

The logo for The Cancer Letter, consisting of the letters 'TCL' in a bold, white, sans-serif font on a red background.

THE CANCER LETTER

Inside information on cancer
research and drug development

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COVID-19 VS. COMMUNITY ONCOLOGY: FLATIRON'S DATA PROVIDES FIRST DAMAGE ASSESSMENT

Community oncology practices in the United States are reeling from a sharp decrease in business—the result of reduced activity and stay-at-home orders across the country to mitigate the spread of SARS-CoV-2.

→ PAGE 5

NSCLC PATIENTS GETTING CHECKPOINT INHIBITORS MORE LIKELY TO DEVELOP PNEUMONITIS, SYAPSE-FDA-AURORA STUDY FINDS

→ PAGE 16

SKIP BURRIS: THESE FEW MONTHS ARE GOING TO SHAPE HEALTH CARE IN THE COMING YEARS

→ PAGE 25

AACR DATA FROM CHINA AND EUROPE AMOUNT TO “TWO DIFFERENT MESSAGES” FOR CANCER PATIENTS WITH COVID-19

→ PAGE 32

UNDER THE ONSLAUGHTS OF COVID-19, MONTEFIORE DEPLOYED A PPE STRATEGY FOR PATIENTS—PREVENT/PROTECT/ENABLE

→ PAGE 56

MaineHealth Physician Recruitment Center



Associate Medical Director, Medical Oncology/Hematology and Cancer Genetics

Many choose to spend their vacations where we call home. Known for rocky coastlines, sandy beaches, sparkling lakes and breathtaking mountains, Maine offers much more to those lucky enough to live, work and raise families here. Come practice in a location that provides unsurpassed natural beauty, safe communities, excellent schools and nearly unlimited four-season outdoor recreation.

We are actively seeking physicians with expertise in general medical oncology/hematology, cancer genetics, and physician leaders as Associate Medical Directors to join Maine Medical Center's Division of Medical Oncology and our expanding statewide oncology program – the MaineHealth Cancer Care Network (MHCCN). The network is a coordinated system of care in which 11 MaineHealth partner hospitals and organizations work together to deliver the highest quality cancer care to patients as close to home as possible. The network provides a complete array of cancer care, including surgery, radiation and chemotherapy.

The MaineHealth Cancer Care Network (MHCCN) is rapidly growing a highly integrated care delivery network across the southern, central, and coastal regions of Maine and eastern New Hampshire. The network is comprised of 11 hospital partners and provides care to more than 6,300 analytic cancer cases annually. Maine Medical Center (MMC), the flagship of MaineHealth's integrated delivery system, an affiliate of Tufts University School of Medicine, has 637 licensed beds and is the state's leading tertiary care hospital and Level I Trauma Center, with a full complement of residencies and fellowships. MHCCN has expanding clinical trials portfolio greatly afforded by our recent inclusion in the NCI's Community Oncology Research Program (NCORP).

We are seeking individuals with a track-record of successful training, scholarship, commitment to cancer clinical trials, and/or clinical care in a progressive academic setting/health system environment.

For more information, please contact Gina Mallozzi, Physician Recruiter at (207) 661-2092 or gmallozzi@mainehealth.org.

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COVER STORY (REAL WORLD EVIDENCE)

- 5** COVID-19 vs. community oncology: Flatiron’s data provides first damage assessment

- 49** Remdesivir established as standard of care for COVID-19, Fauci declares – FDA issues Emergency Use Authorization

REAL-WORLD EVIDENCE

- 16** NSCLC patients getting checkpoint inhibitors more likely to develop pneumonitis, Syapse-FDA-Aurora study finds

GUEST EDITORIAL

- 56** Under the onslaughts of COVID-19, Montefiore deployed a PPE strategy for patients— PREVENT/PROTECT/ENABLE
- 60** The pandemic of COVID-19 and its effect on clinical trials in the community – How do we move forward?
- 62** Cancer doesn’t wait—we are treating cancer patients now

CONVERSATION WITH THE CANCER LETTER

- 25** Skip Burris: These few months are going to shape health care in the coming years

- 64** Dafna Bar-Sagi, Arul Chinnaiyan, Carl June, Christopher Lima, Miriam Merad, and John Schiller are among newly elected NAS members

- 32** AACR data from China and Europe amount to “two different messages” for cancer patients with COVID-19

COVID-19 UPDATES

CONVERSATION WITH THE CANCER LETTER

- 42** With 61,000 people registered, first-ever virtual AACR annual meeting “enthusiastically received”

- 67** FDA grants Emergency Use Authorization for novel, non-implanted device to wean patients off mechanical ventilation
- 67** TGen seeks volunteers for COVID-19 immunity study

CORRECTIONS



Clarification

A guest editorial in *The Cancer Letter* stated that “work has halted on ECOG-ACRIN Cancer Research Group’s landmark Tomosynthesis Mammographic Imaging Screening Trial.” (*The Cancer Letter*, [April 10, 2020](#)) The TMIST breast cancer screening trial is not suspended. TMIST formally remains an ongoing study under the NCI and Cancer Trials Support Unit. Active participation at this time is at the discretion of individual sites. Sites are making critical local operational decisions to help manage any potential influx of COVID-19 patients and maintain the safety of patients and staff. As a result, some sites have suspended non-urgent health care services, such as screening mammography, and research operations.

Correction

A COVID-19 Update on April 24 reported that The Association of American Cancer Institutes annual meeting has moved to a virtual format (*The Cancer Letter*, [April 24, 2020](#)). The Association of American Cancer Institutes’ Clinical Research Innovation (CRI) program has moved its July 7-8 annual meeting to a virtual format. The AACI annual meeting, which takes place Oct. 11-13 in Kansas City, MO, is still scheduled as an in-person meeting at this time.

IN BRIEF

- 68** Kristin Brill named enterprise director of Breast Oncology at SKCC
- 68** UCLA researchers receive \$2.8M NCI grant to develop blood-based test for liver transplant candidate selection
- 68** J&J and Emergent Bio collaborate on coronavirus vaccine candidate
- 69** 2020 Stovall award nominations due May 1

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

- 70** Phase III trial evaluating Libtayo in NSCLC halted because of significant OS improvement
- 70** Lynparza demonstrates OS benefit in phase III prostate cancer trial
- 71** GARNET study demonstrates potential of dostarlimab to treat recurrent or advanced endometrial cancer
- 71** MD Anderson, Ipsen advance therapy with potential benefit for patients with lung, ovarian cancer

- 71** Study: Disruptions in health insurance coverage are common, and affect cancer care and survival
- 72** AI may help brain cancer patients avoid biopsy
- 72** Mouse model study shows promise in treatment of medulloblastoma and ependymoma

DRUGS & TARGETS

- 73** FDA approves GSK’s PARP inhibitor Zejula for first-line maintenance of advanced ovarian cancer
- 74** FDA grants accelerated approval to new dosing regimen for Keytruda
- 74** FDA grants Mobocertinib Breakthrough Therapy Designation in NSCLC designation



Bobby Green, MD
*Chief medical officer,
Senior vice president of clinical oncology,
Flatiron Health*

COVID-19 VS. COMMUNITY ONCOLOGY: FLATIRON'S DATA PROVIDES FIRST DAMAGE ASSESSMENT

By Matthew Bin Han Ong

REAL-WORLD EVIDENCE



Community oncology practices in the United States are reeling from a sharp decrease in business—whether you look at new patients, chemotherapy visits, or non-chemo visits—the result of reduced activity and stay-at-home orders across the country to mitigate the spread of SARS-CoV-2.

Early data compiled by Flatiron Health and made available exclusively to *The Cancer Letter* make it possible to visualize the severe impact of the COVID-19 pandemic on community oncologists. The data, which are derived from 270 oncology practices that use Flatiron's OncoEMR platform, show that:

- Visits from new patients, per week, decreased by about 3,000 from over 8,000 in early February to less than 5,000 toward the end of April, a nearly 40% drop,
- Total patient visits decreased dramatically after March 9—in the five-figure range,
- Patient visits involving chemotherapy were reduced by up to 17% in the Northeast, while non-chemo visits plunged across the country, up to 37%, and
- Cancellations and no-shows nearly doubled, up to 80%.

"I think it's clear there has been a shock to the system," Bobby Green, chief medical officer and senior vice president of clinical oncology at Flatiron, said to *The Cancer Letter*. "We've seen a drop-off in new patient visits. We've seen a drop-off in chemotherapy visits. We've seen

a drop-off in follow-up appointments. We've seen an increase in cancellations.

"This puts many practices at risk," said Green, who is also a practicing medical oncologist at Florida Cancer Specialists and Research Institute. "There's a lot of financial concern that's out there right now about being able to stay open and keep the lights on."

The uptick in adoption and use of telehealth in place of in-person visits is encouraging, although it pales in comparison to the overall decrease in patient volume.

"Telehealth isn't completely making up the difference in our drop in volume, but I do think it's definitely helping," Green said. "We've seen community oncology practices go from zero to 60 in getting telehealth up and running very quickly. I think you may have seen some of the early experimentation in academic centers, but community practices have really, from an operational standpoint, I think, really spun this up pretty quickly."

A recent [report](#) by the Community Oncology Alliance suggests a 20.8% increase in practices merging with or being acquired by other practices and larger corporations over the past two

years. If operations continue to be depressed in the ongoing pandemic or by a resurgence in COVID-19 cases in the coming months, this trend may gain strength, Green said.

"I worry a lot that COVID-19 is going to accelerate things," Green said. "But COVID-19 is having a real impact on hospital systems as well; everyone is hurting right now. So, while this does have the potential to accelerate consolidation, the answer is that we don't know yet, but, yes, I'm worried."

As patients delay diagnoses and visits, longitudinal studies may be needed to understand how the pandemic may be changing trends in cancer mortality, and how contingency therapeutic regimens, i.e. more neoadjuvant chemotherapy ahead of delayed surgeries, are affecting patient outcomes.

"Now the questions are: How long can this last?" Green said. "What's going to happen over the next several months as COVID-19 cases start to decrease? But then, what will happen if we get another COVID-19 wave in the fall? How can practices be prepared?"

Green spoke with Matthew Ong, associate editor of *The Cancer Letter*.

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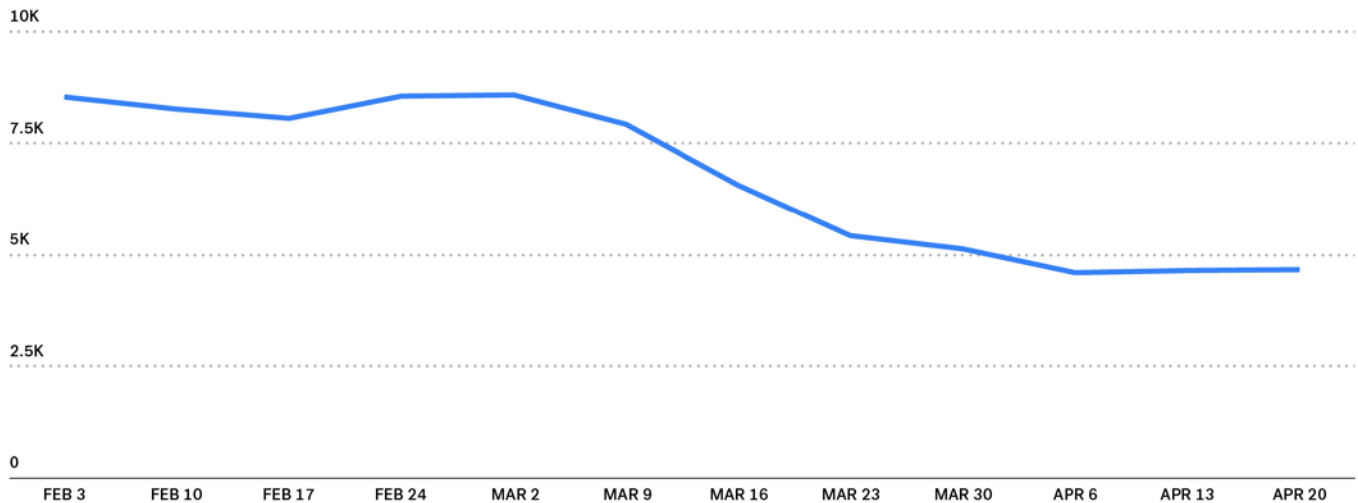
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Green spoke with
Matthew Ong, associate editor of
The Cancer Letter.

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COVID-19 AND U.S. COMMUNITY ONCOLOGY

Trends in new patient visits



The above data are sourced from over 270 community oncology practices that use Flatiron's OncoEMR® platform. The data may not be fully representative of Flatiron's research-grade datasets and should only be considered directional.

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Matthew Ong: Thank you for sharing these early data with us. I have to say, they don't look incredibly encouraging for the community practices represented in your dataset. What are your observations?

Bobby Green: As the EHR provider for our practices, Flatiron is able to see the changes in activity pretty much in real time, and to assess the impact of this extraordinary event both on our services and operations, and on our providers. We feel it is important to share what we have observed.

With that said, from my perspective, there's clearly been a shock to the system.

It's pretty amazing what community oncology practices—independent clin-

ics that vary in size—have continued to do through all of this disruption. They have really stepped up and responded, everything from screening patients, setting up tents outside the clinic, and even helping patients in their cars. Really just continuing to make sure that cancer patients get taken care of.

From our perspective, as a partner and EHR provider to community oncology practices, we've seen a drop-off in new patient visits. We've seen a drop-off in chemotherapy visits. We've seen a drop-off in follow-up appointments. We've seen an increase in cancellations.

Now the questions are: How long can this last? What's going to happen over the next several months as COVID-19 cases start to decrease? But then, what will happen if we get another COVID-19 wave in the fall? How can practices be prepared?

Everyone, I think, expects that there will be a rebound in patient visits. There

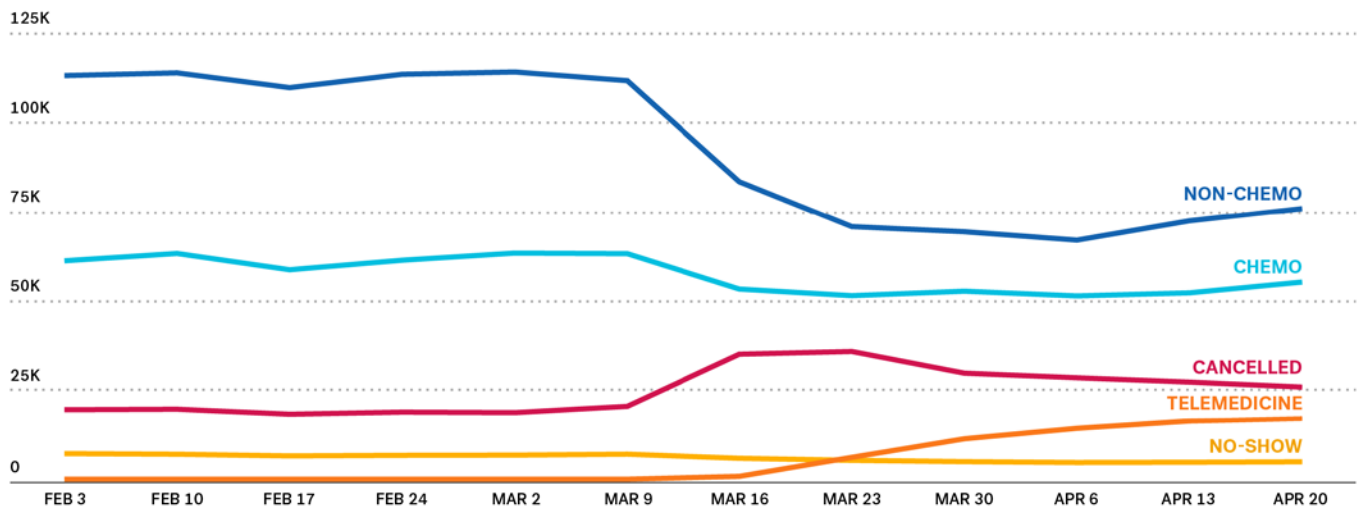
are patients who aren't getting their mammogram and colonoscopies, and so they're not getting diagnosed yet. These people will be getting diagnosed at some point in the future, so many of our practices are expecting to see a wave of new patients as these more elective procedures start to take place.

But I don't think any of us really know what that looks like. What's the timeline? And then, ultimately, what's the lasting impact on practices going to be? Oncology is certainly different than a lot of other medical specialties in that cancer patients need to be treated now.

At the same time, you've read that people aren't showing up at hospitals for strokes, people aren't even showing up for appendicitis, which is just mind-boggling to me. The incidence of appendectomies at hospitals has gone down. What's happening to all those people suffering from appendicitis?

COVID-19 AND U.S. COMMUNITY ONCOLOGY

Trends in patient visit type



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When are we going to start seeing the people who developed a cough that might've been a sign of lung cancer? Or who had a mass that was a lymphoma, who normally would've gone to see their doctor but have delayed it?

What does this mean for the viability of these practices? Specifically, have you seen closures or hospital acquisitions during this time?

BG: I absolutely think this puts many practices at risk. I don't know that we've seen any practices that have closed or been acquired during the pandemic yet, but we do know that this is putting a financial strain on practices, and we certainly hope that this isn't a scenario where large hospital systems use this to further gobble up community practices.

And telehealth doesn't seem to quite be making up the difference, although it is being used. CMS has issued Medicare waivers, but are practices having issues with prior authorizations with private insurers, not to mention building infrastructure and capability for telehealth? What are the challenges that are unique to your cohort here?

BG: Telehealth isn't completely making up the difference in our drop in volume, but I do think it's definitely helping in a couple ways. One is, I think it's giving access to patients who otherwise might not have come into the clinic.

Secondly, it's enabling us to continue to take care of patients who otherwise

would have had to come into the office, but you are able to instead do it remotely to ensure their safety. There are obviously certain things that you can't do via telehealth, but I am very bullish on it.

This pandemic felt like an impetus, a technological pressure test on the system that, I hope, is going to result in telehealth being a lot more prevalent after we're out of this.

CMS has been amazing for all of this by relaxing regulations and making telehealth at this scale available so quickly. I honestly can't say enough about that.

There are many logistical and technological challenges in getting practices and patients set up for telehealth.

Do I have enough WiFi bandwidth in my practice now that we have 15 doctors all live video streaming on and off throughout the day? Does my patient have high-speed internet at home? Does my patient have a smartphone? Does

my patient know how to click on a link and log into a virtual server?

There are definitely those challenges that we need to overcome, but there is a world in which telehealth can ultimately help improve health care disparities.

There are many patients who have to take two buses to get to my clinic, and if there are ways that I can take care of them without them having to do that, that's great. But if they don't have high-speed internet, it's really hard to do a remote visit.

I had a previous conversation with Dr. Ben Neel at NYU about telehealth and he said, "Necessity is the mother of innovation." Large academic centers have been scrambling to scale up their telehealth programs, but how are community practices managing?

BG: This is with my bias as a community oncologist. So, with that asterisk there, I would argue that, actually, community oncology practices are better prepared to deal with things like this.

I think one of the lessons of the whole value-based care experience is that, more often than not, independent practices were able to adapt quickly. We've seen community oncology practices go from zero to 60 in getting telehealth up and running very quickly. I think you may have seen some of the early experimentation in academic centers, but community practices have really, from an operational standpoint, I think, really spun this up pretty quickly.

I see, they may be able to be more nimble and to move faster.

BG: Yes. Four years ago, Bob Kocher, a venture capitalist who worked on the Affordable Care Act in the Obama administration, wrote an editorial in the Wall Street Journal, titled "How I Was Wrong About Obamacare." In the editorial, he wrote how he thought that it was going to be the big academic systems and health centers that were going to be the value-based care innovators, but it turned out that the smaller independent practices have become the innovators.

I think, in some ways, we may be seeing that again here, though this is not to say that academic centers don't also provide an enormous amount of value and of course play a critical role in cancer care.

Definitely. The Northeast appears to stand out in your data, in average decrease in chemo and non-chemo treatments and visits, as well as increase in patient cancellations and no-shows. Is that the New York effect as well as greater compliance with public health guidelines? What is your sense about what's going on here?

BG: The Northeast is just such a hotspot. Many of our Northeastern practices are in the New York City area, in the

COVID-19 AND U.S. COMMUNITY ONCOLOGY

Decrease in chemo and non-chemo patient visits, by region

Difference in daily average volume over the last six weeks compared to the previous six months

REGION	CHEMO	NON-CHEMO
Midwest	-9%	-30%
Northeast	-17%	-37%
South	-3%	-24%
West	-5%	-25%

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boroughs right outside of Manhattan, in the middle of the hot zones. And I think it's a combination of the social distancing and the lockdown. People are scared to go out.

I also think we are seeing these decreases in visits and increases in cancellations because in areas where public transportation is the main mode of transportation, like New York, it becomes harder to go to the clinic when there is a higher risk of contracting the virus.

I'm also concerned about what looks like a big drop in new patient visits, by, what, about 3,000 visits from February to April?

BG: Yes. This is really interesting, and that number is obviously dramatic. And, Matt, while teasing this out will require deeper analysis, I will provide my anecdotal observations.

As you probably know, oncology practices see cancer patients, obviously, but also will see a fair amount of benign hematology. And I am hopeful that a big chunk of those new patients are benign hematology, where they are waiting a month or two months to get to the doctor, which is not as big of a deal as a patient with a new cancer diagnosis.

But, invariably, there will be some patients with new cancer diagnoses, and those might be, "I have a symptom and I just never got to my internist, so I never got diagnosed," and some of those may be because of the drop in "elective procedures," like colonoscopies, mammograms, those types of procedures that would've led to a cancer diagnosis.

And again, I can't tell you what percentage of those make up that drop, but those are the patients who really worry

me. I think what we're looking at here is the short-term immediate impact from an operational standpoint on practices.

There are obviously going to be a lot of medium to long-term questions about how this impacted outcomes, delay in diagnosis and those things that will be critical to answer.

Right, it might be important to understand whether these delays would result in a significant uptick in overall cancer mortality, as a result of the pandemic.

BG: Yes, it's going to be really important. And, again, speaking of health care disparities, what are the demographics of those new patients with cancer who aren't coming in? That worries me as well.

Have you looked at the data on disparities, so far, or what is your sense of it anecdotally?

BG: We haven't really dug into it in detail yet, and it's one of those questions that is hard for me to even suggest anecdotally before doing so. You're trying to guess what you're missing, and we just don't do that.

COVID-19 AND U.S. COMMUNITY ONCOLOGY

Increase in patient cancellations and no-shows, by region

Difference in daily average volume over the last six weeks compared to the previous six months

REGION	CANCELLATIONS & NO-SHOWS
Midwest	+77%
Northeast	+80%
South	+72%
West	+72%

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And, Matt, just as an aside, the dataset that we're looking at here is a cut of our network, it's different from Flatiron's research datasets. Our research datasets are typically much larger—it's a much deeper data set with a lot more clinical information that has been further processed and vetted. So not only is the dataset different, but our objectives in scanning this data are different because here we're doing so as part of our internal operational management and support of our providers.

We've sort of taken a snapshot look here, but we haven't really dug in and cleaned and validated the data in the ways that we would do for an outcomes study. Questions like this, including ones about disparities, are ones that Flatiron is going to be interested in doing down the road once we have developed robust datasets.

Got it. Also, have you seen broad changes in the kinds of treatment regimens that are being used or scheduled? You probably haven't had the time to look at the data on this matter, but for instance, there are considerations for using neoadjuvant treatments because of delays in surgical interventions.

BG: We haven't looked into the data yet, but I've heard the exact same things. Anecdotally, I think that we're seeing increased use of neoadjuvant therapy to try to avoid surgeries and delay of treatments that you might consider "non-essential," though that's not the right word.

At a high level, when you're making a treatment decision for a patient with cancer, you have to look at a bunch of different factors. You have to look

at the risk from the cancer. So, for example, a fast-growing lymphoma to a slow-growing prostate cancer; and you also have to look at what are the other illnesses that the patient may have that could put them at increased risk.

And then, what are the potential risks of therapy versus waiting, or maybe even not treating? In taking care of cancer patients, in general you make decisions based on data, but also based on some uncertainty. That's the art and science of medicine. But COVID-19 has thrown us a whole big curve ball of new uncertainty.

Also, what is Flatiron doing to support its community oncology partners at this time?

BG: We have a whole team spun-up to help support the practices. First of all, the head of our team who supports our practices' revenue cycle management (RCM), Gail Airasian, is the one who kicked off all of this practice analysis that we've shared with you.

Gail and her teams are helping practices with their collections, A/R and appropriate financial analyses. This is of course critically important to help ensure they weather this storm.

We're also providing data to practices to serve as a benchmark, so that they'll be able to compare their data to try to get an understanding of how they are doing vis-a-vis the rest of the country.

We've helped our practices with thinking about how to integrate telehealth into our electronic health record, offering best practices on documentation of telehealth, and other questions that relate to our EHR.

We also have an information center to help our practices understand the changing regulations and what CMS is

doing. We want to make sure they can benefit from what CMS is offering, the small business loans, and other changes being made by the federal government. When there's information about the CARES Act, when HHS was sending out checks to practices, making sure practices were aware of all that information.

We also need to make sure that when, for example, CMS lifted the restrictions on being able to use FaceTime and Skype for telehealth, our practices are made aware.

Also, I think it's really important for us to track the regulations that are changing outside of COVID-19, so for instance, some of the interoperability standards or various other pieces of the puzzle that are being put on temporary pause. Ensuring we're helping our practices keep abreast of the whole picture, I think, is really important.

And by the way, a lot of this is complementary to what the Community Oncology Alliance (COA) has been doing. I think COA, as usual, has been doing a great job here.

I know this isn't addressed in this dataset, but what can you tell us about how your academic partners compare in coping with the pandemic and changes in patient trends? What are the similarities and differences here?

BG: I think the academic centers, both from our experience at Flatiron and everything that I have read, conversations I've had, have in a lot of ways been very, very similar to what community practices are doing; initiating a lot of the same practices like doing standardized screening before coming into the office, not letting people suspected of

being infected into the office, not letting guests accompany patients during visits unless absolutely necessary, making sure that there's appropriate spacing between patients in the infusion room, initiating telehealth. I think all of those things have been similar.

The biggest difference that I can see is most of these academic centers also have an inpatient hospital to deal with as well, and that obviously adds a whole new dimension. So, I think that's been the biggest difference. But in terms of how oncology clinics are operating, it seems to be pretty similar.

So, COA just released a report finding a 20.8% increase in practices merging with, being acquired by other practices or corporate entities, hospitals, etc., over the last two years. Do you expect this trend to be accelerated by COVID-19? And also, what does that statistic tell you about the changing landscape of cancer care?

BG: It worries me. I think we all know that when independent practices go into hospital systems, costs go up. Often, access is harder. And that's not to say that academic medical centers, hospital systems don't play a role in our health care system—of course they do, an important one.

But as we see more of these acquisitions by hospital systems, I don't believe it's good for patients. I worry a lot that the COVID-19 is going to accelerate acquisitions.

But COVID-19 is having a real impact on hospital systems as well; everyone is hurting right now. So, while this does have the potential to accelerate consolidation, the answer is that we don't know yet, but, yes, I'm worried.

Did we miss anything?

BG: One of the things I would share is we hear all of these incredible stories of what's going on in hospitals and in ICUs and what the frontline health care workers are doing. And I think we're also seeing that across our community oncology practices.

Many of our practices have set up access for injections, blood draws and pre-screening in tents outside of their clinic, allowing patients to stay in their cars. I heard one story recently about a patient who needed to get an injection, but obviously did not want to go into the clinic. So nurses from that practice literally came outside in a torrential downpour with no umbrella, no raincoat, to administer this injection to the patient in their car, all to ensure their safety.

There are just so many stories about how people are stepping up and taking care of patients. It's scary going out these days. It's scary being around people. You go to the grocery store, and you get scared.

And I go into my clinic every week, and I see all of the staff in those offices who are there, who are checking in, sitting with patients, taking them back to the infusion room, treating them in the infusion room. These people are all putting themselves at some degree of risk, and that is just an incredible thing to see.

On another note, I've had some funny telehealth interactions. I had a patient come in last Friday when I was in the clinic, someone I was seeing for the first time. And they looked at me and said, "Wow, you look so young." I was wearing a mask.

While that wasn't a telehealth story, I use it because I think it's funny, but also it tells you something about what

the real life in-person visits now look like: you're sitting in an exam room with more space between you and the patient than you normally would have. You're wearing a mask. The patient's wearing a mask.

In some ways, telehealth has started to almost feel more intimate than an in-person visit, because at least you're not wearing a mask and you can see the person sitting across from you.

And of course, telehealth is clearly not for everyone. There are obviously people who need to come into the office or when a physical exam can be really helpful.

But overall I find it's just been such a positive experience, with the asterisk that I mentioned before. There is a risk of increasing disparities for those who don't have high-speed internet or the right technology.

I mean, just like how we once set up a system where pretty much everyone could have a landline phone, and we also set up a system where now pretty much everyone can have a cellphone, even if it's not a smartphone, we need to set up a system where everyone can have high-speed internet and access to video technology to enable telehealth.



I absolutely think this puts many practices at risk. There's a lot of financial concern that's out there right now about being able to stay open and keep the lights on.



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Brown & Hirsh spoke with
Matthew Ong, associate editor of
The Cancer Letter.

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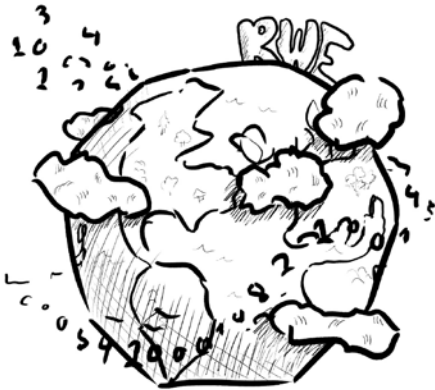
BEATING CANCER WITH LEADING-EDGE RESEARCH.

Cancer hits hard in Kentucky. That's why, every day, the team at Markey steps up, with research projects that include decoding an enzyme that may be behind some resistant strains of prostate cancer. Because we're not just treating cancer today. We're working hard to beat it once and for all.

See how at ukhealthcare.com/beatingcancer



REAL-WORLD EVIDENCE



NSCLC patients getting checkpoint inhibitors more likely to develop pneumonitis, Syapse-FDA-Aurora study finds



Thomas D. Brown, MD, MBA
*Chief medical officer,
Syapse*



Jonathan Hirsch
*Founder and president,
Syapse*

Patients with lung cancer and a history of pneumonitis are more likely to develop treatment-associated pneumonitis later, especially in the course of receiving immune checkpoint inhibitor therapy, according to a new study by Syapse, FDA, and Advocate Aurora Health.

The study, which relies on real-world data, examines the frequency of treatment-associated pneumonitis in patients with advanced non-small cell lung cancer who were treated with immunotherapy or chemotherapy. An abstract was presented April 27 in the Clinical Plenary Session at the American Association for Cancer Research's virtual annual meeting.



This is the first time that someone has done a comprehensive look at the prior medical history of pneumonitis, and looking at the impact of that prior medical history on post-treatment-associated pneumonitis for both therapeutic agents.



—Jonathan Hirsch

In the COVID-19 era, real-world data are playing an increasingly significant role in helping researchers and physicians understand the risks and benefits of

their interventions, as well as how their clinical operations are being affected by broader trends.

The Syapse-FDA-Aurora findings are all the more important, because checkpoint inhibitors—e.g. ipilimumab, atezolizumab, durvalumab, nivolumab, and pembrolizumab—have become the standard of the care in the treatment of many cancers and disease subtypes, especially NSCLC.

Given that the COVID-19 pandemic will likely increase the percentage of the population with a history of pneumonia, studies designed to characterize the safety outcomes of these patients will be critical to informing future clinical practice.

“In neither datasets were there deaths that were attributed directly to the pneumonitis,” Thomas Brown, chief medical officer of Syapse, said to *The Cancer Letter*. “Obviously, pneumonitis can be a serious complication, but the prior history of pneumonitis should not automatically exclude a patient from consideration of receiving immune checkpoint inhibitor therapy.

“We’re intent on expanding the analysis very rapidly to include analyzing patients regarding their past history of pneumonia. This has always been of clinical interest, but increasingly so with the COVID-19 pandemic.”

The Syapse-FDA-Aurora project helps define the utility of real-world evidence in oncology. Using data generated in real time, RWE researchers are demonstrating that they can now rapidly inform the standard of care by eliminating the knowledge gap between outcomes in the real world vs. outcomes from clinical trials used to support drug approval.

“This is the first time that someone has done a comprehensive look at the prior medical history of pneumonitis, and

looking at the impact of that prior medical history on post-treatment-associated pneumonitis for both therapeutic agents,” Jonathan Hirsch, founder and president of Syapse, said to *The Cancer Letter*.

“To be honest, it was the first time that we had really considered a question like this,” Hirsch said. “We were as eager as the FDA to look at the feasibility of an analysis like this in the real-world dataset. Together, we believed that there was room to provide practice-changing knowledge through an analysis like this.”

The study, which was completed within 2.5 months, compares data (N = 1,262) from Advocate Aurora Health in Milwaukee—derived from patients with advanced, stage III and IV NSCLC—with results from clinical trials (N = 6,491). The latter are pooled data from eight randomized aNSCLC trials comparing immune checkpoint inhibitor treatment, both with and without chemotherapy, to chemotherapy.

With conventional retrospective data collection practices, it would’ve taken up to two years to find the sites, wrap up contracting processes, find patients, and obtain and analyze the data, Hirsch said.

“If you look at initiating the research collaboration in mid-August 2019, we were able to have a very impactful project completed and submitted for late-breaking to AACR in mid-January,” Hirsch said. “That’s a pretty rapid turnaround for what turned out to be a high-impact project selected for a clinical plenary, which we were very happy about and honored by. We certainly were not expecting that at the time. I think the topic was highly relevant given the current global pandemic.”

The long-term safety profiles of checkpoint inhibitors are often not fully understood, because of speedy FDA



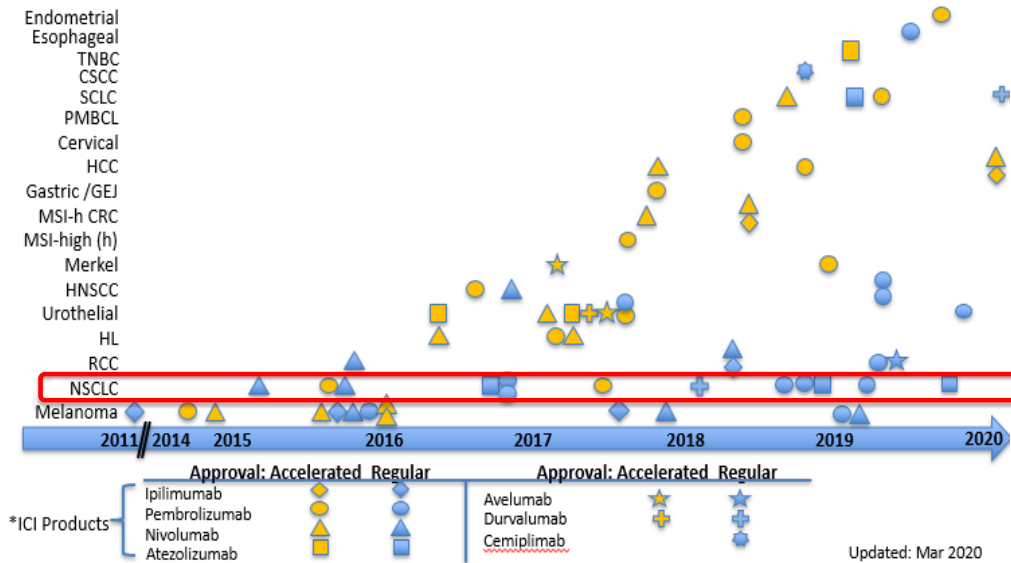
Results: Effect of PMH of Pneumonitis on TAP Incidence in Clinical Trials and RWD

Incidence of TAP point estimate (95% confidence interval)				
PMH of Pn	Clinical Trials		RWD	
	ICI +/- chemotherapy (N=3723)	chemotherapies (N=2768)	ICI +/- chemotherapy (N=615)	chemotherapies (N= 647)
Yes	5/30 16.7% (7.3-33.6%)	2/18 11.1% (3.1-32.8%)	3/21 14.3% (5.0-34.6%)	1/12 8.3% (0.4-35.4%)
CT N=48 RWD N=33				
No	164/3693 4.4% (3.8-5.2%)	27/2750 1.0% (0.7-1.4%)	17/594 2.9% (1.8-4.5%)	14/635 2.2% (1.3-3.7%)
CT N=6443 RWD N=1229				

13



Timeline of ICI* Approvals



Slide courtesy of Dr. Marc Theoret

5

approvals and equally swift uptake by physicians.

“The association between immune checkpoint inhibitor usage and pneumonitis has been reported in a range from 1% to 7% of patients with immune checkpoint inhibitor therapy,” Brown said. “We’re using the classical definition of pneumonitis, meaning non-infectious lung inflammation, and effectively seeing if that prior history of pneumonitis increases the risk of immune checkpoint inhibitor-associated pneumonitis.

“The answer in both the clinical trials and the real world dataset is ‘Yes.’”

A past history of receiving radiation therapy appears to be a crucial predisposing factor for the development of pneumonitis, Brown said.

“It turns out that, amongst the pneumonitis patients, whether you’re talking about a past history of pneumonitis or immune checkpoint inhibitor-associated pneumonitis, a majority of patients in both those groups had a prior history of radiation,” Brown said. “Radiation appears to be an important factor in the story.

“On review of the individual patients, when I say a majority of the patients received prior radiation therapy, in most of those cases, the radiation was felt to be the cause of the pneumonitis, i.e. radiation pneumonitis.

“There’s also a phenomenon called radiation recall that can be triggered by certain drugs. The interaction between the history of radiation therapy, immune checkpoint inhibitor therapy, and chemotherapies, all has to be further sorted out.”

Brown and Hirsch spoke with Matthew Ong, associate editor of *The Cancer Letter*.

Matthew Ong: Congratulations on being selected for the plenary at AACR. This is a milestone in characterizing treatment outcomes with real-world evidence, and benchmarking your findings against results from traditional clinical trials. Can you describe the significance of your project?

Thomas Brown: Thank you. Matt, you have touched on some of the key issues. The overarching issue was to examine an impactful question and compare both the evidence found in clinical trials with that in our real-world dataset.

The specific question is of importance. One way I like to look at this, stepping back a little bit, is that the FDA has been very successful in increasing the efficiency of new drug approvals. There are several paths, as you know, to getting a drug to market nowadays, especially in the cancer realm.

The challenge is that when drugs enter the market, there’s a greater burden on the post-approval period to further clarify safety issues. In particular, especially for those safety issues that play out over time, and also to further clarify the broader therapeutic applications of anticancer drugs.

In this case, we wanted to address, even prior to the pandemic coming into full form, an important topic, which is pneumonitis associated with therapy, with immune checkpoint inhibitors. That association has been well-recognized.

We wanted to, firstly, examine that question overall, in the real-world dataset as compared to clinical trials, but then to also utilize the depth and breadth of the real-world dataset that

we’re working with, to look at a sub-population of patients who had a prior history of pneumonitis.

Now in this case, we’re using the classical definition of pneumonitis, meaning non-infectious lung inflammation, and effectively seeing if that prior history of pneumonitis increases the risk of immune checkpoint inhibitor-associated pneumonitis. The answer in both the clinical trials and the real-world dataset is “Yes.”

We were able to tease out some issues from the real-world data that are of interest. One is, and this was addressed by the discussant during the AACR presentation, that in the real-world dataset we were able to examine patients who had any prior radiation therapy.

It turns out that, amongst the pneumonitis patients, whether you’re talking about a past history of pneumonitis or immune checkpoint inhibitor-associated pneumonitis, a majority of patients in both those groups had a prior history of radiation. Radiation appears to be an important factor in the story. Though this needs further study, we were able to identify this issue through the plumbing of the real-world data.

So, the risk for treatment-associated pneumonitis is higher, in general, for patients who receive checkpoint inhibitors, compared to chemotherapy alone, regardless of prior history of pneumonitis. But what’s new here is that patients with a past history of pneumonitis are at risk of developing it again?

TB: Correct. The association between immune checkpoint inhibitor usage

Results: Overall Treatment Associated Pneumonitis (TAP) Incidence by Study Type and Treatment Arm



Incidence of TAP point estimate (95% confidence interval)			
Clinical Trials (N=6491)		RWD (N=1262)	
ICI +/- chemotherapy (N=3723)	chemotherapies (N=2768)	ICI +/- chemotherapy (N=615)	chemotherapies (N= 647)
169/3723 4.5% (3.9-5.3%)	29/2768 1.0% (0.7-1.5%)	20/615 3.3% (2.1-5.0%)	15/647 2.3% (1.4-3.8%)

12

and pneumonitis has been reported in a range from 1% to 7% of patients with immune checkpoint inhibitor therapy.

The data shows in both the clinical trial set as well as the real-world dataset that there is a similar association with classical chemotherapy and pneumonitis, albeit at a lower level.

Jonathan Hirsch: In addition to the novelty of the clinical trial and real-world comparison on the post-treatment pneumonitis, the novel factor about our work is that this is the first time that someone has done a comprehensive look at the prior medical history of pneumonitis, and looking at the impact of that prior medical history on post-treatment-associated pneumonitis for both therapeutic agents.

TB: As Jon alluded to, during the AACR presentation, there was a discussion session and the discussant labeled this as the first recognition of that association, that is that a past history of pneu-

monitis increases the subsequent risk of immune checkpoint inhibitor associated pneumonitis.

How does past history of radiation therapy worsen the risk for recurrence of pneumonitis in patients undergoing immune checkpoint inhibitor therapy?

TB: That's another important feature of our real-world dataset. On review of the individual patients, when I say a majority of the patients received prior radiation therapy, in most of those cases, the radiation was felt to be the cause of the pneumonitis, i.e. radiation pneumonitis.

There's also a phenomenon called radiation recall that can be triggered by certain drugs. The association between radiation and pneumonitis is

well known. It's something that has a variable time course. The interaction between the history of radiation therapy, immune checkpoint inhibitor therapy, and chemotherapies, all has to be further sorted out.

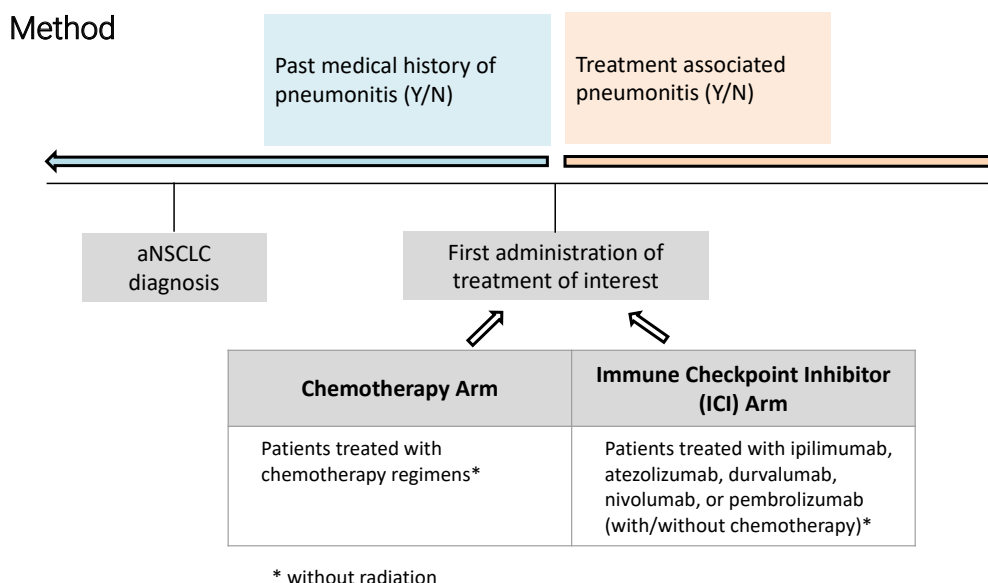
How much does the past history of radiation increase the risk of immune checkpoint inhibitor pneumonitis?

There's been some study of this in the literature, but it's a subject that we plan to further explore. The important elephant in the room, so to speak, is that this particular study focused on pneumonitis and did not include patients with pneumonia, with an infectious cause of lung inflammation.

One would assume that infectious causes of pneumonitis would likely also be associated with an elevated risk of immune checkpoint inhibitor-associated pneumonitis, although our study did not address this. That's certainly a further analysis that we're pursuing.



Analysis Using Real-World Data



11

Did you first see the signal in your real-world datasets, ahead of FDA's analyses of the results from clinical trials? How was the research question formulated?

JH: This is a very interesting example of collaboration between us and the FDA. As you know, we signed our research collaboration with the FDA in August of 2019. Shortly thereafter, the Office of Clinical Pharmacology team members came to us and said that they had this question about pneumonitis in chemo versus checkpoint inhibitors with patients who had a prior medical history of pneumonitis.

They wanted to compare the population of what they're seeing in clinical trials versus real-world data. There were sev-

eral reasons why they had this question. A lot of it had to do with the fact that this was an unanswered question pertaining to the use of checkpoint inhibitors

Together, we believed that there was room to provide practice-changing knowledge through an analysis like this. Part of why they approached us is because, in our discussions with the FDA, one of the attributes that we had highlighted about our real-world data work is the fact that we are working with health systems that see more than just the outpatient cancer journey and health systems, that typically have a relationship with the patient that dates back years, in fact, including before their cancer history.

One of the important facets of something like pneumonitis is the potentially slow onset, or the long development period. In order to really look at this question, you do have to have quite a bit of longitudinality to your data, which also means, for something like metastatic

lung cancer, being able to look way back in not just the patient's treatment journey, but potentially to look back before the patient was diagnosed with cancer.

Because we had discussed with the FDA on this facet of the real-world data we integrate, Qi Liu and her FDA OCP colleagues thought of us when they had this question and approached us about answering it.

To be honest, it was the first time that we had really considered a question like this. We were as eager as the FDA to look at the feasibility of an analysis like this in the real-world dataset. We developed a joint analysis plan and proceeded with joint methodology. One of the really important facets about the analysis in the real-world data was the ability to look at the radiation, and specifically the ability to look at the imaging, to assure that the association of radiation with pneumonitis could be actually verified via the imaging.

It was really a collaborative effort, and one where full credit should go to the FDA for generating the research question and bringing it to us.

TB: The FDA appreciates, as we do, the value of real-world data and real-world evidence in clarifying safety issues, in particular in the post-approval realm. As Jon said, the depth, breadth and longitudinality of the real-world dataset that we have at Syapse is a powerful tool for evaluating a phenomenon like pneumonitis where there is a variable clinical course. Sometimes it appears relatively early, sometimes it appears relatively late.

So, Aurora Health in Milwaukee is your data partner for this project. Did all of the use cases in your dataset come from Aurora Health? I happen to know them and Milwaukee quite well, having lived there.

JH: Yes. In this specific analysis, we wanted to look at the patients being seen at one health system, even though our network is much broader than that.

One of the reasons for this was that we wanted to assure that, with a complicated question such as this, we had clinical partners on the ground who were able to collaboratively work with us to address any specific details with analyzing the population. One of the facets of our work on real-world evidence is that we collaboratively engaged the key opinion leaders at the health systems we work with. We will involve them in the research and analysis that we do.

This is very important in this case because Dr. Mike Thompson, who runs the Precision Medicine Program at Aurora, was a key thought partner in this project, providing guidance to the analysis.

We certainly plan to scale this analysis up to the rest of the network, but in this early analysis, it was very important to be collaboratively working with a KOL at a health system who provided very important guidance as the project shaped over time.

For oncologists reading this story, what do the results of the study mean for the treatment and management of patients with non-small cell lung cancer?

TB: First of all, if you look at the the data and evidence within the clinical trial realm, and look at the data and evidence within the real-world realm, we can say that, while there is an increased risk of immune checkpoint inhibitor-associated pneumonitis when you've had a prior history of pneumonitis, this risk—it appears in both datasets—can be managed.

In neither datasets were there deaths that were attributed directly to the pneumonitis. Obviously, pneumonitis can be a serious complication, but the prior history of pneumonitis should not automatically exclude a patient from consideration of receiving immune checkpoint inhibitor therapy.

What are the mechanisms of action associated with an increased risk of pneumonitis—specifically, with immune checkpoint inhibitors, either as monotherapy or as combination therapy?

TB: The running assumption has been that the mechanism of action is immune-based, i.e. relating to cellular and

cytokine dynamics. The mechanism of action is not completely clear.

As we have discussed, there are multiple factors that can impact the incidence of pneumonitis: the immune checkpoint inhibitor; the classical chemotherapy; past radiation; and, of course, there may be other factors to include any history of pneumonia. Teasing out the mechanism of action is a work in progress.

How should health care providers be thinking about this information as well in the context of COVID-19?

TB: We're intent on expanding the analysis very rapidly to include analyzing patients regarding their past history of pneumonia. This has always been of clinical interest, but increasingly so with the COVID-19 pandemic.

For now, it's important for clinicians to assume that a past history of pneumonia may well have an impact on the incidence and severity of immune checkpoint inhibitor-associated pneumonitis. They should continue to exercise caution in treating patients with a past history of pneumonia, to include a past history of significant respiratory compromise. We hope to further elucidate this topic in the short-term.

You've mentioned probably about a dozen important things that you'd like to build on with this study. What are the next steps?

TB: I think the next steps are basically in three categories. One is to expand the analysis of pneumonitis to include pneumonia, to include infectious caus-

es. The second is to further elucidate the role of radiation therapy by further comparing those patients who received radiation therapy in the past and those who did not.

Then thirdly, looking at a broader range of treatments when one considers treatment-associated pneumonitis. For example, some of the other targeted therapy classes include the tyrosine kinase inhibitors, and beyond.

Did we miss anything?

TB: The importance of this project at a high level is that it's a demonstration of how real-world data and real-world evidence can supplement and add to clinical trial information, particularly in the safety realm, in this post-marketing era.

One of the drivers of our collaboration with the FDA is our mutual recognition that there's an opportunity for real-world data to elucidate safety issues for all the reasons that we've stated.

Jon, do you have anything to add? Also, any updates about your ongoing work on validation of real-world endpoints?

JH: One of the things that excites us about the research collaboration with the FDA is how rapidly we've been able to generate meaningful results. If you look at initiating the research collaboration in mid-August 2019, we were able to have a very impactful project completed and submitted for late-breaking to AACR in mid-January.

That's a pretty rapid turnaround for what turned out to be a high-impact project selected for a clinical plenary,

which we were very happy about and honored by. We certainly were not expecting that at the time. I think the topic was highly relevant given the current global pandemic.

We are moving at a similar pace with our other efforts. As you well know, we have been working on several programs that were announced in the press release, including work on real-world endpoint development and methodology.

We always say "validation" in quotes because we're still trying to figure out what the right word is, working in conjunction with our colleagues at the FDA. That project continues at a rapid pace. We hope to be sharing results on that soon.

We continue to participate in and support the efforts from groups like Friends of Cancer Research, who are working on real-world endpoints as well (*The Cancer Letter*, [Nov. 22, 2019](#)).

I will say that this has taken on an increasing importance as you look at what's happening now with clinical trials in oncology. What we're seeing from the industry, in general, and certainly from the health systems and the life sciences companies that we work with, is that the global COVID-19 pandemic has impacted clinical trial operations.

It has impacted things in such a way that real-world data—and the need to be able to use real-world data in a regulatory setting where one is confident in the underlying methodology and data quality—has taken on increasing importance.

We think that this pandemic is going to accelerate efforts that were already happening, and the use of real-world data in the clinical trials and regulatory realms is one example.

TB: One thing I've learned, to extend on Jon's comments, is the important aspects of utilizing real-world data for

safety issues. My background is in developmental therapeutics, early phase clinical trials, specifically phase I trials.

Even today, when we tend not to have an upper age limit for adult patients' clinical trial eligibility, older patients are not as likely to participate in clinical trials. Real-world data then gives you the ability to look at the entire age spectrum.

Likewise, on the fringes of organ dysfunction, whether one's talking about hepatic, renal, or even bone marrow dysfunction, one can evaluate those patients within a real-world data set, patients who would usually be excluded from a clinical trial.

That is what the real world looks like; right? That broader range of individuals with a wider age distribution, with a wider range of organ function. That's so important as drugs are introduced to the general population at an increasingly rapid pace.



The importance of this project at a high level is that it's a demonstration of how real-world data and real-world evidence can supplement and add to clinical trial information, particularly in the safety realm, in this post-marketing era.



—Thomas Brown

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

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CONVERSATION WITH
THE CANCER LETTER

Skip Burris: These few months are going to shape health care in the coming years

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I worry about some of the smaller practices, with a handful of physicians, and their ability to have staying power through this pandemic, as they may not have the ability to handle the decrease in volume.

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Howard A. “Skip” Burris III, MD, FACP, FASCO
*President, American Society of Clinical Oncology
President, Clinical Operations and Chief Medical Officer
Sarah Cannon, the Cancer Institute of HCA Healthcare
Associate, Tennessee Oncology*

The COVID-19 pandemic will change the structure and economics of clinical care and clinical trials in cancer, said Howard “Skip” Burris, president of clinical operations and chief medical officer of Sarah Cannon, the Cancer Institute of HCA Healthcare.

“The pandemic is going to create an opportunity to look at how oncology should be reimbursed and how a practice is not disadvantaged when they’re able to function electronically in some areas,” said Burris, who is this year’s president of the American Society of Clinical Oncology. “And then I think bigger picture, this pandemic will help us set some health care priorities for the population.

“I’m hopeful that after we get through the storm, there will be a real assessment and look at the data as you alluded to about the need to continue with appropriate cancer screening programs, mammography, colonoscopy, and appropriate CT scans.

“And hopefully, we won’t see too big of a disadvantage coming from procedures being delayed. The information during this time will help confirm what we thought for years—that early detection of cancer really leads to better outcomes. These few months here, I think, are going to greatly shape how we approach health care over the next few years.”

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

Paul Goldberg: First of all, how are you?

Skip Burris: I’m doing well. We are staying fairly busy in continuing to care for our patients. Nashville had a lot of cas-

es, but we have had a fairly low number of hospitalizations and an even lower number of deaths. So, we’ve been a little bit of an outlier as a state.

Nashville had a lot of cases early, but the hospitals have been relatively quiet in comparison to other states. The major hospitals here have been running inpatient COVID-positive numbers in the twenties, with a handful of patients in the intensive care unit.

How about your practice? How about Sarah Cannon?

SB: Our major practices are Tennessee Oncology and Florida Cancer Specialists, where we have the bulk of the patients on clinical trials. We also have research programs in Kansas City, Oklahoma City and Denver.

We have about a dozen COVID-19 positive patients across the practices, and have been fortunate that none have been critically ill. A few staff have been infected, exposed outside of our clinics, but again, nobody critically ill.

The Nashville clinic, where I practice, is relatively quiet, but we are continuing treatment. Surveillance visits have been moved out a few months, and we’re continuing to keep an eye on that timing. The benign hematology has also been moved out. The oral therapies are being handled with telemedicine and shipping the drugs to the patients.

The clinics across our network are steadily functioning, but not overly busy, including chemotherapy rooms. With the lower volume, we are able to successfully implement social distancing measures as well as all the safety precautions of masks, gloves, and hand washing.

What about the financial impact? Are you seeing any?

SB: There is an impact, but it’s a little early to do any calculations. The absolute visits are going to be dropping. We are starting to pick up the telemedicine visits, but it’s probably 50/50 on patients being comfortable with that approach versus simply wanting to push out their visit. The treatments have remained fairly steady in terms of those patients that are on intravenous treatments.

I think the financial impact is not going to be quite as devastating as we had first anticipated. The missed visits will never be made up.

It’s a little bit like the movies and the restaurant business—people are not going to have two dinners at the same place in the same night, or see two movies at the same time—patients are not going to come for two visits to our clinics in a week either. So, I think the financial impact is going to be substantial, but not catastrophic.

I do think it is different for large practices versus the smaller practices. I worry about some of the smaller practices, with a handful of physicians, and their ability to have staying power through this pandemic, as they may not have the ability to handle the decrease in volume.

What about impact on clinical trials, especially drug company trials? We’ve certainly written a lot about NCI trials, but drug company trials, I think haven’t been really gauged yet. What impact do you think this will have on approvals?

SB: It's an interesting question. We have seen big pharma that are conducting global trials pause studies and put a hold on accrual. I think a part of that is making sure that they can get the data.

Also, it was easier to not make site-specific selections and just put a large trial on hold. So, we've seen most of the big pharma react that way.

We have seen a substantial drop in enrollment for phase II/III studies, resulting from at least a third of the clinical trial menu being put on pause.

The other part about the phase II/III side of the businesses is, in many of those scenarios, patients have an option. We have had so many approvals recently. Patients may have an off-study option that might require fewer visits or less travel. I suspect that is impacting accrual as well.

All of those will be detrimental in terms of slowing down trial completion, slowing down approvals.

On the other hand, on the phase I end of the spectrum, where I think the majority of the patients are seeking an investigational treatment and/or a treatment to match their mutation, we have not seen quite the level of decline.

And in particular, we have seen the smaller biotechs continue forward. Many of their phase I trials are at only a handful of sites, making any decisions site-specific.

As you said at the beginning, in terms of approvals, certainly many of the phase II/III studies are going to be slowed substantially. It is also important to note that some of the big academic centers, typically accruing many patients, are in cities hit the hardest by COVID-19, such as New York City, Boston and some of the cities in Europe, which is impacting trials.

You would think that some patients would have to be censored out, because with time to progression, the radiographic metrics, you would pretty much have missed the opportunity to gauge it; right?

SB: Correct. I think it's going to be complex within the phase II/III trials. I was reading *The Cancer Letter* with Matt Ong's interview with Don Berry [*The Cancer Letter*, April 24, 2020], thinking about how individuals will need to come in and really think about how we pool that data and analyze it. But you're exactly right.

The NCI has been great in encouraging taking deviations related to COVID-19 needed to keep the patient on study. We have made a number of operational adjustments including remote data monitoring, shipping pills to keep people on oral therapies, and implementing telemedicine visits.

Certainly, in the phase II/III area, with time to progression studies, there will be an impact, and there will be some complexities in how we analyze that data.

How are academic cancer centers affected?

SB: Probably a lot depends on where they are located geographically. In talking to our colleagues at centers in New York, Boston and New Haven, we know many of those centers have had to stop clinical trial accrual. We are seeing the same thing in much of the East Coast and parts of the West Coast.

Also, there is a tertiary referral travel population. We have seen, at all of our centers, patients being much more hesitant to travel for treatment. I think it will substantially impact analyzing the data from those centers and getting those trial programs up and running.

Some of the academic medical centers have had a higher volume of COVID-19 positive patients. I know I've had some patients that have gone back and forth to MD Anderson, where they are now encouraging patients to stay there in Houston, and not travel for their safety.

This recommendation gets into socioeconomic issues about who can do this relocation and who cannot.

What impact do you think it will have financially on the academic cancer centers?

SB: I think you have to look at an academic medical center as part of a larger hospital. We can break this into different buckets—small community practices will be hit differently than larger community practices that have more synergies.

Larger practices may have better staying power, and, of course the CARES program allows the hospitals to help in some ways. There are some waivers with regard to Stark concerns, and then the ability for some of these practices to participate in the PPP programs for loans and for advanced Medicare payments.

When you think about the hospitals right now, they are essentially doing emergency room care, which has dropped, COVID-19 care that's ongoing, and then cancer care that needs to be done.

The other services generating revenues have slowed down because many of the procedures, such as orthopedics and cardiovascular can be pushed out a few months. We have seen across the country health systems and hospital systems beginning to furlough individuals and take other actions with regard to employment.

I think that this environment is going to be tough for the academic medical centers. Hospitals have multiple sources of revenue, and many of these sources have really been scaled back as patients choose to defer coming in or there are simply not the resources for routine health care.

So, there is redistribution, but is it a net loss?

SB: It will be interesting to see how some of that care comes back. While patients will never make up that cancer visit, the patients who need a hip replacement will schedule their surgery.

The individuals who need a valve replacement will get their cardiac procedure. I think in other specialties there will be a backlog, and it will be interesting as we go through the summer and the fall to see how that is handled. There is some short-term pressure in terms of just how much routine health care has paused or slowed down.

It has been interesting to see the articles talking about all the patients who used to come into the emergency room or the urgent care centers for aches and pains, and how much that has dropped. And then we are going to wonder going forward, will patients be more hesitant to utilize the health care system? Will they think once or twice before coming in?

As you have alluded to, we also have the economic side: we are seeing the unemployment numbers go up, which may have short-term impact as well. We have many Americans, unfortunately, uninsured or with less health insurance than they have had in the past.

What about the impact on community hospitals and for-profit hospitals?

SB: Sarah Cannon's parent company is HCA Healthcare, and they have committed to not laying off anyone through this crisis. HCA Healthcare is a large company, with the financial strength to support pandemic pay programs that will aid employees.

County hospitals or rural community hospitals are impacted on a different level. They already were under economic pressures. I suspect we may see some consolidation and closures of hospitals in rural settings or in places that are geographically disadvantaged.

That issue is going to be a stressor to the system. We already were trying to figure out how to do rural health care before the pandemic, and this crisis has certainly exacerbated the challenge.

Hospitals that do not have a large system to help alleviate some of the stress are going to be struggling to get through the near term.

I was just looking at what seems to be happening in the adjuvant care. There seems to be a shift to neo-adjuvant—because of COVID. Is there data to support this in terms of safety and efficacy?

SB: That is a great question, and I say that because I have asked the same question. In certain settings, such as HER2 positive breast cancer, there are a number of patients who would likely benefit from neoadjuvant therapy, as well as some triple-negative or locally advanced tumors.

There are likely other subsets of breast cancer and other diseases where neoadjuvant therapy makes sense. But by and large, you are correct, that during this COVID-19 crisis, many think it is better to put patients through chemotherapy versus surgery. And that has been greatly debated.

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We already were trying to figure out how to do rural health care before the pandemic, and this crisis has certainly exacerbated the challenge.

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CMS came out with guidelines that put cancer surgery in the Tier Three category, and that seems reasonable. Our motto at Sarah Cannon has been that we are going to stay safe and stay the course.

We have seen a number of surgeries put off, but I do not think I have ever said to a patient with invasive cancer that their surgery is elective. Some are more urgent than others.

The system has made a quick shift to thinking that neoadjuvant therapy is the safest thing to do or the best thing

to do, but there is not a lot of data to back that up in many settings.

We have never really had clinical trials that showed that hormonal therapy was a great neoadjuvant treatment for the hormone-positive breast cancer. It is a real judgment call to put patients through chemotherapy, with myelosuppression and more in this setting.

There were some broad-based recommendations made from several societies that I found interesting, without a lot of data to back them up.

Will we learn from this, or will this be one of those societal experiments that we will never know the impact of?

SB: I hope we can learn from it. We have talked about this topic at ASCO. Under Dr. Richard Schilsky, the CMO, and in conjunction with the leadership, we have launched the [ASCO Survey on COVID-19 in Oncology Registry](#) [*The Cancer Letter*, April 17, 2020] to try to track the patients within our practices that have tested positive.

We are hoping that as we gather data, we can also get some insights to the overall changes in care that took place. CancerLinQ should also provide some of that information as its database has been growing.

You bring up some points that are going to be to key in this issue. Are some of these delays appropriate and what sort of delays are we seeing? Then, on the screening side, we have seen a marked decrease, both from health systems deciding not to have screening clinics open for mammography and colonoscopy, and also the patient population being

unwilling to come in. It will be interesting to track that data.

We should be able to get some large looks at information across the country as we are seeing patients not come in for what are well known and data-proven screening mechanisms that are appropriate for certain cancers.

Is there any insight about immunotherapy versus chemotherapy in patients who are at risk for COVID?

SB: No, we do not have any data, but it's been a question that is going to be asked and looked at with great interest. We had the initial group of data that came out of China and Northern Italy where lung cancer group seemed to do poorly. We do not have the next level of data in terms of immunotherapy and chemotherapy in some of those populations.

I think the most interesting data will be the U.S.

We are hoping within the ASCO registry that we gather a large amount of information and will be able to sort out whether we see a difference between immunotherapy and chemotherapy.

And then, specifically in some other populations, such as the bladder cancer group or some of the other diseases where immunotherapy is used more often.

Theoretically, the checkpoint inhibitors should have been an attractive treatment choice in the COVID-19 setting and one would hope that patients were not disadvantaged by taking those types of therapies.

This sounds like a good real-world evidence question.

SB: Absolutely. We will be aggregating the data as we go. This question might be one place where electronic medical records and the aggregation of data and platforms like CancerLinQ hopefully will really yield some insights.

I think we are going through the sprint phase right now. I'm no expert in infectious diseases, but one would think that now we will move into more of the marathon phase of COVID-19 where we will continue to see pockets of the virus and what happens during the upcoming fall season.

I suspect this virus will be with us for a while at least until we get some vaccines that are effective. So, these early learnings will be very helpful as we think about taking care of patients later in 2020 and then as we move into 2021.

What role have oncologists played—or have the science behind oncology played—in development of treatments? Are you seeing a kind of a merging of oncology with, say, virology with rheumatology?

SB: It is an excellent topic. Because of our research infrastructure and the rapid initiation of a number of COVID-19 trials, Sarah Cannon has been brought to the table to help with the infrastructure support around some of these clinical trials.

Our involvement has quickly led to more conversations, one being convalescent plasma. Our blood cancer doctors and experts that have been doing apheresis and transfusions and infusions for years have been brought in to help operationalize that and work with the Red Cross.

That therapy has been a place where we have seen the hematologists and oncologists brought to the table. Then we have also seen an abundance of potentially helpful therapies in the anti-inflammatory group. We have had some mixed news over the last few days about the IL-6 monoclonal antibodies that we've been using to help cytokine release syndrome.

There is a mix of data about the role of inflammation in COVID-19 analysis. We are seeing conversations about some of the other drugs that are out there such as selinexor, the new myeloma drug and acalabrutinib, the lymphoma drug, those being potentially efficacious in helping with an inflammatory response. So, we are seeing the oncologist being brought to the table to discuss how those therapies might work, how they might be utilized.

It is nice to see our specialists being able to contribute in that regard. Because at the practice level, we have been worried about the cancer patients being a vulnerable population.

So, at our facilities, the cancer doctors have been asked to not go to the hospital, to allow the hospitalist to take care of our patients and to really try to protect the oncologists from being exposed and potentially transmit to our patient population.

But academically, scientifically, intellectually, it has been good to see the conversations ongoing.

What will oncology look like when it's over? Will there be a rebound? So, how will it work? What will it look like?

SB: Being a clinical researcher and involved in drug development throughout my career, I think one positive is going to be what we talked about in terms of modernizing the clinical trial process.

In regard to some types of visits, we know now that we can handle some with telemedicine, which may decrease the burden on the patient. The remote data monitoring has gone very well for our centers.

Decreasing the number of visits, sending out the pills for patients, and using local laboratories are some elements to modernizing the clinical trial process that I think will be attractive.

For some patients who live an hour or so away, and travel is burdensome, I think the idea of decreasing the number of visits will be attractive.

But having oral therapies shipped is going to create some pressure on what the payment model should be. We don't envision a decrease in the need for nurses as they provide critical education and contact for our patients.

The pandemic is going to create an opportunity to look at how oncology should be reimbursed and how a practice is not disadvantaged when they are able to do some things remotely or electronically. And then I think bigger picture, this pandemic will help us set some health care priorities for the population.

I'm hopeful that after we get through the storm, there will be a real assessment and look at the data as you alluded to about the need and benefit to continue with appropriate cancer screening programs, mammography, colonoscopy, and appropriate CT scans.

And hopefully, we won't see too big of a disadvantage coming from procedures being delayed. Hopefully, the information during this time will help confirm what we thought for years—that early detection of cancer really leads to better outcomes.

These few months of the COVID crisis are going to greatly shape how we approach health care over the next few years.

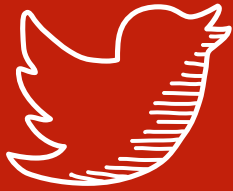
Let's look at their rebound. If it actually happens, you won't have a full rebound, probably, because adjuvant care that's not delivered now is not going to be needed. But there would be a rebound. If there is a rebound, will the same institutions that are now furloughing people be trying to hire them back?

SB: It's interesting to think about how that's going to go. I'm glad that at Sarah Cannon we have not had to furlough anyone.

We've actually had a number of our staff move to a work from home setting to socially distance and create space in the clinical area, and that has actually gone fairly well.

You are right. There are certain segments that we will never catch up on with regard to visits and therapies. I

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think we will get back to business as it was in terms of volumes.

Now, I think there might be some things that are done remotely and through telehealth. We might see a real shift in the workforce assessment. I know that many of these hospitals and many of the cancer centers and health care systems in general are finding out that some of these individuals can work from home. And so, do they all need to be in the office?

So, I think we will see some changes in terms of how the workforce is deployed as well. Patients are still living longer. Our generations have been healthier or seen the continued need for health care as patients are moving into the older ages. We are certainly a long way from having cured cancer.

The number of younger people being affected by cancer continues to be real and continues to be growing. So, I think the need is going to be there.

Is there anything we missed?
Anything we've overlooked?

SB: I think you have hit the big points. It has been interesting being involved with ASCO during this time, to see the thirst for information and the connectivity across the country and across the globe.

Our [ASCO.org](https://www.asco.org) resources have received an incredible number of page views. We went from a few thousand to a 100,000 to 250,000 over the past week. Patients are desperately looking for information and concerned about where they are in their care and the treatment.

We have also been looking at, and it kind of goes to the workforce question,

how often do we need to get together and meet? I think people love the big annual ASCO meeting in Chicago. I know I am particularly sad that we will not be gathering this year. It might be that we see fewer in-person meetings overall. We will certainly see how these virtual meetings go over the next couple months.

We might see a real shift here in terms of how education is done. Even just from this past month, we have gone from being uncomfortable being seen on video to accepting them as part of life.

And we're a very adaptable society, and I think most people are technologically savvy. It's been interesting to see just what has changed over the last 4-6 weeks. We've seen a real culture shift in terms of the willingness to do something via video.

Thank you so much for talking with me.

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It might be that we see fewer in-person meetings overall. We will certainly see how these virtual meetings go over the next couple months.

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AACR data from China and Europe amount to “two different messages” for cancer patients with COVID-19

By Alexandria Carolan

Are COVID-19 patients with cancer at a greater risk of dying than non-cancer patients? Depends on whom you ask.

Researchers from China, Italy, France, Spain, and the United States presented data at the first-ever virtual annual meeting of the [American Association for Cancer Research](#) April 28 that demonstrated very different answers to this question.

“My general view—and I tried to bring it up in the discussion—was that we have two different messages: the one from the two presenters from Wuhan saying that patients with cancer do worse with COVID-19 infections,” Antoni Ribas, president-elect of AACR, said to *The Cancer Letter*. “That contrasts with the data that were provided from Italy, from France, and from Spain—where a cancer diagnosis was not an adverse prognostic factor for having a bad outcome with the COVID-19 infection.”

Ribas is a professor of medicine, professor of surgery, and professor of molecular and medical pharmacology at the University of California Los Angeles, director of the Tumor Immunology

Program at the Jonsson Comprehensive Cancer Center, and chair of the Melanoma Committee at SWOG.

The data presented at an AACR session, titled “COVID-19 and Cancer,” were based on observational cohort studies in cancer patients with COVID-19. Several studies broke down fatality rate by cancer type.

Data from Italy and China earlier in the course of the pandemic suggest that patients with cancer, as with patients with comorbid conditions, are at higher risk for developing severe adverse events and dying after testing positive for SARS-CoV-2 (*The Cancer Letter*, [March 20, April 3, 2020](#)).

Results from Wuhan, published in [Cancer Discovery](#), demonstrated that patients with cancer, specifically those who finished cancer treatment, were more at risk than those who had not gone through cancer treatment.

“This is consistent with what my concerns have been,” Leonard Lichtenfeld, deputy chief medical officer at American Cancer Society, said to *The Cancer Letter*. “The numbers are small, but they confirm the concerns and fears of many of us, that COVID-19 is worse for cancer patients. “Patients who get chemotherapy, or patients who have recovered from lymphoma, still could have some impact on their immune system. And the Wuhan data support that. On the other hand, other data does not support that. So we have a lot to learn.”

Researchers from Gustave Roussy reported that the rate of infection does not seem higher in cancer patients than in the global population, justifying “an optimal management of the cancer patients’ underlying tumor.”

“The bottom line is when we talk about patients with cancer, the ones who are in acute treatment, we all know have to be protected. But we also have a vulnerable population of those who have recovered, who are survivors, who tend

to be older, who had cancer,” Lichtenfeld said. “And that is a group I’m particularly concerned about as we do these opening orders, because they need to understand, their families need to understand.”

Types of cancer most common in Europe could be different from those found in China, observers say.

“Different information from China and from Europe may be based on referral patterns, type of disease, and comorbid conditions,” Ribas said. “In the European series, the patients who had a prior cancer but are not being actively treated for it, did not do worse than the patients who were actively treated unless they had a very recent chemotherapy or a hematologic cancer.”

“It was patients who had comorbid conditions—in particular in the lungs, patients who have chronic lung inflammatory disease are also more likely to have lung cancer, both linked to cigarette smoking,” Ribas said.

Conclusions from the abstracts presented during the COVID-19 and Cancer session follow:

The experience of treating patients with cancer during the COVID-19 pandemic in China, presented by Li Zhang of Tongji Hospital in Wuhan.

“Cancer patients showed aggressive presentation and poor outcomes with the COVID-19 infection. It is recommended that vigorous screening for COVID-19 infection should be performed for cancer patients with anti-tumor. From our limited data, there is no evidence to suggest difference in cancer patients on ICI treatment.”

Patients with cancer appear more vulnerable to SARS-CoV-2: A multi-center study during the COVID-19 outbreak,

presented by Hongbing Cai, of Zhongnan Hospital of Wuhan University, Wuhan.

“Our results showed COVID-19 patients with cancer had higher risks in all severe outcomes. Patients with hematological cancer, lung cancer, or with metastatic cancer (stage IV) had the highest frequency of severe events. Non-metastatic cancer patients experienced similar frequencies of severe conditions to those observed in patients without cancer. Patients who received surgery had higher risks of having severe events, while patients with only radiotherapy did not demonstrate significant differences in severe events when compared to patients without cancer. These findings indicate that cancer patients appear more vulnerable to SARS-CoV-2 outbreak. Since this is the first large cohort study on this topic, our report will provide the much-needed information that will benefit global cancer patients. As such, we believe it is extremely important that our study be disseminated widely to alert clinicians and patients.”

TERAVOLT (Thoracic cancerERS international coVid 19 cOLlaboraTion): First results of a global collaboration to address the impact of COVID-19 in patients with thoracic malignancies, presented by Marina Chiara Garassino of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan.

“Data suggest that due to their cancer diagnosis patients with thoracic malignancies are less likely to be admitted to the intensive care unit and are at increased risk of prolonged hospitalization and mortality from COVID-19 infection. With improved cancer therapeutic options and prognosis, physicians need to balance the individual cancer specific mortality and risk of death when treating patients with COVID-19. TERAVOLT will continue to collect data and to provide data in order to identify characteristics associated to a severe COVID-19

able to help societies to create guidelines tailored on individual risk.”

Experience in using oncology drugs in patients with COVID-19, presented by Paolo A. Ascierto, of Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples.

“The hyperactivation of immune system due to the immunotherapy strategies can develop some conditions which need of immuno-suppressive drugs to reduce the harmful immune reaction. Since the acute respiratory stress syndrome COVID-19 related seems to occur from an excess of cytokine production, we focused our attention on the cytokines storm which probably lead to ARDS by COVID-19 and how to prevent or treat it. We know very well the Cytokine Release Syndrome (CRS), one of the most prominent and well described toxicity from chimeric antigen receptor T cell therapy (CAR-T), as well as from some bispecific antibodies. In particular, we know the key role played by IL-6 in the pathogenesis of these kind of hyperinflammation syndromes. Considering elevated serum concentration of IL-6 and CPR in patients admitted in ICUs department, we started to use monoclonal antibodies against IL6, above all tocilizumab. In Italy we started on 19th of March a phase II study (NCT04317092) which enrolled 330 patients in 24 hours, with the ability of tocilizumab to reduce the one-month mortality rate as main endpoint.”

Outcome of cancer patients infected with COVID-19, including toxicity of cancer treatments, presented by Fabrice Barlesi, of Gustave Roussy Cancer Campus, Villejuif, France.

“Globally, the rate of the SARSCoV-2 infection in our cancer patients’ population does not seem to be higher compared to the global population. We

have not found evidence that COVID-19 is more lethal or aggressive in cancer patients that underwent usual SARS-Cov-2 treatment. We believe that adequate testing and protective measures, along with the low rate of SARS-cov-2-treatment-related adverse events (5.5%), justify an optimal management of the cancer patients' underlying tumor."

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Adapting oncologic practice to COVID-19 outbreak: From outpatient triage to risk assessment for specific treatment in Madrid, presented by Carlos Gomez-Martin, of Octubre University Hospital, Madrid.

"Until data from randomized studies including cancer patients were available, their diagnosis and treatment must be carried out according to the standard of care at all times. Comorbidities and life expectancy conditioned the treatment by the underlying tumor must be taken into account when considering an aggressive treatment (ICU). Based on our data, lung involvement (primary or metastatic), neutropenia and acute respiratory distress syndrome are predictive factors of poor outcome (death) regardless of other conditions. COVID-19 treatment must be multidisciplinary and it should include specific antiviral therapy, supportive treatment, close monitoring of inflammatory parameters, and appropriate use of anticoagulants given the risk of thromboembolic complications in this disease."

AACR record attendance: 61,000 registered

The first-of-its-kind virtual AACR meeting marks the beginning of the 2020 conference season, nearly all of which will take place online this year.

The 61,000 people in attendance was "unexpected," said Anthony Ribas, president-elect of the association. The highest-attended AACR meeting in the

past had about 20,000 in attendance, Ribas said.

"We imposed on ourselves to create something that hasn't been done before, and make it freely available to everyone," Ribas said. "We were excited to provide a scientific program with many sessions but we knew it would be a big challenge to organize it in such a short period of time."

"We're going to emerge out of this and it's going to be the same principles that we've had so far where science and knowledge will allow us to move forward. It will be applied to the COVID-19 pandemic, and it will be applied to cancer research and cancer treatment," Ribas said.

The AACR annual meeting represents the first opportunity for the global cancer research community to share data on COVID-19 and formulate strategies to treat the disease.

Pre-COVID-19, the observational cohort studies presented at the AACR session would have been considered "hypothesis generating," Karen Reckamp, director of Medical Oncology, associate director of Clinical Research, and director of Medical Oncology at the Lung Institute at Cedars-Sinai Medical Center, said to *The Cancer Letter*.

"In the cancer world, there's been very limited data that has helped us to understand how best to treat our patients with cancer," Reckamp said. "Now, when you bring even a little bit of data into that vacuum, you want to fill up the void. I think we have to remember that, even at a place like AACR, generally when we're at those meetings—even a randomized phase III trial can be debated by the scientists that are there to talk about the merits of what might be the gold standard."

Data from countries hit hard with the novel coronavirus can be applied in pan-

demic hotspots in the United States—such as New York.

"It's helpful now that we're getting some data from other centers, and helpful that from other centers around the world, we understand some local issues," Reckamp said. "I think some of the issues brought out by some of the European data, is that when you do have less resources, it really may be that cancer patients may do worse if they're not able to get the resources that are available."

"Also thinking about the New York data, and the social and economic issues faced by patients and issues of diversity, that not everybody has the same access or the same ability to socially isolate—and they may be at more risk," Reckamp said.

During the session, Louis Voigt, an intensivist who is the chair of the Ethics Committee at Memorial Sloan Kettering Cancer Center, reviewed the limited data from his institution.

MSK tested more than 5,000 patients for COVID-19, Voigt said. Of these, 773 patients tested positive, and 327 of them were hospitalized at the cancer center as of April 22. Fifty four percent of the cohort were discharged from the hospital, and 14% died in the hospital, Voigt said. The average full stay was 10 days.

In the ICU, as of April 22, 78 patients were admitted, and 52 of them needed mechanical ventilation. Thirteen patients were extubated, four underwent tracheostomy, 22 had a do not resuscitate order, 15 died in the hospital, and 40% were still receiving care in the ICU. Three patients were discharged.

Voigt provided a summary of what has been published so far for several cohorts of patients in Seattle, the United Kingdom, New York City at Northwell, and in New York City at Memorial Sloan Kettering. The MSK data have not been

MSK Unpublished Partial Data for Hospitalized Patients

Tested >5000 patients

>4200 tests at MSK with first case on March 13, 2020

>140 tests at other hospitals

773 out of 4200 or 18% with COVID-19

As of April 22, 2020

327 unique patients hospitalized at MSK

176 or 54% discharged from the hospital alive

45 or 14% died in hospital

Average hospital LOS of 10 days

>100 or ~31% still in hospital

Data on COVID-19 from Various HCO

Cohort	Critically-ill, n=	MV, n=	Mortality, %	Reference
Seattle-1	21	15	67%	Arentz, JAMA, March 2020
Seattle-2	24	18	56%	Bhatraju, NEJM, March 2020
UK (CNARC)	5578	3186	67%	https://www.icnarc.org , April 17, 2020
NYC Northwell	2634	320	88%	Rihardson, JAMA, April 2020
NYC MSK	78	52	27%	Unpublished Data

MV = Mechanical Ventilation

Courtesy of Prof Elie Azoulay

MSK Data have not yet been validated and should be handled with care!

CLINICAL OUTCOMES IN CANCER PATIENTS WITH COVID-19 BY ZHANG ET AL.

Clinical Outcome (Updated to April 4)

OUTCOME	No. (%)	OUTCOME	No. (%)
Severe events	15 (53.6)	Cause of death	
Clinical outcomes		ARDS	5 (62.5)
Death (Lung 3; prostate 2; liver 1; rectum 1; testis 1)	8 / 28 (28.6)	Septic shock	1 (12.5)
Discharge from hospital (March 4 th)	10 / 28 (35.7)	Pulmonary embolism suspected	1 (12.5)
By April 4 th	14 / 28 (50.0)	Acute myocardial infarction	1 (12.5)
Still hospitalized by April 4	6 / 28 (21.4)	CT scan evaluation	
Duration of hospitalization for those discharged	18.4 (12.8-20.6)	Improvement	13 (46.4)
Duration of hospitalization for those still admitted	29.4 (18.5-42.5)	Unchanged appearance	5 (17.9)
Time from COVID Dx to severe events, days	7.0 (5.0-15.0)	Deterioration	6 (21.4)
		NA	4 (14.3)



*Follow up time, day26 (16.3-34.8) (cutoff on Mar 4)

Zhang L, et al. Ann Oncol. 2020 Mar 23. pii: S0923-7534(20)36383-3.

Source: Presented by Li Zhang at AACR virtual annual meeting I

validated, and should not be considered published or final, Voigt said.

“There was approximately anywhere between 56 and 88% of mortality recorded or reported for patients who required mechanical ventilation. That number contrasts with the 27% recorded mortality for patients with cancer admitted at Memorial Sloan Kettering Cancer Center,” Voigt said. “So, we are still gathering data and analyzing them. I did not present any real demographic variables, cancer types, active cancer directed therapies, CPR, or hematologic complications of aggressive anticoagulation to be followed.”

The MSK data, in combination with data from the other countries, leave researchers with more questions, Voigt said.

How does prior-immunotherapy affect COVID-19 infections? What is the

impact of calibrated or reduced-dose chemotherapy? And what about the socioeconomic status of patients and characteristics of race, ethnicity, or limited-English proficiency?

“The deleterious effects of cancer and COVID-19 appear obvious. In fact, we have a higher incidence of cancer and cancer-related mortality as well as a high incidence of COVID-19 and COVID-19-related mortality, for African Americans and Hispanics, compared to the white population,” Voigt said.

The pandemic has created the perfect condition for suboptimal care and treatment for underserved populations, Voigt said.

“The decisions being made by many health care professionals are sometimes driven by fear and emotions rather than evolving facts,” Voigt said. “That should be a calling to all of us caring

for patients, particularly patients with cancer, because our obligations for a more robust safety net for this vulnerable groups of patients remain, and become, in fact, more needed—as defined by ASCO, by AACR, by ACS and by NCI.”

“We need to be careful, because the reality may be more complex and we need more time and more data,” Voigt said.

Breaking down the data by country

Two of the studies presented during the virtual session were from Wuhan. The first, *The experience of treating patients with cancer during the COVID-19 pandemic in China*, presented by Li Zhang of Tongji Medical College, defined the clinical characteristics of cancer patients with COVID-19 in three Wuhan hospitals from Jan. 13 through Feb. 26.



Severe Events in 105 Cancer Patients for Each Types of Cancer

Cancer types	Total number	Death n%	Average time to death	ICU admission n%	Average time to ICU	Critical symptom n%	Average time to critical	IMV n%	Average time to IMV
Lung cancer	22/20.95%	18.18	16.75/8.17	27.27	10.00/6.82	50.00	8.55/5.71	18.18	14.50/6.98
Gastrointestinal cancer	13/12.38%	7.69	24.0/NA	23.08	9.05/6.16	30.77	8.50/5.85	7.69	22.00/NA
Breast cancer	11/10.48%	0.00	NA/NA	0.00	NA/NA	18.18	12.00/7.00	0.00	NA/NA
Thyroid cancer	11/10.48%	0.00	NA/NA	0.00	NA/NA	9.09	8.00/NA	0.00	NA/NA
Blood cancer	9/8.57%	33.33	19.33/1.89	44.44	2.82/1.80	66.67	3.83/3.08	22.22	9.00/NA
Cervix cancer	6/5.71%	0.00	NA/NA	16.67	4.00/NA	33.33	7.00/3.00	0.00	NA/NA
Esophagus cancer	6/5.71%	16.67	28.00/NA	33.33	9.52/0.50	50.00	7.33/2.05	16.67	16.00/NA
All cancer	105/100%	11.43	19.92/6.13	19.05	6.51/4.16	34.29	7.56/5.2	9.52	14.56/5.68



Source: Presented by Hongbing Cai at AACR virtual annual meeting |

Specifically, the researchers followed 124 cancer patients with immune checkpoint inhibitors, and their families, for their infection rate and clinical outcome. The study included 28 COVID-19 patients who also had cancer, with a median age of 65 years. Seven (25%) of the patients had lung cancer, and eight (28.6%) had been infected while they were in the hospital.

Fifteen (53.6%) patients had severe events with a mortality rate of 28.6%. The last anti-tumor treatment within 14 days from the diagnoses of COVID-19 significantly increased risk of developing severe events (HR=4.079, 95%CI 1.086-15.322, P=0.037). The common chest CT findings were ground-glass opacity (21, 75.0%) and patchy consolidation (13, 46.3%). The patchy consolidation on CT had a higher risk for developing severe events (HR=5.438, 95%CI 1.498-19.748, P=0.010).

Only one patient (1/124, 0.8%), who had been on immune-checkpoint inhibitor treatment for his metastatic hepatocellular carcinoma and tested positive COVID-19 infection, had mild clinic presentation and a short hospital course.

“Cancer patients with COVID-19 presented poor outcomes with higher occurrence of clinical severe events and mortality. The antitumor treatment within 14 days of COVID-19 diagnosis increased the risk of developing severe events,” Zhang said at the session. “Limited information did not suggest cancer patients treated with immune checkpoint inhibitors were more vulnerable to the COVID infection, or with worse outcomes compared to the others.”

The second study, *Patients with cancer appear more vulnerable to SARS-COV-2: A multi-center study during the COVID-19 outbreak*, presented by Hongbing Cai, of Zhongnan Hospital of Wuhan Univer-

sity in Wuhan, observed the effects of COVID-19 on cancer patients, and categorized these by cancer type.

The study included 105 cancer patients and 536 age-matched non-cancer patients with confirmed COVID-19. Results showed COVID-19 patients with cancer had higher risks in all severe outcomes. The most frequent cancer types were lung, 22 (20.95%) of 105 patients, gastrointestinal, 13 (12.38%) of 105 patients, breast 11 (10.48%) of 105 patients, thyroid cancer 11 (10.48%) of 105 patients, and hematological cancer, nine (8.57%) of 105 patients.

Three out of nine patients (33.33%) with hematologic malignancies died. Four out of 22 patients with lung cancer died, with a mortality rate of 8.18%.

“It’s a very small sample size, and it’s heterogeneous,” Noah Merin, assistant

CHARACTERISTICS OF CANCER PATIENTS WITH COVID-19 BY BARLESI ET AL.

Cancer characteristics

		N=137 (%)
Solid tumor, n=119	Breast	23 (19.3%)
	Gastro Intestinal (GI)	18 (15.1%)
	Head and Neck	17 (14.3%)
	Genito-urinary (GU)	17 (14.3%)
	Gynecological	17 (14.3%)
	Thoracic	12 (10.1%)
	Dermatology	9 (7.6%)
	Others (endocrine, CNS, ACUP)	6 (5%)
Hematology, n=24	Mature B cell neoplasms/Myeloma	15 (62.5%)/4 (16.7%)
	Acute Myeloid Leukemia (AML)	4 (16.7%)
	Hodgkin Lymphoma	3 (12.5%)
	Others (MDS)	2 (8.4%)
Current Status (Unk, n=2)	Remission/Curative intent	56 (41.5%)
	Active advanced disease	79 (58.5%)

24/04/2020 Outcomes of cancer patients infected with COVID-19 at Gustave Roussy Cancer Center 11

Source: Presented by Fabrice Barlesi at AACR virtual annual meeting I

professor of medicine in the Clinical Scholar Track Blood and Marrow Transplantation Program at Cedars-Sinai Medical Center, said to *The Cancer Letter*. “Leukemia includes myeloid leukemia as well as one lymphoid leukemia, and then lymphoma and multiple myeloma are both lymphoid malignancies.”

“Those of us who treat hematologic malignancies are really interested to know whether patients who have low neutrophils, so monocytes, patients who may have consequences of myeloid malignancies, or targeting of myeloid diseases, have a different outcome from patients who have lymphoid malignancies,” Merin said. “Because it is a different type of an immunocompromised state that they’re in. It determines whether they have lower T-cell or hemo-immunity, versus lower myeloid immunity.”

The study included a similarly high in-hospital infection rate to the first study, at 19.04% for cancer patients, and 1.49% for non-cancer patients. The study found that We found that patients with metastatic cancer had even higher risks of death (OR 5.58, 95% CI [1.71, 18.23]; $p=0.01$), ICU admission (OR 6.59, 95% CI [2.32, 18.72]; $p<0.01$), having severe conditions (OR 5.97, 95% CI [2.24, 15.91]; $p<0.01$), and use of invasive mechanical ventilation (OR 55.42, 95% CI [13.21, 232.47]; $p<0.01$). In contrast, patients with non-metastatic cancer did not demonstrate statistically significant differences compared with patients without cancer, all with p values > 0.05 .

Additionally, patients who received surgery had higher risks of having severe events, while patients with only radiotherapy did not demonstrate significant differences in severe events when compared to patients without cancer.

“The data from Wuhan, for example, of hospital-acquired infections and patients with cancer were 10 times greater than they were for patients without cancer. In certain cancers, were particularly—COVID-19 was particularly lethal. But again, the numbers were small,” Lichtenfeld said.

Conflicting conclusions from France

Fabrice Barlesi of Gustave Roussy Cancer Center in Villejuif, France, found that the coronavirus didn’t pose a greater risk to cancer patients who underwent treatment for COVID-19.

He presented the findings from the abstract titled *Outcome of cancer patients infected with COVID-19, including toxicity*

COMPLICATIONS IN CANCER PATIENTS WITH COVID-19 BY GARASSINO ET AL.

Complications - no./total no. (%)	All
Pneumonia/Pneumonitis	125/157 (79.6)
ARDS	42/157 (26.8)
Sepsis	8/157 (5.1)
Coagulopathy	8/157 (5.1)
Arrhythmia	3/157 (1.9)
Heart Failure	1/157 (0.6)
Multi-organ Failure	12/157 (7.6)
Bacterial infection	6/157 (3.8)
Other	15/157 (9.6)
Hospitalization -no./total no.(%)	
Yes	152 (76.0)
No	48 (24.0)
Death (during hospitalization, ICU or at home)	
Yes	66/191 (34.6)
No	125/191 (65.4)

Source: Presented by Marina Garassino at AACR virtual annual meeting I

of cancer treatments. At peak infection, more than 13,000 patients were positive for COVID-19 in the Paris area, Barlesi said.

Gustave Roussy tested 1,302 patients for COVID-19, and 12% were found positive. The study included 137 cancer patients diagnosed with COVID-19. The primary endpoint of this analysis was the clinical deterioration, defined as the need for oxygen supplementation of 6 l/min or more, or death of any cause.

Most COVID-19-positive cancer patients were female (58%), with a median age of 61 years, including 36 pts (26%) \geq 70 years. Most frequent underlying cancers were solid tumors (115) including breast (23), gastrointestinal (18), head and neck (17), genitourinary (17), gynecologic (17) malignancies or hemopathies (22).

At time of diagnosis, 79 patients (58%) had metastatic/active cancer, and 56 pts (41%) were considered in remission/treated with curative intent. The diagnosis of SARS-CoV-2 infection was made by RT-PCR or thoracic CT scan alone in 93.4% and 6.6% of the cases, respectively.

Clinical deterioration occurred in 34 pts (24.8%) and was associated with hematological underlying disease, CRP at diagnosis of COVID-19 >50 and the use of cytotoxic chemotherapy within less than three months. At data cut-off April 20, 95 (69.3%), 20 (14.6%), and 22 (16.1%) patients were discharged, had died, or were still hospitalized, respectively, according to the abstract.

All the deaths were considered related to SARS-CoV-2 infection.

TERAVOLT: COVID-19 patients with lung cancer

Given that patients with thoracic malignancies have been shown to be at particularly high-risk—for example, in the Wuhan data—researchers from Italy created a global registry called TERA-VOLT (Thoracic cancerERs international coVid 19 cOLLaboraTion) to provide guidance to oncologists managing thoracic malignancies in the time of COVID-19.

Thoracic cancer patients are thought to be at particular risk given the number of potential risk factors: older age, smoking habits, pre-existing cardio-pulmonary concomitant comorbidities, and intensive therapies administered to treat their illness, Marina Chiara Garassino, of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, said during the session.

Garassino presented *TERAVOLT (Thoracic cancers international coVid 19 cOLlabora-Tion): First results of a global collaboration to address the impact of COVID-19 in patients with thoracic malignancies.*

The TERAVOLT study includes 200 patients who have COVID-19 and thoracic cancers, from eight countries. The median age of patients is 68 years, and 29.5% are women. The most common histology was non-small cell lung cancer, in 75.5% of patients, and small cell lung cancer, in 14.5% of patients. The majority of these patients, 73.5%, had stage IV disease.

Systemic therapies were done in 147 out of 200 (73.5%) patients and included 19%, 32.7% and 23.1% of patients on TKI alone, chemotherapy alone, and immunotherapy alone—13.6% of patients were on a chemotherapy-immunotherapy combination. 152 (76.0%) patients were hospitalized and 66 (33.3%) died. The majority were not offered intensive care therapy.

Univariate analyses revealed that the presence of COPD, was associated with increased risk of hospitalization, and more than one comorbidity with increased risk of hospitalization and death. Tumor type and cancer therapy did not impact survival.

The second study from Italy, *Experience in using oncology drugs in patients with COVID-19*, presented by Paolo A. Ascierto, of Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, focused on treatment of cancer patients with COVID-19.

“It’s important to be cautious and not panic, we need to keep everybody safe, patients and physicians—and we can use drugs that we normally use in oncology to treat the cytokine storm. This treatment will be essential for these patients,” Ascierto said.

Data from Spain

At the Octubre University Hospital in Madrid, 90 of cancer patients admitted to the hospital had been treated for the disease. Carlos Gomez-Martin, of Octubre University Hospital, found that lung, gastrointestinal, and breast were the three most common cancers in 63 observed cancer patients with COVID-19.

Martin presented on the abstract *Adapting oncologic practice to COVID19 outbreak: From outpatient triage to risk assessment for specific treatment in Madrid, Spain.* Of these 63 cancer patients with COVID-19, 52 (82%) had metastatic disease, and 11 (18%) had non-metastatic cancer.

Thirty six patients (58%) were on active chemotherapy, 17 (26%) were on other treatment, and eight (12%) were receiving immunotherapy.

A total of 16 patients (25%) died of COVID-19, with a mean overall survival of 12.4 days. Thirty four (54%) patients developed respiratory failure, and 24 patients (38%) experienced acute respiratory distress syndrome—66% of patients who developed ARDS died.

What does it all mean?

These limited studies provide new information for how oncologists should treat their cancer patients who test positive for COVID-19, but the data are nowhere close to definitive.

“The further you go down into the sub-categories, again, it is information that can help guide you, but it shouldn’t be the only information you follow or be significantly practice-changing,” Reckamp said to *The Cancer Letter*. “It’s helpful now that we’re getting some data from other centers around the world, so we understand some local issues.”



The further you go down into the subcategories, again, it is information that can help guide you, but it shouldn’t be the only information you follow or be significantly practice changing.



—Karen Reckamp

Although there are conflicts in the data—particularly the different outcomes for patients with cancer in China versus Europe—“overall, that data supports what we have been saying and what we have believed. And that is the cancer patients are at greater risk,” Lichtenfeld said to *The Cancer Letter*.

In the United States, the COVID-19 pandemic continues to peak at different times in different states, counties, and communities.

“We’re wondering how to integrate our desire to treat someone with the amount of immunosuppression it causes with the level of activity that’s in their community,” Merin said to *The Cancer Letter*. “In other words, it might be safe for us to do stem cell transplants in Los Angeles, but not in New York.

“How does a national board, a national body, give recommendations at a national level, when the conditions with the outbreaks are so variable across the country?”

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Ribas spoke with
Alexandria Carolan, a reporter
with The Cancer Letter.

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CONVERSATION WITH
THE CANCER LETTER

With 61,000 people registered, first-ever virtual AACR annual meeting “enthusiastically received”

“

It's clear that my term as president of AACR is going to be marked by how to respond to the COVID-19 pandemic. There's no way that we can go on with cancer research and develop new treatments if this pandemic is not under control.

”



Antoni Ribas, MD, PhD

President-elect, AACR;

Professor of medicine, professor of surgery, professor of molecular and medical pharmacology, University of California Los Angeles;

Director, Tumor Immunology Program, Jonsson Comprehensive Cancer Center;

Chair, Melanoma Committee, SWOG

Nobody knew how to even begin to predict the number of people who would register for the first-ever virtual annual meeting of the American Association for Cancer Research.

There was no registration fee, no travel, no need for hotels—but also no revenues for the professional society.

When over 61,000 people registered online from 140 counties—nearly three times the number who usually come to the in-person Annual Meeting—Antoni Ribas, MD, PhD, Program Chair for the AACR Annual Meeting 2020 and AACR President-Elect., was immensely excited that the this first virtual meeting was so enthusiastically received by the global cancer community.

“An AACR Annual Meeting usually draws an attendance of nearly 23,000 scientists and clinicians in all subdisciplines of cancer research. This one had over 61,000 registrants, and at peak sessions, there were about 24,000 people viewing the talks at the same time,” Ribas, a professor of medicine, professor of surgery, and professor of molecular and medical pharmacology at the University of California Los Angeles, director of the Tumor Immunology Program at the Jonsson Comprehensive Cancer Center, and chair of the Melanoma Committee at SWOG, said to *The Cancer Letter*.

“This is unprecedented. I could not have predicted that this would happen,” Ribas said. “We were just trying to make sure that important clinical and scientific information was rapidly disseminated and find the best platform for it to release data that could not wait for a later replacement meeting. It was all done in a short period of time and we were thrilled that the platform held up.”

AACR didn't charge for registration this year. Because of financial and other challenges being faced by cancer

researchers dealing with the COVID-19 crisis, AACR felt that offering the annual meeting free to registrants was an important decision, Ribas said.

According to tax documents, conferences and workshops were the highest source of revenue for the association, contributing \$25.6 million to AACR's \$60.3 million gross receipts in 2018, the most recent year for which a filing is available. This figure includes all conferences and workshops and doesn't include the cost of these events.

The virtual meeting marks the beginning of a transition for oncology conferences from in-person to online—only one change among many that have been made in light of the COVID-19 pandemic. Ribas is expected to be named president of AACR within the next week, and will face the task of leading the organization in a time when the future of clinical trials, drug approvals, and even the number of people in the field are in question.

In July, AACR plans to hold a COVID-19 and Cancer virtual meeting.

“We're going to emerge out of this, and it's going to be the same principles that we've had so far, where science and knowledge will allow us to move forward, and it will be applied to the pandemic, it will be applied to cancer research and to cancer treatment,” Ribas said.

Ribas spoke with Alexandria Carolan, a reporter with *The Cancer Letter*.

Alex Carolan: Based on the meeting this week, what do you think the future of oncology meetings will look like?

Antoni Ribas: This was an unexpected success in regard to the number of registrants. There was no way I could have predicted this huge number if you had asked me a month ago.

This was the first-of-its-kind virtual meeting where AACR was presenting mostly clinical research that needed to be released without delay.

It's usually an important part of the program, and it was exciting to have these top clinical trials presented along with the science behind them for the community to enjoy.

For example, we saw the pembrolizumab every six weeks [regimen] approved by the FDA Tuesday, right after it was presented at the AACR virtual meeting.

There are clinical trials that, once presented, lead to next steps, with people saying that “that's the way to go” or “no, that's not the way to go.”

So, we couldn't just sit on these important data. That's why we imposed on ourselves to create something that hasn't been done before, and make it freely available to everyone.

We were excited to provide a scientific program with many sessions but we knew it would be a big challenge to organize it in such a short period of time.

An AACR Annual Meeting usually draws an attendance of nearly 23,000 scientists and clinicians in all subdisciplines of cancer research. This one had over 61,000 registrants, and at peak sessions, there were about 24,000 people viewing the talks at the same time.

This is unprecedented. I could not have predicted that this would happen. We were just trying to make sure that important clinical and scientific information was rapidly disseminated and find the best platform for it to release data that could not wait for a later replace-

ment meeting. It was all done in a short period of time and we were thrilled that the platform held up.

But overall, the platform held up to the massive audience.

We're in an unprecedented pandemic, and AACR is facing much of the same challenges that the rest of the world is. What's the biggest challenge you'll have to face at AACR once you are president?

AR: It's clear that my term as president of AACR is going to be marked by how to respond to the COVID-19 pandemic.

There's no way that we can go on with cancer research and develop new treatments if this pandemic is not under control. Clearly, cancer will not disappear while there's a coronavirus pandemic, so we have to be able to keep our focus on both diseases.

I think the cancer research field has a lot to contribute to fighting the pandemic, and we need to do that so in order to get on with our mission and our goals.

In regards to cancer, we are suddenly seeing population-level disease drops in mortality, and the quality of drugs and treatment is improving. Will COVID-19 stop this, or slow it?

AR: It will temporarily slow it. The majority of gains of the last several decades in fighting cancer have all been driven by science and applying scientific

knowledge to patients, which is at the core of what our organization does.

Most research labs have been asked to stop what they're doing, because we can't have people working closely together, propagating a virus. It's a logical thing to have social distancing and that we don't continue to work the same way right now, because all we would be doing is feeding the virus as opposed to fighting cancer.

The temporary closing of research labs is a way to fight cancer, because we need to deal with the immediate problem—the pandemic—while at the same time working on cancer.

Labs have been shuttered, because they're considered non-essential right now. What does this mean?

AR: It means that we're fighting in a different way. We have to adapt to this new reality. We cannot have people close together and allow the virus to go from one person to another, making some people really sick as we could then not be fighting cancer.

Meanwhile, patients with cancer continue to have cancer, and that's where we're really struggling to find the right balance between providing care and doing the things that patients need, or exposing them and others to the spread of this virus.

It's a troubling time where patients are afraid to go to have their blood drawn, to go to the clinic to have infusion, to have the surgery that would benefit them in treating their cancer, to have chemotherapy or immunotherapy or radiation therapy. That gives options to the cancer that we would otherwise be treating.

It's very difficult to find this balance, and we're now acting with the idea of a short-term plan, but we don't know what the future holds. If it's going to be longer, then we'll have to change many things that we have been doing.

At the same time, this virus has triggered a lot of innovation in a very short time. It's amazing how we've gone from doing everything in person, face-to-face, having people coming in, flying from other places to just see the doctor—to now having telemedicine for the majority of patients.

I have clinic this afternoon, and the majority of my patient visits are on phone or video calls. We're providing results this way. We're discussing treatments this way. This will trigger more home care, and not having people go to the infusion room, but instead have the infusion brought to them. It's allowing treatments to be given in a different way.

We're decreasing the time that patients are going to see the doctors in person and getting infusions in order to try to decrease the pandemic, and that's why telemedicine will be a lasting benefit from a terrible thing, which is this COVID-19 pandemic.

Do you see oncology being more inclusive with telemedicine in the future? How will this change how you treat patients?

AR: That has two potential answers, because, yes, bringing care to people closer to home will make it more inclusive to more people, but then there are people who are at a disadvantage and more vulnerable with everything that's happening because they do not have access to the internet and to telemedicine do not benefit.

Their care is being delayed until they go and see somebody in person, and these visits are delayed. This virus is disproportionately affecting people with low socioeconomic status and certain ethnicities.

Therefore, the disparities in care are now even more extreme, because the virus is affecting everybody—but the more vulnerable are affected more, because they have less access to care and less ability to do social distancing and to benefit from telemedicine.

We have to be very proactive about this. This is a major problem that all of us are facing in the field. AACR is working on a report about disparities in cancer and health care. A new chapter is going to be added to cover disparities in COVID-19 infections and cancer.

Obviously, these disparities will likely be demonstrated in cancer down the line. What will this look like?

AR: People with comorbid conditions, hypertension, diabetes—especially if not well-controlled—with less access to care are at high risk for complications. It's all these issues that make the vulnerable more vulnerable, especially now.

Let's talk about the research. We've seen growth in cancer care and research, and you said how COVID-19 might slow this. What can AACR do to help?

AR: If we think about this virus and we think about cancer, there are a lot of similarities.

Cancer is a disease of dysfunctional proteins that are doing something that's bad for the body. That's also what the SARS-CoV-2 virus does. It has a series of proteins that infect cells, it starts making dysfunctional proteins that are allowing the virus to expand, and the virus interplays with the inflammatory response and the immune system, the same as cancer cells.

The same principles that have been used to advance treatment of cancer are being used to address the COVID-19 pandemic.

Using drugs that inhibit proteins of the virus is the same concept as a targeted drug for a mutation in cancer, where there's one protein that has certain functions that need to be stopped. Chemists make drugs that specifically block the function of that protein—whether it's a virus protein or a mutated protein—and then it is developed clinically, in clinical trials.

The virus induces inflammatory processes that are leading to worse complications, the respiratory distress syndrome and others.

Those inflammatory processes are the same that cancer cells use to feed themselves to grow within a tumor microenvironment. Then the immune system, the immune cells, the T cells and the B cells, the ones we have learned to unleash to fight cancer, are also the ones that protect us from viral infections.

Sequencing genomes has been mostly applied to cancer, and we're now seeing information about how to use those same sequencing methods to track the virus that also changes over time, as cancer does. I'm sure this sequencing knowledge will help us make better tests that can be done more in parallel, with genetic barcodes, so we can test more people faster, as opposed to looking for parts of the virus with a PCR or an antibody test.

The diagnostics field of cancer can provide a lot of knowledge about how to do these tests in a completely different way that I hope will allow universal testing in the near future.

And what do you expect from NCI during the COVID-19 crisis? How should they respond?

AR: Dr. Dinah Singer, deputy director for scientific strategy and development, gave an address at the end of the AACR virtual meeting, where she assured the attendees that the NCI is very aware of the critical needs that are happening now, where research labs are being closed and people are sent home without active hands-on research.

But there are other ways that they are contributing to all of this. It was clear that the NCI has decided that they do not want to dismantle the cancer research workforce.

The personal costs would be terrible if the cancer research workforce would be abandoned, just because temporarily cancer scientists cannot show up in person to do what—to hold a pipette? But we continue doing research in different ways during this lockdown.

The National Cancer Institute has made it clear that grants will continue, that they will adapt the timelines, and that the expectations for research results will be adjusted—giving assurances that we're fighting the virus and continuing to fight cancer in the same way by putting a hold on in-campus, hands-on research.

With regard to cancer research, obviously cancer isn't going to stop for COVID-19. Patients are still receiving treatment, and their disease still takes priority. But is oncology going to lose trainees to other specialties now that COVID-19 is in play? Is this an issue?

AR: I'm hopeful that this is going to be a period a time—albeit, a painful, very painful one, after which we'll go back to some form of normality whenever we have better testing, vaccines, and treatment for COVID-19.

Once we do that, then I hope that the federal government and everyone in academia and industry will think about what happened and work to prevent another pandemic.

But the value of the things we were doing before the pandemic will not have gone away, and one of the top ones will continue to be fighting cancer. So, I don't think this is going to take people away from careers in cancer research and treatment.

It will just make it difficult for a period of time, the same way our lives have been disrupted in so many other things that we were doing.

How are you and your institution navigating COVID-19? What changes have you made?

AR: We immediately made changes. We tried to have fewer people together and make sure that we safeguard our patients and try to avoid any exposure

of patients to a potential infection, and also the other way around, to protect health care workers from potential infections.

It's now harder to enroll patients in clinical trials, because we have less support staff on site, and we're less able to do tests and scans, biopsies, and infusions. All of this is a detriment to patients whose best option was to be in a clinical trial, and who could benefit in the treatment of the disease.

That is a difficult thing that we're going through. We have not completely closed clinical research; we're maintaining it in a scaled-down process. Within our research groups, we've decided which are the top-priority clinical trials, and what staff was needed to keep them open, and still put patients on studies.

In some places, they've had to completely stop this approach. The peak in Los Angeles and California has not been as bad as in the East Coast, because of early implementation of social distancing—also because our geographical environment and weather allow more social distancing, just naturally.

So, we're not seeing this big influx of patients with COVID-19 infections that could have happened if nothing had been done.

We touched on the labs issue earlier, but have labs at UCLA been shuttered because they're considered non-essential?

AR: Yes. That was the right thing to do. Within a period of three or four days we were asked to close all research labs for non-essential work. If we kept any projects ongoing, we had to justify it and request special permission from our departments and our dean's office.

But we all made a plan on how to continue the essential research and not start new research. We made contingency plans to make sure that people came in sequentially, not in groups, that several people were not in the same room, and that all communications were done electronically by phone, by internet, by email, by Zoom meetings.

All of that has avoided outbreaks in the research labs, which, if that had happened, would have been worse and caused further delay in cancer research.

That's a good point. Could you describe what's going on in clinical trials in the cancer world?

AR: There are different directives that different drug companies have given on how to proceed with their clinical trials.

Most have sent notifications saying, "we understand what you're going through, we understand that it's hard to follow the protocol as it was written at this time."

Not having access to certain things done for research as opposed to strictly patient care, there are going to be deviations to protocols—something we always want to avoid, but now they're really necessary.

There have been organizations that have been even more proactive, like the NCI-funded cooperative groups, the one I know is SWOG, which has provided general directives of what to do during the pandemic.

How patients benefit should be above the protocols to be flexible with skipping visits, sending drugs to the patients' homes, which used to be pro-

hibited. Patients had to come and they had to get their bottle of pills that we had counted. Now we can send them to their homes.

Doing telemedicine visits, as opposed to having people coming to the office, giving infusions of treatments taking into consideration the risk and the benefit based on whether the physician and the patient agree to what is best, which is allowed during this period of time, and the patient will be able to continue the clinical trial and not be kicked out because they missed that time point and then cannot do the next one.

So, all of this evolved very rapidly. What we needed to do was to avoid the propagation of the virus so we could, short-term and long-term, do better for everyone.

And what's happening with drug approvals in oncology?

AR: I assume it's going to be harder to provide the data on clinical trials. The analysis of the data will be harder or delayed.

All the clinical data have to be looked at carefully to be sure that there are no errors and that there's no wrong information being entered—so, you need monitors going to the sites, rolling up their sleeves, and looking at all the source documents. That will not happen for a while.

So, I would assume that some of the clinical trials and approvals may be delayed, but meanwhile, the data that have been generated before can be worked on and analyzed better during this period of time where you're not piling on more information.

I think in the short-term, it should not have an impact on new drug approvals. In the mid-term, we may see a gap and delay in some of the approvals.

Tuesday's session at AACR on COVID-19 and cancer was really interesting because it brought together the perspective of all of these different countries, and how they have been dealing with the virus in regards to cancer. What do the data from yesterday tell us about COVID-19 disease and cancer?

AR: This is something where I pushed for with my colleagues at the AACR. I thought we had to do something like this.

We had to go to the people who have been at the front lines of this problem and who have gathered information, so I contacted colleagues I know and asked to let me know who the best speakers are on various important topics.

I consider all of the people who talked in this session to be true heroes of cancer research. They were risking their lives taking care of patients before they knew what this virus was about, especially the ones from Wuhan and Northern Italy.

Not only did they do this, but they took care to collect information about what was happening to their patients. This all has its benefits and its limitations, because the information cannot be comprehensive at this juncture.

It has the biases of how those patients got to them, what they did or did not collect, and what are potential outcomes of the patients who didn't get to them, which leads to different views that are

probably related to how the data have been available to these investigators.

My general view—and I tried to bring it up in the discussion—was that we have two different messages: the one from the two presenters from Wuhan saying that patients with cancer do worse with COVID-19 infections.

That contrasts with the data that were provided from Italy, from France, and from Spain—where a cancer diagnosis was not an adverse prognostic factor for having a bad outcome with the COVID-19 infection.

It was patients who had comorbid conditions—in particular in the lungs, patients who have chronic lung inflammatory disease are also more likely to have lung cancer, both linked to cigarette smoking. Comorbid conditions like hypertension and obesity also led to higher risk of cancer, and those are also bad risk factors for COVID-19 outcomes.

And then the risk factors that were cancer-specific, like having received chemotherapy within a short period of time, as well as hematological malignancies which commonly receive frequent chemotherapy that leads to decreased white blood cell counts, decreased lymphocytes, that may make it difficult to control virus spread.

I'm going through this long explanation to say that the different information from China and from Europe may be based on referral patterns, type of disease, and comorbid conditions.

In the European series, the patients who had a prior cancer but are not being actively treated for it, did not do worse than the patients who were actively treated unless they had a very recent chemotherapy or a hematologic cancer.

You talked about how you pushed for this session yesterday to bring all these different perspectives together, and as you mentioned, some of them had different conclusions. What does this say about the role AACR meetings have during this pandemic?

AR: I think one of our roles is to disseminate knowledge and provide the forum for reliable information, and that's why we didn't want to have just one presentation from one place.

We wanted to have a balance of all information by going to the people who would more likely have information that could be presented.

We'll have another "COVID-19 and Cancer" session in the June AACR Virtual Meeting, and we're planning a dedicated "COVID-19 and Cancer" conference in July—where we're going to issue a call for abstracts that will be peer-reviewed in the same way that AACR has always done it.

The current information is mostly hypothesis-generating, but it's also providing information on what's happening, so people can incorporate that information and then make prospective plans that will really generate robust new information and help in management and treatment decisions.

Based on the meeting this week, what do you think the future of oncology meetings will look like?

AR: It turns out that people really wanted to get information, and most of it about cancer research and trials results, with a limited set of basic and translational science sessions.

The June 22-24 AACR Virtual Annual Meeting II will be ten times bigger than this one. What will happen next year?

Well, I do not think that in-person meetings will disappear, because there's a lot of other things that go on at an in-person meeting: the networking; the trainees getting to show their data in poster and oral sessions to develop their careers and network with senior investigators; the interactions that occur between industry colleagues and academics, as well as between companies that have a drug or a pathway or a diagnostic because they see each other's data.

That needs to be able to happen, because that has helped the field, so I think there's going to be a hybrid between virtual and in-person meetings, and we'll have to see what's the right balance.

Great. Is there anything else you'd like to add?

AR: We're going to emerge out of this and it's going to be the same principles that we've had so far where science and knowledge will allow us to move forward.

It will be applied to the COVID-19 pandemic, and it will be applied to cancer research and cancer treatment.

Well, thank you so much for taking the time to speak with me, Dr. Ribas.

AR: Thanks for your interest in the AACR and our AACR Virtual Annual Meeting.

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Remdesivir established as standard of care for COVID-19, Fauci declares

FDA issues Emergency Use Authorization

By Matthew Bin Han Ong and Paul Goldberg

Early data from two randomized phase III studies of the antiviral drug remdesivir make it a viable treatment for COVID-19.

FDA May 1 issued an [Emergency Use Authorization for remdesivir](#) for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.

The investigational drug was shown in a clinical trial to shorten the time to recovery in some patients.

“Whenever you have clear-cut evidence that a drug works, you have an ethical obligation to immediately let the people who are in the placebo group know, so that they could have access. And all of the other trials that are taking place, now have a new standard of care,” Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, said in a press conference at the White House April 29, when the two positive studies were reported.

In one of the two studies, an NIH-sponsored randomized, placebo-controlled trial involving over 1,000 hospitalized patients with advanced COVID-19 and lung involvement, patients who received remdesivir recovered faster than similar patients who received placebo (*The Cancer Letter*, [April 24, 2020](#)).

“I do believe that there is most likely a two-step process, with potentially the EUA being granted, and then moving onto the full approval,” Daniel O’Day, Gilead’s CEO and chairman of the board of directors, said in an earnings call April 30.

In another study, conducted by the drug’s sponsor, Gilead Sciences Inc., patients with severe manifestations of COVID-19 receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a five-day

treatment course. The study enrolled 397 patients.

However, in a third trial, conducted in China, remdesivir didn’t produce an advantage in time to clinical improvement in patients with severe COVID-19. [The study](#), in which 237 patients were randomized 2:1 to remdesivir vs. placebo, was published in *The Lancet* on April 29.

“Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early,” the study states, pointing to accrual problems. “Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less.”

According to an [update](#) published on ClinicalTrials.gov, the China trial is one

of two remdesivir trials by the Capital Medical University in Beijing that were ended or halted, because “the epidemic of COVID-19 has been controlled well in China, [and] no eligible patients can be enrolled at present.”

The NIH trial, called the Adaptive COVID-19 Treatment Trial, or ACTT, is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID).

An independent data and safety monitoring board overseeing ACTT met on April 27 to review the data, concluding that remdesivir was better than the standard of care from the perspective of the primary endpoint, time to recovery. Recovery, a metric often used in influenza trials, was defined as being well enough for hospital discharge or returning to normal activity level.

According to preliminary results, patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p < 0.001$). The median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p = 0.059$).

“That’s sort of good. All I saw in the report was that there was no difference, but that meant no statistical difference,” said Don Berry, professor in the Department of Biostatistics and founding chair of that department at MD Anderson Cancer Center, said to *The Cancer Letter*. “In fact, it was a 3%-point difference in mortality, which is suggestive.”

According to NIAID, FDA has been engaged in sustained and ongoing discussions with Gilead regarding making remdesivir available to patients.

“It’s strong enough for what FDA would approve it for,” said Berry, who is also

senior statistical scientist and founder of Berry Consultants, a company that is playing a key role in providing statistical guidance for multiple COVID-19 trials. “They would say this extends or this shortens the time to recovery, and it’s based on the statistical significance of shortening the time to recovery.

“It’s all depending on the indication. It won’t say, ‘Take this if you don’t want to die.’”

The ACTT trial is designed to incorporate additional arms.

“Unlike traditional drug development, we are attempting to evaluate an investigational agent alongside an evolving global pandemic,” Merdad Parsey, Gilead’s chief medical officer, said in a statement. “Multiple concurrent studies are helping inform whether remdesivir is a safe and effective treatment for COVID-19 and how to best utilize the drug.

“These study results complement data from the placebo-controlled study of remdesivir conducted by the National Institute for Allergy and Infectious Diseases and help to determine the optimal duration of treatment with remdesivir.

“The study demonstrates the potential for some patients to be treated with a 5-day regimen, which could significantly expand the number of patients who could be treated with our current supply of remdesivir. This is particularly important in the setting of a pandemic, to help hospitals and health care workers treat more patients in urgent need of care.”

The Gilead trial sought to determine whether a 5-day course is similar to the 10-day regimen. Secondary endpoints were the rates of adverse events and additional measures of clinical response. The trial, which focused solely on patients who had severe manifestations of COVID-19, did not randomize patients

to a control arm, with only placebo or standard of care treatment.

“I guess they felt they couldn’t give placebo, so they were looking at a dose effect or a dose duration effect,” Berry said.

Patients had evidence of pneumonia and reduced oxygen levels that did not require mechanical ventilation at the time of study entry. Clinical improvement was defined as an improvement of two or more points from baseline on a predefined seven-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support and medical care or were discharged from the hospital.

“So, we are, and the team is, in constant information exchange with the agency right now and they’re getting information from us, obviously from NIH on the NIAID trial,” O’Day said. “There’s a big sense of urgency here, I think. FDA understands the importance of reacting quickly to this. And so, it’s intense right now. We think the FDA will move quite quickly on their decision-making on the labeling side.

“We made a decision to donate 1.5 million vials, which was the entirety of our supply through the early summer.”

The time to clinical improvement for 50 percent of patients was 10 days in the 5-day treatment group and 11 days in the 10-day treatment group. More than half of patients in both treatment groups were discharged from the hospital by Day 14 (5-day: 60.0%, $n = 120/200$ vs. 10-day: 52.3% $n = 103/197$; $p = 0.14$). At Day 14, 64.5 percent ($n = 129/200$) of patients in the 5-day treatment group and 53.8 percent ($n = 106/197$) of patients in the 10-day treatment group achieved clinical recovery.

Clinical outcomes varied by geography. Outside of Italy, the overall mortality rate at Day 14 was 7% ($n = 23/320$) across

EFFICACY AND SAFETY RESULTS FROM GILEAD'S PHASE III SIMPLE TRIAL FOR PATIENTS WITH SEVERE MANIFESTATIONS OF COVID-19

	5-Day RDV n=200	10-Day RDV n=197	Baseline Adjusted p-value ¹
Clinical Efficacy Outcomes at Day 14			
≥ 2-point improvement in ordinal scale	129 (65)	107 (54)	0.16
Clinical recovery	129 (65)	106 (54)	0.17
Discharge	120 (60)	103 (52)	0.44
Death	16 (8)	21 (11)	0.70
Safety			
Any adverse event (AE)	141 (71)	145 (74)	0.86
Grade ≥3 study drug-related AE	8 (4)	10 (5)	0.65
Study drug-related serious adverse event (SAE)	3 (2)	4 (2)	0.73
AE leading to discontinuation	9 (5)	20 (10)	0.07

¹Adjusted for baseline clinical status

both treatment groups, with 64 percent (n=205/320) of patients experiencing clinical improvement at Day 14 and 61% (n=196/320) of patients discharged from the hospital.

Key efficacy and safety results from the Gilead study are included in the table above.

This is one of two randomized, open-label, multi-center phase III trials by Gilead for remdesivir in countries with high prevalence of COVID-19 infection.

In this study, an expansion phase of the study was recently added and will enroll an additional 5,600 patients, including patients on mechanical ventilation. The study is being conducted at 180 trial sites around the world, including sites in the United States, China, France, Germany, Hong Kong, Italy, Japan, Korea, the Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan and the United Kingdom.

A second SIMPLE trial is evaluating the safety and efficacy of 5-day and 10-day dosing durations of remdesivir administered intravenously in patients with moderate manifestations of COVID-19,

compared with standard of care. The results from the first 600 patients of this study are expected at the end of May.

Fauci's April 29 remarks in the Oval Office follow:



A trial that the National Institute of Allergy and Infectious Diseases—which is the institute I direct—sponsored, called the Adaptive COVID-19 Treatment Trial, was started in Feb. 21 of this year, and it was a randomized placebo-controlled trial, com-

paring the Gilead drug remdesivir with a placebo.

It was highly powered, with about 1,090-plus individuals, so it is the first truly high-powered, randomized, placebo-controlled trial. It was an international trial involving multiple sites. The primary endpoint was the “time to recovery,” mainly the ability to be discharged.

The data and safety monitoring board ... notified the study team, namely the multiple investigators who are doing the study throughout the world, that the data shows that remdesivir has a clear-cut significant positive effect in diminishing the time to recovery. This is really quite important, for a number of reasons, and I'll give you the data.

It's highly significant. If you look at the time to recovery, being shorter in the remdesivir arm, it was 11 days, compared to 15 days. And that's a p-value, for the scientists who are listening, of 0.001. So, that's something that, although with 31% improvement—doesn't seem like a knockout, 100%—it is a very important proof of

concept. Because what it is proving, is that a drug can block this virus.

The mortality rate trended towards being better, in the sense of less deaths in the remdesivir group—8% vs. 11% in the placebo group. It has not yet reached statistical significance, but the data needs to be further analyzed.

The reason why we're making the announcement now, is something that, I believe, people don't fully appreciate. Whenever you have clear-cut evidence that a drug works, you have an ethical obligation to immediately let the people who are in the placebo group know, so that they could have access. And all of the other trials that are taking place, now have a new standard of care.

So, we would've normally waited several days to dot the i's and cross the t's, but the data are not going to change. Some of the numbers may change a little, but the conclusion will not change.

When I was looking at this data with our team the other night, it was reminiscent of 34 years ago, in 1986, when we were struggling for drugs for HIV, and we had nothing. And there were a lot of anecdotal reports about things that maybe it did work, and maybe not, and people were taking different kinds of drugs.

And we did the first randomized placebo-controlled trial of AZT, which turned out to give an effect that was modest, but that was not the end-game, because building on that every year after, we did better and better. We had better drugs of the same type, and we had drugs against different targets.

This drug happens to be blocking an enzyme that the virus uses, and that's

an RNA polymerase. But there are a lot of other enzymes that the viruses uses that are now going to be targets for this.

This will be the standard of care. And, in fact, when we look at the other trials we're doing, we're going to do trials with another anti-inflammatory, a monoclonal antibody. We're going to now compare the combination of remdesivir with this.

So, as drugs come in, we're going to see if we can add on that. So, bottom line, you're going to be hearing more details about this; this will be submitted to a peer-reviewed journal and will be peer-reviewed appropriately.

But we think it's really opening the door to the fact that we now have the capability of treating [COVID-19], and I guarantee you, as more people, more companies, more investigators get involved, it's going to get better and better.

Excerpts of remarks by Gilead CEO O'Day and CMO Parsey in the April 30 earnings conference call follow:



Dan O'Day: I'll just make a couple of comments, which was also echoed by Dr. [Anthony] Fauci yesterday,

which is, with the NIAID results and the highly statistically significant reduction in "time to recovery," this now changes the landscape for drug development within COVID-19, being that one has to now think about comparing to remdesivir and/or looking at adding to remdesivir, which I think is exactly what the NIH trial is going to do now, and I'm sure all of our collaborators within the drug development space.

We have been working with them, we're going to continue to work with them on the possible hypotheses around how we might be able to consider, just as one reflects upon HIV decades ago, that remdesivir becomes the base therapy, and one looks to try to improve symptomatology improvement, mortality improvement, expanding patient populations, and so, that is yet another factor that will go into how we determine how best to create a sustainable solution for remdesivir.

But, clearly, all those things, we have been thinking about and now we have to accelerate, now that we have these trial results. More to come on that.



Merdad Parsey: Thanks, Dan. The concentration [of remdesivir] that we're looking for, we think our AC50 in human cells is in the tens of nano-

molar range, and we know our serum concentration gets in the micromolar range. And so, we should be more than adequately covered by achieving those levels with the current dosing paradigm that we have, probably by an order of magnitude, or two.

Certainly, in the serum and based on modeled data in non-human primates as well as mice, we see more than adequate concentrations getting into the lungs of those animals and in vivo efficacy in those animals. And I think the clinical benefits we're seeing suggest that that's exactly what's happening in humans as well. I think we're pretty comfortable with where we are in terms of both dosing and exposure, including in the lung.

DO: There's been a surprising consistency across all the different data elements in our clinical program, from compassionate use to interrogating what we know about the China trial, to the [Gilead] severe trial, to the NIAID trial.

In anticipation of more data

MP: We all were using the parallel construct of influenza for our thinking around remdesivir, which was you got to get in really early, given the viral kinetics in influenza, and getting in too late probably won't have much of an impact. That was certainly our expectation.

However, the wild card here, and what I think we're still learning is, what are the viral kinetics in patients with this virus? How long does that last and how quickly does it go up and how quickly can we have an impact on it?

I think the data, essentially, we are seeing efficacy across both patient

populations, but also across trials that are really all tracking in the same direction, as Dan alluded to, so, even if you look at the China data, the hazard ratios for improvement are consistently positive. The study was underpowered, and I think the hazard ratios we'll probably see from the NIAID study are going to be in the same ballpark, but with an appropriate sample size—they're highly statistically significant.

Similarly, I think when we look at the mortality data and when we look at all of those different factors, this virus seems to be behaving differently. Remdesivir seems to be having efficacy in a relatively broad patient population, so I think we're learning as we go.

We'll learn as more and more data are generated; right? We have our moderate data coming up, where we'll be looking at an even less severely ill patient population, so there'll be more data coming out in that population, that they may add to our knowledge base here to understand the spectrum.

And, as we talked about earlier, understanding the efficacy in the subgroups and the NIAID study will be really interesting in this, and we don't have that information yet, so I think all those data will contribute to our overall understanding of, how early do you need to be in? Do patients who have symptoms for less time do better?

Those are certainly the trends, but there are certainly things to be benefited even in patients who have longer duration of symptoms right now.

DO: To clarify the EUA, under an Emergency Use Authorization, one could charge for the product. We made a decision to donate 1.5 million vials, which was the entirety of our

supply through the early summer, and that's for a variety of uses, right? I mean that's for clinical trials, as one would expect not to charge for those, of course; compassionate use, EIT in other countries.

But also available is that supply for regulatory approvals around the world, and then we'll allocate accordingly until its regulatory approvals come online.

So, yes, it is possible to charge. I would just say that our goal here is to get a full approval for remdesivir. We feel the data supports that and an EUA, therefore, is a step to a more formalized approval.

The reason—the agency and we are talking about that—is that these are extraordinary times; right? So, weeks would make a difference to being able to get medicine to patients by enacting an EUA, if that's what the FDA chooses to do prior to another form of approval.

And so, it's a stepwise approach, which allows us to immediately address the humanitarian need, while still pursuing all the aspects of a normal approval, which we are doing with the FDA. So, I think that's probably the most important point.

We will be answering your questions on the sustainable model for remdesivir in the future, in the near future. We just don't have the answers yet, but we deeply respect and appreciate the fact that when we get into millions of doses, we have to have a sustainable economic model that works here, and that achieves access to affordability for patients around the world. So, more to come on that, if I could turn it over to Merdad on the ventilated treatment approach.

Remdesivir in patients on ventilators

MP: The criticality, this comes down to a timing question; right? It really comes down to how long is viral replication ongoing in the lungs of patients, and how quickly do patients deteriorate to needing mechanical ventilation. Certainly, what we're seeing is that patients are very rapidly deteriorating. Some patients deteriorate rapidly.

And so, getting them antiviral therapy in that timeframe, where it seems that there's still viral replication going on, certainly seems to be benefiting those patients. And probably what's going on, and this is speculation on my part, is by limiting the viral replication, you're going to limit the inflammation, you're going to reduce the number of people who develop lung injury, and you're going to get them off the ventilator faster.

So, the discharge rates that we're seeing, where people are being discharged four days earlier, for example, in the NIAID study, underlying that are patients who are deescalating or need oxygenation and that leads them to getting onto room air more quickly. So, there's a time element in all of this that I think is probably where we're benefiting these patients.

Certainly, if you talk about people who've been ventilated for a week or two weeks, there, the question of whether an antiviral would be beneficial, I think, seems more difficult to tie into what's going on. But again, it comes down to understanding the viral kinetics here. And that's a work in progress, I think, for all of us.

Washington, and drug pricing

DO: I think people have come together in a variety of ways and, certainly, that's also occurred to a certain degree in Washington.

I've spent a decent amount of time in Washington over the past several months, certainly before the shelter-in-place, and I think, even then, there is some change in the rhetoric [about drug pricing].

I think for highly innovative, research-based companies that have immediately shifted their efforts to solutions for the coronavirus—it's pretty impressive, actually, to many of the peers in the industry that I stay in very close touch with—have spared no expense to pivot and shift.

I think at the end of the day, I think this will certainly help the industry's reputation. I think the ability to solve a human crisis like this, because of the decades of investment and the at-risk investment that's done by so many companies, people and the general public will see that. And whether that's treatment, different types of treatments or vaccines, I think that'll be the case.

But I think the tone is different in Washington. I think people are very appreciative and concerned about finding solutions here, and it's brought us all together, which I think is a good thing. I'm not suggesting that there won't continue to be focus and pressure on drug pricing.

Of course, there will be, and we continue to work appropriately to make sure that, in particular, the patients that are bearing the brunt, sometimes, of some of the pharmaceutical pricing that legislation has put into place that supports that, and improves that for

patients. And that we lean in as an industry and as a company to give more that flows through to patients.

So, all of those principles, I think, still apply, but it's being done now in a way where we can have an appreciation for the innovation the industry brings. So, more to come and a lot still to happen this year, with the election coming up, and with other things.

But I think, from a Gilead perspective, we stay focused on innovative medicines and making sure we have access programs, on leaning into legislation that supports the innovative industry and that supports reducing patient out-of-pocket costs. And that would be our focus, accordingly. I hope that gives a little bit of an insight.

FDA approval for remdesivir?

DO: We've been in constant dialogue with [FDA] on remdesivir. We have been working with them on the submission.

They've been open to receiving parts of the submission, which has been very helpful under a normal process. Plus, there's the whole EUA process that kind of goes on top of that. So, yes, the answer is, and you can imagine that, obviously, that's been going on for weeks, and, actually, a couple of months now, but in the past 48 hours is increased in intensity.

We are, and the team is, in constant information exchange with the agency right now and they're getting information from us, obviously from NIH on the NIAID trial. There's a big sense of urgency here, I think.

FDA understands the importance of reacting quickly to this. And so, it's intense right now. We think the FDA

will move quite quickly on their decision-making on the labeling side.

MP: This has been an unprecedented time in terms of our interactions with the regulators, both here in the U.S. As well as outside the U.S. It's been really impressive and truly collaborative, working with the NIH and the FDA in parallel over the past couple of months. We talk constantly and the same is true with the EMA. Same is true with Japan. We're talking to all the regulators in parallel. It's been a pretty unique situation and I think everyone understands the gravity. That's been very helpful in moving forward collaboratively.

DO: The discussions are still ongoing in terms of what's required for a formal approval, but I meant to infer that the NIAID data demonstrate safety and efficacy at a highly statistical level, which is usually the barrier for a full approval. So, that's what we're working with them on.

I don't want to get ahead of the agency on that. But again, I do believe that there is most likely a two-step process, with potentially the EUA being granted, and then moving onto the full approval.

Clinical trial endpoints



Diana Brainard [senior vice president of clinical research at Gilead]: In terms of end points, the NIAID study looked at time to clinical recovery, using a seven-point ordinal scale. The ordinal scale is really tracking throughout most of the major clinical trials right now. But as our understanding of the disease has evolved, the types of endpoints using that scale has evolved.

So, NIAID changed to time to clinical recovery, which basically means no longer requiring medical care within the hospital, getting off of oxygen, or discharge. In our moderate study, we're using the ordinal scale as well, but we're looking at the day 11 distribution along that ordinal scale.

So, similar to what we did in our severe study, but looking at day 11 instead of day 14, recognizing that we're looking at a population that's less sick.

The moderate study is looking at patients who are hospitalized, but they're not hypoxic, they're not requiring oxygen. The NIAID study enrolled patients from starting there, but all the way through mechanical ventilation. So, slightly different endpoints for slightly different patient populations, and, most importantly, really looking at different questions.

We're looking at treatment duration. They're looking at primary safety and efficacy with a placebo control.

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GUEST EDITORIAL

Under the onslaughts of COVID-19, Montefiore deployed a PPE strategy for patients—**PREVENT/PROTECT/ENABLE**

March 1, 2020, started as a good day at the Montefiore Einstein Center for Cancer Care in New York.



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As an NCI-designated cancer center based at the Albert Einstein College of Medicine, our accrual to cancer clinical trials reached its highest level in the last decade, and our faculty was leading innovative work at the local and national levels.

The number of cancer patients referred to our system and patients accrued to cancer clinical trials was steadily rising. We were providing state-of-the-art cancer care, collaborating in translational research with scientists at the NCI-designated Einstein Cancer Center, supporting a robust education and training program, and serving our community.

Although these attributes were not unique to our center, a distinguishing feature was that 80% of our patients and trial participants were African-American or Hispanic, and about 25% were living below the federal poverty rate, contributing to success-

ful efforts to secure NCI funding as a minority underserved NCORP.

However, that very day the first documented case of COVID-19 was reported in New York City. Every day since then has brought new challenges and multiple COVID-19 teleconferences.

Fast forward just four-to-six weeks, and our institution was challenged in ways one could not imagine. The census of COVID-19 patients in our three Bronx hospitals swelled to a peak of 1,148, including 241 vented patients in multiple newly constructed ICUs with our EDs seeing more than 500-plus new COVID cases per day.

With up to 1,200 sick calls per day, some of our staff were also becoming ill, some seriously. On Monday, March 30, our community was devastated upon learning of the deaths of our first two associates: a 29-year old clerk and a 73-year old physician—a pediatric neuro-

surgeon who was world renowned for successfully separating conjoined twins.

Many of our trainees and support staff were deployed to cover these new units, and our medical oncology faculty staffed a new COVID-positive inpatient unit while supporting our usual set of inpatient oncology units. All cancer surgeries and most other procedures were cancelled, creating major challenges in developing bridging strategies to surgery.

All research labs were shut down, with the brightest minds on campus locked into endless Zoom meetings for the foreseeable future. While the COVID deluge flooded the entire city of New York, the Bronx was even more seriously impacted, with a higher-than-anticipated proportion of cases and deaths impacting our minority communities.

As bad as it was at the time, our leadership was preparing for the worst that



In addition to facing a cancer diagnosis and now the fear of the pandemic, many of our patients are further burdened with financial challenges, lack of resources and a social support system, emotional burden, loneliness, etc.



was yet to come—a period of unimaginable losses. The five stages of loss are classically listed as denial, anger, bargaining, depression, and acceptance.

No question that most of us have faced many of these stages ourselves over these dizzying times. However, the last stage we seem to have successfully converted into an ongoing phase of “adaptation.” Below we will describe the key steps we have taken in order to keep our patients the safest possible, allow reasonable ongoing clinical care and research while keeping our staff engaged and sane during these most trying times.

Learning from the first major epicenters of COVID-19 in China and Italy, we realized early on that we have to go out of our way to “cocoon” our cancer patients from the epidemic, and one key element of this had to be protecting them from cross-contamination through infected health care workers—ourselves (more than 10% of all infected cases in Italy occurred in HCWs).

Our center therefore very quickly established a core leadership group to implement rapid changes to optimize safety in both the outpatient and inpatient settings. The implemented changes reviewed below could be broken down along the easy and familiar mnemonic put to new use—**PPE- PREVENT, PROTECT, ENABLE**—establishing the best “PPE” we could offer to our patients.

PREVENT

As many centers, we recognized the first obvious step that we could take is minimize exposure of patients to the health care environment. For example, all non-urgent visits/procedures were deferred and visits that did not demand actual physical encounters were converted into telemedicine visits.

Within six weeks, this led to the point that currently approximately 75% of the encounters take place via telemedicine tools. In addition, early assessment of the first wave of COVID-positive cancer patients revealed that elderly, frail patients, and especially those living in residential facilities or being inpatients, were particularly vulnerable resulting in special attention to minimize risk of exposure to such patient groups.

Early steps included the establishment of a completely closed COVID-negative inpatient/transplant unit with admission only following testing and deferral of visits from nursing home patients to our facilities.

PROTECT

Clearly, while telemedicine could be sufficient for some time in certain disciplines, in oncology we had to face balancing the competing risks of potential exposure to COVID-19 versus the risk of delaying needed procedures/treatments. In order to be able to offer critical therapies to our patients, we needed

to convert our practices where we could feel secure of minimizing risk while allowing access.

For this, we made an early decision to consolidate our outpatient practices into a single performance site. Through a herculean effort by staff, we set up a free-standing outpatient facility that provided complete control of access in/out of the building serving as a “fort.” This permitted a screening station to be set up at the entrance supported by the establishment of an urgent care area with rapid COVID testing availability.

Exceeding attention was given to safe practices with full personal protective equipment for staff, limited patient density, physical distancing, and regular terminal cleaning runs. These procedures provided the assurances needed to allow our active oncology practice to continue despite the onslaught of the pandemic. Lastly, protecting our patients from potentially infected but asymptomatic staff was felt to be key as well. For this reason, we established the rule that staff who had worked on inpatient floors could not enter outpatient spaces until after a week of quarantine.

ENABLE

Last but not least, major efforts had to be undertaken then to enable reasonable ongoing clinical care and research. Regular review of appropriate treatment principles in the face of the pandemic has been an important element—converting regimens to require fewer infusional visits, oral regimens, regimens with less immune suppressive side effects, if such could be reasonable chosen, adopting hypo-fractionated radiation courses, etc.

While oncology clinical research clearly had to slow down, it did not stop with continued cautious enrollment of patients into studies offering needed options to our patients. In addition, we

shifted our focus to support COVID-related research for this transitional time with active participation of novel treatment studies, coordinator support of key studies run by our ID and Critical Care Divisions, participation in national and international registries to ensure that we as a team contribute to the emerging knowledge gained as to the interface of COVID-19 and cancer.

Ongoing surveys of the financial burden of cancer treatment have continued to accrue in order to capture how patients and their family support systems are coping with additional impacts of the pandemic. Some of the most accomplished scientists at Einstein have also applied their expertise to development of antiviral and immune approaches directed against SARS-CoV2, the virus causing COVID-19.

Examples include development by the Gavathiotis lab of highly selective drugs against the SARS-CoV-2 protease required for viral replication, generation of CD8 T dubbed “synTacs” (Synapse for T-cell Activation) pioneered by the Almo laboratory that are engineered to destroy SARS-CoV-2, and generation of pathogen-specific B cells from convalescent donors targeting the SARS-CoV2 spike protein by the Chandran, Lia, and Daily labs.

These efforts include collaboration with other basic scientists at Einstein whose work is not cancer-focused and is supported by the center’s shared resources that continue to function and sustain other vital scientific activities at Einstein addressing the Covid-19 pandemic.

Where are we eight weeks later?

After peaking at 2,200 COVID-19 patients in our health system’s nine hospitals serving the Bronx and beyond in mid-April, including over 1,000 at our Bronx hospitals, the trend is reversing

now with 1,300 or so COVID-19 patients still admitted.

Although many have succumbed, more than 4,000 patients have been discharged as of April 25. We are now turning our attention to a fourth component of adaptation:

ENACT

We are setting up a new life recognizing that COVID-19 is certainly here to stay for the coming months. While possibly as many as 20% of the 1.5 million Bronx residents have been exposed, that still leaves 80% still vulnerable for an extended plateau or further waves. Our institution weathered this dramatic storm well—strong leadership and amazing demonstration of the selflessness of our health care workers across the board have shone through this crisis.

Furthermore, we cannot forget another key element of cancer care in this new COVID era:

EMBRACE

In particular, our vulnerable patient population in the Bronx, the poorest county in New York State, is facing unique challenges. In addition to facing a cancer diagnosis and now the fear of the pandemic, many of our patients are further burdened with financial challenges, lack of resources and a social support system, emotional burden, loneliness, etc. The unique aspects of the COVID crisis amplify all of these issues leading to a potential erosion of the patient/health care interface and added alienation.

We as a team are now back full steam, embracing this special challenge and addressing these key issues head-on via providing expanded services ranging from virtual supportive care services to telephonic counseling, bilingual peer

support programs and food delivery through our renowned BOLD program and dedicated social workers.

Now, we need to be able to dig in and focus on this next phase as our staff/trainees/researchers will slowly be returning to home base, and cancer patients will re-emerge in large numbers after an extended period of delaying/deferring care.

What will be the new normal?

Many questions have yet to be answered. Currently, we are establishing new practices as to routine COVID testing for our cancer patients for all new patients before their first visit and monthly for patients on active therapy.

We are setting up a separate infusion unit solely for COVID-positive patients and we have already established separate inpatient areas. When can we resume ancillary services including all diagnostic and surgical procedures so needed to be able to provide comprehensive cancer care?

When can we feel comfortable resuming a full set of research activities? How can we help fellows to get back on track after months-long disruption of their research and training activities? What additional steps will be needed to support our staff who have been so deeply impacted by this crisis, both professionally and personally?

We will find answers to these questions, and we look forward to sharing our experience with others and learning greatly from other centers’ experience as well.

One thing that is for sure—we are fully resolved to continue to focus on adaptation and not acceptance.

Our patients deserve nothing less.



GUEST EDITORIAL

The pandemic of COVID-19 and its effect on clinical trials in the community

How do we move forward?



By James N. Atkins, MD

Co-Principal investigator

Southeast Clinical Oncology Research Consortium NCORP

This pandemic has affected a lot of people, both physicians and patients, physically as well as emotionally.

There are patients who have become afraid to come into the office to see the staff for fear that they would contract the virus. Our patients seem to have more depression, which may stem from a lack of social interaction.

We have all had our practices turned upside-down, we have gone from face-to-face visits, which we love, to computer-to-computer, or phone-to-phone visits. We have seen physician reimbursement plummet and colleagues

stress about their ability to run a private practice.

Physicians have been concerned about their ability to pay the bills as well as their own mortality from this invisible enemy.

We are seeing PTSD in practitioners.

This virus, like cancer, has turned a lot of lives upside-down, and perhaps has shown us what our patients face on a daily basis.

Some patients whom I have seen have been treated on clinical trials in large cities and have been told that they can-

not come back to the city for therapy due to the COVID lockdown. They have been referred to our communities to get their clinical trial therapy.

We are treating patients on clinical trials, but they are on trials that we do not have open. This would have been unheard of a few weeks ago. It would be a major protocol deviation, but should it be? What can we learn—and what should we learn—from this pandemic when it comes to clinical trials and audit time?

Getting patients in to be seen on time (as per protocol) has been more difficult due to patients' fear about going

to the hospital, a doctor's office or the concerns about social distancing on the way to or in the office.

In the past, we could get tests done when we wanted them—within a day or two. Now, a CT scan will have to be classified as STAT in order to get it done on a certain date.

We would never had ordered it STAT in the past, as it may cost more; but now we have to. With COVID, the x-ray departments have changed their protocols so as to have more time available for COVID patients and to conserve supplies. So our patients who need x-rays are delayed.

Some of our nursing staff may have been furloughed or redeployed due the pandemic as the hospitals are losing money and they are trying to maintain a balance sheet that is already negative.

One of the offices in our NCORP have had their staff furloughed, with just a manager left behind, 6 of 19 offices are trying to do 75% to 90% of their work remotely, and 10 of 19 continue to work in-house.

There has been a significant decline in NCTN accruals to clinical trials over the past month nationally. It also seems that there has been a significant decrease in new cancers over the past month as well. The decrease in cancers is probably due to people being afraid to come to see a doctor—or the procedures to diagnose the cancer is considered elective.

Some of the practitioners, doctors included, are afraid to see patients for fear that they may get the virus from the patients and then get sick or die. We are seeing more patients with virtual visits, and this is good in that it does decrease the exposure of our patients to others. However, this makes documenting for clinical trials more difficult.

Those of us treating patients worry about deviations from protocols and the protocol violations that then occur.

The good thing is that there are people in the clinical trial organizations and the NCI who do understand what's going on. We believe that the problems of the pandemic will be considered when it is audit time.

We are having problems getting procedures done like colonoscopies for iron deficiency in the older population, and needle biopsies of lung lesions when we need them. We have found that we have to be more insistent on what we want and when we want it, as others may not understand.

I had a patient who needed a lung biopsy after her third cycles of therapy, and radiology was not very happy, because we already had a diagnosis of lung cancer, we had not been clear enough in our request.

We are also having problems getting tests done within the eligibility time window, just getting pulmonary function tests or a Cardiac Echo may take time.

What can we learn from this pandemic? What can we do to make changes that will improve clinical trials in America? Can we have a system where physicians are approved by some organization as being physicians that have demonstrated good practice with clinical trials and those so designated be allowed to work across trials from different sites?

It seems like we have seen a significant drop in accrual to clinical trials over the past year or two, as trials became more precision-based. COVID has just made this worse.

I fear that we are getting down much closer to 1% of adults going on trials not the 3% of the past. Should a patient be able to go 200-400 miles away to get

started on a trial and then be allowed to get some or all of their follow-up treatment closer to home if it is agreeable with all the providers?

I think it is worth considering.

The easier we make it for a patient to go on a clinical trial and the easier we make it for their follow-up, the better we will do with accrual and changing the therapy for cancer.

If this is a time for change, then we need to re-evaluate the barriers for patients going on trial.

These may range from a lack of clinical trial training in our training programs, to physician apathy and burnout, ability to open trials due to lack of staff, patient trust, and financial support just to name a few.

We have to decide how important it is and whether we want to try to fix it—or whether the status quo is acceptable.



We are treating patients on clinical trials, but they are on trials that we do not have open. This would have been unheard of a few weeks ago. It would be a major protocol deviation, but should it be?





GUEST EDITORIAL

Cancer doesn't wait— we are treating cancer patients now

As part of responding to the COVID-19 pandemic, hospitals across the nation had dramatically reduced their surgery schedules when UC Davis cancer patient Marlene Blake had surgery for breast cancer in March.



By Richard Bold, MD

Physician-in-Chief

Chief, Division of Surgical Oncology,

UC Davis Comprehensive Cancer Center



By Timothy Donahue, MD

Chief of the Division of Surgical Oncology

Vice chair for Surgical Cancer Care, Department of Surgery,

Jonsson Comprehensive Cancer Center at UCLA

Imaging showed she had three masses in one breast and a fourth suspected in the other. Ms. Blake recently celebrated her birthday and shared, “I’m so glad to begin the next year of life without that worry. Whether there’s coronavirus or not, I want to stay healthy.”

Care of pandemic victims has to come first, and all precautions must be taken to minimize the risks to health care providers and other patients. But cancer doesn’t wait for the coronavirus.

According to the American Cancer Society’s Cancer Statistics,¹ 150,000 Americans per month are diagnosed with cancer, and approximately two-thirds—100,000 patients—would require surgery to treat the cancer. These operations are not “elective” in the sense that they are optional or can be delayed unduly. Rather, they are part of responsibly managing patients’ health with treatments that are likely to cure and cannot safely be delayed.

Comprehensive cancer centers are hard at work to provide this sort of care, all while keeping staff and patients safe. Universal masking policies are in place, meaning everyone in the facility must wear a mask at all times. Health care staff members are screening people entering the building for signs of infection and testing all patients for COVID-19 prior to surgery.

The number of visitors is severely restricted. Patients in the waiting area are encouraged to practice physical distancing and wash their hands or use hand sanitizer from the dispensers that are widely available throughout the facility. Medical teams are expanding video visits, allowing patients to securely receive care in the safe environment of their homes.

Our goals today are the same as on any other day: to serve our patients steadfastly, as we strive to end the scourge of cancer. By acting responsibly now, we aim to avoid a “second surge” of cancer patients on the heels of the coronavirus surge, further burdening the health care system as it recovers from the pandemic. We are treating patients now to avoid stressing cancer care resources when the pandemic has ended, but the battle against cancer will still need to be fought.

We are aligned with the Centers For Medicare & Medicaid Services newly updated guidelines, on Sunday, April 19, about re-opening facilities to provide non-emergent non-COVID-19 health care. This would include “procedural care (surgeries and procedures), chronic disease care, and, ultimately, preventive care.”

By not deferring care we will avoid a second surge, and more patients like Marlene Blake can enter the next chapter of life with one less worry during this challenging and unprecedented time.

1. Cancer Statistics Center, American Cancer Society, <https://cancerstatisticscenter.cancer.org/#/>. Among cases diagnosed from 2009 to 2015, followed through 2016. Data sources: Surveillance, Epidemiology, and End Results (SEER) 18 registries, National Cancer Institute.

“

Care of pandemic victims has to come first, and all precautions must be taken to minimize the risks to health care providers and other patients. But cancer doesn’t wait for the coronavirus.

”

Dafna Bar-Sagi, Arul Chinnaiyan, Carl June, Christopher Lima, Miriam Merad, and John Schiller are among newly elected NAS members

The National Academy of Sciences announced the election of 120 members and 26 international members in recognition of their distinguished and continuing achievements in original research.

Newly-elected members bring the total number of active members to 2,403 and the total number of international members to 501. International members are nonvoting members of the academy, with citizenship outside the United States.

Newly-elected members whose work is related to cancer include:

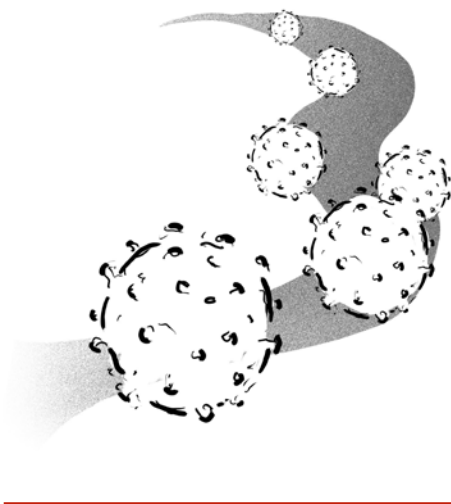
- Bahar, Ivett; John K. Vries Chair and distinguished professor of computational biology, department of computational and systems biology, University of Pittsburgh School of Medicine
- Barkan, Alice; director, department of biology and Institute of Molecular Biology, University of Oregon
- Bar-Sagi, Dafna; senior vice president, vice dean for science, chief scientific officer, and professor, department of biochemistry and molecular pharmacology and department of medicine, New York University School of Medicine
- Bellen, Hugo; investigator, Howard Hughes Medical Institute; and professor, department of molecular and human genetics and department of neuroscience, Baylor College of Medicine
- Carreira, Erick M.; professor of chemistry, department of chemistry and applied biosciences, ETH Zürich, Zurich
- Chang, Howard Y.; professor of dermatology, and director, Center for Personal Dynamic Regulomes Dermatology, Stanford University School of Medicine
- Cheng, Yifan; investigator, Howard Hughes Medical Institute; and professor, department of biochemistry and biophysics, University of California, San Francisco
- Chinnaiyan, Arul M.; investigator, Howard Hughes Medical Institute; and S.P. Hicks Endowed Professor of Pathology, American Cancer Society Research Professor, and director, Michigan Center for Translational Pathology, University of Michigan Medical School
- Christiano, Angela; Rhodebeck Professor of Dermatology and Genetics and Development, departments of dermatology and genetics, Columbia University College of Physicians and Surgeons
- Conaway, Joan W.; investigator, Stowers Institute for Medical Research, Kansas City, Mo.
- Corces, Victor G.; HHMI Professor and Arts and Sciences Distinguished Professor of Biology, department of biology, Emory University
- Diffley, John F.; associate research director, Francis Crick Institute, London

- Fagin, Ronald; IBM Fellow, IBM Almaden Research Center, San Jose, Calif.
- Galli, Giulia; Liew Family Professor of Electronic Structure and Simulations, Institute for Molecular Engineering, The University of Chicago
- Goldstein, Lawrence S.; director, Sanford Consortium for Regenerative Medicine and UCSD Stem Cell Program, and professor, department of cellular and molecular medicine, School of Medicine, University of California, San Diego
- Green, Douglas R.; member and chair, department of immunology, St. Jude Children's Research Hospital
- Habener, Joel F.; professor of medicine, Harvard Medical School; and chief, laboratory of molecular endocrinology, Massachusetts General Hospital
- Howe, Gregg A.; university distinguished professor and MSU foundation professor, MSU-DOE Plant Research Laboratory, department of biochemistry and molecular biology, Michigan State University
- Hurley, James H.; Judy C. Webb Chair and professor of biochemistry, biophysics, and structural biology, department of molecular and cell biology, University of California, Berkeley
- Hwa, Terence T.; co-director, specialization in quantitative biology, and distinguished professor, department and division of biological sciences and department of physics, University of California, San Diego
- Jarzynski, Christopher; distinguished university professor and director, Institute for Physical Science and Technology, department of chemistry and biochemistry, University of Maryland, College Park
- Jenkins, Marc K.; regents professor, department of microbiology and immunology, Center for Immunology, University of Minnesota Medical School, Minneapolis
- June, Carl; Richard W. Vague Professor in Immunotherapy, and director, Center for Cellular Immunotherapies, Perelman School of Medicine, University of Pennsylvania
- Keeney, Scott; investigator, Howard Hughes Medical Institute; and full member, molecular biology program, Memorial Sloan Kettering Cancer Center
- Kirkpatrick, Mark; T.S. Painter Centennial Professorship in Genetics, department of integrative biology, University of Texas, Austin
- Krainer, Adrian R.; St. Giles Foundation Professor, Cold Spring Harbor Laboratory, Cold Spring Harbor
- Kubiak, Clifford P.; distinguished professor of chemistry and biochemistry, department of chemistry and biochemistry, University of California, San Diego
- Lewis, Richard S.; professor of molecular and cellular physiology, Stanford University
- Lieberman, Judy; endowed chair of cellular and molecular medicine, Boston Children's Hospital; and professor, department of pediatrics, Harvard Medical School
- Lima, Christopher D.; investigator, Howard Hughes Medical Institute; and member, Memorial Sloan Kettering Cancer Center
- Lindblad-Toh, Kerstin; professor in comparative genomics, Uppsala University; and scientific director of vertebrate genome biology, The Broad Institute
- Livingstone, Margaret S.; Takeda Professor of Neurobiology, department of neurobiology, Harvard Medical School
- McMahon, Andrew P.; director, Eli and Edythe Broad CIRM Center, provost professor, Keck Professor, and chairman, department of regenerative medicine and stem cell biology, University of Southern California
- Merad, Miriam; professor of immunology and oncological science, co-leader, cancer immunology program, and director, Immunology Institute, Icahn School of Medicine at Mount Sinai
- Miller, Scott J.; Irénée du Pont Professor of Chemistry, department of chemistry, Yale University
- Morrison, Sean J.; investigator, Howard Hughes Medical Institute; and director, Children's Research Institute, University of Texas Southwestern Medical Center
- Orth, Kim; investigator, Howard Hughes Medical Institute; and W.W. Caruth Jr. Scholar in Biomedical Research, Earl A. Forsythe Chair in Biomedical Science, and professor, department of molecular biology, University of Texas Southwestern Medical Center
- Pourquié, Olivier; Burr Professor of Pathology, Brigham and Women's Hospital, and professor of genetics, Harvard Medical School
- Przeworski, Molly; full professor, department of biological sciences and department of systems biology, Columbia University
- Rosen, Michael K.; investigator, Howard Hughes Medical Institute; and professor, department of biochemistry, and chair, department of biophysics, University of Texas Southwestern Medical Center
- Sarnow, Peter; professor of microbiology and immunology, department of microbiology and immunology, Stanford University School of Medicine

- Schier, Alex F.; professor of cell biology and director of Biozentrum, The Center for Molecular Life Sciences, University of Basel
- Schiller, John T.; deputy chief, laboratory of cellular oncology, NIH Distinguished Investigator, and head, neoplastic disease section, Center for Cancer Research, National Cancer Institute, National Institutes of Health.
- Schmid, Sandra L.; professor and chair, department of cell biology, University of Texas Southwestern Medical Center, Dallas
- Schuman, Erin M.; director, Max Planck Institute for Brain Research, Frankfurt
- Smith, George P.; Curators' Distinguished Professor Emeritus, division of biological sciences, University of Missouri
- Smith, Janet L.; professor of biological chemistry, department of biological chemistry, and Margaret J. Hunter Collegiate Professor, Life Sciences Institute, University of Michigan
- Stoneking, Mark; group leader, department of evolutionary genetics, Max Planck Institute for Evolutionary Anthropology, Leipzig
- Stupp, Samuel I.; Board of Trustees Professor of Materials Science and Engineering, Chemistry, Medicine, and Biomedical Engineering, Northwestern University
- Symington, Lorraine S.; full professor, department of microbiology and immunology, Columbia University Medical Center
- Tontonoz, Peter; professor and Frances and Albert Piansky Chair, department of pathology and laboratory medicine, University of California, Los Angeles
- Toste, F. Dean; Gerald E.K. Branch Professor of Chemistry, department of chemistry, University of California, Berkeley
- Tsao, Doris Y.; investigator, Howard Hughes Medical Institute; and professor of biology, California Institute of Technology
- Tycko, Robert; senior investigator, laboratory of chemical physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
- Vaida, Veronica; professor of chemistry, department of chemistry and biochemistry, University of Colorado, Boulder
- Walker, Suzanne; professor of microbiology and immunobiology, Harvard Medical School
- Weber, Elke U.; Gerhard R. Andlinger Professor, departments of psychology and public affairs, Woodrow Wilson School of Public and International Affairs, Princeton University
- Andrews, Brenda J.; professor and director, Terrence Donnelly Center for Cellular and Biomolecular Research, University of Toronto
- Arber, Silvia; senior group leader, Friedrich Miescher Institute, and professor of neurobiology and cell biology, Institute for Biomedical Research, University of Basel
- Barrett, Spencer C.H.; emeritus professor of botany, department of ecology and evolutionary biology, University of Toronto
- Bernards, Rene; professor of molecular carcinogenesis, Utrecht University; and molecular oncologist, The Netherlands Cancer Institute
- Cao, Xiaofeng; co-director, CAS-JIC Centre of Excellence for Plant and Microbial Science; and head, Center for Genome Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences
- Cramer, Patrick; director, Max Planck Institute for Biophysical Chemistry
- Domingo, Esteban; emeritus professor, Severo Ochoa Molecular Biology Center, Spanish National Research Council
- Henzinger, Thomas; university president, Institute for Science and Technology Austria
- Holt, Christine E.; professor emeritus, department of physiology, development, and neuroscience, University of Cambridge
- Hyman, Anthony; director, Max Planck Institute of Molecular Cell Biology and Genetics
- Jorgensen, Bo Barker; professor, department of biology, Center for Geomicrobiology, Aarhus University
- Kay, Lewis E.; professor of biochemistry, molecular genetics, and chemistry, University of Toronto
- Morris, Richard G.M.; professor of neuroscience, Edinburgh Neuroscience, University of Edinburgh
- Nobre, Anna C.; director, Oxford Centre for Human Brain Activity, department of experimental psychology, University of Oxford
- Powrie, Fiona M.; director, Kennedy Institute of Rheumatology, University of Oxford
- Speakman, John R.; professor, University of Aberdeen; and professor, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences

Newly elected international members, their affiliations at the time of election, and their country of citizenship are:

COVID-19 UPDATES



FDA grants Emergency Use Authorization for novel, non-implanted device to wean patients off mechanical ventilation

FDA has issued Emergency Use Authorization for Lungpacer Medical's novel Diaphragmatic Pacing Therapy System (DPTS) for immediate use in patients on invasive mechanical ventilators at high risk of weaning failure, including COVID-19 patients.

"Hospital resources around the world have been under significant strain during the COVID-19 pandemic and ICU beds and mechanical ventilators have been at peak demand. This novel therapy has the potential to wean patients earlier from the ventilator and free up resources during these difficult times," Ali Ataya, assistant professor of medicine, Division of Pulmonary and Critical Care Medicine, University of Florida Health, Gainesville, said in a statement. "We are looking forward as an institu-

tion to start using this technology to help our patients during this pandemic."

Ataya co-authored the publication reporting the results of the RESCUE₁ trial, which demonstrated feasibility, and assessed initial safety and efficacy of the Lungpacer DPTS.

Lungpacer DPTS is the first minimally invasive, temporary, transvenous phrenic-stimulation system cleared through Emergency Use Authorization by the FDA. This non-surgical, non-implanted, diaphragm stimulation therapy is delivered via a central venous catheter, similar to central lines currently placed in mechanically ventilated ICU patients.

The central line is used to deliver both fluids and medications, while also incorporating the capability to activate the diaphragm muscle via transvenous phrenic-nerve stimulation. This stimulation is intended to strengthen a weakened diaphragm, already atrophied by mechanical ventilation and is expected to help patients wean off the ventilator more rapidly.

Reducing time on the ventilator decreases the risk of ventilator-induced lung injury, secondary pneumonias, and poor patient outcomes associated with prolonged mechanical ventilation. Less ventilator time frees up ICU beds, resources and mechanical ventilators, potentially improving ICU throughput and effectively reducing ventilator burden by a projected 26% in patients during this COVID crisis.

TGen seeks volunteers for COVID-19 immunity study

The Translational Genomics Research Institute, an affiliate of City of Hope, is looking for patients recovered from COVID-19 to participate in the [COVID Immunity Study](#).

Participants in The COVID Immunity Study must be U.S. residents, age 18 or older, have tested positive for COVID-19, and then recovered.

This is a research study, and will not be used to diagnose disease among the participants. The study could eventually lead to new methods of diagnosing COVID-19, and help in the development of antibody therapies and vaccines.

"We are using cutting-edge research tools to study, in depth, the immune response to COVID-19," John Altin, assistant professor in TGen's Pathogen and Microbiome Division, the institute's infectious-disease branch in Flagstaff, said in a statement. "Our goal is to enable urgently-needed new diagnostics and treatments for this virus."

David Engelthaler, director of TGen North and Arizona's former state epidemiologist, said the study could help better understand how the virus has moved through our community.

"This will help us learn more about how, when and why we produce antibodies in response to a COVID-19 infection. One class of antibodies tackles the infection first, and then another comes in to finish the job," Engelthaler said in a statement. "Knowing when these different immune responses occur, and how long they last, could help us understand if some patients gain a certain degree of immunity against reinfection. We need to know how that works."

"To supplement this study, I am leading a research project at City of Hope, in collaboration with Dr. Altin's lab, that will hopefully result in the development of a COVID-19 virus antibody neutralization test. Together, these two tests will help us understand what is necessary for immune protection against COVID-19," John Zaia, director of the Center for Gene Therapy at City of Hope, said in a statement.

Those who sign up for TGen's study will be asked to complete a short online health questionnaire. TGen would then mail them a simple blood-spot collection kit. They would be instructed to prick the end of a finger and put a drop of blood on a sample collection card. A week later, they would put another drop of blood on the sample collection card, and then mail the test back to TGen.

"Our approach will not only tell you which proteins are being targeted, but also be able to tell which regions of each protein are being targeted," Altin said. "Each protein can be recognized by many different types of antibodies. By looking at this level of detail, we then could see elements of the antibody response that others might be missing."

J&J and Emergent Bio collaborate on coronavirus vaccine candidate

The Janssen Pharmaceutical Companies of Johnson & Johnson and Emergent BioSolutions Inc. are collaborating to support the manufacturing of Johnson & Johnson's lead investigational COVID-19 vaccine candidate.

Johnson & Johnson said it hopes to supply more than one billion doses of the vaccine globally.

Under the manufacturing agreement, Johnson & Johnson plans to expand drug substance capacity related to the vaccine candidate. Emergent has agreed to provide drug substance manufacturing services with its molecule-to-market CDMO offering. Emergent may provide operations support for commercial manufacturing of Johnson & Johnson's COVID-19 vaccine candidate, using Janssen's AdVac and PER.C6 technologies beginning in 2021.

Johnson & Johnson has begun preparations for clinical vaccine production at its facility in Leiden, the Netherlands, and aims to start phase I human clinical studies of its vaccine candidate in September 2020. Johnson & Johnson will begin production at risk and is committed to bringing an affordable vaccine to the public on a not-for-profit basis for emergency pandemic use.

Johnson & Johnson said it plans to use Janssen's proven AdVac and PER.C6 technologies to develop new vaccine candidates and upscale production of the optimal vaccine candidate. The same technology was used to develop and manufacture the company's investigational Ebola vaccine, and construct RSV and HIV vaccine candidates that are now in phase II or phase III of clinical development.

IN BRIEF



Kristin Brill named enterprise director of Breast Oncology at SKCC

Breast surgeon Kristin L. Brill has joined the Sidney Kimmel Cancer Center—Jef-

erson Health as enterprise director of Breast Oncology.

Particular areas of focus for Brill include young women with breast cancer and those at high risk.



Brill joins SKCC from Cooper University Health Care, where she was head of the Division of Breast Surgery and Director of the Janet Knowles Breast Cancer Center at MD Anderson Cancer Center at Cooper and assistant professor of surgery at Cooper Medical School of Rowan University. She also directed the Breast Surgical Oncology Fellowship at Cooper Medical School and was an adjunct assistant professor in the Department of Surgery at MD Anderson Cancer Center.

UCLA researchers receive \$2.8M NCI grant to develop blood-based test for liver transplant candidate selection

Researchers from the UCLA Jonsson Comprehensive Cancer Center received a \$2.8 million, five-year grant from NCI to help develop a blood-based test to improve the selection and prioritization for patients with liver cancer who need a liver transplantation.

The grant, led by Vatche Agopian, associate professor of surgery, liver and pancreas transplantation; and HR Tseng, professor of molecular and medical pharmacology, helps fill an unmet need for more accurate ways to predict how well patients with hepatocellular carcinoma—the most common form of liver cancer—will do after a liver transplant, using a blood-based assessment of tumor biology to make these predictions.

“For patients with liver cancer whose tumors cannot be surgically removed due to prohibitive underlying liver dysfunction and portal hypertension, liver transplantation becomes their only option for a cure,” Agopian said in a statement. “But current imaging tests do not take into account the tumor biology that actually makes some patients better candidates than others.”

The gold-standard to decide who is a candidate for a successful liver transplant for liver cancer is known as the Milan criteria, which defines a strict tumor size and number criteria.

“Unfortunately, the Milan criteria has numerous limitations,” Agopian said. “On the one hand, up to 20% of patients who meet the Milan criteria still develop post-transplant cancer recurrence, which usually leads to patient death. Conversely, some patients who don’t meet these criteria would potentially have excellent outcomes following liver transplant and are denied the possibility of even having one. These shortcomings of our current patient selection criteria highlight the need for better ways to select candidates for liver transplants.”

The UCLA blood-based test uses circulating tumor cells, which are cancer cells that are released into the bloodstream and have the ability to provide vital information about a person’s specific cancer. The grant will help the team build on their previous research to integrate liver cancer circulating tumor cells to create an assay that will allow them to

look at both cell phenotype and molecular characterization that will help better define patients’ tumor biology.

The UCLA team has created five generations of the novel method they call NanoVelcro, each with different clinical utilities.

“We anticipate that our integrated assay will better assess this risk of tumor progression and prioritize patients to receive a transplant before tumor progression,” Tseng, who led the development of the assay, said in a statement. “Should we confirm our assay outperforms the Milan criteria, this could be a transformative change and paradigm shift in how patients with liver cancer are selected and prioritized for liver transplantation.”

Sungyong You, an assistant professor of surgery and biomedical sciences at Cedars-Sinai Medical Center, will be co-PI on the grant.

2020 Stovall award nominations due May 1

National Coalition for Cancer Survivorship is accepting nominations for the 2020 Ellen L. Stovall Award through May 1.

Anyone can submit a nomination for the 2020 Ellen L. Stovall Award, and submissions from cancer survivors are especially encouraged.

The Ellen L. Stovall Award for Innovation in Patient-Centered Cancer Care honors the legacy of our former CEO, Ellen L. Stovall, a pioneering advocate who dedicated her life to making cancer care better for patients and their families.

Self-nominations are welcome.

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THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP



Phase III trial evaluating Libtayo in NSCLC halted because of significant OS improvement

The primary endpoint of overall survival was met in a phase III trial comparing the PD-1 inhibitor Libtayo (cemiplimab) to platinum-doublet chemotherapy in patients with first-line locally advanced or metastatic non-small cell lung cancer who tested positive for PD-L1 in $\geq 50\%$ of tumor cells.

Libtayo is jointly developed and commercialized by Regeneron and Sanofi under a global collaboration agreement.

Based on a recommendation by the independent data monitoring committee to stop the trial early, the trial will be modified to allow all patients to receive

Libtayo for this investigational use, the companies said. The data will form the basis of regulatory submissions in the U.S. and European Union in 2020.

“While demonstrating a survival benefit in first-line NSCLC has been challenging for immunotherapies, the one FDA-approved anti-PD-1 monotherapy has changed the therapeutic paradigm,” George D. Yancopoulos, co-founder, president and chief scientific officer of Regeneron, said in a statement.

A protocol-specified interim analysis conducted by the independent data monitoring committee demonstrated that patients treated with Libtayo monotherapy had a significant increase in OS. Libtayo decreased the risk of death by 32.4% (HR=0.676; CI:0.525-0.870, $p=0.002$), compared to platinum-doublet chemotherapy, despite a third of patients entering the trial within the past six months and all chemotherapy patients being able to crossover to Libtayo if their disease progressed.

“This is the largest clinical trial evaluating a PD-1 inhibitor as a first-line monotherapy in patients with advanced non-small cell lung cancer with high PD-L1 expression,” John Reed, global head of Research and Development at Sanofi, said in a statement.

Libtayo was invented using Regeneron’s proprietary VelocImmune technology that utilizes a proprietary genetically-engineered mouse platform endowed with a genetically-humanized immune system to produce optimized fully-human antibodies. VelocImmune technology has been used to create

multiple antibodies including Dupixent (dupilumab), Praluent (alirocumab) and Kevzara (sarilumab). Regeneron previously used these technologies to develop a treatment for Ebola virus infection, which is under review by the FDA, and is used in efforts to create preventative and therapeutic medicines for COVID-19.

Lynparza demonstrates OS benefit in phase III prostate cancer trial

The phase III PROfound trial of Lynparza (olaparib) in men with metastatic castration-resistant prostate cancer who have a homologous recombination repair gene mutation and have progressed on prior treatment with new hormonal agent treatments (e.g. enzalutamide and abiraterone) has demonstrated improvement in overall survival.

AstraZeneca and Merck sponsor Lynparza.

Results from the trial showed a statistically significant and clinically meaningful improvement in the key secondary endpoint of overall survival with Lynparza versus enzalutamide or abiraterone in men with mCRPC selected for BRCA1/2 or ATM gene mutations, a subpopulation of HRR gene mutations, the companies said.

The phase III PROfound trial had met its primary endpoint in August 2019, showing significantly improved radiographic progression-free survival in men with

mutations in BRCA1/2 or ATM genes, and had met a key secondary endpoint of rPFS in the overall HRRm population.

GARNET study demonstrates potential of dostarlimab to treat recurrent or advanced endometrial cancer

The GARNET trial demonstrated that dostarlimab, an investigational anti-programmed death-1 (PD-1) monoclonal antibody, provided clinically meaningful results in women with recurrent or advanced mismatch repair-deficient endometrial cancer who progressed on or after a platinum-based regimen.

GlaxoSmithKline plc. is an investigator on the trial.

This updated analysis included patients with dMMR endometrial cancer who had measurable disease at baseline and ≥ 6 months of follow-up by the data cutoff (n=71). Patients received 500 mg of dostarlimab once every three weeks for four doses, followed by 1,000 mg once every six weeks until disease progression. The primary endpoints were confirmed objective response rate and duration of response, as assessed against RECIST v 1.1 by blinded independent central review. GARNET is the largest dataset evaluating an anti-PD-1 in endometrial cancer.

Treatment with dostarlimab showed an ORR of 42% (95% CI; 31-55) and a disease control rate of 58% (95% CI; 45-69). Overall, 13% of patients had a complete response and 30% of patients had a partial response. At the time of data cutoff, with a median follow up of 11.2 months, the median DOR had not been reached (1.87+ to 19.61+ months).

MD Anderson, Ipsen advance therapy with potential benefit for patients with lung, ovarian cancer

Researchers at the MD Anderson Cancer Center's Therapeutics Discovery division and Ipsen Biopharmaceuticals reported the preclinical discovery and early-stage clinical development of IPN60090, a small-molecule inhibitor of the metabolic enzyme glutaminase (GLS1).

IPN60090, now under investigation in a phase I trial, may benefit certain patients with lung and ovarian cancers.

MD Anderson's GLS1 program was initiated and advanced by a team of scientists in the Institute for Applied Cancer Science and Translational Research to Advance Therapeutics and Innovation in Oncology platforms, both engines within Therapeutics Discovery. Development of the program continues in collaboration with Ipsen, which licensed the therapeutic in 2018.

Findings and information about the ongoing trial were presented April 27 at the 2020 American Association for Cancer Research virtual annual meeting I by Jeffrey Kovacs, institute group leader with TRACTION and co-leader of the GLS1 program.

IACS drug-discovery scientists identified IPN60090 as a potent and selective inhibitor of GLS1 suitable for clinical trials, and translational researchers in TRACTION demonstrated its activity against subsets of lung and ovarian cancer preclinical models.

Further analysis revealed biomarkers of response, which have been leveraged to identify patients most likely to benefit.

In lung cancers, mutations in the KEAP1 and NFE2L2 genes, which regulate response to oxidative stress, sensitize cells to treatment with IPN60090. Similarly, low expression of the metabolic protein asparagine synthetase (ASNS) in ovarian cancers predicts response to IPN60090 in preclinical models.

IPN60090 is under investigation in a phase I dose-escalation and dose-expansion study for patients with advanced solid tumors that harbor KEAP1/NFE2L2 mutations or have low ASNS levels.

Study: Disruptions in health insurance coverage are common, and affect cancer care and survival

A new study finds disruptions in health insurance coverage are common in the United States and are associated with poorer cancer care and survival. The study was published in *The Journal of the National Cancer Institute*.

For years, experts have known that lack of health insurance coverage is associated with poor access and receipt of cancer care and survival in the United States. Meanwhile, disruptions in coverage are common among low-income populations and little is known how these disruptions can affect cancer care, from prevention and screening to diagnosis, treatment, and survival.

Disruptions can be caused by gaps in coverage or transitions between types of coverage (e.g., public and private) or between specific health insurance plans.

Researchers, led by American Cancer Society's Robin Yabroff, conducted a systematic review of studies of health

insurance coverage disruptions and cancer care and outcomes published between 1980 and 2019. They identified 29 observational studies for analysis.

In those studies, from 4.3% to 32.8% of adults experienced coverage disruptions. Those with coverage disruptions were less likely to receive cancer prevention or screening, and if diagnosed with cancer, they were more likely to have advanced disease, were less likely to receive treatment, and have worse survival than their counterparts without coverage disruptions.

“Our findings were consistent across multiple cancer sites, with several studies finding a ‘dose-response’ relationship, meaning the longer the disruption, the worse the care,” lead author Yabroff said in a statement. “The consistency of these findings across the cancer control continuum in our review highlights how important it is to minimize breaks in health insurance coverage to address cancer disparities and promote health equity.”

AI may help brain cancer patients avoid biopsy

A study from UT Southwestern researchers shows that artificial intelligence can identify a specific genetic mutation in a glioma tumor simply by examining 3D images of the brain—with more than 97% accuracy.

Such technology could potentially eliminate the common practice of pretreatment surgeries in which glioma samples are taken and analyzed to choose an appropriate therapy.

“Knowing a particular mutation status in gliomas is important in determining

prognosis and treatment strategies,” Joseph Maldjian, chief of neuroradiology at UT Southwestern’s O’Donnell Brain Institute, said in a statement. “The ability to determine this status using just conventional imaging and AI is a great leap forward.”

The study used a deep-learning network and standard MRI to detect the isocitrate dehydrogenase gene, which produces an enzyme that in mutated form may trigger tumor growth in the brain.

Doctors preparing to treat gliomas often have patients undergo surgery to obtain tumor tissue that is then analyzed to determine the IDH mutation status. The prognosis and treatment strategy will vary based on whether a patient has an IDH-mutated glioma.

However, because obtaining an adequate sample can sometimes be time-consuming and risky—particularly if tumors are difficult to access—researchers have been studying non-surgical strategies to identify IDH mutation status.

The study, published this spring in *Neuro-Oncology*, differentiates itself from previous research in three ways:

- The method is highly accurate. Previous techniques have often failed to eclipse 90 percent accuracy.
- Mutation status was determined by analyzing only a single series of MR images, as opposed to multiple image types.
- A single algorithm was required to assess the IDH mutation status in the tumors. Other techniques have required either hand-drawn regions of interest or additional deep-learning models to first identify the boundaries of the tumor then detect potential mutations.

“The beauty of this new deep-learning model is its simplicity and high degree of accuracy,” Maldjian said. “We’ve removed additional pre-processing steps and created an ideal scenario for easily transitioning this into clinical care by using images that are routinely acquired.”

Maldjian’s team developed two deep-learning networks that analyzed imaging data from a publicly available database of more than 200 brain cancer patients from across the U.S.

One network used only one series from the MRI (T2-weighted images), while the other used multiple image types from the MRI. The two networks achieved nearly the same accuracy, suggesting that the process of detecting IDH mutations could be significantly streamlined by using only the T2-weighted images.

Maldjian’s team will next test his deep-learning model on larger datasets for additional validation before deciding whether to incorporate the technique into clinical care.

Meanwhile, researchers are hoping to develop medications to inhibit IDH through ongoing national clinical trials. If effective, these inhibitors could combine with AI-imaging techniques to overhaul how some brain cancers are assessed and treated.

Mouse model study shows promise in treatment of medulloblastoma and ependymoma

Researchers have demonstrated a novel approach in mouse models that delivers appropriately-targeted chimeric antigen receptor CAR T-cell therapy direct-

ly into the cerebrospinal fluid that surrounds the tumor in an effort to treat medulloblastoma and ependymoma.

Researchers at Baylor College of Medicine, Texas Children's Hospital and the Hospital for Sick Children reported their findings in *Nature Medicine*. The findings support further clinical studies to evaluate this strategy to treat pediatric brain cancers. A first-in-child clinical trial is recruiting patients at Texas Children's Hospital and Baylor College of Medicine to test the safety and anti-tumor efficacy of this approach (NCT02442297).

"Recurrences of medulloblastoma and ependymoma can be disseminated throughout the lining of the brain and spinal cord, which are bathed in cerebrospinal fluid. This location offers the opportunity to deliver therapies into the cerebrospinal fluid compartment and could provide a better chance for the therapy to reach and eliminate the tumor than administering it through the bloodstream," co-corresponding author Nabil Ahmed, associate professor of pediatrics and immunology, section of hematology-oncology at Baylor and Texas Children's Hospital, said in a statement.

In the mouse model studies, CAR T cells were administered into the cerebrospinal fluid around the tumor or into the bloodstream of mice harboring multiple patient-derived medulloblastoma and ependymoma tumors. The tumor size and animal survival were studied for about 200 days.

The results showed that administering tumor-specific CAR T cells into the cerebrospinal fluid was more effective than administering them via the blood. The researchers found that combining immunotherapy with azacytidine was significantly more effective than either treatment alone.

DRUGS & TARGETS



FDA approves GSK's PARP inhibitor Zejula for first-line maintenance of advanced ovarian cancer

FDA has approved a supplemental New Drug Application for Zejula (niraparib) an oral, once-daily poly (ADP-ribose) polymerase (PARP) inhibitor, as a monotherapy maintenance treatment for women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy, regardless of biomarker status.

Until now, only 20% of women with ovarian cancer, those with a BRCA mutation, were eligible to be treated with a PARP inhibitor as monotherapy in the first-line maintenance setting.

GlaxoSmithKline sponsors Zejulia.

Efficacy was investigated in PRIMA (NCT02655016), a double-blind, placebo-controlled trial that randomized 733 patients to niraparib or matched

placebo. Patients were in a complete or partial response to first-line platinum-based chemotherapy.

"PRIMA was designed for patients with ovarian cancer who have a high unmet need. The positive data observed regardless of biomarker status in this study is extremely encouraging and suggests benefit beyond the BRCAm population," Bradley Monk, PRIMA investigator, US Oncology, University of Arizona College of Medicine, Phoenix Creighton University School of Medicine at St. Joseph's Hospital Phoenix, said in a statement. "This approval is an important step forward in the treatment of ovarian cancer. In my opinion, maintenance treatment with niraparib should be considered an option for appropriate patients who responded to first-line platinum-based chemotherapy versus active surveillance."

The main efficacy outcome measure, progression-free survival, was first tested in the homologous recombination deficient population, then in the overall population and was determined by blinded independent central review per RECIST 1.1. Tumor samples were tested for homologous recombination deficiency status; homologous recombination deficient was defined by either presence of tumor breast cancer susceptibility gene mutation or genomic instability score ≥ 42 . An FDA-approved companion diagnostic is not required to initiate treatment with ZEJULA for this indication.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to niraparib compared with placebo in the homologous recombination deficient and overall population. Median PFS in the homologous recombination deficient population was 21.9 months (19.3, NE) for patients receiving niraparib compared with 10.4 months (8.1, 12.1) for those receiving placebo (HR 0.43; 95% CI: 0.31, 0.59; $p < 0.0001$). Median PFS in

the overall population was 13.8 months (11.5, 14.9) for patients receiving niraparib compared with 8.2 months (7.3, 8.5) for those receiving placebo (HR 0.62; 95% CI: 0.50, 0.76; $p < 0.0001$).

“It’s so important for patients with ovarian cancer to have treatment options, and this approval is positive news for our community,” Audra Moran, president and CEO, Ovarian Cancer Research Alliance, said in a statement. “PARP inhibitors represent a major advancement in the fight against ovarian cancer, and having a new first-line maintenance option for platinum-responsive advanced ovarian cancer patients—regardless of BRCA mutation status—is especially exciting. We are determined to keep funding research and partnering with scientists who are on the frontline of finding new treatments like this one to help those impacted by this disease.”

PRIMA study results were previously presented at the 2019 European Society for Medical Oncology (ESMO) Congress and published in the *New England Journal of Medicine*.

FDA grants accelerated approval to new dosing regimen for Keytruda

FDA has granted an accelerated approval to a new dosing regimen of 400 mg every six weeks for Keytruda (pembrolizumab) across all currently approved adult indications, in addition to the current 200 mg every three weeks dosing regimen.

Merck sponsors Keytruda.

The approval was based on pharmacokinetic modeling and exposure-response analyses that compared the predicted exposure of pembrolizumab 400 mg every six weeks to observed exposures

of pembrolizumab in patients who received pembrolizumab at 2 mg/kg every three weeks, 200 mg every three weeks, and 10 mg/kg administered every two weeks.

The pharmacokinetic modeling was supported by additional exposure-response analyses across the pembrolizumab development program and an interim analysis of pharmacokinetics and overall response rate in a cohort of patients (Cohort B) enrolled in KEYNOTE-555 (NCT03665597), the company said. Cohort B of Study KEYNOTE-555 was an international, single-arm, multi-center study that enrolled 101 patients with advanced or metastatic melanoma who had not received prior PD-1, PD-L1, or CTLA-4 inhibitors (other than CTLA-4 inhibitors in the adjuvant setting). The ORR was 39% (95% CI: 24, 55) in the first 44 patients enrolled in KEYNOTE-555.

Merck resubmitted supplemental Biologics License Applications to FDA to update the dosing frequency for Keytruda to include a 400 mg Q6W option across all approved adult indications. The results of KEYNOTE-555 supported the resubmission, the company said. In the EU, 400 mg Q6W dosing for Keytruda monotherapy was approved by the European Commission in March 2019.

Results from KEYNOTE-555 Cohort B were presented in an online plenary session at the American Association for Cancer Research virtual annual meeting April 28.

FDA grants Mobocertinib Breakthrough Therapy Designation in NSCLC designation

FDA has granted Breakthrough Therapy Designation to mobocertinib (TAK-

788) for the treatment of patients with metastatic non-small cell lung cancer with epidermal growth factor receptor exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.

Mobocertinib is sponsored by Takeda Pharmaceutical Company Ltd.

There are no approved therapies designed to treat this specific form of NSCLC. Mobocertinib is a small-molecule tyrosine kinase inhibitor designed to selectively target EGFR and human EGFR 2 exon 20 insertion mutations.

The Breakthrough Therapy Designation is based on the overall response rate and the long-term benefit seen in patients who responded in a phase I/II study evaluating the safety and efficacy of mobocertinib in patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations and have been previously treated with systemic chemotherapy.

“Although most EGFR mutations can be targeted by currently available TKIs, people with exon 20 insertion mutations often suffer and feel forgotten since available EGFR inhibitors don’t work well in their cancer,” Jill Feldman, lung cancer patient, advocate, and co-founder of the EGFR Resisters, said in a statement.

Takeda presented development of mobocertinib, including the first public disclosure of the structure, during the American Association for Cancer Research virtual annual meeting I, April 28.