



# TCL

**THE CANCER LETTER**

Inside information on cancer  
research and drug development

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**OUTSTANDING ACADEMIC LEADERSHIP OPPORTUNITY  
DIVISION DIRECTOR, GYNECOLOGICAL ONCOLOGY, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY  
CO-DIRECTOR, WOMEN'S CANCER PROGRAM, CEDARS-SINAI CANCER**

Cedars-Sinai Medical Center, one of the nation's premier healthcare institutions, is conducting a national search for a Division Director, Gynecological Oncology and Co-Director, Women's Cancer Program. Our Gyn-Onc team ranks #5 nationally and #1 in Southern California as the busiest Gyn-Onc surgical service. This is an exciting and transformational time for the cancer enterprise at Cedars-Sinai with its renewed plans and aspirational goals to be a top tier nationally recognized cancer center. Cedars-Sinai Cancer sees over 4800 new cases of cancer per year and is part of Cedars-Sinai Health System, a rapidly expanding vertically integrated health enterprise with practices located in Southern California, including Tower Hematology Oncology, The Angeles Clinic and Research Institute, Cedars-Sinai Valley Oncology Medical Group, the Marina Del Rey Hospital, Hunt Cancer Institute at Torrance Memorial and Cedars-Sinai Medical Center.

Our search will identify an accomplished academic gynecological oncology leader with demonstrated successful leadership experience in division, program or institute (of an NCI designated cancer center) and demonstrated successful research program. The dual role has a reporting relationship to the Chair, Department of Obstetrics and Gynecology and to the Director of the Cancer Center.

**DIRECTOR, DIVISION OF GYNECOLOGICAL ONCOLOGY, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY**

**Position Summary:** Primary responsibilities will be ensuring excellence (clinical, research, education) of the Gynecological Oncology division including but not limited to the following:

**Clinical:** Work with the Chair to actively participate in integration and coordination of pertinent services throughout the Medical Center including growth of clinical volume with focus on quality and safety. Provide vision, oversight and mentoring for the Gyn-Onc division including development of mentoring programs for faculty. Provide Gyn-Onc care with shared coverage with other faculty members.

**Research:** Engage in productive peer-reviewed funded research either basic, translational, population, health services areas and/or clinical trials which support the Department's and Cancer Center's strategic plans. Work to increase divisional research funding from external sponsors including federal, industry and foundation. Provide mentorship and guidance for researchers in the division.

**Education:** Maintain fully accredited fellowship program in Gyn-Onc. Work with residency and fellowship directors regarding Gyn-Onc education for trainees.

**CO-DIRECTOR, WOMEN'S CANCER PROGRAM AT CEDARS-SINAI CANCER**

**Position Summary:** The Women's Cancer Program at Cedars-Sinai Cancer will be co-directed by the Division Director of Gyn-Onc and a faculty member from the Breast Cancer Program. The goals of this position are to bring together faculty with clinical and research programs focused on women's cancers, provide the best collaborative care and facilitate multidisciplinary research in women's cancers across the Cedar-Sinai Health System. The Co-Directors will jointly oversee and collaborate to develop the academic and programmatic aspects of the Women's Cancer Program including but not limited to the following:

**Programmatic:** Provide guidance and oversight to all aspects of Gyn-Onc and Breast Cancer including detection, treatment, prevention, survivorship, healthcare disparities and health policy. Work collaboratively with cancer physicians across the Cedars-Sinai Health System in the development of research and clinical programs.

**Research:** Work to increase number of Gyn-Onc and Breast Cancer clinical trials available to patients and to increase enrollment in these trials across all appropriate Cedars-Sinai clinical sites. Promote and increase academic productivity to ensure increased NIH funding within the Women's Cancer Program.

**Education:** Work with the Associate Director for Education and Training in the Cancer Center to develop strategy for academic excellence in women's cancers education including multi-disciplinary programs for graduate students, medical students, faculty, attending and staff.

As a member of the Cancer Center and the Department of OBGYN leadership teams, the co-directors will be committed to designing and building world class research and clinical programs in Gyn-Onc and Breast Cancer. This includes expanding clinical programs, strategic planning, fiscal responsibility and developing philanthropy.

**Required Qualifications:**

- MD or equivalent degree from an accredited professional school
- Board certified in Gyn-Onc, current California medical license
- California medical license (or eligible for licensure)
- Associate or Professor academic rank
- Five or more years as an established leader of clinical operations with a successful track record demonstrating increased strategic responsibility in a complex, academic healthcare organization
- Leadership roles in professional organizations
- Strong communication, organization and interpersonal skills
- Demonstrated ability to build strong, sustainable partnering relationships
- Demonstrated experience working with and fostering a diverse faculty, staff, and student environment or commitment to do so as a faculty member
- Knowledge and understanding of the trends and forces influencing health care delivery, the provision of care and other emerging issues in today's healthcare environment
- Peer-reviewed research program funding in Gyn-Onc

We are among the nation's leading providers of healthcare services, medical education and medical research, with total annual revenues of \$3.7 billion. Cedars-Sinai is one of the largest non-profit academic medical centers in the U.S. with 886 licensed beds, 2,100 physicians, 3,000 nurses and thousands of other healthcare professionals and staff. Clinical programs range from primary care for preventing, diagnosing and treating common conditions to specialized treatments for rare, complex and advanced illnesses.

**Interested candidates should send their CVs as well as names of three references to  
Dr. Margaret Pisarska c/o angela.russell@cshs.org**

*Cedars-Sinai encourages and welcomes diversity in the workplace AA/EOE*

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# 20-YEAR FOLLOW-UP DATA ARE IN: PROSTATE CANCER PREVENTION WORKS; CONCERNS ABOUT HIGH-GRADE DISEASE DISMISSED



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Prostate cancer is the most common solid tumor in men. It has been estimated that 60-75 percent of men will have histologic evidence of prostate cancer during their lifetime and that 2-4 percent of men will die of the disease. African American men are at a greater risk of diagnosis and death.

While early detection has been found to reduce death from the disease, it comes at a great human cost: 781 men must be screened and 27 men must be treated to prevent one prostate cancer death.

Treatment is associated with significant morbidity, including impotence and incontinence. In the absence of early detection, most men who present with prostate cancer have metastatic disease; once metastases develop, most men will die of prostate cancer within 10 years.

The potential of prostate cancer *prevention* became a possibility in the early 1990's. This concept occurred due to a confluence of events. With the advent of prostate specific antigen (PSA) testing in the mid to late 1980s, the rate of prostate cancer more than doubled in the U.S.

Concurrently, in 1992, the drug finasteride (Proscar) was demonstrated to effectively treat symptoms of prostate enlargement (BPH) and was ultimately found to reduce the risk of complications of BPH. Finasteride is an inhibitor

of the enzyme five alpha-reductase that recapitulates a genetic mutation associated with an absence of development of BPH or prostate cancer.

Another clinical effect of finasteride was the prevention of development of male pattern baldness. With its potential effect on cancer prevention, the Board of Scientific Counsellors of the Division of Cancer Prevention (DCP) of the National Cancer Institute (NCI) recommended the exploration of the first NCI-sponsored clinical trial to determine if prostate cancer could be prevented.

DCP leadership invited Dr. Charles Coltman, group chair of the Southwest Oncology Group (now SWOG Cancer Research Network) to Bethesda to explore possible design options. Dr. Ian Thompson joined Dr. Coltman as the urologic oncologist from SWOG along with Dr. Polly Feigl and Dr. Brent Blumenstein from the SWOG Statistics and Data Management Center.

Others in attendance during the first meeting at the Executive Plaza building included Dr. Otis Brawley (former chief medical officer, American Cancer Society), Dr. Leslie Ford, Dr. Barnett Kramer, and Dr. Peter Greenwald, all from DCP. (Notably, Dr. Coltman passed away in late 2018.) (The Cancer Letter, [Dec. 7, 2018](#))

During this meeting on May 13, 1992, multiple study designs were considered. The initial consideration of prostate cancer mortality as an endpoint was deemed unfeasible as up to 100,000 subjects and 25-30 years of follow-up would be required for such a study.

Since a prostate cancer diagnosis at that time was associated with considerable morbidity (treatment and the side effects of treatment), the study endpoint of prostate cancer prevalence

was selected as one that was meaningful and achievable.

A complicating factor that needed to be accounted for in the design was



The majority of the results of the PCPT are now in. Seven years of treatment with finasteride reduces the risk of prostate cancer by about 25 percent and that reduced risk is durable with 20 years of follow-up. Most tumors that are prevented are low-grade, tumors that are commonly 'observed' at this time.



that the interventional agent (finasteride) affected the primary method of prostate cancer detection (elevated PSA levels), decreasing PSA by about 50 percent and shrinking the prostate gland effecting the sensitivity digital rectal exam (DRE).

The final study design included adjusted blinded PSA values, but because the precise adjustment of PSA was not possible and the DRE effect could not be accounted for, it was determined that the only method of minimizing detection bias caused by the finasteride was to include an end-of-study prostate biopsy in all subjects at the end of their seven-year course of treatment with study drug.

After approval of the study design by the NCI and identification of more than 200 study sites around the U.S. and one site in Canada, training of hundreds of study personnel and principal investigators was conducted in 1993 followed by a press conference at the National Press Club in Washington, D.C.

Within hours, the Cancer Information Service telephone lines were flooded with requests for more information from men interested in study participation.

The PCPT was designed to accrue 18,000 men over a three-year period; due to this intense interest, not only was subject accrual complete in the anticipated three-year period but ultimately, 18,882 men enrolled and were randomized between January 1994 and May 1997.

Over the course of the study, an independent Data Safety and Monitoring Committee evaluated the critical assumptions of the study, adherence of study subjects to the trial, and, importantly, rates of recommended biopsies and prostate cancer in the two study groups: placebo and finasteride.

Two-thirds of the study subjects were randomized in the first year, and seven years later, in 2001, two-thirds of the study subjects were scheduled for their end-of-study biopsy.

On Feb. 21, 2003, during a DSMC meeting, on the basis of an analysis that concluded that further biopsies would not change the results that were reached at that time, the DSMC voted to recom-

mend study closure and to discontinue any further treatment for study subjects who were still on study.

The conclusion was that finasteride significantly reduced the relative risk of prostate cancer, by 24.8 percent, meeting the primary objective of the study. A total of 1,147 prostate cancers were seen with placebo, compared with 803 with finasteride.

Complicating the study finding was a paradox: while prostate cancer risk was reduced significantly, a greater number of high-grade prostate cancers were seen with finasteride. While there were 344 fewer overall cancers, there were 43 more high-grade cancers with finasteride.

The study leadership team decided that the best way to report these findings and to close the study would be to prepare a manuscript for publication that would then go through high-level peer review to optimize the scientific discussion of this paradoxical finding and to release information to participants and institutions concurrently with a fast-track publication.

On July 17, 2003, *The Influence of Finasteride on the Development of Prostate Cancer* was published in *New England Journal of Medicine (NEJM)*. The publication related the significant reduction in risk of prostate cancer, the smaller but statistically-significant increased risk of high-grade cancer, but did not address analyses to explore why these findings may have occurred; these analyses would have to wait for additional data to be collected, cleaned and analyzed.

Concurrent with the *NEJM* manuscript was the publication of an editorial by Dr. Peter Scardino. In that editorial, Dr. Scardino stated that finasteride should not be recommended for prevention of prostate cancer and that further

follow-up would be required to understand the study's findings.

Side effects of finasteride included a small but statistically significant negative impact on sexual function and a small increased risk of breast enlargement.

Over the ensuing years, three key investigations and publications helped us understand why there were more high-grade cancers seen in the finasteride study group.

The first of these was in 2006, when PCPT investigators reported in the *Journal of the National Cancer Institute (JNCI)* that finasteride significantly improved the performance of PSA for prostate cancer detection and for detection of high-grade prostate cancer.

In 2007, the PCPT team reported in *Journal of Urology* that finasteride similarly significantly improved the performance of digital rectal examination for detection of prostate cancer.

Finally, in 2007, a group led by Dr. Scott Lucia, the lead PCPT study pathologist, reported in *JNCI* on the comparison of biopsy and radical prostatectomy tumor grades in the two study arms.

They found that if high grade prostate cancer were truly present (confirmed by radical prostatectomy), it was missed on biopsy 50 percent of the time in men who received placebo, compared to only 30 percent of the time in men who received finasteride.

Several subsequent studies evaluated how these biases (that increased the likelihood of detecting prostate cancer and detecting high-grade cancer in men who received finasteride) would have affected the final study results.

In 2008, in the journal *Cancer Prevention Research*, SWOG biostatistician Dr.

Mary Redman estimated that accounting for these biases, the overall risk of cancer was reduced by 30 percent, and that, although based on small numbers, the risk of high-grade cancer was reduced by 28 percent with finasteride.

In 2010, a group of investigators working with Glaxo Smith Kline, published in *New England Journal of Medicine* the results of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) clinical trial. This study examined the impact of a dual 5-alpha reductase inhibitor--dutasteride--on the risk of prostate cancer in men with elevated PSA levels (2.5 to 10 ng/mL) and a prior negative biopsy.

The authors found that dutasteride reduced the relative risk of prostate cancer by 22.8 percent over four years. While the total number of Gleason 7-10 tumors was similar in the two study arms, there were more Gleason 8-10 tumors in the men receiving dutasteride.

Based on the results of the REDUCE clinical trial, GSK approached the U.S. Food and Drug Administration about placing these results in the product information for dutasteride. Although almost 10 years previously, the significant reduction of prostate cancer that had been identified with finasteride, these results had not been placed in the product information for finasteride, initially manufactured by Merck. Notably, finasteride became a generic drug in October 2014.

In response, the FDA referred the GSK request to the Oncologic Drugs Advisory Committee (ODAC) in late 2010. Merck was requested to also present information related to finasteride at that meeting and Dr. Ian Thompson (study principal investigator) and Dr. Catherine Tangen (study lead statistician) attended.

The ultimate decision was made to not only exclude information related to a reduced risk of prostate cancer with both drugs, but to also place a warning in the product information materials for finasteride stating that there may be an increased risk of high-grade prostate cancer.

The information related to improved detection of prostate cancer and of high-grade prostate cancer was not included.

Over the years following the 2003 release of the original PCPT results that finasteride reduced the risk of prostate cancer by 24.8 percent, despite the enhanced detection of cancer with finasteride, very little interest was seen for the use of this drug to prevent the most common cancer in men.

The most common reason cited was the *potential* increased risk of high-grade cancer that could negate the reduced risk by increasing risk of death from prostate cancer.

In August 2013, PCPT study investigators published long-term survival outcomes of the study in *NEJM*, finding no differences in overall survival in men randomized to finasteride versus placebo.

Subsequently, in 2018, Dr. Joseph Unger and SWOG investigators, after linking PCPT participants with Medicare data, reported on long-term prostate cancer risk in *JNCI*. The investigators found that with up to 20 years of follow-up, the approximately 25 percent reduction in risk was durable.

Understanding that the primary hurdle to the use of finasteride for prevention of prostate cancer was the observed increased number of high-grade cancers and that these high grade cancers could increase the risk of prostate cancer death, SWOG investigators led by

Phyllis Goodman conducted an analysis to answer the question: *what was the impact of seven years of finasteride on PCPT participants risk of prostate cancer death?*

To address the question, PCPT participants were linked to the National Death Index which provided cause of death.

The results were published on Jan. 24, 2019, in *NEJM*. With 296,842 person-years of follow-up and a median follow-up of 18.4 years, of 9,423 men randomized to finasteride, there were 3,048 deaths and 42 deaths due to prostate cancer. By comparison, of 9,457 men randomized to placebo, there were 2,979 deaths of which 56 were due to prostate cancer.

While there was a 25 percent lower risk of prostate cancer on the finasteride arm, with a small number of prostate cancer deaths, this difference was not statistically significant.

Interestingly, of the prostate cancer deaths in which tumor grade was known, more than a third of the men who died of prostate cancer were originally diagnosed with a Gleason  $\leq 6$  tumors, the type of cancer that is reduced significantly with finasteride.

The majority of the results of the PCPT are now in. Seven years of treatment with finasteride reduces the risk of prostate cancer by about 25 percent and that reduced risk is durable with 20 years of follow-up. Most tumors that are prevented are low-grade, tumors that are commonly “observed” at this time, but that are ultimately treated with radical prostatectomy or radical radiation therapy in about half of men. These treatments can have significant side effects, including impotence and incontinence.

Finasteride also improves urinary symptoms in men with BPH and sig-

nificantly reduces the need for treatment of BPH or complications of BPH (such as urinary retention).

The cost of the drug is \$7 to \$8 per month, as it is generic.

Despite significantly fewer cancers in men who receive finasteride, the drug also improves detection of prostate cancer by better performance of PSA testing and of prostate biopsy. From the most recent analysis, we now know that overall survival of men and risk of prostate cancer death is unaffected by finasteride.

As had been anticipated, it would have taken a study many times larger to have been able to detect a statistically significant difference in risk of prostate cancer death.

Historically, one man in six has been diagnosed with prostate cancer in the U.S. A 25 percent reduction in risk with finasteride would have a profound impact on cancer risk and our nation’s war on cancer. That the drug has a relatively low risk of side effects, is inexpensive, and improves urinary function in men who commonly suffer problems from prostate enlargement makes it an even more attractive method of prevention. Men who are most likely to benefit are those who are undergoing PSA testing.

Physicians who are ordering PSA testing for men 55 years of age and older should explain these results to patients and offer the opportunity to reduce their risk of prostate cancer with finasteride.





GUEST EDITORIAL

# The Prostate Cancer Prevention Trial and **nine lessons** in prostate cancer medicine



**Otis W. Brawley**

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Johns Hopkins University*

The publication by Ian M. Thompson and colleagues in last week's New England Journal of Medicine regarding long term follow-up of patients in the NCI-sponsored Prostate Cancer Prevention Trial (PCPT) marks a good opportunity to review and reflect on the history of the trial and the past 30 years of prostate cancer medicine.

George Santayana is oft quoted as saying that "those who do not remember the past are condemned to repeat it." There are many lessons here that should influence our approach to modern health care issues in general and prostate cancer specifically, such that we do not repeat the harm that had been caused by closed-mindedness and ignorance around prostate cancer.

In the 1990's, prostate cancer was (and indeed still is) a significant cause of human suffering. The nineties was a time of prostate cancer hysteria. Society was just starting to talk openly about cancer. Studies indicated prostate specific antigen (PSA) screening could find prostate cancer early. Many public figures were willing to publicly say that they had prostate cancer and PSA screening saved their lives. Many felt an obligation to be an example to save other men. They preached decades-old messages of cancer early detection.

By 1992, patient advocacy was becoming increasingly prominent in AIDS and women's health. Advocacy moved into the prostate cancer arena with formation of a group called Us TOO. The

group advocated for prostate awareness, screening and treatment. Their prejudice toward screening and treatment is understandable due to fear of cancer and the years of messaging regarding early detection.

In the US, hospitals and clinics responded to this hysteria by putting prostate cancer screening and treatment into their business plans. Mass screening in malls and community centers was being advertised. While most thought that they were doing a public service, the fact that screening and treatment were lucrative helped keep health-care providers from questioning their health benefits. It is fascinating that the introduction and use of PSA was more rational in Europe.

## The importance of clinical trials

In early 1990's prostate cancer medicine, few prostate clinical studies had been attempted. There were studies showing that PSA could find localized cancer. No study had been conducted to show that PSA screening saved lives. Indeed, no study had been conducted to show that treatment of localized disease saved lives.

PSA was, and to this day is, FDA-approved for diagnosis of disease in men for whom there is a clinical suspicion of prostate cancer and for following progression of diagnosed disease. It was not—and still is not—FDA-approved for screening.

Prospective randomized trials take a long time. Some felt a sense of urgency, arguing against doing the appropriate clinical trials and staying the course, i.e. continuing to screen and treat, because people are dying.

Truth is, bad or inappropriate medicine can also kill. Medicine's inability to predict effectiveness is fraught with interventions that were thought beneficial, but really caused harm. Fortunately, over the past two decades, well-designed trials definitively demonstrated that:

- Treatment of prostate cancer can prolong survival in 1997. The first study to show a treatment benefit demonstrated that radiation therapy and hormones was better than radiation alone for locally advanced disease. (1)
- Radical prostatectomy for localized disease prevents death in 2002. (2)
- PSA screening combined with treatment saves lives in 2009. (3)
- The majority of men with screened detected prostate cancer do not need treatment in 2016. (4) One screening study, the NCI The

Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, was crippled by the American screening frenzy. (5)

It was hard to convince a man randomized to the control group to not get screening when all of his friends were doing it. Many Americans felt that it was unethical to do a study which required a group randomized to a non-screening arm.

I was involved in the launch of PCPT in 1992. The study was severely criticized by some in the medical community. While some criticism or skepticism is healthy and always legitimate in medicine, the loudest critics of PCPT spoke without decency and often misrepresented the science while denigrating me and the trial. They indicated ignorance of the science. For some, the concept of prevention was neither understood nor valued. They attacked the study because it took away from the "screen, screen, treat!!!" message.

The tendency of "experts" to be extremely vocal often demonstrates ignorance of the science. I have seen it in many cancer screening arguments. As I recall the often impolite, sometimes ad hominem comments from PCPT critics, I am reminded of the Abraham Lincoln quote: "Better to remain silent and be thought a fool than to speak and to remove all doubt."

### Lesson 1: Some so called "expert opinion leaders" are not very expert.

Interestingly, the lay public was very much interested in prevention and frightened of prostate cancer. The fast accrual to PCPT was evidence of this. The trial participants were overwhelmingly educated and middle class. Even a high proportion of the racial minorities on the trial had a graduate degree.

### Lesson 2: Most men will never be diagnosed with prostate cancer.

PCPT was one of the first trials where a special emphasis was placed on accruing minorities and the traditionally underserved. As the trial went on, we learned that poor people are extremely rational. They do not have time to get involved in a study to assess prevention of a disease they are not likely to get.

## The prevention findings

After more than a decade, the study found that 7 years of 5-alpha reductase therapy with finasteride lowers the period prevalence of prostate cancer by 25 percent. (6) It found that 24.4 percent of men on the placebo arm were diagnosed with prostate cancer, compared to 18.4 percent on the treatment arm. PCPT also showed that men taking finasteride and diagnosed with prostate cancer had a higher likelihood of having high grade prostate cancer. This led to the concern that finasteride causes high grade prostate cancer.

A second 5-alpha reductase inhibitor dutasteride was marketed. It was tested in a prospective randomized placebo-controlled prevention study, and it too reduced prostate cancer prevalence with an increase in the proportion of high-grade cancers in those diagnosed while on 5-alpha reductase therapy.(7)

A number of studies pointed away from 5-alpha reductase therapy causing high grade prostate cancer and demonstrated that it improves ability of PSA screening to find high-grade cancers. Despite these data, the FDA required a warning label that finasteride and dutasteride might increase the risk of high-grade prostate cancer. It is unfortunate that the FDA action

came after an Oncologic Drug Advisory Committee (ODAC) meeting in which some of the PCPT critics would not allow presentation and consideration of all of the evidence.

**Lesson 3: It is importance that consensus panels be open-minded and consider all the literature.**

The warning led to lawsuits, as money-hungry attorneys sought prostate cancer patients who had taken these drugs. This scared drug companies from interest in prostate cancer risk reduction.

**Lesson 4: Long-term use of 5-alpha reductase inhibitors reduces risk of prostate cancer and may reduce risk of prostate death.**

**Lesson 5: Treatment with 5-alpha reductase inhibitors improves the operating characteristics of PSA screening.**

The long-term follow-up of participants in the PCPT is the clearest and best evidence that finasteride therapy reduces risk of prostate cancer and that it's safe. It suggests that the effects of finasteride go well beyond the seven-year period of therapy and it may even reduce risk of prostate death. The finding is open to some legitimate skepticism, as follow-up through the National Death Index is not as good as clinical follow-up. Unfortunately, long-term follow-up of NCI clinical trial participants is going away due to budget constraints.

Despite this one weakness, I believe the evidence is sufficient to warrant removal of the FDA warning placed on 5-alpha reductase inhibitors, and the evidence now supports an indication

for prostate cancer risk reduction. The 5-alpha reductase inhibitors are now generic. No drug company has a financial interest in obtaining an indication for prostate cancer risk reduction using finasteride or dutasteride. This is unfortunate for the public health. Perhaps the National Cancer Institute, which started this body of work nearly 30 years ago, will complete it by filing for the indication.

## Prostate cancer screening

The PCPT taught a number of lessons about prostate cancer screening. The placebo arm is one of the best-controlled PSA screened cohorts ever. The study enrolled men with a PSA of 3 ng/ml or less. A reasonable criticism was that the study was trying to prevent prostate cancer in men at low risk of prostate cancer. It was a big surprise that prostate cancer was diagnosed in 24.4 percent of these "low risk" men.

**Lesson 6: Prostate cancer is extremely common in healthy men. We have the technology to diagnose it in at least one in four men in their sixties.**

Of men diagnosed with prostate cancer on the placebo arm, half were diagnosed through PSA screening and half were diagnosed through a biopsy that was called for in all men who had normal PSA screening over the seven years of the trial.

**Lesson 7: PSA screening of "low-risk" men can find a lot of prostate cancer and miss a lot of cancer.**

Indeed, PSA screening missed as much prostate cancer as it found. Prostate cancer can be diagnosed in men with very low PSA level.

**Lesson 8: Most people think every man diagnosed with prostate cancer will die of it if not treated. Fact is, most men who are diagnosed with prostate cancer do not die of it and do not need treatment.**

PCPT showed that 25 percent of men can be diagnosed (half through PSA screening in a seven-year period). The NCI SEER studies suggest that less than 3 percent of men die of prostate cancer. The Schroeder screening study suggests that lifetime risk can be reduced from about 3 percent to about 2.4 percent.

**Lesson 9: Half of all men diagnosed with prostate cancer through screening have a Gleason 6 prostate cancer. A third of those who died of prostate cancer in PCPT initially had a Gleason 6 cancer.**

This demonstrates the need for careful observation of those undergoing surveillance and the need for better laboratory tests to predict significant disease.

We have come a long way in our understanding of prostate cancer since the beginning of PCPT and the publication of the other large prostate cancer trials. We have increased appreciation for the need for rigorous assessment of the literature. We also have increased appreciation of the limits of our knowledge. Most screening recommendations involve informed decision-making. Perhaps the American Society of Clinical Oncology (ASCO) decision aid best explains what is known about prostate cancer screening and treatment.<sup>(9)</sup> Out of 1,000 men age 55 who choose to be screened to age 70, about 96 will be diagnosed with prostate cancer and 4 will ultimately die of the disease.

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- Out of 1,000 men age 55 who choose not to be screened to age 70, about 60 will be diagnosed with prostate cancer and 5 will ultimately die of the disease.
- The 4 deaths per 1,000 vs. 5 deaths per 1000 represents the 20 percent reduction in relative risk of death.

The high number of men who are diagnosed and do not die of prostate cancer indicates that a substantial number of men do not benefit from treatment and again show that the need to be able to identify the men for whom observation is best and the 1 in 1,000 men who will benefit from treatment of localized disease.

In April 2017, the American Urologic Association (AUA), the American Society of Therapeutic Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO) released a joint evidence-based practice guideline on clinically localized prostate cancer. It was later endorsed by the American Society of Clinical Oncology. The guideline stresses the importance of involving the patient in shared decision-making regarding prostate cancer screening and treatment. (9)

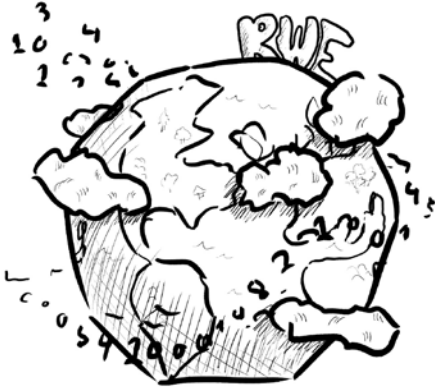
It also stressed the importance of evaluating a cancer for risk of clinical significance and says that active surveillance is the best initial care option for most low-risk localized prostate cancer.

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## REAL-WORLD EVIDENCE



# Gottlieb: FDA to expand real-world data infrastructure to enhance AI capabilities

By Matthew Bin Han Ong

FDA is enhancing its ability to handle real-world evidence by training reviewers in data science via a curriculum on machine learning and artificial intelligence, said FDA Commissioner Scott Gottlieb.

“We’re working to develop new guidance documents to assist sponsors interested in developing and using real-world evidence,” Gottlieb said at a Jan. 28 panel discussion organized by the Bipartisan Policy Center.

“Our ‘Framework for Real-World Evidence Program’ will apply a consistent strategy for harnessing these tools across our drug and biologic review programs,” said Gottlieb, referring to a framework document published last December. The document evaluates the use of RWE to support additional indications for already approved drugs as well as to satisfy drug post-marketing study requirements (The Cancer Letter, [Jan. 4](#)).

“The framework is aimed at leveraging information gathered from patients and the medical community to inform and shape the FDA’s decisions across our drug and biologic development

efforts,” Gottlieb said. “The goal is to develop a path for ensuring that RWE solutions can play a more integral role in drug development and regulatory life cycle at the FDA.

“Today, I’m announcing four additional activities that’ll help FDA and stakeholders advance these opportunities for the benefit of patients.”

FDA plans to:

- Support the seamless integration of digital technologies in clinical trials by developing a framework on how digital systems can be used to enhance the efficient oversight of clinical trials. These technologies present important opportunities to streamline drug trials and improve data site integrity by remotely monitoring data trends, accrual, and integrity over the course of a trial.

- Use digital technologies to bring clinical trials to the patient, rather than always requiring the patient to travel to the investigator. More accessible clinical trials can facilitate participation by more diverse patient populations within diverse community settings where patient care is delivered, and in the process can generate information that’s more representative of the real world and may help providers and patients make more informed treatment decisions.
- Explore how reviewers can have more insight into how labeling changes inform provider prescribing decisions and patient outcomes. The FDA’s Information Exchange and Data Transformation—or INFORMED—is using RWD to examine the impact of a recent FDA labeling change for two approved products from weight-based dosing to flat-dosing of immune check-

point inhibitors. This project is focused on how community practices are adopting the flat dose after the labeling change, and factors that may affect adoption.

- Work with the medical product centers to develop an FDA curriculum on machine learning and artificial intelligence in partnership with external academic partners. The aim of this program is to improve the ability of FDA reviewers and managers to evaluate products that incorporate advanced algorithms and facilitate the FDA's capacity to develop novel regulatory science tools harnessing these approaches.

FDA's Oncology Center of Excellence is working with Friends of Cancer Research, NCI, and others to harmonize reference standards for assessing tumor mutational burden—as determined by multiple proprietary assays—to help identify cancer patients who are more likely to respond to immunotherapy.

Harmonizing the measurement of tumor mutational burden across commercial assays used in routine oncology care can help reduce treatment variability, and improve the utility of TMB as a potential biomarker for enriching clinical trials that are designed to test immunotherapies.

OCE is also working on a project exploring whether it's possible to use real world endpoints, such as time to treatment discontinuation (TTD), as a potential real-world endpoint for pragmatic randomized clinical trials, for FDA approved therapies in the post-market setting.

“Through ‘Project: Switch,’ OCE is investigating whether well-matched contemporaneous synthetic control arms based on prior clinical trials can be used to make inferences regarding the effect of a new drug, or whether a synthetic control could be used to compare data to active control arms

in ongoing randomized controlled trials in rare tumor types where the standard of care remained stagnant, and the prognosis is especially poor,” Gottlieb said.

FDA's framework for RWE, created in response to a mandate in the 21st Century Cures, spells out the agency's thinking on the types of guidances that need to be developed before RWE can be routinely used in regulatory science (The Cancer Letter, [Jan. 4](#)).

“We really need people to weigh in on the guidances, because one thing I did learn at FDA, pretty much if the FDA says something, the industry is going to do it,” former FDA Commissioner Robert Califf said at the meeting Jan. 28. “So, we'd like to get those guidances right.

“I'm very excited that Amy Abernethy is coming to the FDA [as principal deputy commissioner]. She is an expert on this, I have every confidence that she'll help guide us through this.” (The Cancer Letter, [Jan. 4](#)).

There is a need to better understand AI algorithms, and whether they generate results that are replicable, said former FDA Commissioner Mark McClellan, who is also a former commissioner for the Centers for Medicare and Medicaid Services.

“It's great to see the progress that's happening at FDA,” McClellan said at the meeting. “I think Rob [Califf]'s vision for what the future ought to look like, which is a lot of data from a wide variety of sources, including many that a lot of people in the health care industry aren't really thinking about as important sources of health relevant information—that is the right vision. I think we're still a long way from getting there. So, great vision, great potential.”

Using real-world data effectively is akin to monitoring jet engines to prevent plane crashes, said Andrew von

Eschenbach, former FDA commissioner and former NCI director.

“People won't die, because planes don't crash. GE has a system in which their jet engines have an incredible number of sensors that are in those engines and they're sensing and monitoring those engines in real time, and so they know in real time if there's anything going wrong,” von Eschenbach said at the meeting.

“I think what we have is the opportunity with the kinds of tools that are now becoming available, be they sensors in humans, or the opportunity to access the data that's coming in both real time and retrospectively, we're going to be able to prevent problems. We're going to be able to see ahead, just like they can, and not only retrospectively correct what's going on, but prospectively be able to create what needs to be created to save lives.”



I think what we have is the opportunity with the kinds of tools that are now becoming available, be they sensors in humans, or the opportunity to access the data that's coming in both real time and retrospectively, we're going to be able to prevent problems.



—Andrew von Eschenbach

# Industry a no-show as Sens. Grassley and Wyden hold hearing on drug pricing

By Claire Dietz

Earlier this week, the Senate Committee on Finance convened what is likely to be the first in a series of hearings focused on the rising costs of prescription drugs, oncology drugs among them.

“This hearing is not a one-off,” Sen. Ron Wyden (D-OR), the committee’s ranking member, said at the hearing Jan. 29. “This is the first in a series we will hold on this topic. So, nobody is going away, and even if it means using our power to compel the drug company CEOs to show up, they will come before this committee. The crisis of prescription drug costs threatens too many lives and bankrupts too many people for the Congress to tolerate this ducking and weaving by the companies that caused it.”

Several pharmaceutical companies were invited to testify—two said they would show up, but none were seen at the Dirksen Senate Office Building on the day of the hearing.

“I want to express my displeasure at the lack of cooperation from the pharmaceutical manufacturers recently,” said Sen. Chuck Grassley (R-IA), the

committee’s chair, who, like Wyden, is known for his penchant for political theater. “The companies that declined said they would discuss their ideas in private, but not in public. One company mentioned that testifying before the committee would create a language barrier problem. That is not what I mean when I talk about transparency.”

The drug industry lobbying association PhRMA declined to comment. Biotechnology Innovation Organization, another trade association, didn’t respond to an email from The Cancer Letter.

At the hearing, Wyden said he plans to take a closer look at why drug manufacturers have “unchecked power” when setting prices.

“I’m especially troubled by health care middlemen who skim off enormous sums of money, when there’s scant evidence they’re getting patients a bet-

ter deal,” Wyden said. “That sure looks like it’s the case with pharmacy benefit managers. Called PBMs, they’re supposed to negotiate better deals, but the reality is, they take a big cut and inflate list prices.”

Early in his career, Wyden, then a House member, challenged the pricing of Bristol-Myers Squibb drug Taxol (paclitaxel), arguing that the drug, developed through a Cooperative Research and Development Agreement with NCI, had enabled the company to, as he put it, “price gouge.”

Wyden’s efforts resulted in a “reasonable pricing clause” for drugs developed through collaboration between NIH and pharmaceutical companies.

The clause was ultimately removed from NIH reauthorization, as companies complained that working with government researchers had become

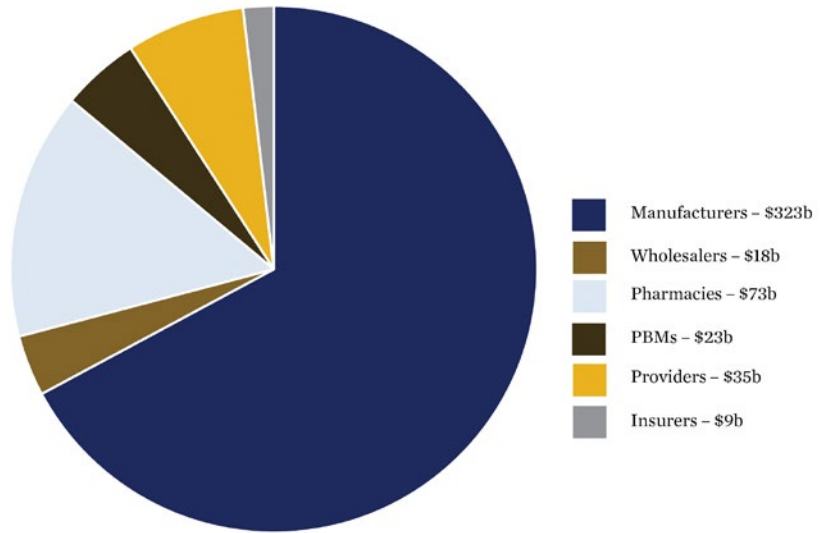
unsustainable. Wyden has famously made tobacco executives testify under oath about the link between tobacco and cancer. Similarly, he made oil company executives testify on the link between fossil fuels and global warming. It's unlikely in the extreme that pharma executives want to play part in a similar show.

The prices of cancer drugs are increasing at an unsustainable rate, Peter Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, said in his testimony at the hearing. Bach runs the Drug Pricing Lab, which is funded by the Laura and John Arnold Foundation, Kaiser Permanente, and MSK.

The largest share of pharmaceutical product revenues goes to drug manufacturers, Bach testified. In 2016, out of \$500 billion in total spending, \$323 billion—about two-thirds—went to industry, Bach said. The rest of the revenues were retained by wholesalers, pharmacies, PBMs, providers, and insurers. The text of Bach's study is posted [here](#).

"An organizing theme of the pharmaceutical supply chain is that all participants benefit as both drug prices and total spending rise," Bach said. "Pharmaceutical corporations logically seek to profit by charging high prices, but ideally the other parties in the supply chain would serve as a countervailing force to push prices down.

"Pharmaceutical products are often marked up in percentage terms as they pass through the supply chain," Bach said. "This means that more expensive drugs on average bring larger profits. This pattern applies to wholesalers and pharmacies. It also applies to physicians and hospitals when they use expensive infused drugs covered by Medicare Part B. This is because the reimbursement formula for Part B drugs



Source: Peter Bach

includes a mark-up over the average acquisition price of the drug."

Bach's full testimony can be found [here](#).

As a result, physicians are significantly more likely to mark up prices, Bach's study shows.

"We recently reviewed studies that examine whether or not the profit potential for various [Medicare] Part B drugs influences prescribing; across the studies we examined, the conclusion was consistent that they do," Bach said. "On the margin, physicians will prescribe the more profitable of drugs when there are options to choose from. Aaron Mitchell and colleagues published a review of this topic as well. [These] authors graded the quality of the literature along with summarizing its findings and arrived at the same conclusion. Physicians systematically select more profitable drugs to prescribe when they are able to choose among clinically substitutable options."

This preference was also noted in hospital outpatient departments.

"My team conducted an analysis that showed that among treatments in oncology that are not recommended and that involve expensive Part B drugs, the likelihood that these treatments were administered was higher in physician offices than hospital outpatient departments across all the clinical scenarios we examined, a finding that was robust to clinical severity risk adjustment." Bach said.

Douglas Holtz-Eakin, president of American Action Forum, said debates on drug pricing should focus on the "high-value," not "low cost" of drugs.

"Particularly with oncology drugs, it is important to make sure that the cost of the treatments correlates to the value," Holtz-Eakin said at the hearing. "Remember that the goal is not low cost, it is high value. It is easy to have low-cost drugs; they, however, may not do much good. Conversely, it might make sense



to spend more for a drug if its therapeutic benefits are high enough.”

The American Action Forum is an affiliate of American Action Network, which, according to its website, is an “action tank” that will create, encourage and promote center-right policies based on the principles of freedom, limited government, American exceptionalism, and strong national security. The American Action Network’s primary goal is to put our center-right ideas into action by engaging the hearts and minds of the American people and spurring them into active participation in our democracy.”

“Policymakers should first identify the ‘actual problem’ in the debate on drug pricing, Holtz-Eakin said.

“There is little consensus in the term ‘rising drug costs,’ making it difficult to determine if there is an actual policy problem, its size, or its scope,” Holtz-Eakin said. “Rising drug costs could also mean an increase in overall prescription drug expenditures, whether in dollar figures or as a percentage of National Health Expenditures,” Holtz-Eakin said. “Because spending is a function of both price and quantity, this could result from increased utilization due to rising national reliance on prescription drugs or broader access to them.”

The long-term financing of cures is the industry’s way of framing the issue backwards, with the goal of protecting their revenues, Bach said.

“‘Value-based pricing’ has been proposed by a number of analysts for new branded drugs with no competition,” he said. “Today we often end up with drugs priced at levels well beyond what their benefits justify. We then see payers attempt to counteract these high prices. Payers insert barriers to access including shifting costs to out of pocket, delaying access through utilization

management, and generally thinning the quality of the insurance benefit for patients who most need insurance.”

In cases where pharmaceutical companies are able to extend drug patents and prevent generic versions from entering the market, they have monopoly over drug prices.



**Pharmaceutical corporations logically seek to profit by charging high prices, but ideally the other parties in the supply chain would serve as a countervailing force to push prices down.**

– Peter Bach



“When companies say we need to change our payment system to afford their new high-priced treatments, they are framing the issue backwards,” he said. “Prices for monopoly goods are dictated primarily by what payers are willing to pay for them, as the companies do not face traditional market competition that would put downward pressure on their prices.

“So, when companies call for long term financing to pay them for their treatments, they are inventing a means by which the market can pay them more than they would get without such a system. But in viewing this proposal, it is important to keep in mind that these drugs do not inherently cost \$1 million or \$2 million dollars. Rather, it is policy choices that will dictate what they cost, policy should not configure to what the corporations want them to cost.”

Bach proposed what he refers to as “The Netflix Model,” which would allow states to procure highly priced Hepati-

tis C medication at a flat subscription payment over a set number of years.

Mark Miller, executive vice president of health care at the Arnold Ventures, previously known as the Laura and John Arnold Foundation, said the “virtuous cycle” of pharmaceutical companies maintains these monopolies.

“Instead of encouraging research into the next generation of cures, firms with drugs approved by the FDA are incentivized to hold on to their monopolies as long as possible and deploy as many anti-competitive tactics as possible to ensure generics or biosimilars are not available,” Miller said.

“Of the roughly 100 best selling drugs, nearly 80 percent obtained an additional patent to extend their monopoly period at least once,” he said. “Nearly 50 percent extended it more than once. For the 12 top selling drugs in the United States, manufacturers filed, on average, 125 patent applications and were granted 71. For these same drugs, invoice prices have increased by 68 percent.”

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## IN BRIEF



## Califano named physician-in-chief of Moores Cancer Center



Joseph Califano was named physician-in-chief of Moores Cancer Center at UC San Diego Health. Califano will retain his roles as professor of surgery and director of the Head and Neck Cancer Center as well as maintain an active clinical practice in head and neck surgery.

His principal role will be to oversee clinical operations related to Moores Cancer Center and all related inpatient

and outpatient oncology services at UC San Diego Health, as well as operations with affiliates and outreach clinics.

In this role, Califano will be directly responsible to Scott Lippman, director of Moores Cancer Center, or as delegated to Catriona Jamieson, deputy director of Moores Cancer Center.

For ambulatory clinic operations, Califano will have a reporting relationship to Christopher Kane, chief executive officer, UC San Diego Health Physician Group. For hospital-based services and quality initiatives, he will also have a reporting relationship to Thomas Moore, MD, interim chief medical officer.

As physician in chief, Califano will be appointed to the Cancer Center Executive Committee and will work in partnership with Julie Croner, chief administrative officer, on operational and strategic opportunities that further the mission and vision of the cancer center, including reviewing and redesigning the organizational structure for cancer center medical leadership, advising on clinical faculty recruitments and resource allocation, standardizing cancer center processes and procedures and coordinating with cancer center leaders for clinical research and education efforts.

Additionally, Califano will be responsible for service line performance, collaborating with ancillary services including radiology and pathology/laboratory, leading the oversight committee for Moores Cancer Center psychology and psychiatry services, overseeing clinical quality and patient satisfaction in conjunction with the chief medical officer, managing approvals for charity care, high cost drugs, and inpatient imaging, advancing the agenda of cancer center quality and value, and appointing a new director of quality.

As well, Califano will participate in Board of Visitors and philanthropy

meetings and cancer center and health system strategic planning as well as oversee clinical space planning, including for new facilities and service offerings. He will also collaborate with chairs and division chiefs as it relates to the clinical faculty practice within the cancer center.

Califano will be directly responsible for:

- Oversight of disease team leaders and cancer cabinet in collaboration with Croner and Razelle Kurzrock, senior deputy director of clinical research, including goal setting and annual review;
- Oversight of clinic medical directors in collaboration with Kane and Croner, including goal setting and annual review;
- Oversight of hospital medical directors in collaboration with Moore, including goal setting and annual review.

## NYU receives anonymous \$75M gift to establish center for blood cancers

NYU Langone Health's Laura and Isaac Perlmutter Cancer Center announced a transformational philanthropic gift to establish a Center for Blood Cancers that will house a new, world-class program for multiple myeloma care and research, along with its other blood cancer programs. The new center will significantly expand Perlmutter Cancer Center's capacity to study and treat blood cancers.

The \$75 million gift was donated anonymously in support of Perlmutter Cancer Center's campaign to enhance its state-of-the-art research and clinical space.



The new center will expand services for patients, bolster new and ongoing research efforts, and provide expanded educational resources for students and faculty at NYU School of Medicine. Lab space and cell processing within the Center for Blood Cancers will be increased considerably, and infusion and exam rooms will be added to ensure efficient patient flow.

In addition to bolstering multiple myeloma research and care, the new center will expand research capabilities focusing on clinical trial recruitment and efforts to identify markers for different cancer types to recognize blood cancers at its earliest stages. Enhanced educational opportunities in this area will now be available as well for fellows at NYU School of Medicine.

“There is a pressing need for more research in the areas of early diagnosis and prevention of blood cancers,” says Benjamin Neel, director of Perlmutter Cancer Center. “As a nationally recognized cancer center, we are proud to continue to be on the leading edge of research and clinical care in this area. This gift will help us attract new talent, leaders, and added expertise to further our mission to prevent and treat these deadly diseases.”

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## Ross Mitchell named artificial intelligence officer at Moffitt

Ross Mitchell has joined Moffitt Cancer Center as the artificial intelligence officer.

In this new role, he will lead the cancer center’s efforts to develop digital tools and technologies that utilize computer science to improve the efficiency and quality of cancer care.

Mitchell is also a senior member of Moffitt’s Department of Biostatistics and Bioinformatics and will collabo-

rate with fellow research faculty to optimize projects utilizing artificial intelligence applications.

“Data science is a growing area in cancer research and care. Through the analysis of data, we can better predict outcomes to assist with informed decision-making. Mitchell will help Moffitt identify those business and clinical opportunities where predictive analytics, machine learning and other advanced technologies can be used to improve our patient experience,” said Dana Rollison, vice president, chief data officer and associate center director of Data Science at Moffitt. “He will also bring this skillset to our research enterprise.”

Mitchell comes to Moffitt from the Mayo Clinic in Scottsdale, where he led multiple medical imaging informatics initiatives such as the application of machine learning in brain tumor imaging.

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## Sagar Lonial awarded Gray Family Chair in Cancer at Winship



Sagar Lonial, chief medical officer for Winship Cancer Institute of Emory University and chairman of the Department of Hematology and Medical Oncology, was presented with

the Anne and Bernard Gray Family Chair in Cancer.

The endowment honors the life of Gray’s sister, Karen Ammons Howell, who died of breast cancer.

Lonial is an expert in the biology and care of patients with multiple myeloma. His most recent research focuses on combining novel agents as therapy for myeloma patients and how to identify new targets and treatment strategies for patients with high-risk myeloma.

He was principal investigator on two large studies of novel monoclonal antibodies, both of which led to FDA approval. The research team he developed has contributed to all the major FDA approvals for myeloma therapeutics over the past decade. Lonial is currently leading a global genome sequencing study for patients with newly diagnosed myeloma.

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## Silvia Formenti and Heather McArthur awarded SU2C Laura Ziskin Prize

Stand Up To Cancer has awarded the 2019 Laura Ziskin Prize in Translational Research to two clinical investigators who will join in a bi-coastal collaboration to use radiation and immunotherapy pre-operatively to help the body create its own vaccine to fight breast cancer. A clinical trial is currently in development.

The prize was awarded at the 2019 SU2C Scientific Summit in Santa Monica.

Award winners Silvia Formenti of Weill Cornell Medicine Sandra and Edward Meyer Cancer Center in New York City and Heather McArthur of Cedars Sinai in Los Angeles will share a \$250,000 grant for their year-long project. They



will be working with a team of immunologists, bioinformatics specialists and biostatisticians.

“These two doctors, with their complementary backgrounds, have serious potential to develop treatment protocols that could provide better outcomes for breast cancer patients and perhaps reduce mortality,” said the selection committee chair John Glaspy, professor of medicine at the Jonsson Comprehensive Cancer Center of the University of California, Los Angeles School of Medicine.

Formenti is a recognized leader in breast cancer research and an international expert in the use of radiation therapy for cancer treatment. Her work in radiation biology demonstrates the efficacy of combining radiation therapy with immunotherapy to control cancer cell growth in solid tumors. It aims to have patients create a personalized immunotherapy by recruiting their immune system to reject an individual tumor. Formenti has translated preclinical work to clinical trials in metastatic breast cancer, lung cancer and melanoma. Her work has opened a new field of application for radiotherapy, whereby localized radiation can be used as an adjuvant to immunotherapy of solid tumors and lymphomas.

McArthur researches novel immuno-oncology strategies for treating breast cancer, with a specific interest in multidisciplinary approaches. She is currently evaluating the impact of tumor destruction with cryoablation or radiation in combination with immune stimulation for the treatment of women with early-stage breast cancer. By augmenting one’s immune response to the unique biologic features of one’s tumor, it is hoped that an affected individual may develop long-term immunity against their tumor.

## Helen Heslop named by SU2C to lead ‘Dream Team’



Stand Up To Cancer has awarded an \$8 million grant to a top team of scientists to develop therapies that use a person’s immune cells to recognize and attack T-cell lymphoma.

Helen Heslop, of Baylor College of Medicine, will direct the team and Gianpietro Dotti, of University of North Carolina Lineberger Comprehensive Cancer Center, will serve as co-leader of the grant.

The team is trying to find a way to develop CAR-T therapies covering the entire spectrum of T-cell lymphomas including an “off-the-shelf” basis so they will be available to more patients at lower cost. The team is also working to identify biomarkers that will help track the effectiveness of the therapy, and is evaluating a novel small molecule that shows encouraging activity in reducing the size of T-cell lymphomas.

The team is named in memory of Meg Vosburg, a lifelong learner, educator, and humanitarian, who died from T-cell lymphoma in 2018 at the age of 51. The SU2C Meg Vosburg T-Cell Lymphoma Dream Team will develop and study chimeric antigen receptor

T-cell therapies, which involve modifying a person’s immune cells to treat T-cell lymphoma.

The multi-institutional Dream Team includes six researchers from UNC Lineberger: Anne Beaven, investigator; Gianpietro Dotti, co-leader; Paul Eldridge, investigator; Natalie Grover, young investigator; Joel Parker, investigator; and Barbara Savoldo, investigator.

Patty Spears, who chairs the UNC Lineberger Patient Research Advocacy Group, was appointed as advocate. The team’s other members are from the Wake Forest Baptist Medical Center Comprehensive Cancer Center, Baylor College of Medicine and MD Anderson Cancer Center.

SU2C made the announcement at its 2019 Scientific Summit in Santa Monica, CA.

## Robert Prins receives grant to research brain tumor treatments



Robert Prins, professor of neurosurgery and molecular and medical pharmacology in the David Geffen School of Medicine at UCLA, has been award-

ed a \$750,000 grant to support research in developing immunotherapies for brain tumors.

The grant was sponsored by the Brain Tumor Funders' Collaborative, a partnership between six private philanthropic and advocacy organizations dedicated to accelerating progress in brain tumor research by supporting research and collaborations.

While there have been many advancements in cancer treatments in the past 20 years, there has been limited treatment developments for people with malignant gliomas.

Prins, an immunologist in the UCLA Jonsson Comprehensive Cancer Center and member researcher with the Parker Institute for Cancer Immunotherapy Center at UCLA, and members of the UCLA Brain Tumor Center are finding new ways to treat this deadly brain tumor by studying immune-based therapies.

Researchers are studying a new combination therapy using checkpoint blockade in conjunction with a personalized dendritic cell vaccine, which was developed at UCLA, for people diagnosed with glioblastoma. Prins and his team hope by combining the two treatments they will be able to create a new way to treat people with brain cancer, as well as develop new ways to track the immune response.

## Johns Hopkins Greenberg Bladder Cancer Institute Awards focused on bladder cancer in women

The Johns Hopkins Greenberg Bladder Cancer Institute has awarded research grants to four projects focused on un-

derstanding how treatment of bladder cancer affects women, why the disease has a less favorable outcome for women than men, and how biology could play a role in offering new targets for cancer therapy.

The institute encourages new strategies for combating bladder cancer and rewards those areas of innovative study with grants of \$25,000 to \$50,000.

"Bladder cancer presents different clinical challenges in men and women. It is diagnosed more often in men, but on average, women develop more aggressive disease," David McConkey, director of the Greenberg Bladder Cancer Institute, said in a statement. "Identifying the root causes of these discrepancies is a top priority for ongoing research. We also need to optimize our surgical approaches in men and women to ensure that we are obtaining the best possible outcomes. The projects we are funding this year directly address both of these priorities."

The Greenberg Bladder Cancer Institute recently launched a women's bladder program at the Johns Hopkins Kimmel Cancer Center. Jean Hoffman-Censits and Armine Smith will lead the program.

Two of the projects awarded research grants are looking at how bladder cancer treatment impacts the sexual health of women and how women are counseled after undergoing radical cystectomy.

- **Natasha Gupta** is a resident at the Brady Urological Institute at the Johns Hopkins University School of Medicine. Her project aims to examine the components of sexual health and dysfunction among women with bladder cancer who undergo radical cystectomy, as well as the counseling patients receive regarding these issues.

Gupta and her team will also study national practice patterns among

urologists regarding radical cystectomy in women and counseling about sexual dysfunction. They are conducting in-depth interviews with patients and their partners about these issues.

Gupta hopes a better understanding of sexual health and dysfunction in women with bladder cancer will lead to improved decision making about treatment and better management of sexual dysfunction in patients who undergo radical cystectomy for bladder cancer.

- **Sima Porten** is a member of the urologic oncology team at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco. **Sumeet Bhanvadia** is an assistant professor of clinical urology at the Keck School of Medicine at the University of Southern California. The two want to do an in-depth assessment of sexual outcomes among women after radical cystectomy to understand the extent of sexual dysfunction and its impact on patients and their partners.

Their pilot study hopes to generate data to develop a quantitative measure of degrees of sexual dysfunction and quality of life issues among women with bladder cancer. This information can be used to develop alternative treatment plans and properly prepare patients for what they may experience after radical cystectomy.

- **Margaret Knowles**, at the University of Leeds, and **Benjamin Hopkins**, a Ph.D. student at Leeds, have identified biological differences between cultured normal cells from the bladders of men and women.

"Such differences may have a major influence on the process of tumor development," Knowles said. "This award will allow us to examine normal cells directly isolated

from the bladders of normal males and females to determine whether such differences also exist within the body.”

While acknowledging that different exposure risks have been highlighted, Knowles and her team suggest a complete explanation for the gender-related differences in bladder tumor behavior relates to genetic and epigenetic distinctions in these tumors, and such differences may develop because of inherent differences in the biology of the normal male and female bladder. Their goal is to make it possible for treatments to target the specific biology of tumors, taking into account any gender-related differences.

- **Jenny Southgate**, director of the Jack Birch Unit for Molecular Carcinogenesis at the University of York, and **Simon Baker**, deputy director of the Jack Birch Unit, are examining how the skin layers inside the bladder—known as urothelial cells—develop and how those cells have genetic qualities seen in some subsets of bladder cancer.

Southgate and Baker will look at receptors in the urothelial cells—turning them on and off—to discover what role they may have in tumor development. They believe their work will provide new insights into bladder cancer subtypes and a new understanding of urothelial biology.

## ASCO names advance of the year: progress in treating rare cancers

Over the past year, major research advances provided new treatment options for patients with rare, difficult-to-treat cancers. In recognition of these achievements, the American Society of Clinical Oncology names “Prog-

ress in Treating Rare Cancers” as the Advance of the Year. To continue the forward momentum, ASCO also debuts its list of Research Priorities to accelerate progress against cancer. These and additional milestones in cancer research are featured in ASCO’s annual Clinical Cancer Advances report.

Although rare cancers account for about 20 percent of all cancers diagnosed in the United States each year, treatment progress has lagged behind that of more common forms of the disease. In the past year, however, research and regulatory achievements in five rare cancers were particularly impactful and together comprise ASCO’s Advance of the Year:

**Anaplastic Thyroid Carcinoma:** FDA approved the first treatment for this form of thyroid cancer in nearly 50 years, a targeted therapy combination of dabrafenib (Tafinlar) plus trametinib (Mekinist) for patients with BRAF-mutated ATC. This approach produced tumor shrinkage in over two-thirds of study participants.

**Desmoid Tumors:** Sorafenib (Nexavar) became the first treatment to improve progression-free survival for patients with this rare form of sarcoma.

**Midgut Neuroendocrine Tumors:** FDA approved 177Lu-Dotatate (Lutathera), which delivers targeted radiation to tumor cells, based on research showing it lowers the risk of disease progression or death by 79% for patients with advanced disease.

**Uterine Serous Carcinoma:** Trastuzumab (Herceptin) was shown to slow progression of HER2-positive uterine serous carcinoma, one of the most aggressive forms of endometrial cancer.

**Tenosynovial Giant Cell Tumor:** Research identified the first promising therapy, pexidartinib, for this rare can-

cer of the joints, producing responses in nearly 40% of patients.

This progress could not have come about without decades of sustained federal support for clinical cancer research. Several ongoing research initiatives sponsored by the National Institutes of Health have yielded key insights for rare cancers, and three of the five studies featured as part of the Advance of the Year received funding from the U.S. government. Nine Research Priorities to Advance Progress Against Cancer.

For the first time, ASCO has identified specific areas to focus future cancer research efforts. These priorities, listed in no particular order, represent areas of vital unmet need or knowledge gaps that could significantly improve clinical decision-making. ASCO’s Research Priorities include:

- Identify strategies that better predict response to immunotherapies
- Better define the patient populations that benefit from post-operative (adjuvant) therapy
- Translate innovations in cellular therapies to solid tumors
- Increase precision medicine research and treatment approaches in pediatric cancers
- Optimize care for older adults with cancer
- Increase equitable access to cancer clinical trials
- Reduce the long-term consequences of cancer treatment
- Reduce obesity and its impact on cancer incidence and outcomes
- Identify strategies to detect and treat premalignant lesions.

# THE CLINICAL CANCER LETTER



## TRIALS & TRIBULATIONS

# Glioblastoma patient is first to receive treatment under Right to Try. Our question is Why?



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A University of California, Irvine patient with glioblastoma recently received an experimental cancer vaccine from the U.S. subsidiary of Brussels-based Epitopoietic Research Corp. (ERC-USA). While most cases of patients receiving experimental medical treatment are not particularly newsworthy, this one was.

This anonymous patient is billed as the first to receive an investigational medical product under the Right to Try Act of 2017, a law signed by President Trump last May that claims to give seriously ill patients easier access to investigational medicines. Given the historic nature of this claim, and the likelihood that many cancer patients have encountered this news, we would like to unpack this story.

We've previously discussed why patients that have run out of approved treatments to try and that cannot participate in a clinical trial may find the right to try (RTT) pathway attractive. The president claimed that the law would give “hundreds of thousands” of patients access to drugs in the development pipeline. Sen. Ron Johnson (R-WI), the main RTT proponent in Congress, claimed that patients who were “running out of time” could be saved and their hope restored with a federal right to try law.

But these statements fail to acknowledge, firstly, that patients have been able to access experimental medical products outside of clinical trials through FDA's expanded access pathway for over 30 years. Secondly, the primary reason more patients do not obtain access through the expanded access pathway is that companies have the right to decline requests for their experimental products and often do so.

The key difference between right to try and expanded access is that the latter pathway requires oversight by FDA and an IRB. Involvement of these enti-

ties may involve paperwork (although less than many imagine), but they also serve to protect patients from harm and exploitation that may occur from those who wish to capitalize upon patient desperation.

Right to try proponents incorrectly assert that expanded access is slow and denies many patient requests. However, the agency allows over 99% of the requests it receives to proceed. (FDA does not review the request until after a company has agreed to provide the product.) Emergency requests can be handled over the phone and reviewed within one day; non-emergency requests are, on median, reviewed within eight days.

FDA reviewers, who have access to confidential information on investigational medical products, can provide valuable information to the patient's physician on the proposed treatment plan, and, in some cases, are able to identify an approved drug or a clinical trial for which the patient is eligible. Furthermore, the main reason for patients' inability to access an investigational medical product is company unwillingness—not obstacles arising from FDA or IRB. Thus, positing that RTT will ameliorate non-trial access to investigational drugs is akin to saying that treatment for a broken arm will heal a leg wound.

Nevertheless, in addition to the federal RTT law, 41 states have enacted their own version of the law. While they all are called “right to try,” none of them confer any increased access to patients; indeed, they have been mocked as “right to beg” laws. Patients didn't need a new law to enable them to request access to investigational products from the companies developing them.

We've argued that right to try laws would not meaningfully improve patient access to experimental medicines and could increase patient harms, both

from physical risks associated with investigational medical products and due to exploitation. Numerous patient advocacy and physician organizations have echoed these concerns, including the American Society for Clinical Oncology, the American Cancer Society Cancer Action Network, Breast Cancer Action, and the National Organization for Rare Disorders.

At best, the laws won't help patients; at worst, they could permit unscrupulous and unethical entities to sell ineffective treatments to desperate patients. (There are limits to what a company may charge a patient for an unapproved medical product, but no rules on what ancillary costs may be charged for labs, clinic visits, monitoring, etc.) Why, then, would a—by all appearances—legitimate company developing a vaccine that may help many future glioblastoma patients agree to provide its product-in-development to a patient via the RTT pathway?

We have not spoken to the doctor, patient, or institution involved. We base our analysis on media reports, conversations with the reporters who filed those stories, and contact with the company.

The patient received the investigational vaccine, which is in phase II testing in the U.S., through the California state RTT law. The company has provided its product in the U.S. via expanded access previously. In this case, the patient reportedly asked to receive the vaccine specifically through RTT. The patient's doctor was willing to use the RTT pathway, as she viewed it as less onerous than expanded access. But a closer look reveals none of this is as clear-cut as it may seem.

While the main thrust of the RTT approach is to cut FDA and an IRB out of non-trial access to an investigational medical product, the myriad RTT laws have different provisions.

According to information on its [website](#), UC Irvine follows the statutory requirements of [California's RTT law](#), which mandates more stringent reporting and informed consent requirements than does the federal RTT law. Because of the patient protections embedded in California's version of RTT, UC Irvine's IRB could ensure that the patient was informed of any alternative treatments and their right to stop the experimental treatment or seek palliative care. It must be underscored that this case was handled in accordance with California's RTT law, which is unique: as such, we cannot conclude from this event how right to try would be handled elsewhere.

Further complicating the narrative of this case, ERC-USA [notified FDA](#) that it planned to treat a patient under the Right to Try Act. Prior contact with FDA is explicitly not a part of either the federal or California RTT law; the goal of the RTT laws was to cut FDA out of single patient access to experimental treatments outside of clinical trials.

FDA's acknowledgement of ERC-USA's communication to the agency occurred in July 2018—nearly six months before the patient began receiving treatment in late November. Presumably, it took time to create a personalized vaccine for the patient; nevertheless, this lengthy delay underscores the absurdity of RTT advocates' central claim—that FDA's expanded access pathway was too slow.

This case of RTT included additional “add-ons” not specified in any RTT law. This complexity has not been explained in most media coverage. Given that the Right to Try Act of 2017 was the only piece of legislation explicitly mentioned in the 2017 State of the Union address, it is reasonable to assume the president will mention this recent usage of RTT in the forthcoming State of the Union address.

If so, we expect more patients will believe RTT may offer them access to experimental treatments. Yet, according to very recent reporting from [STAT News' Nicholas Florko](#), several people with ALS who were very hopeful that RTT would offer them access to investigational treatments—including one of the patients for whom the federal law was named—have yet to receive anything via this pathway.



**At best, the laws won't help patients; at worst, they could permit unscrupulous and unethical entities to sell ineffective treatments to desperate patients.**



There are many other life-threatening diseases, but this situation starkly illustrates that, right to try is not working as many advocates hoped it would. (Except for Sen. Johnson, RTT's chief advocate in the Senate, who [stated](#) that it “is actually really performing the way I intended it to.”) There are numerous reasons why companies that understand the difference between expanded access and RTT are unwilling to use the later pathway, the starkest of which is that if anything bad were to happen to a patient who received an experimental agent, the company wants to be able to remind FDA that it, too, signed off on the use of the product in that patient.

The safest and most societally beneficial way for patients to get access to experimental treatments is by participating in a clinical trial. But when clinical trial participation is not feasible, some patients may wish to try an experimental product in hope of receiving medical benefit. Some companies may be

willing to provide their drugs-in-development for this purpose. There exists a decades-old way for this to happen: expanded access. It has evolved over time and continues to do so.

For example, in 2017 [FDA changed the rules to allow one IRB member to review a single patient expanded access request](#), rather than requiring full board review. The year before that,

FDA streamlined its single patient expanded access request form to a two-page document. There are still changes that can be made to optimize expanded access for all stakeholders; however, creating a co-existing pathway for access with different rules is not helpful.

At present, patients with life-threatening conditions have 43 different pathways—expanded access, federal right to try, and the 41 state laws—through which they can access an experimental medical product.

In an area already rife with confusion, right to try laws are only making it more difficult to navigate seeking non-trial access to unapproved agents. To help patients with no other possible treatment options who wish to try experimental treatments, we need one system that works for everyone.

Using RTT laws moves us further away from that possibility.

## CLINICAL ROUNDUP



## Study incorporates patient feedback into better cancer treatments

A study now underway aims to better incorporate patient feedback into clinical trials that help determine which new cancer treatments will be approved for use.

The project, supported by a five-year, \$3.4 million grant from NCI, involves statisticians, clinicians and patient advocates. The team is analyzing data from previous and ongoing clinical trials to design new statistical measurement criteria for assessing how well trial participants tolerate experimental therapies.

“There is a pressing need to include the patient’s voice in the evaluation of the toxicity and tolerability of new cancer treatments,” said André Rogatko, director of the Biostatistics and Bioinformatics Research Center at Cedars-Sinai Cancer. “As a consequence of our work, we expect that the future reporting of results from cancer treatment trials can include better evaluations.”

Rogatko is co-leading the study along with Patricia Ganz, professor of Med-

icine in the David Geffen School of Medicine at UCLA.

New experimental cancer treatments are raising hopes among clinicians and patients for longer survival times and cures. But clinical trials that test such treatments also need to analyze the impact on patients of potentially harsh side effects, known as adverse events, Rogatko said. These side effects may include pain, fatigue, nausea, heart palpitations, skin reactions, mood changes, memory impairment and sexual dysfunction, among others.

“A big unknown is how adverse events affect patients over longer periods of time, particularly in immunotherapy, in which we only recently are learning about long-term toxicity and how it affects quality of life,” Rogatko said.

“As we continue to improve immunotherapy and now combine it with other therapies to make it more effective, we will have to carefully study side effects so that we design combinations that are both more effective and less toxic. That would be a real advance, and this work will help with reaching this goal,” said Dan Theodorescu, director of Cedars-Sinai Cancer.

In recent years, federal agencies have stressed the importance of increased data collection and scrutiny of adverse events experienced by patients while undergoing cancer treatments. The new study aims to advance that effort.

One goal of the study is to use existing and new methods for describing toxicity to show and foretell adverse events. The second goal is to predict the toxicity in a given clinical trial and whether a patient will complete the treatment.

Investigators are using a toxicity index previously developed by Rogatko plus PRO-CTCAE, a set of patient-reported outcome measures designed by the National Cancer Institute to evaluate symptomatic toxicity in patients in

cancer clinical trials. The study takes advantage of data from three ongoing immunotherapy trials and three completed National Surgical Adjuvant Breast and Bowel Project trials.

Although the study’s research methods involve highly technical statistical analysis, the emphasis is on improving quality of life for cancer patients, Rogatko said. “We have a chance to give patients more power in how they want to be treated.”

**Funding:** Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number U01CA232859. The grant was awarded in September, and the study will conclude in August 2023.

## Patients getting placebo allowed to cross to Erleada as TITAN results unblinded

The Janssen Pharmaceutical Companies of Johnson & Johnson announced unblinding of the phase III TITAN study evaluating Erleada (apalutamide) plus androgen deprivation therapy in the treatment of patients with metastatic castration-sensitive prostate cancer.

The decision resulted from an Independent Data Monitoring Committee recommendation coinciding with a pre-planned analysis that showed the dual primary endpoints were both achieved, significantly improving radiographic progression-free survival and overall survival.

Based on these results, the IDMC recommended that patients in the placebo plus ADT group be given the opportunity to cross over to treatment with Erleada plus ADT. Patients will contin-

ue to be followed for OS and long-term safety as part of the TITAN study.

“The TITAN study was designed to evaluate the efficacy and safety of Erleada in combination with androgen deprivation therapy in patients with newly-diagnosed metastatic castration-sensitive prostate cancer, regardless of the extent of their disease,” said Margaret Yu, vice president, Oncology Clinical Development, Janssen Research & Development.

Results from the TITAN study will be submitted for presentation at an upcoming medical congress. Applications seeking regulatory approval of Erleada supported by data from the phase III TITAN study are planned for 2019, the company said.

TITAN is a phase III randomized, placebo-controlled, double-blind study in men who were newly diagnosed with metastatic disease, regardless of prognostic risk, volume of disease, prior treatment with docetaxel or treatment of localized disease.

More than 1,050 patients with mCSPC were randomized to receive either Erleada plus ADT, or placebo plus ADT. Participants were treated until disease progression or the occurrence of unacceptable treatment related toxicity, or end of treatment.

The dual primary endpoints of the study are rPFS and OS.<sup>4</sup> Secondary endpoints of the study include time to chemotherapy, time to pain progression, time to chronic opioid use and time to skeletal related event. For additional study information, visit [ClinicalTrials.gov](http://ClinicalTrials.gov).

Erleada (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer. It became the first treatment to receive FDA approval for this disease state on Feb. 14, 2018.

The NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer include apalutamide as a treatment option for patients with non-metastatic CRPC with a category 1 recommendation (especially for those with a PSA doubling time  $\leq 10$  months)\*.

Additionally, the American Urological Association Guidelines for Castration-Resistant Prostate Cancer were updated to include apalutamide with continued ADT as a treatment option that clinicians should offer to patients with asymptomatic nmCRPC. It is included as one of the options clinicians should offer to patients with nmCRPC who are at high-risk for developing metastatic disease (Standard; Evidence Level Grade A).

## Antioxidants may enhance chemotherapy treatment for brain tumor

Findings from a pilot study at the University of Missouri School of Medicine show antioxidants such as alpha-lipoic acid may show promise working in tandem with temozolomide to further slow brain tumor growth in glioblastoma.

“Temozolomide is the most common first-line chemotherapy agent for patients with glioblastoma,” said Scott Litofsky, professor and chief of neurological surgery at the MU School of Medicine. “Before temozolomide was available, the median survival for glioblastoma was about nine months. With temozolomide, survival increased to about 14 months. Many patients also take over-the-counter supplements in addition to their temozolomide treatment. We wanted to know whether these supplements assist or hinder chemotherapy treatments.”

Litofsky’s research team studied one glioblastoma cell line taken from consenting patients and another purchased from American Tissue Culture Collection. The researchers pre-treated the glioblastoma cell lines with varying concentrations of one of three anti-oxidants—vitamin D3, melatonin or alpha-lipoic acid—for 72 hours followed by a 72-hour treatment with temozolomide.

The researchers found using the antioxidants in combination with the drug slowed cancer cell growth at varying levels. Specifically:

- Vitamin D3 alone did not affect the glioblastoma cells but did have a slight benefit when offered in combination with temozolomide.
- Melatonin alone decreased cancer cell growth in the pre-treatment phase by more than 60 percent, but showed no significant slowing of cell growth in combination with chemotherapy treatment.
- Alpha-lipoic acid reduced cell growth by more than 50 percent in both the pre-treatment and chemotherapy phase compared to the control in one cell line, and 44 percent in the other.
- Both melatonin and alpha-lipoic acid significantly enhanced the effectiveness of temozolomide’s ability to destroy cancer cells.

“The dose of alpha-lipoic acid that we used in our cell cultures is a dose that can be attainable when a person takes the antioxidant orally,” said Dianne McConnell, senior research specialist in the Division of Neurological Surgery at the MU School of Medicine. “Alpha-lipoic acid showed in our study that it may affect the cells that escape treatment with chemotherapy. If the alpha-lipoic acid can decrease the growth of those cells by the time they do the next dose of chemotherapy, the tumor can’t grow, and chemotherapy might be more effective.”



Although these results show promise, more studies are necessary before determining the effectiveness of combining antioxidants with temozolomide to treat glioblastoma in humans. The researchers' next step is to test alpha-lipoic acid in tandem with temozolomide in mice.

In addition to Litofsky and McConnell, the study authors include Joe McGreevy, University of Missouri School of Medicine, and Macy Williams, undergraduate student, University of Missouri.

Their study, "Do Antioxidants Vitamin D3, Melatonin, and Alpha-Lipoic Acid Have Synergistic Effects with Temozolomide on Cultured Glioblastoma Cells?" was recently published by the journal *Medicines*.

Research reported in this publication was supported by Head for the Cure Foundation and Stand Up to Cancer.

## DRUGS & TARGETS



## Lung-MAP precision medicine trial expands

The Lung Cancer Master Protocol is undergoing a major expansion to include patients with all non-small cell lung cancers.

The trial previously tested treatments for people with advanced stage squamous cell lung cancer. The trial is now open to all types of advanced stage non-small cell lung cancers. NSCLC makes up about 85 percent of all lung cancer diagnoses in the U.S.

This month, Lung-MAP will undergo other key changes. These include:

A new screening protocol to include the addition of liquid biopsies, as well as a streamlined informed consent form that combines screening and prescreening—a step that will make it easier to enroll patients.

Two new drug sub-studies, one testing a PARP inhibitor and another testing a PD-L1 and VEGF inhibitor in combination scheduled to open in early 2019. Two more sub-studies are in development and are scheduled to open in late summer 2019.

A new mandate that requires hospitals, clinics, and other sites that open the trial to use the NCI's Central Institutional Review Board to oversee trial changes, another move to speed the process of opening the trial at sites and registering patients.

Lung-MAP is the first large-scale precision medicine trial in lung cancer backed by the NCI and the first major NCI cancer trial to test multiple treatments, simultaneously, under one "umbrella" design.

Lung-MAP is also a groundbreaking public-private partnership, one that includes the NCI and its National Clinical Trials Network including SWOG Cancer Research Network, Friends of Cancer Research, the Foundation for the National Institutes of Health, Foundation Medicine, and pharmaceutical companies which provided their drugs for the study, and several lung cancer advocacy organizations.

Since it launched in June 2014, Lung-MAP has registered more than 1,700

patients across the country. Trial leaders have worked with 10 pharmaceutical partners, in coordination with the FNIIH, to launch nine studies, six of which are completed.

The new trial is also addressing questions about the efficacy of immunotherapies and immunotherapy combinations and the validity of new biomarkers. The trial has also produced insights into the conduct of large-scale precision medicine trials, including tissue sampling and banking, genetic screening, and patient communication, its sponsors say.

## Alimta + Keytruda and platinum chemo for NSCLC gets FDA label expansion

Eli Lilly and Co. said FDA has granted approval for a new indication for Alimta (pemetrexed for injection) in combination with Keytruda (pembrolizumab), developed and marketed by Merck, and platinum chemotherapy for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer, with no EGFR or ALK genomic tumor aberrations.

This indication is approved based on data from Merck's phase III KEY-NOTE-189 trial, which enrolled patients regardless of PD-L1 expression and had dual primary endpoints of overall survival and progression-free survival.

Alimta in combination with pembrolizumab and carboplatin was first approved in June 2018 under the FDA's accelerated approval process for the first-line treatment of patients with metastatic nonsquamous NSCLC, based on tumor response rates and PFS data from the phase II study KEY-NOTE-021 (Cohort G1).

In accordance with the accelerated approval process, continued approval was contingent upon verification and description of clinical benefit, which has now been demonstrated in the KEYNOTE-189 trial and has resulted in the FDA converting the accelerated approval to full approval.

“KEYNOTE-189 demonstrated an exceptional effect of the Alimta-pembrolizumab-platinum chemotherapy combination in the first-line setting, offering significantly improved survival in patients with metastatic non-squamous non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations,” Anne White, president, Lilly Oncology, said in a statement. “This new indication reinforces Lilly’s continued commitment to providing practice-changing treatment options that can make a meaningful difference for people living with lung cancer.”

Alimta is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed. See additional Important Safety Information below.

On Aug. 20, 2018, Merck’s pembrolizumab was approved by FDA for this indication, based on data from the KEYNOTE-189 study, which demonstrated that treatment with Alimta in combination with pembrolizumab plus platinum-based chemotherapy resulted in significantly longer OS and PFS than Alimta plus platinum chemotherapy with placebo.

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## Trovagene and PoC Capital agree to fund clinical development of onvansertib in metastatic colorectal cancer

Trovagene Inc. announced an agreement with PoC Capital to fund clinical

development of onvansertib, Trovagene’s first-in-class, 3rd generation oral and highly selective Polo-like Kinase 1 inhibitor in a phase Ib/II clinical trial in patients with metastatic colorectal cancer.

Trovagene submitted an Investigational New Drug application and protocol to the FDA on Dec. 19, 2018, and received a “study may proceed” notification from the FDA, 28-days later, on Jan. 16, 2019.

The trial will be conducted at two prestigious cancer centers in the U.S.; USC Norris Comprehensive Cancer Center and Mayo Clinic. Onvansertib, its lead drug candidate, is a first-in-class, 3rd generation, highly-selective oral Polo-like Kinase 1 Inhibitor. The company currently has two ongoing open-label clinical trials: a phase Ib/II trial in acute myeloid leukemia and a phase II trial in metastatic castration-resistant prostate cancer.

In this open-label, phase Ib/II trial, onvansertib in combination with standard-of-care FOLFIRI and Avastin is being evaluated for safety and efficacy. The trial, “A phase Ib/II Study of Onvansertib (PCM-075) in Combination with FOLFIRI and Bevacizumab for Second-Line Treatment of Metastatic Colorectal Cancer in Patients with a Kras Mutation”, will enroll up to 44 patients with a Kras mutation and histologically confirmed metastatic and unresectable disease.

In addition, patients must have failed treatment or be intolerant of FOLF-OX (fluoropyrimidine and oxaliplatin) with or without Avastin (bevacizumab). The trial is being conducted at two prestigious cancer centers: USC Norris Comprehensive Cancer Center and The Mayo Clinic Arizona.

Onvansertib is a first-in-class, 3rd generation, oral and highly-selective adenosine triphosphate competitive inhibitor of the serine/threonine polo-like-kinase 1 enzyme, which is

over-expressed in multiple cancers, including leukemias, lymphomas and solid tumors.

Separate studies with other PLK inhibitors have shown that inhibition of polo-like-kinases can lead to tumor cell death, including a phase II study in AML where response rates of up to 31% were observed when combined with a standard therapy for AML (low-dose cytarabine-LDAC) versus treatment with LDAC alone with a 13.3% response rate.

A phase I open-label, dose escalation safety study of onvansertib has been completed in patients with advanced metastatic solid tumor cancers and published in *Investigational New Drugs*. The maximum tolerated dose or recommended phase II dose in this trial was 24 mg/m<sup>2</sup>.

Onvansertib targets the PLK1 isoform only, is orally administered, has a 24-hour drug half-life with only mild to moderate side effects reported. Trovagene believes that targeting only PLK1 and having a favorable safety and tolerability profile, along with an improved dose/scheduling regimen will significantly improve on the outcome observed in previous studies with a former panPLK inhibitor in AML.

Onvansertib has demonstrated synergy in preclinical studies with numerous chemotherapies and targeted therapeutics used to treat leukemias, lymphomas and solid tumor cancers, including FLT3 and HDAC inhibitors, taxanes, and cytotoxins.

Trovagene believes the combination of its targeted PLK1 inhibitor, onvansertib, with other compounds has the potential to improve clinical efficacy in AML, metastatic castration-resistant prostate cancer, non-Hodgkin lymphoma, triple negative breast cancer, as well as other types of cancer.

Trovagene has an ongoing phase Ib/II clinical trial of onvansertib in com-

ination with low-dose cytarabine or decitabine in patients with relapsed or refractory AML that was accepted by the National Library of Medicine and is now publicly viewable on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

The NCT number assigned by [clinicaltrials.gov](http://clinicaltrials.gov) for this study is NCT03303339. Onvansertib has been granted Orphan

Drug Designation by the FDA in the U.S. and by the EC in the European Union for the treatment of patients with AML.

Trovagene has an ongoing phase II clinical trial of onvansertib in combination with Zytiga (abiraterone acetate)/prednisone in patients with metastatic castration-resistant prostate cancer who are showing signs of early progressive

disease (rise in PSA but minimally symptomatic or asymptomatic) while currently receiving Zytiga.

The trial was accepted by the National Library of Medicine and is now publicly viewable on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). The NCT number assigned by [clinicaltrials.gov](http://clinicaltrials.gov) for this study is (NCT03414034).

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