JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Clinical Cancer Advances 2013: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

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Published online ahead of print at www.jco.org on December 10, 2013.

*Executive editor.

†Specialty editor.

Supported in part by the Conquer Cancer Foundation Mission Endowment.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2013.53.7076

A MESSAGE FROM ASCO'S PRESIDENT

Since its founding in 1964, the American Society of Clinical Oncology (ASCO) has been committed to improving cancer outcomes through research and the delivery of quality care. Research is the bedrock of discovering better treatments—providing hope to the millions of individuals who face a cancer diagnosis each year.

The studies featured in "Clinical Cancer Advances 2013: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology" represent the invaluable contributions of thousands of patients who participate in clinical trials and the scientists who conduct basic and clinical research. The insights described in this report, such as how cancers hide from the immune system and why cancers may become resistant to targeted drugs, enable us to envision a future in which cancer will be even more controllable and preventable.

The scientific process is thoughtful, deliberate, and sometimes slow, but each advance, while helping patients, now also points toward new research questions and unexplored opportunities. Both dramatic and subtle breakthroughs occur so that progress against cancer typically builds over many years. Success requires vision, persistence, and a long-term commitment to supporting cancer research and training.

Our nation's longstanding investment in federally funded cancer research has contributed significantly to a growing array of effective new treatments and a much deeper understanding of the drivers of cancer. But despite this progress, our position as a world leader in advancing medical knowledge and our ability to attract the most promising and talented investigators are now threatened by an acute problem: Federal funding for cancer research has steadily eroded over the past decade, and only 15% of the ever-shrinking budget is actually spent on clinical trials. This dismal reality threatens the pace of progress against cancer and undermines our ability to address the continuing needs of our patients.

Despite this extremely challenging economic environment, we continue to make progress. Maintaining and accelerating that progress require that we keep our eyes on the future and pursue a path that builds on the stunning successes of the past. We must continue to show our policymakers the successes in cancer survival and quality of life (QOL) they have enabled, emphasizing the need to sustain our national investment in the remarkably productive US cancer research enterprise.

We must also look to innovative methods for transforming how we care for—and learn from—patients with cancer. Consider, for example, that fewer than 5% of adult patients with cancer currently participate in clinical trials. What if we were able to draw lessons from the other 95%? This possibility led ASCO this year to launch CancerLinQ, a groundbreaking health information technology initiative that will provide physicians with access to vast quantities of clinical data about real-world patients and help achieve higher quality, higher value cancer care.

As you read the following pages, I hope our collective progress against cancer over the past year inspires you. More importantly, I hope the pride you feel motivates you to help us accelerate the pace of scientific advancement.

Clifford A. Hudis, MD, FACP

President

American Society of Clinical Oncology

J Clin Oncol 31. © 2013 by American Society of Clinical Oncology

EXECUTIVE SUMMARY

"Clinical Cancer Advances 2013: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology" marks the annual assessment by the American Society of Clinical Oncology (ASCO) of the advances in cancer research with the greatest potential to improve patient care and quality of life.

This year's report features 76 studies. Many studies highlighted capitalize on our growing understanding of tumor biology and genomics that paves the way to the development of new therapy approaches for treatment-resistant and rare cancers. Marked progress has been achieved in overcoming treatment resistance through precision medicine and immunotherapy. The report also features the year's most important cancer policy developments and clinical practice guidelines (Table 1) that are likely to influence cancer care delivery in the near term.

Preserving our nation's investment in cancer research is absolutely necessary to maintain and increase the momentum that brings new and improved treatments to the growing numbers of people with cancer. Although major advances were seen across the treatment spectrum, the report this year focuses on how this investment pays off in two increasingly important research fields: cancer genomics and screening.

Cancer in the United States

- Approximately 1.6 million new cancer cases will be diagnosed this year in the United States. Over the most recent 10 years for which data are available—2000 through 2009—the overall incidence rate of all cancers combined decreased slightly in men (by 0.8% per year) and remained stable in women. Among some ethnic groups, however, cancer incidence rates are on the rise. For example, childhood cancer incidence rates increased for African American and Hispanic children but remained stable for children of all other racial and ethnic groups.

- Although overall cancer-related death rates continue to decline in the United States—by 1.5% per year during the period from 2000 through 2009—cancer remains the second most common cause of death, accounting for nearly one in four deaths. An estimated 580,000 Americans will lose their lives to cancer in 2013.

Cancer Genomics Paves the Way to Precision Medicine

Genomic information is increasingly being used in the clinic to make treatment decisions for individual patients. Over the past decade, modern genomic technology has enabled accumulation of massive amounts of data on the molecular underpinnings of tumor development and growth. Leading this effort is The Cancer Genome Atlas (TCGA) research network, launched by the National Institutes of Health (NIH) in 2009, which aims to explore the entire spectrum of genomic changes involved in human cancer. TCGA researchers are charting genomic changes in more than 20 different cancer types. Their findings are made readily available to the worldwide research community, accelerating development of new targeted therapies. In 2013, TCGA network reported results of comprehensive molecular analyses of kidney and endometrial cancers as well as acute myeloid leukemia (AML).

Many studies featured in the report this year showcase how genomic research is being applied to personalized therapy approaches, ultimately improving outcomes for patients. For example, large-scale genomic profiling has identified genetic changes that drive tumor development, pinpointing potential new prognostic markers and drug targets in brain, kidney, and head and neck cancers. Researchers have identified new molecular subtypes of endometrial cancer and glioblastoma (GBM). The federally funded Lung Cancer Research Consortium reported on genomic testing for genes that drive lung cancer and matching patients with the best available targeted therapies and clinical trials. Finally, an important genomic study revealed that changes in one specific gene may be associated with resistance to chemotherapy in some children with acute lymphocytic leukemia (ALL).

Table 1. ASCO Clinical Practice Guidelines and Endorsements, October 2012 to October 2013

Guideline Title	Publication Date
ASCO Endorsement: Guideline for the Management of Fever and Neutropenia in Children With Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation	January 14, 2013
Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: ASCO Clinical Practice Guideline	February 20, 2013
Breast Cancer Follow-Up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	March 1, 2013
Central Venous Catheter Care for the Patient With Cancer: ASCO Clinical Practice Guideline	April 1, 2013
Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Practice Guideline Update	June 10, 2013
Fertility Preservation in Patients With Cancer: ASCO Guideline Update	July 1, 2013
Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline	August 10, 2013

Abbreviation: ASCO, American Society of Clinical Oncology.

New Cancer Screening Paradigms Could Drastically Reduce Disparities

Cancer screening programs allow for early detection of cancer, which often substantially improves the likelihood of successful treatment and long-term survival. Unfortunately, screening is not accessible to all people, because of barriers such as lack of infrastructure, resources, health insurance, and health education.

Two pivotal reports this year describe new cancer screening models designed to reduce economic and racial disparities in cancer outcomes. A study involving more than 150,000 women in India

demonstrated that cervical cancer screening using simple vinegar and delivered by primary health workers is effective and feasible. If implemented, the strategy could save more than 70,000 women's lives per year in low-resource countries where Pap and human papillomavirus (HPV) testing are largely unavailable. An innovative, state-funded, colorectal cancer screening and treatment program in Delaware has nearly eliminated disparities in outcomes for African Americans, without increasing overall health care costs in its first 10 years of operation. The program may serve as a model for other states to eliminate disparities in colorectal cancer.

New Success at Harnessing the Power of the Immune System

Over millions of years, our immune system has evolved into a robust yet highly adaptable defense barrier against disease. Unfortunately, a natural immune response to cancer is not typical, because of various molecular mechanisms by which tumors either hide from or suppress any effective immune response. This year brought encouraging results, with two clever strategies to unlock and enhance the ability of the immune system to fight cancer.

Several early studies confirmed that the programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) pathway plays a critical role in the immune response to certain forms of cancer. New targeted drugs that block the PD-1 protein on immune cells or the PD-L1 protein on cancer cells resulted in rapid and long-lasting tumor shrinkage in patients with advanced melanoma.

Another new immunotherapy approach involves collecting T cells from an individual patient, genetically engineering them in the laboratory so they can find and dock onto the patient's tumor cells, growing those cells in large numbers, and reinfusing them into the patient. Findings from three small studies in adults and children with chemotherapy-resistant ALL suggest that this experimental therapy may help such patients live longer.

Approvals Result in New Treatment Options for Common and Rare Cancers

Between October 2012 and October 2013, based on compelling evidence of benefit shown in clinical trials, the US Food and Drug Administration (FDA) approved nine new anticancer drugs to treat patients with advanced and/or treatment-resistant chronic myeloid leukemia (CML; omacetaxine mepesuccinate and ponatinib), multiple myeloma (pomalidomide), medullary thyroid cancer (cabozantinib), breast cancer (ado-trastuzumab emtansine), prostate cancer (radium-223 [^{223}Ra] dichloride), melanoma (dabrafenib and trametinib), and non–small-cell lung cancer (NSCLC; afatinib). This remarkable number of new drug approvals in a 12-month period is indicative of vigorous drug development activity and improvements in regulatory processes, including accelerated approval, and special effort within the FDA. In addition, the new FDA breakthrough therapy designation, established by Congress in 2012, is designed to speed development of new treatments that may lead to substantial improvement over existing therapies. From October 2012 to September 6, 2013, the FDA has granted 26 breakthrough therapy designations, with the largest disease area for cancer therapies. Most of the newly approved agents are targeted drugs that block the activity of specific proteins (ie, kinases) that fuel cancer growth. This year's approvals also include agents in other classes of drugs (eg, radiopharmaceuticals, immunomodulatory agents, and protein translation inhibitors).

Conquer Cancer Foundation

- The Conquer Cancer Foundation of the American Society of Clinical Oncology (ASCO) directly funded two of the research studies featured in this year's report: first, preclinical research on how a new targeted therapy called AGI-5198 inhibits growth of cancerous cells in glioma, and second, a clinical trial showing that a new kinase inhibitor, cabozantinib, results in an antitumor effect and reduction of circulating tumor cells in advanced prostate cancer.

- The Conquer Cancer Foundation was created by the world's foremost cancer physicians of ASCO to seek dramatic advances in the prevention, treatment, and cures of all types of cancer. With the vision of a world free from the fear of cancer, the foundation works to conquer this disease by funding breakthrough cancer research and sharing cutting-edge knowledge with patients and physicians worldwide, by improving quality of and access to care, and by enhancing quality of life for all who are touched by cancer. Over 30 years, more than $83 million in funding has been provided through the Conquer Cancer Foundation Grants and Awards Program to support clinical and translational scientists at all levels of their careers, working around the globe to address the full spectrum of oncology—from prevention through survivorship and end-of-life care—for nearly every cancer type.

In addition, the FDA has expanded indications for six existing anticancer agents, offering new treatment options for patients with mantle-cell lymphoma (lenalidomide), NSCLC (paclitaxel protein-bound particles and erlotinib), prostate cancer (abiraterone acetate), GI stromal tumors (GISTs; regorafenib), and giant-cell tumor of the bone (GCTB; denosumab; Table 2).

About Clinical Cancer Advances

ASCO developed this annual report, now in its ninth year, to document the important progress being made in clinical cancer research and to highlight emerging trends in the field. Clinical Cancer Advances (CCA) reports serve to outline to the public the progress achieved against cancer by reviewing the major advances in clinical cancer research and care each year. As a whole, this document attests to the current state of the science and reflects on where cancer research is heading in the near future.

The content of the CCA report was developed through a peer-review process, under the direction of an 18-person editorial board composed of prominent oncologists with expertise in areas pertinent to each section of the report. The editors reviewed research published in peer-reviewed scientific or medical journals and presented at major scientific meetings over a 1-year period (October 2012 to September

Table 2. FDA Approvals of Anticancer Agents, October 2012 to October 2013

Generic Name	Trade Name	Indications	Date of Approval
Newly approved agents			
Omacetaxine mepesuccinate	Synribo	For the treatment of adult patients with chronic- or accelerated-phase CML with resistance and/or intolerance to ≥ 2 TKIs	October 26, 2012
Cabozantinib	Cometriq	For the treatment of patients with progressive metastatic medullary thyroid cancer	November 29, 2012
Ponatinib	Iclusig	For the treatment of adult patients with chronic-, accelerated-, or blast-phase CML resistant or intolerant to prior TKI therapy or Ph-positive ALL resistant or intolerant to prior TKI therapy	December 14, 2012
Pomalidomide	Pomalyst	For the treatment of patients with multiple myeloma who have received ≥ 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy	February 8, 2013
Ado-trastuzumab emtansine	Kadcyla	For use as a single agent for the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination	February 22, 2013
Radium-223 dichloride	Xofigo	For the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease	May 15, 2013
Dabrafenib	Tafinlar	For the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	May 29, 2013
Trametinib	Mekinist	For the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutation as detected by an FDA-approved test	May 29, 2013
Afatinib	Gilotrif	For the first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test	July 12, 2013
Expanded indications for existing agents			
Paclitaxel protein-bound particles	Abraxane	For use in combination with carboplatin for the initial treatment of patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or radiation therapy	October 11, 2012
Abiraterone acetate	Zytiga	For use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer	December 10, 2012
Regorafenib	Stivarga	To treat patients with advanced GISTs that cannot be surgically removed and who no longer respond to other FDA-approved treatments for this disease	February 25, 2013
Erlotinib	Tarceva	For the first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations	May 13, 2013
Denosumab	Xgeva	For the treatment of adults and skeletally mature adolescents with giant-cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity	June 13, 2013
Lenalidomide	Revlimid	For the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib	June 5, 2013
Paclitaxel protein-bound particles	Abraxane	For the treatment of patients with late-stage (metastatic) pancreatic cancer	September 6, 2013

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; FDA, US Food and Drug Administration; GIST, GI stromal tumor; HER2, human epidermal growth factor receptor 2; MCL, mantle-cell lymphoma; NSCLC, non–small-cell lung cancer; Ph, Philadelphia chromosome; TKI, tyrosine kinase inhibitor.

2013). To strengthen the quality and scientific validity of the report, this year we have added an advisory group of experts (one for each section). The editorial advisors (listed in the Acknowledgment, online only) provided an additional round of review within their practice specialties to ensure the advances meet the prespecified selection criteria and that no important advances have been omitted.

The research reviewed in this report covers the full range of clinical research disciplines: prevention, screening, treatment, patient and survivor care, biomarkers, tumor biology, and cancer disparities.

This report is intended for anyone with an interest in cancer care, including oncologists, oncology trainees, other medical professionals, patients, caregivers, news media, policymakers, and cancer advocacy organizations.

About ASCO

ASCO is the world's leading professional oncology society committed to conquering cancer through research, education, prevention, and delivery of high-quality patient care. ASCO is unique in that we are the only organization that encompasses all oncology subspecialties, allowing our members to grow from the professional and personal expertise of their colleagues worldwide and across disciplines. With more than 30,000 members, ASCO is dedicated to providing the highest-quality resources in education, policy, the pioneering of clinical research, and above all the advancement of care for patients with cancer. For ASCO information and resources, visit www.asco.org. Cancer information for the lay public is available at www.cancer.net.

POLICY PERSPECTIVE: RENEWING THE NATION'S COMMITMENT TO CLINICAL CANCER RESEARCH

In large measure, as a result of our nation's investment in cancer research during the past four decades, we know more than ever about what triggers cancer development and growth, and we have made tremendous strides in improving patient care, survival, and QOL. Since the 1990s, cancer death rates have declined 21% among men and 12% among women, and more than 13 million cancer survivors are alive in the United States today.

The expansion of our understanding of cancer at the molecular level is nothing short of remarkable. Researchers have identified hundreds of molecular changes that cause cancer and developed many new targeted treatments that home in on many of those changes. Some new treatments essentially turn cancer into a chronic disease, stalling additional growth with maintenance therapy. In other cases, new therapies are opening up the prospect of long-term survival and even cure.

Also, in recent years, as more people survive cancer and more individualized treatment is possible, greater attention has been paid to the quality and value of health care, leading to innovative solutions for quality improvement.

2013: Sequestration Cuts Research Grants and Clinical Trials

In the United States, cancer research is critically dependent on federal funding of NIH and the National Cancer Institute (NCI). Federal funding underpins the cancer clinical trials system and is particularly important in supporting research that industry typically does not pursue, including nonregulatory studies comparing several different therapies head to head, combination therapy approaches (eg, surgery, chemotherapy, and radiation), studies on reducing treatment dose or altering the schedule while preserving efficacy, and studies of rare cancers, cancer disparities, prevention and screening, and quality and cost of care. In fact, approximately one third of the advances featured in this report have been funded through NIH grants.

However, this vital research is facing its greatest threat in a generation. The federal budget sequester enacted in 2013 triggered across-the-board cuts to ongoing research across the United States. In particular, NIH cut existing grants by 10% and eliminated from consideration 700 viable research projects that otherwise would have been funded.[1] NCI, which provides most of the federal funding for cancer research in the United States and is the largest component of NIH, cut funding by at least 6% percent for existing grants, cancer centers, and other research programs. Research and development contracts were cut by 8.5%.

This recent budget reduction falls on a pattern of flat funding over the past decade. Although Congress enacted a 5-year doubling of the NIH budget in 1998, funding for NIH has been effectively undoubled since that time. Including the cuts from sequestration, the NIH budget has declined by more than 22% ($6.1 billion) over the last decade, after adjusting for inflation. The number of new grants supported by NIH is at its lowest level since 1998, with only

National Institutes of Health Budget Cuts

- With the National Institutes of Health (NIH) budget providing support for approximately 300,000 research personnel who are employed at more than 2,500 universities and research institutions throughout the country, the bleak funding picture is having real-life consequences for the cancer research enterprise in the United States (http://www.nih.gov/about/budget.htm).
- At the Moffitt Cancer Center (Tampa, FL), researchers saw their budget reduced by $1.7 million when the sequestration cuts took effect. A large project studying lung cancer was not renewed and had to be curtailed (Perry M: Tampa Bay Tribune, August 26, 2013).
- The Mayo Clinic (headquartered in Rochester, MN) lost $23 million in federal research funding because of the sequester in fiscal year 2013 (Mayo Clinic Public Affairs, personal communication, September 26, 2013).
- The state of New Jersey lost $12 million in NIH funding (Waldron K: NJ1015.com, August 19, 2013).
- Approximately 750 fewer new patients were expected to be enrolled onto all clinical trials at the NIH Clinical Center hospital (Bethesda, MD) in 2013 (http://www.nih.gov/news/health/jun2013/nih-03.htm).

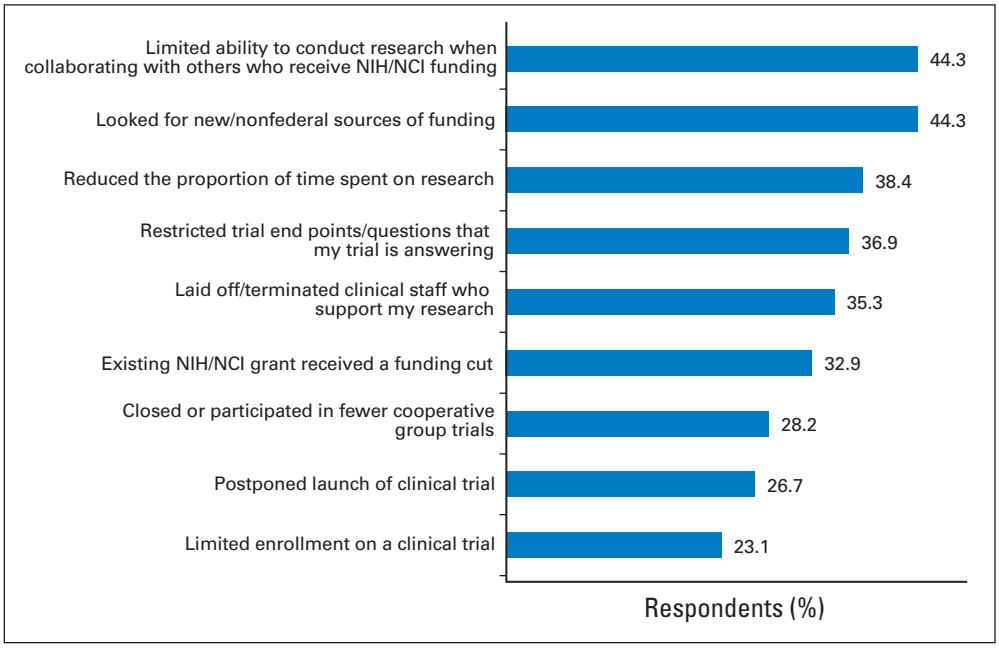

Fig 1. An American Society of Clinical Oncology survey of United States–based members conducted in August 2013 found that federal budget cuts to the National Institutes of Health (NIH) have severely affected the ability of members to conduct cancer research. Of the 345 respondents, 60% conduct their research at academic institutions, 35% at National Cancer Institute (NCI)–designated cancer centers, and the remainder at a community hospital, private practice, or Veterans Administration hospital. A majority of respondents (80%) engage in clinical or patient-centered research.

one in six highly ranked grant proposals currently receiving funding. This low funding rate is discouraging to researchers and slows progress against cancer.

No institution receiving NIH grant support has been spared in these budget cuts. Laboratory technicians and postdoctoral students are being laid off. Translational research—the research that advances basic science into development of new therapies—is being delayed. Long-planned clinical trials are not able to open for patient enrollment.

ASCO members reported that this year's funding cuts have had a devastating impact on their research and ability to make progress against cancer (Fig 1). In fact, 75% of the ASCO members who responded to an August 2013 survey said that since October 2012, the current federal funding situation is having a direct impact on their ability to conduct cancer research, and 38% said their time spent on research has been reduced. In addition, 35% reported having to lay off research staff, 28% are participating in fewer federally funded clinical trials, and 26% have delayed the launch of a clinical trial.

Yet, the worst is still to come. If Congress does not reverse the sequester for NIH and NCI, the across-the-board budget cuts will continue through 2021. These reductions will undermine the nation's biomedical research enterprise, threatening our traditional global leadership in this important area.

Supporting the National Clinical Trials Network

Since 1955, the NCI Clinical Trials Cooperative Group Program has served as the leading network for federally funded cancer clinical research in the United States. Enrolling approximately 20,000 patients onto clinical trials each year—and involving 14,000 clinical researchers at 3,100 institutions and community practices in the United States—the NCI cooperative groups have developed innovative and effective therapies for a variety of cancers and provided essential training for young clinical researchers. The existence of the cooperative group program has helped ensure that innovative clinical trials are available to patients in nearly every community in which cancer care is offered.

In an effort to strengthen the cooperative group system and improve efficiency, NCI set in motion in 2010 a major consolidation of the nine cooperative groups studying adult cancers into the new National Clinical Trials Network. The new network, consisting of four adult cancer groups and the existing Children's Oncology Group, is designed to conduct highly efficient clinical trials of therapies that target the molecular mutations that drive cancer development.

However, cooperative group program funding has been falling and, when adjusted for inflation, is at approximately the same level it was in 1999. As a result, patient enrollment onto clinical trials has dropped from a high of more than 29,000 patients per year in 2009 to fewer than 20,000 per year today (Fig 2).[2]

Clearly, clinical research productivity—and resulting information that could help oncologists offer better therapies to their patients—has been severely affected by federal budget cuts. Recognizing the critical role that the National Clinical Trials Network plays in studying important research questions and bringing new treatments to individuals with cancer, ASCO earlier this year called on Congress to increase funding for the network.[1]

Patient Access to Clinical Trials: Good News, Bad News

Clinical trials represent a vitally important lynchpin in the development and testing of new cancer therapies, diagnostic tools, and prevention methods.

Removing a critical obstacle to patients interested in participating in clinical trials, the Patient Protection and Affordable Care Act included an important provision to require coverage of routine medical costs for individuals participating in approved research studies. The law includes stringent requirements that will take effect for all new health plans offered after January 1, 2014.

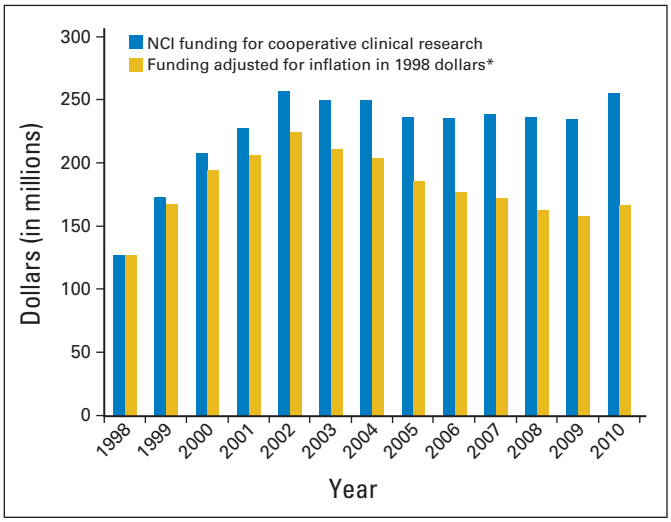

Fig 2. National Cancer Institute (NCI) cooperative clinical research funding comparing actual funding with funding adjusted for biomedical inflation in 1998 US dollars. Funding for the NCI Clinical Trials Cooperative Group (now known as the National Clinical Trials Network) program has not kept pace with inflation. Data adapted.[2] (*) Calculations based on the National Institutes of Health Biomedical Research and Development Price Index (http://officeofbudget.od.nih.gov/gbiPriceIndexes.html).

Regrettably, federal agencies decided to leave the implementation details of this provision up to individual states, which is likely to produce a patchwork of uneven and unpredictable coverage that may confuse patients and their health care providers and delay access to potentially life-extending research. ASCO is developing informational brochures for patients and clinicians to explain the provision but also believes that additional guidance from the federal government would be beneficial.

Quality Cancer Care

- In today's policy environment, which is absorbed by budget deficits and funding cuts, greater attention is being paid to quality and value in health care, including cancer care. The American Society of Clinical Oncology (ASCO) was one of 15 sponsoring organizations of an Institute of Medicine report issued in September, entitled "Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis," which examines opportunities for and challenges to delivering high-quality cancer care and provides recommendations for improving the quality of cancer care in the United States.

- ASCO is at the leading edge of this movement and over the past year has made huge strides in its two major initiatives that have the potential to significantly improve cancer care: CancerLinQ and the Quality Oncology Practice Initiative (QOPI).

Joining more than 50 other organizations earlier this year, ASCO called on the US Department of Health and Human Services and Department of Labor to issue clear federal guidance to ensure that the new law is implemented consistently and fairly.

The organizations urged federal guidance to clarify that potential complications arising from clinical trials would be covered under routine costs, patients would not be required to travel unreasonable distances to enroll onto trials, and a patient's health care professional would determine whether his or her condition is life threatening. ASCO and others also called for safeguards to protect patients from administrative delays that would affect their ability to enroll onto trials.

Moving Forward With the ASCO Cancer Research Blueprint

Significant progress has been made in advancing the vision of ASCO for transforming clinical cancer research in the United States and speeding the creation of effective new therapies for patients—articulated in the ASCO 2011 report "Accelerating Progress Against Cancer: ASCO's Blueprint for Transforming Clinical and Translational Cancer Research."

Since issuing the report, ASCO has worked with partners, including the FDA and NCI, to drive the recommendations of the report forward. At its 2013 annual meeting, ASCO provided an update on its initiatives to articulate desired end points of clinical trials that would produce results that are clinically meaningful to patients, develop recommendations to avoid unnecessary exclusion of patients from trials, and work with the FDA to streamline data collection and advance the development and use of end points that would allow clinical trials to demonstrate safety and efficacy earlier. Sustained federal funding will be critical to the success of these scientific and regulatory efforts that will contribute to achieving the blueprint vision of a more flexible, nimble, and efficient clinical cancer research system adapted to the molecular era.

ASCO's Call to Action

What will it take to transform today's scientific discoveries into effective therapies for people with cancer? The scientific and clinical workforces are currently adequate, but ongoing and increasing support will be needed to ensure that we can meet the increase in demand anticipated as the US population ages, as the number of cancer survivors increases, and as expanded coverage is available through the Affordable Care Act. The basic and clinical research infrastructures are well established. Initiatives to ensure quality of care and rapid learning to improve outcomes are under way. All that is missing is the political will to renew our nation's historic investment in life-extending cancer research. That commitment was clear in 1971, when the National Cancer Act was enacted. It was clear in 1998, when Congress voted to double the NIH budget. Flat funding and cuts from sequestration mean that NIH funding has not kept pace with the increasing cost of conducting research or with the growing need for advances as more Americans are diagnosed with cancer.

The future of federal funding for cancer research remains uncertain. Meanwhile, as researchers are forced to delay or halt promising studies, and the next generation of investigators may be leaving the field because of low prospects of obtaining support, the slowdown in biomedical research threatens to undermine the country's leading role in biomedical research.

CancerLinQ for Higher Quality, Higher Value Cancer Care

- In 2013, the American Society of Clinical Oncology (ASCO) initiated development of the full CancerLinQ system, a groundbreaking health information technology (HIT) initiative to achieve higher quality, higher value cancer care with better outcomes for patients. The multiphase development process will encompass a series of successively more powerful quality improvement tools for physicians, with the first components becoming available by early 2015.
- CancerLinQ will transform cancer care by unlocking vast quantities of information that are now lost to file cabinets and unconnected servers. Instead of learning from the 3% to 5% of patients in clinical trials, we will learn from the routine care given to every patient—and improve quality and value of care for all patients. CancerLinQ will place a new universe of practical insights at the fingertips of:
  - Physicians: Access to up-to-the-minute, individualized decision support based on published reports and real-world experience
  - Patients: Access to personalized treatment information from their medical team
  - Researchers: Access to information from a massive body of deidentified data on patient care and results to conduct secondary analytics
- In March, ASCO announced the successful completion of the CancerLinQ prototype, which demonstrated the feasibility of an HIT-based learning health system (http://www.iom.edu/Reports/2012/Best-Care-at-Lower-Cost-The-Path-to-Continuously-Learning-Health-Care-in-America.aspx). The prototype was completed in just 8 months and included more than 170,000 deidentified (ie, anonymous) medical records of patients with breast cancer provided by oncology practices across the United States.
- The first components of CancerLinQ will center on providing next-generation quality measurement that builds on the ASCO Quality Oncology Practice Initiative (QOPI). Future components will encompass more powerful quality improvement tools, real-time clinical decision support, and analysis of thousands of patient outcomes to create a continuous cycle of learning. CancerLinQ is supported by the ASCO Conquer Cancer Foundation and is a project of the ASCO Institute for Quality. For more information, please visit www.asco.org/cancerlinq.

Quality Oncology Practice Initiative Positioned to Serve As Model Clinical Registry

- A provision in the American Taxpayer Relief Act of 2012—passed at the end of December 2012 to avert the fiscal cliff—may allow oncology practices to meet their Physician Quality Reporting System (PQRS) requirements by participating in the American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative (QOPI) starting in 2014. QOPI is a national quality assessment and improvement program involving more than 800 registered oncology practices across the country that is designed to measure care provided in outpatient oncology practices against evidence-based and expert consensus care recommendations, thereby informing quality improvement activities.
- The law allows physicians to meet their PQRS requirements through participation in clinical data registries approved by the US Department of Health and Human Services. ASCO worked with other medical specialty societies to achieve bipartisan support for this key provision.
- ASCO has formally recommended that the Centers for Medicare and Medicaid Services (CMS) use QOPI as a model clinical registry and continues to work with CMS to make this possibility a reality.

ASCO urges Congress and the Administration to:

- Provide a fiscal year 2014 appropriation of $32 billion for NIH, including $5.2 billion for NCI, to ensure progress continues to be made in cancer research
- Increase funding for the NCI National Clinical Trials Network
- Avoid future sequestration budget cuts for NIH and NCI
- Issue clear federal guidance on the clinical trial provision of the Patient Protection and Affordable Care Act

ASCO encourages its members to communicate with their legislators through the ASCO Alert Congress Today (ACT) Network. By joining the ACT Network, ASCO members can e-mail legislators directly from the Web site and receive action alerts and information on important legislation.

People with cancer today and those facing a diagnosis in the future are depending on the ability of scientists and clinicians to make progress against cancer. Can they also count on Congress and the Administration for support?

PREVENTION AND SCREENING

Cancer prevention and screening efforts have contributed to a steady decline in cancer incidence and death rates. Researchers are continuously exploring new and improved screening and prevention strategies, and in recent years, attention has been turned to the balance of

benefits and potential risks associated with screening as well as disparities in access to screening.

One study this year examined data from the first round of large-scale, nationwide lung screening using low-dose computed tomography (CT), confirming that this strategy is superior to chest x-ray screening and that its benefits for heavy smokers clearly outweigh any potential risk. Another large-scale, randomized study demonstrated that daily multivitamins provide a slight but statistically significant reduction in total cancer risk for middle-age and older men. An annual report on the status of cancer in the United States found that although overall cancer death rates are declining in all ethnic and age groups, the incidence of certain HPV-related cancers is increasing, underscoring the need to intensify appropriate prevention efforts, such as HPV vaccination. Finally, long-term survival data from a prostate cancer prevention study have reduced concerns about increased incidence of high-grade prostate cancer associated with the preventive drug finasteride.

Advances

Large study evaluates impact of low-dose CT screening for lung cancer on diagnosis and treatment: Results inform future screening programs. Lung cancer is the leading cause of cancer-related death worldwide. Because it is usually diagnosed at an advanced stage, only approximately 16% of patients are still alive 5 years after their diagnosis. Earlier detection through screening, however, substantially increases the odds of favorable treatment outcomes and longer survival. Several large, federally funded clinical trials have explored lung cancer screening strategies, particularly for current and former cigarette smokers, who have a significantly elevated risk of developing lung cancer. This increased lung cancer risk persists for several decades after a person has stopped smoking.

Annual chest x-ray examinations were once a common lung cancer screening strategy, especially for smokers. However, results from the large PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening) clinical trial showed that annual lung cancer screening with chest x-ray examinations does not provide a survival advantage compared with usual care. However, the NLST (National Lung Screening Trial) showed that annual screening with low-dose CT (LDCT) leads to a 20% reduction in lung cancer mortality relative to screening with chest x-ray examinations. On the basis of these findings, current clinical practice guidelines, including those from ASCO, recommend using LDCT for individuals who are current or former smokers.

Two recent publications describe the screening, diagnosis, and limited treatment results from the initial round of screening in the NLST (this research was funded in part through contracts with NIH).[3,4] The findings will inform and improve lung cancer screening programs. A total of 53,439 participants were randomly assigned to annual LDCT or chest x-ray screening for 3 years. The participants were older persons (age range, 55 to 74 years) who were current heavy smokers or had been smokers within the previous 15 years. The NLST researchers found approximately 15% to 20% fewer lung cancer deaths among study participants screened with LDCT relative to chest x-ray over an average of 6.5 years in the trial follow-up period. In addition, all-cause mortality, not a primary end point, was 6.7% lower in those screened with LDCT relative to those screened with chest x-ray.

LDCT screening also led to more follow-up tests; a total of 10,313 imaging procedures were performed in this group compared with 3,657 imaging procedures in the x-ray group. The risk from additional radiation received through multiple CT scans is of concern. However, researchers estimate that in NLST, the benefit of preventing lung cancer far outweighed the radiation risk. For younger individuals or those with lower risk of lung cancer (nonsmokers), however, potential radiation risks may substantially outweigh the benefits.

On the basis of these findings, the US Preventive Services Task Force (USPSTF) endorsed CT screening for patients at high risk of developing lung cancer.[5] The USPSTF estimates that lung cancer screening conducted according to recommendations (ie, annual screening in current or former smokers of $>$ 30 pack-years, smoked in past 15 years) results in a 14% reduction in lung cancer mortality, or an estimated 521 lung cancer deaths prevented per a population of 100,000.

These findings will inform the implementation of nationwide lung cancer screening programs. It is still unclear if a screening program such as that used in the NLST would be effective when adopted in the broader community, outside of academic centers with considerable expertise in the management of thoracic malignancies. Quality CT screening requires highly skilled personnel and costly scanners typically available only at large hospitals and academic centers. Further research is needed to assess the cost effectiveness of large-scale lung cancer screening using LDCT.

Daily multivitamins modestly reduce the risk of cancer in men. It is estimated that at least one third of US adults regularly take multivitamin supplements. Many studies have explored potential cancer prevention effects of individual vitamins, and the findings have been mixed. To date, observational studies have not provided evidence that long-term multivitamin use protects against cancer or reduces cancer deaths.

However, last year, the Physicians Health Study II found that daily intake of multivitamins provides a small but statistically significant reduction in total cancer risk for men age 50 years or older.[6] This is the first and only large, randomized, placebo-controlled clinical trial to our knowledge testing long-term effects of common multivitamins for the prevention of chronic diseases, including cancer.

A total of 14,641 US male physicians were randomly assigned to daily multivitamin or placebo. Over a median follow-up period of 11.2 years, 2,669 men were diagnosed with cancer. Men taking multivitamins had a small but statistically significant reduction in the incidence of total cancer; 1,290 (17.6%) of 7,317 men were diagnosed with cancer in the multivitamin group compared with 1,379 (18.8%) of 7,324 men in the placebo group. Among the 1,312 men with a history of cancer at study entry, daily multivitamins were also associated with lower rates of total cancer compared with placebo (14.7% *v* 19%). There was no significant effect of daily multivitamin use on the development of any specific form of cancer (including colon and prostate cancers), nor did it reduce cancer mortality.

The findings of this study suggest that a broader combination of low-dose vitamins and minerals may be more effective than high doses of individual vitamins, some of which were tested in prior clinical trials.

Incidence rates for two HPV-associated cancers are rising: HPV vaccination coverage remains uneven across the United States. This year's "Report to the Nation on the Status of Cancer" features data on cancer incidence and death rates in the United States from 1975 through 2009 (this study was funded in part by grants from the National Institutes of Health).[7] The data were collected from the

Centers for Disease Control and Prevention, NCI, and the North American Association of Central Cancer Registries. The findings show that among adults, death rates for all cancers decreased 1.5% per year from 2000 to 2009. Among children age 0 to 19 years, cancer death rates decreased even more (2% per year) in the same timeframe. Overall cancer incidence rates decreased in men but remained stable in women.

This year's report specifically explores the burden and trends in HPV-associated cancers. From 2000 to 2009, the report describes an increase in incidence rates for HPV-associated cancers in certain demographic groups. These include oropharynx cancers among white men and women, anal cancer among white and African American men and women, and cancer of the vulva among African American and white women. In contrast, cervical cancer rates decreased for women of all racial and ethnic groups, suggesting that access to screening is growing and potentially that HPV vaccination is paying off.

In the same report, researchers also assessed the prevalence of HPV vaccination in 2008 and 2010 and of Pap testing during 2010, using data from national surveys. Routine HPV vaccination is currently recommended for all girls and boys age 11 to 12 years as well as for older adolescent women and men who were not vaccinated previously. Nationwide, researchers found that only 32% of girls age 13 to 17 years had completed the three-dose series of the HPV vaccine, and vaccination rates were significantly lower among the uninsured (14.1%) and in some Southern states (20% in Alabama and Mississippi). Those states also had the lowest prevalence of Pap testing and highest cervical cancer rates.

This report highlights encouraging trends regarding the overall decline of cancer death rates. The increase in certain HPV-associated cancers, however, underscores the need for additional prevention efforts, including increased access to HPV vaccination nationwide.

Prevention of prostate cancer. The Prostate Cancer Prevention Trial, begun in 1993, randomly assigned 18,882 men to the 5-alpha reductase inhibitor finasteride or placebo and in 2003 reported the results: a 25% reduction in risk of prostate cancer (803 of 4,368 in finasteride group *v* 1,147 of 4,692 in placebo group) but a numerically smaller yet statistically significant increased risk of high-grade cancers (280 in finasteride group *v* 237 in placebo group). This increased risk of high-grade tumors generally precluded interest in use of this medication to reduce the risk of prostate cancer, which affects approximately one in six men in their lifetime. Subsequent studies suggested that the increased risk of high-grade cancer resulted from increased sensitivity of detection of high-grade disease, through better detection with prostate-specific antigen (PSA) and prostate biopsy.

With up to 18 years of follow-up, using the Social Security Death Index to assess survival, the researchers asked whether survival was affected by finasteride, potentially caused by the higher number of high-grade cancers (this study was funded in part by a grant from NIH).[8] Comparing finasteride and placebo groups, survival was identical. Cancer survival (both low and high grade) was similar in both study groups. Examining all men enrolled, the risk reduction for prostate cancer was 30%; the risk reduction of low-grade cancer was 43%.

These outcomes must be understood against the backdrop of PSA testing, which is not recommended by the USPSTF, primarily because of the risk of detection of low-grade cancers that may lead to unnecessary treatment and associated adverse effects. If low-grade cancers are managed with active surveillance, anxiety, cost, and morbidity are high. If a man opts for PSA testing, concurrent use of finasteride results in a 43% reduction in detection of potentially inconsequential cancers while preserving detection of high-grade, potentially lethal cancers, resulting in equivalent survival. Adverse effects of finasteride include decreased libido, erectile dysfunction, and gynecomastia (breast enlargement). Benefits include reduction in benign prostatic hyperplasia (prostate enlargement) symptoms, need for surgery for prostatic obstruction, and urinary retention.

TUMOR BIOLOGY AND DEVELOPMENTAL THERAPEUTICS

Our growing understanding of tumor biology is helping guide treatment selection for individual patients and steering the direction of new drug development. Today's integrated and high-throughput technologies can relatively quickly render comprehensive molecular portraits of tumors. Analysis of these data may lead to identification of new tumor subtypes, markers of therapy response, and potential new drug targets.

Remarkable advances in the tumor biology field this year affirm that research is fulfilling the promise of precision medicine, where patients' outcomes are maximized by matching treatments to the specific molecular makeup of their tumor.

This year, a large, federally funded genomic profiling study depicted a detailed landscape of molecular abnormalities in AML, offering new biologic insights that will help with tumor classification and selection of therapy. Researchers have also identified a highly sensitive blood marker of therapy response in women with metastatic breast cancer, offering a much-needed noninvasive but reliable method of monitoring treatment effectiveness. A small study pinpointed the genetic abnormality that potentially makes some patients with colorectal cancer resistant to epidermal growth factor receptor (EGFR) –targeted therapy and showed that this resistance can be overcome through the use of MET inhibitors. Finally, researchers found that many different forms of cancer harbor fibroblast growth factor receptor (*FGFR*) gene fusions, leading to abnormal hybrid proteins. Further research may demonstrate if FGFR inhibitors can be an effective treatment for tumors bearing these fusions.

Advances

Genomic profiling provides new insights into molecular abnormalities in AML. AML is classified by genetic changes found in leukemia cells. Some of these changes are detected by looking at the chromosomes of dividing cells (karyotype) under a microscope, whereas other changes are found only through molecular tests and genomic profiling. Physicians routinely assess chromosomal changes in patients' leukemia cells to determine the best course of therapy, because specific changes are linked to prognosis and the likelihood that treatment will be effective against AML in an individual patient.

This year, researchers published findings from a comprehensive genome analysis of 200 tumor samples from adults with de novo AML, a subtype associated with recurrent genetic abnormalities in leukemia cells (this study was funded in part by a grant from NIH).[9] The study, performed by TCGA Research Network, revealed that a complex interplay of genetic abnormalities contributes to development of de novo AML. On average, 13 mutations were identified per patient

sample. A total of 23 genes were significantly mutated (higher-than-expected mutation prevalence) across all tumor samples; these included genes that are well known as being relevant to AML as well as several genes that have only recently been linked to AML development. Another 237 genes were mutated in two or more samples. Nearly all (99%) of the samples had at least one mutation in one of the nine biologic function categories linked to AML development. Researchers found that some genetic changes occurred together, suggesting the existence of biologic relationships among several genes and categories.

This study deepens our understanding of molecular changes involved in AML development. The databases from this study are available to researchers around the world to serve as a foundation for future studies on molecular classification of risk, which may ultimately lead to improvements in therapy approaches for patients with AML.

Circulating tumor DNA: A potential new marker of treatment response in metastatic breast cancer. Monitoring treatment response (ie, tumor shrinkage) in patients with cancer is important to avoid continuing ineffective therapies and prevent unnecessary adverse effects. Treatment response monitoring is also critical in clinical testing of new therapies. For women with metastatic breast cancer, treatment response is generally assessed by medical imaging and by blood tests for cancer antigen 15-3 (CA 15-3), but these methods often fail to detect small changes in tumor burden.

In recent years, circulating tumor cells (CTCs) have emerged as a promising new biomarker in women with metastatic breast cancer, with elevated levels of CTCs being associated with a worse prognosis.[10] However, the only FDA-approved test for CTC detection is often not sensitive enough to detect small changes in tumor burden.

This year, however, researchers identified a potential new biomarker in metastatic breast cancer: circulating tumor DNA.[11] Circulating tumor DNAs are essentially fragments of cell-free DNA that the primary tumor sheds into the bloodstream. The fragments contain some of the same genetic changes that are found in the primary tumor.

To detect circulating tumor DNA fragments, researchers first identified genetic changes in the primary tumor and then designed personalized assays for monitoring levels of circulating tumor DNA. In this study, researchers directly compared the sensitivity of circulating tumor DNA with other biomarkers (CA 15-3 and CTCs) and medical imaging for monitoring treatment response in 30 women with metastatic breast cancer. Circulating tumor DNA showed a greater correlation with tumor burden than either CA 15-3 or CTCs. Circulating tumor DNA was detected in 29 (97%) of 30 of women, whereas CA 15-3 and CTCs were detected in 21 (78%) of 27 and in 26 (87%) of 30 women, respectively. Circulating tumor DNA also provided the earliest measure of tumor response in 10 (53%) of 19 women, and higher levels were associated with worse survival, confirming that it may be valuable as a prognostic marker.

This proof-of-concept study is one of the first attempts to assess circulating tumor DNA as a biomarker in breast cancer. The findings show that it is more sensitive than other circulating biomarkers and often provides an earlier indication of treatment response.

Small study uncovers the potential underlying cause of treatment resistance in some patients with colorectal cancer. EGFR-targeted antibodies, such as cetuximab and panitumumab, are effective in some patients with advanced colorectal cancer without mutations in the *KRAS* gene. Unfortunately, nearly all patients eventually develop resistance to this type of treatment. There are no other treatment options for such patients. It is known that in approximately half of patient cases, resistance arises from new mutations in the *KRAS* gene, but the molecular basis of resistance in other patients has been unclear.

This year, a new, small study reported that having extra copies of a gene called *MET* may be linked to resistance to EGFR-targeted therapy in tumors that do not have *KRAS* mutations.[12] Extra copies of *MET* were detected in tumors of three patients with anti-EGFR resistance as well as in CTCs collected from the patients' blood. The ability to detect *MET* gene changes in the blood offers the opportunity to monitor drug resistance and tumor recurrence in a non-invasive way. Researchers also previously showed in animal studies using patient-derived tumor tissue that resistance to EGFR-targeted therapy can be overcome with the use of MET kinase inhibitors. These findings indicate that a subset of patients who are resistant to anti-EGFR therapies as a result of *MET* gene amplification may benefit from MET inhibitors. Several MET inhibitors are already being tested in clinical trials.

New gene abnormality detected in multiple cancers, offering opportunity for personalized treatment. Gene fusion is a type of genetic abnormality that is rather common in cancer, occurring when parts of two different genes join together to form a new gene, which results in a hybrid protein. The *BCR-ABL* gene fusion in CML was one of the first gene fusions discovered in a cancer. Over the past decade, researchers have detected various gene fusions in prostate, lung, breast, colon, thyroid, and other cancers. In many cases, the fusions are successfully treated with targeted therapies directed against the hybrid protein.

In a two-part analysis this year, scientists reported that many different tumor types harbor *FGFR* gene fusions.[13] First, *FGFR* gene fusions were identified in tumor specimens from four patients with advanced cancer using a combination of DNA and RNA sequencing technologies. This included patients with cholangiocarcinoma, breast cancer, and prostate cancer. A subsequent analysis of genomic data on approximately 2,400 tumors and cell lines from University of Michigan and TCGA databases identified 24 additional occurrences of *FGFR* gene fusions. *FGFR* was found joined to a dozen different partner genes, and three different *FGFR* subtypes were found in the gene fusions. *FGFR* fusions were detected in a diverse array of common and rare cancer types, including cholangiocarcinoma, GBM, and breast, prostate, thyroid, bladder, oral, head and neck, and lung cancers.

The findings indicate that patients with a wide variety of tumor types may benefit from FGFR-targeted therapies, such as the experimental agent PD173074 and pazopanib. Additional FGFR-targeting drugs are currently in clinical testing.

BLOOD AND LYMPHATIC CANCERS

Cancers of the blood and lymphatic system include leukemia, lymphoma, and multiple myeloma. The most common blood cancer, leukemia, includes several distinct diseases: ALL, chronic lymphocytic leukemia (CLL), AML, and CML. Lymphoma is subclassified into Hodgkin lymphoma and non-Hodgkin lymphoma, which includes mantle-cell lymphoma.

This year, investigators reported encouraging results in clinical trials that tested new targeted treatments and immunotherapies for

patients with treatment-resistant or relapsed CLL, mantle-cell lymphoma, and ALL. Another important study identified a genetic marker that seems to define a new molecular subset of blood cancers. The findings may inform personalized treatment options for patients with rare forms of leukemia. Researchers also reported on a new technique that may improve the success of umbilical cord blood transplantation for patients with high-risk blood cancer who do not have donor relatives available. Over the past year, the FDA approved four new drugs for patients with difficult-to-treat forms of leukemia and lymphoma.

Advances

Ibrutinib shows promising anticancer effects in patients with treatment-resistant CLL or mantle-cell lymphoma. Ibrutinib is an investigational oral drug that targets and blocks an enzyme called Bruton's tyrosine kinase. This enzyme plays a critical role in the growth and survival of B-cell cancers, including CLL and mantle-cell lymphoma. Two early-stage studies this year reported encouraging activity of ibrutinib in patients with treatment-resistant CLL and mantle-cell lymphoma. These patients are in urgent need of new and effective treatments, because standard treatments—chemotherapy and rituximab—are not curative and are associated with significant toxicity.

The first study included 81 patients with relapsed or treatment-resistant CLL or small lymphocytic lymphoma whose disease had progressed despite an average of four prior chemotherapy treatments; this study was funded in part by a grant from NIH).[14] Patients were treated with two different doses of ibrutinib. More than two thirds of patients (71%), including those with high-risk genetic markers, had tumor shrinkage. After a median follow-up of more than 2 years, an estimated 75% of patients had no disease progression, and 83% were still alive. The adverse effects were generally mild and included diarrhea, fatigue, and upper respiratory infection. The findings of this phase Ib/II study demonstrate that the targeted drug, ibrutinib, leads to long-lasting remissions in a large proportion of patients with relapsed or treatment-resistant CLL and small lymphocytic lymphoma who would have previously been treated with often-toxic chemotherapy.

In the second study, 111 elderly patients with relapsed or treatment-resistant intermediate- or high-risk mantle-cell lymphoma were treated with a single dose of ibrutinib.[15] Mantle-cell lymphoma is a rare but difficult-to-treat form of lymphoma that often affects older patients.

The study participants had received a median of three prior therapies. Tumor shrinkage was observed in 68% of patients, with 21% achieving complete remissions; the responses lasted 17.5 months on average. Importantly, researchers observed responses among patients with clinical risk factors associated with chemotherapy resistance. The estimated progression-free survival of patients in the study was 13.9 months. At 18 months, an estimated 58% of patients were still alive. These results are significantly better than what is achievable with available salvage therapy options. The most common adverse effects were moderate diarrhea, fatigue, and nausea. A small number of patients experienced serious adverse effects related to blood count changes.

Taken together, these two studies suggest that ibrutinib should be explored further as an effective and less toxic therapy option for patients with relapsed or treatment-resistant CLL, small lymphocytic lymphoma, and mantle-cell lymphoma. Having a less toxic therapy option is particularly important for elderly patients, who account for the majority of patients with CLL. Given the relatively mild adverse effects, it may be possible to combine ibrutinib with other therapies such as monoclonal antibodies to further increase efficacy. Randomized clinical trials of ibrutinib in patients with CLL and small lymphocytic lymphoma are already under way.

Study identifies a new molecular subset of blood cancers and promising options for personalized therapy. Identifying key molecular changes that drive cancer development and growth is necessary for development of new targeted therapies and personalized treatment plans. The molecular causes of many blood cancers are unknown. A genomic profiling study reported on critical genetic changes in two such diseases—chronic neutrophilic leukemia (CNL) and atypical (*BCR-ABL1* negative) CML—offering promising new leads on potential targeted treatment options (this study was funded in part by a grant from NIH).[16]

Researchers examined leukemia cell samples from 27 patients and found specific mutations in a gene called colony-stimulating factor 3 receptor (*CSF3R*) in 16 patients (59%). Two classes of *CSF3R* mutations were identified, each linked to the activation of two distinct pathways: SRC family-TNK2 and JAK. Laboratory testing of several tyrosine kinase inhibitors (TKIs) in *CSF3R*-positive leukemia cells showed that the TNK2 inhibitor dasatinib and JAK inhibitor ruxolitinib blocked the growth of cells harboring specific *CSF3R* mutations. Researchers subsequently explored whether ruxolitinib had antitumor effects in patients. A patient with leukemia harboring a JAK-activating mutation experienced significant clinical improvement after treatment with ruxolitinib.

These findings indicate that *CSF3R*-positive CML and CNL represent a new molecular subset of blood cancers. Incorporation of *CSF3R* mutation testing into diagnostic criteria for these diseases would help identify patients who may benefit from specific TKIs. Encouraging activity of the JAK inhibitor ruxolitinib in a patient harboring a JAK pathway–activating *CSF3R* mutation constitutes a proof of principle, warranting further investigation of TKIs for the treatment of patients with *CSF3R*-positive leukemia.

Early study shows engineered T cells are effective in aggressive, chemotherapy-resistant ALL. B-precursor ALL is the most common subtype of ALL. Patients with chemotherapy-resistant ALL have a poor prognosis, despite the use of intensive treatments, such as hematopoietic stem-cell transplantation. More effective therapies are urgently needed for this patient population. A new type of immunotherapy, known as chimeric antigen receptor-modified T cells, has shown promising activity in patients with CLL. Early results of a small study reported this year suggest that this therapy may also be effective in adults with relapsed and chemotherapy-resistant ALL. This treatment involves collecting immune T cells from a patient, genetically engineering them in the laboratory so that they can attach to specific proteins on the patient's tumor cells, growing the engineered T cells in large numbers, and finally infusing them back into the patient.

In the study, all five enrolled adult patients with relapsed B-cell ALL quickly experienced complete remissions with treatment using this type of T-cell immunotherapy (in one patient, remission occurred only 8 days after receiving the therapy; this study was funded in part by a grant from NIH).[17] Four patients subsequently received hematopoietic stem-cell transplantation; one of those patients died 2 months

after receiving T-cell therapy, and the other three were still in remission at the time this study was published. The fifth patient experienced a relapse 90 days after receiving T-cell therapy. The treatment was well tolerated.

These early findings indicate that chimeric antigen receptor–modified T cells may be a promising new treatment option and a bridge to potentially curative therapy for patients with aggressive, relapsed, and chemotherapy-resistant ALL. A similar approach has yielded encouraging results in another small study involving children with chemotherapy-resistant or relapsed ALL (see Pediatric Cancers section; this study was funded in part by a grant from NIH).[18]

New methodology may improve cord blood transplantation outcomes in adults with high-risk blood cancer. Blood stem-cell transplantation is a standard treatment for patients with a variety of high-risk blood cancers. The source of stem cells is typically bone marrow or peripheral blood from a family member donor, if available. Umbilical cord blood from unrelated donors may be used for patients who do not have a matched, related donor available, because more donor-recipient mismatches are allowed. However, cord blood contains fewer stem cells than bone marrow and peripheral blood and often leads to more transplantation-related complications as well as increased health care costs. A study this year reported a new methodology that promises to improve the effectiveness of cord blood transplantation (this study was funded in part by a grant from NIH).[19]

During a typical transplantation, adult patients may receive two units of cord blood (blood from two different umbilical cords) in an attempt to expedite engraftment—the process in which the transplanted stem cells find their way to the bone marrow of the large bones of the body and begin to produce new blood cells (including neutrophils and platelets). In this study, to increase the number of stem cells available for transplantation, researchers took one unit of cord blood and stimulated the growth of additional cord blood cells in the laboratory by adding another type of cell, called mesenchymal cells. After 2 weeks, 31 patients received these cultured cord blood cells alongside a second unit of matched, unmanipulated cord blood. Researchers then assessed the median time to engraftment.

Successful engraftments in this group of patients were compared with outcomes in 80 historical controls who had received two units of unmanipulated cord blood. The median time to engraftment was substantially shorter in the study cohort than in the historical controls (15 *v* 21 days for neutrophils and 42 *v* 49 days for platelets). This resulted in a faster recovery for patients in the study cohort. The rates of serious adverse effects were similar in both groups.

These findings indicate that this new method of increasing cord blood cell numbers before transplantation is safe and effective. It seems that this technique also improves engraftment success over the standard method, but a true head-to-head comparison of the two approaches is needed to confirm this result, and a randomized study comparing these two strategies is under way.

FDA approves two new drugs for adult patients with CML. In October last year, the FDA approved omacetaxine mepesuccinate for patients with chronic- or accelerated-phase CML whose cancer progressed after treatment with at least two drugs from a class called TKIs.[20] The new drug blocks certain proteins that promote the development of cancerous cells. The approval was granted under the FDA accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate end point that is reasonably likely to predict a clinical benefit for patients. In two different cohorts, 14% to 18% of patients responded to treatment with omacetaxine mepesuccinate. This approval offers a new treatment option for patients with CML who are resistant to or cannot tolerate other FDA-approved drugs.

In December of last year, the FDA approved ponatinib for adult patients with chronic-phase, accelerated-phase, or blast-phase CML resistant or intolerant to prior TKI therapy and for patients with Philadelphia chromosome–positive ALL.[21] The approval, also granted under the accelerated approval program, was based on the results of a multicenter, international, single-arm clinical trial of 449 patients with disease resistant or intolerant to prior TKI therapy, in which 54% of patients responded to ponatinib. This approval is important because it provides a treatment option for patients with two rare forms of leukemia that are resistant to other therapies.

FDA approves pomalidomide for patients with multiple myeloma. In February, the FDA approved pomalidomide for patients with multiple myeloma whose disease progressed despite having received at least two prior therapies, including lenalidomide and bortezomib.[22] Pomalidomide modulates the body's immune system to destroy cancerous cells and inhibit their growth. This new drug was also approved under the FDA accelerated approval program based on the results of a clinical trial showing that 7.4% of patients treated with pomalidomide alone experienced partial or complete disease remission. The approval provides an additional treatment option for patients who have not responded to other drugs.

FDA approves lenalidomide for patients with mantle-cell lymphoma. In June, the FDA approved lenalidomide for patients with mantle-cell lymphoma whose disease relapsed or progressed despite two prior therapies, one of which included bortezomib.[23] Lenalidomide also modulates the immune system to destroy cancerous cells and inhibit their growth. The approval was based on results of a single-arm, multicenter clinical trial of 134 patients with mantle-cell lymphoma who had relapsed after treatment with or were resistant to bortezomib or a bortezomib-containing regimen. In the study, 26% of patients responded to the drug, and 7% experienced complete remissions. The approval provides a new therapy option for patients with difficult-to-treat mantle-cell lymphoma. The agent was previously approved for patients with multiple myeloma and myelodysplastic syndromes.

BREAST CANCER

It is estimated that approximately one in eight US women will develop invasive breast cancer in her lifetime. Breast cancer is also the second-leading cause of cancer-related death in US women. Researchers are continuously working on ways to provide individualized treatment options that maximize chances of long-term survival while preserving the patient's QOL as much as possible.

This year brought a new strategy that promises to help reduce the risk of breast cancer recurrence after surgery—longer-term tamoxifen therapy (10 years instead of the traditional 5)—for women with early-stage, estrogen receptor (ER) –positive breast cancer.

Another study showed that two commonly used postoperative (adjuvant) chemotherapy regimens for early-stage breast cancer have comparable effectiveness in reducing recurrence but differ in severity

of adverse effects, suggesting that women can safely opt for the treatment with fewer adverse effects.

Advances

Longer-term tamoxifen therapy substantially reduces risks of breast cancer recurrence and death. Thousands of women worldwide take tamoxifen to reduce cancer recurrence and mortality after surgery for hormone receptor–positive, early-stage breast cancer. Results from two large randomized phase III clinical trials indicate that taking tamoxifen for 10 years, instead of 5 years as currently recommended, further reduces the risks of breast cancer recurrence and death for this population of women.

In both studies, women with ER-positive breast cancer who had been taking tamoxifen for 5 years were randomly assigned to continue treatment with tamoxifen for another 5 years or to discontinue. In the first study, ATLAS (Adjuvant Tamoxifen, Longer Against Shorter), 3,428 women were assigned to 10 years of tamoxifen therapy, and 3,418 stopped therapy at 5 years. Researchers observed that both breast cancer recurrence and breast cancer death rates were lower in the 10-year versus 5-year tamoxifen group (18% *v* 20.8% and 9.6% *v* 11.6%, respectively).[24] The overall mortality rate was also lower in the 10-year group (18.6% *v* 21.1%).

The second study, aTTom (Adjuvant Tamoxifen: To Offer More?), observed approximately 5,000 British women for more than 10 years after they were randomly assigned to either stop or continue tamoxifen therapy.[25] Treatment duration had little effect on breast cancer recurrence or death rates in years 5 to 9 after diagnosis. However, during the second decade after diagnosis, women who continued tamoxifen therapy for 10 years had a 25% lower breast cancer recurrence rate and 23% lower breast cancer mortality rate compared with women who underwent 5 years of treatment. In this study, the 10-year treatment did not have a significant impact on overall mortality.

When taken together, the findings from the two studies suggest that longer-duration tamoxifen decreases breast cancer recurrence over several years after diagnosis. This will likely change the patterns of care for women with hormone receptor–positive breast cancer and is especially relevant for young, premenopausal women who are at high risk of recurrence.

Weekly adjuvant paclitaxel therapy has comparable efficacy but fewer side effects than the biweekly regimen. Paclitaxel is a long-standing component of postoperative (adjuvant) breast cancer treatment. The drug is typically administered to patients either every week at a lower dose or every 2 weeks at a higher dose. A randomized phase III clinical trial conducted by a federally funded cooperative group in the United States formally assessed, for the first time to our knowledge, the efficacy and adverse effects of these two widely used treatment regimens (this study was funded in part by a grant from NIH).[26]

Researchers found that among the 2,716 patients treated in the study, the two treatment regimens resulted in equivalent 5-year progression-free survival rates (82% and 81% for the weekly and every-2-weeks regimens, respectively). However, there were differences in the type and severity of adverse effects; the every-2-week schedule was associated with a slightly higher frequency of allergic reactions (1.4% *v* 0.6%), musculoskeletal pain (11% *v* 3%), and peripheral neuropathy (17% *v* 10%) compared with the weekly schedule, whereas weekly paclitaxel more frequently lowered WBC counts, which was not unexpected, because this approach does not include treatment that boosts WBC production. These findings will likely motivate many physicians to use weekly dosing preferentially.

FDA approves ado-trastuzumab emtansine for patients with human epidermal growth factor receptor 2–positive, metastatic breast cancer. In February, the FDA approved ado-trastuzumab emtansine as a single agent for treatment of patients with human epidermal growth factor receptor 2 (HER2) –positive, metastatic breast cancer who previously received trastuzumab and a taxane.[27] The agent consists of two chemically linked anticancer drugs: the anti-HER2 antibody trastuzumab and the chemotherapy drug emtansine. The approval was based on a randomized, multicenter, open-label clinical trial that enrolled 991 patients with HER2-positive metastatic breast cancer.[28] The approval provides an additional treatment option for women with late-stage HER2-positive breast cancer.

CNS CANCERS

Cancers of the CNS include those of the brain and spinal cord. Significant progress in basic, translational, and clinical research on brain cancer was achieved this year.

A preclinical study provided proof of concept that targeting mutated isocitrate dehydrogenase (IDH) proteins is a viable strategy for slowing the growth of gliomas. Two large-scale molecular profiling studies identified new mutations in meningioma and new biologic subgroups of GBM. The findings may lead to development of new prognostic markers and targeted therapies. Long-term follow-up results from two clinical trials in patients with oligodendroglioma confirm that the combination of chemotherapy and radiation provides a remarkable survival advantage compared with radiation alone for patients harboring 1p/19q chromosomal codeletions in their tumors.

Advances

New investigational drug blocks growth of glioma cells harboring IDH1 *gene mutations.* Many cancers, particularly glioma and acute myelogenous leukemia, harbor mutations in a gene for an enzyme called IDH1. These mutations trigger changes in gene expression patterns, which ultimately lead to tumor development. *IDH1* mutations prevent glioma cell differentiation—the process by which immature cells become mature cells with specific functions. This year, researchers reported data from a preclinical study showing that a new investigational drug may be able to reverse the effects of mutated *IDH1* (this study was funded in part by the 2009 Conquer Cancer Foundation of ASCO Advanced Clinical Research Award in Glioma to author Ingo Mellinghoff and by a grant from NIH).[29]

The drug, termed AGI-5198, selectively blocked an IDH1 variant with a specific mutation in glioma cells grown in the laboratory. The blockage disrupted the function of the abnormal IDH1 enzyme, so it could no longer make R-2-hydroxyglutarate, a metabolite that promotes tumor growth. This in turn led to expression of genes involved in cell differentiation. Although the blockade of mutated *IDH1* slowed the growth of glioma cells harboring the specific *IDH1* mutation, it had no effect on the growth of glioma cells with normal (wild type) *IDH1*. The findings provide proof of concept that mutant *IDH* is therapeutically targetable and show that targeting the metabolic effect of *IDH1* mutations can affect glioma tumor biology, slowing tumor growth.

Large genomic analysis identifies recurrent mutations in meningioma, some potentially treatable with existing targeted therapies. Meningioma is the most common primary brain tumor. The tumor develops in the meninges, which are the thin membranes that surround and protect the brain and spinal cord. Meningioma is usually slow growing, but it may cause significant symptoms as it grows and presses on the brain or spinal cord. In some patients, meningiomas cannot be surgically removed, and chemotherapy is largely ineffective. Such patients are in urgent need of new treatment options. A large-scale genomic study this year identified several new mutations in a common subtype of meningioma, promising potential opportunities for targeted treatment of this disease.[30]

Researchers conducted a genomic analysis of 300 non-NF2 meningiomas, a subtype that accounts for roughly half of all meningioma patient cases. The patient cases of meningioma included in this study were nearly always low grade, chromosomally stable, and originating from the medial skull. Mutations in a gene called *TRAF7* were present in nearly one fourth of non-NF2 meningiomas. Those mutations frequently coincided with mutations in two other genes, *KLF4* and *AKT1*. Finally, approximately 5% of patients had mutations in the *SMO* gene. Those four genes are implicated in distinct biologic pathways linked to tumor development and growth. These findings provide new insight into tumor biology of meningioma, identify new molecular subtypes, and suggest new avenues for targeted therapy. Some of the mutations may be amenable to treatment with targeted drugs currently in clinical development (eg, SMO inhibitors, AKT inhibitors).

Comprehensive molecular profiling identifies six distinct GBM subgroups across the entire age spectrum. GBM is the most common and most devastating malignant brain tumor, with fewer than 10% of patients alive 5 years after diagnosis. Researchers have recently discovered age-specific molecular differences that suggest that pediatric GBM is biologically distinct from the adult form of the disease. These data were confirmed by results of a comprehensive molecular analysis of GBMs from 77 adults and 59 children and complementary data from genomic profiles of 74 adult GBM specimens generated by TCGA.[31]

The findings suggest that GBM can be classified into six biologic subgroups, which are indistinguishable by looking at the tumor tissue under a microscope. The six subgroups differ in patterns of DNA methylation, a process that controls gene expression levels in a cell without affecting the DNA sequence. The methylation patterns are associated with mutations in specific genes, gene copy number changes, and key clinical parameters. In addition, investigators found that 30% to 40% of pediatric and young adult GBMs have recurrent and mutually exclusive mutations in either *H3F3A* or *IDH1* genes as well as abnormal DNA methylation patterns, confirming that pediatric GBM is biologically distinct from the adult form of the disease. Two different *H3F3A* mutations were detected in those patients, each associated with a distinct DNA methylation pattern and specific anatomic location of the tumor. This study provides much-needed new insight into the biology of GBM. The findings may lead to development of new prognostic biomarkers and subgroup-specific treatments.

Late results from two clinical trials delineate benefits of chemotherapy and radiation in patients with oligodendroglioma. Anaplastic oligodendroglioma (AO) is a small subset of glioma, the most common form of primary brain cancer in adults. Chemotherapy works well in AO, especially in patients who have codeletions in chromosomes 1p and 19q, but it has historically been unclear if adding radiation therapy (RT) would further prolong overall survival. Results of two long-term follow-up studies indicate that combined treatment delays tumor growth and extends survival, although the benefit may be limited to patients with 1p/19q codeletions.

In the first study, patients with AO were randomly assigned to receive PCV (procarbazine, lomustine, and vincristine) chemotherapy immediately followed by RT (148 patients) or RT alone (143 patients; this study was funded in part by a grant from NIH).[32] Patients were observed for a median period of 11.3 years. For the entire cohort of patients, the median overall survival was comparable between the two groups (4.6 years for PCV plus RT *v* 4.7 years for RT alone). However, an analysis of a subgroup of 126 patients with the 1p/19q codeletion found that they lived much longer than other patients, regardless of treatment received. For those patients, the median survival was 14.7 years with the combination treatment and 7.3 years with RT alone. For patients lacking 1p/19q codeletions, there were no differences in median survival with respect to treatment arms. These findings are supported by long-term follow-up results of another phase III trial in patients with AO.[33]

In this second study, 368 adult patients with newly diagnosed AO were randomly assigned to receive RT alone or RT followed by PCV. Patients were observed for a median period of 11.7 years. Overall survival was significantly longer for patients who received the combination treatment compared with those who received RT alone (42.3 *v* 30.6 months). Progression-free survival was also longer in the combination arm compared with the RT arm (24.3 *v* 13.2 months). The 80 patients with 1p/19q codeletions seemed to benefit most from the combination treatment (overall survival not reached for the combination arm *v* 112 months in the RT arm).

The initial publication of results from these studies in 2006 did not show survival differences. However, this longer follow-up shows that there is a marked increase in median survival for patients with 1p/19q codeletions who are treated with a combination of chemotherapy and RT. The 1p/19q codeletion is both prognostic and predictive of survival. Taken together, the results of these two studies will change the standard of care for patients with AO with 1p/19q codeletions to use of RT and chemotherapy instead of RT alone.

GI CANCERS

GI cancers include those of the esophagus, stomach, liver, pancreas, biliary tract, small bowel, appendix, colon, rectum, and anus. This year, researchers reported significant advances in some of the most difficult-to-treat GI cancers: neuroendocrine tumors, colorectal cancer, and pancreatic cancer.

One study reported that the hormonal drug octreotide improves survival for some patients with advanced midgut neuroendocrine tumors, a rare form of GI cancer. A landmark study in patients with advanced and inoperable colorectal cancer establishes capecitabine and bevacizumab as a new standard maintenance treatment. A retrospective analysis of genetic changes in tumors of patients with metastatic colorectal cancer identifies new mutations that predict lack of response to the targeted drug panitumumab. Finally, two large studies of patients with pancreatic cancer point to new, life-prolonging treatment options: nab-paclitaxel plus gemcitabine and S-1.

Advances

Octreotide LAR prolongs overall survival in some patients with a rare form of GI cancer. Neuroendocrine tumors begin in the hormone-producing cells of the body's neuroendocrine system. Neuroendocrine cells are found throughout the body, including the GI tract (stomach, intestine, appendix, colon, or rectum). They perform specific functions, such as controlling the speed at which food is moved through the GI tract. An estimated 8,000 people in the United States are diagnosed with a neuroendocrine tumor that starts in the GI tract each year. These patients often have significant disease burden and symptoms but few standard therapy options.

An earlier study showed that a drug called octreotide LAR substantially prolongs time to disease progression in patients with metastatic midgut neuroendocrine tumors. This year, researchers reported longer-term follow-up data from that same clinical trial, finding that octreotide LAR also extends overall survival in a subset of patients.[34] Between 2001 and 2008, 85 patients were randomly assigned to receive octreotide LAR or placebo. Patients whose disease progressed while receiving placebo crossed over to octreotide. Poststudy treatment was at the discretion of the local investigator.

By January 2013, the median overall survival in the placebo arm was 84 months and was not reached in the octreotide LAR arm, meaning that overall survival in that arm will exceed 84 months, but longer follow-up is needed to determine the median overall survival in that arm. The drug was most beneficial for patients with a hepatic load (ie, percent of the liver that is replaced by cancer) less than or equal to 10% (ie, limited tumor spread to the liver) at study entry. In that subset of 64 patients, the median overall survival was 80.5 months in the placebo arm and not reached in the octreotide arm. Octreotide LAR did not extend overall survival in the high–hepatic load subgroup.

The benefit of octreotide in patients with midgut neuroendocrine tumors has been debated for some time. These encouraging findings will motivate many physicians to start using octreotide LAR, particularly in patients with a low hepatic load.

Maintenance treatment with capecitabine and bevacizumab extends overall survival in patients with inoperable metastatic colorectal cancer. Chemotherapy in combination with bevacizumab is a standard first-line therapy for patients with metastatic colorectal cancer. However, there has been great debate as to how best to use the agents to optimize both efficacy and toxicity.

To address this question, Dutch researchers conducted a phase III clinical trial comparing the efficacy of maintenance treatment with the chemotherapeutic drug capecitabine and bevacizumab versus observation in 558 previously untreated patients with inoperable metastatic colorectal cancer that had not worsened after six cycles of induction treatment with CAPOX-B (capecitabine, oxaliplatin, and bevacizumab).[35] Compared with patients in the observation group, patients in the maintenance treatment group experienced a substantially longer time to first progression (7.1 *v* 4.1 months). On disease progression, patients in both groups received CAPOX-B, which temporarily stalled tumor growth. It took longer for the disease to progress again in the maintenance group than in the observation group (11.5 *v* 15.4 months). The median overall survival in the maintenance group was 21.7 months compared with 17.9 months in the observation group. Toxicity was minor with maintenance treatment. This study establishes capecitabine and bevacizumab as a standard maintenance therapy in colorectal cancer.

Patients with colorectal cancer harboring NRAS *mutations are unlikely to benefit from panitumumab.* Panitumumab is an antibody drug that targets EGFR. It has been approved by the FDA for the treatment of metastatic colorectal cancers, but only in patients without mutations in the KRAS protein, because mutations in *KRAS* render the drug ineffective. Patients are routinely tested for *KRAS* mutations before deciding on panitumumab therapy.

New results reported this year, however, indicate that mutations in a related protein, NRAS, also interfere with the efficacy of panitumumab.[36] In a retrospective analysis of data from a phase III clinical trial comparing panitumumab plus FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin) chemotherapy and FOLFOX alone, investigators assessed the impact of specific *KRAS*, *NRAS*, and *BRAF* gene mutations on overall survival in 641 patients with metastatic colorectal cancer. Among the 512 patients with no mutations in either *NRAS* or *KRAS* genes, the addition of panitumumab improved both median overall survival (26.0 *v* 20.2 months) and median progression-free survival (10.1 *v* 7.9 months). However, there was no benefit with panitumumab for patients harboring mutations in *KRAS* or *NRAS*; in fact, patients with these mutations did worse with combination treatment than those treated with FOLFOX alone (overall survival: 15.6 months for panitumumab plus FOLFOX *v* 19.2 months for FOLFOX alone). In this analysis, *BRAF* gene mutations were not associated with patient survival. These findings suggest that patients should be tested for both *KRAS* and *NRAS* mutations before receiving panitumumab to avoid the adverse effects and costs of a potentially ineffective treatment. Approximately 40% of patients have *KRAS* mutations, and 10% have *NRAS* mutations.

Large phase III study establishes a new standard treatment option for patients with metastatic pancreatic cancer. In the United States, pancreatic cancer is the fourth-leading cause of cancer-related death. More than half of patients are diagnosed at an advanced stage, for which the 5-year survival rate is less than 2%. Chemotherapy with gemcitabine is a standard treatment for advanced pancreatic cancer. Adding other drugs to gemcitabine, such as erlotinib or capecitabine, has been shown to help some patients live longer. Findings from a large international study published this year establish a new gemcitabine combination for this group of patients.[37]

In the study, 861 patients with pancreatic cancer that had spread to the liver were randomly assigned to receive nab-paclitaxel (paclitaxel protein-bound particles) plus gemcitabine or gemcitabine alone. Patients who received the combination treatment had a higher response rate (23% *v* 7%), longer median overall survival (8.5 *v* 6.7 months), and longer progression-free survival (5.5 *v* 3.7 months) compared with patients who received gemcitabine only. These results establish gemcitabine plus nab-paclitaxel as a new standard treatment option for patients with metastatic pancreatic cancer. In September, based on the findings of this study, the FDA approved nab-paclitaxel for treatment of patients with metastatic pancreatic cancer.[38]

Postoperative treatment with S-1 chemotherapy reduces relapses and extends survival in Asian patients with pancreatic cancer. After surgery for advanced pancreatic cancer, patients typically receive gemcitabine, which has been shown to lengthen survival by several months compared with surgery alone. Interim results from a phase III clinical trial of 385 patients with stage I to III pancreatic adenocarcinoma reported this year suggest that another chemotherapy drug, S-1, substantially improves survival compared with gemcitabine in Asian patients.[39]

In the study, conducted in Japan, patients were randomly assigned to receive gemcitabine or S-1 after surgery. Patients who received S-1 had a 44% lower risk of dying compared with patients treated with gemcitabine. The 2-year survival rates were 70% and 53% for S-1 and gemcitabine, respectively. Relapse rates were also lower in the S-1 arm. The 2-year relapse-free survival rates were 49% and 29% for S-1 and gemcitabine, respectively.

These findings demonstrate that S-1 is superior to the current standard postoperative (adjuvant) therapy for advanced pancreatic cancer, warranting serious consideration of S-1 as a new standard of care for this population of patients.

In Japan and some other countries, S-1 has been approved to treat several cancers, including stomach, colorectal, pancreatic, biliary, head and neck, NSCLC, and metastatic breast cancers. Although S-1 is not yet FDA approved in the United States for any indication, it is being explored in several clinical trials. The active component of S-1, tegafur, is converted in the bloodstream to fluorouracil, which is FDA approved to treat pancreatic cancer. Previous studies have shown that S-1 is more toxic for patients of European descent, requiring use of lower doses.

GENITOURINARY CANCERS

Genitourinary cancers include those in the prostate, testis, kidney, bladder, ureter, and urethra. Prostate cancer is by far the most common type of genitourinary cancer and consequently the focus of intensive clinical research.

This year, there were two notable advances that may affect the care of patients with castration-resistant prostate cancer (CRPC): one, early clinical results pointing to a promising new treatment option for this disease, and two, insight into the molecular mechanisms that drive resistance to androgen-deprivation therapy. This year also brought important advances in kidney cancer research. A large comparative-effectiveness study determined that the targeted drugs pazopanib and sunitinib significantly differ in adverse effects, although they provide similar survival benefit. A small, early study identified a promising new immunotherapy for patients with advanced renal cell carcinoma (RCC). Finally, a large-scale comprehensive molecular analysis of clear-cell RCC identified frequent changes in genes and pathways as well as molecular signatures associated with survival. The findings will inform development of new treatment strategies for this disease.

Advances

Multitargeted drug cabozantinib has impressive antitumor activity in patients with advanced prostate cancer. Advanced prostate cancer most frequently spreads to the bone. Bone metastases are a major challenge in the care of patients with CRPC. Results of two phase II studies published this year show that a new TKI, cabozantinib, helps stall disease progression and causes dramatic and rapid shrinkage of tumor lesions on bone scans as well as rapid declines in pain intensity and CTC levels.

Cabozantinib is an oral drug that blocks MET and vascular endothelial growth factor receptor 2 (VEGFR2), two proteins that play critical roles in CRPC development and progression. A total of 171 men with progressing CRPC were enrolled onto the first study.[40] All men received cabozantinib for the first 12 weeks. Nine (5%) of the men had a confirmed response within the first 12 weeks, 127 (75%) had stable disease, and 18 (11%) experienced disease progression. To explore whether continuation of cabozantib treatment delays disease progression, 31 of the men who had stable disease at 12 weeks were randomly assigned to cabozantinib or placebo. In that subgroup, cabozantinib significantly prolonged progression-free survival (23.9 weeks for cabozantinib *v* 5.9 weeks for placebo). Given the remarkable results observed with cabozantinib, the study was halted early based on strong antitumor activity, and 57 patients continued open-label treatment with the drug.

Researchers also observed that cabozantinib treatment had a substantial effect on shrinking CRPC metastases in the bones and decreasing bone pain. At the beginning of the study, 149 men had evidence of bone metastases. After therapy, bone lesions had shrunk on scans in 79 (68%) of men, with complete disappearance of metastases in 12% of men. This was accompanied by a reduction in bone pain in 67% of men and decrease or discontinuation of pain medication in 56% of men. More than 70% of men had shrinkage of soft tissue tumor lesions.

Retrospective analysis of data from a separate nonrandomized phase II study of cabozantinib in 144 men with CRPC that had progressed despite prior treatment with docetaxel showed an association between overall survival and decrease of bone metastases on scans, reduction in pain intensity, and decrease in CTC counts.[41] The two phase II studies used a daily cabozantib dose of 100 mg, which was associated with serious adverse effects in some patients, requiring dose reductions. To determine if lower doses would reduce adverse effects while preserving the efficacy of the drug, another study explored three lower cabozantinib doses (60, 40, and 20 mg; this study was funded in part by the 2009 Career Development Award of the ASCO Conquer Cancer Foundation to author Richard J. Lee).[42] Researchers determined that the dose of 40 mg daily was associated with significant reductions of bone metastases on scans and was better tolerated than the 100-mg dose used in prior studies. These results informed the design of two ongoing phase III studies assessing the impact of cabozantinib on overall survival in men with CRPC. More research is also needed to explore the balance between decreased pain and adverse effects of therapy and identify strategies for management of adverse effects.

Innovative research model identifies the molecular basis of resistance to androgen deprivation in prostate cancer: New opportunities for tailored treatment. Androgens are male hormones that fuel the growth of prostate tumors. Androgen-deprivation therapies are generally effective against prostate cancer, but some men develop resistance to this form of therapy. Androgen-resistant prostate cancer is also known as CRPC. To gain deeper insight into the molecular changes that underlie development of CRPC, researchers undertook an innovative, coclinical approach; they integrated data from genetically engineered prostate cancer mouse models with clinical data from tissue samples of men with CRPC.[43]

In the study, published this year, hundreds of genetically engineered mice were treated with androgen-deprivation therapy. The mice were observed using CT–positron emission tomography and/or magnetic resonance imaging (MRI) scans, and researchers performed genetic, molecular, and pathologic analyses of their tumors, which led to the identification of a three-gene (*XAF1*, *XIAP*, and *SRD5A1*) signature predictive of CRPC. Importantly, combined blocking of *XIAP*, *SRD5A1*, and androgen receptor pathways with targeted drugs reversed resistance to androgen-deprivation therapy. Researchers

subsequently confirmed that the same signature was associated with resistance to androgen-deprivation therapy in human patients. These results will help stratify patients for clinical trials based on genetic and molecular criteria and may offer the opportunity for development of new personalized treatments for patients with late-stage prostate cancer.

Pazopanib and sunitinib have similar efficacy in metastatic RCC, but sunitinib has more adverse effects. Advanced RCC is generally resistant to chemotherapy, and patients with this disease are in need of new treatment options. Two drugs from the TKI family, sunitinib and pazopanib, are among the recently approved targeted agents for use in first-line therapy in patients with metastatic RCC. Comparison across different clinical trials has suggested that the two drugs have similar benefits but differ in severity and types of adverse effects. This year, researchers published results from the first head-to-head comparison to our knowledge of efficacy and safety of sunitinib versus pazopanib in this patient population.[44]

In this phase III study, 1,110 patients with clear-cell, metastatic RCC were randomly assigned to receive pazopanib or sunitinib. Tumor shrinkage occurred in 31% in the pazopanib group and 24% in the sunitinib group. Disease progression was observed in 60% of patients in the pazopanib group and 58% in the sunitinib group, and progression-free survival periods were comparable (8.4 months for pazopanib *v* 9.5 months for sunitinib). The median overall survival was not significantly different between the two groups (28.4 months for pazopanib *v* 29.3 months for sunitinib). Compared with patients in the pazopanib group, patients in the sunitinib group had a higher incidence of severe fatigue and hand-foot syndrome as well as higher risk for laboratory abnormalities (low blood counts). In contrast, patients in the pazopanib group had a higher risk of liver function abnormalities. During the first 6 months of treatment, patients receiving pazopanib had better health-related QOL (HRQOL) compared with those receiving sunitinib. Overall, these findings indicate that pazopanib provides a survival benefit similar to that of sunitinib but is associated with fewer serious adverse effects, which translates into improved QOL for patients and savings in costs associated with managing adverse effects.

New anti–PD-L1 drug shows promising activity in advanced RCC. This year, researchers reported results from an ongoing phase I expansion study of the investigational drug MPDL3280A—an engineered PD-L1–targeted antibody—in patients with metastatic RCC that had worsened despite several prior treatments.[45]

PD-L1 is a protein located on tumor cells, which some tumors use to avoid attacks from the patient's own immune system. When MPDL3280A attaches to PD-L1, the cancer can no longer hide from the patient's immune system, allowing the body's T cells to fight the cancer. Fifty-three patients were treated with four different doses of MPDL3280A. Tumor shrinkage was observed across all dose levels, and all responses were ongoing at the time of data analysis. The responses were associated with expression of PD-L1 and interleukin-17 markers in the tumor. At 24 weeks of treatment, 50% of patients had no signs of disease progression. The new drug was well tolerated, and no treatment-related deaths occurred. These early findings indicate that MPDL3280A warrants further research in patients with advanced RCC.

Molecular profiling identifies potential new therapeutic targets in clear-cell RCC. Clear-cell RCC is the most common form of kidney cancer. Researchers have recently identified changes in several pathways that seem to be involved in clear-cell RCC development and progression. Results of a comprehensive genomic analysis of more than 400 clear-cell RCC tumors were reported this year (this study was funded in part by a grant from NIH).[46]

This comprehensive study assessed clinical and pathologic features, genomic alterations, DNA methylation profiles (epigenetic changes), and RNA and proteomic signatures. Researchers identified 19 significantly mutated genes. The VHL/HIF, PI3K/AKT, and DNA methylation pathways were frequently altered, suggesting that these pathways might be viable therapeutic targets. The study also revealed several molecular signatures associated with survival. Abnormal levels of genes involved in cell metabolism were associated with worse survival. These findings point to new avenues for development of targeted treatments for clear-cell RCC.

FDA approves abiraterone acetate for patients with advanced CRPC. In December of last year, the FDA approved abiraterone acetate for use in combination with prednisone in patients with advanced CRPC.[47] The drug decreases the production of testosterone. The approval was based on a study of 1,088 men with late-stage CRPC who had not previously received chemotherapy. Participants received either abiraterone or placebo in combination with prednisone. Patients who received abiraterone had a median overall survival of 35.3 months compared with 30.1 months for those receiving placebo. The FDA had previously approved the drug for use in patients whose prostate cancer progressed after treatment with docetaxel. This approval provides patients the option of receiving abiraterone earlier in the course of treatment.

FDA approves ^{223}Ra for patients with advanced CRPC. In May, the FDA approved ^{223}Ra-dichloride for the treatment of patients with CRPC with symptomatic, painful bone metastases and no known visceral metastatic disease.[48] The approval was based on a large, randomized clinical trial in patients with metastatic CRPC who experienced a statistically significant improvement in overall survival with ^{223}Ra compared with placebo (14.0 *v* 11.2 months).[49] This approval offers a new standard treatment option for these patients.

GYNECOLOGIC CANCERS

Gynecologic cancers include cancers of the cervix, uterus, ovaries, fallopian tubes, peritoneum, vagina, and vulva. This year brought advances that are beginning to deliver on the promise of precision medicine, with genetic tools and molecularly targeted therapies that may improve treatment selection and outcomes in several notoriously hard-to-treat cancers. A comprehensive molecular analysis of endometrial cancers provides detailed insight into the biology of the disease, helping improve tumor classification and guide therapy selection. A small, early-stage study reported a promising new targeted treatment option for a form of ovarian cancer that is resistant to chemotherapy. Finally, for the first time to our knowledge, researchers reported on a life-extending treatment for advanced and relapsed cervical cancer, a disease that claims a quarter of a million lives worldwide each year.

Advances

Comprehensive molecular analysis of endometrial cancers refines tumor classification, helping guide individualized treatment selection. Endometrial (uterine) cancer is the most common gynecologic cancer

and the fourth most common malignancy among US women. Endometrial cancers are a diverse group of cancers that are histologically classified as endometrioid, serous, clear cell, neuroendocrine, mixed, and undifferentiated. Endometrioid adenocarcinomas are further histologically classified with grading on a three-tier system: grade 1 (low), 2 (moderate), or 3 (high). Endometrial cancers can be challenging to classify, often resulting in disagreement among pathologists on the histologic subtype diagnosis. Histologic classification is also imperfect at predicting clinical and genomic characteristics. Because of this, histologic classification systems have limitations in determining treatment selection and directing patients to clinical trials.

To improve the current classification system, TCGA Research Network conducted a comprehensive genomic and proteomic analysis of 373 endometrial cancers, including low-grade endometrioid, high-grade endometrioid, and serous tumors (this study was funded in part by a grant from NIH).[50] This molecular classification provides an additional layer of biologic characterization that complements the current classification system based on histology alone.

The analysis identifies four subcategories of serous and endometrioid tumors based on genomic characteristics: *POLE* ultramutated, microsatellite instability hypermutated, copy number low, and copy number high.

Approximately 25% of tumors that the pathologists classified as high-grade endometrioid tumors had molecular characteristics that were actually similar to uterine serous carcinomas, including frequent mutations of the *TP53* gene and gene copy number changes. This finding suggests that this subset of patients with endometrioid cancer may benefit from treatment paradigms similar to those used for serous cancers. The molecular data collected in this study also provide opportunities for future clinical trials and drug development.

Phase II study shows selumetinib has promising activity against low-grade serous ovarian cancer. Epithelial ovarian cancer is a general term for tumors that arise from the fallopian tubes, ovaries, endometrium, or peritoneal cavity. There are several distinct histologic types of epithelial ovarian cancer, including high-grade serous, low-grade serous, clear cell, mucinous, and endometrioid. Low-grade serous ovarian cancer is particularly challenging to treat, because it tends to be resistant to chemotherapy and hormonal therapy.

Results of a phase II, single-arm study reported this year point to the promising activity of selumetinib for women with recurrent low-grade serous ovarian carcinoma (this study was funded in part by a grant from NIH).[51] Selumetinib is an oral drug that blocks MEK1 and MEK2 kinases in the mitogen-activated protein kinase (MAPK) pathway, which is frequently altered in this disease.

In this study, eight (15%) of 52 of women experienced measurable tumor shrinkage, and one had a complete remission. In addition, 34 women (65%) had stable disease. The drug was generally well tolerated, and there were no treatment-related deaths. Although larger studies are needed to confirm MEK inhibition, these findings indicate that MAPK pathway–targeting therapies are a promising strategy for this group of patients.

Study of bevacizumab combination therapy finds survival benefit for women with metastatic or relapsed cervical cancer. In the developed world, cervical cancer is typically diagnosed at an early stage, when it is amenable to treatment with surgery alone or multimodality treatment, and most patients achieve good outcomes. Patients with advanced cervical cancer, on the other hand, have limited options, and median survival with the standard treatment is approximately 1 year. Approximately 4,000 women in the United States die as a result of the disease each year.

A landmark study reported this year shows, for the first time to our knowledge, that the targeted therapy bevacizumab substantially extends survival for women with metastatic or relapsed cervical cancer (this study was funded in part by a grant from NIH).[52] In this phase III study performed by the federally funded Gynecologic Oncology Group, 452 women were randomly assigned to treatment with one of two standard chemotherapy regimens alone or a combination of either standard chemotherapy regimen and bevacizumab. Bevacizumab works by blocking the growth and maintenance of tumor blood vessels. The two chemotherapy regimens tested were cisplatin plus paclitaxel and topotecan plus paclitaxel.

No significant differences in survival were observed between the two chemotherapy arms, but the median survival for women who received the bevacizumab combination was 17.0 months versus 13.3 months for those who received chemotherapy alone. Tumor shrinkage rates were also higher with bevacizumab combination therapy compared with chemotherapy alone (48% *v* 36%). Bevacizumab is currently approved by the FDA for treatment of several advanced cancers, but it has not to date received approval for any gynecologic cancer.

HEAD AND NECK CANCERS

Head and neck cancers arise in the nasal cavity, sinuses, mouth, lips, salivary glands, throat, and larynx (voicebox) and are predominately squamous cell carcinomas. They are relatively rare in the United States, accounting for 5% of all cancer cases. However, their incidence is rising, in large part because of HPV infection, smoking, and heavy alcohol consumption. Worldwide, head and neck cancers are the sixth most common type of cancer, with more than 70% of patient cases occurring in developing countries.

Thyroid cancer forms in the thyroid gland, a small organ at the base of the throat that makes hormones that help control heart rate, blood pressure, body temperature, and weight. Although also rare, the overall incidence of thyroid cancer in the United States has increased over the past two decades. In fact, its incidence is rising faster than all cancers, also occurring more frequently in women than in men. It is thought that this is in part the result of earlier detection; however, the increase in mortality as well as the increase of larger tumors suggests that there may be additional factors behind the increase.

This year brought important advances in treatment for thyroid and head and neck cancers as well as new insight into HPV-positive oropharyngeal cancer (OPC) risk. Findings from a landmark study suggest that the targeted drug sorafenib may be the first active drug identified in more than four decades for a rare form of treatment-resistant thyroid cancer. Researchers found that spouses of patients with HPV-positive OPC have low prevalence of oral HPV infection, reducing anxiety about their own HPV-related cancer risk. A genomic analysis of head and neck squamous carcinoma tissue identified several promising new drug targets that warrant further exploration.

Advances

Sorafenib stalls growth of treatment-resistant thyroid cancer. Differentiated thyroid cancers (DTCs), which start in follicular cells of the thyroid, account for 85% of the 60,000 thyroid cancer patient cases

diagnosed each year in the United States. The majority of patients with DTC can be cured with a combination of surgery and radioiodine therapy. Unfortunately, roughly 5% to 15% of patients with advanced DTC develop treatment resistance and disease progression. Previously, there were no effective treatments for these patients, but this year, a phase III study found that a drug called sorafenib delays disease progression for this population of patients.[53]

Sorafenib is an oral drug that blocks two cancer-related pathways: VEGFR and RAF kinase. The drug is currently FDA approved for the treatment of advanced kidney and liver cancers.

A total of 417 patients with locally advanced or metastatic, radioiodine-resistant DTC were randomly assigned to treatment with sorafenib or placebo. Patients in the placebo arm were allowed to cross over to the sorafenib arm on disease progression. The median progression-free survival was 10.8 months in the sorafenib arm compared with 5.8 months in the placebo arm. Tumor shrinkage of 30% or more occurred in 12% of patients receiving sorafenib arm but in only 0.5% of those receiving placebo. An additional 42% of patients in the sorafenib arm had no disease progression for 6 months or longer. Longer follow-up is required to determine the effect of sorafenib on overall survival. Further analysis of data from this study is planned to find markers for identifying patients who are likely to respond well to sorafenib and those who may need additional therapy. If approved by the FDA, sorafenib would become the first new active drug for this form of thyroid cancer in 40 years.

Spouses of patients with HPV-positive OPC do not have increased oral HPV infections. OPC begins in the middle area of the throat, from the tonsils to the voicebox. OPC is approximately twice as common in men than in women, and research indicates that infection with HPV is a risk factor for OPC. HPV is most commonly passed from person to person during sexual activity, including oral intercourse. Consequently, patients with HPV-positive OPC and their spouses often worry about oral HPV transmission and wonder about the spouses' own cancer risk. However, findings from a new study provide reassurance that the risk of developing HPV-positive OPC is low for spouses.[54]

The study included 147 patients with HPV-positive OPC and 83 spouses or partners. Patients with OPC were predominantly male, and the spouses or partners were predominantly female. Researchers collected oral rinse samples at diagnosis and again 1 year later. HPV DNA was detected in 66% of patients with HPV-positive OPC at diagnosis, but only 7% of those patients still had an oral HPV infection 1 year later. The overall prevalence of HPV infection among the partners was 7.2%. The prevalence among the 75 female partners was 5%, which is comparable to the prevalence among women in the general population (4% based on previously published data). The prevalence among the small number of male partners assessed in this study was also similar to that among men in the general population, although it was higher than in the female population. HPV16, the subtype responsible for most cases of HPV-positive OPC, was detected in 54% of patients with HPV-positive OPC but in only 2.7% of female partners and in none of the male partners. These findings indicate that the risk of developing HPV-positive OPC remains low for both female and male partners of patients diagnosed with HPV-positive OPC. Couples who have been together for several years can be reassured that they need not change their intimate behavior after one partner's diagnosis of HPV-positive OPC.

Genomic profiling identifies several potential new drug targets in head and neck squamous cell carcinoma. Most head and neck cancers are squamous cell carcinomas, meaning they begin in the flat, squamous cells that make up the thin surface layer (called the epithelium) of the structures in the head and neck. Targeted therapy development for this type of cancer has been limited, because little is known about the genetic changes that fuel the growth of this disease. This year, a genomic profiling study identified recurrent genetic abnormalities that could potentially be targeted and blocked by existing drugs.[55]

Researchers screened tumor and matched healthy tissue from 120 patients for mutations in 60 cancer-related protein kinases. Novel mutations and gene copy number changes were detected in 45% of the tumors, including abnormalities in FGFR1, FGFR2, DDR2, EPHA2, and PI3K pathways. These findings warrant further investigation of these potential new targets in clinical trials. Drugs targeting some of these pathways are already available in the clinic. Agents that target these pathways will need to be studied in the context of current therapeutic regiments. Similar mutations were previously reported in lung squamous cell carcinoma and are already being explored as therapeutic targets.

FDA approves cabozantinib for patients with medullary thyroid cancer. In November last year, the FDA approved cabozantinib for treatment of patients with metastatic medullary thyroid cancer.[56] Cabozantinib blocks abnormal kinase proteins involved in the development and growth of medullary cancer cells. The approval was based on the demonstration of improved progression-free survival observed in an international randomized, placebo-controlled trial enrolling 330 patients with metastatic medullary thyroid cancer, highlighted in last year's CCA report. The approval provides an additional treatment option for this rare disease.

LUNG CANCERS

Lung cancers are a group of diseases, each defined by specific biologic processes that determine their clinical picture and responsiveness to therapy. Lung cancers are the primary cause of cancer-related death among men and women in the United States. More than 220,000 adults are diagnosed with lung cancers every year, and only 16% survive 5 years. Although cigarette smoking causes most lung cancers, more than 80% of patients diagnosed this year had either never smoked cigarettes or stopped smoking, sometimes decades earlier.

Discovery of key genes and proteins that spark and fuel lung cancers (ie, driver genes) has shifted the focus of lung cancer treatment toward targeted therapies. This year, strategies of screening for genetic changes in lung tumors and matching patients to appropriate targeted treatments were reported, thus delivering on the promise of personalized medicine. Early results showed encouraging antitumor effects of dabrafenib against *BRAF*-positive lung cancers and LDK378 and AF802 for *ALK*-positive lung cancers.

Advances

Genomic testing helps physicians match patients with targeted treatments and clinical trials: Leads to improved lung cancer survival. In 2009, NCI, using funds from the American Relief and Recovery Act, established the Lung Cancer Mutation Consortium, a national initiative to prospectively examine tumors from persons with lung adenocarcinomas for targetable genetic mutations and match patients to the

best possible therapies based on these results. Today, the consortium includes 16 cancer centers across the United States. This year, researchers reported results from the program, showing for the first time to our knowledge that this approach prolongs survival (this study was funded in part by a grant from NIH).[57]

A total of 1,007 patients with metastatic adenocarcinomas (the most common subtype of NSCLC) were tested for at least one genomic mutation, and 733 underwent testing for all 10 known lung cancer oncogenic drivers: *KRAS*, *EGFR*, *HER2*, *BRAF*, *PIK3CA*, *AKT1*, *MEK1*, *NRAS*, *ALK*, and *MET*. A driver was detected in 622 (62%) of 1,007 patients with at least one gene tested, and 465 (63%) of 733 patients who underwent testing for all 10 genes. Mutations in *KRAS*, *EGFR*, and *ALK* genes accounted for approximately half of all driver mutations detected. Twenty-nine patients (4%) had mutations in two driver genes.

These findings were then used to select available targeted therapies or appropriate clinical trials testing new targeted therapies in 279 patients with a driver mutation. Clinical follow-up and treatment information was assessed for 938 patients. Among the 622 patients with a driver mutation detected, those treated with targeted therapy (264 patients) had a median survival of 3.5 years, and those who did not have a targeted therapy available (313 patients) had a median survival of 2.4 years. The 361 patients without identified driver mutations had a median survival of 2.1 years. This study demonstrates that close to two thirds of all patients with lung adenocarcinomas harbor mutations in known lung cancer driver genes and that matching patients with treatments targeted specifically to those drivers leads to improvements in survival.

Success of the French nationwide screening for six driver mutations in patients with lung cancer. Another study this year affirms the feasibility and value of nationwide routine screening for driver mutations in patients with lung cancer.[58] The French National Cancer Institute recently began routine screening of patients with advanced NSCLC for mutations in six genes: *EGFR*, *ALK*, *HER2*, *KRAS*, *BRAF*, and *PI3KCA*. This study reported encouraging results of the genomic testing, along with epidemiologic, clinical, and therapeutic outcomes for the first 10,000 patients screened. Patients were mainly former smokers (83%) and had stage IV disease. *KRAS* and *EGFR* gene mutations accounted for the majority of genetic changes detected, found in 27% and 9% of patients, respectively. At the time of this analysis, treatment data were available for 19% of the patients. Among those patients, 57% received a targeted treatment selected according to the molecular profile of their tumor. This French program represents the largest molecular marker study in patients with advanced NSCLC conducted to date. The findings provide important evidence of the feasibility and value of nationwide, routine, multiplexed screening for patients with NSCLC, and longer-term data will demonstrate how this approach affects patient outcomes overall.

Results from a phase II study show dabrafenib has antitumor activity in patients with BRAF *V600E–mutant NSCLC.* Nearly 3,000 patients with lung adenocarcinomas diagnosed each year in the United States have tumors that carry a mutation called V600E *BRAF*. The *BRAF* gene makes a protein that affects how cancer cells divide and grow. An oral drug that blocks the BRAF protein, dabrafenib, has recently shown dramatic effects in patients with *BRAF* V600E–positive metastatic melanoma. This year, researchers reported early results from the first clinical trial to our knowledge to show activity of dabrafenib in patients with lung cancer.[59]

Seven (54%) of 13 patients experienced major tumor shrinkage. Currently, the best traditional single-agent chemotherapy drugs shrink lung cancers approximately 15% of the time and lead to severe adverse effects, such as hair loss, vomiting, and nerve damage. The longest duration of response to dabrafenib to date is 11 months. Eleven patients remained on therapy at the time of reporting. Dabrafenib was better tolerated than traditional chemotherapies, with adverse effects similar to those observed in patients with melanoma (decreased appetite, fatigue, weakness, and nausea). On the basis of these early results, the study continues into its second stage, enrolling additional patients with stage IV NSCLC.

New screening strategies identify RET *and* ROS1 *gene alterations in patients with advanced lung cancers.* *RET* and *ROS1* genes fuel the development and growth of lung adenocarcinomas. The most common type of *RET* and *ROS1* abnormalities are gene fusions, where sequences of two unrelated genes are linked, leading to production of abnormal hybrid proteins. *RET* and *ROS1* fusions occur in 2,000 to 3,000 patients with lung cancer overall. Screening for these fusions is not yet routine, although drugs targeting those abnormalities are already being tested in clinical trials and have been approved to treat other types of cancers.

Two studies this year reported on a new screening paradigm that focuses on patients whose tumors are most likely to harbor *RET* and *ROS1* fusions: individuals who are never-smokers and those without other cancer driver oncogenes. Screening is performed using a common diagnostic technique known as fluorescence in situ hybridization (FISH), specifically modified to detect gene fusions.

In the first study, researchers looked for specific *RET* gene fusions in 51 patients with lung adenocarcinoma who did not carry mutations in the *EGFR*, *KRAS*, *ALK*, or *ROS1* gene (this study was funded in part by a grant from NIH).[60] The patients were mostly never-smokers. Eight (15%) of 51 patients had *RET* gene abnormalities, including gene fusions and extra copies of the gene. The study confirms that the FISH technique can efficiently detect multiple types of *RET* abnormalities in lung adenocarcinomas and shows that *RET* abnormalities are more common among tumors that are negative for other lung cancer oncogenic drivers.

The second study screened never-smokers for *RET* and *ROS1* gene fusions using FISH and two other molecular techniques.[61] Patients had advanced lung adenocarcinoma without mutations in *EGFR*, *KRAS*, *NRAS*, *BRAF*, *HER2*, *PIK3CA*, *MEK1*, *AKT*, or *ALK*. A *RET* or *ROS1* fusion was detected in 10 (31%) of 32 patients screened. Patients with *RET*-positive tumors were enrolled onto a phase II clinical trial of cabozantinib, and those with *ROS1*-positive tumors were enrolled onto a phase I study of crizotinib, which blocks ROS1, ALK, and MET proteins. Cabozantinib blocks several tyrosine kinases, including RET, and is approved for the treatment of medullary thyroid cancer. Two of five patients treated with cabozantinib and one of five treated with crizotinib experienced some tumor shrinkage. Further evidence of the benefit of crizotinib in patients with *ROS1*-positive lung cancer was presented at the 2013 ASCO annual meeting, showing substantial tumor shrinkage in 14 (56%) of 25 patients.[62]

Taken together, the results of the studies confirm that *RET* and *ROS1* fusions occur more frequently among patients with no other known mutations in lung cancer genes than in the general population of patients with lung cancer. These findings suggest that patients whose tumors do not harbor mutations in other lung cancer genes should be screened for *ROS1* and *RET* gene fusions and considered for

treatment with drugs that block these targets. This work further demonstrates how research continues to lead to the discovery of additional drivers that permit the concept of personalized care to be applied to more and more persons with lung cancer.

FDA approves albumin-bound paclitaxel, erlotinib, and afatinib for patients with metastatic NSCLC. Albumin-bound paclitaxel was approved for use in combination with carboplatin for patients with NSCLC who are not candidates for curative surgery or RT. The approval was based on a phase III study showing that the new drug resulted in tumor shrinkage in a greater proportion of patients than that with standard paclitaxel.[63] The FDA approved erlotinib[64] in May and afatinib[65] in July for the initial treatment of patients with lung cancers harboring *EGFR* mutations. The approval of erlotinib was based on the results of a randomized, multicenter, open-label study comparing erlotinib with platinum-based doublet chemotherapy in patients with metastatic NSCLC whose tumors had specific *EGFR* mutations. The study showed that cancer progression was delayed by 5.2 months in patients receiving erlotinib compared with those receiving chemotherapy. The approval of afatinib was based on randomized clinical trial showing that afatinib delayed disease progression by 4.2 months compared with chemotherapy. Afatinib and erlotinib are both TKIs that block proteins that promote the development of cancer cells.

MELANOMA

Advanced-stage melanoma is the leading cause of death resulting from skin cancer and among the deadliest cancers overall. This year brought significant advances in targeted and immunotherapy treatment options for patients with metastatic or inoperable melanoma.

An important study showed that blocking BRAF and MEK pathways concurrently is a safe and effective approach for treating *BRAF*-mutated melanoma. Several early-phase studies demonstrated that targeting the PD-1/PD-L1 pathway—a strategy that helps patients' own immune system fight cancer—leads to rapid and lasting tumor shrinkage in a large proportion of patients. Finally, lasting antitumor responses were observed in a phase III study of an innovative immunotherapy approach that uses an engineered virus to produce an anticancer drug inside the tumor.

Advances

Two new targeted treatments approved for certain patients with inoperable or metastatic melanoma: Combination of same drugs shows promise in early study. Approximately half of melanoma tumors harbor a mutation in the *BRAF* gene, which activates the MEK pathway. Tumors with such mutations are generally resistant to standard therapies, but in May this year, the FDA approved two new treatment options.[66]

Dabrafenib, an inhibitor of the BRAF protein, was approved to treat only patients with inoperable or metastatic melanoma harboring the *BRAF* V600E gene mutation. Trametinib, a MEK inhibitor, was approved to treat patients whose advanced or inoperable tumor expresses the *BRAF* V600E or V600K gene mutation. Both drugs are approved only for use as single agents.

In addition, this year, researchers reported findings from a phase I/II study assessing the efficacy of combination treatment with trametinib and dabrafinib in patients with *BRAF*-mutated melanoma resistant to dabrafenib or vemurafenib (another *BRAF*-targeted therapy) and in those who had never been treated with a BRAF inhibitor.[67]

Among the 69 patients in the BRAF inhibitor–resistant group, 38% had experienced tumor shrinkage with single-agent treatment, but their disease eventually worsened. On treatment with the dabrafenib plus trametinib combination, the median tumor shrinkage rate was up to 15%, and the median progression-free survival was 3.6 months. Among the 78 patients who had not previously received a BRAF inhibitor, the median tumor shrinkage rate was up to 76%, and the median progression-free survival was up to 10.8 months. These early findings show that the combination of these two drugs is much more effective in patients receiving the treatment as first-line therapy, as compared with patients who had acquired resistance to BRAF inhibitors. These preliminary data also suggest that BRAF inhibitor/MEK inhibitor combination therapy is superior to BRAF inhibitor single-agent treatment in patients who had not previously received BRAF inhibitor therapy.

Encouraging results regarding new PD-1–targeted immunotherapies for patients with advanced melanoma. The PD-1/PD-L1 pathway plays an essential role in the body's immune response to cancer. New targeted treatments that block either the PD-1 (located on the surface of immune cells) or PD-L1 protein (located on the surface of certain cancer cells) are showing promising activity in a number of cancer types. In melanoma, two early-stage studies offer particularly encouraging results with drugs blocking PD-1, a strategy that boosts the ability of the immune system to fight cancer.

Long-term follow-up results from an expanded phase I study indicate that the investigational drug nivolumab produces lasting remissions in patients with stage IV melanoma.[68] In this study, 107 patients were treated with five different doses of nivolumab. All patients had disease that worsened despite extensive prior standard systemic therapies. Overall, 33 (31%) of 107 patients experienced significant tumor shrinkage (30% or more), and responses were seen at all doses. The 2-year survival rate was 44%. The median overall survival across all doses was 16.8 months; it was 20.3 months for the dose chosen for study in subsequent phase III clinical trials.

Although this was an early-phase, nonrandomized study, it included a considerable number of patients, and the durability of responses is a sign of promising clinical activity, with median overall survival exceeding that seen with the most recently approved melanoma drugs.

Another PD-1 targeting agent, lambrolizumab, has also shown encouraging antitumor effects in patients with advanced melanoma, including those whose disease progressed despite treatment with ipilimumab.[69] A total of 135 patients with metastatic or inoperable melanoma were treated with different doses of lambrolizumab in this study. Of those, 48 patients had previously received ipilimumab.

The overall response (tumor shrinkage) rate across all doses was 38%, and the highest response rate was 58%. The responses were durable in most patients, lasting 11 months on average. The response rates did not differ with regard to prior ipilimumab therapy. The overall median progression-free survival was longer than 7 months. The adverse effects were generally mild. The early findings indicate that lambolizumab is safe and shows strong and lasting antitumor effects in patients with advanced melanoma, including those resistant to the standard immunotherapy drug ipilimumab.

Phase I study suggests ipilimumab and nivolumab may be better together than alone. Both nivolumab and ipilimumab are antibody

drugs that target gatekeepers or checkpoints (PD-1 and CTLA-4, respectively) on immune cells, which otherwise inhibit the immune system from fighting melanomas. Ipilimumab has previously been shown to prolong overall survival, and lasting antitumor effects have been observed in phase I studies with nivolumab. A proof-of-principle study reported this year shows that concurrent use of the two antibodies leads to rapid and lasting tumor shrinkage in up to 50% of patients with advanced melanoma.[70]

Patients with inoperable stage III or IV melanoma who had undergone up to three prior therapies were enrolled onto the study. A total of 53 patients received concurrent treatment with the two drugs, and 33 received sequenced treatment. The overall tumor shrinkage rate among patients who received concurrent treatment was 40%, with the highest rate of 53% seen in patients treated with the highest dose of both drugs. The tumor shrinkage rate in the sequenced treatment group was 20%. Sixteen (31%) of 53 patients who received concurrent therapy experienced marked tumor shrinkage of more than 80% at 12 weeks of treatment. Adverse effects were manageable and did not affect the positive therapeutic activity for the majority of the patients in this study.

The findings provide a strong rationale for studying the combination of ipilimumab and nivolumab in first-line therapies for patients with advanced melanoma. A randomized phase III study assessing the efficacy of concurrent treatment with nivolumab and ipilimumab, compared with nivolumab or ipilimumab alone, has been initiated.

Early study validates PD-L1 as an important new treatment target for patients with difficult-to-treat melanoma. Patients with metastatic melanoma often have elevated levels of PD-L1 protein in their tumors. When PD-L1 attaches to its receptor PD-1 on immune cells, tumors are able to hide from the immune system; drugs that target either PD-L1 or PD-1 inhibit this interaction. Researchers reported interim results from a phase I expansion study evaluating the safety and activity of MPDL3280A, an engineered antibody that blocks PD-L1 from attaching to PD-1 in patients with advanced melanoma.[71]

A total of 45 patients with metastatic melanoma were treated with different doses of the anti–PD-L1 antibody. Nine (26%) of 35 evaluable patients experienced tumor shrinkage, some within days of starting treatment. In this study, treatment seemed more effective in patients who had PD-L1 detected in their tumor specimens. The drug was generally well tolerated, and no treatment-related deaths occurred. The findings provide a strong rationale for further assessment of MPDL3280A as a single agent as well as in combination with other drugs.

Tumor vaccine may be better than granulocyte-macrophage colony-stimulating factor for treatment of patients with inoperable melanoma. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a growth factor commonly used to stimulate WBC recovery after chemotherapy or stem-cell transplantation. The agent has also recently been explored as an immunotherapy option for the treatment of melanoma. Interim results from a phase III study comparing GM-CSF with talimogene laherparepvec (T-VEC), a GM-CSF vaccine, suggest that the latter is more effective in patients with inoperable melanoma.[72]

T-VEC is an immunotherapy derived from herpes simplex virus type 1. The virus is genetically engineered to replicate and produce GM-CSF when injected into the tumor. In the study, 295 patients with inoperable stage III or IV melanoma received T-VEC, and 141 received GM-CSF. Overall tumor shrinkage rates were notably higher with T-VEC than with GM-CSF (26% *v* 6%). Durable responses were observed in 16% of patients who received T-VEC but in only 2% of those who received GM-CSF. Interim overall survival data showed a trend in favor of T-VEC. T-VEC was generally well tolerated, but serious adverse effects occurred more frequently among patients receiving T-VEC than among those treated with GM-CSF. Although there was an overall survival trend, mature overall survival data will be necessary to determine the role of T-VEC therapy in the rapidly advancing armamentarium for metastatic melanoma treatment.

PEDIATRIC CANCERS

Although cancer is uncommon in children—occurring in one to two in 10,000 children each year—it is still the leading cause of disease-related death in children younger than age 14 years. Overall long-term survival rates for childhood cancer have improved steadily. In the 1950s, fewer than 10% of patients were cured, but today cure rates are approaching 80%. Unfortunately, a significant percentage of patients have tumors that remain resistant to available therapies, and new options are urgently needed.

This year, results reported from two early-stage clinical trials point to promising new therapies for patients with treatment-resistant ALL, large-cell lymphoma, and certain solid tumors. Additionally, there have been important advances stemming from genomic analyses of childhood cancers. Large-scale sequencing efforts have led to the discovery of mutations that are shared among tumor types and among tumors of different histologies. These results have led to the development of new molecularly targeted drugs and new classification schemes that classify tumors by the genetic changes occurring in them rather than by the way tumor tissue looks under a microscope.

In a perfect world, all subtypes of a given tumor would contain the same mutated gene, such as occurs in CML. In this case, a targeted therapy can be used for all patients with the disease. To date, it seems that some human cancers are highly personal such that tumors of a given histologic subtype from individual patients contain unique genetic profiles, whereas in some tumor types, such as melanoma, the same genetic mutation is present in many patients. The studies highlighted here confirm these observations. One genomic study found that recurrent genetic changes in high-risk neuroblastoma are uncommon, suggesting that development of new targeted drugs for this disease will be challenging. Another genomic study provided insight into the biologic causes of chemotherapy resistance among some patients with ALL, uncovering a potential new treatment target. A final study identified new genetic changes in childhood low-grade glioma (LGG) and low-grade glioneuronal tumors that may inform the development of new molecularly targeted treatments.

Advances

Experimental therapy shows promising effects in relapsed and treatment-resistant pediatric ALL. ALL is the most common form of childhood cancer. The hallmark of this disease is uncontrolled growth of early precursor lymphocytes (usually B lymphocytes in 85% of cases and T cells in 15%). Although long-term survival rates are high with current treatments (> 85% of patients live longer than 5 years),

approximately one in five patients relapses. Children with relapsed and chemotherapy-resistant B– and T–precursor cell ALL have a poor prognosis. This aggressive cancer is typically treated with high-dose regimens of chemotherapy and radiation, including hematopoietic stem-cell transplantation. Such aggressive regimens have not cured the majority of patients, prompting the search for novel approaches. Early results from the first two children treated with a new experimental therapy point to a potentially effective alternative option for these patients (this study was funded in part by a grant from NIH).[18]

In this new approach, which was tested in childhood ALL for the first time to our knowledge, T cells taken from a patient's own blood are reengineered in a laboratory to recognize and attach to CD19, a protein that is found only on the surface of B cells. These modified T cells are reinfused back into the patient, where they multiply and attack cancerous B cells. The first two children who received this treatment experienced a complete remission. In the first patient, the remission lasted 11 months, and the treatment precluded the need for donor stem-cell transplantation. The second patient had a relapse approximately 2 months after treatment. These early results show promise that in the future, engineered T cells may become a radical new strategy for advanced, treatment-resistant ALL.

Large-scale study depicts the landscape of genetic changes in high-risk neuroblastoma. Scientists are increasingly using genome sequencing tools to uncover new drug targets for some of the most difficult-to-treat malignancies, such as high-risk neuroblastoma. Neuroblastoma is predominantly a tumor of early childhood, with two thirds of patient cases presenting in children age 5 years or younger. Only 30% to 50% of children with high-risk neuroblastoma remain alive 5 years after diagnosis.

This year, researchers reported results of a comprehensive assessment of genetic changes in 240 patients with high-risk neuroblastoma (this study was funded in part by a grant from NIH).[73] Although recurrent changes were detected in several genes, including *ALK*, *PTPN11*, *ATRX*, *MYCN*, and *NRAS*, the overall frequency of genetic mutations in this patient population was relatively low. This is a somewhat sobering finding in the DNA century and a challenge for current targeted approaches that rely on frequently altered genes. However, individual mutations may converge on common pathways, and additional work is under way to explore this possibility.

Crizotinib shows promising antitumor activity in young patients with treatment-resistant solid tumors and anaplastic large-cell lymphoma. *ALK* gene alterations have been detected in various forms of cancer, including anaplastic large-cell lymphoma (ALCL), inflammatory myofibroblastic tumors, NSCLC, and neuroblastoma. The targeted drug crizotinib, which blocks ROS1, MET, and ALK proteins, was recently approved by the FDA for the treatment of ALK-positive NSCLC.

Updated findings from a phase I clinical trial reported this year indicate that crizotinib has antitumor activity in children with cancers harboring *ALK* gene alterations, particularly ALCL and inflammatory myofibroblastic tumors, a form of soft tissue sarcoma (this study was funded in part by a grant from NIH).[74] Further investigation is needed to confirm activity in ALK-positive childhood neuroblastoma. Seventy-nine patients, age 1 to 22 years, were enrolled onto the study. The patients had treatment-resistant or relapsed solid or CNS tumors or ALCL resistant to standard therapies.

Tumor shrinkage was observed in 14 of 79 patients overall (eight of nine patients with ALCL, three of seven with inflammatory myofibroblastic tumor, one of two with NSCLC, and two of 34 with neuroblastoma). Seven of nine patients with ALCL experienced a complete remission. Antitumor activity was higher among patients with confirmed *ALK* gene abnormalities in their tumor (eight of nine patients with ALCL, one of 11 with neuroblastoma, three of seven with inflammatory myofibroblastic tumor, and one of two with NSCLC). This study demonstrates that ALK-targeted therapy is a promising approach for the treatment of pediatric cancers, specifically ALCL and inflammatory myofibroblastic tumors that frequently harbor *ALK* gene abnormalities and are dependent on this activation. If these early findings are confirmed in larger clinical trials, crizotinib may become part of first-line therapy for children with these diseases. The antitumor effects of crizotinib in the small percentage of children with neuroblastoma whose tumor contains *ALK* mutations are promising in preclinical studies, and two ongoing clinical trials are exploring the safety of this drug in this patient population.

Genomic studies uncover an alteration that makes some patients with ALL resistant to chemotherapy. Approximately one in five children with ALL do not achieve complete remission or experience a relapse despite intensive chemotherapy, and those patients have a poor prognosis. Treatment resistance and relapse are the greatest challenges in the fight against this disease. The biologic factors causing this resistance have been unknown.

This year, researchers reported findings from two studies suggesting that resistance of ALL to chemotherapy may be linked to mutations in a gene that encodes a protein called NT5C2. In the first study, researchers determined that mutated *NT5C2* was associated with inactivation of chemotherapy drugs 6-mercaptopurine and 6-thioguanine in 20 (19%) of 103 patients with relapsed T-cell ALL and one (3%) of 35 patients with relapsed B–precursor cell ALL.[75] A second study identified *NT5C2* alterations in two (20%) of 10 patients with relapsed childhood B–precursor cell ALL; researchers subsequently detected *NT5C2* alterations in five of 61 additional specimens.[76] All patients harboring those alterations experienced a relapse within 36 months of initial diagnosis. These two studies provide significant insight into the biologic basis of chemotherapy resistance and potential new treatment approaches.

Study reveals new genetic changes in pediatric LGG and low-grade glioneuronal tumors. LGGs are the most common childhood brain tumors, with more than 1,000 new patient cases diagnosed in the United States each year. LGGs can form in various parts of the brain or spinal cord, and they typically grow slowly. For patients with tumors that can be completely removed through surgery, the 10-year survival rate is approximately 90%. Tumors that are not amenable to surgery are typically treated with combination chemotherapy and radiation.

So far, little has been known about molecular abnormalities that drive LGG formation. A new genomic study published this year, however, identifies a range of genetic alterations that may contribute to the development of these tumors as well as the more rare subtype, low-grade glioneuronal tumors.[77] New alterations involving *BRAF*, *RAF1*, *FGFR1*, *MYB*, *MYBL1*, *H3F3A*, and *ATRX* genes were detected in 39 of 151 tumor specimens. The findings point to potential new therapeutic targets across the full spectrum of this most common brain tumor in children. For example, BRAF inhibitors have been used successfully in adult cancers, especially melanoma.

SARCOMA

Sarcoma encompasses approximately 50 different cancers that arise from cartilage, muscle, fat, blood vessels, or other connective or supportive tissue. The disease is especially complex, because each of these sarcoma subtypes is biologically and molecularly distinct, and these tumors are generally resistant to chemotherapy. Because it is a rare disease—accounting for just 1% of cancers in adults—research funding for new sarcoma treatments is rather limited, and progress against this disease has been difficult. This year brought three treatment advances that will improve the care of patients with a form of sarcoma called GISTs and soft tissue sarcoma. One study demonstrated circulating tumor DNA collected from patients' blood may help guide targeted treatment selection, potentially sparing patients with GISTs of the need for repeated, painful tumor biopsies. A randomized study showed that patients with GISTs whose disease progressed despite standard treatment with imatinib and sunitinib may benefit from a second course of imatinib treatment. Findings from a phase III study indicate that doxorubicin alone is as beneficial as, but less toxic than, doxorubicin plus ifosfamide as first-line therapy for patients with advanced soft tissue sarcoma. In addition, the FDA approved two new drugs for sarcoma: regorafenib for patients with advanced, inoperable, treatment-resistant GISTs and denosumab for patients with giant-cell tumor of the bone (GCTB). This adds new agents to the growing collection of targeted drugs now available for the treatment of this disease.

Advances

Circulating tumor DNA is a potential alternative to tumor biopsy for analyzing GIST markers, which may also predict treatment response. Determining the genetic makeup of patients' tumors allows for selection of optimal targeted therapy for patients with a range of cancers. This year, researchers reported that analysis of markers in tumor DNA collected from patients' blood may reduce or eliminate the need for painful, repeated tissue biopsies in patients with treatment-resistant GISTs and that such markers are tied to treatment response.[78]

Circulating tumor DNA and tumor tissue DNA were collected from 163 and 102 patients, respectively, and analyzed for mutations. Mutations were detected in *KIT*, *PDGFRA*, and *KRAS* genes. Researchers demonstrated that the types and frequencies of genetic changes were similar in circulating tumor DNA and in DNA extracted from tumor biopsy specimens. For example, *KIT* gene mutations were detected in 58% of circulating tumor DNA samples and 66% of tumor samples.

Certain mutations detected in tumor samples and circulating DNA samples were associated with better response to targeted treatments. Specifically, patients with specific *KIT* mutations responded better to imatinib than to sunitinib. The only patient with a *KRAS* mutation did not respond well to sunitinib, imatinib, or regorafenib. These findings indicate that for those patients in whom circulating DNA can be detected, this method of *KIT* analysis provides a noninvasive alternative to biopsy and can potentially be used for prognosis and selection of optimal therapy.

Study confirms re-treatment with imatinib offers modest gains for patients with advanced GISTs. Patients with GISTs whose disease worsens after first-line treatment with the standard TKI imatinib or sunitinib often receive a second round of treatment with imatinib, because GISTs progress quickly after all TKIs are discontinued. This year, researchers from Seoul, South Korea, reported results of the first study to our knowledge to formally evaluate the efficacy of re-treatment with imatinib.[79]

A total of 81 patients with metastatic and/or inoperable GISTs were randomly assigned to receive best supportive care and imatinib or best supportive care and placebo. All patients enrolled had disease that responded to but eventually progressed during first-line imatinib therapy and were resistant to sunitinib. Regorafenib was not available to this patient population. Patients were allowed to cross over from the placebo group to the imatinib group on disease progression. Researchers observed small but significant improvements in median progression-free survival (1.8 *v* 0.9 months). The median overall survival was 7.5 months in the placebo group and 8.2 months in the imatinib group. The findings provide evidence that resumption of imatinib in patients with GISTs whose cancer progressed with prior imatinib and sunitinib therapy can result in a clinical benefit when no other treatment options are available.

In patients with soft tissue sarcoma, treatment with doxorubicin in combination with intensive ifosfamide does not improve survival compared with doxorubicin alone. Findings from nonrandomized studies have suggested that adding high-dose ifosfamide to standard doxorubicin chemotherapy may improve treatment outcomes for patients with soft tissue sarcoma. However, results of a European randomized phase III study demonstrate that this combination regimen does not improve overall survival over standard doxorubicin alone and is associated with more adverse effects.[80]

In the study, 455 patients with locally advanced or metastatic soft tissue sarcoma were randomly assigned to first-line treatment with doxorubicin alone or doxorubicin plus ifosfamide. There were no differences in overall survival rates at 2 years (31% in doxorubicin arm *v* 28% in combination arm). The progression-free survival, however, was significantly longer in the combination arm (7.4 months) compared with the single-agent arm (4.6 months). Response rates (complete and partial) were also greater with the combination as compared with the single agent (26% *v* 14%). However, serious adverse effects, including anemia (35% *v* 5%) and febrile neutropenia (46% *v* 14%), were more common in the combination arm.

This study indicates that treatment with this intensive combination regimen should not be routinely used in the palliative setting, thus sparing patients from higher-toxicity therapy that will not improve their survival. The findings reinforce that doxorubicin alone should remain the control-arm treatment for future randomized studies of first-line chemotherapy in patients with advanced soft tissue sarcoma.

FDA approves regorafenib for patients with advanced, inoperable, and treatment-resistant GISTs. In February, the FDA approved regorafenib for treatment of patients with advanced GISTs that cannot be surgically removed and have progressed despite treatment with other FDA-approved drugs for this disease.[81] Regorafenib blocks several enzymes that promote cancer growth. The safety and effectiveness of regorafenib for this use were evaluated in a randomized, placebo-controlled, clinical study of 199 patients with GISTs that could not be surgically removed and that progressed after treatment with imatinib or sunitinib. Progression-free survival was nearly four-fold longer in the regorafenib group than in the placebo group (4.8 *v* 0.9 months). The approval provides an important new treatment option for patients with GISTs resistant to other available therapies.

FDA approves denosumab for patients with GCTB. In June, the FDA approved denosumab for treatment of patients with GCTB, a rare and usually noncancerous tumor.[82] In most cases, GCTB does not spread to other parts of the body but destroys normal bone as it grows, causing pain, limited range of motion, and bone fractures. Rarely, GCTB can transform into a cancerous tumor and spread to the lungs. Denosumab is an antibody that targets a protein essential for maintenance of healthy bone. The safety and effectiveness of denosumab for GCTB were established in two clinical trials that enrolled a total of 305 adult or adolescent patients, of whom 47 experienced tumor shrinkage. Denosumab is approved for use in patients whose tumors cannot be surgically removed or in cases where surgery may result in loss of limb or joint removal. This approval provides a new treatment option for such patients.

PATIENT AND SURVIVOR CARE

Research on patient and survivor care helps address a wide range of challenges, including optimal treatment selection, assessment of short- and long-term risks of treatments, symptom control, and general improvement in quality of life.

An important study this year clarifies the effectiveness of intravenous calcium and magnesium for preventing sensory neurotoxicity, a debilitating adverse effect of oxaliplatin chemotherapy. Another study provides the first prospective evidence for the benefit of yearly breast MRI screening in addition to mammography for women treated with chest radiation for Hodgkin lymphoma. Finally, a large survey of US adolescent and young adult (AYA) patients with cancer provides new insights into the detrimental effects of cancer on various aspects of QOL and identifies particularly vulnerable subgroups. The findings will inform future research and development of targeted interventions for this age group.

Advances

Intravenous calcium and magnesium do not reduce oxaliplatin-induced sensory neurotoxicity. Oxaliplatin chemotherapy is commonly used in adjuvant and palliative treatment regimens for colorectal cancer, such as FOLFOX. Unfortunately, oxaliplatin sometimes triggers sensory neurotoxicity, causing some patients to stop therapy early. Symptoms of acute (temporary) sensory neurotoxicity include jaw spasms, muscle cramps, and stiffness in hands or feet. Chronic sensory neurotoxicity manifests as numbness and tingling in hands and feet and burning/shooting pain.

A previous randomized study suggested that infusion of calcium and magnesium may reduce oxaliplatin-induced sensory neuropathy in patients with colorectal cancer. However, some physicians remained skeptical about the findings because the study was small and terminated prematurely. This year, researchers reported results of a larger, placebo-controlled study, showing that calcium and magnesium infusion does not protect patients against oxaliplatin-related sensory neurotoxicity (this study was funded in part by a grant from NIH).[83] In the study, 353 patients with colorectal cancer undergoing FOLFOX therapy were randomly assigned to one of three arms to receive: intravenous calcium and magnesium before and after oxaliplatin, calcium and magnesium before oxaliplatin and placebo after oxaliplatin, or placebo before and after oxaliplatin. There were no significant differences in neuropathy scores among study arms. The findings should resolve the debate and spare patients from this ineffective and time-consuming treatment.

Study provides evidence supporting dual breast cancer screening with MRI and mammography in survivors of Hodgkin lymphoma. Women who undergo chest radiation to treat Hodgkin lymphoma at a young age have a significantly increased risk for developing breast cancer later in life. It is estimated that a woman treated for Hodgkin lymphoma at age 25 years has a 10.7% risk of developing breast cancer by the age of 35 years and a 24.6% risk by the age of 45 years. This risk is comparable to that of *BRCA1* and *BRCA2* mutation carriers.

In women with a family history of or genetic predisposition for breast cancer, breast MRI has been shown to be more sensitive than mammography and better at detecting early-stage disease. Oncology and radiology organizations also currently recommend this approach for women with a history of chest radiation for Hodgkin lymphoma, but these recommendations are largely based on consensus expert opinion rather than clinical evidence.

This year, researchers reported results from the first prospective clinical trial to our knowledge to compare mammography and breast MRI in this patient population.[84] The study enrolled 148 women age 35 years or younger who had undergone chest radiation for Hodgkin lymphoma more than 8 years earlier. The women received yearly mammography and breast MRI screening for a period of 3 years. On the basis of the results of the screening, a total of 63 biopsies were performed, 18 of which were positive for breast cancer. Of those, five malignancies were detected by MRI alone, six by mammography only, and seven by both modalities. Four of the five patient cases detected by MRI and missed by mammography were early stage (preinvasive). Although this study did not find MRI to be more sensitive than mammography overall in the Hodgkin lymphoma survivor population, the fact that MRI may help detect more early-stage patient cases supports the use of MRI screening in addition to mammography in this group of women. More research is needed to identify a subgroup of patients for whom dual screening would be particularly beneficial. A randomized clinical trial, which would provide the most definitive evidence, would be difficult to conduct in this small population of patients.

Study helps identify vulnerable AYA cancer survivors needing additional support. In the United States, approximately 70,000 AYAs are diagnosed with cancer each year, and this number is growing. Although outcomes are typically poorer overall for patients in this age group than among younger or older patients, AYAs with cancer also face unique challenges, such as major life transitions (eg, completing education, moving out of the parental home, and becoming financially independent) and require specific psychosocial support.

To gain more insight into this problem, researchers surveyed 523 AYA patients with cancer, age 15 to 39 years at diagnosis. The findings of the survey—called the AYA HOPE survey—were reported this year (this study was funded in part by a grant from NIH).[85] Overall, AYAs with cancer had significantly worse HRQOL compared with published data on general and healthy populations of similar age. HRQOL was particularly affected among patients currently undergoing treatment, with current or recent symptoms, or lacking health insurance. Specifically, researchers observed: Hispanic patients, patients with sarcoma, and those with a high school or lower education level reported worse physical health; teenage patients reported worse physical and work/school functioning compared with older patients; and unmarried patients reported worse mental health.

The findings from this study suggest that cancer in AYAs has a major impact on fatigue, physical and social functioning, limitations in emotional roles, and mental health. Researchers concluded that particular attention needs to be paid to the vulnerable subgroups identified by this study. More research is also needed on long-term effects of cancer on HRQOL outcomes to inform appropriate interventions for AYAs.

QUALITY CANCER CARE

Ensuring consistent delivery of high-quality cancer care to patients is among the highest priorities in oncology practice and policy today. Efforts to understand the unique characteristics of all patients—including not only their biology but also their values and priorities about treatment—can assure personalized and appropriate shared decision making.

Toward these goals, a host of tools have been developed and tested, including clinical practice guidelines, decision aids, and educational programs. Major strides have been made in improving QOL and enhancing communication between providers and patients. However, there is still progress to be made.

Several studies this past year evaluated processes in oncology care delivery where system improvements can enhance the ability to provide value to patients. Evaluations of clinical practice guideline use found that guideline adherence improves outcomes, but often guidelines are not followed. Off-label use of chemotherapy is widespread and accounts for substantial US national spending, although approximately half of this use is consistent with guideline recommendations. Hospice services, widely acknowledged in past years as beneficial to patients with advanced cancers, are underused in underserved populations. Across patients, the goals of care are often misunderstood, suggesting the need for educational and communication tools. Organizations have released prototypes of new health information technologies that promise to transform patient care in the future.

Advances

Adherence to antibiotic guidelines improves outcomes in febrile neutropenia. Adherence to guideline-recommended antibiotic use was measured among 25,000 patients hospitalized with febrile neutropenia between 2000 and 2010 (this study was funded in part by a grant from NIH).[86] Febrile neutropenia occurs when patients develop fever along with abnormally low levels of WBCs called neutrophils. Guideline-recommended antibiotics were administered to 79% of patients, empiric vancomycin (which is not recommended generally) to 37%, and GCSF (which also is not generally recommended and increases cost) to 63% during the 10-year period. Vancomycin use actually increased during the observation period from 17% to 55%, whereas GCSF use decreased from 73% to 55%. Among low-risk patients with febrile neutropenia, prompt initiation of guideline-based antibiotics significantly decreased discharge to a nursing facility and improved survival. This study demonstrates that guideline-adherent practice is associated with better outcomes. Such adherence is reasonable as a quality indicator and might be enhanced through educational programs and automated reminders in electronic order entry systems.

Many clinical practice guidelines do not adhere to national methodologic standards. Cancer clinical practice guidelines produced between 2005 and 2010 were analyzed for compliance with recently published methodologic standards from the Institute of Medicine.[87] Only half of guidelines addressed conflicts of interest, most did not comply with standards for inclusion of patient and public involvement in the development or review process, and most did not specify a process for updating. On the positive side, many did comply with standards for transparency, articulation of recommendations, and use of external review. Specific developers of guidelines were not compared with one another. This analysis suggests that producers of guidelines and users of guidelines should pay heed to methodologic considerations and similarly that the Institute of Medicine recommendations should be revisited to assess if they are realistic or should be revised.

Off-label use accounts for one third of chemotherapy prescribing but is guideline supported only half the time. The extent of off-label chemotherapy use in a group of community oncology practices was evaluated, including cost and adherence to National Comprehensive Cancer Network (NCCN) guidelines.[88] Off-label use accounts for 30% of prescribing, with approximately half of off-label use adhering to NCCN guidelines. Total national spending on chemotherapy amounts to $12 billion, of which off-label use accounts for $4.5 billion (within which $2.5 billion accounts for drugs that are not NCCN supported). Concerns have been raised by policymakers, payers, and patient advocacy groups about the cost and safety of off-label chemotherapy use in the United States. Future work is recommended to evaluate these non–NCCN-supported approaches to evaluate how often their use is inappropriate or potentially harmful.

Hospice services are underused by Medicaid patients. The value of hospice services for patients with advanced cancers is increasingly recognized, with prior studies showing benefits in survival and QOL among patients with lung cancer. ASCO previously issued a provisional clinical opinion recommending the expansion of palliative care services for patients with advanced cancers.[89] A study comparing rates of hospice use in California and New York for patients enrolled in Medicare versus Medicaid found substantially lower use of hospice in Medicaid programs (this study was funded in part by a grant from NIH).[90] Approximately 50% of patients with stage IV lung cancer in Medicare programs used hospice, compared with only approximately one quarter of those in Medicaid. Most Medicaid patient deaths occurred in acute-care facilities (which increases cost) or at home with no hospice (which increases morbidity). The study demonstrates the need to develop infrastructure that offers hospice services to patients in both Medicare and Medicaid programs, particularly the latter.

When patients are faced with a diagnosis of advanced cancer, ASCO recommends that physicians initiate candid discussions soon after the diagnosis about the full range of treatment options, including palliative therapies. Ensuring that people live their final days in comfort and dignity is a key responsibility of cancer care providers. ASCO recommendations state that patients have a right to make informed choices about their care, and oncologists must lead the way in discussing the full range of care options to ensure that patients' choices are honored.

ASCO offers a guide to help patients with advanced cancer broach difficult conversations about their prognosis, treatment, and palliative care options with their physicians (www.cancer.net/advancedcancer).

Patients often do not understand the goals of cancer treatment. Effectively communicating the goals of treatment to patients with

advanced cancers is an essential component of oncology care. A study involving more than 1,000 patients nationally, as part of CanCORS (Cancer Care Outcomes Research and Surveillance), found that approximately 70% of patients with lung cancer and 80% of patients with colorectal cancer did not understand that they had incurable disease and that the goal of treatment was palliation (this study was funded in part by a grant from NIH).[91] It is not clear why there is such a substantial disconnect in patients' understanding of treatment goals, but this raises questions about how information is communicated and whether patients are adequately informed to make treatment decisions currently. Nonwhite and Hispanic patients have worse levels of understanding, although educational level, functional status, and degree of patient participation in decision making do not affect results.

New health information technologies harness big data to support clinical decisions. There is growing interest to improve quality of care by aggregating and rapidly analyzing large data sets. Linking electronic health records, improving how we use practice guidelines, and better understanding the patient perspective can enhance how cancer treatments are developed, delivered, and used in clinical practice. It is estimated that the amount of medical information available in medical journals and electronic medical records doubles every 5 years. Several initiatives are underway to develop information technology strategies to rapidly analyze these big data to assist in decision making for the individual patient.

In early 2013, ASCO announced the launch of a prototype for a rapid learning health system called CancerLinQ (more information provided in Policy Perspective: Renewing the Nation's Commitment to Clinical Cancer Research). CancerLinQ is being designed to aggregate and analyze cancer data from many sources (eg, electronic health records, pharmacy records, or imaging data from multiple sources), with the goal to deliver clinical decision support to physicians, provide real-time quality reporting based on established guidelines, and allow data mining to develop new insights and hypotheses. Other organizations are developing related resources, such as the Watson project by IBM, which aims to provide individualized treatment plans based on knowledge gathered from patient cases, practice patterns, guidelines, and published literature.[92] Although nascent, the hope of these and related initiatives is that the quality of available information and standards for care delivery will be improved for all patients.

CANCER DISPARITIES

Although cancer care overall has improved tremendously in recent decades, not all patients have benefited equally from advances in cancer prevention, screening, and treatment. The causes of disparities are complex, ranging from socioeconomic to biologic factors. This year brought several important advances in the effort to reduce cancer disparities.

A landmark study in India demonstrated that a simple, low-cost cervical cancer screening strategy delivered by community-based primary health workers may substantially reduce the cervical cancer burden in India and worldwide. One study reported on a statewide screening and treatment program in Delaware that dramatically reduced colorectal cancer incidence and mortality rates for African Americans in a single decade. Another study reported that a patient navigation program in Ohio had an impressive impact on reducing the time to diagnosis for low-income patients with abnormal findings on cancer screening tests or cancer-related symptoms. A large-scale genomic analysis identified biologic reasons underlying the survival disparity for African American children with neuroblastoma. Finally, new research results suggest that current recommendations for active surveillance may not be adequate for some African American men with low-risk prostate cancer.

Advances

Affordable, easily implementable cervical cancer screening strategy promises to save thousands of women in India and other low-resource countries. Since the introduction of routine Pap screening, cervical cancer incidence and death rates have been reduced by 80% in the developed world. However, cervical cancer is still the leading cause of cancer death among women in many low-resource countries, where there is little or no access to Pap screening because of a lack of laboratory facilities and medical professionals. In India alone, cervical cancer claims more than 77,000 lives every year. Results of a large clinical trial released this year point to the first cost-effective and widely implementable screening strategy, which could ultimately reduce cervical cancer deaths in India by one third (this study was funded in part by a grant from NIH).[93]

Researchers used a simple, low-cost screening method, known as visual inspection with acetic acid (VIA), which involves applying vinegar to the cervix using a cotton swab. After 60 seconds, the cervix is examined with the naked eye. Precancerous tissue turns white when vinegar is applied, whereas healthy tissue does not change color. VIA was performed by primary health workers—young women from local communities with at least a 10th grade education—who are essentially the only health professionals available to deliver VIA screening in remote and rural parts of India. The health workers received 4 weeks of intensive training at the beginning of the study.

Women with no prior history of cancer were randomly assigned to biennial screening with VIA (75,360 women) or no screening (control group; 76,178 women). Both groups received at least one round of education about cervical cancer and screening. All study participants were offered free cervical cancer treatment, if diagnosed. VIA screening resulted in a 31% reduction in cervical cancer death rates (from 16.2 per 100,000 to 11.1 per 100,000). In addition, more women in the screening group were diagnosed with earlier-stage disease than in the control group.

The findings represent an important step forward in reducing the cervical cancer burden in India and other low-resource countries. The researchers estimated that the strategy may lead to the prevention of 22,000 cervical cancer deaths every year in India and more than 73,000 worldwide.

Innovative Delaware cancer screening and treatment program dramatically reduces colorectal cancer disparities among African Americans. Colorectal cancer is the third most common cancer in the United States, with more than 102,000 new patient cases diagnosed each year. However, it remains one of the few cancers highly preventable through routine screening. However, African Americans continue to have worse outcomes from this disease compared with other ethnic groups. There are multiple putative reasons for this disparity, including lower rates of screening and lower rates of follow-up for abnormalities found on screening among African Americans.

A study published this year reported on a Delaware program that has nearly eliminated statewide disparities in outcomes for African American patients with colorectal cancer, without increasing overall

health care costs.[94] In 2002, the Delaware Cancer Consortium launched a statewide, comprehensive colorectal cancer screening program that included patient navigation, case management, reimbursement for colorectal cancer screening, and up to 2 years of cancer treatment for the uninsured and underinsured. The overall colorectal cancer screening (with colonoscopy or sigmoidoscopy) rate for Delaware residents age 50 years or older increased from 57% in 2001 to 74% in 2009. In the same time period, the screening rate for African Americans increased from 48% to 74%, equal to the rate among whites. Cancer incidence rates declined for all groups but more so for African Americans (from 66.99 per 100,000 to 44.3 per 100,000). The colorectal cancer mortality rate declined 42% for African Americans, resulting in a rate almost equal to that among whites. In addition, the percentage of cancers diagnosed at an early stage for African Americans increased from 15% in 2001 to 50% in 2009. Researchers estimated that the state program saved approximately $8.5 million annually from reduced incidence of cancers that would have required aggressive therapy. The success of this comprehensive program may serve as a model for other states for eliminating disparities in colorectal cancer.

Patient navigation program reduces health disparities for low-income patients with abnormal cancer screening tests or symptoms. Patient navigation—the process by which an individual guides a patient through the complex cancer care system to help ensure timely diagnosis and treatment—was introduced in the early 1990s as an intervention for reducing health care disparities. There are many models of patient navigation, but few have been carefully evaluated. Last year, researchers reported encouraging results of a study that assessed the Ohio American Cancer Society model of patient navigation (the Ohio Patient Navigation Research Program) in terms of its ability to reduce time to diagnostic resolution among persons with abnormal breast, cervical, or colorectal cancer screening tests or symptoms.[95]

A total of 862 patients from 18 clinics were randomly assigned to patient navigation or usual care. The time periods between detection of an abnormal finding and establishing a diagnosis were documented from medical record review. The diagnostic resolution rate (time to establishing a diagnosis or ruling one out) at 15 months was 65% higher in the patient navigation arm compared with the usual care arm. The greatest impact was seen in the first 6 months among low-income patients. The findings show that patient navigation, if performed in a standardized way, can help reduce the time to resolution of abnormal tests or symptoms and thereby potentially improve a range of cancer-related outcomes, but more research is needed to assess the impact of patient navigation on clinical outcomes. The study also provides evidence for how future studies can be refined to evaluate patient navigation programs in the most cost-effective and patient-specific way.

Genomic analysis identifies biologic causes of survival disparities among African American patients with neuroblastoma. Neuroblastoma is a cancer that begins in the nerve tissue of adrenal glands. It is one of the most common types of childhood cancer, with approximately 650 new patient cases per year in the United States. African American patients with neuroblastoma are more likely to be diagnosed with high-risk disease and have worse outcomes than white patients. Little is known about the underlying causes of racial and ethnic disparities in neuroblastoma survival. A genomic study published last year provides insight into the relationship between genetic variations and ethnic disparities in neuroblastoma outcomes.[96]

In this study, 2,709 patients with neuroblastoma were classified by their genomic ethnic ancestry (European, African, Hispanic, and Asian). Researchers confirmed that African ancestry was associated with high-risk neuroblastoma and shorter event-free survival (ie, length of time after patient completes treatment and recurrence of cancer or symptoms). One specific genetic variant, *SPAG16*, was found to be significantly associated with high-risk disease in patients of European and African ancestry and was more common among African American patients. These results indicate that a common genetic variant contributes to ethnic disparities in neuroblastoma survival. The study affirms the value of genomic profiling in identifying potential biologic mechanisms behind observed cancer survival differences, which may ultimately be used to develop new, more effective therapies.

Study suggests that current recommendations for active surveillance may not be adequate for African Americans with low-risk prostate cancer. African American men have higher incidence of prostate cancer and worse outcomes after initial treatment, regardless of cancer stage. Overall, up to 19% of men with prostate cancer have low-risk disease at diagnosis.

Current NCCN guidelines for men with low-risk prostate cancer and life expectancy of fewer than 20 years recommend active surveillance (watchful waiting) instead of treatment for men of all races, because it reduces the risk of overtreatment of slow-growing cancers while allowing time for intervention if cancer gets worse. These recommendations, however, are based on patient cohorts with small numbers of minority men and therefore may not be ideally suited for minority populations. A retrospective study, published this year, examined actual pathology reports after prostate removal surgery for 1,473 white and 256 African American men who met NCCN criteria for low-risk disease (this study was funded in part by a grant from NIH).[97]

Researchers found that African Americans had poorer cancer-related outcomes after prostate surgery compared with white men. In addition, they were more likely to have their cancer grade (Gleason score) upgraded after surgery than white men, higher rates of cancer spread beyond the prostate, and higher risk of biochemical recurrence (return of elevated PSA levels after surgery). After a median follow-up period of 3 years, however, there were no racial differences in metastasis-free, cancer-specific, or overall survival. Although it is not clear whether these results will lead to a modification of the NCCN guidelines, more research is needed to address race-specific recommendations for entering active surveillance. The study underscores the importance of having adequate racial and ethnic diversity in future study cohorts so that guidelines are applicable across racial and ethnic lines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Nicholas J. Vogelzang, US Oncology (C) **Consultant or Advisory Role:** Sylvia Adams, GlaxoSmithKline (C); Marcia S. Brose, AstraZeneca (C), Bayer Schering Pharma (C), Bristol-Myers Squibb (C), Exelixis (C), Onyx Pharmaceuticals (C), Eisai (C); Mark R. Gilbert, EMD Serono (C), Merck (C), Genentech (C), Bristol-Meyers Squibb (C), Abbott Laboratories (C), Novartis (C); Mark G. Kris, BIND Biosciences (C), Boehringer Ingelheim (C), Chugai Pharmaceutical (C), Clovis Oncology (C), Covidien (C), Millennium Pharmaceuticals (C), Genentech (C), Pfizer (C), Threshold Pharmaceuticals (C), ARIAD Pharmaceuticals (C); John L. Marshall, Amgen (C), Genentech (C), Bayer HealthCare Pharmaceuticals (C), Onyx Pharmaceuticals (C); Blasé Polite, Quintiles (C); Gary K. Schwartz, Novartis (C), Pfizer (C), Tragara Pharmaceuticals (C); Nicholas J. Vogelzang, Novartis (C), Dendreon (C), GlaxoSmithKline (C), Pfizer (C), Bayer HealthCare Pharmaceuticals (C), Astellas Pharma (C), Janssen Pharmaceuticals (C) **Stock Ownership:** None **Honoraria:** Marcia S. Brose, Onyx Pharmaceuticals, Bayer Schering Pharma; Mark R. Gilbert, Merck, Genentech, EMD Serono; Mark G. Kris, Boehringer Ingelheim, Novartis; John L. Marshall, Amgen, Genentech, Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals; Steven J. O'Day, Bristol-Myers Squibb, Merck, Roche; Blasé Polite, Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals **Research Funding:** Marcia S. Brose, Bayer Schering Pharma, Exelixis, ImClone Systems, Novartis, Plexxikon, Roche, Genentech, Onyx Pharmaceuticals, Eisai; Mark R. Gilbert, GlaxoSmithKline, Genentech, Merck; Mark G. Kris, Boehringer Ingelheim, Pfizer, PUMA; John L. Marshall, Boehringer Ingelheim, Bristol-Myers Squibb, Roche, sanofi-aventis, Pfizer; Steven J. O'Day, Merck, Novartis, Bristol-Myers Squibb; Blasé Polite, Merck; Gary K. Schwartz, Novartis; Sunil Sharma, Novartis, Pfizer, GlaxoSmithKline, Millennium Pharmaceuticals; Bruce J. Roth, Exelixis, Medivation, Oncogenix **Expert Testimony:** None **Patents:** William L. Carroll **Other Remuneration:** Marcos de Lima, Mesoblast (travel support)

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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Acknowledgment

We thank Peter Bach, MD, MAPP; Ezra Cohen, MD; Susan M. Domchek, MD; Robert Dreicer, MD; Lee M. Ellis, MD; Patricia Ganz, MD; Sergio A. Giralt, MD; Heinz-Josef Lenz, MD, FACP; David I. Quinn, MBBS, PhD, FRACP; Charles M. Rudin, MD, PhD; Christopher W. Ryan, MD; Julian C. Schink, MD; Jeffrey A. Sosman, MD; Debu Tripathy, MD; Christina I. Tsien, MD; and Clare J. Twist, MD, for their help in selecting research advances to include in this report.