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**THE CANCER LETTER**

Inside information on cancer research and drug development

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## **WHY AUSTERITY MEASURES AMID CONGRESSIONAL GENEROSITY? SHARPLESS EXPLAINS THE COUNTERINTUITIVE**

In recent years, NCI spending on extramural research has been following the same trajectory as Congressional appropriations for the institute: up, up, up.

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**Assistant Director / Associate Director for Research Administration  
UPMC Hillman Cancer Center, Pittsburgh, PA**

UPMC Hillman Cancer Center (Hillman) seeks a talented and experienced individual to step into a highly supportive environment as Assistant/Associate Director (AD) for Research Administration. This is a very exciting time for a new AD for Administration to join Hillman. Hillman is strongly supported by UPMC and the University of Pittsburgh School of Medicine. The Hillman Foundation recently committed a large amount of continued support for our Center over the next 10 years. The new AD will collaborate with Hillman CC members to promote and invest these funds in strategic new projects, recruits, shared resources, and pilot programs. With our re-naming as UPMC Hillman Cancer Center, a new Director, and upcoming expansion of space for Hillman researchers, Hillman is unified and supportive of cancer research, prevention and therapy.

The AD for Research Administration reports directly to the Deputy Director for Research Administration and is a member of Hillman's leadership team. Primary duties and responsibilities include: oversight and management of Hillman facilities, scientific shared resources, development, facilitation and support of multi-component team science cancer research programs as well as spearheading internal and external collaborative research endeavors. To meet the position requirements, the AD for Research Administration will collaborate with a team of administrators and PhD-level scientists, coordinate vision setting and strategic planning; support and participate in CCSG Research Program and Shared Resource activities; develop operational and administrative policies and procedures; work with the Hillman Fiscal Office to develop budgets and monitor spending; develop staff and space utilization plans; oversee facility operations; and communicate research outcomes to Hillman investigators, the NCI, and the public. To facilitate and advance Hillman science, the AD will also: coordinate CCSG preparation and submission; grow the funded research base, with emphasis on multi-disciplinary collaboration with internal and external investigators; work with the Hillman Development Office to promote and increase philanthropic donations; assist in recruitment of faculty.

Located in the City of Pittsburgh's Shadyside neighborhood, (Pittsburgh is routinely ranked as one of the top-most livable and affordable U.S. cities), Hillman is a National Cancer Institute (NCI)-designated matrix cancer center focused on state-of-the-art cancer research, training the next generation of cancer researchers, and community outreach. In 2015, Hillman celebrated its 30<sup>th</sup> anniversary and the renewal of its 5-year NCI Cancer Center Support Grant (CCSG). Hillman has over 330 members, 10 scientific programs, 13 CCSG-supported shared resources, and an FY17 institutional funding base of nearly \$157 million. In FY16 the University of Pittsburgh ranked #5 in overall NIH funding. During its 2015 CCSG review, Hillman Research Administration scored exceptional.

Candidates for the position must have a PhD or master's degree in business, administration, policy, or other research administration-relevant field. Candidates also must have 5+ years in research administration, which includes an understanding of the regulatory requirements and complexities pertaining to animal and clinical research; familiarity with NCI CCSG requirements; experience with NCI-funded cancer centers; and excellent written and oral communication, computer, people management, and interpersonal skills. Candidate will be an Assistant or Associate Professor commensurate with experience.

The successful candidate will be hired as an employee of the University of Pittsburgh, with a very competitive salary and benefits package (see [www.hr.pitt.edu/benefits](http://www.hr.pitt.edu/benefits)). The University of Pittsburgh is an equal opportunity employer. EEO / AA / M / F / Vets / Disabled

To apply for the position of Associate Director for Research Administration at UPMC Hillman Cancer Center, please send a 1-page personal statement highlighting your qualifications and experience, along with your CV or resume, to Hillman Director Robert L. Ferris, MD, PhD (care of [thompsonla3@upmc.edu](mailto:thompsonla3@upmc.edu)).

**Robert L. Ferris., MD, PhD, Director, UPMC Hillman Cancer Center  
C/O Lola Thompson, 5150 Centre Avenue, Suite 500  
Pittsburgh, PA 15232**

## In this issue

### Editor & Publisher

Paul Goldberg

### Reporter

Matthew Bin Han Ong

### Reporter

Claire Dietz

### Designer

Jacqueline Ong

### Illustrator & Operations Manager

Katherine Goldberg

### Web Developer

David Koh

### Editorial, Subscriptions and Customer Service

PO Box 9905 -  
Washington, DC 20016

**T** 202-362-1809

**F** 202-379-1787

**W** [www.cancerletter.com](http://www.cancerletter.com)

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**WHY AUSTERITY MEASURES AMID  
CONGRESSIONAL GENEROSITY?  
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COUNTERINTUITIVE**

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Sharpless spoke with  
Paul Goldberg, editor and  
publisher of The Cancer Letter,  
and Matthew Ong, a reporter  
with The Cancer Letter.

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## CONVERSATION WITH THE CANCER LETTER

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If we didn't make adjustments for fiscal year 2019—modest reductions to operating budgets for NCI divisions, reducing new, non-modular ROIs by an additional two percent, and reducing many noncompeting grants by 3 percent — paylines would be lower still.

”

In recent years, NCI spending on extramural research has been following the same trajectory as Congressional appropriations for the institute: up, up, up.

This expansion resulted from a strategy by NCI Director Ned Sharpless and his recent predecessors to grow investigator-initiated research and the cancer centers. Now, growth has slowed, as out-year grant payments place a limit on the number of new grants NCI is able to issue in 2019.

On top of that, NCI is contending with a rising number of grant applications, propelled by the availability of funds and new possibilities in the field. As the denominator—the pool of applicants—rises, the applicants' success rates, or paylines, would plummet.

With fiscal pressures rising, something had to give, and NCI Director Sharpless recently opted to trim the institute's intramural spending in order to maintain the paylines.

Since making this choice, forum after forum, Sharpless has been explaining a notion that some might regard as counterintuitive: that NCI has to take austerity measures in the midst of a years-long stretch of healthy appropriations.

Sharpless started his Explaining Tour at the meeting of the National Cancer Advisory Board and the Board of Scientific Advisors last December (The Cancer Letter, [Dec. 7](#), 2018). He returned to the lectern on Jan. 25, hosting a Town Hall at NCI to explain his rationale for the cuts.

A webcast of his remarks is posted [here](#).

Earlier this week, Sharpless sat down for a chat with The Cancer Letter as well.

In fiscal 2018, Sharpless increased funding for the Research Project Grant

pool by \$146 million, providing the largest increase to the pool since 2003 (The Cancer Letter, [March 30](#), 2018).

These increases on the extramural side come at a price: all internal operating budgets of NCI divisions, offices and centers are subjected to a 5-percent cut, across-the-board in FY19.

“Because of the success of cancer research, we're having so many people in our field and we're getting so many great ideas. We've had this very sharp uptick in the number of grant applications we're receiving for certain kinds of grants like the R01 award,” Sharpless said to The Cancer Letter. “Grants are up nearly 60 percent since 2009 and nearly 50 percent since 2013.

“The NCI leaders agree that we want these grants coming in and we'd like people to send their ideas for funding. We want to try to support them and really support innovation to the extent possible. And I think there's buy-in on why we have to do this.

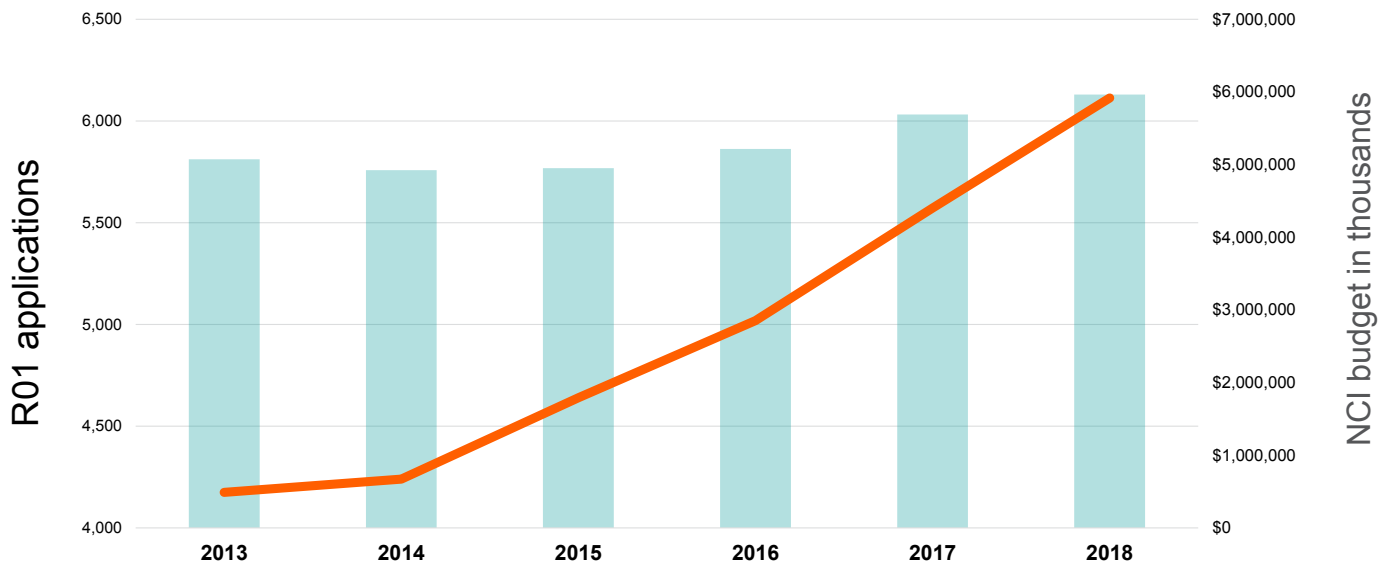
“Any cut at all is different from the status quo and it is causing some hardship. I think that no one's enthusiastic about this, but I think everybody understands the issue.

“I think if we didn't make adjustments for fiscal year 2019—modest reductions to operating budgets for NCI divisions, reducing new, non-modular ROIs by an additional two percent, and reducing many noncompeting grants by 3 percent—paylines would be lower still.”

In an email sent to members of NCI's advisory committees in December, NCI Director Ned Sharpless summarized the budgetary changes:

- Make internal budget adjustments across NCI, including all divisions, offices and centers, which will operate at 95 percent of FY 2018 levels.

## NCI Budget & R01 Grant Applications



NIH NATIONAL CANCER INSTITUTE

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- Fund non-competing grant continuations at 97 percent of the committed level, with the exception of Cancer Center Support Grants, Cancer Moonshot grants, and NRSA awards.
- Change the funding policy reduction to competing new and renewing grants (Type 1s and Type 2s) by 2 percent compared to FY 2018, from 17 percent to 19 percent.
- Fund new grants up to and including the 8th percentile.
- Maintain the [early-stage investigator] payline at 14 percent or better.

Sharpless spoke with Paul Goldberg, editor and publisher of The Cancer Letter, and Matthew Ong, a reporter with The Cancer Letter.

**Paul Goldberg:** How is NCI doing this year? Is the shutdown affecting you?

**Ned Sharpless:** NCI is open. We received our funding, as you know, at the beginning of the fiscal year and we're able to do our scientific mission and continue to really carry out and support the stunning, breathtaking progress that's going on in cancer. We are grateful to be able to continue our work and we recognize the disruption many of our colleagues in other agencies are facing.

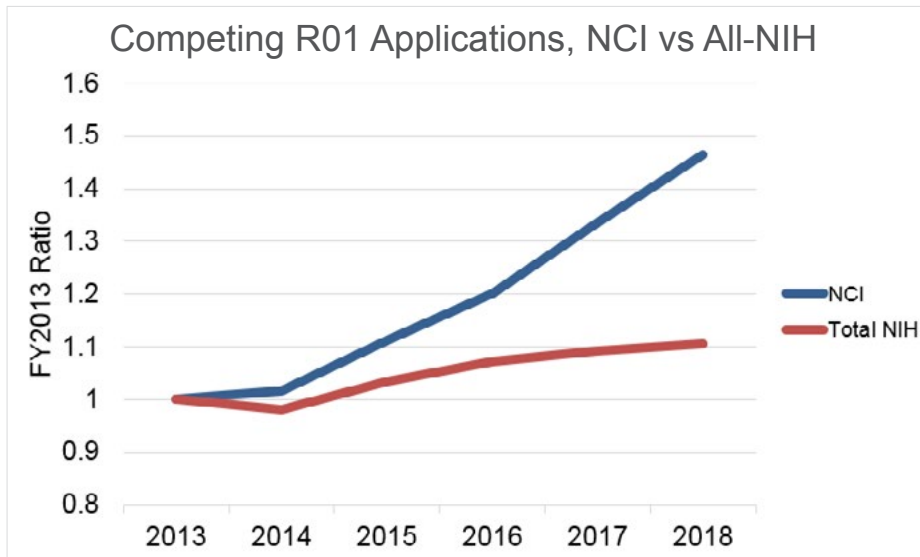
We had a bit of concern about our ability to convene meetings that have to be published in the Federal Register. We think we've resolved that issue. We believe for present time, at least, we'll be able to convene our relevant councils on time.

As the partial shutdown continues, going forward we will be placing a high level of scrutiny on some of our activities such as travel. I will be canceling my trips until the current situation is resolved and I will be asking the NCI staff to carefully consider planned travel and limit trips to those that are mission-critical and time-sensitive. I do not anticipate that will distract significantly from our scientific mission or our scientists' ability to do their work.

**Matthew Ong:** You had a Town Hall today. What's the news?

**NS:** As you know, we had a bit of truth-telling at the most recent joint National Cancer Advisory Board and Board of Scientific Advisors meeting about the state of the NCI budget. The budget is in many ways good—we certainly are not complaining about \$180 million increase we got this year. There

## Dramatic Increase in R01 Applications Since 2013



FY	R01 applications to NCI	R01 applications to NIH (total)
2013	4,175	27,939
2014	4,240	27,399
2015	4,640	28,873
2016	5,019	29,968
2017	5,572	30,516
2018	6,113	30,874

are some things, some trends within cancer research in general that are contingent on the NCI and that have led to moving funds around within the NCI. I wanted to better explain why we're doing that.

Basically, the news is that because of the success of cancer research, we're having so many people in our field and we're getting so many great ideas. We've had this very sharp uptick in the number of grant applications we're receiving for certain kinds of grants like the R01 award. Grants are up nearly 60 percent since 2009 and nearly 50 percent since 2013.

This is really strong increase, but it's not been seen across the rest of the NIH. We think that's because scientists are being drawn to cancer research by the scientific opportunity there. This is mirrored in pharma as they are devoting more resources to oncology and away from other therapeutic areas. I consider that good news. That's a sign of

a vibrant, healthy field where, new scientific ideas would be brought to bear.

But the problem you see right away is if your budget goes up 20 percent since 2009 and your grant applications go up 60 percent since 2009—you know this math—then, that's going to lead paylines to go down despite the fact that we're putting more and more money into the RPG pool every year.

In 2018, we had the biggest increase in the RPG pool since 2003 a \$120 million-plus increase in the RPG pool. And this year, we hope to put an additional \$100 million or more into the RPG pool, even though, as you know, the increase to our budget this year is roughly \$180 million dollars, but \$100 million of that is for the Moonshot. We will use the Moonshot funding for Moonshot purposes, so really, the increase to our general appropriation this year is \$80 million, and we plan to put more than that into the RPG pool.

**PG:** What's your goal for a success rate? I mean, you're having a really good problem.

**NS:** I agree, Paul. And thank you for discussing it that way. Some people trying to get an R01 from the NCI, may not necessarily see it as a good problem, but I have to keep reminding people that in some ways, it is.

But I think paylines last year were 9 percent that translated into a 12 percent success rate. We think paylines and success rates will both go down slightly in 2019.

And I think if we didn't make adjustments for fiscal year 2019—modest reductions to operating budgets for NCI divisions, reducing new, non-modular R01s by an additional two percent, and reducing many noncompeting



## Protect the RPG pool

1. Increase total dollars in the RPG pool by \$100 million over the FY 2018 level.
2. Reduce most awards that are extensions (continuations of existing grants) by 3%.
3. Adjust R01 payline to the 8th percentile (from the 9th in FY 2018).
4. Other modest reductions will be applied to certain grant types.

grants by 3 percent—paylines would be lower still.

The adjustments we're making adjustments allow NCI to put more money into the RPG pool and keep the payline as healthy as possible.

**MO:** How are the “haircuts”—as Harold Varmus used to call them—for NCI’s budget proceeding? Have they been enacted?

**NS:** We are enacting them. I’m having discussions with all division directors about how they’re experiencing the cuts to their operating budget. Grants and salaries are exempted from the division cuts. So, the cuts to the actual divisions are smaller than you might imagine.

But the traditions at the NCI for the last few years have been for the budgets to go up. So, any cut at all is different from the status quo and it is causing some hardship. I think that no one’s enthusiastic about this, but I think everybody understands the issue. We’ve discussed these data about increasing grants internally and everyone agrees it’s a good problem, as we said, so, the NCI leaders agree that we want these grants coming in and we’d like people to send their ideas for funding.

We want to try to support them and really support innovation to the extent possible. And therefore, I think the purpose of the haircuts, as you called them, is well understood. And I think there’s buy-in on why we have to do this.

**PG:** And also, of course, NCI has the largest intramural program at NIH, the last time I checked. So, there’s some room there, potentially.

**NS:** A criticism lobbed at the NCI from the extramural world sometimes is we don’t have the means to really evaluate ongoing programs and decrease them or terminate them when timely. These haircuts really forced the division chiefs to do that to some extent. I’m asking them to find the savings in their division and they are using this opportunity to really think about what their priorities are. So, in some ways it’s not unhealthy for an organization that can do things like this.

## Stay true to the vision of the Cancer Moonshot

Funds appropriated by Congress for the Cancer Moonshot (\$400 million in FY 2019) will be spent exclusively to support research activities that implement the recommendations of the Blue Ribbon Panel.

Extensions or continuations of existing grants awarded for Cancer Moonshot research will not be subject to the 3% reduction applied to other continuing grants.



We decided to not to apply the cuts to cancer centers. The cancer centers are very good investments for the NCI. I've traveled to most of the cancer centers and I think for every dollar we spend there, they bring in—in some places it's \$5, in some places a lot more than that.



**MO:** Are the percentages still the same? Five percent cuts to the NCI divisions, offices, and centers, and 3 percent cuts to the noncompeting awards?

**NS:** The three percent cut only applies to certain types of noncompeting, continuing awards. First off, let me say what we're not cutting. We're not cutting training grants, cancer center support grants, SBIRs, the Moonshot, and very specific small awards. But beyond that, all the other continuing RPGs are getting cut.

There are two main reasons why we decided to not to apply the cuts to cancer centers. The cancer centers are very good investments for the NCI. I've traveled to most of the cancer centers and I think for every dollar we spend there, they bring in—in some places it's \$5, in some places a lot more than that.

So, it is a highly leveraged funding. But the other reason and probably the more important one, frankly, is that [former NCI Director] Harold Var-mus asked to refine to cancer center funding model.

There were years of discussion about this and we finally hit upon a plan that would involve increasing the funding of small centers. So that plan was to be implemented over five years as each of the existing centers come in for recompetition.

We're committed to that plan and we're only one year into it. This is a difficult funding model to implement and now that it has started, I don't feel like it's time to back away from it yet.

So, the cancer centers are a good investment and we're going to continue to maintain our commitment to the funding model. Now I can't say, if we were to have an even more difficult budget year next year that the cancer centers would always be off the table.

## Continue to prioritize ESIs

Maintain the payline for ESIs at the 14<sup>th</sup> percentile

Extensions or continuations of existing grants for research training programs (e.g. T-, F- and K-awards) will not be subject to the 3% reduction applied to other continuing grants.

But I think for this year, at least, we've preserved them.

**PG:** How is NCI using this year's Moonshot funds? At \$400 million, it's the largest authorization in the seven-year lifespan of the initiative.

**NS:** That's right. First off, we are using the Moonshot funds for the purposes identified by the Blue Ribbon Panel. As you know, science evolves and some of the opportunities look a little different today than they did three or four years ago. For the most part we are trying to hew as closely as possible to the plan established by the vision identified by the Blue Ribbon Panel.

In other words, we're sticking to the Moonshot goals. As you know, there's flexibility in the funding that allows us to fully fund certain grants in the

first year and we could carry over other funds as needed. And so that flexibility is really important this year, because \$400 million is the high watermark, next year it goes to \$200 million.

We have to plan for that so that we can experience that in a way that's not fiscally irresponsible for the NCI. As you know, most of the awards, even though we do have the ability to pre-fund the grants to be funded over multiple years. And so, the things we award this year will have significant out-year costs, so we have to plan for that too.

Therefore, I would say that there will be a lot of new funding announcements this year along the lines of the Moonshot goals. You have the 10 recommendations from the Blue Ribbon Panel. But this will be the last big year for the Moonshot. Next year, we will have some monies for new initiatives.

This will not be the last year of new initiatives in the Moonshot, but it'll be less because next year, the proportion

of the budget consumed by our costs will be a lot higher. So, I've been telling people that are interested in getting funding that they carefully look at the RFAs on the Moonshot website, because there are several open now and there'll be a lot of additional ones opening this year.

**MO:** So, basically it sounds like this year's Moonshot increase allows the institute to jumpstart funding for more projects and RFAs?

**NS:** That's right. I think the 10 recommendations of the Blue Ribbon Panel are really exciting. There's some great stuff in there and we have been working diligently on new concepts that will be published this year. The Blue Ribbon Panel's vision was a good one and it allows us to really dedicate very targeted funding to important, mostly transla-

tional, initiatives. The idea is getting cutting-edge science into patient care as rapidly as possible.

**PG:** In JAMA this week, you co-wrote a piece with Jim Doroshov in which you described the NCI approach to modernizing clinical trials. Could you recap the institute's new approach to clinical trials? How is it being done and what might be the impact on the groups and the cancer centers?

**NS:** I think this is such an important topic. When I talk to colleagues at cancer centers, I hear a lot of frustration, but also just a lot of questions, a lot of lack of clarity.

It seems like people don't understand what the NCI's vision is for clinical trials. So, I think we have to admit, as a specialty, that clinical trials have really changed in oncology and that's a good thing. It reflects scientific progress and better drugs for patients with less toxicity.

But it does mean we have to do things differently. And there are a lot of people who liked doing things the old way and so that's a little uncomfortable for some of them and getting them to buy into these changes is really the NCI director's job. We're trying to make the point in a number of ways—different structures of trials, things like the NCI-MATCH trial or Lung-MAP, or the DART trial, it's trying to not compete with industry but complement industry.

So, we have to accept that industry sponsors fund the majority of clinical trials in oncology in the United States. NCI has to really decide what are the kinds of trials that it should do with our considerable investment. We spend a lot of money on clinical trials, but that

money should be complimentary to what is being spent by industry, not competitive.

So, I thought about a lot of what these trials are, things like deescalation studies and multimodality trials, and trials that combine different agents from multiple companies that are hard for them to do for a variety of reasons. And really that's sort of the sweet spot for the NCI to be involved.

And then, as you know, we are putting more funding into clinical trials and we believe that the clinical trials infrastructure has been under-resourced and we are trying to address that issue. We were able to add \$10 million to the National Clinical Trials Network, for example, last year. I hope to be able to do the same this year. I don't know if that will be enough.

I hope even in future years we will be able to add more money to NCTN, but at least for the first two years, so far so good. We're also adding new money, I hope this year, to the NCORP. The NCI Community Oncology Research Program has become a really important venue to do many trials that are a good fit for community oncology, and that, additionally needs more support.

**MO:** What do we need to know about NCI's efforts on Big Data over the past year? Are you also expanding the institute's work on real-world evidence?

**NS:** It's an area where there's a lot going on and we have a lot of dynamic, interesting initiatives, but I think some of them are a little less visible, because they tend to be weedy infrastructure stuff like building a different computer architecture that makes the data much more useful.

I'm not sure people notice unless they are direct consumers of that data on a day-to-day basis. But we've begun to implement this cancer research data commons framework. So, we took the success of what started with The Cancer Genome Atlas and then became the Genomic Data Commons, and realized that single node can be replicated for other kinds of data—data commons for imaging and data commons for proteomic data, and data commons for a variety of other sorts of data.

And then, that can all be shared and linked through a common metadata data aggregator. We believe the framework for using this will be these cloud initiatives that the NCI supported over the last few years, the so-called cloud pilots that we now call the cloud resources, because we've been very successful and we continue to support that.

So, we have a pretty clear vision for how we're going to get more data to our academic investigators as quickly as possible, but the details of each node matter, like how do you get the clinical annotation for the genomic data—that turns out to be an authority problem that we are talking with industry and academic partners about how to do that better. We have a real focus on working with the FDA and we've had a lot of lively, ongoing discussions with Sean Khozin and colleagues at the FDA about how the NCI can use some of their pristine and wonderful trials data for our purposes. I think the FDA's enthusiastic about that.

I also believe, with Amy Abernethy coming to be the deputy commissioner [at FDA]—she's a longtime friend of mine, but she's also somebody who really understands Big Data at a very sophisticated level, given her background in Flatiron—I think will be a real champion for data usage between the FDA and NCI.

And then, lastly, and perhaps most importantly in data, I'm about to hire a



new director for the Center for Biomedical Informatics and Information Technology. Although the title sounds a little weedy, I really envision that person being the visionary, data strategist for the National Cancer Institute, and so, that person will be very important to figure out where we need to be in 20 years.

**PG:** Can you tell us who that is?

**NS:** I've been interviewing candidates. I will say the application pool is very strong. The search committee was led by Stephen Chanock and they've produced a great roster for me to interview. I'm midway through the interviews and I'm sure we're going to find somebody great.

**PG:** You've laid out your vision for the institute since you've become director—how are these priorities coming along? How's your checklist looking?

**NS:** You know, some checks are bigger than others, pun intended. I have been encouraged. I feel like the extramural community has bought into these key focus areas (big data, clinical trials, workforce development, and basic science).

What I'm finding is a lot of people saying, "How can we help? And if you're interested in Big Data, you should do this." For example, I was at the Broad Institute and they have a lot of great ideas on how the NCI could do data differently. And so, we really need to take advice from the extramural community, be educated by them.

I've become very fond lately of this Harry Truman quote: "Doing the right thing is easy. Knowing what the right thing to do is hard." We have a lot of

laudable things we want to do, but exactly how you're making them happen mechanically can be challenging.

I also feel like the intramural program is very strong and continues to advance these sorts of scientific areas where the intramural program is really well suited to do that. I feel like my efforts to get out within the intramural program and meet people and have a lab on campus and to really understand what's causing difficulties for the scientists, has gone over well.

And then, I'm also now becoming more involved with the NIH Clinical Center which has a lingering set of issues. As you may know, the NIH suffered a tremendous loss late last year when Steve Katz passed away. Steve was the director of NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases and served as the chair of NIH's Clinical Center Governing Board for many years. [NIH Director] Francis Collins has asked me to take over that chair role for the clinical center because of my passion on this topic, so I hope to continue to support the intramural program and the clinical center as much as possible. And I think that has been very appreciated in my first year at the NCI.

**MO:** Do you have any new plans or goals for NCI in the new calendar year? Anything you didn't see before that you see now?

**NS:** I think they will look new to some people, because they will be the extension of the things that we've said from day one we're trying to do, but I think we'll now start to see some of those things happen.

We've discussed a lot about new funding announcements, and for the Moon-

shot, some of those will actually come to fruition this year. And as you've probably followed, a few of those topics were particular challenging if you had a lot of feedback in discussion with the NCAB to get those cleared and the BSA to get this cleared.

I think now I'm very excited about some of these things that will be coming out this year. I think the continued focus on clinical trials is starting to play positively and then, we have some new stuff in the works that hopefully we'll be able to talk about more as they come to pass. But they will be, in a way, hopefully surprising new visions, but also hopefully unsurprising and is exactly in line with the things we said we will do.

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

**NS:** The state of the NCI is good. As we've discussed, in 2019, NCI will increase support for cancer research through RPGs, we'll stay true to the vision of the Cancer Moonshot, and we'll continue to support early-stage investigators and cancer centers.

Any downward trend in the payline is concerning, but it has to be seen as a good problem. The field is vibrant, and competition is good for science. Good cancer science will ultimately benefit patients.

I don't know if you saw Gideon Blumenthal and Rick Pazdur's [article](#) in *Nature Reviews Oncology* that came out Tuesday, but it shows all these drugs approved. It's just remarkable and that doesn't happen by accident. That certainly doesn't happen solely by industry.

If you look at those drugs, many of them are the result of long, detailed, basic science and clinical trials funded by the NCI. And so, I think we can claim a lot of credit for that success there.



# FDA approves 19 new cancer drugs and biologics in 2018—and don't forget two new endpoints and “real-time” review

By Claire Dietz and Matthew Bin Han Ong

Last year, FDA approved 19 applications for new cancer drug and biologics as well as 38 supplemental indications and four biosimilars, agency officials said.

“These advances in anticancer therapy included a landmark approval of the first histology-agnostic, biomarker-defined new molecular entity and approvals based on real-time data review and novel end points,” Gideon Blumenthal, acting deputy director of FDA’s Office of Hematology and Oncology Products and Richard Pazdur, director of the Oncology Center of Excellence at FDA, wrote in a Jan. 22 [commentary](#) published in *Nature Reviews*.

Overall, in 2018, FDA approved [59 novel drugs](#), breaking its record of 53 drugs in 1996—with the largest share of approvals being in oncology.

In one of the highlights in cancer, in November 2018, the agency approved larotrectinib, the first ever oral tyrosine kinase inhibitor for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic recep-

tor tyrosine kinase gene fusion without a known acquired resistance mutation (*The Cancer Letter*, [Nov. 11, 2018](#)).

“If you look at the rank-and-file signaling stuff, all these things in the RTK pathway, the NCI intramural scientists had been a big part of that,” NCI Director Ned Sharpless said to *The Cancer Letter*. “Obviously, just getting back from the University of Pennsylvania and spending time with Carl June, you know, CAR-T cells, they were freaking science fiction like three years ago. It’s unbelievable.”

“That’s going to change oncology and those things were certainly really heavily supported extramurally and intramurally by the NCI. It’s just remarkable and that doesn’t happen by accident and that certainly doesn’t happen solely by industry.”

Also, FDA has developed two new endpoints:

- Metastasis-free survival, a prolonged delay in the development of metastatic disease as an objective and clinically relevant outcome (*The Cancer Letter*, [July 20, 2018](#)). The MFS endpoint was used to approve apalutamide and enzalutamide.
- Minimal residual disease, for the approval of blinatumomab for B cell-precursor acute lymphoblastic leukemia (*The Cancer Letter*, [March 9, 2018](#)).

Blinatumomab was indicated for adult and pediatric patients “who were in first or second complete remission with minimal residual disease  $\geq 0.1\%$  on the basis of the MRD response rate—that is, the achievement of undetectable MRD after one cycle of treatment us-

ing a test with a sensitivity of 0.01%,” Blumenthal and Pazdur wrote.

FDA has approved several agents using Real-Time Oncology Review, a pilot review program. In November, the agency expanded the approved use of Adcetris (brentuximab vedotin) injection in combination with chemotherapy for adult patients with certain types of peripheral T-cell lymphoma (The Cancer Letter, [Nov. 16, 2018](#)).

In the commentary, Blumenthal and Pazdur listed a number of significant approvals, including many molecularly targeted therapies:

- Novel small-molecule tropomyosin receptor kinase inhibitor larotrectinib, for treatment of pediatric/adult patients with unresectable or metastatic NTRK gene fusion-positive solid tumors, irrespective of tumor histology. In the main study, the confirmed ORR in 55 patients was at 75%, and 39% of responses lasted for at least a year
- 12 tumor types were represented, from non-small cell lung cancer to infantile fibrosarcoma
- Talazoparib and olaparib, for metastatic breast cancer with deleterious germline BRCA mutations
- Lorlatinib, for metastatic, ALK-rearranged NSCLC
- Dacomitinib, afatinib, and osimertinib, for metastatic NSCLC with EGFR aberrations
- Encorafenib plus binimetinib, for advanced-stage BRAFV600E/K; and dabrafenib plus trametinib for the adjuvant treatment of BRAFV600E/K-mutant melanoma
- Gilteritinib or ivosidenib monotherapy for patients with relapsed and/or refractory FLT3-mutant or IDH1-mutant AML
- Glasdegib or venetoclax in combination with low-dose cytarabine, for patients with newly diagnosed AML 75 years and over who have co-morbidities precluding intensive chemotherapy
- Apalutamide and enzalutamide, metastatic free survival in non-metastatic castration-resistant prostate cancer
- Blinatumomab, for adult/pediatric patients with B cell-precursor acute lymphoblastic leukemia in first or second remission with minimal residual disease
- ClonoSEQ, a next-generation sequencing assay, for the detection and monitoring of MRD in patients with ALL or multiple myeloma
- Label expansion for tisagenlecleucel, a chimeric antigen receptor T cell product, to include some patients with relapsed/refractory large B cell lymphoma
- Cemiplimab-rwlc, a PD-1 antibody, for advanced-stage cutaneous squamous cell cancer
- Label expansions for several anti-PD-1 or anti-PD-L1 antibodies, as monotherapies or in combination with chemotherapy or anti-cytotoxic T lymphocyte antigen 4 (CTLA-4)
- Label restrictions for pembrolizumab and atezolizumab, in the initial treatment of advanced-stage cisplatin-ineligible patients with PD-L1-positive tumors according to FDA-approved companion diagnostics or those ineligible for any platinum-containing chemotherapy (regardless of PD-L1 expression).

A list of cancer indications approved in 2018 follows.

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Obviously, just getting back from the University of Pennsylvania and spending time with Carl June, you know, CAR-T cells, they were freaking science fiction like three years ago. It's unbelievable.

”

– Ned Sharpless

**SUMMARY OF FDA ONCOLOGY DRUG APPROVALS IN 2018 (IN DECREASING CHRONOLOGICAL ORDER)** – Source: FDA

Drug	Indication	Type	Comments
Pembrolizumab	Adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma	Supplement	PR, AA
Olaparib	First-line maintenance treatment of patients with newly diagnosed BRCA-mutated advanced-stage ovarian cancer	Supplement	PR, AAid
Calaspargase pegol-mknl	As a component of a multi-agent chemotherapeutic regimen for patients with ALL	New	—
Tagraxofusp-erzs	Adult and paediatric patients aged $\geq 2$ years with blastic plasmacytoid dendritic cell neoplasms	New	PR, BTd, OD
Trastuzumab-pkrb	Trastuzumab biosimilar for use in patients with HER2-overexpressing breast cancer	Biosimilar	—
Atezolizumab	In combination with bevacizumab, paclitaxel, and carboplatin for first-line metastatic non-squamous NSCLC	Supplement	PR
Gilteritinib	Relapsed and/or refractory FLT3-mutant AML	New	FTD, PR, OD, CoDx
Rituximab-abbs	Rituximab biosimilar for patients with CD20-positive, B cell NHL to be used as a single agent or in combination with chemotherapy	Biosimilar	—
Larotrectinib	Adult and paediatric patients with advanced-stage or metastatic solid tumours that have a NTRK gene fusion who have no satisfactory alternative treatments	New	BTd, PR, AA, OD
Venetoclax	In combination with azacytidine or decitabine or LDAC for newly diagnosed AML in patients $\geq 75$ years of age or in those with comorbidities precluding intensive induction chemotherapy	Supplement	BTd, PR, AA, OD
Glasdegib	In combination with LDAC for newly diagnosed AML in patients $\geq 75$ years of age or in those with comorbidities precluding intensive induction chemotherapy	New	PR, OD
Emapalumab	Adult and paediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease or who are intolerant of conventional HLH therapy	New	BTd, PR, OD
Brentuximab vedotin	In combination with chemotherapy for adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T cell lymphoma	Supplement	BTd, RTOR, PR, AAid
Pembrolizumab	HCC previously treated with sorafenib	Supplement	PR, AA
Lorlatinib	Metastatic ALK-positive NSCLC after disease progression on another ALK inhibitor	New	BTd, PR, AA, CoDx, OD
Pembrolizumab	In combination with carboplatin and paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC	Supplement	PR
Talazoparib	Deleterious or suspected deleterious germline BRCA- mutated, HER2-negative, locally advanced or metastatic breast cancer	New	PR, CoDx
Cemiplimab-rwlc	Metastatic or locally advanced cutaneous squamous cell carcinoma	New	BTd, PR
Dacomitinib	First-line treatment of metastatic NSCLC with an EGFR exon 19 deletion or exon 21 L858R substitution	New	PR, OD, CoDx
Duvelisib	Relapsed and/or refractory CLL, SLL or FL after at least two prior therapies	New	PR, OD

Moxetumomab pasudotox-tdfk	Relapsed and/or refractory hairy cell leukaemia after at least two prior systemic therapies, including a purine nucleoside analogue	New	PR, FTD, OD
Pembrolizumab	In combination with platinum and pemetrexed for the first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK aberrations	Supplement	RTOR, PR
Pembrolizumab	Label update: restricted use to patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (CPS $\geq 10$ ), or those who are not eligible for any platinum-containing chemotherapy	Supplement	CoDx
Atezolizumab	Updated Label: restricted use to patients with locally advanced-stage or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (stained tumour-infiltrating immune cells covering $\geq 5\%$ of the tumour area), or those who are not eligible for any platinum-containing chemotherapy	Supplement	CoDx
Nivolumab	Metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy	Supplement	PR, AA
Lenvatinib	First-line treatment of patients with unresectable HCC	Supplement	—
Mogamulizumab-kpkc	Relapsed and/or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy	New	BTD, PR, OD
Iobenguane I-131	Adult and paediatric patients (aged $\geq 12$ years) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy	New	BTD, PR, FTD, OD
Ivosidenib	Relapsed and/or refractory AML with a sensitizing IDH1 mutation	New	PR, FTD, OD, CoDx
Ribociclib	In combination with an aromatase inhibitor as initial endocrine-based therapy for premenopausal or perimenopausal women with HR-negative, HER2-negative advanced-stage or metastatic breast cancer	Supplement	PR, FTD, RTOR, AAid
Enzalutamide	Non-metastatic CRPC	Supplement	—
Ipilimumab	In combination with nivolumab for patients aged $\geq 12$ years with MSI-H or dMMR mCRC that has progressed following fluoropyrimidine, oxaliplatin and irinotecan therapy	Supplement	BTD, PR, AA
Nivolumab	In combination with ipilimumab for patients aged $\geq 12$ years with MSI-H or dMMR mCRC that has progressed following fluoropyrimidine, oxaliplatin and irinotecan therapy	Supplement	BTD, PR, AA
Encorafenib	In combination with binimetinib for patients with unresectable or metastatic BRAFV600E/K-mutant melanoma	New	CoDx, OD
Binimetinib	In combination with encorafenib for patients with unresectable or metastatic BRAFV600E/K-mutant melanoma	New	CoDx, OD
Pembrolizumab	Adult and paediatric patients with refractory primary mediastinal B cell lymphoma	Supplement	PR, OD, AA
Bevacizumab	In combination with carboplatin and paclitaxel after initial surgical resection of stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer	Supplement	OD
Pembrolizumab	Recurrent or metastatic cervical cancer that has progression on or after chemotherapy and has expression of PD-L1 (CPS $\geq 1$ )	Supplement	PR, AA, CoDX

Venetoclax	CLL or SLL with or without 17p deletion after at least one prior therapy	Supplement	BTD, PR
Pegfilgrastim-jmdb	Pegfilgrastim (Neulasta ) biosimilar	Biosimilar	—
Epoetin alfa-epbx	Epoetin alfa (Epogen /Procrit ) biosimilar	Biosimilar	—
Dabrafenib	In combination with trametinib for anaplastic thyroid cancer with BRAFV600E mutation	Supplement	BTD, PR, OD
Trametinib	In combination with dabrafenib for anaplastic thyroid cancer with BRAFV600E mutation	Supplement	BTD, PR, OD
Tisagenlecleucel	Adult patients with relapsed and/or refractory large B cell lymphoma after two or more lines of systemic therapy	Supplement	BTD, PR, OD
Dabrafenib	In combination with trametinib for adjuvant treatment of BRAFV600E/K-mutant melanoma with lymph node involvement	Supplement	BTD, PR, CoDx
Trametinib	In combination with dabrafenib for adjuvant treatment of BRAFV600E/K-mutant melanoma with lymph node involvement	Supplement	BTD, PR, CoDx
Osimertinib	First-line treatment of metastatic NSCLC with an EGFR exon 19 deletion or exon 21 L858R substitution	Supplement	BTD, PR, CoDx
Ipilimumab	In combination with nivolumab for intermediate or poor risk, previously untreated advanced-stage RCC	Supplement	BTD, PR
Nivolumab	In combination with ipilimumab for intermediate or poor risk, previously untreated advanced-stage RCC	Supplement	BTD, PR
Everolimus tablets for oral suspension	Adjunctive treatment of adult and paediatric patients aged $\geq 2$ years with TSC-associated partial-onset seizures	Supplement	—
Rucaparib	Maintenance treatment of recurrent ovarian, fallopian tube or primary peritoneal cancer after a complete or partial response to platinum-based chemotherapy	Supplement	PR
Blinatumomab	Adult and paediatric patients with B cell-precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%	Supplement	PR, OD, AA
Nilotinib	Paediatric patients aged $\geq 1$ year with newly diagnosed Ph+ CML-CP or those with Ph+ CML-CP that is resistant to, or who are intolerant of, prior TKI therapy	Supplement	PR, OD
Brentuximab vedotin	Previously untreated stage III or IV cHL, in combination with chemotherapy	Supplement	BTD, PR
Abemaciclib	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with HR-negative, HER2-negative advanced-stage or metastatic breast cancer	Supplement	PR
Durvalumab	Unresectable stage III NSCLC that has not progressed following concurrent platinum-based chemotherapy and radiation therapy	Supplement	BTD, PR
Apalutamide	Non-metastatic CRPC	New	PR
Abiraterone acetate	Non-metastatic CSPC	Supplement	PR
Lutetium Lu-177 dotatate	Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours, including foregut, midgut and hindgut neuroendocrine tumours	New	PR, OD
Afatinib	Broadened indication in the first-line treatment of metastatic NSCLC 'non-resistant' EGFR mutations other than exon 19 deletions or exon 21 L858R substitution	Supplement	PR, OD, CoDx
Olaparib	Deleterious or suspected deleterious germline BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer	Supplement	PR, CoDx



# CONQUERING CANCER IN KENTUCKY

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

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CONVERSATION WITH  
THE CANCER LETTER

## Brawley aims to create a “huge collaboration” in research on disparities

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I am going to focus on the large number of lives lost because of lack of good care as well as wasted medical care that often feels good, but is not based in good science and is really a waste of resources that increases the number of people with poor outcomes.

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**Otis Brawley**

*Associate director for community outreach and engagement,  
JHU's Bloomberg School of Public Health,  
Johns Hopkins Kimmel Cancer Center.*

Otis W. Brawley was named the Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University.

Brawley will lead a broad interdisciplinary research effort of cancer health disparities at JHU's Bloomberg School of Public Health and the Johns Hopkins Kimmel Cancer Center, focusing on disparities in the prevention, detection, and treatment of cancer in the U.S. and worldwide.

In his role as the associate director for community outreach and engagement at Hopkins, Brawley will focus on programs for underserved populations throughout the cancer center's catchment area. Also, he will teach undergraduate and graduate students in the Department of Epidemiology in the Bloomberg School, the Department of Oncology at the School of Medicine, and the university's Krieger School of Arts and Sciences.

And he will see patients. "I will continue to see patients for as long as I am a physician," said Brawley, who will be seeing prostate cancer patients. "Seeing patients is what keeps me grounded."

Brawley was most recently the chief medical and scientific officer for the American Cancer Society (The Cancer Letter, [Nov. 9, 2018](#)). He is also a former director of the Georgia Cancer Center at Grady Memorial Hospital in Atlanta and former professor of oncology and hematology and deputy director for cancer control at the Winship Cancer Institute at Emory University.

Brawley is a member of the National Academy of Medicine and a recent recipient of the Martin D. Abeloff Award for Excellence in Public Health and Cancer Control from the Maryland State Council of Cancer Control.

"My jobs are to do outreach and engagement, to do health practices work,

to continue much of the health disparities work that I had already been doing at the American Cancer Society," Brawley said. "I anticipate that moving to Hopkins will allow me to have some academic freedoms to get involved in the political process, influence policy in ways that you just cannot do from a not-for-profit foundation."

Brawley is the 39th Bloomberg Distinguished Professor at Hopkins. The program is backed by a \$350 million gift from Michael R. Bloomberg, a Johns Hopkins alumnus, founder of Bloomberg Philanthropies, World Health Organization Global Ambassador for Noncommunicable Diseases, UN Secretary-General's Special Envoy for Climate Action, and former New York City mayor.

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

**Paul Goldberg:** First a trick question: What do Michael Bloomberg, Sidney Kimmel and David Koch have in common?

**Otis Brawley:** It is ironic that those three names would be in my letterhead. I am the Michael Bloomberg Distinguished Professor in the Sidney Kimmel Cancer Center, sitting in the David H. Koch Cancer Research Building.

**So, what is the job?**

**OB:** I have been given a tremendous opportunity, and that opportunity is to come to Johns Hopkins and work with some amazing people, some amazing people who do great epidemiology, great prevention work, great outreach,

great advocacy—and come here and work with them, and actually try to explain to the people of Baltimore, the people of Maryland, and the American people how you can apply good science to oncology, to cancer medicine, to public health and how we can reduce the rate of death from cancer by applying good science.

At the same time, I have an opportunity to show them how we are slowing down our progress in cancer by applying bad science.

**What's the war chest for this?**

**OB:** In many respects, the war chest is of infinite depth. In many respects, the well is unlimited. What I have are resources of a number of incredibly gifted people here at Hopkins.

The attraction of coming to Hopkins was, there already is just an amazing group of people working here doing health disparities research, doing health practices research, and I get to come here and work with the A-team.

These are folks, many of whom I have known and admired for my entire career, some of whom I have had the opportunity to work with very successfully. And now, I get to work with them on a daily basis.

**Are you going to be focusing this group that's already there, plus building onto it?**

**OB:** We have the opportunity to work with the current group as well as to bring additional talent in, and really build an institute that will be looking at community outreach, health practices and cancer control.



So, you're recruiting?

**OB:** Yes.

What are the jobs? How many people?

**OB:** That has not been totally determined yet. But I can tell you I already have office space. That's a big thing in the academia.

Yes, the Koch building.

**OB:** The first day I arrived, they said, "Oh, here's your office, and here's several additional offices for faculty members, and here's some cubicles for graduate students."

That way I have space both in the medical school, and I have space in the School of Public Health.

So, you're focusing the outreach and engagement, among other things; right?

**OB:** My jobs are to do outreach and engagement, to do health practices work, to continue much of the health disparities work that I had already been doing at the American Cancer Society.

I anticipate that moving to Hopkins will allow me to have some academic freedoms to get involved in the polit-

ical process, influence policy in ways that you just cannot do from a not-for-profit foundation.

Can you tell me, roughly, what you think the low hanging fruit would be?

**OB:** Well, clearly low hanging fruit is, you know, I have a number of contacts in Washington. I talk to a number of elected officials as well as policymakers on a regular basis. I've been doing that for 20-plus years. Now I'm very close to Washington, and I think I can speak more openly and freely with those policymakers.

And publish?

**OB:** I also have the ability to write and to publish.

How then, can one center move the needle on problems that are so engrained?

**OB:** I don't think it's actually just one center that can move the needle.

I'm hoping that there's a community of cancer control expertise across the country at a number of places and I'm hoping that from this position I'm going to be able to work with cancer control experts across the country and organize all of this.

And, you know, I'm not suggesting that we're going to create a union of cancer

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Too much of what I hear of called 'cancer control' is not based in science, and actually increases disparate and poor outcomes for blacks and for whites; for the rich and for the poor. What this country needs is some leadership in implementing cancer control based in scientific fact. And that's what I plan on doing.

”



control experts, but we're going to create a huge collaboration.

And part of the job is not just outreach into the community of Baltimore, Md. That is a big part of it. I actually look at being able to work in Baltimore, Md, and use that as a laboratory to demonstrate what things can be done in terms of cancer control and education, as well as in terms of changing the communities' outlook on health care.

But I also think that we, as a group of cancer control experts, can really come together from universities far and wide. You know, there's some amazing talent in cancer control, which is really a discipline that came up in the 1970s out of the National Cancer Act.

We are at a point in time where we have defined many of the causes of cancer, and now we just have to organize ourselves and constructively start applying what we know in cancer control science.

I am going to focus on the large number of lives lost because of lack of good care as well as wasted medical care that often feels good, but is not based in good science and is really a waste of resources that increases the number of people with poor outcomes.

**Well, if I may express an opinion, it's good to see NCI require outreach and engagement in such a very clear way, because here is the institute basically saying, "Go out there and help somebody."**

**OB:** There's some very, very smart people at the National Cancer Institute who understand science, who understand cancer control.

I think what you see, is one of the most important moves that the National Cancer Institute has made over the last 40 years. They are calling the cancer centers to get involved in community outreach and engagement.

And it is the National Cancer Institute telling its 60-plus NCI designated cancer centers, "You need to give to your communities, you need to take what we as a community of scientists have discovered and be a tool to implement that good science in your communities."

**And Baltimore is one fine place to do it.**

**OB:** That's right.

**Well, anything we missed?**

**OB:** Too much of what I hear of called "cancer control" is not based in science, and actually increases disparate and poor outcomes for blacks and for whites; for the rich and for the poor. What this country needs is some leadership in implementing cancer control based in scientific fact. And that's what I plan on doing.

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## IN BRIEF



## Rosanna Morris named chief operating officer at MD Anderson



Rosanna Morris was named chief operating officer at MD Anderson Cancer Center.

Morris currently is president of Beaumont Hospital, Royal Oak. The hos-

pital is part of Beaumont Health, Michigan's largest health system, which has 38,000 employees and 187 health centers.

Morris, a registered nurse, will begin her new duties overseeing inpatient and outpatient operations on April 22.

"Rosanna brings a demonstrated ability to rally people around delivering high quality care in the safest, most efficient and effective manner while exceeding patient expectations," said Peter Pisters, president of MD Anderson, to whom Morris will report. "She will work closely with me and our chief medical executive to oversee MD Anderson's clinical enterprise. We welcome her to MD Anderson and our executive leadership team."

Morris also has held a number of executive and clinical positions at Nebraska Medicine in Omaha; Avera McKennan Hospital and University Health Center in Sioux Falls, S.D.; Bert Fish Medical Center in New Smyrna, Fla.; and Stanford University.

## Health groups call for speedy end of shutdown

In a letter to the White House and Congressional leaders, 46 health groups urges an end to the government shutdown.

The text of the letter, dated Jan. 22, follows:

Dear Mr. President, Speaker Pelosi, Leader McConnell, Leader Schumer, and Leader McCarthy,

The undersigned organizations, representing millions of American patients, caregivers, healthcare providers, and researchers write to raise alarm at the continued gov-

ernment shutdown--particularly its impact on the U.S. Food and Drug Administration.

The work of the FDA to protect the health and wellbeing of our nation cannot be overstated. The agency regulates one quarter of the U.S. economy, ensures a safe food supply, protects patients from contaminated and unsafe medical products and, importantly, is the catalyst for expediting lifesaving therapies to patients.

On behalf of patients across this country, we are greatly concerned that the agency is currently not fully funded, and thousands of vital FDA employees are not working or able to operate at full capacity. While we applaud Commissioner Gottlieb, FDA leadership, and "essential staff" for truly heroic work to keep many aspects of its mission functioning, we fear that this continued shutdown not only puts the current health and safety of Americans at risk, but has begun to put future scientific discovery and innovation in jeopardy.

The ongoing government shutdown forces the FDA to make difficult choices regarding to which essential functions its greatly reduced resources are directed. These are decisions that never should have to be made—the health and safety of Americans today should never be weighed against the prospect of new life-saving therapies for patients. Tragically, that is what is happening.

We ask that the President and Congress act immediately to bring the FDA back to its full capacity. Americans' health and patients' futures are at stake."

## **Kyn Therapeutics partners with Celgene to develop immuno-oncology therapies**

Kyn Therapeutics said it has entered into a global strategic collaboration with Celgene Corp.

The goal of the collaboration is to develop novel immuno-oncology therapies through uniting Kyn's immuno-oncology expertise and pipeline with Celgene's capabilities for developing and commercializing medicines in areas of high unmet medical need. The collaboration begins with an upfront payment and an equity investment by Celgene, which receives exclusive options to license Kyn's aryl hydrocarbon receptor antagonist program and its kynurenine-degrading enzyme program.

AHR and kynurenine are associated with immunosuppression in a range of tumor types through multiple cellular metabolic mechanisms that modulate both innate and adaptive immunity. These attributes make them compelling targets for investigative therapies, in particular in patients who do not fully benefit from current treatments like checkpoint inhibitors.

Under the agreement, Kyn will receive an upfront cash payment of \$80 million and an equity investment from Celgene for exclusive options to globally license the Kynase and AHR antagonist programs.

For each program, Kyn is responsible for R&D activities through phase Ib, at which time Celgene can opt in to lead and fund global development and commercialization of the licensed programs. If successful, Kyn is eligible for substantial clinical, regulatory and commercial milestone payments. Kyn will also receive tiered royalties on worldwide net sales on products resulting from development of the licensed programs.

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## FUNDING OPPORTUNITIES



## Colorectal Cancer Alliance announces funding recipients for colon and rectal cancer research needs

Colorectal Cancer Alliance is providing a total of \$625,000 in grants to four researchers, including one advancing personalized treatment options for rectal cancer patients and three seeking to understand the root cause of rising colorectal cancer rates in patients under age 50.

Grant recipients include:

- J. Joshua Smith of Memorial Sloan Kettering Cancer Center who will build on his previous research using patient-specific rectal cancer organoids to grow human-specific rectal cancer models in mice as a platform for developing personalized treatments.
- Robin B. Mendelson of Memorial Sloan Kettering Cancer Center who will describe the gut microbiome of patients under age of 50, comparing them to the microbiomes of

older people with colorectal cancer and the microbiomes of younger healthy people.

- Joshua Meyer of Fox Chase Cancer Center who will describe the genetic and genomic features of colorectal cancer patients young and old, and thoroughly characterize the biology of young-onset colorectal in patients under 50 years old.
- Rosa Maria Munoz Xicola of the Yale School of Medicine will provide essential knowledge on how the APC-negative subset of colorectal cancers develop, which is crucial in the development of effective early detection tests and treatments. Xicola will also investigate whether the APC-negative subset disproportionately affects African Americans and young people.

The Colorectal Cancer Alliance is now accepting [applications](#) for its prevention research grants. The application deadline is 11:59 p.m., Monday, March 18, 2019.

## Funding opportunities for FY19–DOD Breast Cancer Research Program

The FY19 Defense Appropriation provides \$130 million to the Department of Defense Breast Cancer Research Program to support innovative, high-impact research with clinical relevance that will accelerate progress to end breast cancer for Service members, Veterans, and the general public.

FY19 BCRP Program Announcements and General Application Instructions for the following award mechanisms are posted on the Grants.gov website.

Applications submitted to the FY19 BCRP must address one or more of the following overarching challenges:

- Prevent breast cancer (primary prevention)
- Identify determinants of breast cancer initiation, risk, or susceptibility
- Distinguish deadly from non-deadly breast cancers
- Conquer the problems of overdiagnosis and overtreatment
- Identify what drives breast cancer growth; determine how to stop it
- Identify why some breast cancers become metastatic
- Determine why/how breast cancer cells lie dormant for years and then re-emerge; determine how to prevent lethal recurrence
- Revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival
- Eliminate the mortality associated with metastatic breast cancer

<https://cdmrp.army.mil/funding/bcrp>



# THE CLINICAL CANCER LETTER

## CLINICAL ROUNDUP



### Finasteride found to be safe, effective prevention for prostate cancer

Finasteride, a generic hormone-blocking drug, was found to reduce the risk of prostate cancer by 25 percent in the landmark Prostate Cancer Prevention Trial.

Long-term data, initially published in the *New England Journal of Medicine* in 2003, show that reduction in prostate cancer risk has continued, and fewer than 100 men on the trial died from the disease.

SWOG Cancer Research Network, an international cancer clinical trials group funded by the NCI opened the PCPT for enrollment 25 years ago. The PCPT enrolled 18,882 men from 1993 to 1997, making it one of the largest prostate cancer clinical trials ever conducted.

New results, which reported participant deaths over two decades, show that finasteride has the lasting effect of reducing prostate cancer risk. Results also eliminate concerns over initial findings of a possible risk of more aggressive cancers with finasteride use.

“Finasteride is safe, inexpensive, and effective as a preventive strategy for prostate cancer,” said Ian Thompson, principal investigator of the PCPT for SWOG. “Doctors should share these results with men who get regular prostate-specific antigen tests that screen for the presence of prostate cancer. The drug will have its greatest effect in this group of men.”

Thompson is chair of SWOG’s genitourinary cancer committee and serves as president of CHRISTUS Santa Rosa Hospital Medical Center in San Antonio, Tex., and as emeritus professor at the University of Texas Health Science Center.

Along with SWOG biostatisticians Catherine Tangen, and Phyllis Goodman, of Fred Hutchinson Cancer Research Center, Thompson sought to determine whether the increased number of high-grade cancers detected through the PCPT years ago would result in more prostate cancer deaths over time.

SWOG published the first PCPT results in 2003. Investigators reported a significant, positive result: finasteride reduced prostate cancer risk by 25 percent. But the study also cast a shadow on the drug, the first 5-alpha-reductase inhibitor which targets and blocks the action of androgen, like testosterone and is commonly used to treat lower

urinary tract problems in men and also male pattern baldness.

The results showed that finasteride increased the number of high-grade prostate cancers, a finding that resulted in a drug label warning posted by FDA. That warning remains in effect.

Thompson, Tangen, and Goodman matched participants to the National Death Index, a centralized database of death record information managed by the U.S. Centers for Disease Control and Prevention.

This analysis allowed the SWOG team to determine if a trial participant had died, and if so, the cause of death. With almost 300,000 person-years of follow-up and a median follow-up of 18.4 years, they found 42 deaths due to prostate cancer on the finasteride arm and 56 on the placebo arm. Thus, there was no statistically significant increased risk of prostate cancer death with finasteride.

In the *NEJM* letter, the team notes that a cheap, reliable prostate cancer prevention drug will have a big impact on public health. Due to a rise in screening for the disease, prostate cancer diagnoses are on the rise, with the American Cancer Society estimating that 164,690 American men would be diagnosed in 2018.

While many of these cancers will be slow-growing, and not life-threatening, they are still often treated with surgery and radiation, resulting in common complications such as impotence and incontinence.



“There are significant negative consequences to patients’ health and quality of life that can result from prostate cancer treatment, as well as to their finances and their peace of mind,” Thompson said. “If we can save people from surgeries, and scores of examinations and tests, and spare them from living for years with fear, we should. The best-case scenario for patients is prevention, and this trial has found an inexpensive medication that gets us there.”

NCI and the NIH funded the study through grants CA037429 and CA182883.

## Remote participation enables patients with ALK-positive lung cancer to enroll in study of treatment resistance

The Addario Lung Cancer Medical Institute and researchers from the Dana-Farber Cancer Institute are launching a novel nationwide study to understand why treatment resistance develops in a specific group of lung cancer patients.

The Study of Plasma Next Generation Sequencing for Remote Assessment, Characterization, Evaluation of Patients with ALK Drug Resistance uses the latest gene-sequencing technology on blood plasma of patients with a rare form of lung cancer.

The SPACEWALK study seeks to better understand the molecular causes of drug resistance to help doctors determine if switching to a different ALK inhibitor could prove beneficial.

Advances in gene-sequencing now allow doctors to understand a tumor’s genetic composition from a sample of a patient’s blood, sometimes called a

“liquid biopsy.” In the past, genomic analysis required patients to undergo an invasive biopsy to collect tumor tissue for testing.

With a liquid biopsy, doctors can analyze tumor DNA shed into the bloodstream, which means patients only need to go through a simple blood test. By using liquid biopsies, with blood samples shipped for analysis, the study enables patients across the country to participate. A study open to patients throughout the U.S. is especially important in conducting a meaningful study of uncommon conditions.

To learn more about this study, click [here](#).

## Servier & Taiho present Lonsurf data at ASCO 2019 GI Symposium

Note: The Cancer Letter has previously published information regarding this and can be found [here](#).

Servier and Taiho Oncology Inc., said the safety and efficacy data in the gastrectomy patient subgroup of the global phase III trial TAGS evaluating Lonsurf (trifluridine/tipiracil, TAS-102) in patients with metastatic gastric cancer are consistent with the overall study results published in *The Lancet Oncology*. These data were highlighted in an oral presentation at the ASCO 2019 Gastrointestinal Cancers Symposium.

In TAGS, 221 (44%) of the 507 randomized mGC patients had undergone prior gastrectomy (147 LONSURF, 74 placebo), which is reflective of the real-world patient population diagnosed with mGC. The results confirmed that trifluridine/tipiracil prolonged survival versus placebo regardless of prior gastrectomy.

The overall results of TAGS demonstrated that patients treated with oral trifluridine/tipiracil showed a clinically meaningful and statistically significant improvement in overall survival compared with placebo and a 31 percent risk reduction of death (HR 0.69 one sided  $p=0.00029$ ), which translated into a prolonged median survival of 2.1 months (5.7 months for trifluridine/tipiracil versus 3.6 months for placebo).

Trifluridine/tipiracil is indicated in E.U. for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapies, anti-VEGF agents, and anti- EGFR agents.

Applications for an additional indication in mGC for LONSURF are under review by health authorities in Japan, the US and the EU.

TAS-102 Gastric Study is a Taiho-sponsored pivotal phase III, multinational, randomized, double-blind study evaluating trifluridine/tipiracil, also known as TAS-102, plus best supportive care versus placebo plus BSC in patients with metastatic gastric cancer, including gastroesophageal junction cancer, refractory to standard treatments.

The primary endpoint in the TAGS trial is OS, and the main secondary endpoint measures include progression-free survival, and safety and tolerability, as well as quality of life.

TAGS enrolled 507 adult patients with metastatic gastric cancer who had previously received at least two prior regimens for advanced disease. The study was conducted in Belarus, the European Union, Israel, Japan, Russia, Turkey and the United States.

In Japan, Taiho Pharmaceutical Co., Ltd. has been marketing Lonsurf for the treatment of unresectable advanced or recurrent colorectal cancer since 2014.

In the U.S., beginning in 2015, Taiho Oncology Inc., began marketing the drug for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

In June 2015, Taiho and Servier entered into an exclusive license agreement for the co-development and commercialization of Lonsurf in Europe and other countries outside of the US, Canada, Mexico and Asia.

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## New test for esophageal cancer could save millions of lives

Stephen Meltzer, a professor of medicine and oncology at the Johns Hopkins University School of Medicine, along with a team of researchers, clinicians and biomedical engineers have created a test—the “EsophaCap”—that uses specific genetic biomarkers to detect dangerous changes in the cells that line the inside of the esophagus. The paper was published in *Clinical Cancer Research*.

Previous studies have demonstrated Meltzer’s biomarkers’ ability to detect a condition called Barrett’s esophagus, which causes the body to replace the tissue that lines the organ with cells that can turn cancerous.

But large-scale methods to deploy those biomarkers as a screening tool have been elusive until now.

The principle behind the EsophaCap is simple, said Meltzer. The patient swallows a small capsule that has a long string attached to it. After the capsule makes its way down the esophagus and into the stomach, the gelatin coating on the capsule begins to dissolve.

From that capsule emerges a 2-centimeter polyurethane sponge, still attached to the string, much of which still hangs from the patient’s mouth.

The screener gently pulls the string and the sponge begins its return journey, out of the stomach, into the esophagus and, finally, out of the patient’s mouth.

As it makes its way up, the sponge comes into contact with the entire length and breadth of the esophagus, collecting genetic material all along the way. Then, as the sponge nears the top, the screener gives a final gentle tug, popping the sponge past the organ’s upper sphincter muscle. The sponge emerges loaded with genetic material that holds the key to the patient’s esophageal health.

The sponge is then sent to a company that performs simple genetic tests on the material to determine the patient’s risk for esophageal cancer.

In previous research, Meltzer has performed rigorous testing on the set of genetic biomarkers he uses to diagnose Barrett’s esophagus. The gene combination of p16, NELL1, AKAP12 and TAC1 has yielded a sensitivity of nearly 92 percent and has offered reliable diagnoses.

Medicine has never had routine screening methods for the disease. Both endoscopy and biopsy are less-than-ideal, since they’re inexact, expensive and rely on random tissue samples, rather than material from the whole esophagus lining.

“It’s actually possible to miss early cancerous cells using endoscopy with biopsy and most patients with Barrett’s don’t ever undergo endoscopy,” said Meltzer. “Right now, we’re confident that we have the tools to identify this type of cancer. But we previously lacked a way to collect enough genetic material to confidently determine

a patient’s diagnosis. We believe that EsophaCap now provides a solution to this serious problem.”

Meltzer administered the EsophaCap test to 94 people over the course of the study. Eighty-five percent of subjects were able to swallow the capsule, with 100 percent successful sponge retrieval.

Endoscopic evaluation of the patients after EsophaCap administration, Meltzer reported, showed no evidence of bleeding, pain, trauma or other adverse reactions to the test.

In the journal article, Meltzer reports that of the patients able to swallow the capsule, nearly half would be diagnosed with Barrett’s esophagus—a rate far higher than that of the general U.S. population. He notes that most patients enrolled in the study were being treated for gastrointestinal symptoms.

This work was supported by NIH (Grants CA211457 and DK118250), the Emerson Cancer Research Fund and a Discovery Award from The Johns Hopkins University School of Medicine. Stephen Meltzer is the Harry and Betty Myerberg-Thomas R. Hendrix Professor and an American Cancer Society Clinical Research Professor. Zhixiong Wang was supported by a Scholarship from the China Scholarship Council (CSC) and the 3-3 Fund from the First Affiliated Hospital of Sun Yat-sen University.

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## AbbVie’s Imbruvica fails late-stage pancreatic cancer study

AbbVie announced an update on the phase III RESOLVE trial (PCYC-1137) of ibrutinib (Imbruvica) in combination with chemotherapy agents nab-paclitaxel and irinotecan.

taxel and gemcitabine versus placebo in combination with these chemotherapy agents in patients with metastatic pancreatic adenocarcinoma.

PCYC-1137 evaluated the efficacy of ibrutinib in combination with nab-paclitaxel and gemcitabine for the first-line treatment of patients with metastatic pancreatic cancer.

Patients were randomized 1:1 to receive ibrutinib and nab-paclitaxel and gemcitabine combination treatment arm (n=211 study patients) versus the placebo and nab-paclitaxel and gemcitabine combination treatment arm (n=213 study patients).

At conclusion, the study did not meet its primary endpoint of improving progression-free survival or overall survival benefit among the study population. Safety data collected from the study were consistent with the existing safety information for the study therapies.

The full results from this trial will be submitted for publication to a future scientific conference and/or a peer-reviewed medical journal.

PCYC-1137 is a Pharmacyclics sponsored randomized, multicenter, double-blind, placebo-controlled, phase III study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine, in the first-line treatment of patients with metastatic pancreatic adenocarcinoma.

Imbruvica is a first-in-class Bruton's tyrosine kinase inhibitor jointly developed and commercialized by Pharmacyclics LLC. Imbruvica has been available in the U.S. since 2013 and is FDA-approved for use in five B-cell blood cancers, as well as in chronic graft-versus-host-disease for a total of nine FDA-approved indications.

## DRUGS & TARGETS



## European Commission authorizes Rubraca tablets in ovarian cancer

The European Commission approved the use of Rubraca (rucaparib) for a second indication, as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The drug is sponsored by Clovis Oncology Inc.

This expands Rubraca's indication beyond its initial marketing authorization in Europe granted in May 2018 and with this label expansion, rucaparib is now available to patients regardless of their BRCA mutation status.

Rucaparib was the first PARP inhibitor licensed for an ovarian cancer treatment indication in the EU and is now the first to be available for both treatment and maintenance treatment among eligible patients.

The EC authorization is based on data from the phase III ARIEL3 clinical trial, which found that rucaparib significantly improved progression-free survival in all ovarian cancer patient populations studied.

The ARIEL3 trial was a double-blind, placebo-controlled clinical trial of rucaparib that enrolled 564 women with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy. Patients were randomized (2:1) to receive rucaparib tablets 600mg twice daily (n=375) or placebo (n=189).

ARIEL3 successfully achieved its primary endpoint, of extending investigator-assessed progression-free survival versus placebo in all patients treated (intention-to-treat), population, regardless of BRCA status; the key secondary endpoint of extending PFS as assessed by independent radiological review was also achieved.

An exploratory analysis of patients in the ITT population with measurable disease at baseline showed a tumor response was reported in 18% (95% CI 12%–26%) of patients (n=26) on rucaparib compared to 8% (95% CI 3% – 17%) of patients (n=5) on placebo (p value = 0.0069), including 10 patients (7%) in the rucaparib group who achieved a complete remission.

## Bristol-Myers Squibb withdraws U.S. application for Opdivo + Yervoy in first-line lung cancer

Following recent discussions with FDA, Bristol-Myers Squibb announced the voluntary withdrawal of the sBLA for the Opdivo and low-dose Yervoy (ipilimumab) combination for treatment of



first-line advanced non-small cell lung cancer in patients with tumor mutational burden  $\geq 10$  mutations/megabase.

In October 2018, the company announced the submission of an exploratory overall survival analysis for the TMB  $< 10$  mut/Mb subgroup to the FDA. The FDA determined at that time, that the submission of this new information constituted a major amendment to the sBLA and extended the review period by three months, moving the Prescription Drug User Fee Act date to May 20, 2019.

After recent discussions with the FDA, the company believes further evidence on the relationship between TMB and PD-L1 is required to fully evaluate the impact of Opdivo plus Yervoy on OS in first-line NSCLC patients.

This analysis will require availability of the final data from Checkmate -227, Part 1a (Opdivo plus low-dose Yervoy or Opdivo monotherapy versus chemotherapy in patients whose tumors express PD-L1), which the company anticipates will be available in the first-half of 2019. Since these data from Checkmate -227, Part 1a, will not be available within the review cycle of the current application the company decided to withdraw.

In January, the company announced the European Commission approved the combination of Opdivo plus Yervoy for the first-line treatment of patients with intermediate- and poor-risk advanced renal cell carcinoma.

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## FDA finalizes policy on labeling for accelerated approval drugs

FDA issued the final guidance, Labeling for Human Prescription Drug and

Biological Products Approved Under the Accelerated Approval Pathway, that aims to assist sponsors of drug and biological products in developing the Indications and Usage section of product labeling for products approved under the accelerated approval pathway.

The accelerated approval pathway is one of several approaches used by the FDA to expedite the development of drugs for serious or life-threatening diseases and conditions.

The FDA may grant accelerated approval to a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments.

This guidance focuses on how accelerated approval is represented in the Indications and Usage section of product labeling and offers recommendations to sponsors on language that best conveys different circumstances specific to accelerated approval.

During this period without a FY19 appropriation for the FDA, the agency has been focused on making sure it continues critical aspects of its work, to the extent permitted by law.

At this time, for products covered by a user fee program, our review of existing medical product applications and associated policy development regarding FDA review is funded by limited carryover user fee balances. The

FDA will continue to update the public on how it's approaching the work.

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## FDA grants Illumina's TruSight Assay Breakthrough Device designation

FDA has granted Breakthrough Device Designation for Illumina's its pan-cancer assay.

Currently in development, with plans to be marketed as TruSight Oncology Comprehensive, the assay is based on the content of Illumina's TruSight Oncology 500, designed to detect known and emerging solid tumor biomarkers. Illumina is seeking FDA approval of the assay as a companion diagnostic.

The assay utilizes both DNA and RNA from tumor samples to identify key somatic variants underlying tumor progression. These variants include small DNA variants, fusions, and splice variants, as well as immunotherapy-associated biomarkers such as tumor mutational burden and microsatellite instability, features that are potentially key biomarkers for immunotherapies.

The Breakthrough Device Program, which supersedes the FDA's Expedited Access Pathway, is designed for certain medical devices and device-led combination products that provide for more effective treatment in diagnosing life-threatening or irreversibly debilitating diseases or conditions.

The Breakthrough Devices Program contains features of the EAP, as well as the Innovation Pathway, both of which were intended to facilitate the development and expedite the review of breakthrough technologies.

With Breakthrough Device Designation, Illumina's assay will receive pri-

ority review, meaning that the review of the submission is prioritized in the queue and will receive additional review resources, as needed.

## Amgen's Blincyto approved in Europe for leukemia

Amgen said the European Commission has approved an expanded indication for Blincyto (blinatumomab) monotherapy to include adult patients with Philadelphia chromosome negative CD19 positive B-cell precursor acute lymphoblastic leukemia in first or second complete remission with minimal residual disease greater than or equal to 0.1 percent.

The approval was based on data from the phase II BLAST study in frontline and relapsed/refractory ALL, the largest prospective trial for MRD-positive ALL ever conducted. Blincyto, a bispecific CD19-directed CD3 T cell engager, is the first BiTE immunotherapy to receive regulatory approval globally.

In that study, Blincyto induced a complete MRD response, or no detectable MRD, in 78 percent of patients within one treatment cycle. Safety results among MRD-positive patients were consistent with the known safety profile of Blincyto in relapsed or refractory B-cell precursor ALL.

Approval via the centralized procedure allows for obtaining a marketing authorization from the EC, which is valid in all EU and European Economic Area-European Free Trade Association states, including Norway, Iceland and Liechtenstein.

In March 2018, FDA approved Blincyto for the treatment of adults and children with B-cell precursor ALL in first or

second complete remission with MRD greater than or equal to 0.1 percent.

Blincyto is the first immunotherapy from Amgen's BiTE platform. BiTE antibody construct technology, pioneered by Amgen, is an innovative treatment approach that helps the body's immune system attack cancer cells without the removal of immune cells from the patient. Amgen is studying a number of "off-the-shelf" investigational BiTE immunotherapies, with distinct targets, across a range of hematologic and solid tumors.

The BLAST study is the largest ever prospective trial in patients with MRD-positive ALL. It is an open-label, multicenter, single-arm, phase II study evaluating the efficacy, safety and tolerability of Blincyto in adult patients with MRD-positive B-cell precursor ALL in complete hematologic remission after three or more cycles of intensive chemotherapy.

Patients received continuous IV infusion of Blincyto 15 µg/m<sup>2</sup>/d for four weeks, followed by two weeks off. Patients received up to four cycles of treatment and could undergo hematopoietic stem cell transplantation at any time after the first cycle, if eligible.

Efficacy was based on achievement of undetectable MRD within one cycle of Blincyto treatment and hematological relapse-free survival. Additional secondary endpoints included incidence and severity of adverse events, overall survival, time to hematological remission and duration of complete MRD response.

Blincyto is a bispecific CD19-directed CD3 T cell engager immunotherapy that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of effector T cells. Blincyto was granted breakthrough therapy and priority re-

view designations by the FDA in 2014, and carries full approval in the U.S. for the treatment of relapsed or refractory B-cell precursor ALL in adults and children.

In the U.S., Blincyto is also approved for the treatment of adults and children with B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1 percent. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. In the EU, Blincyto is indicated for the treatment of adults with Ph- relapsed or refractory B-precursor ALL and for the treatment of Ph- CD19 positive B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1 percent.

## Genmab initiates of FDA submission for expansion of daratumumab in multiple myeloma

Genmab said its licensing partner, Janssen Biotech, Inc. has submitted the first part of a regulatory submission to FDA for a label expansion to include the use of daratumumab in combination with lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

FDA plans to review this application under their Real-Time Oncology Review



pilot program. Inclusion in the RTOR pilot program does not guarantee or increase the probability of approval of this supplemental Biologics License Application. In August 2012, Genmab granted Janssen an exclusive worldwide license to develop, manufacture and commercialize daratumumab.

The submission package is based on data from the phase III MAIA (MMY3008) study of daratumumab in combination with lenalidomide and dexamethasone as treatment for patients with newly diagnosed multiple myeloma, who are not candidates for high dose chemotherapy and ASCT.

The phase III study (NCT02252172) is a randomized, open-label, multicenter study that includes 737 newly diagnosed patients with multiple myeloma who are not candidates for high dose chemotherapy and ASCT.

Patients were randomized to receive either daratumumab in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone. In the daratumumab treatment arm, patients received 16 milligrams per kilogram (mg/kg) weekly for first 8 weeks (Cycles 1 and 2), every other week for 16 weeks (Cycles 3 to 6) and then every 4 weeks (Cycle 7 and beyond) until progression of disease or unacceptable toxicity. Lenalidomide was administered at 25 mg orally on days 1 through 21 of each 28-day cycle, and dexamethasone was administered at 40 mg once a week for both treatment arms.

Participants in both treatment arms will continue treatment with lenalidomide and dexamethasone until disease progression or unacceptable toxicity. The primary endpoint of the study is progression free survival.

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