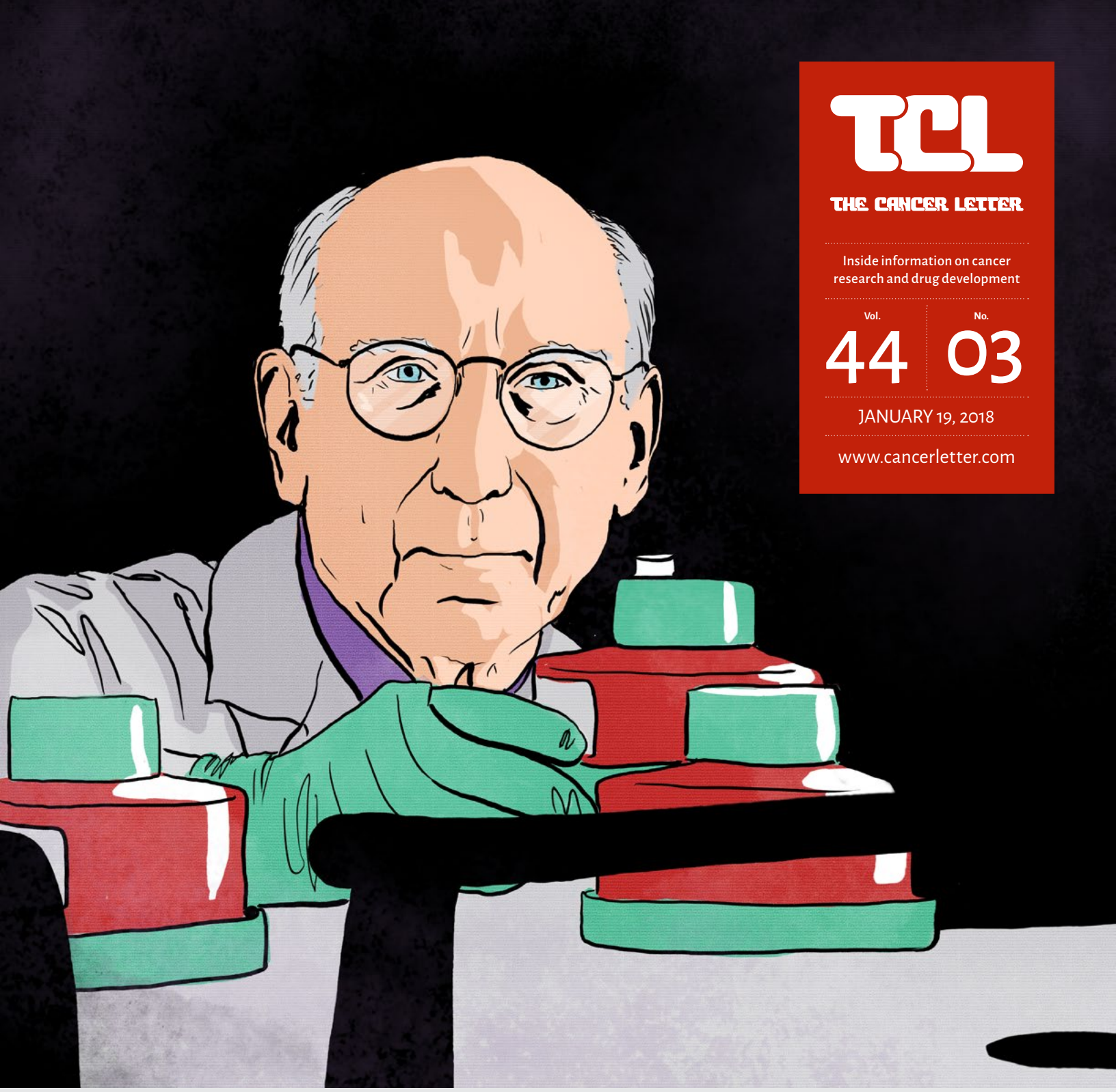

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A UNIQUE DRUG FOR EACH PATIENT: A PARADIGM SHIFT IN CANCER THERAPY

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→ PAGE 4

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GUEST EDITORIAL

A UNIQUE DRUG FOR EACH PATIENT: A PARADIGM SHIFT IN CANCER THERAPY

The recent FDA approvals of a cell/gene therapy for patients with advanced B cell malignancies provide a glimpse into a paradigm shift in the treatment of hematologic and solid cancers, the creation of a new drug unique to each cancer patient.

By Steven A. Rosenberg
Chief, Surgery Branch, senior investigator and head of the Tumor Immunology Section, Center for Cancer Research, National Cancer Institute, National Institutes of Health

In 2010, the Surgery Branch at the National Cancer Institute first reported the regression of advanced lymphoma in a patient infused in 2009 with his own lymphocytes genetically engineered to express a chimeric antigen receptor (CAR) that recognized CD19, a cell surface molecule expressed on B cell malignancies and normal B cells.

This patient experienced a complete cancer regression that has lasted over 8 years. Other groups at Memorial Sloan Kettering Cancer Center, the University of Pennsylvania and other academic medical centers demonstrated similarly impressive results with CD19-CAR T cells in patients with B-cell malignancies leading to multi-institutional trials sponsored by Kite Pharma and Novartis. The CD19-CAR T cell approach became the first cell and gene therapy approved by the FDA for patients with cancer.

Immunotherapy using a patient's own anti-tumor lymphocytes, naturally arising in the host or genetically engineered in the laboratory to attack cancer, is a new approach to drug development that represents a convergence of work in two areas of immunotherapy.

In 1988, we showed that T cell transfer using a patient's own tumor infiltrating lymphocytes (TIL) expanded in vitro could mediate regression of metastatic melanoma. Refinements to this treatment achieved complete, sustained regressions in about 30% of these patients.

In 2006, pilot studies showed that cancer regression could occur in patients with metastatic melanoma following infusion of autologous, anti-tumor lymphocytes created in the laboratory by transduction of genes encoding highly avid T cell receptors (TCRs) that recognized shared, non-mutated melanocyte antigens such as MART-1 and gp100.

Severe autoimmunity was observed in these trials due to the expression of these antigens on normal melanocytes in the skin, eye and ear. Tumor regression and severe colitis were seen in colon cancer patients receiving T cells transduced with genes encoding TCRs that recognized non-mutated carcinoembryonic antigen (CEA) thus emphasizing the difficulties encountered when targeting antigens expressed on normal tissues.

The lack of normal tissue toxicities seen in melanoma patients responding to TIL administration thus led us to explore the role of cancer mutations as possible cancer antigens.

To identify the prevalence of possible cancer antigens on common epithelial cancers we developed high-throughput screening methods to identify cancer mutations that were immunogenic, i.e. recognized by the patient's T-lymphocytes.

In studies of tumors from over 100 patients with a variety of metastatic epithelial cancer types we found that about 70-80% of patients mounted T cell responses to cancer specific mutations. An average of 1-2 % of mutations in each patient were recognized by the immune system.

Surprisingly, the overwhelming majority of these immune responses arose from random somatic mutations unique to that cancer and not shared by other cancers though rarely shared mutations encoded by "hotspots" in genes known to play a role in oncogenesis, such as KRAS or p53, were recognized.

The targeting of mutated proteins appears to be the "final common pathway" underlying the effectiveness of all natural immunotherapies including IL-2, checkpoint modulators and TIL.

These insights led us to develop immunotherapies based on the transfer of autologous T cells enriched for reactivity against cancer mutations unique to that cancer—a highly personalized treatment in which lymphocytes are used as a new drug unique for each patient.

Whole exome and RNA sequencing of tumor and normal tissue can identify all mutations expressed by the cancer in 10-14 days. Autologous lymphocytes and their TCRs reactive with these mutations can be isolated and used to generate large numbers of tumor-reactive lymphocytes for treatment.

In encouraging early reports using the transfer of mutation-reactive, autologous lymphocytes, objective regressions have been seen in isolated patients with several types of metastatic epithelial cancers including those arising in bile ducts, colon, cervix and breast. Since all cancers contain mutations, this approach is a potential "blueprint" for the treatment of most cancer types.

The creation of an individual drug for each patient represents a considerable departure from the established norm in drug development. Traditional pharmaceutical companies depend on the development of "drugs in a vial" applicable to large numbers of patients and easily distributed widely.

The development of the first vial can cost hundreds of millions of dollars and can be commercially pursued if subsequent vials can be produced for a few pennies or dollars. This approach using cytotoxic or targeted agents has largely failed to cure patients with metastatic solid tumors, and. although life can be prolonged, virtually all patients with detectable metastatic epithelial cancers will die of their disease despite the best available treatments.

Existing off-the-shelf immunotherapies have limited efficacy against the common epithelial cancers that kill over 90% of patients that die of cancer in the U.S. every year (estimated to be about 600,000 deaths in 2018). The in-

troduction of checkpoint modulators is an important step in the development of immunotherapy, especially in patients with melanoma, though complete responses remain infrequent for the solid epithelial cancers.

The complexity and expense of individualized cancer treatments have discouraged large pharmaceutical companies from developing the new cell-based strategies described here. Further complexity derives from the need to utilize natural TCR-based rather than simpler CAR-based treatments. CARs depend on the antigen binding properties of monoclonal antibodies and can only target the subset of proteins expressed on the cell surface and these are very rarely mutated.

It has been over 40 years since the description of monoclonal antibodies and, despite considerable effort, none have been found uniquely reactive with shared antigens on the surface of cancer cells from solid tumors. Targeting non-mutated cell surface proteins can lead to life-threatening destruction of normal tissues.

The biology of cancer is complex and effective treatments may involve more than swallowing a pill or receiving the infusion of a "one-fits-all" drug. Infusion of anti-tumor lymphocytes is a "living treatment" often administered only once since the anti-tumor cells can expand a thousand-fold in the week after administration and survive in the patient for years.

Cell therapies will be expensive, but medical care dollars can be saved if curative treatments can be developed using this approach rather than having patients spend hundreds of thousands of dollars to move from one expensive, minimally effective treatment to another.

The developmental stages of cell therapies for cancer have largely been performed by academic groups that face increasing obstacles to progress. Many research institutions seeking to develop and improve cell therapies require investigators developing individual treatments for a single patient with a lethal disease to meet Good Manufacturing Practice regulations similar to those required by drug companies preparing a "one-size-fits-all" drug for millions of patients.

These institutional requirements appear to exceed guidance by the FDA that allow more flexibility for small academic groups engaged in phase I cell transfer studies for limited numbers of patients. The FDA guidance is vague, however, and clarification by the FDA of the requirements for cell transfer investigative trials could unleash additional clinical research in this area.

their own procedures and receive Investigational New Drug (IND) approval from the FDA, a laborious, expensive and time-consuming process beyond the means of most clinical centers. A practical model for treatment, pioneered by Kite Pharma and Novartis, is the development of central laboratories that can receive lymphocytes and/or tumors and prepare the "personalized drug" as cryopreserved cells for delivery to the home institution for infusion.

The exquisite specificity and sensitivity of the immune system, capable of recognizing single amino acid changes in a long intracellular protein has opened a new paradigm in cancer treatment—the ultimate "personalized" therapy using a patient's own cells to recognize mutations unique to the patient's cancer.

> "Immunotherapy using a patient's own anti-tumor lymphocytes, naturally arising in the host or genetically engineered in the laboratory to attack cancer, is a new approach to drug development that represents a convergence of work in two areas of immunotherapy."

Related to this issue is the need for the development of automated, "hands-off" techniques for the many repetitive manipulations involved in the identification, isolation and growth of mutation-reactive lymphocytes.

The generation and administration of cells at each institution to treat their own patients is necessary for discovery and innovation in cell-based therapies but is not likely to bring personalized cell therapies to large populations in need since for this purpose each institution would have to develop and validate

Much remains to be done to make this new approach better, simpler and faster. In the 16th century, Francis Bacon, a philosopher/scientist, warned, "Ye that will not apply new remedies must expect new evils for time is the great innovator."

The views expressed here are my own and do not necessarily reflect the views of the NCI or NIH.

NEWS ANALYSIS

As government shutdown looms, don't lose sight of bigger battle over appropriations, sequestration

By Paul Goldberg

As the rancor in Washington continues to escalate from bickering to a war on many fronts, the deadline approaches for the end of a continuing resolution that keeps the federal government open until Jan. 19.

Government operations for the fiscal year, which began on Oct. 1, have been funded through a succession of three CRs.

At this writing, the House has passed a four-week stopgap CR that doesn't include a provision to allow children of undocumented residents to stay in the country. When the bill got to the Senate, Democrats balked, setting off a feverish last-minute round of negotiations with the White House.

At 1 p.m. Jan. 19, NCI staff members were told to monitor a website for news—and to plan to return to work on Monday.

"The current Continuing Resolution ends at midnight today and we are currently awaiting guidance on whether the federal government will shut down," the email reads. "We anticipate additional information later this afternoon. Regardless of whether there's a shutdown, anticipate that you will need to report to work on Monday morning, January 22, as normal. We will also post important information on myNCI."

Under the best-case scenario for NIH and NCI, the House and Senate leaders would set their battles aside to pass the fourth CR and finalize a deal on a bipartisan budget agreement that would take the first steps toward an "omnibus" appropriations bill to fund federal agencies for the rest of the FY 2018.

Nobody likes CRs. For government programs, CRs mean flat funding. That's a problem for NIH, which is poised to get a $2 billion raise.

Congressional leadership and the White House have been negotiating a two-year budget agreement that would cover the rest of fiscal year 2018 as well as 2019. At this writing, that deal seems more elusive than ever.

Allowing a shutdown to happen would be a gamble for both parties, with midterm elections only nine months away, and election-year posturing has lent intensity to the budgetary debates.

The fortunes of military and civilian discretionary programs seem to be intertwined tighter than ever before. Both sides seem to agree that in the short term (meaning the waning hours of the current CR) and in the long term (a real budget deal), Congress must raise the spending caps imposed under the 2011 Budget Control Act.

However, the sides cannot agree on which side—civilian programs or the military—would get more from the raise. Democrats want the money from

the raised caps to be apportioned dollar for dollar. Republicans want more money for the military.

If they fail to come to an agreement, sequestration would set in and cuts to military and civilian programs would be made across the board.

This battle is playing out in short-term battles over the CR as well.

Several Republican hawks in Congress have indicated that they are reluctant to vote for another CR, because CRs keep budgetary increases from getting to the military. According to their logic, forcing a shutdown would lend new urgency to deal-making, which could at the very least include raises—called "anomalies"—being built into the CR on the military side.

Today, legislators are in an uproar over Deferred Action for Childhood Arrivals program that affects children brought to the U.S. by parents who had immigrated here illegally. The fight was further fueled by President Trump's recent comment about immigration from "shithole countries," and neither party seems to be showing the will to set aside their disagreements.

In addition to DACA, Congress is divided over disaster relief, measures to stabilize the Affordable Care Act, and the Children's Health Insurance Program, which is set to expire in March.

The administration first said it would be willing to sign a stopgap bill that includes CHIP, but on Jan. 18, Trump tweeted that "CHIP should be part of a long term solution, not a 30 Day, or short term, extension!" The tweet, naturally deepened the state of disarray in the negotiations. Later in the day, the president said "it's up to the Democrats" to avert the shutdown.

NIH has a lot at stake. The research institution is poised to receive its third-in-a-row $2 billion raise. If assurances from Congressional leaders are to be believed, the support for the measure to continue to boost NIH funding remains strong and bipartisan.

Congressional leaders, including both House Appropriations Labor-HHS-Education Subcommittee Chairman Tom Cole (R-OK) and Senate Appropriations Labor-HHS-Ed Subcommittee Chairman Roy Blunt (R-MO), have assured biomedical research groups that Congressional resolve to continue to grow NIH hasn't gone away.

The divide in Washington is more than just partisan and more than just civilian vs. military. The divide is also between Republican-controlled Congress and the Trump White House. Last March, the Trump Administration budget proposal sought to slash the NIH budget by 21 percent (The Cancer Letter, March 17, 2017; April 7, 2017; May 26, 2017). Under the proposal, indirect costs would have been capped at 10 percent, a level that would have crippled research at academic institutions (The Cancer Letter, March 2, 2017).

> The medical research community is also facing a complicated and worrisome challenge in the form of the spending caps that are currently in place for FY 2018.
>
> *– Michael Caligiuri*

The proposal energized the NIH supporters on both sides of the aisle, and instead of the cut, Congressional bills ended up giving NIH a $2 billion increase (The Cancer Letter, June 23, 2017; March 17, 2017; May 5, 2017). The indirect costs provision didn't make it into the bill.

With the 2019 budget proposal two months away, it would be unrealistic to expect that the Trump administration will propose a raise or even flat funding, which means the schisms in Washington will deepen.

In a guest editorial last July, Michael Caligiuri, president of the American Association for Cancer Research and president of City of Hope National Medical Center, urged that spending caps be removed and that spending for domestic and research programs be increased dollar for dollar for military and domestic discretionary programs (The Cancer Letter, July 21, 2017).

"The medical research community is also facing a complicated and worrisome challenge in the form of the spending caps that are currently in place for FY 2018," Caligiuri wrote. "If the NIH, NCI, the FDA, and other vitally important scientific agencies are to receive the resources that are necessary to drive advances across the clinical cancer care spectrum and save an increasing number of lives from cancer, it's going to require that Congress negotiate a bipartisan budget deal to raise the discretionary budget caps for FY 2018.

"There's an effort to break the caps on the defense side of the budget, while leaving the non-defense side of the budget caps in place. With regards to

this proposal, we agree with Rep. Nita Lowey (D-NY), the top Democrat on the House Appropriations Committee, who said, 'It is clearly time to lift the budget caps in FY 2018, but for more than just the Pentagon.'

"As Rep. Lowey has stated, the non-defense discretionary side of the budget ledger should grow at a comparable rate in order to support vital research and patient needs, as these and other programs 'need attention just as badly as we need new jets, tanks, and ships.' "

While Trump's budget proposal for the current year has slated biomedical research for draconian cuts, the administration's appointments for key posts in areas affecting cancer have been sound and widely praised: Ned Sharpless for NCI, Francis Collins for NIH, and Scott Gottlieb for FDA.

He has appointed Alex Azar, a former Eli Lilly executive, to lead HHS. The Senate Finance Committee Jan. 17 approved Azar's candidacy in a 15-12 vote and clearing the way to a vote by the full Senate.

Trump's first HHS secretary, Tom Price, a former House member, resigned under pressure in the midst of an investigation of his use of charter planes.

In an earlier hearing, Azar acknowledged that drug prices are a genuine problem.

IN BRIEF

Allison, Bax, Doudna and Chang receive NAS prizes

James Allison, of MD Anderson Cancer Center, will receive the Jessie Stevenson Kovalenko Medal from the National Academy of Sciences.

Altogether, 19 individuals with awards in recognition of their extraordinary scientific achievements in a wide range of fields spanning the physical, biological, and medical sciences. The winners will be honored in a ceremony April 29, during the National Academy of Sciences' 155th annual meeting.

Allison's research has had a vast impact on cancer therapy and the evolution of the entire field of cancer immunology. In 1983, Allison reported on the protein structure of T cell receptor, providing one of the earliest looks at the molecules involved in T cell function.

This led to the discovery of two molecules related to the activation of T cells, CD28 and CTLA-4, the second of which functions as an inhibitor that restricts T cell responses. In 1996 Allison showed that blocking CTLA-4 led to tumor rejection in mice. This opened up the field of "immune checkpoint therapy," a paradigm shift in cancer treatment which targeted the immune system rather than tumors themselves.

After several years of clinical trials, CTLA-4 was approved as a standard treatment for patients with metastatic melanoma. It is currently being tested in several additional forms of tumors and has already benefitted the lives of tens of thousands of patients.

The Jessie Stevenson Kovalenko Medal is awarded every two years for outstanding research in the medical sciences. The award is presented with a medal, a $25,000 prize and $50,000 to support the recipient's research.

Adriaan Bax, an NIH Distinguished Investigator, will receive the 2018 NAS Award for Scientific Reviewing.

Bax is responsible for transforming Nuclear Magnetic Resonance spectroscopy into a powerful and readily accessible tool for the study of the structure, function, and dynamics of biological macromolecules. His development of a constant stream of novel methods has led to important advances in our basic understanding of how biological systems work at the molecular level.

Bax has published more than 400 original research articles on NMR methods and applications. His book, "Two-Dimensional Nuclear Magnetic Resonance in Liquids," was the springboard for the widespread evolution of this technology.

His conceptual innovations and pioneering experimental methodologies have been widely adopted by chemistry and structural biology laboratories, influencing research in both academic institutions and the worldwide pharmacological industry. Beyond development of the technology itself, Bax has applied NMR to a wide range of biomedical problems, with important discoveries on proteins related to HIV and Parkinson's disease.

The 2018 NAS Award for Scientific Reviewing recognizes authors, whose reviews in structural biology have synthesized extensive and difficult material, rendering a significant service to science and influencing the course of scientific thought. The award is sponsored entirely by Annual Reviews and is presented with a $20,000 prize.

Jennifer A. Doudna, principal investigator at University of California, Berkeley, will receive the 2018 NAS Award in Chemical Sciences.

Following pioneering discoveries on how RNA can fold to function in complex ways, Doudna, along with Emmanuelle Charpentier, invented the technology for efficient site-specific genome engineering using the CRISPR/Cas9 nucleases for genome editing—a breakthrough technology which has had an immediate and wide impact on all areas of both basic and applied life sciences.

CRISPR genome editing allows precise changing of the DNA code in human cells, as well as in those of other multicellular organisms. It has the potential to create new defenses against human viruses or to correct mutated human genes and provides methods to reshape the biosphere for the benefit of the environment and human societies. CRISPR genome editing has already been adopted by tens of thousands of laboratories around the world, where it has enabled and stimulated diverse experiments that were never before simple to conduct or possible to conceive.

The NAS Award in Chemical Sciences is presented annually to honor innovative research in the chemical sciences that contributes to a better understanding of the natural sciences and to the benefit of humanity. The NAS Award in Chemical Sciences was established in 1978 and supported by Occidental Petroleum Corporation from 1978 to 1996. The Merck Company Foundation assumed sponsorship in 1999. The award is presented with a medal and a $15,000 prize.

Howard Y. Chang, Howard Y. Chang, Stanford University School of Medicine, will receive the 2018 NAS Award in Molecular Biology.

Chang is a physician-scientist who made major contributions to genome science in his discoveries about a new class of genes called long noncoding RNAs, which are pervasive in the human genome.

Long noncoding RNAs are important causes of cancer metastasis and other human diseases, as well as development and aging. His work showed that long noncoding RNAs can act as guides, scaffolds, or decoys between DNA and enzyme machines.

These discoveries themselves would not have been possible without Dr. Chang's invention of new genomic technologies such as ATAC-seq, which maps open chromatic sites with enzymes that copy and paste DNA, and ChIRP-seq, which maps RNA occupancy sites on the genome. ATAC-seq in particular has revolutionized the field of epigenetics, improving the ability to map active DNA elements by 1 million-fold in sensitivity and 100-fold in speed. Dr. Chang's genomic technologies have already been widely adopted by investigators in thousands of labs around the world and have revolutionized the study of many human diseases and model organisms.

The NAS Award in Molecular Biology is supported by Pfizer Inc. and recognizes a recent notable discovery in molecular biology by a young scientist (defined as no older than 45) who is a citizen of the United States. The award is presented with a medal and a $25,000 prize.

Kathy Albain receives first Huizenga Family Endowed Chair at Loyola University Chicago

Kathy Albain was named the inaugural Huizenga Family Endowed Chair in Oncology Research at Loyola University Chicago Stritch School of Medicine.

The endowed chair will enable Albain to devote more time to cancer research, and is recognition of the outstanding contributions she has made as a physician, researcher, teacher and mentor. The chair is funded by Heidi Huizenga, one of Albain's grateful patients, her husband Peter, and her family.

Albain is a professor in the division of hematology/oncology in the department of medicine of Loyola University Chicago Stritch School of Medicine. She is director of Loyola Cardinal Bernardin Cancer Center's breast clinical research program, co-director of the multidisciplinary breast oncology center and director of the thoracic oncology program.

Albain is a leader in national clinical trials of new treatments for breast and lung cancer as well as cancer survivorship research.

ACS CAN: Cancer patients should be exempt from possible Medicaid work requirements

The Centers for Medicare and Medicaid Services issued guidance allowing states to require "able-bodied" adults to work, participate in job training or volunteer in order to receive Medicaid health benefits.

As part of the guidance, CMS exempts children, pregnant women, the disabled and those who are deemed, "medically frail," however the guidance does not clearly define who would be considered medically frail.

A statement from Chris Hansen, president of the American Cancer Society Cancer Action Network follows:

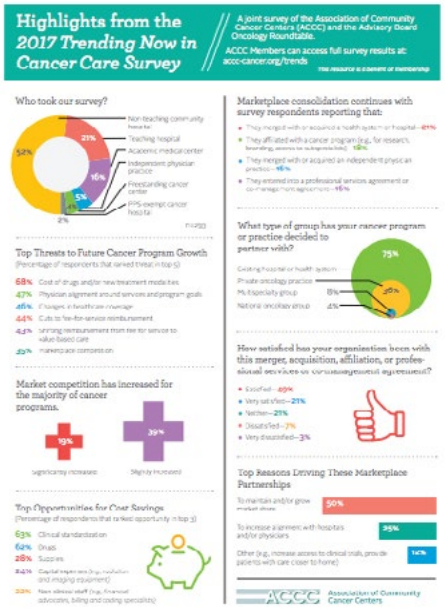
"Today's guidance could mean a significant change to one of America's most essential safety-net programs. Medicaid serves as a vital lifeline that provides health care coverage to more than 2.3 million low-income Americans with a history of cancer.

"Many cancer patients in active treatment are often unable to work or require significant accommodations to their work schedules due to that treatment. It is unclear from the guidance what standards states would use to define "medically frail."

Research suggests between 40 and 85 percent of cancer patients stop working while receiving cancer treatment, with absences ranging from 45 days to six months. Additionally, evidence shows that patients who have recently completed treatment may need additional time to recover and transition back into the workplace.

"We strongly urge CMS to require states exempt people with serious, complex medical conditions, particularly cancer patients and recent survivors from any work requirements…"

ACCC's 2017 survey: cost of treatment is top threat to cancer program growth



Amidst a dramatically changing healthcare landscape and increasingly competitive market, the Association of Community Cancer Centers eighth annual Trending Now in Cancer Care survey, which was conducted in partnership with Advisory Board's Oncology Roundtable, identifies current and emerging trends across U.S. cancer programs.

When asked to identify the top threats to future cancer program growth, 68 percent of respondents selected cost of drugs and/or new treatment modalities as the number one threat, 47 percent named physician alignment around services and program goals, and 46 percent cited changes in healthcare coverage.

Respondents also identified cuts to fee-for-service reimbursement and the move to value-based care as significant threats to cancer program growth. One in three reported marketplace competition as a top threat. More than 290 respondents from 209 organizations participated in the 2017 survey.

Asked to identify their greatest opportunities for cost savings, respondents overwhelmingly pointed toward clinical standardization (63%) and drugs (62%). Providers see clinical standardization as a way to help reduce variation in care and eliminate duplicative services, thereby realizing cost savings.

Nearly 30 percent of respondents intend to improve clinical standardization by adopting clinical pathways for medical oncology, either vendor sponsored or homegrown. One in four survey respondents expect to realize cost savings by reducing capital expenses, such as radiation and imaging equipment.

The ACCC Trending Now in Cancer Care survey provides insights into nationwide developments in the business of cancer care. With today's cancer patients acting more like consumers with a say in where they receive care, cancer programs continue to grow their service lines to meet this demand for personalized, patient-centered care, specifically around symptom management and survivorship.

The survey results also reveal trends around market consolidation and the rise in marketplace partnerships, participation in value-based contracts, and barriers to meeting accreditation and quality reporting requirements.

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THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Blood test for eight cancer types provides framework for early detection

Johns Hopkins Kimmel Cancer Center researchers developed a single blood test that screens for eight common cancer types and helps identify the location of the cancer.

The test, called CancerSEEK, is a noninvasive, multianalyte test that simultaneously evaluates levels of eight cancer proteins and the presence of cancer gene mutations from circulating DNA in the blood.

The test is aimed at screening for eight common cancer types that account for more than 60 percent of cancer deaths in the U.S. Five of the cancers covered by the test currently have no screening test.

"The use of a combination of selected biomarkers for early detection has the potential to change the way we screen for cancer, and it is based on the same rationale for using combinations of drugs to treat cancers," said Nickolas Papadopoulos, senior author and professor of oncology and pathology.

The findings were published online by Science on Jan. 18.

The investigators initially explored several hundred genes and 40 protein markers, whittling the number down to segments of 16 genes and eight proteins. They point out that this molecular test is solely aimed at cancer screening and, therefore, is different from other molecular tests, which rely on analyzing large numbers of cancer-driving genes to identify therapeutically actionable targets.

In the study, the test had greater than 99 percent specificity for cancer.

The test was evaluated on 1,005 patients with nonmetastatic, stages I to III cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung or breast. The median overall sensitivity, or the ability to find cancer, was 70 percent and ranged from a high of 98 percent for ovarian cancer to a low of 33 percent for breast cancer. For the five cancers that have no screening tests—ovarian, liver, stomach, pancreatic and esophageal cancers—sensitivity ranged from 69 percent to 98 percent.

"A novelty of our classification method is that it combines the probability of observing various DNA mutations together with the levels of several proteins in order to make the final call," said Cristian Tomasetti, associate professor of oncology and biostatistics, who developed the algorithm. "Another new aspect of our approach is that it uses machine learning to enable the test to accurately determine the location of a tumor down to a small number of anatomic sites in 83 percent of patients."

Although the current test does not pick up every cancer, it identifies many cancers that would likely otherwise go undetected.

"Many of the most promising cancer treatments we have today only benefit a small minority of cancer patients, and we consider them major breakthroughs. If we are going to make progress in early cancer detection, we have to begin looking at it in a more realistic way, recognizing that no test will detect all cancers," says Bert Vogelstein, co-director of the Ludwig Center, Clayton Professor of Oncology and Howard Hughes Medical Institute investigator.

To zero in on the analytes for the CancerSEEK test, the research team pulled data from more than three decades of cancer genetics research generated at their Ludwig Center at Johns Hopkins, where the first genetic blueprints for cancer were created, as well as data from many other institutions.

The investigators said the CancerSEEK test will eventually cost less than $500. Additional testing is underway.

Study shows screening population for select genes is a cost-effective solution

A study published in the Journal of the National Cancer Institute indicates that screening the general population for mutations in specific genes is a more cost-effective way to detect people at risk and prevents more breast and ovarian cancers compared to only screening patients with a personal or family history of these diseases.

Current guidelines recommend that only those with a personal or family history that could indicate a greater risk of developing cancer be tested for gene mutations that can cause the disease. However, the successful use of testing for high-risk groups has led many to consider extending genetic testing for cancer to the whole population.

Recent technological advances in genomic medicine make large-scale genetic testing possible. The new study evaluated the cost effectiveness of screening the general population for ovarian and breast cancer genes, compared to only screening high-risk people. It found that population-based testing for mutations in specific genes in women over 30 years old was cost effective and prevented more cancers and deaths than only carrying out genetic testing in women whose personal or family history indicated a greater risk of developing cancer.

Mutations that cause cancer can occur in many people with no history to indicate a risk. These people are therefore not included in screening programs that target high-risk patients and the mutations remain undetected. The researchers of the new study estimate that implementing a program to test all women over the age of 30 could result in thousands fewer cases of ovarian and breast cancer in women in the US and UK.

The paper "Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women" is available at the Journal of the National Cancer Institute.

Polygenic hazard score predicts when men develop prostate cancer

An international team, led by researchers at the University of California San Diego School of Medicine, has developed a genetic tool for predicting age of onset of aggressive prostate cancer.

The tool, described in the Jan. 11 online issue of the BMJ (formerly the British Medical Journal), may potentially be used to help guide decisions about who to screen for prostate cancer and at what age.

Currently, detection of prostate cancer relies primarily upon the prostate-specific antigen screening blood test. But PSA testing is not good as a screening tool. While it reduces deaths from prostate cancer, indiscriminate PSA screening also produces false positive results and encourages over-detection of non-aggressive, slow-growing tumors.

Tyler Seibert, chief resident physician in the Department of Radiation Medicine and Applied Sciences at UC San Diego School of Medicine, senior author Anders Dale, professor and co-director of the Center for Translational Imaging and Precision Medicine at UC San Diego School of Medicine, and colleagues in Europe, Australia and the United States, used genome-wide association studies to determine whether a man's genetic predisposition to developing prostate cancer could be used to predict his risk of developing the aggressive and lethal form of the disease.

GWAS search individual genomes for small variations, called single-nucleotide polymorphisms, that occur more frequently in people with a particular disease than in people without the disease. Hundreds or thousands of SNPs can be evaluated at the same time in large groups of people. In this case, researchers used data from over 200,000 SNPs from 31,747 men of European ancestry participating in the ongoing international PRACTICAL consortium project.

Using a method developed at UC San Diego, the researchers combined information from GWAS and epidemiological surveys to assess quantification for genetic risk at age of disease onset.

Genotype, prostate cancer status and age were analyzed to select SNPs associated with prostate cancer diagnosis. Then the data was incorporated into the polygenic hazard score, which involves survival analysis to estimate SNPs' effects on age at diagnosis of aggressive prostate cancer.

The results led to a polygenic hazard score for prostate cancer that can estimate individual genetic risk. This score was then tested against an independent dataset, from the recent UK ProtecT trial, for validation.

The study authors note that an individual's genotype does not change with age, so the polygenic hazard score can be calculated at any time and used as a tool for men deciding whether and when to undergo screening for prostate cancer. This is especially critical for men at risk of developing prostate cancer at a very young age, before standard guidelines recommend consideration of screening.

Exelixis and Ipsen announce phase III trial results of Cabozantinib in advanced hepatocellular carcinoma

Exelixis Inc. and Ipsen announced detailed results of the pivotal phase III CELESTIAL trial in patients with previously treated advanced hepatocellular carcinoma, which will be presented in a late-breaking oral session at the 2018 ASCO-GI Symposium.

In CELESTIAL, cabozantinib provided a statistically significant and clinically meaningful improvement versus placebo in overall survival, the trial's primary endpoint, at the planned second interim analysis (pre-specified critical p-value ≤ 0.021) for the population of second- and third-line patients enrolled in this study.

Median OS was 10.2 months with cabozantinib versus 8.0 months with placebo (HR 0.76, 95 percent CI 0.63-0.92; p=0.0049). Median progression-free survival was more than doubled, at 5.2 months with cabozantinib and 1.9 months with placebo (HR 0.44, 95 percent CI 0.36-0.52; p<0.0001).

Objective response rates per RECIST 1.1 were 4 percent with cabozantinib and 0.4 percent with placebo (p=0.0086). Disease control (partial response or stable disease) was achieved by 64 percent of the cabozantinib group compared with 33 percent of the placebo group.

In a subgroup analysis of patients whose only prior therapy for advanced HCC was sorafenib (70 percent of patients in the study), median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (HR 0.70, 95 percent CI 0.55-0.88). Median PFS in the subgroup was 5.5 months with cabozantinib versus 1.9 months with placebo (HR 0.40, 95 percent CI 0.32-0.50). Adverse events were consistent with the known safety profile of cabozantinib.

The most common (≥10 percent) grade III or IV adverse events in the cabozantinib group compared to the placebo group were palmar-plantar erythrodysesthesia (17 percent vs. 0 percent), hypertension (16 percent vs. 2 percent), increased aspartate aminotransferase (12 percent vs. 7 percent), fatigue (10 percent vs. 4 percent), and diarrhea (10 percent vs. 2 percent).

Treatment-related grade V adverse events occurred in six patients in the cabozantinib group (hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism and hepatorenal syndrome) and in one patient in the placebo group.

Sixteen percent of patients in the cabozantinib arm and three percent of patients in the placebo arm discontinued treatment due to treatment-related adverse events.

CELESTIAL is a randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC conducted at more than 100 sites globally in 19 countries.

The trial was designed to enroll 760 patients with advanced HCC who received prior sorafenib and may have received up to two prior systemic cancer therapies for HCC and had adequate liver function. Enrollment of the trial was completed in September 2017.

Patients were randomized 2:1 to receive 60 mg of cabozantinib once daily or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia versus other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms during the blinded treatment phase of the trial.

The primary endpoint for the trial is OS, and secondary endpoints include objective response rate and PFS. Exploratory endpoints include patient-reported outcomes, biomarkers and safety.

Based on available clinical trial data from various published trials conducted in the second-line setting of advanced HCC, the CELESTIAL trial design assumed a median OS of 8.2 months for the placebo arm.

A total of 621 events provide the study with 90 percent power to detect a 32 percent increase in median OS (HR = 0.76) at the final analysis. Two interim analyses were planned and conducted at approximately 50 percent and 75 percent of the planned 621 events.

At the first interim analysis conducted by the independent data monitoring committee the observed hazard ratio was 0.71 and the p-value was 0.0041, which did not cross the stopping boundary for the first interim analysis (p ≤ 0.0037).

On Oct. 16, 2017, Exelixis announced that the independent data monitoring committee recommended that the trial be stopped for efficacy following review of the second planned interim analysis, as the trial had met its primary endpoint of OS (pre-specified critical p-value ≤ 0.021).

In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC.

DRUGS & TARGETS

Foundation Medicine and Pfizer form partnership to develop companion diagnostics

Foundation Medicine Inc. said the company has entered into a broad partnership with Pfizer Inc.

The partnership focuses on development, regulatory support and commercialization of companion diagnostics that will be included in updates to FoundationOne CDx.

FoundationOne CDx is Foundation Medicine's FDA-approved comprehensive genomic profiling assay for all solid tumors that incorporates multiple companion diagnostics.

Pfizer will also benefit from access to FoundationInsights, Foundation Medicine's data analytics platform, to facilitate novel biomarker discovery and to optimize clinical trial design. The unique combination of FoundationInsights and FoundationOne CDx will potentially enable Pfizer to leverage Foundation Medicine's platform technology to accelerate discovery and development of precision oncology therapeutics.

Pfizer currently has 10 FDA-approved oncology medicines that treat a diverse array of solid tumors and hematologic malignancies. In addition, its oncology pipeline includes 17 assets in clinical development and 19 phase III studies.

FoundationOne CDx assesses all classes of genomic alterations in 324 genes known to drive cancer growth, providing potentially actionable information to help guide treatment decisions. It also reports genomic biomarkers, such as microsatellite instability and tumor mutational burden, that can help inform the use of immunotherapies; genomic alterations in other genes relevant to patient management; and relevant clinical trial information.

As such, it is designed to help streamline companion diagnostic development, mitigate risk and advance targeted therapy development. Currently FoundationOne CDx is FDA-approved as a CGP assay for all solid tumors and a broad companion diagnostic for patients with certain types of non-small cell lung cancer, melanoma, colorectal cancer, ovarian cancer or breast cancer to identify those patients who may benefit from treatment with one of 17 on-label targeted therapies.

Concurrent with FDA approval, the Centers for Medicare & Medicaid Services issued a preliminary National Coverage Determination for FoundationOne CDx. The draft NCD would provide coverage for FDA-approved companion diagnostic claims, as well as a pathway for additional coverage with evidence development in other solid tumor types. The final policy is expected to issue during the first quarter of 2018 following public comment on the preliminary NCD and an administrative period.

FoundationOne CDx is a sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability and tumor mutational burden using DNA isolated from formalin-fixed paraffin embedded tumor tissue specimens.

FoundationOne CDx is intended as a companion diagnostic to identify patients who may benefit from treatment with certain targeted therapies in accordance with their approved therapeutic product labeling.

Additionally, FoundationOne CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

FDA approves addition of overall survival data to Kyprolis

FDA has approved the supplemental New Drug Application to add overall survival data from the phase III head-to-head ENDEAVOR trial to the Prescribing Information for Kyprolis (carfilzomib).

Data added to the label demonstrated that Kyprolis and dexamethasone reduced the risk of death by 21 percent and increased OS by 7.6 months versus Velcade (bortezomib) and dexamethasone in patients with relapsed or refractory multiple myeloma (median OS 47.6 months for Kd versus 40.0 months for Vd, HR=0.79; p=0.01).

The NCCN Clinical Practice Guidelines in Oncology list Kd as the only preferred doublet regimen at relapse for multiple myeloma. Full OS results from the

ENDEAVOR trial were published earlier this year in The Lancet Oncology.

Adverse events observed in this updated analysis were consistent with those previously reported for ENDEAVOR. The most common adverse events (greater than or equal to 20 percent) in the Kyprolis arm were anemia, diarrhea, pyrexia, dyspnea, fatigue, hypertension, cough, insomnia, upper respiratory tract infection, peripheral edema, nausea, bronchitis, asthenia, back pain, thrombocytopenia and headache.

Since its approval in 2012, more than 50,000 patients worldwide have received Kyprolis. The Kyprolis clinical program continues to focus on providing treatment options for physicians and patients for this frequently relapsing and difficult-to-treat cancer. Kyprolis is available for patients whose myeloma has relapsed or become resistant to another treatment and continues to be studied in a range of combinations and patient populations.

The randomized ENDEAVOR (RandomizEd, OpeN Label, Phase III Study of Carfilzomib Plus DExamethAsone Vs Bortezomib Plus DexamethasOne in Patients With Relapsed Multiple Myeloma) trial of 929 patients evaluated Kyprolis in combination with low-dose dexamethasone, versus Velcade with low-dose dexamethasone in relapsed or refractory patients who previously received at least one, but not more than three, prior therapeutic regimens.

The primary endpoint of the trial was progression-free survival, defined as the time from treatment initiation to disease progression or death. The primary analysis was published in *The Lancet Oncology* and is described in the Prescribing Information.

Patients received treatment until progression with Kyprolis as a 30-minute infusion on days 1, 2, 8, 9, 15 and 16 of 28 day treatment cycles, along with low-dose dexamethasone (20 mg). For cycle one only, Kyprolis was administered at 20 mg/m2 on days 1 and 2, and if tolerated was escalated to 56 mg/m2 from day 8 of cycle one onwards. Patients who received Velcade (1.3 mg/m2) with low-dose dexamethasone (20 mg) were treated with Velcade administered subcutaneously or intravenously at the discretion of the investigator and in accordance with regional regulatory approval of Velcade. More than 75 percent of the patients in the control arm received Velcade subcutaneously.

Novartis granted FDA Priority Review for Kymriah for adults with r/r DLBCL

Novartis said its supplemental Biologics License Application for Kymriah (tisagenlecleucel) suspension for intravenous infusion, formerly CTL019, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for or relapse after autologous stem cell transplant (ASCT) has been accepted by FDA for Priority Review.

In addition, the European Medicines Agency has granted accelerated assessment to the Marketing Authorization Application for Kymriah for the treatment of children and young adults with r/r B-cell acute lymphoblastic leukemia and for adult patients with r/r DLBCL who are ineligible for ASCT.

Kymriah became the first CAR-T cell therapy to receive regulatory approval when it was approved by the FDA in August 2017 for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Kymriah uses the 4-1BB costimulatory domain in its chimeric antigen receptor to enhance cellular expansion and persistence. In 2012, Novartis and the University of Pennsylvania entered into a global collaboration to further research, develop and commercialize CAR-T cell therapies, including Kymriah, for the investigational treatment of cancers.

The regulatory applications in the US and EU are based on data from the Novartis-sponsored global clinical trial program of Kymriah in children and young adults with r/r B-cell ALL and adult patients with r/r DLBCL demonstrating the efficacy and safety of Kymriah across studies. Results from the pivotal phase II JULIET clinical trial served as the basis of the sBLA and MAA (applications submitted by pharmaceutical companies to health authorities when seeking approval of a new product) for Kymriah in adult patients with r/r DLCBL. Results from the pivotal phase II ELIANA study were submitted as part of the MAA for Kymriah in children and young adults with r/r B-cell ALL.

JULIET is the first multi-center global registration study for Kymriah in adult patients with r/r DLBCL. JULIET is the largest study examining a CAR-T therapy in DLBCL, enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan and Europe, including: Austria, France, Germany, Italy, Norway and the Netherlands. Data from the six-month primary analysis of JULIET were presented at the annual meeting of the American Society of Hematology (ASH) in December 2017.

ELIANA is the first pediatric global CAR-T cell therapy registration trial, examining patients in 25 centers in the US, Canada, Australia, Japan, and the EU, including: Austria, Belgium, France, Germany, Italy Norway, and Spain.

CTEP PROTOCOLS

NCI CTEP-Approved Trials for January

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month.

For further information, contact the principal investigator listed.

Phase I - 10080
Phase I Study of Recombinant Interleukin 15 in Combination with Checkpoint Inhibitors Nivolumab and Ipilimumab in Subjects with Refractory Cancers

National Cancer Institute
Developmental Therapeutics Clinic
Chen, A P
(240) 781-3320

Phase I - ABTC-1604
Phase 0/I Study of AMG 232 Concentrations in Brain Tissue in Patients with Recurrent Glioblastoma and of AMG 232 in Combination with Radiation in Patients with Newly Diagnosed Glioblastoma and Unmethylated MGMT Promoters

Adult Brain Tumor Consortium
Alexander, Brian Michael
(617) 732-7560

Phase I - AMC-S007
Longitudinal Quality of Life Study Among Participants with AIDS-Associated Kaposi Sarcoma

Bugando Medical Centre, in Mwanza, Tanzania
AIDS Malignancy Consortium
Schroeder, Kristin Marie
(919) 668-6288

Phase II - 10139
A Randomized Phase 2 Study of Atezolizumab in Combination with Cobimetinib Versus Atezolizumab Monotherapy in Participants with Unresectable Cholangiocarcinoma

JHU Sidney Kimmel Comprehensive Cancer Center LAO
Azad, Nilofer Saba
(410) 614-9169

Phase II - EA5161
Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) Alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

ECOG-ACRIN Cancer Research Group
Leal, Ticiana A.
(608) 263-9063

Phase II - EA8153
Cabazitaxel with Abiraterone Versus Abiraterone Alone Randomized Trial for Extensive Disease Following Docetaxel: The CHAARTED2 Trial

ECOG-ACRIN Cancer Research Group
Kyriakopoulos, Christos
(608) 263-0786

Phase II/III - NRG-HN004
Randomized Phase II/III Trial of Radiotherapy with Concurrent MEDI4736 (Durvalumab) Vs. Radiotherapy with Concurrent Cetuximab in Patients with Stage III-IVB Head and Neck Cancer with a Contraindication to Cisplatin

NRG Oncology
Mell, Loren K.
(858) 246-0471

Phase II/III - S1612
A Randomized Phase II/III Trial of "Novel Therapeutics" Versus Azacitidine in Newly Diagnosed Patients with Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS), Age 60 or Older (LEAP: Less-Intense AML Platform Trial)

SWOG
Michaelis, Laura Christian
(414) 805-1118

Phase Other - AALL17B7-Q
Germline TP53 and ETV6 Mutations in Acute Lymphoblastic Leukemia

Children's Oncology Group
Yang, Jun J.
(901) 595-2517

Phase Other - AALL17B8-Q
Dissecting the Prognostic Impact of the Pediatric B-ALL Immune Microenvironment Using Single-Cell Approaches

Children's Oncology Group
Carroll, William L.
(212) 263-9947

Phase Other - WF-30917CD
A Stepped-Care Telehealth Approach to Treat Distress in Rural Cancer Survivors

Wake Forest NCORP Research Base
Danhauer, Suzanne C.
(336) 716-7980