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"CALL ME DOCTOR" HOW WOMEN IN ONCOLOGY ARE FIGHTING FOR CULTURAL CHANGE

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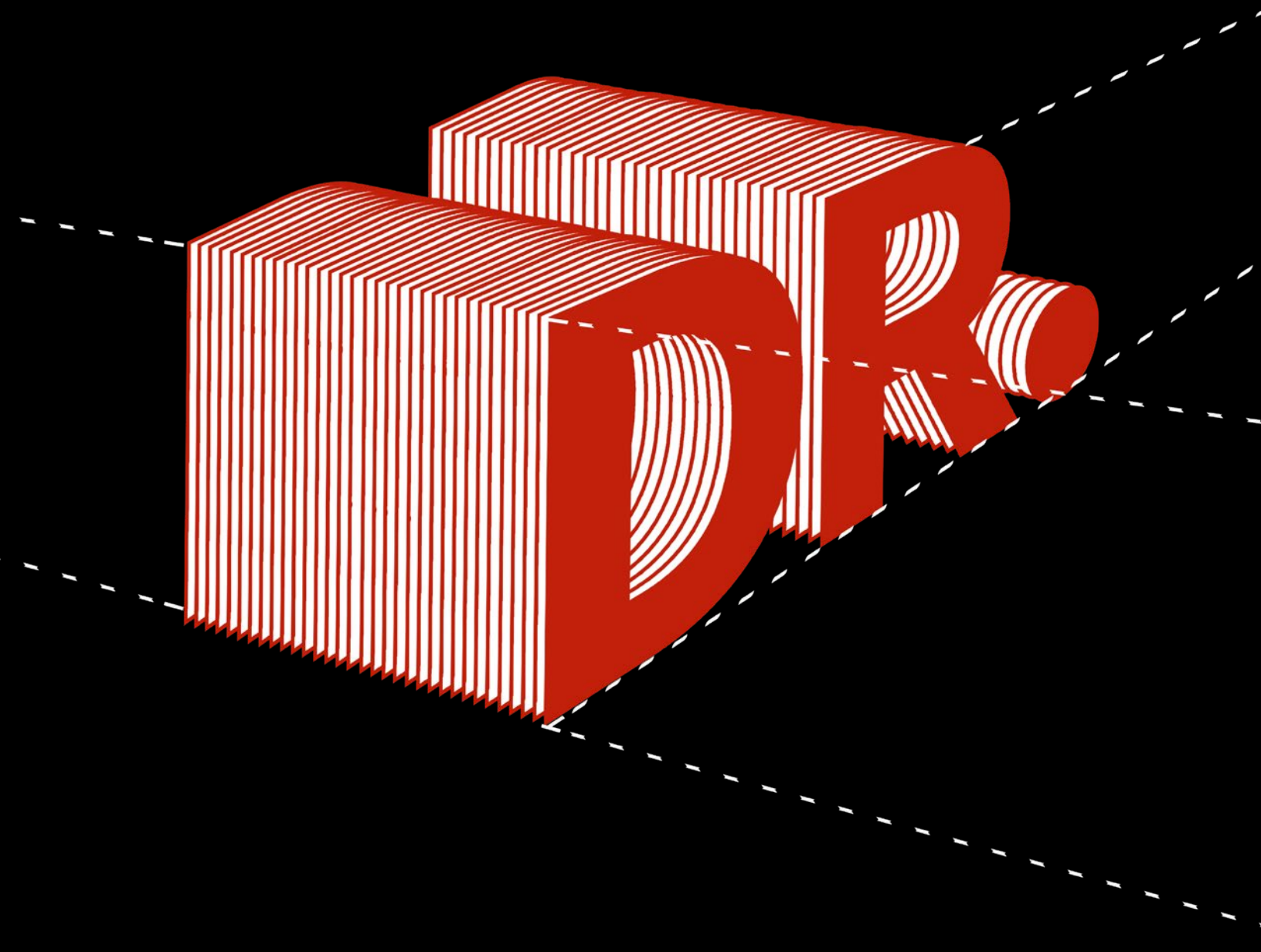
"CALL ME DOCTOR"

HOW WOMEN IN ONCOLOGY ARE FIGHTING FOR CULTURAL CHANGE

By Alexandria Carolan



A sense of foreboding descended on Narjust Duma as she sat at a presentation on drug-induced toxicities. The year was 2018, Duma was a 31-year-old second-year fellow at Mayo Clinic, and her discomfort stemmed from something other than the subject matter discussed.

Duma was attending a panel at the annual meeting of the American Society of Clinical Oncology, and on the stage were three physicians—one woman and two men.

The session chair, a man, introduced himself and the other man presenter by name and title. The woman—whom Duma knew to have the most experience and deepest understanding of the subject—was introduced by first name only.

Duma was taken aback.

Narjust Duma, lead author of a study that is changing culture at oncology meetings.

Is oncology a field where men are introduced as "Drs. X, Y and Z," while women get a "Jenny" or "Rashmi," or "Heidi"? If this woman, despite being renowned for her expertise, can be so casually stripped of her title, how can a young oncologist like Duma hope to earn the same respect as a man with the same credentials?

"As she was being introduced by her first name—and she's a full professor—I was thinking, then what are the hopes for me?" Duma said recently to *The Cancer Letter.*

The thought set off a firestorm, inspiring policy change throughout academic oncology, but it came at a price—harassment.

Duma was familiar with a 2017 study published outside oncology: The study gauged bias in introductions of speakers at grand rounds at Mayo, Duma's institution at the time. (Another study later exposed this behavior in introductions at the 2017 annual meeting of the American Society of Colon and Rectal Surgeons).

Could something similar be happening at ASCO, the largest international oncology conference?

As a Latina in medicine, Duma felt this all the more acutely. "On top of being a woman, and also a minority—that really scared me." Of 688,468 practicing physicians, only 5.2% identify as Hispanic, according to a study published in *JAMA Internal Medicine* in 2015.

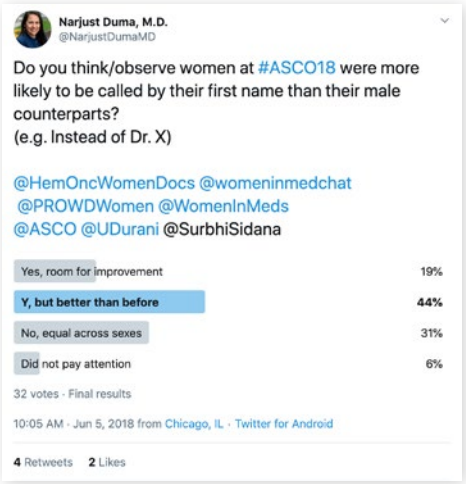
"I'm a fellow. I'm almost done doing all this training that takes forever, and now this is stripping me of my title," thought Duma, now an assistant professor and thoracic oncologist at Carbone Cancer Center at the University of Wisconsin-Madison.

"What is the future if this is happening right now? Is this just me?"

How pervasive is this bias, and how high does this problem reach in the field's hierarchy?

At 9:05 a.m. CT, June 5, 2018, with the session still in progress, Duma tweeted out a question: "Do you think/observe women at #ASCO18 were more likely to be called by their first name than their male counterparts? (e.g., Instead of Dr. X)."

The Twitterverse answered. In this initial straw poll, the majority—63%—said yes.



The answers inspired Duma to dig deeper. In response to her poll, other researchers approached Duma with suggestions to study this question with scientific rigor.

A year after her tweet, Duma presented their results at a session titled "Evaluating Unconscious Bias: Speaker Introductions at an International Oncology Conference" at the 2019 ASCO annual meeting.

The Duma et al. study, published Oct. 11 in *The Journal of Clinical Oncology*, confirmed the results of the informal Twitter poll.

Women leaders in oncology said to *The Cancer Letter* that the Duma et al. findings confirm an open secret, amplifying it from whispered anecdotes and online chatter to robust data capable of informing policy and changing culture.

Informal introductions signal a lack of respect, which perpetuates gender disparities in health care. Unconscious or not, this bias could well have been holding women back for decades, even as more women than men continue to enroll in medical schools.

"Differential formality in speaker introductions may amplify isolation, marginalization, and professional discomfiture expressed by women faculty in academic medicine," Duma et al. wrote, citing the Mayo study, which was published in 2017.

In 1960, 6% of all practicing physicians were women; in 2000, the proportion of women rose to about 30%. In 2017, the number of women enrolling in medical schools in the United States exceeded the number of men, at 50.7%.

Despite this increase, women make up only 42% of faculty at U.S. medical schools, 25% of full professors, and only 19% of department or division chairs. In the 2018 Association of American Medical Colleges report, the average rate of promotion of women to associate professor was significantly lower than that of their men peers, 41% versus 59%.

Nine of the 71 NCI-designated cancer centers are led by women directors—less than 13%.

"One of the things I think is probably underappreciated is how few women cancer center directors there are of the 71 NCI-designated cancer centers," said Karen Knudsen, director of Sidney Kimmel Cancer Center, professor in the Department of Cancer Biology at Jefferson Medical College of Thomas Jefferson, and chair of Cancer Biology.

The Duma et al. paper led to immediate change.

Several directors of cancer centers said they are talking about the study with their faculty and staff, and ASCO has implemented a rule that will require all chairs at scientific, educational, and policy sessions to introduce speakers formally, with their full professional titles.

The study brings about awareness, a crucial first step to achieving gender equity, Knudsen said.

"I view this study as part of that effort to try to enlighten women to say that they can and should be seen in a gender neutral way as capable leaders," Knudsen said. "If that starts as part of an awareness, that there is an unconscious bias in terms of using titles, then it's a small step toward the greater good of really achieving parity in the workforce."

Seven prominent women leaders in oncology—Knudsen, Cheryl Willman, Reshma Jagsi, Nancy Davidson, Cornelia Ulrich, Caryn Lerman, and Sharon Stack—spoke with *The Cancer Letter* about their experiences with gender

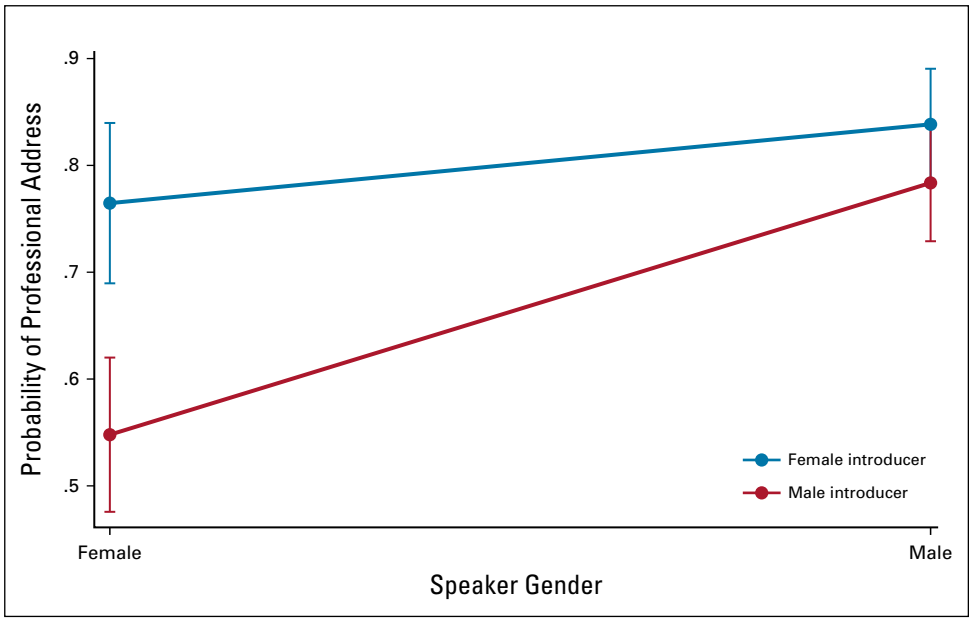


FIG 2. Interaction of speaker gender with introducer gender.

bias, implicit and explicit. Their stories appear on page 16.

"It's important that we are mindful, and are working towards a really true, equal environment," said Ulrich, director of the Comprehensive Cancer Center at Huntsman Cancer Institute and the Jon M. and Karen Huntsman Presidential Professor in Cancer Research.

"That means that if there are multiple speakers, that all the men and women are equally introduced either by their first names or all by their last name—that there are no differences made. What we should say is that the professional titles are critical."

In "Evaluating Unconscious Bias: Speaker Introductions at an International Oncology Conference," Duma et al. analyzed 781 introductions from the 2017 and 2018 ASCO annual meetings, finding that women speakers were addressed less often by their professional title, compared with men speakers, 62% versus 81%.

Men were less likely to use a professional title when introducing women speakers, compared with women who introduced men speakers, 53% versus 80%, the study found. Men introducers were more likely to address women speakers by first name only, compared with men introducers, 24% versus 7%.

Duma's name is now likely to be recognized at conferences.

"Shoot, she's the one with the paper," a man researcher at another oncology conference must have thought while introducing her, according to Duma. Unfortunately, he introduced her by her nickname, NJ, an abbreviation of her first name.

"He corrected it right away and said, 'Dr. Duma.' So, that was enough for me to say that our paper has an impact," Duma said. "Because, yeah, I have been introduced as 'NJ' way too many times.

"If somebody introduces me as NJ in front of a conference instead of 'Dr. Duma,' the audience won't take me as seriously," Duma said. "And that's actually even worse than introducing me by my first name—if I'm introduced by nickname."

The Wolf Pack

When Miriam Knoll saw Duma's Twitter poll on June 5, 2018, she immediately recognized its significance.

"Hey—Great poll," Knoll, medical director of the Department of Radiation Oncology at Hackensack University Medical Center/Mountainside, wrote to Duma over direct message.

Duma's Twitter poll reminded Knoll of a daily affliction—being just "Miriam" in the professional setting.

"This is probably something we can formally study—ex: review the videos from the plenaries," Knoll wrote. "To get the actual data…"

Gender bias in introductions wasn't an issue that had been formally recognized and discussed openly in public with other doctors—men doctors, Knoll said.

"Every woman physician that I had spoken to, ever, not just in oncology, has said that this is something that they've witnessed—that they are addressed, introduced, responded to by their first name and not by 'doctor,' and that's in stark contrast to their male colleagues," Knoll said to *The Cancer Letter.*

"It's informally in the hospital. It's in writing. In response to emails. And this, specifically, you'll notice, is not by people that we know well. It's not by friends and colleagues. It's by people that we don't know," Knoll said.

Before Duma's hypothesis, before her data, before the policy changes, there was a secret, invite-only Facebook group called the Wolf Pack. Today, with 1,563 in the pack, women in hematology and oncology continue to get together to discuss clinical questions, exchange career advice, and talk through issues of gender bias.

> "Every woman physician that I had spoken to, ever, not just in oncology, has said that this is something that they've witnessed—that they are addressed, introduced, responded to by their first name and not by 'doctor,' and that's in stark contrast to their male colleagues."
>
> *– Miriam Knoll*

"Two years ago, you could talk about the Wolf Pack, but you couldn't talk too much," said Duma, a pack member since 2017. "It was like the Illuminati."

In 2016, Knoll noted that child care wasn't available at ASCO—an issue she voiced in the group, and again in a blog she published in *ASCO Connection.* She later turned her hypothesis into a scientific survey with another Wolf-Packer, Reshma Jagsi, and published the 2019 results, titled "Association of Gender

and Parenthood With Conference Attendance Among Early Career Oncologists" in *JAMA Oncology*.

Jagsi is a professor, deputy chair, and residency program director in the Department of Radiation Oncology, and director of the Center for Bioethics and Social Sciences in Medicine at the University of Michigan. She is also a member of the ASCO board of directors.

"It is difficult as a parent, specifically, to attend conferences," said Knoll, who is also the senior author on the Duma et al. paper. "Female oncologists really want to go, they want to be there. And they think that it's important. And ASCO decided to offer onsite childcare, and they did. That policy implementation—which was so important—happened."

ASCO offered free onsite child care for the first time at the 2019 meeting.

Social media was the key for women to connect and describe this form of bias, Knoll said.

Since Duma first joined, the Wolf Pack has become more well-known. At ASCO 2019, women in the Wolf Pack identified one another by placing a red circle on their badges. They were a team.

"[This study] is really a great example of building consensus on social media and recognizing yourself in others," Knoll said. "Because what social media allows is to comment on, 'I noticed something that you may have been feeling and wondering about for a long time, but thought maybe it was only yourself, and then you realize that, no, this is something that other women, other doctors are feeling as well.'"

On June 3, 2019, a full year after Duma ran her poll on Twitter and first connected with Knoll, they presented their findings together in a Clinical Science Symposia session at ASCO.

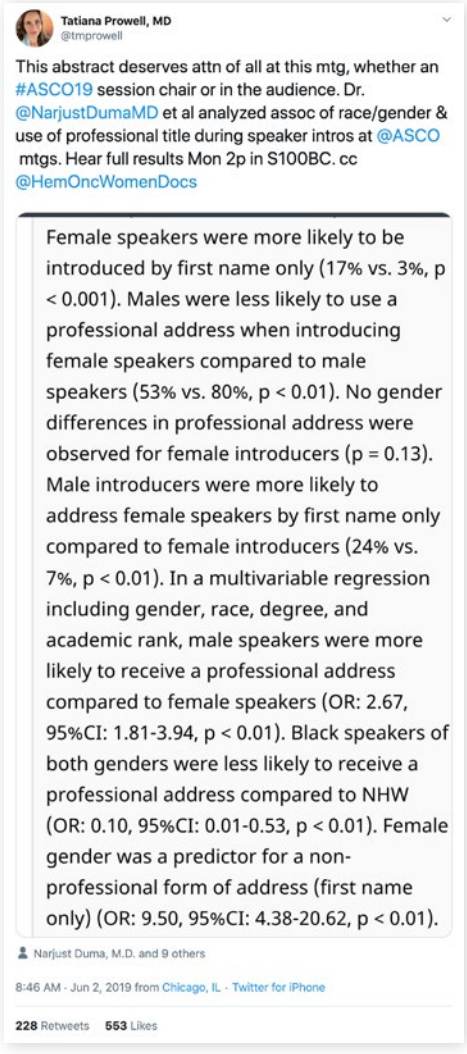
"This abstract deserves attn of all at this mtg"

On June 2, a day before Duma's presentation, a tweet from Tatiana Prowell drew the ire of online trolls.

Prowell, a breast oncologist at FDA and associate professor of oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, was one of four who retweeted Duma's initial Twitter poll.

Prowell is part of the Wolf Pack and is active in the #MedTwitter community.

Aware that sessions on diversity-related issues are often not well-attended at conferences, Prowell, at the time the chair-elect of the society's Annual Meeting Education Committee, wanted to drum up attendance for Duma's presentation.



At 7:46 A.M. CT on June 2, Prowell tweeted: "This abstract deserves attn of all at this mtg, whether an #ASCO19 session chair or in the audience. Dr. @NarjustDumaMD et al analyzed assoc of race/gender & use of professional title during speaker intros at @ASCO mtgs. Hear full results Mon 2p in S100BC. cc @HemOncWomenDocs."

Prowell's tweet, which contains the abstract, has received 228 retweets and 554 likes.

"I wanted to be sure people came to the session, so I tweeted about it before the session took place to try to get people in the room," Prowell said to *The Cancer Letter*. "Because I thought—the authors have done this important work, everyone in this meeting is going to see speakers introduced, or introduce speakers, or be introduced—or all of the above. They need to be in the room to be made aware of this—acutely, during this meeting. Before it's over."

Initially, there was a lot of support for the tweet and a lot of support for the results. "Men and women were congratulating [the authors] for doing the painstaking work of going back and watching all of the videos from all of the sessions from two years of annual meeting," Prowell said.

Prowell's tweet offered no further interpretation of the data. She didn't point fingers, didn't make accusations. No men were attacked, but some might have thought they were:

"#metwomovemrnt. Enough with political correctness."

"... And amazingly, these are supposedly the country's intellectual elite, MDs and PhDs. What a mess the rest of the country must be. Or who knows, maybe it's better..."

"When did we as scientists begin addressing criticisms of supposed

scientific studies by name calling? And where does medical science go in an environment where this attitude is commonplace?"

"Is it a good idea to encourage documentation of gender inequality?"

Duma continues to receive online hate mail.

"I want to call it how it is—harassment—because it was crazy," Duma said. Prominent faculty members from other institutions sent Duma messages advising her to "stick to lung cancer" and telling her that she "was a good researcher until now."

> I want to call it how it is—harassment—because it was crazy.
>
> – *Narjust Duma*

"People were saying, this is an insult to intellectuality, this isn't science," Duma said. "Some of them were comparing me to the anti-vaccination movement. It came from everywhere, from a lot of different types of people. I did delete a lot of the messages on Twitter because I didn't want to see them."

As a taxpayer-funded employee, Prowell believes she should be accessible to the public. Her Twitter settings allow anyone to send her private messages, which were often more hurtful than the public replies.

"I was honestly surprised that the tweet generated that much attention, let alone controversy. It's science and not really that different from any other study I might tweet about to my mind," Prowell said.

Duma received hundreds of direct messages on Twitter. She received emails to her institutional address. People who didn't even know her, who declined to reveal their names publicly, took the time to dig for her information and contact her directly.

"People were a little bit more cruel by email. Because it is not out there, so you feel more free to say whatever," Duma said.

She was weeks away from finishing her training—"I was still a fellow, and I think trainees are considered to be a protected population," Duma said. "We're learning. We are still young."

Before the study was published, Duma was most-commonly accused of dividing the ASCO community. "The other most common message was that we were cherry picking the data—when we reviewed all of the videos. Not one, all of them."

Some of the messages received by women in the Twitter conversation appeared to be threatening.

"I got a string of emojis that included a dagger, a heart, and a crying face," Prowell said.

Security guards

On June 3, Duma was in no position to put the uproar in perspective. This was her first-ever oral presentation.

There were about 40 people in attendance. About 25 of them were women from the Wolf Pack. There were about half-a-dozen men, Prowell estimates.

Of 2,511 videos reviewed from ASCO's 2017 and 2018 annual meetings, 781 met inclusion criteria. Women were addressed less often by their professional title, compared with men speakers (62% v 81%; P , .001). Men were less likely to use a professional address when introducing women speakers, compared with women introducing men speakers (53% v 80%; P , .01).

When women performed speaker introductions, no gender differences in professional address were observed (75% v 82%; P = .13). Women speakers were more likely to be introduced by first name only (17% v 3%; P , .001). Men introducers were more likely to address women speakers by first name only compared with women introducers (24% v 7%; P , .01).

In a multivariable regression including gender, degree, academic rank, and geographic location of the speaker's institution, men speakers were more likely to receive a professional address compared with women speakers (odds ratio, 2.43; 95% CI, 1.71 to 3.47; P , .01).

The study's conclusion: "When introduced by men, female speakers were less likely to receive a professional address and more likely to be introduced by first name only compared with their male peers."

The presentation seemed to have gone smoothly. After the talk, while Duma was in conversation with ASCO staff members about reporting the harassment, she noticed two security guards stationed by the door.

"I learned that the ASCO team had brought some guards, just to be safe. I think it was two people. It wasn't the detail of Queen Elizabeth," Duma said.

ASCO brought in security guards specifically because of the harassment she received.

"'Ay dios mio, thank God you told me after my presentation,'" Duma thought, relieved she hadn't been distracted while focusing on the data. "I didn't think anybody would get physical with us, but we were just afraid that somebody would be aggressive. This is the first time this type of data was ever presented at ASCO."

ASCO also sent cease-and-desist letters to the perpetrators.

"ASCO staff spontaneously reached out to let me know they were monitoring the conversation taking place on Twitter," Prowell said. "They were very focused on ensuring a safe environment for everyone, which I appreciated."

ASCO has since implemented directives for how to introduce speakers at all future meetings. The society plans to train all chairs on unconscious bias ahead of the 2020 annual meeting, Jamie H. Von Roenn, vice president of education, science and professional development at ASCO, said to *The Cancer Letter.*

"The results of this study and some discussions that were ongoing regarding ASCO's commitment to gender equity across its programs—which the board has been following for a couple years—really led to this change," Von Roenn said.

ASCO's action on gender bias is part of a larger cultural shift, including the recent introduction of free onsite child care and private nursing rooms during the 2019 meeting, and a larger focus

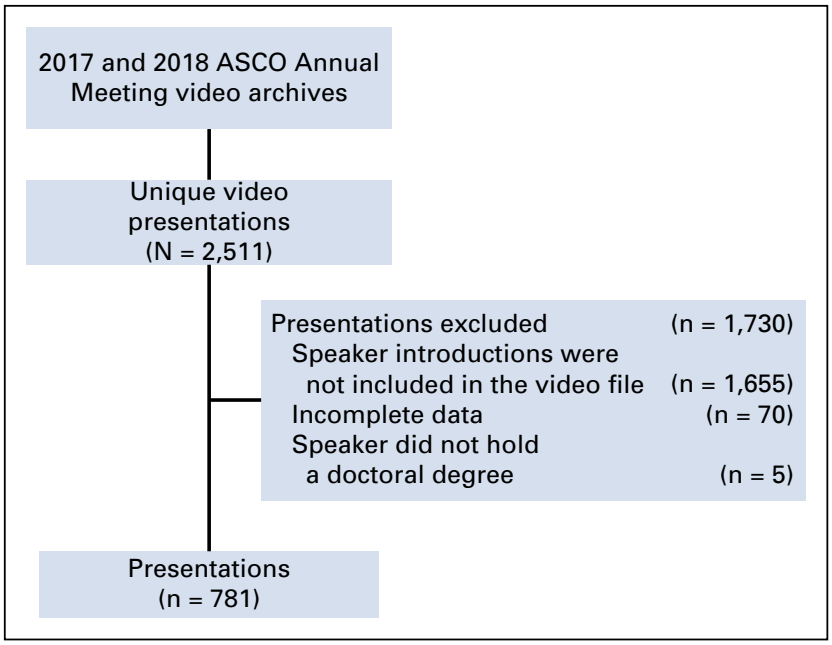


FIG 1. Consort diagram depicting the selection of video files from the 2017 and 2018 ASCO Annual Meetings.

TABLE 1. Characteristics of Speakers at the 2017 and 2018 ASCO Annual Meeting

	Female Speaker, n = 322	Male Speaker, n = 459	
Characteristic	**No. (%)**	**No. (%)**	***P***
Year			.80
2017	176 (55)	255 (56)	
2018	146 (45)	204 (44)	
Session area			< .01
Hematology	34 (11)	48 (10)	
Oncology	161 (50)	250 (55)	
Care delivery/medical education/survivorship	99 (31)	87 (19)	
Basic sciences/early drug development	27 (8)	66 (14)	
Missing/unknown	1 (< 1)	8 (2)	
Academic degree			< .01
MD	232 (72)	291 (63)	
MD/PhD	56 (17)	137 (30)	
PhD	25 (8)	25 (5)	
Other	9 (2)	6 (1)	
Academic rank of speaker			.03
Instructor	4 (1)	7 (2)	
Assistant professor	51 (16)	55 (12)	
Associate professor	83 (26)	98 (21)	
Professor/emeritus	99 (31)	192 (42)	
Nonacademic	11 (3)	13 (3)	
Other/unknown	55 (17)	65 (14)	
Missing	19 (6)	27 (6)	
Geographic region of speaker's institution			.06
United States	249 (77)	339 (74)	
Europe	48 (15)	80 (17)	
Canada	15 (5)	14 (3)	
Australia	5 (2)	3 (1)	
Asia	3 (1)	19 (4)	
Africa	2 (1)	1 (< 1)	
Central America/South America/Caribbean	0 (0)	3 (1)	
Medical trainee	10 (3)	10 (2)	.42

Abbreviations: MD, Doctor of Medicine; PhD, Doctor of Philosophy.

The Language of Respect

Health care professionals working in the field of oncology have respect for patients, families, and colleagues as a core tenet of practice and research. Unfortunately, the language of oncology does not always convey or represent that level of respect. In language about patients, this is likely not a result of intent, but an issue of shorthand communication, phraseology that made its way into modern parlance many years ago, and a lack of awareness.

Recent evidence[1] has shown that there is inconsistency in demonstrating appropriate respect in the forms of address used to introduce faculty at the ASCO Annual Meeting. It is essential that all faculty are introduced and addressed in a professional manner; the form of address should not be different based on gender, race, ethnicity, or seniority.

The American Society of Clinical Oncology and its 2019-2020 President and Annual Meeting leadership are committed to developing new norms that reflect appropriate respect for patients, families, advocates, and health care providers. To that end, we are providing this summary guidance to our faculty with some critical points to keep in mind and put into practice – at our Meeting and in all communications. There is certainly more language that may be considered disrespectful and/or offensive. Our goal is to begin the journey and to continue to evolve.

Directive: Demonstrate Respect for Patients and Families

Do not Blame Patients

- Patients do not fail therapies; therapies fail patients.
    - *Wrong*: "Six patients failed to respond to [study drug]." **or** "Six patients failed treatment."
    - *Instead*: "[Study drug] did not yield a response in six patients" **or** "Six patients had tumors that did not respond to [study drug]."
    - *Wrong*: "## number of patients were screen failures."; *Instead*: "## number of patients were not eligible for the study."

Respect the Role of the Patient

- Doctors do not manage patients; doctors manage disease/therapies.
    - Use the word "treat" when referring to patients, as in "the experimental drug was used to treat six patients."
    - Only use the word "manage" when referring to the disease, as in "steroids were used to manage brain metastases."

Do not Dehumanize Patients

- Do not use a disease or condition on its own to refer to a patient.
    - Do not use the adjective form of diseases or conditions alone to refer to a person, as in "12 diabetics were included"; *Instead*: "12 patients with diabetes were included."
- Do not use language that implies that the patient is the disease.
    - *Wrong*: "The study included 250 EGFR mutants…"
    - *Instead*: "The study included 250 patients whose tumors had EGFR mutations" **or** "The study included 250 patients with EGFR-mutated tumors."
    - *Wrong*: "The patient progressed…"; *Instead*: "The cancer/tumor progressed…" **or** "The patient experienced disease progression…"

Use Accurate Language Throughout the Session

- "Risk reduction" is the appropriate term for strategies that lessen the risk of developing cancer but do not necessarily prevent it.

Directive: Demonstrate Respect for Colleagues

- All chairs, faculty, presenters, and panelists, including patients and advocates, who have a doctoral degree (e.g., MD, PhD, ScD, PharmD) should be introduced and addressed as Dr. Full Name or Dr. Last Name.
- All other chairs, faculty, presenters, and panelists (including patients and advocates) should be introduced and addressed as Mr./Ms. Full Name or Mr./Ms. Last Name.
- These forms of address should continue during Q&A and panel discussions, regardless of whether the faculty know one another. The key element is *consistency of address among all panelists*.
- We will ask all faculty to commit to use of a professional form of address when accepting their session invitations. Chairs will be asked to briefly reiterate this policy with all faculty in their session immediately prior to the start of the session.

[1] Evaluating unconscious bias: Speaker introductions at an international oncology conference.
Narjust Duma et al., Journal of Clinical Oncology 2019 37:15_suppl, 10503-10503

on patient-first language. The Duma et al. study is directly cited in ASCO's recently published instructions written by Prowell and ASCO staff on meeting language: "The Language of Respect."

ASCO will provide training for abstract reviewers, Von Roenn said, which will make them aware of how gender can influence how a reviewer evaluates an abstract.

"The more we can do to level the playing field, the better care we can provide," she said.

How unconscious is "unconscious"?

Two other studies have found the same form of bias in other medical specialties:

- A study published in the *Journal of Women's Health* in 2017, "Speaker introductions at internal medicine grand rounds: Forms of address reveal gender bias," honed in on speaker introductions at Mayo Clinic's grand rounds. The Mayo study found women introducers were more likely to use professional titles when introducing any speaker during the first form of address compared with men introducers (96.2% vs. 65.6%).
- Another study, published in *Diseases of the Colon & Rectum* in 2017, found women moderators were more likely to use formal introductions, compared to men moderators at the 2017 American Society of Colon and Rectal Surgeons' annual meeting (68.7% vs. 54.0%). Men moderators were significantly less likely to formally introduce a woman versus a man speaker (36.4% vs. 59.2%).

"Studies like this are so important to show people these small unconscious biases, and how they can cumulatively have a significant effect, such that we're never going to achieve equity unless we're mindful of them and target them," Jagsi said to *The Cancer Letter*. "Kudos to Dr. Duma for extending this to the setting of ASCO speaker introduction.

"It's a brilliant idea to take a look at this and she, again, followed the very rigorous approach that Dr. Sharonne Hayes [senior author of the Mayo study] had established when she had done the Grand Rounds study, where she had mixed gender coders who were coding the introductions to remove the impact of any kind of bias. And, really, she did a well done study in a really important setting to study," Jagsi said.

The retrospective analysis used by Duma et al. solidified the study's findings, Sharon Stack, Ann F. Dunne & Elizabeth Riley Director of Harper Cancer Research Institute, Kleiderer-Pezold Professor of Biochemistry, Department of Chemistry & Biochemistry at the University of Notre Dame, said to *The Cancer Letter*.

"Things can't be changed if you say, 'Oh, I think there's an issue with the way people are being introduced,' … the participants were not aware that this study was going on because this was retrospective data. [The researchers] could really go back and analyze it in a completely unbiased way," Stack said. "I think that makes the data even stronger. The data were unequivocable, and the ranges were not subtle."

On its face, "unconscious" bias may amount to a benefit of the doubt. If the issue is so pervasive, how could men—and less often, women—not be aware of it?

"It's not that we think or suspect that there is overt discrimination, overt sexism, or a concerted effort to disrespect women," Knoll said. "What is happening, clearly, is an unconscious bias. It's unconscious inequity. It's not that someone is looking to discredit women, but clearly there's a difference between how men and women oncologists are being introduced."

These behaviors are not intentional, said Jagsi, who is a founding member of Time's Up Healthcare, a part of Time's Up, an organization that advocates for causes that include gender equality in the workforce. "By and large, these are unconscious biases, and they're called unconscious, because they are not conscious," she said. "And the purpose of studies like these are to identify them so they can be targeted."

> "What is happening, clearly, is an unconscious bias. It's unconscious inequity."
>
> *– Miriam Knoll*

Bias and prejudice have been the subject of extensive research in psychology, sociology, and anthropology. Gender bias in medicine and health care is now receiving increasing scrutiny.

So, is the gender discrepancy in introductions truly "unconscious," in psychological terms?

In the social sciences, bias is generally considered to be either "implicit" (i.e. subconscious or unconscious) or "explicit" (conscious). Implicit biases are thought to develop from the continual association of a social group (such as "men") with either a trait (such as "competent") or attitude (good/bad), experts say.

"People reveal [implicit bias] unintentionally through their actions, without being aware of it, to culture, the set of meanings, symbolisms, and expecta-

tions based on what we are conditioned to give meaning to," Dawne Moon, an associate professor of sociology in the Department of Social and Cultural Sciences at Marquette University, said to *The Cancer Letter.*

Moon provides an analogy:

In the same way that a driver would stop (habit of thought) when the traffic light turns red (culturally-defined meaning), perceptions of someone's sex and gender can trigger psychological processes (chains of associations) at a lower level of awareness.

"What level of non-consciousness that operates on, I couldn't really say. It wouldn't be as a result of repression, though," Moon said. "It would have to do with the social construction of symbolic associations in the brain."

Introductions are "an objective measure of formality, an objective measure of professional respect. It's really a great way to document and show unconscious bias," Knoll said.

Every time a woman physician is stripped of a title her men colleagues get to keep, it perpetuates the falsehood that men are better, UMich's Jagsi said.

"If it's sowing an unconscious seed that man is worthy of respect and dignity, it is suggesting in some way that the woman is less significantly accomplished as a professional," Jagsi said.

These implicit gender biases can be changed, Moon said.

"Those chains of association can be examined, rethought, and challenged," Moon said. "Just because we tend to think 'doctor = man' and 'nurse = woman' doesn't mean we can't—with either intrinsic or extrinsic motivation—catch ourselves and remake those chains of association."

Heidi and Howard

It's not a coincidence that Duma's study is published in the #MeToo era, said Ally Coll, a lawyer, president and founder of The Purple Campaign, a Washington non-profit that seeks to prevent workplace sexual harassment by implementing stronger corporate policies.

"This is a moment where people across all industries and professions are recognizing the way that gender discrimination plays out in a professional setting," Coll said.

[Disclosure: Coll is a step-daughter of Paul Goldberg, editor and publisher of *The Cancer Letter*]

When a moderator introduces a woman speaker without her title or biography, the woman's expertise can be undermined, Coll said.

"Women get penalized when they have to share their own bio or say their own title to get that credibility—people often, because of unconscious bias, they'll perceive that as negative—as too self-promoting or selfish. Or they'll hold it against women in a way that they don't with men," Coll said.

For example, in a 2003 experiment that has become known as the Heidi / Howard study, Harvard Business School students were presented with a case study of a successful entrepreneur based on Silicon Valley venture capitalist Heidi Roizen.

Both cohorts were given the same profile: one named "Heidi" and the other "Howard."

Students in both groups ranked Heidi and Howard as equally accomplished, but Howard was seen as an appealing colleague, while Heidi was regarded as selfish or unpleasant.

"When I'm involved in panels or other events, it is a better practice for the

moderator or the introducer to do that work for the panelist, rather than my having to say that to prove my credentials to the room," Coll said.

The audience responds differently if Coll were to introduce herself.

"They're going to have a higher likelihood of seeing it as bragging, or selfish, or self-promoting in a negative way. And I think that the Heidi / Howard study shows that when men have to do that, they don't have necessarily the same backlash effect," she added. "This might seem like a little thing, but it's not."

Recognition by title at conferences have an effect on acknowledgement in other professional settings, Coll said.

"That's why it's so important for people in a workplace setting, whether that's events or in hiring, in promotion decisions, to create neutral processes that everyone just has to follow," Coll said. "When you leave things for individual discretion, that's when unconscious bias can come out—and we see that in decisions around hiring a lot."

Women directors of cancer centers who spoke with *The Cancer Letter* are addressing gender bias in their institutions.

Knudsen, who has previously been on many NCI site visits, said she had always noticed the discrepancy in who is addressed by name and title and who isn't.

She was part of the decision to make sure all faculty and staff referred to each other by their title at a recent NCI site visit at Thomas Jefferson.

"We did it because we wanted there to be continuity in how we discussed and talked about each other," Knudsen said. "So, we said, 'Look, it has to be one or the other—we were either going to use first names or we were going to use titles. And we elected to use titles."

NCI remarked on the consistent use of titles—regardless of gender—at Thomas Jefferson.

"I like to think we're leading the way on this, and it just is a small step toward what we want to achieve—parity," Knudsen said.

Despite ASCO's new policies and heightened engagement on the issue, the problem persists, and is not unique to the "international oncology conference."

On Dec. 11, Prowell spoke with this reporter while attending the San Antonio Breast Cancer Symposium.

"I saw multiple female speakers in one session addressed at the podium by first name only from the floor microphones. This did not happen to any of the men in the session," Prowell said. "I don't believe anyone doing this intends any disrespect. It's unconscious bias.

"Fortunately, now that we are all aware of it, we can work towards solutions."

Have you ever felt disrespected or unsafe because of your gender in a professional setting in health care?

We want to hear about your experiences. Please fill out our **short survey**.

The Cancer Letter will not use any identifying details without your consent. Any data that we publish will be de-identified and anonymized, including the names of any institutions.

Editor's note: *The Cancer Letter* does not use titles and honorifics in its reporting, per the AP Stylebook.

Katie Goldberg and Matthew Ong contributed to this story.

Don't call me Karen, Cheryl, Nancy, Reshma, Cornelia, Caryn, Sharon, ... call me "Doctor."

A study that found gender bias in introductions of women speakers has awakened memories of decades of disrespect, women leaders in oncology said to *The Cancer Letter.*

The study, led by Narjust Duma, an assistant professor and thoracic oncologist at Carbone Cancer Center at the University of Wisconsin-Madison, analyzed 781 introductions from the 2017 and 2018 ASCO annual meetings.

Women speakers were addressed less often by their professional title compared with men speakers, 62% versus 81%, the study found.

Men were less likely to use a professional title when introducing women speakers compared with women who introduced men speakers, 53% versus 80%.

Men introducers were more likely to address women speakers by first name only compared with women introducers.

Women leaders in oncology said they've been aware of this bias throughout their careers.

All the women we spoke with said that since the paper was published in the *Journal of Clinical Oncology* in October, they have been taking efforts to make sure the next generation of women in oncology are treated with respect.

Karen E. Knudsen, MBA, PhD
Executive vice president of oncology services, Jefferson Health
Enterprise director, Sidney Kimmel Cancer Center
Hillary Koprowski Professor and Chair, Department of Cancer Biology,
Thomas Jefferson University
Chair, Cancer Biology

> It's something we can change, and it's easy to change ... It's a call to action.

Karen E. Knudsen laughed knowingly when she first read the title of the Duma et al. paper: "Evaluating Unconscious Bias: Speaker Introductions at an International Oncology Conference."

"I mean, I sighed, and then I chuckled—because I thought 'Oh yeah, I know this story,'" Knudsen said. "This happens all the time. it happens more frequently than it should in a variety of different formats."

Knudsen wasn't surprised at all. Why?

"I'm a woman in academic medicine. This happens to me too regularly. If it is the case that I am introduced as Karen instead of, you know, 'Dr. Smith,' that automatically, unconsciously, puts us on a different playing field. I'm not seen or viewed in the same light."

At conferences, Knudsen said she is referred to as "Karen" frequently. As the 2020 chair of the ASCO Genitourinary Symposium and AACR Advances in Prostate Research, she is planning to draw attention to this issue.

"I will and I have taken more notice of it in regard to conferences. Prior to the article I might not have thought to," Knudsen said. "I'm really appreciative of the fact that this group got together, documented probably what many of us already held to be true, because they raised awareness. To me, that's the real benefit in this article, because it's something we can change, and it's easy to change ... It's a call to action. It's something we could easily modify in our behavior starting today."

Knudsen said she has distributed the paper to faculty and staff at Thomas Jefferson.

"[This study is] a small step toward the greater good of really achieving parity in the workforce," Knudsen said. "If the end goal is parity in the workforce, especially in leadership, then it has to start in the beginning. That means that everyone is viewed based on the merit of what it is that they have accomplished and what their contribution is to the workplace and to the field."

Nine of the 71 NCI-designated cancer centers are headed by women directors, and the number of women in deputy-director positions at cancer centers is alarmingly low.

"I'm always impressed by how many people who ask 'What's it like to be a PhD and a cancer center director,' when at last count I think there's something like 16 or 17 non-MD cancer center directors," Knudsen said. "There are a lot of us. No one ever says 'Wow, isn't it interesting there are so few women [cancer center directors]'—except the women."

During the last NCI site visit to Thomas Jefferson, Knudsen and her leadership team required that all doctors would be addressed by title, regardless of gender. The decision was made before she read the Duma et al. study.

"We did it, because we wanted there to be continuity in how we discussed and talked about each other," Knudsen said. "So we said, 'Look, it has to be one or the other—we were either going to use first names or we were going to use titles.' And we elected to use titles."

It made a difference.

"I remember an unnamed person from the NCI who was at the site visit saying to us, 'Wow, we really remarked at how consistent your team was of using titles for everyone,'" Knudsen said. "I've been on a lot of site visits, and I've seen a lot of variances. So, I like to think we're leading the way on this, and it just is a small step toward what we want to achieve—parity."

Cheryl L. Willman, MD
Distinguished Professor of Pathology and Internal Medicine, The Maurice and Marguerite Liberman Distinguished Endowed Chair in Cancer Research
Director & CEO, University of New Mexico Comprehensive Cancer Center

> “I’ll see my male colleagues referred to as ‘Dr. So-and-so,’ and I’m referred to as my first name, despite the fact that I’m one of the most experienced and longest-serving cancer center directors.”

Cheryl L. Willman has been referred to by her first name since she was in medical school at Mayo Clinic in 1981. She was referred to by her first name during her residency at the University of New Mexico School of Medicine in 1984 as well. To this day, men colleagues often refer to her as just “Cheryl” at meetings of directors of cancer centers as well as on NCI advisory boards.

“I’ll see my male colleagues referred to as ‘Dr. So-and-so,’ and I’m referred to as my first name, despite the fact that I’m one of the most experienced and longest-serving cancer center directors,” Willman said.

One surgeon Willman encountered on cardiovascular rotation during her training holds a place of distinction in a parade of rogues:

“He would say that the women on the team should—I don’t think he ever said ‘girls,’ which was good, but he did say that the women on the team should wave palm fronds when he walked into the room with his patients—as a joke. But it’s really not a joke; right? You just realize that in that environment, you’re not going to say anything.”

As Willman moved up the ranks, she observed gender bias in the institutions where she worked.

“Surprisingly to me—as you rise higher in national groups, like the NCI Board of Scientific Counselors and the Board of Scientific Advisors, even our center directors meeting—it was shocking to me to see this still going.”

Willman circulated the Duma et al. study to her institution’s committee of chairs and health science center—“to make a point.”

“We’ve talked about this in our meetings. I find that particularly men constantly forget; it’s part of their own acculturation. They just need constant reminders,” Willman said. “I find, with gentle reminders, or modeling appropriate behavior when I refer to my female colleagues by their title, men actually pick up on that pretty quickly.”

Formal introductions are essential at international meetings, because they imply respect, Willman said.

“To me, a failure to do that is an indication that the person doesn’t have an equal respect for the achievements of a woman who is serving in the same role. And that’s really disappointing,” she said.

A few years ago, at an American Association for Cancer Research meeting, Willman led a program about women in leadership, where women trainees, residents and fellows raised concerns about informal introductions in professional settings.

“They had actually noticed during the meeting that women were too often referred to in—they used the word pejorative fashion—by first name, or not fully acknowledged with their title and their institution when they were a speaker,” Willman said. “It just makes you realize sometimes what you’re up against. And it’s disappointing.”

In surveys conducted at the University of New Mexico, women have said they are less likely to raise concerns of unconscious bias in regard to gender, race or ethnicity.

“They feel that will harm them,” Willman said. “While I think the conversation has evolved and improved to where I would be comfortable—but I’m a pretty senior leader.”

The best way to call out this behavior?

“Usually, gently and with a smile on my face,” Willman said. “If I’m angry about an issue, which I may feel inside, then the power of my words is lost. If I’m gentle about an issue and speak quietly, and sort of have a smile on my face, it makes everyone uncomfortable, and it has an impact,” Willman said.

“Whether people in the room roll their eyes and say ‘There goes Cheryl again,’ you know, too bad. That’s my role.”

Nancy E. Davidson, MD
Senior vice president,
Director and member,
Clinical Research Division, Fred Hutchinson Cancer Research Center
Raisbeck Endowed Chair for Collaborative Research, Fred Hutch
President and executive director, Seattle Cancer Care Alliance
Professor and head of medical oncology, University of Washington

Before Nancy E. Davidson read the Duma et al. study, she thought that the discrepancy in introductions—addressing women by first name, no honorific—was a once-in-a-while mishap.

She has since thought about incorporating the results into her daily work, and she suspects the implications of the study aren't limited to oncology.

"I like to think that I've been very good at [introductions]," Davidson said. "But I'm trying to be more thoughtful and mindful about this going forward, to make sure that I always emphasize this."

Recently, Davidson introduced a young faculty member during a meeting at her institution.

> "You know, I'm established. I can live with this, [but] the notion that we're giving this message to somebody who is just starting her career strikes me as very distressing for our profession."

"It's obvious to me that the person giving this talk is a physician, but she is a she, and she's a woman of color, and that's the kind of situation where you want to make sure that you really do emphasize her title and her credentials," Davidson said. "That this is 'Dr. So-and-so,' and she got her bachelor's degree here, and her medical degree there, and her training here, and now she has this faculty position—to make sure that it's really clear that this is a person who is qualified and credentialed, and an authority on this topic that you're going to hear about so that there's no ambiguity."

Davidson experienced gender bias earlier this year, when she was on a panel at a local business conference:

"When we were all introduced to come up to the panel, the five men were introduced by their first and last names: 'Dr. John Smith, etc.' The two women were introduced as 'Nancy' and 'Mary.'"

Davidson and "Mary," both well-established in their fields, "walked up there together and said, 'Wow, we don't even get our last names?'" Davidson said. "I was impressed by how that really diminished the qualifications of both of the women who were up there. I would say that this is a pretty pervasive problem."

In another instance, at a philanthropic award event she attended in Seattle, Davidson witnessed an even more distressing display of disrespect.

All but one of the award recipients were men.

"The woman with her PhD was not recognized as 'doctor,' but all of the other people, who were men, were recognized as 'doctor'—'Dr. Smith this, Dr. Smith that,'" Davidson said. "They went through her whole biography and at the end said: 'Jane Smith' is getting this award.'"

The problem isn't limited to large medical conferences. Rather, "it's permeating our society at large," Davidson said.

"You know, I'm established. I can live with this," she said. "[But] the notion that we're giving this message to somebody who is just starting her career strikes me as very distressing for our profession."

The Duma et al. study "brings a large data set to the table for us to look at. To me, it validates what we might have felt in these one-off situations, and says it's actually a more common problem than I could've imagined," Davidson said. "Big data leads to knowledge—so I think these data have allowed us to really know more about the problem. And knowledge is going to hopefully lead to solutions."

Reshma Jagsi, MD, DPhil
Deputy chair, Radiation Oncology
Newman Family Professor of Radiation Oncology
Residency Program Director
Director, Center for Bioethics and Social Sciences,
University of Michigan
Member of the ASCO Board of Directors

> Showing the data can be so important in leading to behavior change of pushing people along that spectrum, from precontemplation to contemplation, to actually realizing there's a problem here.

"For years I've been told it's all in my head," Reshma Jagsi said.

Of course, she understood that she was being asked to accept being called "Reshma" in the same professional settings where her men colleagues got the honorific "Dr." Of course, it wasn't in her head, but here, in the Duma et al. study, the data dispel gaslighting decisively, once and for all.

Just the other day, an administrator referred to Jagsi as Reshma three times in an email. That would have been just fine had the same email not bestowed a "Dr." upon her men colleagues.

"I felt really disrespected," Jagsi said. "I am the deputy chair of this department. One of the four doctors that was mentioned was the chair, but the other faculty members were not senior to me, and arguably were junior to me."

Younger doctors tell Jagsi that they deal with this nonsense daily.

"Most of my female residents tell me they introduced themselves as doctor 'last name' to try to avoid that," Jagsi said. "And even when they do that, sometimes patients will call them by their first name."

The Duma et al. study is indicative of "a deep phenomenon that extends well beyond introductions at formal academic events—this is symptomatic of a very deep issue rooted in our culture," Jagsi said.

Ultimately, the discrepancy in title introductions causes a "downstream impact of gender inequity in leadership," Jagsi said.

"What this study is elucidating is a mechanism by which one of many mechanisms that contributes to the disparity that we see at senior levels because it does matter what one is called," she said. "It influences the way that others respond in the audience when someone is introduced as someone worthy of respect versus introduced in a more informal way."

The issue is personal, too.

"I have a white male husband who doesn't have the same lived experience that I do," Jagsi said. "He is able to appreciate what that must be like, and really, showing the data can be so important in leading to behavior change of pushing people along that spectrum, from precontemplation to contemplation, to actually realizing there's a problem here.

"There is something going on here that is disadvantaging women."

Cornelia Ulrich, PhD
Jon M. and Karen Huntsman Presidential Professor in Cancer Research
Director, Comprehensive Cancer Center at Huntsman Cancer Institute

> We all have to pay attention to the power of language, because that's what we use and that's what we as humans respond to.

Cornelia Ulrich grew up with a language that excludes women from professional roles, including those in medicine.

"The German language, in Germany itself, is entirely male-centric," Ulrich said. "Every prescription note will refer to the physician as the male physician. Every document will refer to that physician as the male physician, and also to the male patient.

"The reason that is given is that it's very cumbersome to use both the male and female form, and it clearly will extend the text."

The Duma et al. paper points to an all-too-familiar feeling of exclusion, reminding Ulrich of a lack of recognition and respect—that women don't belong here.

"It does result overall in women being presented, perhaps, with less credibility and respect— and unintentionally so," Ulrich said. "It's important that we are mindful, and are working towards a really true, equal environment.

"That means that if there are multiple speakers, that all the men and women are equally introduced either by their first names or all by their last name—that there are no differences made. What we should say is that the professional titles are critical."

Whether it's an issue of the German language or first-name introductions, "it's so important that we actually pay attention to that, because the effects are there," Ulrich said.

"[Language] is something that I think has a huge impact, subconsciously, already on young women and children. Because they do not identify themselves with the role, or the trade around them that are usually professional roles."

A man colleague was the first to send Ulrich the Duma et al. study.

"It certainly made me aware of something that I didn't anticipate to be such a big difference. I'll pay more attention to it, both when I introduce myself or when I get introduced," Ulrich said.

When it comes to language, Ulrich's solution is to teach her German-speaking students to include male and female pronouns, or to use a neutral plural pronoun.

The best way to create equality in introductions is to point out the problem, Ulrich said.

"The more we can find ways to highlight these facts and bring it up in a neutral, observing way— and there are many men who are very eager to also change this and getting them on board and involved—the better," she said.

Before she moved to the United States, Ulrich hadn't realized how male-centric the German language is.

"When I came to the U.S., I read children's books to my kids. And it was very funny, because in my mind, in my German mind, it was so clear that the male pronoun would be used for something," Ulrich said. "And then, all of a sudden, it said 'she.' And I felt like I stumbled over it so many times, because it was an incongruence with my role understanding. It made me really aware of that.

"We all have to pay attention to the power of language, because that's what we use and that's what we as humans respond to."

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Caryn Lerman, PhD
Professor of psychiatry and the behavioral sciences
H. Leslie Hoffman and Elaine S. Hoffman Chair in Cancer Research
Director, University of Southern California Norris Comprehensive Cancer Center

> "I think having tangible evidence is useful, because there's something actionable in this. There's something we can do about it."

Caryn Lerman hasn't noticed gender bias in introductions at conferences, but she has witnessed it elsewhere—and not just in oncology.

"I've observed it anecdotally in how announcements are made, perhaps of new faculty appointments, where men might be more often referred to as 'doctor,' and women by their first names," Lerman said.

The Duma et al. paper proves that it's a systemic problem, Lerman said.

"It makes us all aware of it, men and women, aware of our biases—gender biases, or other biases," she said. "In academic settings, we value data to inform on whether our perceptions are validated with evidence. And I think having tangible evidence is useful, because there's something actionable in this. There's something we can do about it."

For Lerman, like others, "it's an important issue professionally, to show the same level of respect for women and men."

If Lerman has experienced an informal introduction, she hasn't noticed it.

"I can't say that I have experienced it myself or been aware of it for myself, maybe because I share the same unconscious bias. But I haven't perceived it for myself," Lerman said. "It may be because I tend to be more informal in my style, and so it probably wouldn't have bothered me personally."

Why, then, are women introduced by their first names, instead of by professional title?

"Perhaps women, in general, tend to be less formal in their interactions; perhaps they invite that lack of formality, perhaps they don't," she said. "I'm not suggesting that that's the case, but I think that it would be interesting to gather data from women about their preferences for titles.

"If you consider women in leadership positions, how likely are men versus women to say that they are comfortable with having their direct reports call them by their first name instead of by doctor? That would be evidence.

"We have to study it in some way to know why this is reflected in titles."

The next steps in documenting gender bias could be to evaluate the impact of bias training and workshops, Lerman said. ASCO is implementing implicit gender bias workshops ahead of the 2020 annual meeting, in addition to providing session chairs with instructions on how to introduce speakers.

"It would be interesting to actually look at changes in how male versus female leaders are referred to before and after training, either in written announcements or as they're announced to the podium in a conference," Lerman said.

"I don't believe at all that there is malice on the part of our male colleagues, or any intention to diminish women in any way in this setting," she said. "I think it would be interesting to do a survey and try to explore what might be behind this."

Sharon Stack, PhD
Kleiderer-Pezold Professor of Biochemistry
Ann F. Dunne & Elizabeth Riley Director,
Harper Cancer Research Institute,
Department of Chemistry & Biochemistry,
University of Notre Dame

> As a senior scientist, I think we have the responsibility to call it out when we see it. You're almost complicit if you don't call it out.

Impressed by the Duma et al. study, Sharon Stack sent the paper to the diversity committee in the Department of Chemistry and Biochemistry at Notre Dame.

"THIS IS CRAZY," one person replied.

"Yes it is," Stack concurred. "The data were unequivocable, and the ranges were not subtle."

The department chair said he would discuss the paper at the department's next faculty meeting.

"I'm going to be more aware of it, going forward, and I think this is an important issue with all unconscious bias, whether it's based on gender or race," Stack said.

Implicit bias extends further than just introductions, and men aren't the only perpetrators, Stack said.

"There are dinosaurs of both genders, and I think the problem is we're not waiting for these dinosaurs to die off, we're still making new dinosaurs," Stack said.

As a basic scientist, Stack is used to a lack of formality at the smaller conferences she attends.

"The impact of not using that honorific title of doctor is probably magnified in the medical community relative to basic science community," Stack said.

Junior faculty feel the adverse effects of bias more acutely, because they aren't in a position of power, Stack said.

"But as a senior scientist, I think we have the responsibility to call it out when we see it," Stack said. "You're almost complicit if you don't call it out. And whether that makes you sound like a complainer—I think it's important for us, as established scientists in the field, to call out instances of bias when we see it, and make our colleagues aware that this is not OK."

Studies that demonstrate these types of unconscious bias "are really important," she said.

"Until you actually measure it—and it's really hard to measure that—then you can't really say whether or not it's the case," Stack said. "This is one of the things where you say 'OK, now we have the data, what are we going to do about it?'"

Have you ever felt disrespected or unsafe because of your gender in a professional setting in health care?

We want to hear about your experiences. Please fill out our short survey.

The Cancer Letter will not use any identifying details without your consent. Any data that we publish will be de-identified and anonymized, including the names of any institutions.

IN BRIEF

Senate confirms Stephen Hahn as FDA commissioner

The Senate Dec. 12 voted 72-18 to confirm Stephen Hahn as FDA commissioner.

Hahn, 59, is chief medical executive at MD Anderson Cancer Center and professor in the Department of Radiation Oncology.

On Dec. 3, members of the Senate Committee on Health Education Labor and Pensions voted 18-5 to confirm Hahn (*The Cancer Letter*, Dec. 6). The White House announced its intention to nominate Hahn Nov. 1 (*The Cancer Letter*, Sept. 6, Nov. 1).

In his Senate confirmation hearing Nov. 20, Hahn acknowledged that the rise in e-cigarette use among youths "is an important, urgent crisis in this country," but made no specific pledges as Democratic and Republican Senate members pressed him on whether he would resist pressure from the administration and lobbying groups. (*The Cancer Letter*, Nov. 22).

Once sworn in, Hahn will become the 24th FDA commissioner, succeeding Scott Gottlieb.

Moderate levels of alcohol consumption linked to higher risk of some cancers, NCI writes in JAMA

Even moderate levels of alcohol consumption appear to be associated with a higher risk of some cancers—including cancers of the female breast—as well as adverse cardiovascular health effects, NCI researchers wrote in JAMA.

The article, "Alcohol and Cancer: Research and Clinical Implications," is co-authored by three associate directors in the Division of Cancer Control and Population Sciences at NCI.

The paper highlights the low awareness of the association between alcohol use and cancer and makes a call for increasing clinician knowledge and patient-provider communication regarding the effects of alcohol on cancer. The authors also supports increased focus and research on the harms of moderate drinking, in addition to the more commonly studied harms from risky drinking and alcohol use disorders.

Alcohol is associated with almost 90,000 cases of cancer of the oral cavity, throat, liver, female breast, and colorectum per year. Awareness of this relationship is low not only in the U.S., but worldwide. The paper also notes evidence that reductions in alcohol use are associated with decreased cancer mortality.

MSK to open David H. Koch Center for Cancer Care in January 2020

Memorial Sloan Kettering Cancer Center Dec. 10 marked the opening of David H. Koch Center for Cancer Care, a $1.5 billion cancer treatment facility, a 750,000-square-foot building which will open for patient care next month.

Located on East 74th Street between York Avenue and the FDR Drive, the David H. Koch Center for Cancer Care at MSK is staffed by 1,300 employees who will work with up to 1,300 patients daily. The outpatient facility occupies 25 floors, with 231 exam rooms, 110 infusion rooms, 37 procedure rooms, and 16 inpatient beds for those requiring a short stay.

Nearly every aspect of cancer care across numerous specialties will be available under one roof, including hematologic oncology, interventional radiology, dermatology, and endocrine, head and neck, pulmonary, and thoracic cancers, as well as phase I clinical trials and more.

The facility stems from the record donation of $150 million from the late David H. Koch, who served as a long-time member of the MSK Boards of Overseers and Managers. His gift represents the largest single donation in MSK's histo-

ry, and his lifelong gifts and pledges to the institution total $230 million. These include funds to establish the David H. Koch Center for the Immunologic Control of Cancer, and three chairs including the David H. Koch Chair.

Thomas Jefferson University receives $70 million for new biomedical research building

Thomas Jefferson University has received a $70 million gift from Sidney and Caroline Kimmel for The Caroline Kimmel Biomedical Research Building, which will expand Jefferson's research capacity.

The Kimmels are philanthropists with a history of supporting medicine and the arts for many years in Sidney Kimmel's native Philadelphia. They have given more than $200 million over the years to Thomas Jefferson University.

In 1970, Kimmel established his own clothing line, Jones New York. The Jones Group was sold for $2.2 billion in 2014.

Edmondo Robinson named chief digital innovation officer at Moffitt

Edmondo Robinson was named senior vice president and chief digital innovation officer at Moffitt Cancer Center.

Robinson, who brings over 16 years of clinical and technology experience to Moffitt, will oversee Moffitt's portfolio of digital innovation, including the development and commercialization of health products, tools and technology. With this new role, Moffitt aims to create and test new services, programs, partnerships and technologies that leverage digital innovations, while challenging the status quo to reduce the cost of care, improve quality, increase access to care and enhance the patient experience.

Previously, Robinson was the chief transformation officer and senior vice president of consumerism at ChristianaCare, where he was responsible for the transformation of health care delivery to advance population health initiatives and the move from volume-based to value-based care.

Robinson is an associate professor of medicine at Thomas Jefferson University's Sidney Kimmel Medical College. He holds a medical degree from UCLA; an MBA from The Wharton School of the University of Pennsylvania; and a master's degree in health policy research also from the University of Pennsylvania.

Winship realigns its research programs to increase impact

Winship Cancer Institute of Emory University has been granted formal approval from NCI to realign the four research programs funded by its NCI Cancer Center Support Grant.

The realignment creates a new Cancer Immunology Research Program, which builds on Winship's growing strengths in cancer immunology and the integration of immunology research efforts across Emory University.

"This realignment will open up more collaborative possibilities for our faculty and focus our efforts on research that advances cancer discoveries," said Kimberly F. Kerstann, Winship senior director for research administration.

Madhav Dhodapkar, who joined in 2018 as inaugural director of the Winship Center for Cancer Immunology, and Rafi Ahmed, director of the Emory Vaccine Center, will lead this new program. The program will include translational physicians and scientists at Winship as well as from the Emory Vaccine Center and the Department of Immunology and Microbiology.

The realignment also creates another entity, the Cell and Molecular Biology Research Program, led by Jing Chen, and Wei Zhou. The research themes for the CMB program are cancer cell metabolism, cancer cell stress and survival, mechanisms of invasion and metastasis, and gene regulation.

Members of the former Cancer Cell Biology and Cancer Genetics and Epigenetics programs will migrate to the new CI and CMB programs. The other two Winship research programs will continue under the same names: Discovery and Developmental Therapeutics Research Program, led by Haian Fu, and Taofeek Owonikoko; and the Cancer Prevention and Control Research Program, led by Timothy L. Lash, and Mylin Torres.

The benefit to patients will be significant because these research programs go to the core of how scientific discovery advances the prevention, detection, and treatment of cancer.

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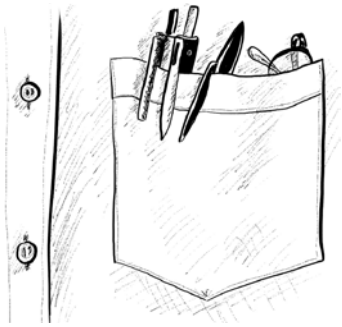
THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

Nobel Prize Award: Impact of Clinical Care?

Ilene Sussman, PhD
Executive director, VHL Alliance

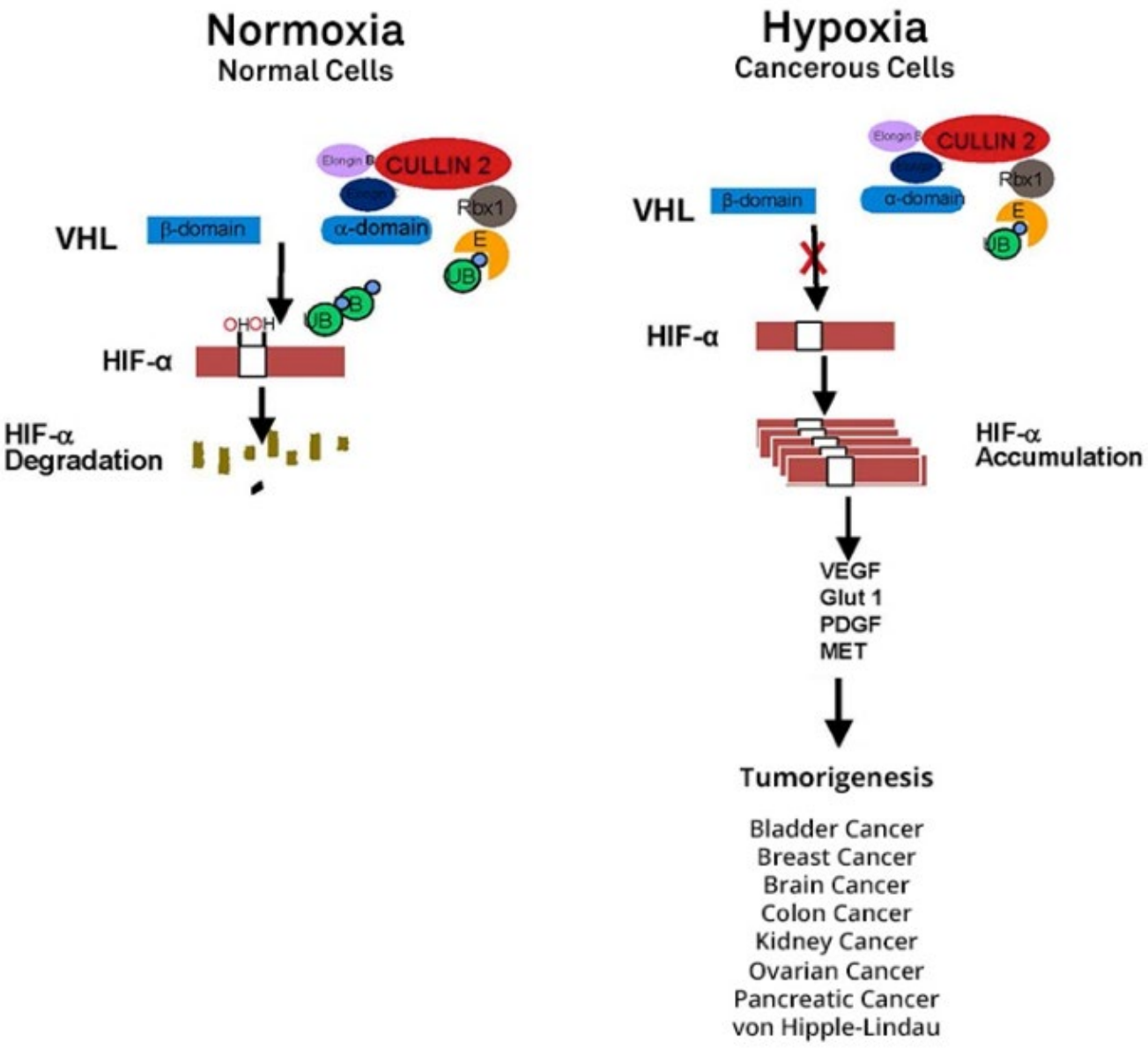
On December 10, 2019, Dr. William G. Kaelin, Jr, Sir Peter J. Ratcliffe, and Dr. Gregg L. Semenza officially received the title of Nobel Laureate in Medicine.

Together, these esteemed researchers provided an understanding of how cells can sense and adapt to changing oxygen levels and how this results in cancer, such as in brain, bladder, breast, colon, ovarian, kidney, and pancreatic cancers.

When cells perceive a lack of oxygen (hypoxia), such as through a defect in the tumor suppressor gene (*VHL*), the transcription factor, HIF (Hypoxia-Inducible Factor), is not allowed to bind to the VHL protein. HIF is thus protected from degradation.

The accumulation of HIF results in the overexpression of various cellular growth factors (VEGF, PGDF) and a change in the ways cells utilize glucose and generate energy. These changes, in turn, lead to an over production of blood vessels, which ultimately leads to tumorigenesis. Understanding how to overcome the HIF accumulation and the cell's perception of hypoxia, is key to preventing tumor development and growth.

The work of these three men, particularly Dr. Kaelin, has focused on the *VHL* gene. In Dr. Kaelin's research is cause for opti-



mism, not only for the 200,000 people suffering from VHL (von Hippel-Lindau disease) around the world, but also for those facing other cancer diagnoses.

VHL is a genetic form of cancer. VHL patients battle a series of tumors in up to 10 parts of the body throughout their lives. Tumors can develop in the brain, spine, retina, kidney, pancreas, adrenal gland, inner ear, reproductive tract, liver, and lung. Lack of timely intervention can often lead to morbidity and mortality.

As stated by Dr. Kaelin, "When you are studying about von Hippel-Lindau disease, you are not just studying about [the] …. disease … you are also now touching other diseases as well, where we can use the *VHL* gene to understand what is happening." As such, the understanding of HIF involvement in tumorigenesis provides hope for the 40% of the world's population who will be diagnosed with cancer at some point in their lives.

The VHL Alliance (VHLA, vhl.org) has been working for decades with cadres of research professionals and members of the medical community around the world to better understand the *VHL* gene and its impact on cancer development. The VHL Alliance funds research in numerous areas including work related to that of the newest Nobel Laureates.

Thanks to this research, the FDA has approved eight drugs for the treatment of kidney and breast cancers. These agents target the regulation of cellular growth factors (the downstream consequence of elevated HIF levels).

A HIF inhibitor is currently in clinical trials for VHL and metastatic kidney cancer. Due to our current understanding of HIF, there is reason to believe that this treatment may be effective in other forms of cancer, as well.

The question remains how to overcome the barriers to diagnosis and treatment that do and will continue to impede maximum benefit of this science and resulting medical treatments. This is particularly true when considering rare diseases such as VHL.

VHLA categorizes people with VHL into three groups:

1. People who are aware and undertake a proactive approach to monitoring their disease and lesion growth in order to achieve a better clinical outcome;
2. People who disregard their medical condition out of lack of knowledge, anxiety about the unknown, and/or lack of medical options other than surgical intervention;
3. People who remain undiagnosed, often despite the presence of manifestations and the existence of genetic testing.

A person's primary physician can be a key influencer in someone's approach to diagnosis and medical care. Knowledge about the various VHL manifestations along with an understanding of the reasons behind VHL surveillance guidelines are helpful in encouraging a patient to be more proactive in managing their disease.

Understanding the complexity of VHL and the need for the involvement of multiple medical specialties should galvanize clinicians to encourage their patients to seek care at a VHL Clinical Care Center.

In addition, there is hope that advances in science, followed by the development and approval of non-invasive medical options with minimal side-effects, will inspire people to be more proactive in managing their disease.

In VHLA's experience, a primary factor behind an absence of diagnosis is a lack of information by one's clinical team. This is no surprise that, due to low prevalence rates, VHL is categorized as one of over 7,000 currently identified rare diseases. It is unrealistic for anyone to know every detail about them all.

Additionally, the medical field generally does not think in terms of outliers ("Zebras" – the analogy in the rare disease world). It is because of this deficiency that actively engaged and highly knowledgeable VHL patients are often forced to educate their medical team.

Utilizing material related to the recent Nobel Prize in Medicine, and in particular, Dr. Kaelin's Nobel Prize lecture, provides a perfect backdrop to making sure that this prestigious award impacts clinical care.

This Nobel Prize give us an opportunity to educate present and future clinicians and health care providers about VHL and the importance of proactive surveillance as a key to improved outcomes.

This includes the VHL Alliance's educational materials (vhl.org/VHL101, vhl.org/VHLvideo, vhl.org/clinicians/diagnosis, vhl.org/screening-guidelines, vhl.org/referral-criteria)—we also hold educational meetings and work with medical societies in order to increase awareness about VHL disease.

References:

1. *Zhong H, De Marzo AM, Laughner E, Lin M, Hilton DA, Zagzag D, Buechler P, Isaacs WB, Semenza GL, Simons JW. Cancer Research 59, 5830 (1999)*
2. *Talks KL, Turley H, Gatter KC, Maxell PH, Pugh CW, Ratcliffe PJ, Harris AL. Am J Pathol 157, 411 (2000)*
3. *Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, Salic A, Asara JM, Lane, WS, Kaelin WG. Science 292, 464 (2001)*
4. *William G. Kaelin – Nobel Lecture. NobelPrize.org. Nobel Media AB 2019. Mon. 9 Dec 2019. https://www.nobelprize.org/prizes/medicine/2019/kaelin/lecture/*

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

PD-1 inhibitor treatment prior to stem cell transplant is safe, effective in classic Hodgkin lymphoma

A new analysis shows that a donor stem cell transplant following treatment with an immune checkpoint inhibitor is generally safe and produces good outcomes for patients with Hodgkin lymphoma, easing concerns that these patients are at heightened risk for severe immune-related complications.

The study, presented at the 61st American Society of Hematology Annual Meeting by Reid Merryman, attending physician in the Lymphoma Program at Dana-Farber Cancer Institute, also found that post-transplant treatment with the drug cyclophosphamide may lead to improved results for many patients.

The study focused on the safety of donor stem cell transplantation in patients with classic Hodgkin lymphoma who were previously treated with a PD-1 inhibitor, a drug that unleashes an immune system attack on tumor cells. While PD-1 inhibitors produce responses in about 70% of these patients, many develop resistance to the drugs within a few years. For that reason, patients are often recommended for a donor stem cell transplant, which can cure the disease.

Because PD-1 inhibitors let loose an immune system attack, there had been concerns of immune-related problems such as acute graft-versus-host disease, in which immune cells from transplanted tissue attack patients' normal, healthy tissue. Several previous studies, including one by Dana-Farber investigators, seemed to justify those concerns, but the studies enrolled relatively small numbers of patients and had a short follow-up period.

The new study pooled data from 150 patients at 26 transplant centers across the U.S. and Europe who had undergone a donor cell transplant after a median of 10 doses of a PD-1 or PD-L1 inhibitor. Fifty-nine percent of the patients were treated with cyclophosphamide to lower their risk of GVHD.

At a median of two years after their transplant, 79% of the patients were alive and 65% had no evidence of lymphoma. Twenty-one percent had relapsed. Six months post-transplant, 39% of patients had developed acute GVHD, including 8% who had severe, life-threatening acute GVHD--a rate that was lower than in previous, smaller studies, Merryman noted. Investigators found that patients treated with cyclophosphamide post-transplant generally fared better and had lower rates of chronic GVHD and relapse.

"Our results indicate that treatment with a PD-1 or PD-L1 inhibitor in advance of a donor stem cell transplant is safe and can provide good outcomes for these patients," said Merryman, "and inclusion of cyclophosphamide treatment as part of GVHD prevention may provide an additional benefit."

BMS's liso-cel met primary, secondary endpoints in TRANSCEND NHL 001

Bristol-Myers Squibb Co. said the pivotal study of lisocabtagene maraleucel (liso-cel) an investigational CD19-directed CAR T-cell therapy with a defined composition of purified CD8+ and CD4+ CAR T cells in relapsed/refractory large B-cell lymphomas (TRANSCEND NHL 001) met its primary and secondary endpoints while demonstrating durable responses.

The data were presented during an oral session at the 2019 ASH annual meeting.

"Longer-term follow-up from the TRANSCEND study shows that liso-cel resulted in a rapid, high rate of durable complete responses with low incidence of severe cytokine release syndrome and neurologic events in two and 10 percent, respectively, among patients

with relapsed/refractory large B-cell lymphomas," said Jeremy Abramson, associate professor of medicine at Harvard Medical School and director of the Lymphoma Center at Massachusetts General Hospital. "Additionally, responses with liso-cel were seen across patient groups including high-risk patients such as those with refractory disease, older patients and those with high tumor burden."

In the study, 344 patients were leukapheresed and 269 patients received liso-cel at one of three dose levels (50 x 106 n=51; 100 x 106 n=177; and 150 x 106 n=41). There were 25 patients that received nonconforming product and there were two instances where product could not be manufactured. Patients were heavily pretreated and had aggressive disease with a median of three prior therapies including 35% with prior autologous or allogeneic hematopoietic stem cell transplant and 67% with chemotherapy-refractory disease. Bridging therapy was administered to 59% of patients.

Among patients evaluable for efficacy (n=256), the overall response rate was 73% (187/256, 95% CI: 67 – 78) with 53% of patients (136/256, 95% CI: 47 – 59) achieving a complete response. Responses were similar across all patient subgroups. The median duration of response for all patients was not reached (95% CI: 8.6 months – NR) at a median follow-up of 12 months (95% CI: 11.2 – 16.7). Median progression-free survival was 6.8 months (95% CI: 3.3 – 14.1) and median overall survival was 21.1 months (95% CI: 13.3 – NR). The median PFS and OS for patients who achieved a CR was not reached with 65.1% of patients progression free and 85.5% of patients alive at 12 months, respectively.

BMS said that based on results from TRANSCEND NHL 001 it expects to complete the submission of a Biologics License Application to FDA by the end of the year.

Phase II KarMMa study of ide-cel in relapsed, refractory multiple myeloma meets ORR primary endpoint

Results from the KarMMa study, a pivotal, open-label, single arm, multicenter, phase II study of idecabtagene vicleucel met its primary endpoint of overall response rate in the treatment of relapsed and refractory multiple myeloma.

The study is sponsored by Bristol-Myers Squibb Co. and bluebird bio Inc.

KarMMa, which evaluated the efficacy and safety of the companies' lead investigational BCMA-targeted chimeric antigen receptor CAR T-cell therapy candidate for patients with relapsed and refractory multiple myeloma also met a key secondary endpoint, complete response rate.

The primary endpoint overall response rate was 73.4% (n=94/128) across three doses. The response rate was dose-dependent, 50.0% (n=2/4) in the lowest, 68.6% (n=48/70) in the middle and 81.5% (n=44/54) in the highest. The complete response rates were 25%, 28.6% and 35.2%, respectively.

Median duration of response was 10.6 months and median progression-free survival was 8.6 months.

KarMMa enrolled 140 patients, of whom 128 patients were treated with ide-cel across the target dose levels of 150-450 x 106 CAR+ T cells. All treated patients were exposed to at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and all were refractory to their last regimen. Ninety-four percent of patients were refractory to an anti-CD38 antibody and 84% percent were triple refractory (refractory to an IMiD agent, PI and anti-CD38 antibody).

The median follow-up duration for all subjects was 11.3 months.

Overall, the safety results were consistent with those observed in the phase 1 CRB-401 study, which evaluated the preliminary safety and efficacy of ide-cel.

"For multiple myeloma patients who have relapsed and become refractory to current treatment options, there remains a high unmet need, as these patients typically experience low response rates, short response durations and poor survival," Kristen Hege, senior vice president of Hematology/Oncology and Cell Therapy and Early Clinical Development for Bristol-Myers Squibb, said in a statement.

"The KarMMa study provides further support for ide-cel as a potential therapeutic option in this heavily pre-treated patient population, and we are encouraged by these data, especially the outcomes observed at the highest target dose of 450 x 106 CAR+ T cells," Hege said.
"We are actively preparing for submission of these data to health authorities for proposed initial registration of ide-cel as a first-in-class BCMA-targeted CAR T-cell therapy."

Seattle Genetics announces positive OS, PFS, ORR for tucatinib in HER2+ breast cancer

Seattle Genetics Inc. announced positive pivotal data from the HER2CLIMB trial evaluating tucatinib in patients with HER2-positive metastatic breast cancer.

"Tucatinib demonstrated a statistically significant and clinically meaningful

benefit in overall survival, progression-free survival and objective response rate compared to the control arm," said Roger Dansey, chief medical officer at Seattle Genetics. "We plan to submit a New Drug Application to FDA and a Marketing Authorization Application to the European Medicines Agency by the first quarter of 2020, with the goal of bringing a much-needed new medicine to patients."

The results were presented at the 2019 San Antonio Breast Cancer Symposium and published in the New England Journal of Medicine. The data presented include the primary endpoint of PFS as assessed by blinded independent central review in the first 480 patients enrolled in the trial. HER2CLIMB enrolled a total of 612 patients to support the analyses of key secondary endpoints, including OS as well as PFS in patients with brain metastases at baseline.

The HER2CLIMB trial compared tucatinib in combination with trastuzumab and capecitabine to trastuzumab and capecitabine alone in patients with unresectable locally advanced or metastatic HER2-positive breast cancer. Patients had previously received trastuzumab, pertuzumab and ado-trastuzumab emtansine. Patients had received a median of four prior lines of therapy overall and three lines in the metastatic setting.

Forty-seven percent of the patients enrolled in the trial had brain metastases at the time
of enrollment. HER2CLIMB is the first randomized pivotal trial completed to enroll patients with metastatic HER2-positive breast cancer who have untreated or previously treated and progressing brain metastases.

Tucatinib is an oral, small molecule tyrosine kinase inhibitor that is highly selective for HER2.

"Following progression on trastuzumab, pertuzumab and T-DM1 in the metastatic HER2-positive breast cancer setting, there is no single standard of care regimen and clinical trial participation is often strongly encouraged. There is a significant unmet medical need for these patients, particularly those who develop brain metastases," said Rashmi Murthy, assistant professor, Department of Breast Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center.

"The addition of tucatinib to the commonly used combination of trastuzumab and capecitabine improved overall survival, reducing the risk of death by 34 percent compared to trastuzumab and capecitabine alone. The results from HER2CLIMB demonstrate tucatinib has the potential to become a new treatment option for patients who have been previously treated with multiple anti-HER2 agents, including patients with and without brain metastases."

ctDNA may help predict recurrence in patient with early triple-negative breast cancer

The presence of circulating tumor DNA in early-stage triple-negative breast cancer helped predict the risk of recurrence in women who had undergone surgery after neoadjuvant chemotherapy, a study found.

The results of the study—funded by the Vera Bradley Foundation for Breast Cancer and the Indiana University Grand Challenge Precision Health Initiative—were presented at the 2019 San Antonio Breast Cancer Symposium. The trial was managed by the Hoosier Cancer Research Network and enrolled at 26 sites across the U.S.

In this study, the authors and colleagues analyzed plasma samples that had been collected from patients enrolled in the BRE12-158 clinical trial, which studied genomically directed therapy versus physician's choice of treatment after preoperative chemotherapy in patients with triple-negative breast cancer. The trial enrolled 196 women, and ctDNA was sequenced in 142 patients using the FoundationOne Liquid Test.

Mutated ctDNA was detected in 90 of the patients, representing 63 percent. TP53 was the most commonly mutated gene, followed by others that are commonly associated with breast cancer.

At 17.2 months of follow-up, detection of ctDNA was significantly associated with inferior distant disease-free survival. Patients with ctDNA had a median DDFS of 32.5 months, while the patients without ctDNA had not reached the median.

At 24 months, the DDFS probability was 56 percent in ctDNA-positive patients, compared with 81 percent in ctDNA-negative patients. In multivariate analysis, when the researchers controlled for factors including residual cancer burden; tumor size, grade, and stage; age; and race, detection of ctDNA remained independently associated with inferior DDFS. Overall, ctDNA-positive patients were three times as likely to have distant disease recurrence than ctDNA-negative patients.

Detection of ctDNA was also associated with inferior overall survival; ctDNA-positive patients had 4.1 times increased risk of death compared with ctDNA-negative patients.

"This study establishes that triple-negative breast cancer patients who have ctDNA after neoadjuvant therapy have a higher risk of recurrence," Schneider said. "This may set the stage for further clinical trials for these high-risk patients, evaluating novel ways to prevent recurrence."

The authors said a clinical trial expected to begin in 2020 will further examine ctDNA's potential in guiding therapy for those patients who are at high risk of recurrence. They also noted that sequencing technology is developing rapidly, and will likely become more sensitive and more specific over time.

"For patients who have triple-negative breast cancer with residual disease, the risk of recurrence is exceptionally high," said the study's senior author, Bryan P. Schneider, professor of medicine and medical and molecular genetics at Indiana University School of Medicine. "Novel therapies and technologies are critical, including those that can potentially predict the risk of relapse."

ctDNA, or tumor DNA derived from plasma, is being explored as a way to detect cancer, guide treatment, and monitor patients during remission. The presence of ctDNA can signal the presence of cancer.

Conversely, the authors—researchers in the Indiana University Melvin and Bren Simon Cancer Center and the Vera Bradley Foundation Center for Breast Cancer Research—said that superior outcomes for those who did not have ctDNA could potentially set the stage for clinical studies evaluating the ability to reduce post-surgical treatment for these patients.

The diagnostic used in the study was Foundation Medicine's FoundationOne Liquid Test.

Extended follow-up phase III data underscore sustained efficacy and safety of Imbruvica in CLL

The phase III E1912 clinical study showed superior progression-free survival and overall survival in patients with chronic lymphocytic leukemia new to treatment.

AbbVie sponsors the study, which was designed and conducted by the ECOG-ACRIN Cancer Research Group and sponsored by NCI.

These results demonstrated the benefits of Imbruvica (ibrutinib) plus rituximab compared to a standard chemoimmunotherapy regimen of fludarabine, cyclophosphamide and rituximab for previously untreated patients with CLL aged 70 years or younger, the company said.

These results were presented Dec. 7 at the American Society of Hematology annual meeting, and served as the basis of the recent supplemental New Drug Application FDA, to expand the Imbruvica prescribing label in CLL.

Additionally, a new integrated analysis of up to six years of long-term follow-up from the phase III RESONATE and RESONATE-2 studies will be presented on Dec. 8 at ASH, evaluating the use of Imbruvica monotherapy in previously untreated patients. Results showed better PFS, OS and overall response rate, with good tolerability compared to use in the relapsed/refractory setting.

"These latest findings add to the extensive clinical evidence supporting the use of Imbruvica, the most comprehensively studied BTK inhibitor in CLL, as both a single-agent and as a combination regimen to improve patient outcomes in early lines of treatment, which has previously been reserved for chemoimmunotherapy," Danelle James, Imbruvica Clinical Development Lead of Pharmacyclics LLC, an AbbVie company, said in a statement.

"Phase III RESONATE and RESONATE-2 trials have proven to be cornerstone studies that have significantly advanced the treatment of CLL among a variety of patients—and the latest data presented at this year's ASH Annual Meeting demonstrate using IMBRUVICA alone and earlier in CLL treatment results in improved patient outcomes," Paul M. Barr, study investigator of the Phase III RESONATE and RESONATE-2 trials, and associate professor of medicine, Hematology/Oncology at the Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, said in a statement. "These results reaffirm the sustained disease control and safety profile of Imbruvica and further support its use as a chemotherapy-free option for previously untreated patients living with this common form of adult leukemia."

Imbruvica is a once-daily, first-in-class BTK inhibitor that is administered orally, and is jointly developed and commercialized by Pharmacyclics LLC, an AbbVie company, and Janssen Biotech, Inc.

Phase III TOURMALINE-AL1 trial of Ninlaro in patients with amyloidosis didn't meet one of two primary endpoints

TOURMALINE-AL1 trial, a phase III, randomized clinical trial evaluating the effect of Ninlaro (ixazomib) in combination with dexamethasone, did not meet the first of the two primary endpoints of significant improvement in overall hematologic response in patients with relapsed or refractory systemic light-chain amyloidosis.

The study is sponsored by Takeda Pharmaceutical Co. The results were presented during an oral session at the 61st American Society of Hematology annual meeting.

Hematologic responses were seen in 53% versus 51% of patients receiving

Ninlaro plus dexamethasone versus physician's choice (odds ratio 1.10 [95% CI 0.60-2.01], p=0.762) as assessed by an adjudication committee. The second primary endpoint of two-year vital organ deterioration or death was not mature at the time of analysis. Other endpoints studied including vital organ progression free survival, hematologic PFS, time to treatment failure and time to subsequent therapy were numerically higher in the Ninlaro plus dexamethasone arm compared to the physician's choice arm.

Takeda said the company is committed to making data available to researchers to continue investigation of this disease. Ninlaro is not approved as a treatment for AL amyloidosis.

"AL amyloidosis is a rare condition, for which prognosis and patient outcomes are poor. Current treatments are often retrofitted from therapies used for multiple myeloma," said Angela Dispenzieri, Mayo Clinic, and the trial's principal investigator and lead author. "For a phase III study that did not meet its primary endpoint, this trial provides interesting information for this community and for future studies. Ongoing research and development to investigate potential treatment options for this underserved patient population is critical."

Phase III SOPHIA study shows margetuximab didn't reach significance for OS in HER2+ metastatic breast cancer

MacroGenics Inc. has presented updated results from the phase III SOPHIA study comparing margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in patients with HER2-positive metastatic breast cancer who have previously been treated with anti-HER2-targeted therapies.

Margetuximab is an investigational, immune-enhancing monoclonal antibody derived from the company's proprietary Fc-engineering technology platform. The data were presented during an oral session at the San Antonio Breast Cancer Symposium by Hope Rugo, director, Breast Oncology and Clinical Trials Education, University of California San Francisco Helen Diller Family Comprehensive Cancer Center.

Overall survival results favored margetuximab plus chemotherapy compared with trastuzumab and chemotherapy in the intention-to-treat population; however, these data did not reach statistical significance at this second interim analysis as of a September 2019 cut-off after 270 events (median OS=21.6 months versus 19.8 months; hazard ratio [HR]=0.89; 95% CI: 0.69-1.13; P=0.326).

The final pre-specified OS analysis is planned after 385 events have accrued, which is projected to occur in the second half of 2020. A pre-specified exploratory objective of the study was to evaluate the effect of CD16A (Fcγ receptor) allelic variation on margetuximab activity.

Among the genetically defined subpopulation of patients carrying a CD16A 158F allele, who represent approximately 85% of the human (and SOPHIA study) population, the median OS at the second interim analysis was prolonged by 4.3 months in the margetuximab arm compared to the trastuzumab arm (23.7 months versus 19.4 months; HR=0.79; 95% CI: 0.61-1.04; nominal P=0.087). Among the approximately 15% of patients who were homozygous for the CD16A 158V allele, the trastuzumab arm performed better than the margetuximab arm.

"Patients with later stage HER2-positive metastatic breast cancer need access to new therapies. The updated SOPHIA study results presented today at the second interim survival analysis showed a trend in overall survival favoring margetuximab and are encouraging. Furthermore, margetuximab is the only HER2-targeted agent to show PFS superiority versus trastuzumab in a head-to-head Phase 3 clinical trial," Rugo said. "The SOPHIA study also includes a pre-specified analysis of CD16A genotype as a predictor of anti-HER2 antibody efficacy, which although exploratory, is the first such prospective clinical analysis and suggests differential benefit in this population."

As previously reported, margetuximab plus chemotherapy showed a statistically significant improvement in independently-assessed progression-free survival compared to trastuzumab plus chemotherapy in this study as of an October 2018 cut-off after 256 events (median PFS=5.8 months versus 4.9 months; HR=0.76; 95% CI: 0.59-0.98; P=0.033).

An updated investigator-assessed analysis as of a September 2019 cut-off showed consistent results after 430 PFS events (median PFS=5.7 months in the margetuximab arm versus 4.4 in the trastuzumab arm; HR=0.71; nominal P=0.0006). Similarly, at the time of this updated analysis, additional patients were evaluable for response in the ITT population.

Investigator-assessed objective response rate was 25.2% (95% CI: 20.1-30.9%) in the margetuximab arm compared to 13.7% (95% CI: 9.8–18.4%) in the trastuzumab (nominal P=0.0006). The clinical benefit rate (CBR, which includes CR+PR+SD>6 months, was 48.1% (95% CI: 42.0-54.3%) in the margetuximab arm versus 35.6% (95% CI: 29.9-41.6%) in the trastuzumab arm (nominal P=0.0025).

Margetuximab plus chemotherapy has shown a safety profile generally comparable to that of trastuzumab plus chemotherapy in this study. As of the

April 2019 cut-off for safety, Grade 3 or greater adverse events occurred in 142 (54%) patients on the margetuximab arm compared to 140 (53%) patients on the trastuzumab arm. Serious adverse events occurred in 43 (16%) patients on the margetuximab arm compared to 49 (18%) patients on the trastuzumab arm.

Infusion-related reactions were more common with margetuximab treatment than with trastuzumab (13% versus 3%) and were mostly Grade 1 or 2 and associated with the first dose. A substudy evaluating shorter, 30-minute infusions of margetuximab in Cycle 2 and beyond showed no effect on safety outcomes, as well as risk or severity of IRR.

Keytruda improved OS in frontline metastatic NSCLC regardless of KRAS status

Keytruda (pembrolizumab) showed improvements in overall survival, progression-free survival and objective response rate as monotherapy for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer whose tumors expressed PD-L1 (tumor proportion score [TPS] ≥1%), regardless of KRAS mutational status.

These findings, which are based on an exploratory analysis of the pivotal phase III KEYNOTE-042 trial, were presented in a proffered paper presentation (Abstract #LBA4) at the European Society for Medical Oncology Immuno-Oncology Congress 2019 in Geneva.

"KRAS mutations occur in approximately 20% of people with non-small cell lung cancer, and some previous studies have suggested that these mutations are associated with a poorer response to treatment," said Jonathan Cheng, vice president, oncology clinical research, Merck Research Laboratories. "It was therefore encouraging to see in this exploratory analysis that Keytruda monotherapy was associated with a survival benefit in certain patients with metastatic nonsquamous non-small cell lung cancer, regardless of KRAS mutational status."

The objective of the exploratory analysis was to assess the prevalence of KRAS mutations and their association with efficacy in the KEYNOTE-042 trial. Of the 1,274 untreated patients with metastatic nonsquamous NSCLC whose tumors expressed PD-L1 (TPS ≥1%) enrolled in KEYNOTE-042, 301 patients had KRAS evaluable data (n=232 without any KRAS mutation; n=69 with any KRAS mutation, including n=29 with the KRAS G12C mutation).

Tissue tumor mutational burden (tTMB) and KRAS mutational status were determined by whole-exome sequencing (WES) of tumor tissue and matched normal DNA (blood). Patients were randomized 1:1 to receive Keytruda 200 mg intravenously every three weeks (n=637) or investigator's choice of chemotherapy (pemetrexed or paclitaxel) (n=637). Treatment continued until progression of disease or unacceptable toxicity. The primary endpoint was OS with a TPS of ≥50%, ≥20% and ≥1%, which were assessed sequentially. The secondary endpoints were PFS and ORR.

Findings from this exploratory analysis showed that Keytruda monotherapy was associated with improved clinical outcomes, regardless of KRAS mutational status, in patients with metastatic nonsquamous NSCLC versus chemotherapy. In this analysis, Keytruda reduced the risk of death by 58% (HR=0.42 [95% CI, 0.22-0.81]) in patients with any KRAS mutation and by 72% (HR=0.28 [95% CI, 0.09-0.86]) in patients with the KRAS G12C mutation compared to chemotherapy.

Venetoclax in reduced-intensity transplant conditioning regimen in high-risk myeloid cancers shows promise

For patients with high-risk myeloid cancers undergoing a donor stem cell transplant, adding the targeted drug venetoclax to a reduced-intensity drug regimen prior to transplant is safe and does not impair the ability of the donor cells to take root in recipients' bodies, a study led by Dana-Farber Cancer Institute researchers suggests.

The study was presented at the 61st American Society of Hematology annual meeting.

The findings provide support for the use of venetoclax prior to transplant as a way to increase the chances of transplant success in this group of patients, said Jacqueline S. Garcia, physician in the Adult Leukemia Program at Dana-Farber and first author of the study.

While a donor stem cell transplant can cure myeloid malignancies such as acute myeloid leukemia and myelodysplastic syndrome, patients whose tumor cells carry certain genetic mutations or chromosomal abnormalities have a high risk of relapsing after transplant. A variety of approaches to lowering the chance of relapse are under study. One involves using venetoclax, which prompts cancer cell death by blocking the BCL-2 protein, as part of the conditioning regimen patients receive in preparation for a donor stem cell transplant.

The new study focused on patients who underwent reduced-intensity conditioning regimens, which use lower, less

toxic doses of chemotherapy and radiation therapy. While such regimens kill fewer cancer cells than traditional "myeloablative" treatments, they are milder on the body and are used in patients over age 60.

"In previous research, we have shown that adding venetoclax to leukemia drugs produces a very large increase in anti-leukemia activity," Garcia remarked. "We hypothesized that venetoclax would promote the anti-leukemic effect of conditioning chemotherapy and therefore reduce the risk of relapse without producing undue toxicity."

The study involved nine patients with high-risk AML or MDS who were recommended for a donor stem cell transplant. In a phase I clinical trial, they received venetoclax along with the chemotherapy drugs fludarabine and busulfex as a conditioning regimen and then underwent a donor stem cell transplant.

"We found that venetoclax can be safely added to standard reduced-intensity conditioning without impeding the ability of donor neutrophils [a type of white blood cell] to engraft," Garcia stated.

Because patients are just six months removed from transplant, it is too early to know if the new regimen reduced the chance of relapse, Garcia noted, but the fact that the donor cells have engrafted—evidenced by patients' blood counts—is an encouraging sign. There has not been a signal of toxicity in excess of what is expected with standard reduced-intensity conditioning, including rates of graft-versus-host disease. To further minimize the potential for relapse, the trial is under an amendment to allow trial participants to receive post transplant maintenance therapy of low dose venetoclax and the chemotherapy drug azacytidine.

DRUGS & TARGETS

FDA issues draft guidance to foster pediatric oncology product development

FDA issued a draft guidance document, "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act."

The draft guidance addresses early planning for pediatric evaluation of molecularly targeted oncology drugs for which original new drug applications and biologics license applications are expected to be submitted to the FDA on or after Aug. 18, 2020, in accordance with section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which was amended by the FDA Reauthorization Act of 2017 (FDARA).

The draft guidance provides the pharmaceutical industry, clinical investigators and institutional review boards with information to facilitate pediatric studies of molecularly targeted oncology drugs.

Specifically, if an original NDA or BLA is for a new active ingredient, and the drug that is the subject of the application is intended for treatment of an adult cancer and directed at a molecular target the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the required molecularly targeted pediatric cancer investigation must be submitted with the marketing application, unless this requirement is waived or deferred.

The draft guidance describes lists, which the FDA sometimes refers to as "The Relevant Molecular Target List" and "The Non-Relevant Molecular Target Leading to Waiver List," that the FDA plans to update regularly, and that are intended to serve as a guide to sponsors as they consider development plans for new targeted drugs and the need for early pediatric assessments.

"Traditionally, drug development for pediatric cancers lagged, in part, because the requirements to study new cancer drugs in children have been based on whether the cancer occurs in children — and many adult cancers rarely occur in children," Acting FDA Commissioner Adm. Brett P. Giroir said in a statement. "New, targeted oncology drugs being developed for adult cancers may prove effective in the treatment of some cancers occurring primarily in pediatric patients with similar molecular targets.

"Thanks to amendments to the Federal Food, Drug, and Cosmetic Act made by the FDA Reauthorization Act of 2017, we have a new mechanism to require the evaluation of certain novel cancer medicines for potential pediatric treatment. Our new draft guidance addresses implementation of these amendments, which we anticipate will facilitate early pediatric assessment of certain targeted cancer drugs and accelerate the development of new, safe and effective therapies for pediatric patients."

FDA approves Avsola for same indications as Remicade

FDA approved Avsola (infliximab-axxq) for all approved indications of the reference product, Remicade (infliximab), including treatment of moderate-to-severe rheumatoid arthritis, moderate-to-severe Crohn's Disease in the adult and pediatric population, moderate-to-severe ulcerative colitis in the adult and pediatric population, chronic severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis.

Avsola is sponsored by Amgen.

Avsola, an anti-tumor necrosis factor alpha monoclonal antibody, was proven to be highly similar to Remicade with no clinically meaningful differences based on a totality of evidence which included comparative analytical, nonclinical and clinical data. The data package was composed of, in part, results from a pharmacokinetic similarity study conducted in healthy subjects, and a comparative clinical study conducted in patients with moderate to severe RA.

The randomized, double-blind comparative clinical study evaluated the efficacy and safety of Avsola compared to Remicade in patients with moderate-to-severe RA. There were 558 patients enrolled and randomized (1:1) to receive either Avsola or Remicade at a dose of 3 mg/kg administered as an infusion on day one, at weeks two and six, and every eight weeks thereafter.

The primary endpoint was the response difference of 20% improvement in American College of Rheumatology core set measurements at week 22. Key secondary endpoints included DAS28-CRP change from baseline, RD of ACR20, ACR50 and ACR70 at weeks two, six, 14, 22, 30, 34, 38, 46 and 50. The study also incorporated the evaluation of a single transition in 119 subjects from Remicade to AVSOLA at week 22, which demonstrated similar safety and immunogenicity in patients who were previously on Remicade.

Amgen has a total of 10 biosimilars in its portfolio, four of which have been approved in the United States, and three that are approved in the European Union.

FDA grants Janssen's BCMA CAR-T therapy JNJ-4528 Breakthrough Therapy Designation for multiple myeloma indication

FDA granted Breakthrough Therapy Designation for the Janssen Pharmaceutical Companies of Johnson & Johnson's JNJ-68284528 (JNJ-4528), an investigational B cell maturation antigen-directed chimeric antigen receptor T-cell therapy in previously treated patients with multiple myeloma.

The Breakthrough Therapy Designation is supported by data from the phase Ib/II CARTITUDE-1 study (NCT03548207), an open-label, multicenter clinical trial evaluating the safety and efficacy of JNJ-4528 in adults with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy or are double refractory to a proteasome inhibitor and an immunomodulatory drug; have received a PI, IMiD and an anti-CD38 antibody; and who progressed on or within 12 months of their last line of therapy.

Currently active in the United States, the primary objective of the phase Ib portion of the study is to characterize the safety of JNJ-4528 and confirm the dose for future clinical trials. Phase II is evaluating efficacy with a primary endpoint of overall response rate, as defined by the International Myeloma Working Group response criteria, as well as duration of response and overall tolerability.

Initial data from the CARTITUDE-1 study were presented at the American Society of Hematology Annual Meeting.

The CARTITUDE-1 study design was informed by the phase I LEGEND-2 study (NCT03090659), the first-in-human study with LCAR-B38M CAR-T cells. In February 2019, FDA granted Janssen an Orphan Drug Designation for JNJ-4528. On April 3, 2019, Janssen announced the European Medicines Agency granted a PRIME designation for JNJ-4528 based on the CARTITUDE-1 and LEGEND-2 studies.

JNJ-4528, a structurally differentiated CAR-T with two BCMA-targeting single domain antibodies, identifies the investigational product being studied in the U.S. and Europe.

LCAR-B38M, which has the same CAR construct, identifies the investigational product in China. In December 2017, Janssen signed an agreement with Legend Biotech to jointly develop and commercialize LCAR-B38M in multiple myeloma. In China, the Phase II CARTIFAN-1 confirmatory trial (NCT03758417), sponsored by Nanjing Legend Biotech Co. Ltd. in collaboration with Janssen, is actively recruiting to further evaluate LCAR-B38M in patients with advanced relapsed or refractory multiple myeloma.