Molecule, an inhibitor of TCR signaling. TCR signaling is responsible for the graft vs. host disease, and tampering or eliminating its signaling could therefore reduce or eliminate GvHD.

In CYAD101, the TIM peptide is encoded alongside the CAR construct allowing allogeneic T cell production through a single transduction step. CYAD-101 benefits from using a manufacturing process that is highly similar to Celyad's well established process for its clinical autologous CAR-T cell products.

While autologous CAR-T therapies now have well established efficacy in

B cell malignancies, the approach can be more challenging for some patients, especially those where the quality of the apheresis is poor.

Keytruda approved in China for advanced melanoma

The China National Drug Administration approved Merck's Keytruda for the treatment of adult patients with unresectable or metastatic melanoma following failure of one prior line of therapy. This is the first approval of an anti-PD-1 therapy for advanced melanoma in China.

The approval of Keytruda in China was based on overall response rate data from the phase Ib KEYNOTE-151 study, which evaluated Keytruda monotherapy in Chinese patients with previously treated locally advanced or metastatic melanoma who received one prior line of systemic therapy.

In 2018, the CNDA granted priority review status to Keytruda, which accelerated the approval process by allowing for simultaneous clinical validation for the first time – creating an industry leading approval turnaround time for imported cancer medicine in China.

KEYNOTE-151 is an open-label, single-arm, multi-center, phase Ib trial evaluating Keytruda monotherapy in 103 Chinese patients with previously treated locally advanced or metastatic melanoma who received one prior line of systemic therapy.

Patients were enrolled to receive KEYTRUDA at a dose of 2 mg/kg every three weeks. The primary efficacy outcome measure was ORR as assessed by Blinded Independent Central Review using RECIST 1.1. Secondary efficacy outcome measures were duration of response and progression-free survival (as assessed by BICR per RECIST 1.1 and irRECIST), ORR (as assessed by BICR per irRECIST) and overall survival.

BMS, Tsinghua University to develop therapies for autoimmune diseases, cancer

Bristol-Myers Squibb Co. and Tsinghua University have entered into a collaboration to discover therapeutic agents against novel targets for autoimmune diseases and cancers.

The collaboration brings together BMS and Tsinghua University's scientific expertise and capabilities with a focus on validating new targets and generating early drug candidates for clinical development.

Under the collaboration, The Innovation Center for Immune Therapy of Tsinghua University will conduct research on projects and BMS will have an option to exclusively license therapeutic agents discovered by Tsinghua University.

The collaboration is an expansion of an existing relationship between Bristol-Myers Squibb and Tsinghua University that began in 2012, which focused on autoimmune target discovery, structural biology research, as well as the science of mapping the 3D protein structure of biological molecular targets.