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BEYOND MORPHOLOGY: FDA MULLS ACUTE LYMPHOBLASTIC LEUKEMIA DRUG BASED ON ELIMINATION OF "MINIMAL RESIDUAL DISEASE"

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UPMC | HILLMAN CANCER CENTER

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 Associate Director (AD) / Deputy Director (DD) 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 / DD will help promote and invest these funds in 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 and therapy.

The AD for Research Administration reports directly to the Hillman Director, and is a member of Hillman's executive leadership team. Duties and responsibilities include:

- supervising a supporting team of administrators and PhD-level scientists,
- coordinating vision setting and strategic planning; overseeing CCSG Programs and Shared Resources;
- developing Center policies and procedures;
- working with the Hillman Fiscal Office to develop budgets and monitor spending; developing staffing and space utilization plans and overseeing facility operations;
- managing Hillman's membership and grants portfolio; and
- communicating research outcomes to Hillman investigators, the NCI, and the public.

To facilitate and advance Hillman science, the AD / DD will also:

- coordinate CCSG preparation and submission;
- grow the funded research base, with emphasis on multi-disciplinary collaboration;
- 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 30th 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.

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BEYOND MORPHOLOGY: FDA MULLS ACUTE LYMPHOBLASTIC LEUKEMIA DRUG BASED ON ELIMINATION OF "MINIMAL RESIDUAL DISEASE"

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee March 7 voted to accept the metric of "minimal residual disease," or MRD, as a basis for approval of a drug for the treatment of acute lymphoblastic leukemia.

In an 8:4 vote, the committee recommended broadening the indication for the Amgen drug Blincyto (blinatumomab) to include the treatment of MRD-positive B-cell precursor ALL.

ALL is a small indication. There are about 2,500 new cases among adults in the US, and about half of these patients are found to be MRD-positive after initial chemotherapy. Since not all of these patients are offered treatment for MRD, the indication likely applies to several hundred new patients per year.

However, MRD is a factor in all forms of leukemia, multiple myeloma, some lymphomas, and, potentially, via measurement of tumor-associated cell-free DNA, in solid tumors.

The agency didn't specify to the public—nor, presumably, to the committee members—whether it's considering a full approval or an accelerated approval for the indication.

ODAC's recommendation signals a significant evolution in the agency's approval criteria since historically—from the 1950s on—approvals of therapies for the treatment of ALL have been based on measures demonstrating achievement and maintanence morphological complete remission.

While drugs were being approved based on these criteria, hematologist/oncologists who treat ALL have been using MRD to determine the patients' risk of recurrence and thus guide treatment decisions. If FDA follows the committee's advice, which it almost certainly will, the approval of this supplemental Biologics License Application will mark the first-ever approval of a treatment targeting MRD.

Blincyto, which is sponsored by Amgen, is a bispecific CD19-directed CD3 T cell engager.

Though having MRD after initial therapy for ALL is bad, it's not known whether eliminating it would improve the patients' outcomes.

Worse, it's not clear whether questions related to the role of MRD could ever be answered conclusively, and, more than anything, ODAC discussion pointed to the challenge of making regulatory decisions in the midst of a permanent revolution driven by technology. As science and technology changes, scientific questions are being rendered moot before answers are able to emerge.

"Yes, MRD is bad, and MRD does define a high-risk population, but we do not know the appropriate cutoff," said Andy Chen, leader of the Lymphoma

Program at the Oregon Health & Science University Knight Cancer Institute, who served as a temporary voting member of the committee.

"Even though we know that MRD is bad and it defines a poor risk group, we don't really have randomized data yet to say that eradication of MRD improves outcomes, and that leads to the second part of this question—and that's a more difficult question for us—is whether or not this presentation here is strong enough in the absence of that," said Chen, who voted against approval.

FDA seemed disinclined to put all the cards on the table. The words "reasonably likely to predict," which signal that the agency is considering an accelerated approval, were never uttered. This could be only because the agency wasn't interested in hearing the ensuing discussion about surrogacy.

However, some interesting dance steps could be observed.

Richard Pazdur, director of the FDA Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products, prompted the sponsor to describe the confirmatory trials that would tease out the role of blinatumomab treatment and of transplantation in the MRD-positive population.

Sponsors rarely volunteer such information so as not to prompt ODAC members to say, "Well, the trials are ongoing, so why not wait? Come back in a few years." Since the indication is rare—there are just a few hundred such cases a year—the wait would take the sponsor well into the 2020s.

The randomized trials addressing the question of transplantation are ECOG1910 and COGAALL1331. The agency usually requests that confirmatory trials be in progress if an application is to qualify for an accelerated approval.

In another hint that the agency may be thinking of an accelerated approval, the committee was asked whether "blinatumomab provides a potential benefit that outweighs the risks from the treatment." The word "potential" could be interpreted as code for "reasonably likely to predict."

Blincyto was granted an accelerated approval in December 2014 for the treatment of Philadelphia chromosome-negative relapsed or refractory BCP ALL on the basis of the CR rate, duration of CR, and proportion of patients with an MRD-negative CR or CR with partial hematological recovery (CRh) within two cycles of treatment in a single-arm trial.

In July 2017, the agent received a regular approval for treatment of relapsed or refractory BCP ALL in adults and children.

ODAC members struggled with Amgen's data in part because about 77 percent of the MRD-positive patients went on to receive transplants after treatment with Blincyto. The contribution of transplants ultimately confounded the result of the Blincyto trial.

"There is no drug that's ever been approved in ALL that specified whether a transplant should subsequently be performed or not," said Aaron Logan, assistant professor of clinical medicine in the Division of Hematology/Oncology at the UCSF Helen Diller Comprehensive Cancer Center. Logan presented the clinical perspective as part of the Amgen presentation.

"The way I view this is this is a decision that needs to be individualized, and that individualized decision makes the assessment of the role of the transplantation as is trying to be performed today very complicated, because transplantation is not two buckets," Logan said to the advisory committee. "It's not no-transplant or transplant. It's no-transplant or which of these 12 different kinds of transplants did the patient undergo? Was it myeloablative? Was it reduced-intensity? What kind of donor did you use? How did you manage the immune suppression after the transplant?

> "I think, clearly, the field is moving from the days of laying on of hands, radiographic evaluation, microscopic evaluation, and now molecular determinations of disease and disease response, and that's going to become incredibly, and increasingly, important over the next decade."
>
> *– Gary Gordon*

"And were your decisions about any of these things informed by your knowledge of the patient's MRD? In the current era, all of those things are influenced for every patient on an individual basis by knowledge of their MRD.

"Our field has already accepted 10-4 as a threshold for specifying patients as being high-risk for relapse. If they remain MRD-positive at the time of the transplant, we are less likely to do a reduced-intensity transplant. If they remain MRD-positive at 10-4 or higher after transplant, we are more likely to rapidly taper their immune suppression. These are things that cannot be captured by the type of analyses presented

today, and therefore I don't think that this should be the focus of the discussion.

"The discussion should be, 'Did this drug take a high-risk population—MRD-positive patients—and enable them to go on to potentially curative therapy?' I think it has been demonstrated that a very high percentage of patients have been able to go on to a potentially curative allogeneic transplantation."

Amgen's application appears to have been inspired in part by a paper by Don Berry et al. that appeared in JAMA Oncology last year. The paper presented a meta-analysis of 39 publications based on data on 13,637 patients.

"The value of having achieved MRD negativity is substantial in both pediatric and adult patients with ALL," the paper concludes. "These results are consistent across therapies, methods of and times of MRD assessment, cutoff levels, and disease subtypes. Minimal residual disease status warrants consideration as an early measure of disease response for evaluating new therapies, improving the efficiency of clinical trials, accelerating drug development, and for regulatory approval.

"A caveat is that an accelerated approval of a particular new drug using an intermediate endpoint, such as MRD, would require confirmation using traditional efficacy endpoints."

The FDA analysis of this paper points out that the authors had pooled "nonrandomized responder analyses, i.e., irrespective of treatment received, patients with MRD-negative disease have longer [event-free survival] and [overall survival]."

"Additionally, because the analysis included studies with different cut-offs to determine MRD-negativity, the results do not address what level of MRD identifies the high-risk group or what level of MRD identifies the group with good long-term prognosis," the agency's report states. "Further, because the description of the patient population did not include whether patients were in Complete Remission 1 or later, whether the patients had true CR or marrow remission with incomplete hematologic recovery, or how [hematopoietic stem cell transplantation] use was addressed, it is not clear to what population specifically these results would apply."

Amgen's data was based on the BLAST trial, which—despite being the largest prospective trial in patients with MRD-positive ALL—was a single-arm phase II study. As such, the trial couldn't measure progression in a convincing manner. Instead, the sponsor presented a propensity score analysis comparing outcomes with a historical control cohort.

The BLAST study [MT103-203] was a single-arm trial of up to 4 cycles of blinatumomab for treatment of patients with BCP ALL in CR or CR with partial platelet recovery and MRD > 0.1%. The primary efficacy endpoint of MT103-203 was complete MRD response (defined as absence of detectable MRD using an assay with a sensitivity < 0.01%) after 1 cycle of blinatumomab.

There were 116 patients treated with blinatumomab. From this group, FDA identified 87 patients in CR with hematologic recovery and baseline MRD > 0.1%, including 61 patients in CR1, 25 in CR2 and 1 in CR3. A complete MRD response was achieved by 69 patients (79%; 95% CI: 70%, 88%).

The estimated median hematological RFS was 22.3 months (25.6 months for patients in CR1 and 11.0 months for patients in CR2 or CR3).

A propensity score analysis for the patients in first remission (with or without hematopoietic recovery) in Study MT103-203 and in Study 20120148, a larger retrospective cohort study sponsored by Amgen, demonstrated that the RFS for the patients treated with blinatumomab was significantly greater than in the historical controls (p<0.0001 by log-rank; median 35.2 months vs 8.3 months, respectively).

How ODAC voted—and why

FDA asked the Oncologic Drugs Advisory committee to discuss a possible threshold for MRD cutoff. The Amgen study included patients with MRD > 0.1%. Committee members said they didn't feel comfortable setting the cutoff threshold.

The voting question read: "Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD > 0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment?"

Gary Gordon
Acting industry representative
vice president of oncology development
AbbVie Inc.

As a non-voting member, I would like to congratulate and thank FDA and the sponsor for bringing forward and advancing the consideration of minimal residual disease and how we really begin to integrate this into assessing patients, considering how we use it to make decisions around therapy, and ultimately how it will potentially become an outcome measure for clinical care.

I think, clearly, the field is moving from the days of laying on of hands, radiographic evaluation, microscopic evaluation, and now molecular determinations of disease and disease response, and that's going to become incredibly, and increasingly, important over the next decade.

Christopher Hourigan
Chief, Myeloid Malignancies Section
National Heart, Lung and Blood Institute

I voted Yes. I share the desire to have randomized study and better quality evidence about the confounding impacts of transplant, but I believe MRD-positive patients need treatment now, and want to have options for them while we're working out the confounding influence of transplant.

Andy Chen
Leader, Lymphoma Program
Knight Cancer Institute
Oregon Health & Science University

I voted No. I do believe that MRD is an important marker, and it should be used in studies going forward.

I thought that the results from this phase II study was too confounded by transplant to say, for certain, that there's a significant clinical benefit, and I thought the numbers for patients who did not get transplant were too small to make any conclusion.

Anthony Sung
Assistant professor of medicine
Division of Hematologic Malignancies and Cellular Therapy
Duke Cancer Institute

I voted Yes.

I do think that there was significant data that was presented that showed that use of this drug in this setting is able to convert patients from an MRD-positive status to an MRD-negative status.

I think that there was data presented that was suggestive that having an MRD-negative status is beneficial, regardless of whether or not you're going to transplant after receiving blinatumomab.

I do know that the reason I voted yes, however, was because the question was worded as a "potential benefit."

I do not think, as Dr. Chen mentioned, that there is significant evidence suggesting that this is, for sure, definitively the way that we should go, in terms of treatment. I also think that it's important to look at the data from the randomized trials that were upcoming, that were discussed, because I don't think that, for example, if this was a question of whether or not it should be approved for this indication, I probably would have voted no in that setting, but I do think there's enough data to suggest a potential benefit.

The other thing that I would like to comment is I would like to see more data about the potential adverse effects in patients who receive blinatumomab and then go on to transplant, because I feel that was not adequately presented, and as one person earlier in the conversation noted, a lot of the historical data was from 2000, where transplant in 2000 is very different from transplant in 2009, which is very different from transplant now.

And so, I think a more granular look at that detail and data is needed.

Arthur Flatau
Patient representative
Austin, Texas

I voted Yes. I think that, as Dr. Sung said, patients probably benefit from being MRD-negative going to transplant. I don't think that patients who are MRD-positive after the chemotherapy and then get Blincyto and become MRD-negative are quite the same, but it still looks like there's some benefit over not being MRD-positive at the time of transplant.

So that's why I voted yes. And I would like to add I'd like to see more randomized trials; I agree with that.

Courtney Preusse
Consumer representative
senior research administrator and CLIA operations director
Clinical Research Division Fred Hutchinson Cancer Research Center

I also voted Yes. I thought that the survival benefit in MRD-positive patients was there, although we can't exactly quantify it, and we don't know what the exact MRD cutoff is.

We don't know how much MRD you can live with and not relapse. I felt that the data was sufficient, in the 10-1 to 10-4 population, to provide this additional treatment option to patients and their providers.

Susan Halabi
Professor of biostatistics and bioinformatics
Duke University Medical Center

I voted No, contrary to my previous peers.

And the reason I voted no was mostly because I wasn't totally convinced that you can interpret the data, because the outcomes are being confounded due to HSCT, which limits, obviously, the interpretations of the results, and even though the study met its primary endpoint, I believe that additional follow-up are needed for the 203 study and additional analysis may help to adjust for confounding.

Vassilliki Papadimitrakopoulou
Professor of medicine
MD Anderson Cancer Center
Department of Thoracic Head & Neck Medical Oncology

I also voted No, and it was because mostly a question of interpretation of the intent of the question here.

My interpretation of the intent was that we were asked to vote on this, and the question was indicative of our intent to improve the drug in this indication. Therefore, that tainted my vote, although I think there is potential benefit, and I think there is plenty of data, and a clear benefit for this patient to have some therapy in the setting of MRD, I do not feel that we have the exact definition of the population that benefits.

For example, it was adequately phrased CR1 versus later CR, and also the confounding factor of transplant, as everybody else mentioned, was not clarified by the analysis. It was not feasible to clarify it, I think.

Bruce J. Roth
Chairperson
professor of medicine,
Division of Oncology
Washington University School of Medicine St. Louis

I ended up voting Yes. I actually wanted to vote Yes and No, and then I wanted to abstain. I voted Yes, because I think it met the primary endpoint, I think fairly impressive, almost 80% of the people MRD converted, and also voted yes kind of in the back of my mind for the patients who do not have transplant as an option, as another option to reduce MRD, and hopefully have something else available down the road.

The No part of my brain said that I am not convinced of clinical benefit from what was presented, and I think it was an impossible task to take this heterogeneous group of historical controls and try get anything out, and that's, in fact, I believe what happened. I'd be very interested to see the results for the upcoming randomized trials to confirm that that MRD conversion actually does end up resulting in improved clinical benefit.

Philip Hoffman
Professor of medicine
The University of Chicago
Section of Hematology/Oncology
Department of Medicine

I voted Yes. I think, perhaps the most simplistic way, after hearing the data and reviewing this, that the drug is currently approved for treating refractory ALL, and the way I see it, MRD-positive is a form of refractory ALL.

It's a different mechanism of measurement, as we've heard, and it will probably get, as has been discussed, even more sensitive over time, but I think that that is an indicator of persistent and refractory disease, and I would be swayed by the predominance of clinical evidence that even with using it as a bridge transplant, that it was still valuable, since patients who get transplanted and are MRD-positive going in, have a less good outcome than those who go in MRD-negative.

Grzegorz Nowakowski
Associate professor of medicine and oncology
Mayo Clinic Rochester

I voted Yes, really on the three pillars.

One, is that MRD used to be clearly predicting or identifying patients at the risk of relapse. We can argue about a cutoff, but multiple publications and data show that MRD is important in ALL.

Secondly, 203 study demonstrated that blinatumomab can actually convert patients from being MRD-positive to negative, and does it in a significant proportion of the patients.

The problem, thirdly, was the clinical benefit. And here, just like others, I struggled a lot with the conversion from MRD-positive to negative truly corresponds to a clinical benefit. But I think, overall, looking at the evidence, there is a reasonable probability that indeed it does help.

Finally, biologically, I think about being MRD-positive like almost being tied to the railroad tracks, and

you see this train coming, and you see the lights far, far away, and you can think about this, "I'm going to wait until the train comes closer and use my ammunition then, or maybe I try to do something earlier to stop this train," and biologically I cannot help thinking that early intervention could be of help here.

David Harrington
Professor of statistics and biostatistics
Dana-Farber Cancer Institute
Harvard T.H. Chan School
of Public Health

Apparently, Dr. Roth and I agree on everything except the vote.

I voted No, and I voted No, primarily because, for me, there is still uncertain benefit in the patients who are eligible for transplant after their CR.

I don't think of the subgroup, necessarily, as the ones who got transplant, but the ones who, you know, after that CR, could get transplant. I think that what's difficult to sort out here, is that different analyses show a different level of benefit for blinatumomab before the transplant.

So, for me, it doesn't quite reach the level of labeling evidence.

I think that in most trials, most of us are willing to approve an indication when a subset that you're particularly worried about is small, but this is a large subset, and it leaves sort of open the question of whether they should be treated or go right to transplant.

There was a claim that, one hopes, that the deeper the response that inducing less residual disease prior to transplant will lead to a longer and better outcome for transplant, but I think that remains to be shown.

Catherine Bollard
Bosworth Chair for Cancer Biology
Director, Center for Cancer
and Immunology
Research professor of pediatrics
and microbiology, immunology
and tropical medicine
Children's National Health System
The George Washington
University School of Medicine
and Health Sciences

I voted Yes. Again, like Dr. Sung, the keyword for me, in this question, was "potential benefit" that outweighs the risks from the treatment.

I think we all agree that MRD-positive patients need treatment. The sponsor gave a very good risk-benefit ratio, I think the study met its primary endpoint, and, for me, the data they showed in response to my question about the patients who did not go on to BMTs, and those 22% responding patients who did not go on to BMT, they clearly had an excellent RFS, especially compared to the absolutely dismal prognosis or outcome for the patients who did not respond and did not go onto transplant.

Obviously, we will await the data of the COG and ECOG randomized trials, and my one caveat would be, as we move, if we do move forward in this MRD setting, that we do need to look at the incidence of CD19-negative disease and the non-responders understanding that there are other CD19-directed therapies these patients might not be eligible for after this therapy.

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GUEST EDITORIAL

Beyond #MeToo: Sexual Harassment in Biomedicine

The fight against sexual misconduct in the workplace has transcended Hollywood and become a major issue across industries.

By Kelly McBride Folkers
Research associate at the Division of Medical Ethics at the NYU School of Medicine.

Biomedical research and academic medicine are not immune to problems with sexual harassment. In early 2016, Reshma Jagsi surveyed 1,000 men and women on sexual harassment in biomedical research labs, and her study revealed that the proportion of women who reported workplace sexual harassment was one in three. I am one of those women. And I have some ideas about what ought to be done to stop harassment.

Despite the widespread nature of sexual harassment, it's not always easy to identify. The subtle, garden-variety acts of misogyny are the ones that slowly chip away at female scientists, healthcare providers, postdocs, and graduate students. The regularity of these instances is only made worse by the fact that leadership in academia is still predominantly male.

And it is a concern. While women are entering biomedicine in equal numbers to men, women are more likely than men to quit academia at the postdoc level. There is some evidence to suggest that men and women alike demonstrate a gender bias that negatively affects the hiring and retaining of women in science. A randomized, double-blind study of science faculty from research-intensive universities were asked to evaluate sample application materials for a lab manager position in which identical applicants were randomly assigned a male or female name. Male and female professors rated male applicants more highly. They were inclined to offer male applicants higher salaries and more career mentoring opportunities than their female counterparts.

Sexual harassment happens in hospitals, labs, and academic departments to women at all stages of their careers. On her first week on the job, a friend of mine who is an OB tech, said that she

was informed that a male colleague would probably rub her shoulders and wolf-whistle when she walked by him, but "that's just what he does." Others I spoke to relayed similar outrages. A clinical research coordinator reported that a male physician asked her why she doesn't wear more makeup. A professor, at a conference at which she was invited to speak, was assumed to be a male colleague's girlfriend and sexual partner. A male superior told a research technician that if he weren't married, he'd sleep with her. A male postdoc told a group of women at a lab meeting that "the problem with women in science" is their inability to control their emotions.

Harassment in academic settings isn't necessarily overtly sexual, either. Before I transitioned to a career in medical ethics, I was a lab manager at a cancer research institution. At one point, I was the only staff member without a PhD employed by this particular lab. A postdoc got my personal phone number and began texting me at odd hours to grill me about happenings in the lab. He would check the log books on weekends to learn when I was working, confronting me about how much time I spent with lab animals or passaging cells. He subjected me to verbal abuse, standing over me at my desk and screaming at me to show him my personal emails.

When you work in a lab, you often share small spaces with lab mates for long periods of time, waiting for a reaction to occur or observing a lab animal after a procedure. After he loomed over my desk (a lá Donald Trump stalking Hillary Clinton on the debate stage), I told my boss that I no longer felt safe at work. My boss had a casual conversation with the postdoc, but much of the behavior didn't stop. I can't help but feel that had I been male and part of this lab's boys' club atmosphere, I might have stayed in my position. But in a group of people who had completed more of their education than I had—who didn't consider themselves my peers—I felt alone. The lab's atmosphere was not conducive to my learning or the lab's success.

I decided to leave and enroll in my graduate program full time. I finished my degree, and I now work as a researcher in a department where a great number of my colleagues are female. The men in my department are prime examples of how male allies should act—and if they are intimidated by the women in our office, they don't show it. But as I have spoken to more and more men and women in science, I know that this workplace gender makeup isn't the norm.

While #MeToo has been a revolutionary moment for women across industries to finally speak out about their consistently present discomfort at work, the campaign's end goal hasn't been clear. Publicly naming accusers focuses the movement on the lurid details of men's bad behavior, instead of correcting the wrongs of the experience of women—and in some cases, men—who have been harassed on the job.

Academic institutions can and should be doing more to support a diverse female workforce, and this includes providing resources to women regardless of their educational level. Others have argued for harsher punishments for assailants of campus sexual assault, while also providing supportive care and resources for survivors during an investigation. While such policies are crucial to bringing perpetrators of sexual violence to justice, institutional policies should be implemented in a way that takes seriously the veracity of reported instances of workplace harassment on academic and research-intensive campuses, even if an institution's policy does not classify the situation as sexual assault.

Many cases of sexual harassment go unreported. When women do report sexual harassment, they often experience tangibly negative fallout. In my case, I sacrificed a competitive salary and tuition benefits so that I wouldn't suffer from daily verbal abuse. An Equal Employment Opportunity Commission study stated that 75 percent of women who report sexual harassment face some kind of retaliation, including damage to their professional reputation and ostracism in the workplace. Taking accusations of harassment seriously means actively involving those who come forward in decisions on how to appropriately and justly hold perpetrators accountable, giving accusers a sense of empowerment over a situation for which they are not at fault.

In an effort to deter sexual harassment in scientific research, the National Science Foundation recently announced a new set of policies that allow the suspension or elimination of research grants after an institution completes an investigation into an accusation of sexual harassment. While this policy creates serious consequences for sexual harassers that should be in place, the policy puts the onus on institutions receiving grant money to report confirmed cases of harassment. It doesn't—and can't—address those sexual harassment cases that are swept under the rug, often to protect men who procure large amounts of NSF funding. If other federal funding agencies follow suit, the NSF reporting requirements may indeed be bolstered.

Serious consequences for sexual harassers, such as suspension or termination from a position, are necessary to foster a safe workplace for women, but they aren't sufficient to ensure that a workplace remains that way. They don't fix a deeply engrained, underlying cultural phenomenon: Biomedical science, like many other disciplines, is often sexist. Far fewer women than men apply for NIH funding. In 2014, women only constituted about 30 percent of NIH research grant project principal investigators. There has

never been a female director of the National Cancer Institute. A lack of gender diversity in scientific leadership positions may help explain why women are still not accurately represented in clinical trials, despite federal efforts to increase women's participation in research studies for new treatments. And as the current administration slowly chips away at protections for women's healthcare services and federal regulations that prohibit discrimination in health insurance coverage on the basis of sex, there has never been a time where we need women in scientific leadership positions more.

When I reflect on my career in academia so far, I have benefitted from the mentorship of women.

My undergraduate research advisor, whom I still consult for advice, became a role model for how to be a woman in science, balancing the expectations of motherhood and family with advancing in her career. My co-workers continue to provide this mentorship, particularly as I move forward with my education in the coming years. I fear that other women may not have this support and are struggling in a field that has long been dominated by men. To date, several initiatives that would have required or incentivized the creation of committees to mentor junior faculty members seeking first government grants have garnered, at best, lukewarm support.

In addition to handing serious consequences to harassers and perpetrators of sexual misconduct in the workplace, institutions must prioritize mentorship for and among women. One method of accomplishing this goal is by fostering institutional events where female scientists can interact, discussing the stressors of their work and gender-related problems they encounter. In such a setting, early career academics can seek out advice from women in more advanced positions, which would be particularly helpful for those who work under male principal investigators.

Women of color, foreign-born scientists, and LGBTQ+ people may face additional struggles in the workplace. Specific resources for them, including the availability of a confidential space in which to voice their concerns, must also be a part of institutionally supported mentorship programs.

While most institutions provide staff members with training courses and employee assistance programs for short-term mental health issues, people appointed to fixed-term academic positions, like postdocs, may not have the same human resources support.

The success of a postdoc almost entirely depends upon the principal investigator, which could prove disastrous for a postdoc's future career if the principal investigator is ill-equipped to handle reports of harassment on the job. Anecdotally, postdocs receive far fewer employment benefits than staff members. The entire workforce at an institution, regardless of the individual's position as a staff member, postdoc, or professor, should have access to an employee assistance program that will help those suffering from harassment.

On the flip side, my harasser may have benefitted from counseling to prevent more women from being sexually harassed, if only my former employer mandated such a program for postdocs who behave badly.

Sexual harassment is a symptom of implicit biases, or attitudes that affect our understanding of others in an unconscious manner. Implicit biases are thought to contribute to relatively automatic behaviors, which is why some legislators have suggested that training on implicit bias be incorporated into law enforcement education to combat police violence against the African American community.

The aggregate of individual implicit biases against women in science has been documented, and one 2008 study suggested that these biases are predictive of gender differences in math and science achievement between male and female students. It's important to note that research studies have been unable to demonstrate that men are more apt in mathematics or science than women; any differences in performance are the result of self-fulfilling beliefs that women lack requisite skills to succeed in these academic disciplines. There may be a role in biomedicine for implicit bias training, aimed at connecting underlying, unconscious beliefs about gender roles with the substantial consequences of those beliefs, which affect women in science and medicine negatively.

Training isn't and won't be enough to change workplace culture by itself. Shifts in cultural thought happen over time through sustained individual effort to combat implicit bias. In the meantime, institutions must prioritize proactive solutions for gender inequity in biomedicine, in addition to taking seriously events that unequivocally cross a line.

Creating a new culture of inclusion in biomedicine will take years. But, I am hopeful that #MeToo will encourage more women to speak up and move up in the biomedical arena, taking us several steps closer to finally breaking the glass ceiling.

Kelly McBride Folkers is a research associate at the Division of Medical Ethics at the NYU School of Medicine. *The author would like to thank Arthur Caplan, the Drs. William F. and Virginia Connolly Mitty Professor of Bioethics at NYU School of Medicine, for comments on earlier drafts of this piece.*

IN BRIEF

Ashley named director of Tisch Brain Tumor Center at Duke

David Ashley was named director of the Preston Robert Tisch Brain Tumor Center at Duke. Ashley follows Darell Bigner, who became director emeritus on Feb. 1.

Bigner will continue to lead the work with the modified poliovirus in an expanding range of glioma and other cancers, including breast carcinoma and melanoma.

Before leaving Australia to join Duke in 2017 as professor of neurosurgery and director of the pediatric neuro-oncology program in the Department of Neurosurgery, Ashley had served as chair of the Department of Medicine at Deakin University, the program director of Cancer Services University Hospital Barwon Health, and executive director of the Western Alliance Academic Health Science Centre.

He was also a director of the Victorian Cancer Agency Consultative Council, director of Clinical Trials Australia, and has been an Academy member of the Australian National Health and Medical Research Council since 2010. Ashley also served as associate professor and director of the Children's Cancer Center at the Royal Children's Hospital in Melbourne, the largest children's cancer treatment center in Australia.

Ashley is credentialed in both pediatric and adult oncology practice. His peer-reviewed publication record is diverse and includes laboratory-based cancer research, clinical trials, public health and psycho-oncology research.

His primary academic focus in brain tumors has been tumor immunology and the genomics and epigenetics of cancer. His achievements in research have led to change in practice in the care of children and adults with brain tumors including the introduction of new standards of practice for the delivery of systemic therapy.

Wolin named director at Center for Carcinoid and Neuroendocrine Tumors at Mt. Sinai

Edward Wolin was named director of the Mount Sinai Center for Carcinoid and Neuroendocrine Tumors.

The multidisciplinary center includes Mount Sinai specialists in gastroenterology, surgical oncology, hepatobiliary surgery, thoracic surgery, nuclear medicine, cardiology, medical oncology, radiology, pathology, endocrinology, and nutrition.

Wolin, who will also be a professor of medicine (hematology and medical oncology) at the Icahn School of Medicine at Mount Sinai, brings a robust research program that includes clinical trials aimed at finding the most effective treatments, including immunotherapy, biologic agents, targeted radiation therapy, and new approaches in molecular imaging for diagnosis.

He becomes the second director of the center which was founded by Richard Warner, professor of medicine (gastroenterology), a pioneer in neuroendocrine tumor research and treatment.

Wolin will lead the center along with Michelle Kang Kim, associate professor of medicine (gastroenterology), and who will serve as associate director after previously serving as interim director.

Wolin was most recently director of the Neuroendocrine Tumor Program at Montefiore Einstein Center for Cancer Care. He has pioneered innovative therapies with novel somatostatin analogs, mTOR inhibitors, anti-angiogenic drugs, and peptide receptor radiotherapy.

He was previously director of neuroendocrine tumor programs at the University of Kentucky Medical Center and Cedars-Sinai Medical Center in Los Angeles, where he founded and directed one of the then-largest carcinoid and neuroendocrine tumor programs in the country.

Wolin serves as co-medical director for the Carcinoid Cancer Foundation and on the Carcinoid Cancer Research Grants Scientific Review Committee for the American Association for Cancer Research.

Cleary named director of IU Walther Supportive Oncology Program

Walther Supportive Oncology Program at Indiana University School of Medicine has named James Cleary as director, where he will join the faculty in July to lead the program and will hold the Walther Senior Chair in Supportive Oncology. He will also be a professor of medicine.

An Australian-trained medical oncologist and palliative care physician, Cleary, who has been in the United States for 24 years, is recognized globally for his expertise in palliative care medicine and cancer pain.

He is currently a professor of medicine at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin. He also is a palliative care physician with the UW Health palliative care program, which he started in 1996.

In 2011, he stepped down as medical director of the clinical program to commit more of his efforts to improving global palliative care. He has been director of the Pain and Policy Studies Group, a World Health Organization Collaborating Center for Pain Policy & Palliative Care at the UW Carbone Cancer Center, for the past seven years.

He earned his medical degree from the University of Adelaide in South Australia, and he completed his medical oncology fellowship (Fellow of the Australasian College of Physicians) at the Royal Adelaide Hospital. He was a founding fellow of the Australasian Chapter of Palliative Medicine through his oncology training and laboratory work in opioid pharmacogenetics.

Cleary's research has been extensively supported by grants from the National Institutes of Health/National Cancer Institute, Livestrong, the Open Society Institute and others.

IU School of Medicine recently received a $14 million gift from the Walther Cancer Foundation to create a supportive oncology program that goes beyond standard therapies such as surgery, chemotherapy, and radiation and seeks to care for a patient's overall physical, mental, and spiritual well-being. The program is named the Walther Supportive Oncology Program in recognition of the foundation's generosity.

FUNDING OPPORTUNITIES

DOD Health Program Anticipated Funding Opportunities for FY 2018

Due to the current Continuing Resolution, the FY18 Defense Appropriations bill has not been passed. Although funds have not been appropriated for the Department of Defense Peer Reviewed Cancer Research Program, the PRCRP is providing the information in this pre-announcement to allow investigators time to plan and develop ideas for submission to the anticipated FY18 funding opportunities.

FY18 PRCRP Program Announcements and General Application Instructions for the following award mechanisms are anticipated to be posted on Grants.gov in April 2018. Pre-application and application deadlines will be available when the Program Announcements are released.

This pre-announcement should not be construed as an obligation by the Government, and funding of research projects received in response to these Program Announcements is contingent on the availability of Federal funds appropriated for the PRCRP.

As directed by the Office of the Assistant Secretary of Defense for Health Affairs, the Defense Health Agency, J9, Research and Development Directorate manages the Defense Health Program Research, Development, Test, and Evaluation appropriation. The managing agent for the anticipated Program Announcements/Funding Opportunities is the Congressionally Directed Medical Research Programs.

Congressionally Directed Topic Areas: To be considered for funding, applications for the FY18 PRCRP must address at least one of the Topic Areas as directed by Congress. Research applications in the areas of breast, prostate, lung (excluding mesothelioma), kidney, or ovarian cancer will not be accepted.

As of the release date of this pre-announcement, the FY18 PRCRP Topic Areas have not been finalized. This pre-announcement should not be construed as an obligation by the Government to include any of these topic areas or others in the FY18 PRCRP. The potential FY18 PRCRP Topic Areas are:

- Bladder cancer
- Listeria-based regimens for cancer
- Myeloma
- Brain cancer
- Liver cancer
- Neuroblastoma
- Cancer in children, adolescents, and young adults*
- Lymphoma
- Pancreatic cancer
- Colorectal cancer
- Melanoma and other skin cancers
- Pediatric brain tumors
- Immunotherapy†
- Mesothelioma
- Stomach cancer

*The definition of adolescents and young adults is derived from the National Cancer Institute and can be considered to be people between the ages of 15-39 years. Cancers studied under this Topic Area should be within the scope of the Congressional language and the intent of the Program Announcement(s)

†As derived from the National Cancer Institute Dictionary of Cancer terms. Immunotherapy is a type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer. Cancers studied under this Topic Area should be within the scope of the Congressional language and the intent of the Program Announcement(s).

The FY18 PRCRP Military Relevance Focus Areas are listed below:

To address the cancer health needs of both deployed and non-deployed personnel, their dependents, retirees, and Veterans, the FY18 PRCRP seeks to support studies that are responsive to at least one of Military Relevance Focus Areas listed below:

- Militarily relevant risk factors associated with cancer (e.g., ionizing radiation, chemicals, infectious agents, environmental carcinogens, and stress)
- Gaps in cancer prevention, screening, early detection, diagnosis, treatment, and/or survivorship that may impact mission readiness and the health and well-being of military members, Veterans, and their beneficiaries and the general public

Career Development Award

Principal Investigator: Independent early-career investigator within 10 years after completion of his/her terminal degree (excluding time spent in residency or on family medical leave) by the time of the application submission deadline.

Career Guide: Investigators at or above the level of Associate Professor (or equivalent); must have a proven publication and funding record in cancer research:

- Letter of Intent is required. An invitation to submit a full application is not required.
- Supports independent, early-career investigators to conduct impactful research with the mentorship of an experienced cancer researcher.
- Must address at least one of the FY18 PRCRP Topic Areas.
- Must address at least one of the FY18 PRCRP Military Relevance Focus Areas.
- Preliminary data are not required.
- Clinical trials are not allowed.
- Maximum funding for the entire period of performance is **$360,000** for direct costs (plus indirect costs).
- Maximum period of performance is 3 years.

Idea Award with Special Focus

- Independent investigator with a faculty-level appointment (or equivalent)
- Preproposal is required; application submission is by invitation only.
- Supports innovative, untested, high-risk/potentially high-reward concepts, theories, paradigms, and/or methods in cancer research relevant to Service members, their families, and other military beneficiaries.
- Emphasis on innovation and military relevance/impact.
- Must address at least one of the FY18 PRCRP Topic Areas.
- Must address at least one of the FY18 PRCRP Military Relevance Focus Areas.
- Preliminary data are not required.
- Clinical trials are not allowed.
- Maximum funding for the entire period of performance is **$400,000** for direct costs (plus indirect costs).
- Maximum period of performance is 2 years.

Translational Team Science Award

- At least two and up to three PIs must partner in one overarching correlative or translational research study.
- At least one of the PIs is encouraged to be a military or Department of Veterans Affairs investigator.
- Preproposal is required; application submission is by invitation only.
- Emphasizes multi-PI, multidisciplinary collaborations.
- Supports translational studies associated with an ongoing or completed clinical trial and/or translational study that can lead to a future clinical trial or clinical application in cancer research relevant to Service members, their families, and other military beneficiaries.
- Not intended to support high throughput screenings, sequencing, etc.
- Must address at least one of the FY18 PRCRP Topic Areas.
- Must address at least one of the FY18 PRCRP Military Relevance Focus Areas.
- Preliminary data are required.
- Maximum funding for the entire period of performance is **$1,000,000** for direct costs (plus indirect costs).
- Maximum period of performance is 4 years.

A pre-application is required and must be submitted through the electronic Biomedical Research Application Portal prior to the pre-application deadline. All applications must conform to the final Program Announcements and General Application Instructions that will be available for electronic downloading from the Grants.gov website.

The application package containing the required forms for each award mechanism will also be found on Grants.gov. A listing of all CDMRP funding opportunities can be obtained on the Grants.gov website by performing a basic search using CFDA Number 12.420.

Applications must be submitted through the federal government's single-entry portal, Grants.gov. Submission deadlines are not available until the Program Announcements are released. For email notification when Program Announcements are released, subscribe to program-specific news and updates under "Email Subscriptions" on the eBRAP homepage. For more information about the PRCRP or other CDMRP-administered programs, please visit the CDMRP website.

THE CLINICAL CANCER LETTER

CONVERSATION WITH THE CANCER LETTER

BMS's Farajallah: Opdivo is the only PD-1 inhibitor approved for four-week dosing

Awny Farajallah
Vice president and head of U.S. Medical Oncology at Bristol-Myers Squibb

Q & A

Farajallah spoke with Matthew Ong, a reporter at The Cancer Letter.

FDA has approved a supplemental Biologics License Application updating the Opdivo (nivolumab) dosing schedule to include 480 mg infused every four weeks for a majority of approved indications.

Opdivo can now be infused over 30-minutes across all approved indications, instead of over an hour, said Awny Farajallah, vice president and head of U.S. Medical Oncology at Bristol-Myers Squibb.

"I think the significance is this should give patients and providers an option," Farajallah said. "If they want to monitor the patient more closely, then they go with the two-week therapy, and if their patient is stable, then they go with four weeks."

The four-week dosing option is approved for the following indications:

- Metastatic melanoma (monotherapy or monotherapy phase after combination treatment with Yervoy [ipilimumab]),
- Previously treated metastatic non-small cell lung cancer,
- Advanced renal cell carcinoma following prior anti-angiogenic therapy,
- Previously treated locally advanced or metastatic urothelial carcinoma following disease progression during or after platinum-based chemotherapy,
- Classical Hodgkin lymphoma following relapse/progression after autologous hematopoietic stem cell transplantation and brentuximab vedotin, or three or more lines of systemic therapy that includes autologous HSCT,
- Recurrent/metastatic squamous cell carcinoma of the head and neck following platinum-based therapy,
- Hepatocellular carcinoma after prior sorafenib therapy, and
- Adjuvant therapy for patients with completely resected melanoma with lymph node involvement or metastatic disease.

PD-1/PD-L1-based therapies have become the standard of care, especially in the non-small cell lung cancer setting, where almost 40 percent of patients are treated with these drugs across all lines (The Cancer Letter, June 2, 2017).

Farajallah spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: How is the new four-week dosing option different from how Opdivo was used previously?

Awny Farajallah: Our previous indications or previous dosing was actually every two weeks, so we did not have the flexibility of Q4W that we recently received the last couple of days.

We went from every two weeks to every four weeks, but with the understanding that it's not a switch—we still can provide the drug every two weeks or every four weeks if you so choose. Basically, it is dependent on the patient situation. The provider and the patient would decide and allow flexibility between the two doses.

If the patient has a recent diagnosis and he or she needs closer follow-up, then two-week dosing may be appropriate if the physician chooses to do so. If the patient has been stable and clinically doing well, then maybe a four-week dosing would be the choice of the physician at the time. That flexibility for the patient depending on the clinical status is really going to be a provider decision.

> "We definitely heavily invest in real-world evidence generation at multiple levels, not just at the patient-reported outcomes, which are incorporated in every clinical trial that we have. But also understanding how our drugs are behaving in the real world, especially in populations that we have not studied in the clinical trials, and try to generate data on this."

Currently, Opdivo is the only immuno-oncology agent that is approved for a four-week infusion, which is different from other IO agents that are currently available to patients.

I think the significance is this should give patients and providers an option. If they want to monitor the patient more closely, then they go with the two-week therapy, and if their patient is stable, then they go with four weeks.

Additionally, the update included a 30-minute infusion rather than a 60-minute infusion, so the original dosing was to infuse Opdivo over 60 minutes. But now, it allows for a shorter time of preparation, shorter time for the patient in the clinic in the infusion chair, which is significant for the patient, of course.

A good number of pharmaceutical companies with cancer portfolios are stepping up their work on real-world evidence and patient-reported outcomes. What are BMS's efforts on that front?

AF: We definitely heavily invest in real-world evidence generation at multiple levels, not just at the patient-reported outcomes, which are incorporated in every clinical trial that we have. But also understanding how our drugs are behaving in the real world, especially in populations that we have not studied in the clinical trials, and try to generate data on this.

We have heavy investment from the research standpoint as well as, again, looking at when to partner externally when we don't have the right datasets, etc. to be able to answer the clinical questions that we're looking to answer.

What else is coming along in BMS's oncology pipeline?

AF: There's a lot going on. We're really looking at cancer from all angles. The mission of the company is to leave no cancer patient behind.

Our pipeline has 18 clinical-stage assets currently that we're studying across 50 tumor types—research from early development, translational medicine, and full clinical development. We also have a robust discovery pipeline as well that we're looking at other mechanisms of action to bring to the clinic.

In addition to that, our focus is really bringing the right treatment to the right patient at the right time, and how do you select those regimens and those drugs for the patients with those robust biomarkers. When we don't have the assets that we think have a good mechanism of action, we actively engage in clinical collaborations or licensing.

As you probably have seen, we have announced the clinical collaboration recently with Nektar Therapeutics to co-develop and do a clinical development plan for their lead immuno-oncology program, NKTR-214, a CD122-biased agonist. So, this is an example of us looking at an established mechanism of action that's proven in the clinic to see how to combine it with our current portfolio.

That's kind of the big picture. Going to your question about regulatory approvals that we may expect, as you know, we have an active ongoing discussion with FDA that we have announced around our potential first-line renal-cell carcinoma combination therapy. We certainly are hopeful that this will move forward.

CLINICAL ROUNDUP

Roswell Park ovarian cancer registry data links ovarian and testicular cancer

Using data from a large ovarian cancer registry, a research team from Roswell Park Comprehensive Cancer Center uncovered a link between testicular cancer and familial ovarian cancer that may be attributable to genetic factors on the X chromosome.

The Familial Ovarian Cancer Registry at Roswell Park was established in 1981 and contains clinical and epidemiological information from 2,636 families with multiple cases of ovarian cancer. The overall goal of this registry is to identify all of the genes responsible for ovarian cancer development so that women who are genetically predisposed to the disease can be identified and monitored carefully.

Using Familial Ovarian Cancer Registry data, the Roswell Park investigators took a closer look at the family histories of 34 men with testicular cancer who were in the registry. These men with testicular cancer were more likely than men with other cancers to have a mother or sister with ovarian cancer.

None of the men with testicular cancer who were included in the registry had a paternal grandmother with ovarian cancer, lending support to the theory that the genes driving testicular cancer development may be X-linked.

Based on the results of this study, the Familial Ovarian Cancer Registry will now include all patients with at least one case of testicular cancer and re-contact existing families to update their information.

Although more studies are needed to further explore the link between testicular and ovarian cancers, this registry may provide new insight into the etiology and transmission of both cancers and identify gene targets for prevention and therapy.

The study, "Hereditary association between testicular cancer and familial ovarian cancer: A Familial Ovarian Cancer Registry study," was published in Cancer Epidemiology and is available at sciencedirect.com.