Editors

EXECUTIVE EDITORS
Gregory Masters, MD, FACP, FASCO, Helen F. Graham Cancer Center
Jyoti D. Patel, MD, Northwestern University

SPECIALTY EDITORS
Howard H. Bailey, MD, University of Wisconsin Hospital and Clinics
Marcia S. Brose, MD, PhD, University of Pennsylvania Abramson Cancer Center
Harold Burstein, MD, PhD, FASCO, Dana Farber Cancer Institute
Lisa Diller, MD, Dana Farber Cancer Institute
Don S. Dizon, MD, Massachusetts General Hospital
Howard A. Fine, MD, New York University Langone Medical Center
Gregory P. Kalemkerian, MD, University of Michigan Health System
Mark Moasser, MD, University of California San Francisco School of Medicine
Michael N. Neuss, MD, Vanderbilt-Ingram Cancer Center
Steven J. O'Day, MD, Beverly Hills Health Center
Olatoyosi Odenike, MD, University of Chicago
Charles J. Ryan, MD, University of California San Francisco
Gary K. Schwartz, MD, Columbia University Medical Center
Alan P. Venook, MD, University of California San Francisco
Sandra L. Wong, MD, University of Michigan

ASCO PRESIDENT
Peter Paul Yu, MD, FACP, FASCO, Palo Alto Medical Foundation

ASCO PRESIDENT-ELECT
Julie M. Vose, MD, MBA, FASCO, University of Nebraska Medical Center

ASCO CHIEF EXECUTIVE OFFICER
Allen S. Lichter, MD, FASCO

ASCO CHIEF MEDICAL OFFICER
Richard Schilsky, MD, FACP, FASCO
# CLINICAL CANCER ADVANCES 2015

**PRESIDENT’S LETTER** .................................................................................................................. 2

**EXECUTIVE SUMMARY** .............................................................................................................. 3

**ADVANCE OF THE YEAR** .............................................................................................................. 8

**ADVANCES IN PREVENTION AND SCREENING** ........................................................................ 11

**ADVANCES IN TREATMENT** ........................................................................................................ 14
  - Combination Therapy .................................................................................................................. 14
  - Targeted Therapy ......................................................................................................................... 15
  - Immunotherapy ............................................................................................................................ 17

**ADVANCES IN PATIENT CARE** .................................................................................................... 20

**ADVANCES IN TUMOR BIOLOGY** .................................................................................................. 24

**HOW FAR WE’VE COME: A DECADE IN REVIEW** .................................................................... 28

**THE 10-YEAR HORIZON** ............................................................................................................... 34

**APPENDIX: ADDITIONAL NOTABLE ADVANCES** ...................................................................... 37

**REFERENCES** .................................................................................................................................. 40

**GLOSSARY** ..................................................................................................................................... 42

**ASCO RESOURCES** ......................................................................................................................... 45
Ten years ago, the American Society of Clinical Oncology (ASCO) first announced the year’s biggest cancer research advances in the inaugural issue of Clinical Cancer Advances. Looking back at a decade of reports, it is exciting to see how transformative those years have been. Clinical Cancer Advances has documented the dawn of precision cancer medicine, the advent of effective new cancer prevention strategies, major improvements in the management of treatment adverse effects, and many other critical advances.

Although all research achievements in this annual report are important, it often seems that one rises above the rest, whether because of its tremendous impact on patient care, its pioneering science, or its cross-cutting significance. So, as Clinical Cancer Advances enters its second decade, we are highlighting the year’s standout achievement with a new feature: ASCO’s Advance of the Year.

For 2015, ASCO’s Advance of the Year is the transformation of treatment for chronic lymphocytic leukemia (CLL). CLL is the most common adult leukemia, and it disproportionately affects the elderly. Yet, until the past year, many older patients were without treatment options, because existing therapies caused severe, even life-threatening, adverse effects for those who were frail or had other major health problems. But 2014 brought stunning new possibilities with the introduction of four new drugs that are both highly effective and far easier on patients. These therapies have filled a major unmet need for those with newly diagnosed or resistant disease, making treatment—and remission—possible for more patients than ever.

This advance also speaks to the importance of value in cancer care. Value is a major focus for ASCO, because clinical benefit, toxicity, and cost must all be factored into shared decision making to determine the best treatment options for patients. ASCO is working to develop a physician-guided tool that will help patients evaluate new treatment options such as those highlighted in this report.

Another big change with this year’s report is that clinical research advances are ordered thematically, rather than by disease area. And within each thematic section, the report not only highlights recent advances, but identifies emerging trends as well. Clinical Cancer Advances also continues its emphasis on the unique and vital role of federally funded cancer research. In this year’s report, almost a third of the studies featured were supported by federal research dollars. One featured study revealed one of the biggest survival gains ever observed in men with advanced prostate cancer. Another found a simple, affordable new way to preserve fertility for women with early-stage breast cancer, while others helped deliver new therapies for hard-to-treat diseases like brain cancer. For more than 40 years, the National Cancer Institute has funded many more clinical studies like these, answering critical cancer care questions that might otherwise have been ignored.

Despite these achievements, federal investment in research has stagnated over the past 10 years, resulting in a 23% loss in purchasing power for the National Institutes of Health. In practical terms, this means promising research is going unfunded, new studies are being scaled back, fewer patients have the opportunity to participate in clinical trials, and future meaningful advances against cancer may be few and far between—unless our nation renews its commitment to fighting cancer.

Advances in health information technology (IT)—including projects like ASCO’s CancerLinQ™—can help overcome some of these challenges. Such technologies will enable us to capture data and learn from every patient, ultimately helping make clinical trials faster and smarter. But we cannot count on health IT alone.

As with any major anniversary, we are reminded that history judges us by our achievements. In oncology, Clinical Cancer Advances documents a decade of remarkable research advances, with progress building on progress over time. Now is the time to increase our nation’s investment to ensure we can build on these advances well into the future.

Peter Paul Yu, MD, FACP, FASCO
President
American Society of Clinical Oncology
Executive Summary

Clinical cancer research has yielded tremendous gains, leading to longer survival and better quality of life for the more than half a million Americans diagnosed with the disease each year. Great strides in cancer prevention have further decreased the burden of the disease. Cancer death rates in the United States have declined 20% from their peak in 1991 (215.1 per 100,000 population) to 2010 (171.8 per 100,000 population).1 Today, there are a record 14.5 million cancer survivors alive in the United States.

Now in its 10th year, the American Society of Clinical Oncology’s (ASCO’s) report, “Clinical Cancer Advances 2015: An Annual Report on Progress Against Cancer,” for the first time identifies ASCO’s Advance of the Year. Other new features in this special anniversary issue include: A Decade in Review, which recounts the biggest changes in cancer care since this report’s introduction; The 10-Year Horizon, which previews trends likely to shape the next decade of cancer care; and a special series of research, which highlights exciting new leads for treatment of rare cancers.

In keeping with this report’s tradition, we explore the clinical advances of the prior year that stand to make the biggest impact on improving cancer prevention, treatment, and care. The following is a summary of some of the most exciting trends and developments.

ADVANCE OF THE YEAR: GAINS IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

In just over a year’s time, treatment for chronic lymphocytic leukemia (CLL), the most common form of adult leukemia, was transformed through the approval of four new therapy options. All the new treatments are easier to tolerate than prior therapies, making treatment possible for more patients than ever—especially elderly patients who account for the majority of patients with CLL and had urgently needed new, less toxic options.

For previously untreated patients who were unable to tolerate the adverse effects of standard CLL treatments, the two different immunotherapy drugs, obinutuzumab and ofatumumab, given in combination with the standard chemotherapy chlorambucil, delay disease progression by roughly a year.

And there is also good news for patients with previously treated CLL that has become resistant to standard treatment or relapsed. New targeted drugs, ibrutinib and idelalisib, which block different molecular pathways that control leukemia growth, are the first effective therapies for these patients. According to striking early clinical trial results, these drugs have the potential to transform CLL therapy, potentially eliminating the need for chemotherapy, the adverse effects of which are too difficult to bear for many elderly patients with CLL.

PRECISION MEDICINE RESEARCH BRINGS NEW THERAPIES TARGETING IMMUNE SYSTEM AND CANCER CELLS

Once a distant goal, precision medicine—an approach where treatments are matched to the genetic makeup of the patient and his or her tumor—is a common strategy for many patients with cancer today. Precision medicine allows
for better treatment outcomes and fewer adverse effects compared with other approaches, such as chemotherapy. This new reality is the fruit of decades of dedicated research on the biology of cancer.

From January through October 2014, the US Food and Drug Administration (FDA) approved seven new drugs that target either cancer-driving proteins on the surface of or inside cancer cells or molecules on immune system cells (Table 1). Four new uses for previously approved drugs were also approved. The new approvals bring hope for patients with hard-to-treat types of melanoma and lung, stomach, blood, and cervical cancers.

**GENOMIC DISCOVERIES PROVIDE NEW LEADS FOR CANCER PREVENTION AND THERAPY**

Modern high-throughput technologies provide extensive molecular information on tumors, which is analyzed to gain a deeper understanding of genetic factors that trigger and sustain cancer growth. This ever-growing knowledge advances patient care in many different ways—from guiding day-to-day treatment decisions for individual patients to steering the direction of new drug development.

Two recent studies brought intriguing new insights, which may have implications for cancer prevention and therapy in the future. In the first study, researchers were able to link known cancer triggers, such as tobacco and sun tanning, to specific sets of genetic changes or mutational signatures in tumor tissue. In another study, similar mutational signatures were sometimes found in entirely different types of cancer. This finding suggests that treatment for a cancer is more dependent on mutations in a tumor than on the organ in which the cancer arises. For example, this may mean that patients with bladder cancer who have a specific mutational

<table>
<thead>
<tr>
<th>TABLE 1. FDA APPROVALS OF ANTICANCER THERAPIES, JANUARY – OCTOBER 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEWLY APPROVED AGENTS</strong></td>
</tr>
<tr>
<td><strong>Generic Name</strong></td>
</tr>
<tr>
<td>Ofatumumab</td>
</tr>
<tr>
<td>Ramucirumab</td>
</tr>
<tr>
<td>Siltuximab</td>
</tr>
<tr>
<td>Ceritinib</td>
</tr>
<tr>
<td>Belinostat</td>
</tr>
<tr>
<td>Idelalisib</td>
</tr>
<tr>
<td>Pembrolizumab</td>
</tr>
</tbody>
</table>

| **NEW USES FOR EXISTING AGENTS**                                |
| **Generic Name** | **Trade Name** | **Indications** | **Drug Target** | **Date of Approval** |
| Trametinib and dabrafenib in combination | Mekinist and Tafinlar | Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation | MEK and BRAF | January 10, 2014 |
| Ibrutinib        | Imbruvica      | CLL | BTK | February 12, 2014 |
| Mercaptopurine   | Purixan        | Oral suspension for ALL as part of a combination regimen | n/a | April 28, 2014 |
| Bevacizumab for intravenous infusion | Avastin        | Metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan | VEGF | August 14, 2014 |

Abbreviations: ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; FDA, US Food and Drug Administration; GEJ, gastroesophageal junction; HDAC, histone deacetylase; IL, interleukin; MCD, multicentric Castleman’s disease; NSCLC, non–small-cell lung cancer; PD-1, programmed death-1; PI3Kδ, phosphatidylinositol 3-kinase; PTCL, peripheral T-cell lymphoma; VEGFR, vascular endothelial growth factor receptor.
signature that is found in lung cancer should be treated more like patients with lung cancer, rather than like other patients with bladder cancer. This potentially has broad applications for our approach to cancer therapy, but more research is needed to confirm this intriguing possibility.

FEDERAL RESEARCH DOLLARS ANSWER KEY QUESTIONS IN CANCER CARE

Much of the progress in this report and in past reports was made possible by federal investment in clinical cancer research. In fact, roughly a third of the advances highlighted in this year’s report were backed in whole or in part by federal funding from the US National Institutes of Health and the National Cancer Institute. Some of the most exciting discoveries include:

- Adding generic chemotherapy to standard advanced prostate cancer treatment yields one of the biggest survival gains ever seen in this disease

ASCO Calls for Increased Federal Investment in Medical Research Innovation

In testimony submitted to the US Senate Committee on Appropriations, 2013 to 2014 ASCO President Clifford A. Hudis, MD, FACP, urged Congress to step up the need for further investment in medical research:

Federal funding in medical research is needed to study topics that the private sector typically doesn’t pursue, such as comparisons of different but already approved drugs, improving the quality and value of patient care, reducing cancer disparities, and developing cancer screening and prevention strategies.

At the same time, the NIH also takes on high-risk, high-reward research that cannot be done at its earliest stages by industry. This often groundbreaking work is many times picked up by the private sector and translated into lifesaving cures and economic growth.

An important consequence of NIH investment in research is that it is also a driving factor in many local economies. Fully 80% of NIH funding is distributed throughout the United States, and it is estimated that every dollar of NIH grant funding creates $2.21 of spending on jobs and businesses in our communities.

Domestically, declining federal funding for clinical trials, coupled with the rising costs of increasingly complex studies, will severely harm the nation’s clinical research enterprise by limiting opportunities for innovation and demoralizing young clinical investigators. As opportunities to develop and lead trials diminish and institutional pressures to generate research funding and clinical revenue continue to grow, young investigators may leave the field of research, or choose to pursue research opportunities in other countries. Not only does this threaten our progress against cancer, but it also diminishes the overall scientific workforce in America.

Because of the incredible scientific opportunities facing us and the current threats to this opportunity, ASCO urges the Committee to provide the necessary investments to the NIH, NCI, and US Food and Drug Administration in fiscal year 2015 to protect innovation. Specially, we offer the following recommendations for FY 2015 funding:

- National Institutes of Health (NIH): $32 billion
- National Cancer Institute (NCI): $5.26 billion
- US Food and Drug Administration (FDA): $2.784 billion

• Adding a generic, low-cost hormone treatment to standard chemotherapy helps preserve fertility of young women with breast cancer undergoing chemotherapy and extend their lives
• Combining standard radiation therapy with chemotherapy adds years of life to patients with a class of brain cancers called low-grade glioma
• Identifying ways to maximize benefits and reduce potential risks from low-dose computed tomography (CT) lung cancer screening
• New, molecularly targeted drugs help overcome treatment resistance in lung cancer

But despite this record of success, the future of the US federal cancer research enterprise faces critical challenges that must be addressed by policymakers, together with the cancer community, so that this pace of research progress can continue, or even accelerate, for the next 10 years (Fig 1).

ABOUT CLINICAL CANCER ADVANCES
ASCO developed this annual report, now in its 10th year, to document the important progress being made in clinical cancer research and to highlight emerging trends in the field. Clinical Cancer Advances serves to outline to the public 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 envisions future directions of cancer research.

The content of Clinical Cancer Advances was developed through a peer-review process, under the direction of an 18-person editorial board comprising prominent oncologists with expertise in a wide range of oncology subspecialties. The editors reviewed research published in peer-reviewed scientific and medical journals and presented at major scientific meetings over a 1-year period (October 2013 to September 2014). The research reviewed in this report covers the full range of clinical research disciplines: prevention, screening, treatment, patient and survivor care, and tumor biology.

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 it is the only organization that encompasses all oncology subspecialties, allowing ASCO members to grow from the professional and personal expertise of their colleagues worldwide and across disciplines. With more than 35,000 members in 100+ countries, ASCO is dedicated to providing the highest-quality resources in education, policy, the pioneering of clinical research, and, above all, advancing the care for patients with cancer. For ASCO information and resources, visit www.asco.org. Cancer information for patients, caregivers, and others interested in learning more is available at www.cancer.net.

The Conquer Cancer Foundation was created by the world’s foremost cancer physicians of ASCO to seek dramatic advances in the prevention, treatment, and cure of all types of cancer. Toward the vision of a world free from the fear of cancer, the foundation works to conquer this disease by funding breakthrough cancer research, sharing cutting-edge knowledge with patients and physicians worldwide, and improving quality of care and access to care, enhancing the lives of all who are touched by cancer.

Over 30 years, more than $89 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. Foundation grants have helped researchers launch successful careers and make discoveries that benefit patients with cancer. Many of the studies featured in this year’s Clinical Cancer Advances report were led by past foundation grant recipients who have continued their careers in oncology research, dedicated to improving the lives of people living with cancer.

“Clinical Cancer Advances 2015: ASCO’s Annual Report on Progress Against Cancer” was also funded in part by the Conquer Cancer Foundation Mission Endowment Fund.
Fig 1. Decreased federal funding threatens cancer research.

**CANCER RESEARCH PROGRESS THREATENED**

**Cancer touches us all.** The need for continued progress is urgent and growing.

Over **1.6 MILLION AMERICANS** received a new cancer diagnosis in the past year. By 2030, this number will increase **45%**.

Nearly **1 in every 4 deaths** in the U.S. is caused by cancer.

Yet federal funding for cancer research is at the **lowest point in decades**...

...Putting U.S. scientific leadership in jeopardy.

**NIH research funding cuts harm us all**

**FEWER CLINICAL TRIAL OPTIONS FOR CANCER PATIENTS**
- Patient Enrollment in NIH’s Clinical Trials Network
- **29,000 patients** in 2009
- **20,000 patients** in 2013

**NEW TREATMENTS DELAYED**
- U.S. oncologists report:
  - **75%** current funding situation is directly impacting their ability to conduct cancer research
  - **38%** reduced time spent on research
  - **26%** delayed launching a clinical trial

**HARM TO LOCAL ECONOMIES**
- For every one NIH grant dollar cut, **$2.21 will be lost** in local economies through lost business activity, jobs, and wages.

**ASCO is calling on Congress to provide a strong investment for NIH in 2016 to sustain the search for cures.**

**For more information, go to:** [www.CancerProgress.Net](http://www.CancerProgress.Net)

**Sources:**
4. AAAS Science and Technology Policy Fellows. Funding Cancer Research [Fact Sheet]. Published June 1, 2014.
5. AAAS Science and Technology Policy Fellows. Funding Cancer Research [Fact Sheet]. Published June 1, 2014.
In just over a year’s time, cancer research has brought four new therapy options that fill a major treatment need for patients with CLL, the most common form of adult leukemia. The new approaches—which include both targeted drugs and immunotherapies—are poised to dramatically improve survival and quality of life for many patients with this form of blood cancer.

According to the Leukemia and Lymphoma Society, in 2014, an estimated 15,700 people in the United States were diagnosed with CLL, most of whom were elderly (the average age of diagnosis is 70 years). An estimated 119,386 people were living with (or in remission from) CLL in the United States as of January 1, 2010.

CLL is a disease in which B lymphocytes, a type of WBC, grow abnormally and build up in the body. CLL is typically slower growing than other leukemias, and survival ranges from approximately 1 year to more than 20 to 30 years.

The treatment of CLL depends on stage, risk status, and the patient’s overall health. Although treatment is often effective, no standard therapy can cure CLL. The goal of treatment is long-term remission. Because CLL develops slowly in approximately half of patients, active surveillance (watchful waiting) may be recommended for some. For patients who have symptoms or worsening blood counts, immediate treatment is recommended. Treatments include chemotherapy, targeted drugs, and bone marrow transplantation. Although these treatments can help control the disease well, many patients cannot tolerate the adverse effects of the current, often quite toxic, therapy approaches. These patients are in dire need of new options.

The standard treatment for CLL has been a combination of chemotherapy (fludarabine/cyclophosphamide) and immunotherapy (rituximab), which aims to achieve long-term remission. Although such treatment can be highly effective, most older adults are unable to tolerate it because of severe adverse effects.

Four new treatments approved in 2013/2014 have fewer adverse effects compared with standard therapy and are effective for patients with newly diagnosed leukemia and those with relapsed or treatment-resistant disease.

**TWO EFFECTIVE TREATMENT OPTIONS FOR PATIENTS WITH NEWLY DIAGNOSED CLL**

Patients with newly diagnosed, previously untreated CLL gained two new treatment options that are far more effective than existing drugs, extending the time to disease progression by a full year, on average. Both of these drugs are immunotherapies.

In November 2013, the FDA approved obinutuzumab, used in combination with the standard CLL chemotherapy drug chlorambucil, for previously untreated CLL.

Obinutuzumab is an immunotherapy drug that works by helping certain cells in the immune system attack cancer.
cells. The approval was based on a clinical trial in 365 patients that showed that the combination of obinutuzumab and chlorambucil was more effective than chlorambucil alone (which has been a standard treatment for CLL for decades, more recently in combination with rituximab). This study focused on patients with coexisting medical conditions that ruled out standard chemotherapy and immunotherapy approaches because of safety concerns. The new treatment more than doubled the average time to disease progression, from 11 to 23 months. In the second stage of this study, the obinutuzumab-chlorambucil combination was compared with the chlorambucil-rituximab combination as first-line therapy. Again, patients treated with the obinutuzumab combination experienced a much longer time to disease progression (27 v 11 months).3

Obinutuzumab represents an important new first-line therapy option for patients with CLL. It was the first drug with breakthrough therapy designation to receive FDA approval. The breakthrough therapy designation is one of four existing expedited review programs for serious conditions or life-threatening conditions. If a drug is designated as a breakthrough therapy, the FDA will expedite the development and review of such a drug, helping patients gain access to promising new therapies faster.

Shortly thereafter, the FDA approved a second antibody drug, ofatumumab, also for use in combination with chlorambucil. The drug is approved for patients with previously untreated CLL for whom the standard, fludarabine-based chemotherapy approaches are considered inappropriate, based on older age or comorbidities, because of the prospect of encountering serious adverse effects.4 Ofatumumab works by flagging leukemia cells for destruction by the immune system. When the drug attaches to a protein on B cells called CD20, it makes them more susceptible to immune system attack.

Ofatumumab also received a breakthrough therapy designation; it had been previously approved for patients with CLL that is resistant to standard chemotherapy. The recent approval of ofatumumab for first-line therapy was based on a clinical trial in approximately 450 patients showing that the combination of ofatumumab and chlorambucil was superior to single-agent chlorambucil; the average time to disease progression was 22.4 months for patients who received the combination versus 13.1 months for those who received chlorambucil alone.6

TWO DRUGS FOR RELAPSED AND TREATMENT-RESISTANT CLL OFFER NEW ALTERNATIVES TO CHEMOTHERAPY

New therapies also became available for patients who had already received at least one prior treatment and whose disease had worsened or come back. The treatments address a major unmet clinical need, offering hope to patients who previously had limited options. The two new treatments are targeted therapies that are so effective, they promise to transform CLL care, offering the possibility of forgoing difficult-to-tolerate chemotherapy.

In February 2014, the FDA granted accelerated approval for a new targeted drug for CLL, ibrutinib.5 Ibrutinib is a kinase inhibitor, which blocks Bruton's tyrosine kinase, a key protein that allows lymphoid cells to grow and divide.

Full approval was granted in July 2014 based on early results from a clinical trial finding that ibrutinib is superior to ofatumumab (approved in 2009 as a standard therapy for relapsed CLL), increasing response rates, time to disease progression, and overall survival for patients. At 12 months of follow-up, 90% of patients in the ibrutinib group were still alive, compared with 81% of patients in the ofatumumab group.6 Just as important, the therapy was well tolerated by patients, causing few serious adverse effects.

In addition, the FDA granted approval of ibrutinib for the treatment of patients with CLL with a genetic alteration called 17p deletion, which is associated with a poor prognosis and resistance to standard chemotherapy and immunotherapy approaches.7

The approval of ibrutinib represents a major step forward for the treatment of CLL overall, particularly for patients who previously had few options, including high-risk subgroups and older adults with the disease who are often not candidates for standard intensive chemotherapies. It is predicted that, given the striking activity of ibrutinib as a stand-alone therapy, combinations of ibrutinib with other drugs may ultimately obviate the need for standard chemotherapy, even in the first-line setting in CLL (ie, for newly diagnosed, previously untreated patients).
Also in July, the FDA approved another targeted drug, idelalisib, for three types of blood cancers, including for use in combination with rituximab for patients with relapsed CLL for whom rituximab therapy or standard chemotherapy alone would not be appropriate because of other existing medical conditions. The approval was based on a clinical trial that was stopped early when it showed that the idelalisib and rituximab combination was much more effective than placebo plus rituximab. Preliminary results showed that patients treated with the idelalisib combination lived on average 10.7 months without the disease progressing, compared with approximately 5.5 months for participants treated with the placebo plus rituximab combination. Idelalisib also worked incredibly fast, showing benefits in as a little as 1 week in some patients.

Idelalisib is a first-in-class oral drug that blocks an enzyme called PI3Kδ, a protein that plays a role in the survival, growth, and spread of B cells. A number of ongoing clinical trials are investigating idelalisib in combination with other agents in various settings, including the first-line treatment of CLL.

In summary, these newly approved therapies demonstrate progress against a difficult and common type of leukemia and present effective and tolerable new options for patients with CLL. Ibrutinib and similar targeted therapeutics such as idelalisib have the potential to transform the face of CLL therapy. Ongoing studies will show whether incorporation of these agents into the first-line therapy setting will ultimately eliminate the need for chemotherapy in CLL.
It is estimated that one of two people born today will be diagnosed with cancer in his or her lifetime. In the United States, a quarter of all deaths are related to cancer. Despite tremendous advances in treatment, avoiding cancer altogether remains the best weapon against the disease. People can substantially decrease the risk of getting cancer by changing their lifestyle (exercising regularly, maintaining a healthy weight, having a balanced diet) and avoiding things known to cause cancer, such as cigarette smoking and exposure to ultraviolet light.

Growing research evidence suggests that being overweight or obese increases one’s risk of developing many types of cancer, and can also complicate treatment and worsen outcomes after a cancer diagnosis. Obesity is quickly overtaking tobacco as the leading preventable cause of cancer. As many as 84,000 cancer diagnoses each year are attributed to obesity, and obesity or excess weight contributes to up to one in five cancer-related deaths. If current obesity trends continue, it is estimated there could be an additional 500,000 cases of cancer by 2030. The good news is that scientists are beginning to understand the biological factors underlying the association between obesity and cancer. The ultimate goal is to combine this knowledge with healthy lifestyle interventions to reduce obesity’s impact on the nation’s cancer burden.

Specific drugs are already recommended to people at increased risk for certain types of cancer, such as breast and ovarian cancers. Early results from an ongoing study point to a promising new way to prevent the development of breast cancer after menopause among high-risk women.

Another important strategy for reducing cancer deaths is screening, which can find pre-cancerous conditions or cancer at an early stage, substantially increasing the chances for successful treatment and longer survival.

Several cancer screening tests are routinely performed in the United States: mammography (for breast cancer), colonoscopy (for colon and rectal cancers), and Pap and human papillomavirus (HPV) tests (for cervical cancer). In 2013, the US Preventive Services Task Force (USPSTF) endorsed annual low-dose CT lung cancer screening for current and former heavy smokers. In 2014, the task force issued a formal set of recommendations regarding this screening. Additional recent research will help improve the efficacy of low-dose CT lung cancer screening and reduce potential harms by identifying the populations that stand to benefit the most from screening, and developing ways to reduce false-positive screening results.

For additional advances in cancer prevention and screening, please see Appendix Table A1.

**HORMONE DRUG HALVES THE RISK OF BREAST CANCER AFTER MENOPAUSE**

This past year brought an important new cancer prevention option for women who have completed menopause and are at increased risk for developing breast cancer. According to initial results from a study of roughly 4,000 high-risk women, a hormonal pill called anastrazole reduced the risk of breast cancer by nearly 50% over a 5-year period—only 2% of the women in the anastrazole group developed breast cancer compared to 4% of the women in the placebo group. The study participants were felt to be at high risk for developing breast cancer based upon the following factors:
high breast density, family history of breast cancer, and personal history of benign breast disease. Although it is difficult to compare results from different clinical trials, anastrazole seems to work as well if not better than other breast cancer prevention drugs, such as tamoxifen, raloxifene, and exemestane.

The adverse effects of anastrazole were mild overall, and more than two-thirds of the women remained on the treatment for the recommended 5 years. Anastrazole did not increase the risk of heart attacks or fractures compared to placebo, although there was an increase in the number of patients who experienced joint and muscle pain and hot flashes/night sweats. In addition, the two adverse effects that are of particular concern for women taking tamoxifen—blood clots and endometrial cancer—did not increase with anastrazole compared to placebo.

A similar benefit provided by anastrazole is its ability to reduce the risk of breast cancer recurrence after surgery in premenopausal women. However, like tamoxifen and raloxifene, anastrazole is currently not FDA approved for breast cancer prevention.

Anastrazole is already used to treat forms of breast cancer that are fueled by estrogen, but it is not yet FDA approved for breast cancer prevention. Like exemestane, anastrazole belongs to a class of drugs known as aromatase inhibitors, which block the enzyme that makes estrogen. Aromatase inhibitors have primarily been used in postmenopausal women, because their use requires that women have a low level of estrogen (however, a recent study showed that, when combined with ovarian suppression, aromatase inhibitors can also reduce the risk of breast cancer recurrence after surgery in premenopausal women). Tamoxifen and raloxifene—the only two drugs currently approved by the FDA to prevent breast cancer—can be used in both pre- and postmenopausal women. They work by blocking estrogen from attaching to breast cancer cells.

Researchers will continue to observe women in this study to monitor long-term adverse effects and determine if the halving of risk of developing breast cancer by taking anastrazole persists after the women stop taking the drug. Longer follow-up will also reveal whether the reduction in breast cancer diagnoses will translate into fewer breast cancer deaths.

Lung cancer is the leading cause of cancer-related death in the world. One of the many reasons for this is that only 25% of patients are diagnosed with early-stage disease that is potentially curable with surgery. Early detection is an important strategy for reducing lung cancer death rates.

Given that cigarette smoking increases lung cancer risk by 20-fold—a risk that persists for years after a person has stopped smoking—smokers are the primary focus for lung cancer screening programs. In 2014, the USPSTF issued the first formal guidance on low-dose CT lung cancer screening, which prevents 20% more lung cancer deaths compared to the chest x-ray. Several recent studies shed light on the benefits and risks of such screenings—including the risk of false-positive findings and the association between lung cancer screening and increased smoking cessation rates.

In March 2014, the USPSTF published recommendations on lung cancer screening, urging annual screening with low-dose CT for those age 55 to 80 years who have a 30-pack-year smoking history (for example, a person could have a 30-pack-year history by smoking one pack a day for 30 years or two packs a day for 15 years) and currently smoke or have quit within the past 15 years.

These recommendations are an important step toward eventual widespread implementation of low-dose CT lung cancer screening in the United States and securing related health insurance coverage, both of which would have a dramatic impact on reducing lung cancer deaths.
New Research Weighs Benefits and Harms of Screening

In 2011, researchers reported results from the National Lung Screening Trial (NLST) showing that screening with low-dose CT prevents death in one of 320 people screened, but the false-positive rate was high, with 96% of screen-detected abnormalities representing benign lesions (not lung cancer). Since that landmark study, researchers have been looking more closely at the risks and benefits associated with such screening. This research will be critical in informing the design and implementation of nationwide lung cancer screening programs in the future.

Another recent federally funded study explored whether the benefits and harms of low-dose CT screening in the NLST varied according to lung-cancer death risk. It found that the 60% of participants with the highest risk for lung-cancer death, based on factors such as age, body-mass index, family history of lung cancer, pack-years of smoking, years since smoking cessation, and emphysema diagnosis, accounted for the great majority (88%) of the lung-cancer deaths prevented by the screening. By contrast, the 20% of participants with the lowest risk of lung-cancer death accounted for only 1% of prevented deaths. These data support refining lung cancer screening criteria to target the highest-risk individuals who stand to benefit the most from lung cancer screening.

Another study, which developed statistical models of screening harms and benefits, affirmed the overall benefits of low-dose CT lung cancer screening. The model predicted that 497 deaths would be averted and 5,250 life-years gained per 100,000 people screened. Half of the lung cancers would be detected at an early, more treatable stage. Nevertheless, investigators also noted important screening-related risks, including 67,550 false-positive tests, 910 biopsies or surgeries of benign abnormalities, and 190 overdiagnosed lung cancers (tumors that may never cause any symptoms during a person’s lifetime). False-positive results and overdiagnoses are important potential harms of cancer screening because they contribute to patient anxiety and add to the cost of additional testing.

A recent study addressed the problem of false-positive findings by developing a new diagnostic blood test for lung cancer. The experimental test is noninvasive; it only requires a blood sample, rather than a painful and risky biopsy. By analyzing molecules called microRNA in a patient’s blood, physicians can determine if the abnormality detected on a scan is truly lung cancer. In a large validation study, combination of the microRNA test and low-dose CT resulted in a five-fold reduction of false-positive screening rates (from 19.4% to 3.7%).

Lung Cancer Screening Boosts Smoking Cessation Rates

Another important benefit of lung cancer screening programs that has emerged is their possible positive effect on smoking cessation. NLST researchers found that smoking cessation was strongly associated with the severity of abnormalities detected in the previous year’s screening; patients were most likely to quit smoking if the screening detected an abnormality that was suspicious for lung cancer and was new or changed from the previous screen. They were least likely to quit if the abnormality detected was not suspicious for cancer. The differences in smoking cessation rates persisted for up to 5 years after the last screen.

The USPSTF recommends counseling and intervention for smoking cessation in all people undergoing lung cancer screening. Integration of smoking cessation programs within lung cancer screening programs would likely further reduce smoking-related deaths.
Over the last year, significant progress has been made in the treatment of both common and rare cancers, leading to longer patient survival and improved quality of life. Advances ranged from targeted therapies for disease settings where previously no effective treatments existed to exciting progress in immunotherapy—an area of research that had seen little success until recent years. In addition, the strategy of combining different types of therapy showed powerful results in two large-scale, federally funded studies; combination of a chemotherapy drug with standard hormone therapy brought the longest survival improvement for patients with advanced prostate cancer, and adding radiotherapy to standard chemotherapy extended the lives of patients with a class of brain cancers called glioma by 5 years.

For additional notable advances in cancer treatment, please see Appendix Table A1.

**COMBINATION THERAPY APPROACHES EXTEND SURVIVAL IN BRAIN AND PROSTATE CANCERS**

Combination therapy—treatment strategies that combine multiple drugs or different types of therapies—has proven enormously effective against many types of cancer. However, because each therapy adds adverse effects, the balance of risks and benefits for every combination has to be carefully evaluated in clinical trials. Researchers have recently reported the remarkable success of two different combination therapy approaches for patients with brain and prostate cancers.

**Chemotherapy and Radiotherapy Combination Adds 5 Years in Survival for Patients with Low-Grade Glioma**

For the past 30 years, radiotherapy has been the standard first-line treatment for patients with low-grade glioma. A glioma is a tumor that grows from a glial cell, a supportive cell in the brain. A glioma is given a grade, which is a measure of how much the tumor resembles normal brain tissue. Low-grade (grade 2) glioma grows slowly. It accounts for 3% of all brain tumors.

Recently, a federally funded study of 250 patients with glioma (grade 2 astrocytoma, oligoastrocytoma, or oligodendrogloma) showed that adding chemotherapy to radiotherapy extends patient survival by roughly 5.5 years compared to radiotherapy alone. On average, patients treated with radiotherapy alone survived 7.8 years, and those who received the radiotherapy along with a specific chemotherapy drug regimen called PCV (procarbazine, lomustine, and vincristine) lived 13.3 years. Combination treatment also resulted in a 10-year delay in disease progression, compared to a 4-year delay with radiotherapy alone.

Until this study, the use of chemotherapy as an upfront treatment for low-grade glioma had been controversial because of the lack of robust clinical trial evidence showing that chemotherapy benefits such patients at any point in the disease process. Based on the dramatic survival improvements observed in this study, combination of PCV chemotherapy and radiotherapy will likely become a standard treatment approach for patients with low-grade glioma.
However, more research is needed to determine which subgroups of patients stand to benefit the most from the addition of chemotherapy. Since this study started more than 15 years ago, the chemotherapy drug temozolomide has largely replaced PCV chemotherapy for the treatment of more advanced glioma. Future research will have to address the role of temozolomide in low-grade glioma.

**First-Line Chemotherapy Added to Standard Hormone Therapy Improves Survival for Men With Advanced Prostate Cancer**

Prostate cancer growth is fueled by male hormones (androgens). The goal of hormone therapy for prostate cancer, also known as androgen-deprivation therapy (ADT), is to reduce androgen levels in the body. ADT alone has been the standard first-line treatment for advanced prostate cancer since the 1950s. Although this approach is initially effective, the disease often becomes resistant to ADT.

Historically, chemotherapy would be initiated only after the disease worsened despite ADT. But early findings from a federally funded study of newly diagnosed metastatic prostate cancer suggest that starting chemotherapy earlier can substantially improve outcomes. The study, which included 790 men with hormone-sensitive disease, found that men lived on average 10 months longer if treated in the first-line setting with ADT plus chemotherapy rather than with ADT alone.

This pivotal study is the first to identify a strategy that prolongs survival in newly diagnosed metastatic prostate cancer. The substantial benefit of early chemotherapy warrants this combination treatment being a new standard option, at least for men who have extensive disease and are fit for chemotherapy.

**TARGETED THERAPY**

Targeted therapy is a treatment that targets specific molecules in or on cancer cells, or in the tumor’s immediate surroundings. This type of approach blocks the growth and spread of cancer cells while limiting damage to healthy cells.

**New Hope for Overcoming Treatment Resistance in Lung Cancer**

In the United States alone, lung cancer takes more than 150,000 lives each year, accounting for nearly a third of all cancer deaths. Our growing understanding of lung cancer biology is steadily opening new avenues for development of therapies for difficult-to-treat types of lung cancer.

Targeted therapies are now standard for patients with non-small-cell lung cancer (NSCLC), the most common type of lung cancer. Erlotinib and afatinib are recommended as first-line treatments for patients harboring mutations in the epidermal growth factor receptor (EGFR) gene (found in 10% to 15% of white and 40% of Asian patients with NSCLC), and crizotinib is recommended for patients with rare alterations in the ALK gene (present in approximately 5% of patients with NSCLC). All three drugs are initially effective, with close to two thirds of patients experiencing tumor shrinkage; however, all patients eventually develop resistance to the targeted treatments. In approximately half of patients, the cancer starts growing again, usually within a year. These patients are in urgent need of new treatments.

New hope came recently with the introduction of two experimental EGFR drugs specifically designed for patients with resistance to existing EGFR therapies, and approval of the first effective drug for patients with difficult-to-treat forms of anaplastic lymphoma kinase (ALK)–positive lung cancer.

**Quest to Overcome EGFR Inhibitor Resistance.** In recent years, scientists have begun to unravel the causes of targeted therapy resistance, spurring development of next-generation drugs that specifically target the resistance-related genetic mutations. It is now known that approximately half of patients with NSCLC harboring mutated EGFR develop an additional EGFR mutation, known as T790M, which is thought to be responsible for resistance to EGFR-targeted therapy. Early, but promising, results from two phase I clinical trials in patients with T790M mutations whose disease worsened after initial EGFR-targeted therapy and who had no other standard treatment options were presented recently. The studies tested experimental drugs AZD9291 and CO-1686, both of which were designed to specifically target the T790M resistance mutation. Remarkably, approximately 50% of T790M–positive patients who received AZD9291 and close to 60% of those who received CO-1686 experienced tumor shrinkage. Longer-term follow-up will continue to see if the drugs lead to improvements in overall survival.

Importantly, because the drugs AZD9291 and CO-1686 are designed to target mutant EGFR, they have a much weaker effect on the normal EGFR in the body and thus cause fewer
debilitating adverse effects, including diarrhea, skin rash, and acne.

**New Second-Line Treatment Option for ALK-Positive NSCLC.** In April 2014, the FDA approved ceritinib, a new treatment for patients with ALK-positive lung cancer that worsened despite the ALK-targeted drug crizotinib (approved in 2013) and for patients who are unable to tolerate crizotinib. Tumors with ALK mutations depend on ALK proteins for growth and survival. Crizotinib can delay tumor growth by 8 to 10 months in patients with ALK-positive NSCLC that responds to the treatment. But approximately a third of patients with ALK alterations acquire additional genetic abnormalities, including new mutations in the gene or an increased number of copies of the ALK gene, which make their tumors resistant to crizotinib.

Ceritinib was approved under the FDA’s accelerated approval program, which provides earlier patient access to promising new drugs while the drug manufacturers conduct confirmatory clinical trials. Prior laboratory tests had shown that ceritinib is 20× more potent than crizotinib in blocking the mutated ALK protein. Ceritinib’s approval was based on an early-stage clinical study involving 122 patients with ALK-positive, late-stage NSCLC. More than half of the patients with NSCLC that had worsened after initial treatment with crizotinib experienced tumor shrinkage with ceritinib, including patients with ALK-resistance mutations. The drug was also effective in patients who had not received prior crizotinib treatment.

Taken together, these early findings prove that drugs designed to overcome resistance pathways can, in select groups of patients, have substantial benefits, which include not only delaying disease progression but also reducing adverse effects. The importance of this research extends beyond lung cancer because resistance to molecularly targeted therapies occurs in all types of cancer.

**FDA Approves First Treatment for Chemotherapy-Resistant, Advanced Stomach Cancer**

In April 2014, the FDA approved ramucirumab for the treatment of advanced stomach cancer or gastroesophageal junction adenocarcinoma, a form of cancer located in the region where the esophagus joins the stomach. This marked the first FDA-approved treatment for patients with advanced stomach cancer that worsened during or after chemotherapy. Patients with advanced stomach cancer have had few options for treatment of this aggressive and often symptomatic cancer.

The approval was based on evidence from a clinical study in 355 patients that identified the first survival gain in a decade for patients in this setting. Compared with patients who received placebo, patients treated with ramucirumab had longer survival (5.2 v 3.8 months, on average).

Ramucirumab belongs to a class of cancer drugs known as angiogenesis inhibitors, which work by blocking the blood supply to the tumor. Because a tumor needs the nutrients delivered by blood vessels to grow and spread, the goal of antiangiogenesis therapies is to starve the tumor.

This study was the first to show that an angiogenesis inhibitor can be effective as a standalone therapy in a GI cancer. Ramucirumab and other drugs targeting angiogenesis are expected to bring substantial improvements in outcomes for this group of patients in the near future.

**Lenvatinib: A New Option for a Difficult-to-Treat Thyroid Cancer**

Differentiated thyroid cancer is the most common type of thyroid cancer. It is generally curable with surgery and radiiodine therapy (RAI), but 5% to 15% of patients with this disease develop resistance to RAI. Results from a study of 400 patients indicate that the targeted drug lenvatinib could...
become a new, effective treatment option for patients with differentiated thyroid cancer that is resistant to RAI therapy.24 The study showed that, compared with patients who received placebo, patients treated with lenvatinib experienced a roughly 15-month delay in disease progression, on average, and the drug caused tumor shrinkage in approximately two thirds of patients.

Lenvatinib belongs to a class of drugs known as tyrosine kinase inhibitors. This drug blocks several different proteins in cancer cells, including vascular endothelial growth factor receptors (VEGFRs) 1-3, fibroblast growth factor receptors (FGFRs) 1-4, platelet-derived growth factor receptor (PDGFR) beta, KIT, and RET. It is also being explored for treatment of liver, lung, kidney, and other cancers. Lenvatinib is only the second active treatment for patients with RAI-resistant thyroid cancer. Another targeted drug, sorafenib, was approved for the same population of patients in 2013.

CANCER IMMUNOTHERAPY

Immunotherapy is a type of cancer treatment designed to boost the body’s natural defenses against cancer. It uses materials either made by the body or in a laboratory to improve, target, or restore immune system function. There are several types of immunotherapy, including antibodies, cell-based immunotherapies, and cancer vaccines. Immunotherapies can work in different ways: by stopping or slowing the growth of cancer cells, stopping cancer from spreading to other parts of the body, or helping the immune system increase its effectiveness at eliminating cancer cells by increasing the killing power of immune cells or flagging cancer cells for destruction.

Researchers have reported remarkable results with both antibody and cell-based immunotherapy approaches, with successes ranging from a 25% reduction in melanoma recurrence after surgery to delaying advanced lung cancer progression by 9 months. In addition, two new, cutting-edge therapies have led to complete remission of acute lymphocytic leukemia (ALL) in children and adults.

Immunotherapy Ipilimumab Reduces Recurrence Risk for Earlier-Stage Melanoma

During the past 30 years, the annual incidence of melanoma, the most deadly form of skin cancer, has increased by more than 60% in the United States. Researchers have been intensifying efforts to develop more effective treatments.

Immunotherapy is emerging as a breakthrough approach, particularly for advanced-stage melanoma. One of the first immunotherapy drugs, ipilimumab, was approved by the FDA in 2011 for melanoma that cannot be surgically removed or has spread to distant sites in the body. Ipilimumab is an antibody that attaches to a protein called CTLA-4 on cancer-killing T cells. The drug essentially releases the brakes on the immune system, springing the T cells into an attack against the tumor.

Researchers will continue observing patients in this study to see if the treatment improves long-term survival. Further research is needed to fully assess the balance of benefits and risks associated with ipilimumab.

Immunotherapy Makes Steady Headway in Lung Cancer

Recent years have brought some of the most promising signs of research success to date, with new immunotherapy approaches for lung cancer. New targeted drugs act on the so-called immune checkpoints—proteins that control the immune system’s ability to attack and kill cancer cells—and strong responses are being reported in as many as two thirds of patients treated.

The programmed death-1 (PD-1)/PD-1 ligand (PD-L1) pathway in particular emerged as an important therapeutic target when researchers discovered that disrupting the interaction between PD-1 and PD-L1 activates cancer-killing T cells. Drugs that block either the PD-1 protein (located on the surface of T cells) or the PD-L1 protein (located on the surface of cancer cells) are showing encouraging activity in a range of cancer types, including lung cancer. Early results from four clinical studies of such treatments in patients with NSCLC were presented recently.
In the first trial, nearly half of the first 45 patients with advanced NSCLC who received the anti-PD-1 antibody drug MK-3475 as first-line therapy responded to the drug.26 The treatment delayed disease progression by 37 weeks, on average, and serious adverse effects were uncommon.

Another study helped confirm researchers’ suspicions that drugs targeting the PD-1/PD-L1 pathway are most effective in patients whose tumor cells make PD-L1. In a population of 200 previously treated patients with lung cancer, higher levels of PD-L1 in the tumor were associated with better responses to MK-3475; 23% of patients with PD-L1-positive tumors (PD-L1 detected in at least 5% of tumor cells) experienced tumor shrinkage versus 9% of those with PD-L1-negative tumors.27

A third study reported results of another PD-1-targeted drug, nivolumab, used as first-line therapy in 20 patients with NSCLC.28 Remarkably, 30% of the patients responded to nivolumab overall. The response rate was 67% in patients with PD-L1-positive tumors (PD-L1 detected in at least 5% of tumor cells), but no response was seen in the patients with PD-L1-negative tumors or unknown PD-L1 status. Among the patients with PD-L1-positive tumors that responded to the nivolumab, cancer progression was delayed by 36 weeks on average.

A fourth study presented results on an anti-PD-L1 antibody, MEDI4736, reporting that 16% of patients with NSCLC (either previously treated or untreated) experienced tumor shrinkage.29 In this small, 20-patient study, researchers also observed a dramatic difference in response rates based on PD-L1 levels in the tumor. Overall, the response rates were 25% with PD-L1-positive tumors and only 3% in the 29 patients with PD-L1-negative tumors.

Taken together, these four early studies demonstrate a clear and consistent response to both first-line and subsequent therapies with PD-1/PD-L1-targeted drugs in patients with NSCLC. As of October 2014, none of these drugs had been approved for the treatment of lung cancer, although MK-3475 (pembrolizumab) was granted FDA approval for the treatment of advanced melanoma. This body of research also suggests that patients with higher levels of PD-L1 should be preferentially selected for further study with these promising immunotherapy drugs because they stand to benefit the most. However, further validation of PD-L1 as a predictor of response to PD-1/PD-L1 therapies will be required before such testing is implemented in routine clinical practice.

**Tumor-Directed T-Cell Therapy: Early Signs of a Breakthrough for Relapsed Leukemia**

Patients with B-cell ALL, the most common type of ALL, have limited treatment options after their cancer becomes resistant to chemotherapy. Even with intensive treatments such as hematopoietic stem-cell transplantation, long-term survival rates are low.

A new type of immunotherapy, known as chimeric antigen receptor-modified (CAR) T-cell therapy, is beginning to look promising, not only for ALL, but also for CLL.

CAR T-cell therapy is a one-time treatment that does not require surgery. In the first step, blood is pumped out of a patient’s body and sent through a machine that separates out T cells. The blood is then returned to the body intravenously. The patient then undergoes chemotherapy while his or her T cells are reprogrammed in the laboratory.

Essentially, scientists design and insert a manmade gene into each T cell. As a result, the reprogrammed T cells, or CAR T cells, start making proteins that will allow them to find and attach to specific molecules called antigens on cancer cells. CAR T cells are grown in large quantities in the laboratory and then infused into the patient, where they continue to live and grow, multiplying thousands of times. When CAR T cells attach to specific antigens on cancer cells, they become primed for elimination of those cells.

Findings from two small studies indicate that CAR T-cell therapy directed against the CD19 antigen on B cells may be the first effective treatment for relapsed ALL in both adults and children.

In the first study, 16 adults with relapsed or chemotherapy-resistant B-cell ALL were treated with a new, CD19-directed CAR T-cell therapy called 19-28z CAR T-cell therapy.10 Complete cancer remissions occurred in 88% of the patients, including the high-risk patients with Philadelphia chromosome-positive disease. Remarkably, patients started responding to therapy as early as 7 to 10 days after CAR T-cell infusion. These encouraging results warrant further investigation of targeted T-cell therapy for B-cell ALL in larger clinical trials.

In late 2013, another research team reported on a different CD19-directed CAR T-cell therapy, called CTL019, in children and adults with relapsed or treatment-resistant ALL.11 The approach is similar to 19-28z CAR T-cell therapy but involves a different kind of genetic reprogramming. Early results were promising; 14 of the first 20 patients treated in the study experienced complete remission of the disease. CTL019 received FDA breakthrough therapy designation in July 2014. The designation supports advancement of CTL019 in additional clinical trials and underscores its potential to become a lifesaving therapy for patients with relapsed/refractory ALL, who are in urgent need of new treatment options.
At this time, access to both 19-28z CAR CD19 and CTL019 CAR T-cell therapies is available only through clinical trials. Ongoing research is exploring the CAR T-cell technologies for a variety of cancer types.

**PROGRESS IN RARE CANCERS**

**First Viable Alternative to Surgery for a Rare and Crippling Joint Disease**

Early results from two small studies provide a new direction in cancer therapy—targeting a protein known as CSF-R1. The studies explored new drugs that were developed based on the discovery of this protein’s role in a rare joint disease called pigmented villonodular synovitis (PVNS).

PVNS is a rare disease, diagnosed in only approximately 600 Americans each year and tending to occur in younger people. It causes gradual destruction of the joints from benign tumors that form in them. PVNS typically affects the hip or knee, causing pain, swelling, and reduced mobility. There is no effective treatment besides surgery, which can range from joint replacement to limb amputations, in severe cases.

But according to new research, patients with PVNS may soon have two new treatment options in the form of simple pills. In a small study of patients with advanced PVNS, a drug called PLX3397 led to tumor shrinkage in 11 of 14 patients, who also experienced moderate to marked improvements in pain, joint stiffness, and daily activities. PLX3397 targets CSF-R1 and two other molecules in tumor cells. In another study, seven of 10 patients with PVNS treated with an anti-CSF-R1 antibody called RG7155 experienced tumor shrinkage.

Although the effectiveness of these new treatments has yet to be confirmed in larger studies, these early findings offer hope of relief from debilitating adverse effects of PVNS and the possibility of avoiding joint replacement or amputation.

**Early Study Suggests Bevacizumab May Be a Promising Treatment for a Rare Form of Ovarian Cancer**

Early results from a federally funded study indicate that the targeted drug bevacizumab is active against recurrent sex cord-stromal tumors of the ovary, a rare form of ovarian cancer. Bevacizumab works by cutting off the blood supply to the tumors. It is FDA approved for treatment of certain types of colorectal, kidney, lung, and brain cancers.

There has been little medical research on this disease to date, and consequently there is little evidence to guide treatment decisions, particularly for patients who experience a relapse. The study reports that bevacizumab shrunk tumors in six of 36 patients and delayed disease progression for approximately 9 months, on average. Although still preliminary, the results are promising enough to warrant further investigation of bevacizumab in this setting.

“The today, because of medical research, we now have smart drugs, drugs that will attack fast-growing cancer cells, without attacking fast-growing healthy cells...What we know also, from cancer research, is the only failure in that research is when you quit or you are forced to quit because of lack of funding. A lot of these new drugs that are coming to market today have been in various phases of discovery for the past 20 years, so to sustain cancer research is to produce promising new therapies, but to also encourage young researchers to stay in the field. That is our obligation, as Democrats and Republicans of this body, in recognizing that we must fully fund the National Institutes of Health and the National Cancer Institute.”

**REP. BRIAN HIGGINS (D-NY); US HOUSE OF REPRESENTATIVES SPECIAL ORDER ON MAY 8, 2014, IN HONOR OF ASCO’S 50TH ANNIVERSARY**
In addition to active treatment, a primary focus of cancer care is maximizing patients’ quality of life and symptom control. Researchers continue to pursue a wide range of strategies, including optimal treatment selection, assessment of short- and long-term risks and adverse effects of treatments, symptom control, and general improvement in quality of life.

One recent study confirmed that incorporating palliative care early in the course of the disease improves patient well-being on many levels, and another identified an effective and easy option for preserving fertility in women undergoing treatment for breast cancer. There has also been renewed focus on reducing racial disparities in cancer burden and outcomes.

For additional notable advances in patient care, please see Appendix Table A1.

**EARLY INITIATION OF PALLIATIVE CARE IMPROVES PATIENT WELL-BEING**

Recent research has shown that palliative care services not only improve physical symptoms and emotional and mental well-being for patients with advanced cancer, but can also extend life. However, palliative care is often offered too late in the course of the disease—typically in the last 2 months of life, after all curative treatments have been exhausted.

A recent study of nearly 500 patients underscores the importance of early palliative care for patients with advanced cancer.36 Compared with patients who received standard cancer care only, patients who also received palliative care services had improvements in several aspects of quality of life—spiritual well-being, quality of life at the end of life, and optimism—compared with patients who received standard care only.

**ASCO Cancer Survivorship Compendium Provides Practical Practice Tools**

In 2014, ASCO released a compendium of practice tools and resources to help oncologists develop and improve cancer survivorship care programs, especially for patients who have completed curative-intent treatment or who have transitioned to maintenance therapy.

With approximately 14 million cancer survivors in the United States, oncology providers play a crucial role in coordinating long-term follow-up care for the survivor population. High-quality survivorship care often includes screening and prevention of new and recurring cancers, managing psychosocial effects of cancer and financial or insurance concerns, and providing guidance regarding diet and exercise.

ASCO’s downloadable booklet, “Providing High Quality Survivorship Care in Practice: An ASCO Guide,” includes information on the key components of survivorship care, different models of care delivery, and a needs assessment to help users determine which model of delivery may best serve their patients. Both the guide and the ASCO Cancer Survivorship Compendium are available at www.asco.org/survivorship. A booklet and additional information is available for patients at www.cancer.net/survivorship.
GOOD NEWS FOR WOMEN HOPING TO HAVE A BABY AFTER BREAST CANCER TREATMENT

Premature ovarian failure (early menopause) is a common adverse effect in young women undergoing chemotherapy for breast cancer, often making it impossible for women to become pregnant after treatment. Two studies reported a promising new way to preserve fertility, by simply adding a hormone drug to chemotherapy.

Luteinizing hormone-releasing hormones (LHRHs) temporarily shut down ovarian function, essentially putting the patient into a postmenopausal state. It is speculated that this protects follicles (developing eggs) from chemotherapy damage. These medications are widely used to control ovulation timing for infertility treatments, such as in vitro fertilization. LHRH drugs are also widely used as hormonal therapies for advanced prostate and breast cancers.

In the first study, researchers showed that adding the hormone drug goserelin to standard chemotherapy cut the rate of ovarian failure or early menopause at 2 years after chemotherapy to 8% (the rate was 22% for women...
who received standard chemotherapy alone. In the study, the combination treatment approach resulted in successful pregnancies in 22 (88%) of the 25 women who attempted pregnancy, compared with 12 (67%) of 18 women who attempted pregnancy after receiving standard chemotherapy alone. The hormonal treatment did not increase the risk of miscarriage, pregnancy termination, or delivery complications, and it even extended women's survival, compared with chemotherapy alone. Although these early findings are promising, it is important to note that the study included only women with hormone receptor-negative disease, which accounts for the minority of women with breast cancer.

Another study last year reported similarly encouraging results for women with hormone receptor–positive breast cancer. It tested the effect of a similar hormonal drug, triptorelin, on preventing ovarian failure in women with early-stage breast cancer undergoing chemotherapy (80% of the study participants had hormone receptor–positive disease). After an average follow-up period of 7.3 years, there were eight pregnancies among the 148 women who received chemotherapy plus triptorelin and four pregnancies among the 133 women who received chemotherapy alone. Triptorelin did not affect survival.

ASCO REPORT OFFERS STEPS TO HELP ENSURE PATIENTS' ACCESS TO CANCER CARE IN THE UNITED STATES

In March 2014, ASCO published its inaugural issue of “The State of Cancer Care in America, 2014.” This landmark report examines a series of threats facing patients’ access to cancer care in the next decade, when the number of new cancer cases is set to rise by as much as 42%, largely as a result of the aging of the US population as well as lifestyle changes. These threats include a potential shortage of oncologists over the next decade, especially in rural areas, and concerns about the long-term viability of small and midsize practices, which serve more than one-third of new patients. This first ASCO report on the state of the US cancer care system also recommends specific steps for federal policy makers and the cancer community to help preserve patient access to cancer care, while improving the quality of care and slowing a projected rise in costs.

ASCO’s report also addresses many of the challenges highlighted in an important 2013 Institute of Medicine report on the quality of cancer care in the United States. That report recommends strategies for improving cancer care, grounded in six components of high-quality patient care: engaged patients; an adequately staffed, trained, and coordinated workforce; evidence-based cancer care; a learning health care IT system; translation of research evidence into practice, quality measurement, and performance improvement; and accessible, affordable cancer care.

Appropriate Inclusion of Women and Minorities in Clinical Trials Is Still a Challenge

Minorities are disproportionately burdened with cancer and yet are under-represented in clinical trials. The National Institutes of Health (NIH) Revitalization Act of 1993 mandated appropriate representation of women and racial/ethnic minorities in NIH-funded clinical research studies; however, the proportion of racial/ethnic minorities participating in cancer clinical trials is persistently lower than the proportion of minorities in the overall US population. Without adequate participation in clinical trials, it is expected that disparities in cancer burden will increase for minorities.

A recent study evaluated the impact of the NIH Revitalization Act on minority participation in National Cancer Institute (NCI)-sponsored clinical trials (Chen MS et al: Cancer 120:1091-1096, 2014 [suppl]). There were five key findings from the study: (1) few cancer clinical trials (< 2% of NCI’s trials) focus primarily on racial/ethnic populations; (2) the proportion of minority adults enrolled onto cancer clinical trials is not adequate nor representative of the US population with cancer; (3) there is scarcity of usable data about racial/ethnic minority populations—only 20% of randomized controlled trials published in high-impact oncology journals reported results by race or ethnicity; (4) barriers for minority participation in cancer clinical trials persist (including mistrust of research, cost, transportation, and differences in cultural perspectives); and (5) evidence is accumulating on the increasing value of participation in cancer clinical trials, as racial/ethnic diversity in molecular tumor characteristics and drug processing is found to play a significant role in cancer outcomes. Together, these findings underscore the need to increase minority participation in clinical trials, and appropriate policy changes are warranted.
CancerLinQ™ Development Underway

Efforts are underway to build on the rapidly advancing fields of cancer science and information technology, thus putting big data to work. The ASCO Institute for Quality is leading the development of CancerLinQ™, a cutting-edge health information technology platform that will revolutionize how we care for people with cancer. Instead of learning only from the 3% to 5% of patients in clinical trials, we will also learn from the routine care given to each of the millions of individual patients living with cancer nationwide, improving the quality and value of cancer care for all.

Once complete, CancerLinQ™ will aggregate and analyze a massive web of real-world cancer care data in order to:

- **Provide real-time quality feedback to providers**: CancerLinQ™ will enable oncology practices to measure how their care compares against guidelines and compares to their peers based on aggregated reports of quality, offering instant feedback and guidance for improvement.
- **Feed personalized insights to doctors**: CancerLinQ’s real-time clinical decision support will help physicians choose the right therapy at the right time for each patient, based on clinical guidelines and the experiences of many similar patients.
- **Uncover patterns that can improve care**: Powerful analytic tools will reveal new, previously unseen patterns in patient characteristics, treatments and outcomes that can lead to improvements in care.

The development of CancerLinQ™ is well underway. In September, ASCO announced that it is working with 15 “vanguard practices” from all across the United States to implement the first components of CancerLinQ™. As part of the development process, the vanguard practices will begin transferring data into the system. Their feedback and their needs will help determine the ultimate shape of the CancerLinQ™ solution, with the first version expected to be released in 2015.

CancerLinQ™ is supported by the Conquer Cancer Foundation of the American Society of Clinical Oncology. CancerLinQ™ is a project of CancerLinQ, LLC. For more information, please visit: www.CancerLinQ.org.

ASCO Provides Online Resource That Examines the Impact of the Affordable Care Act on Cancer Care

Major provisions of the Patient Protection and Affordable Care Act of 2010 (ACA) were implemented in 2014, with a far-reaching impact on health care providers and patients. Under the ACA, most US citizens and legal residents are now required to have health insurance or face penalties. Exchanges have been established in all 50 states to provide a mechanism for the uninsured to shop for coverage. In addition to implementing requirements under the new law, oncology practices are treating considerably more patients with these new exchange-based plans and adapting to changes in numerous existing plans.

ASCO has established an online ACA resource center, which provides details about the law, new requirements for practices, and effects on patients and patient coverage. ASCO provides additional information about the ACA for patients with cancer, available at Cancer.Net (www.cancer.net/affordablecareact).
Advances in Tumor Biology

Understanding the biologic processes that trigger and sustain cancer is critical to fulfilling the promise of precision medicine, whereby treatments are individualized to match the molecular makeup of both the patient and the tumor. Over the last decade, we have seen rapid expansion of knowledge in this field of research—from the identification of the plethora of cancer-related genes and molecular pathways to the discovery of numerous new cancer subtypes. With today’s advanced technologies, researchers have in-depth molecular analyses of cancer tissues and cells at their fingertips.

There has been exciting recent progress in understanding tumor biology and the interaction between tumors and their environment (surrounding blood vessels, immune cells, and other cells). Pivotal, large-scale genetic research on thousands of cancer specimens, representing many different forms of the disease, brought new insights that will help improve cancer diagnostics and provide clues for new therapy development. Additional genetic studies identified potential new therapeutic targets for rare, difficult-to-treat forms of childhood cancer and ovarian cancer.

Building on the recent discovery of abnormalities in the androgen receptor found in some patients with prostate cancer, researchers also unveiled the first blood test to potentially help identify patients who are unlikely to respond to standard hormone therapy that targets this receptor—a finding that could ultimately help spare many from ineffective treatment and adverse effects.

And finally, two studies reported the first evidence that certain bacteria in the gut play active roles in the fight against cancer, enhancing the immune response to cancer and increasing the efficacy of cancer therapy.

For additional notable advances in tumor biology, please see Appendix Table A1.

GENETIC RESEARCH PAVES THE WAY TO IMPROVED CANCER DIAGNOSTICS AND THERAPY

One of the greatest advances in cancer research has been the realization that abnormalities or mutations in the genetic material of a normal cell can lead to cancer. Because cells use genes as instructions for making proteins, genetic mutations can cause cells to make abnormal amounts of certain proteins or produce proteins that do not function as they should. This can disrupt normal cell behavior in a number of ways and ultimately lead to the development of cancer.

Large Genomic Study Offers Clues About Molecular Origins of Cancer

Although it is known that genetic mutations are the root cause of all cancers, scientists still have a rather limited understanding of the processes that bring about such abnormalities. A recent analysis of close to 5 million mutations from roughly 7,000 cancers offers new clues about the molecular origins of many types of cancer. Researchers identified 20 distinct combinations of mutations, which researchers refer to as mutational signatures. Based on prior research, they were able to link some of these mutational signatures to known genetic...
mutation triggers, such as tobacco, ultraviolet light exposure, certain drugs, and defects in the cell’s DNA repair machinery. They also found certain signatures that were associated with the age of the patient at diagnosis. Still, some signatures could not be linked to a specific cause.

Interestingly, researchers also found that many different cancers had mutations caused by rogue activity of enzymes that are normally involved in gene shuffling during antibody production in immune system cells. This raises the intriguing possibility that some cancers may begin as collateral damage from an immune response to a virus or another infectious agent, but further research is needed to confirm this hypothesis. Taken together, these new insights may have implications for cancer prevention and therapy in the future.

**Same Sets of Genetic Changes Found in Completely Unrelated Cancer Types; Possible Implications for Treatment**

Over the past few years, large-scale genomics projects such as The Cancer Genome Atlas (TCGA) have revealed that cancers from the same tissue can be distinguished into subtypes based on their genomic profile—information on the complete genetic material of a tumor, including all molecular alterations. Based on this research, new cancer drugs are being designed to target groups of patients with particular cancer subtypes.

A landmark study moves us another step closer to defining cancers based on their genomic profile.41 Eleven major molecular subtypes emerged from an analysis of molecular data from approximately 3,500 patients with 12 different forms of cancer. Researchers noted that most cancers that originated from the same tissue or organ had similar genomic profiles; however, in approximately one in 10 cases, the genomic profile of a tumor was distinct from other cancer specimens derived from the same tissue. Moreover, the same genomic profiles were sometimes found in tumor specimens from different tissues. For example, some bladder cancer cases had a genomic profile that was more similar to some lung cancers and head and neck cancers than to other bladder cancers. This may suggest that patients should ultimately be treated based on the genomic profile of the cancer they have, rather than the site of origin of the cancer.

Genomic profiling represents an intriguing alternative to the standard, centuries-old classification of cancers based on their tissue of origin. As of yet, however, we need additional research to verify that treating patients according to the genomic profile of their tumor yields better results than treating them according to their pathologic diagnosis. The first step is to convert genomic profiling from research tests to clinical tests so that tumors can routinely be classified according to their molecular profile at the time of diagnosis; this step alone may take several years.

**BLOOD TEST PREDICTS RESISTANCE TO PROSTATE CANCER THERAPY**

A recent study indicates that an experimental blood test may help identify men with prostate cancer who are resistant to the widely used hormone drugs enzalutamide and abiraterone, which target the androgen receptor.42 The test detects an abnormal, truncated form of the androgen receptor in circulating tumor cells (CTCs). Prior research has shown that this abnormal receptor is missing a piece onto which these drugs normally dock.

**ASCO Urges Raising the Bar for Cancer Clinical Trials, Issues Guidance on Clinical Trial Design to Achieve Meaningful Results for Patients**

In a special article published in March 2014 in *Journal of Clinical Oncology*, ASCO outlined overall survival goals for cancer clinical trials that researchers should aim for—and patients should expect. The recommendations provide examples of clinically meaningful outcomes in advanced pancreatic, lung, breast, and colon cancers.

“We’re urging our colleagues to implement clinical trials that, if successful, would provide a significant and clinically meaningful improvement in survival,” said Lee M. Ellis, MD, FASCO, immediate past chair of the ASCO Cancer Research Committee and lead author of the article. “People with cancer are living longer due to new therapies that target specific molecular drivers of cancer. As our understanding of the molecular drivers of cancer expands, we should be able to design clinical trials that achieve better results.”
In the study, 62 men with metastatic castration-resistant prostate cancer were tested for the presence of the truncated androgen receptor before, during, and after treatment with either enzalutamide or abiraterone. The truncated receptor was detected in roughly 40% of patients treated with enzalutamide and 20% of those treated with abiraterone. In both treatment groups, patients with the truncated receptor experienced less benefit from the drugs than those with a normal androgen receptor.

Should future research confirm these findings, wider use of this test could lead to avoidance of unnecessary treatment in a large group of men who carry this abnormality.

GUT BACTERIA NOT MERE BYSTANDERS IN CANCER

Increasing evidence suggests that the human body has a mutually beneficial relationship with the trillions of bacteria in the gut. It is also apparent now that those microscopic intestinal tenants play roles in certain diseases, including cancer. Two recent studies in mice reported, for the first time, that bacteria in the gut enhance the body’s immune response to cancer, mobilizing immune cells to kill cancer cells, not just in the gut but throughout the body as well. The researchers also found that the bacteria affect the efficacy of three different cancer treatments.

In the first study, tumor-bearing mice were treated with immunotherapy—drugs that stimulate the immune system to attack cancer cells. The drugs initially shrank tumors in most mice, but when researchers treated some of the mice with antibiotics, essentially eradicating the gut bacteria, the mice stopped responding to the immunotherapy, and tumors started growing again. The findings suggest that the gut bacteria somehow prime the immune cells inside a tumor to respond to immunotherapy. Similar findings were observed with the chemotherapy drug oxaliplatin (commonly used to treat colorectal and stomach cancers); its efficacy was greatly diminished when gut bacteria were eradicated with antibiotics.

Another research team found that gut bacteria also boost the effectiveness of another common cancer drug, cyclophosphamide, which works in part by boosting the body’s immune response to cancer. Cyclophosphamide damages the lining of the intestine, allowing gut bacteria to travel deeper into the gut, as well as the spleen and lymph nodes, where they stimulate two types of cancer-killing immune cells. Mice treated with antibiotics had a drastically weaker immune response to cancer, and the tumors were resistant to cyclophosphamide.

If these intriguing early findings are confirmed in human studies, it is possible that the presence—or absence—of specific species of gut bacteria in a patient will be taken into consideration when selecting a cancer therapy. One day, it may even be possible to somehow manipulate such microorganisms to improve the immune response to cancer and the efficacy of certain cancer therapies. That day, however, is still far in the future, because there are many unanswered research questions. For example, it is still unclear which bacterial species are responsible for improved cancer treatment responses and which are responsible for boosting immune system attacks on cancer.

PROGRESS IN RARE CANCERS
Promising Lead for Development of New Therapies for a Rare Childhood Cancer

A recent laboratory study investigating the genetic origins of the two major types of rhabdomyosarcoma (RMS)—alveolar and embryonal—found that they harbor distinct genetic alterations. RMS is a rare cancer that forms in a certain type of muscle tissue that can be found anywhere in the body. The disease is most commonly seen in children age 1 to 5 years, but it can also occur in teens and adults. Standard treatments for this disease include chemotherapy, radiation therapy, and surgery. No targeted therapies have yet proven successful for RMS.

The study found that embryonal RMS had a higher number of genetic changes overall than alveolar RMS and harbored abnormalities in the RAS pathway, which is involved in cellular responses to oxidative stress (damage from molecules called free radicals). Oxidative stress is thought to be the root cause of aging and is implicated in dozens of diseases, including cancer. RAS pathway abnormalities were not found in alveolar RMS.

These findings point to a potential new therapeutic
direction for embryonal RMS with drugs that target oxidative stress and the promise of a first targeted therapy for this disease.

**Genomic Research Identifies New Therapeutic Targets in Fatal Childhood Brain Cancer**

Two studies published back-to-back reports on new genetic alterations in a rare form of brain cancer called diffuse intrinsic pontine glioma (DIPG)—a disease in desperate need of a cure.46,47 Scientists found that approximately one in five patients with DIPG carry mutations in a gene called activin receptor (ACVR1). This is the first time such mutations have been found in a cancer. They also identified three molecularly distinct subtypes of the disease.

DIPG accounts for 10% to 15% of all CNS tumors in children, and it usually strikes children age 5 to 9 years. The tumor forms in the brainstem, which controls vital body functions such as breathing. Because of its location in the brain, it is not suitable for surgery. Current treatments are not effective, and long-term survival is rare; most children live only 9 to 12 months after diagnosis. The new findings from the genomic analyses suggest possible therapeutic interventions that could be tested in the future and offer hope for improving treatment outcomes for DIPG.

**New Research Reveals Genetic Causes of a Rare Ovarian Cancer Affecting Young Women**

Three research teams have simultaneously reported on genetic mutations detected among women in families with a rare but aggressive type of ovarian cancer called small-cell carcinoma of hypercalcemic type.48-50 As a result of the mutations, cells in the body stop making a protein called SMARCA4, and this is thought to be the major cause of the disease. The finding could result in improvement in genetic counseling for women at risk of this cancer and guide development of new targeted treatment approaches for this disease.

This devastating cancer primarily affects girls and women younger than age 40 years (the average age at diagnosis is 23 years). Although the disease initially responds to chemotherapy, it inevitably returns, and women typically die within a year from diagnosis.
How Far We’ve Come: A Decade in Review

The field of oncology has witnessed a steady flow of exciting developments since ASCO released the first Clinical Cancer Advances report in 2005. Since then, more than 60 anticancer drugs have been approved by the FDA (Fig 2), and a deeper understanding of tumor biology has begun generating a whole range of new, molecularly targeted drugs that have transformed the care of thousands of patients with difficult-to-treat cancers. Entire new classes of drugs have emerged, each homing in on a specific molecule or group of molecules required for tumor survival, growth, or spread.

Ten years ago, the National Institutes of Health initiated the TCGA project, the first and most comprehensive undertaking of its kind. The TCGA Research Network has thus far yielded complete molecular portraits of 10 different types of cancer. Today, the TCGA and other large-scale programs are providing invaluable information that can help improve patient outcomes in a number of ways, from matching patients to existing targeted treatments, to identifying new cancer-driving genetic abnormalities that could be targeted with new drugs.

After decades of modest progress, in the last few years, the field has witnessed remarkable successes with antibody immunotherapies, first in advanced melanoma and later in a range of other cancers, including the most common type of lung cancer. These new therapies have been able to significantly extend survival for patients who previously had no effective treatment options, and recent long-term studies indicate that antibody immunotherapies can continue keeping tumor growth in check for years after completion of the treatment.

Another kind of immunotherapy, which reprograms the body’s own immune cells to attack cancer, is also showing promise in certain blood cancers, as well as in a range of solid tumors.

The last decade has also marked the approvals of the first cancer prevention vaccine (Gardasil for cervical cancer). Ongoing clinical trials are exploring vaccines for other types of cancer.

And finally, during this time, large-scale screening studies have brought important new evidence that has helped shape screening practices for some of the most common cancers, including lung, breast, and prostate cancers.
RAPID ASCENT OF TARGETED THERAPIES

Over the last decade, we have seen a steady and sharp increase in the number of new targeted therapies approved by the FDA, strongly outpacing new chemotherapy drug development (Fig 3). Roughly 40 new targeted drugs became available in this time period, and many of them transformed the patterns of care, dramatically improving outcomes for patients with a wide range of cancers.

New Drugs Starve Tumors

The introduction of angiogenesis inhibitors, a class of drugs designed to slow the growth of new blood vessels to the tumor, proved to be critical for the successful treatment of many advanced and aggressive cancers. The first such drug, bevacizumab, was approved by the FDA in 2004 for the treatment of advanced colorectal cancer, and it has since been approved for use in certain lung, kidney, ovarian, and brain cancers. Subsequently, other angiogenesis inhibitors—axitinib, cabozantinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib, and ziv-aflibercept—have also improved the treatment of advanced kidney, pancreatic, colorectal, and thyroid cancers; GI stromal tumors; and sarcoma.

EGFR Inhibitors: Targeting a Key Cancer Survival Pathway

Another major targeted therapy class comprises drugs that disrupt key cell signaling pathways—molecular communication networks that control cancer cell growth. One such pathway is controlled by a protein called EGFR. The first EGFR-directed drug, gefitinib, was approved in 2003 for the treatment of NSCLC. Two years later, the FDA approved a second EGFR drug, cetuximab, for the treatment of advanced colorectal cancer, and a similar drug, panitumumab, was approved in 2006. However, in 2008, new research revealed that colorectal cancers with mutations in a gene called KRAS are resistant to cetuximab and panitumumab. This discovery prompted routine testing for KRAS mutations to ensure the two drugs are used only for patients who stand to benefit from them, while sparing other patients the adverse effects and costs of an ineffective treatment.

In 2004 and 2005, the FDA approved another EGFR inhibitor, erlotinib, for the treatment of NSCLC and advanced pancreatic cancer. Most recently, in 2013, the FDA approved afatinib for patients with advanced NSCLC who have specific alterations in the EGFR gene. Other EGFR-targeting drugs are being investigated in ongoing clinical trials.

New HER2 Therapies Bring Continued Breakthroughs in Breast Cancer Care

Approximately 15 years ago, scientists discovered the first targeted treatment for an aggressive form of breast cancer characterized by excess levels of a protein called human epidermal growth factor receptor 2 (HER2) in the tumor. Approximately 15% to 20% of women diagnosed with breast cancer harbor this genetic abnormality (HER2-positive cancer). Like its cousin EGFR, HER2 tells cancer cells to keep growing. Since then, research has yielded four additional HER2-targeted treatments that improve survival for women with HER2-positive breast cancer.

The first HER2 drug, trastuzumab, dramatically improved survival for women with advanced, HER2-positive breast cancer, when combined with chemotherapy. In 2006, trastuzumab was also approved for use in women with early-stage HER2-positive breast cancer to reduce risk of recurrence after surgery.

Recently, a major clinical trial found that a two-pronged attack on HER2 was better than trastuzumab alone, leading to the 2012 FDA approval of a second HER2 drug, pertuzumab, for use in combination with trastuzumab for women with advanced HER2-positive breast cancer, and in
2013 for the treatment of early-stage disease. The same year saw approval of trastuzumab emtansine or T-DM1, a treatment that consists of trastuzumab chemically linked to a chemotherapy drug. This combination treatment is not only more effective than either drug alone but also allows precise delivery of chemotherapy to breast cancer cells, sparing healthy tissues from adverse effects. This is now the preferred treatment for HER2-positive breast cancer that has worsened despite multiple lines of prior treatment.

The fourth HER2 drug, lapatinib (approved in 2007), is effective against both HER2-positive and hormone receptor-positive/HER2-positive metastatic breast cancers when used in combination with an aromatase inhibitor.

**Drugs Targeting Multiple Molecular Pathways: A Rising Trend**

Researchers are discovering increasing numbers of cancer treatments that can block more than one molecular target or pathway at the same time, making them powerful weapons against cancer. For example, vandetanib (approved in 2011 for the treatment of thyroid cancer) blocks EGFR, VEGFR (a protein involved in the growth of tumor blood vessels), and RET. The colorectal cancer drug regorafenib (approved in 2012) blocks six different cancer pathways: VEGFR1-3, TIE2, PDGFR, FGFR, KIT, and RET.

**New Targets, New Drugs**

Research on potential targets for new cancer drugs continues with unabated intensity. In 2013 and 2014, the FDA approved trametinib and dabrafenib, respectively, drugs that are effective against melanoma with a specific change in the BRAF gene, which controls the MEK pathway. Crizotinib (approved in 2013) targets an ALK gene alteration, found in some types of lung and childhood cancers. Temsirolimus (approved in 2007) and everolimus (approved in 2012) block the so-called mammalian target of rapamycin (mTOR) pathway, which controls the growth of many types of cancer, including breast, pancreatic, and kidney cancers. Everolimus is one of the first effective targeted drugs for HER2-negative breast cancer, which accounts for the majority of breast cancer cases. It is approved for use in postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer, in combination with an aromatase inhibitor. Nilotinib (approved in 2007) and dasatinib (approved in 2010) target BCR-ABL, a specific protein found only in some forms of leukemia.

**MAPPING THE CANCER GENOME: THE PATH TO PRECISION MEDICINE**

Genetic abnormalities or mistakes in the DNA can cause cells to make too much of a certain protein or produce a defective protein that does not work as it should. This may, in turn, lead to some cells growing out of control, forming tumors. Cancer cells have dozens of mutations. Identifying genetic abnormalities that drive cancer development and growth is the foundation for precision medicine, whereby treatments are tailored to the genetic makeup of the tumor. In some instances, genomic testing is already being used routinely in the clinic to match patients to available molecularly targeted therapies, as is the case with KRAS testing in colorectal cancer, HER2 testing in breast cancer, and EGFR and ALK testing in lung cancer. New targeted therapies are sometimes approved along with companion diagnostic tests.

Over the last decade, large-scale molecular analyses of hundreds of different cancer specimens have yielded a wealth of new knowledge that helps answer a range of clinical and research questions—from predicting a tumor’s response to specific treatment to identifying new drug targets in cancer cells.

**Large-Scale Genome Analyses**

The year 2005 marked the launch of the TCGA project, a landmark federally funded effort to map the full molecular landscape of 20 different forms of cancer, which includes investigation of the genome (ie, the complete DNA sequence) and the functional products of genes—RNA molecules (the transcriptome) and proteins (the proteome). Hundreds of cancer tissue specimens are analyzed and carefully compared with matched healthy tissue specimens. The project involves a large number of investigators around the world who are working to identify new molecular targets that can guide development of effective new treatments, discover new biomarkers for monitoring disease progression, assess risk of relapse, identify new cancer subtypes, select the optimal therapy for an individual patient, and predict the likelihood of response to a specific therapy.

To date, the TCGA Research Network has completed comprehensive molecular analyses of 10 different types of cancer: brain cancer (glioblastoma), ovarian cancer, colon cancer, rectal cancer, lung cancer, breast cancer, leukemia...
(acute myelocytic leukemia), uterine (endometrial) cancer, kidney cancer, and bladder cancer.

Two other large-scale programs, the Pediatric Cancer Genome Project and the International Cancer Genome Consortium, are also cataloguing the genomic landscape of many types of cancer. Such comprehensive analyses are the most in-depth investigations of their kind. The insights gained may help explain why some patients with seemingly identical tumors benefit from therapy and others do not, but outcomes of therapy depend not only on the tumor but also on patient characteristics. For example, researchers have identified inherited genetic variants that affect how the body responds to certain medicines and radiation therapy and whether a patient is at an increased risk for experiencing treatment adverse effects.

**Beyond Genes: The Epigenome**

Although it has long been known that changes in the so-called letters of the DNA (genetic sequence) are linked to cancer development, only in the last decade have scientists begun to unravel the missing link between the environment, genome, and disease: the epigenome.

The epigenome is a collection of chemical marks that sit on top of the DNA strands. Each cell in the body has a specific epigenetic pattern that controls which genes are turned on and which are turned off, and consequently which proteins are made. So, although cells throughout the body have the same DNA sequences, distinct epigenetic patterns enable cells to perform highly diverse and specialized functions in different tissues.

It is now recognized that epigenetic abnormalities underlie many diseases, including cancer. For example, certain epigenetic abnormalities cause reduced levels of DNA repair proteins, which lead to accumulation of DNA damage, including cancer-causing mutations. Using advanced technologies, researchers can now detect when the DNA of a cancer cell has more or fewer of these chemical marks, or has them in different places, compared with the DNA of a healthy cell of the same tissue. Ongoing studies are exploring the use of epigenetic profiling for cancer detection and diagnosis, identification of new disease subtypes, and prediction and monitoring of response to therapy. Several cancer drugs that target epigenetic changes have already been approved by the FDA.

**Revving Up the Immune System Against Cancer**

WBCs called T cells play an important role in fighting cancer. In 2011, the FDA approved ipilimumab, a breakthrough therapy for melanoma. It was the first treatment to prolong survival for patients with late-stage disease. Ipilimumab is an immunotherapy that targets a protein on T cells called CTLA-4, releasing the breaks on cancer-killing T cells. In clinical trials, patients experienced fast and dramatic tumor shrinkage, and benefits of the drug lasted long after the completion of treatment (for several years in some patients).

Other so-called immune checkpoint inhibitors have been developed since, specifically those that act on the PD-1/PD-L1 pathway, which helps tumors hide from the immune system. The FDA has granted breakthrough therapy status to PD-1 blockers nivolumab and MK-3475, both of which showed unprecedented results in recent early clinical trials in patients with melanoma (nivolumab was also effective against kidney and lung cancers). In September 2014, MK-3475 (pembrolizumab) became the first PD-1–targeted drug to receive FDA approval. PD-L1–targeting drug MPDL3280A has also shown promising effects against advanced melanoma in clinical trials. Recent research suggests that combining two different checkpoint inhibitors or adding an immune-boosting drug, such as interferon or interleukin, to a checkpoint inhibitor may offer even more striking benefits to patients.

**Adoptive Cell Therapies**

Experimental approaches called adoptive cell therapies (ACTs) have given new hope to patients with cancers that are particularly resistant to standard treatments, with some patients experiencing complete and long-lasting remissions.
The strategy involves collecting cancer-killing T cells from the patient's blood or tumor, growing them in the laboratory in large quantities (billions of cells), and reinfusing them into the patient. Some approaches have the added step of genetically reprogramming the patient's T cells to attack tumor cells. Although no ACTs have been FDA approved to date, patients may be able to access a number of early clinical trials testing such therapies in various types of cancer, including melanoma, leukemia, and cervical, ovarian, pancreatic, prostate, esophageal, and lung cancers.

SIGNIFICANT QUALITY-OF-LIFE IMPROVEMENTS FOR PATIENTS AND SURVIVORS

Over the past decade, research has brought a range of new options that improve patients’ quality of life at every step of cancer care, from diagnosis through survivorship. In addition, a new emphasis on early integration of palliative care into active cancer care is helping many patients—especially those with advanced cancer—live longer and better.

Easing Cancer-Related Adverse Effects

New strategies for managing adverse effects have dramatically improved patients’ quality of life, during and after treatment. For example, two separate studies showed that the antidepressant drug duloxetine and the antipsychotic drug olanzapine are effective options for preventing two common adverse effects of chemotherapy—peripheral neuropathy and nausea. Another trial brought a novel approach for treatment of two other common but often undertreated cancer symptoms—depression and pain. It demonstrated that automated symptom monitoring coupled with telephone calls from a trained nurse care manager can substantially reduce depression and improve cancer-related pain control.

There is increasing evidence of the power of nonmedical approaches, such as acupuncture and yoga, for enhancing patient and survivor physical and psychological well-being. The benefits include decreased fatigue and pain, improvement of sleep quality, and reduced use of narcotics and sleeping pills.

Integrating Palliative Care Earlier in Cancer Care

In 2010, a pivotal clinical trial showed that incorporating palliative care early in the course of treatment for advanced lung cancer dramatically improved patients’ quality of life and extended survival by several months over patients who received active treatment alone.52 Furthermore, patients who received early palliative care were less likely to undergo aggressive care at the end of life, such as resuscitation. The study spurred a wave of new attention to the untapped potential of palliative care for patients with advanced cancer and reinvigorated efforts to reduce use of aggressive treatment and other measures in patients’ final weeks of life.

MAJOR DEVELOPMENTS IN CANCER PREVENTION AND SCREENING

Cancer prevention and screening efforts have had powerful effects, contributing to steady declines in cancer incidence and mortality. Over the past 10 years, major clinical trials have revealed effective new screening strategies, raised important questions about other longstanding screening approaches, and identified new ways to prevent cancer.

New Options for Cervical Cancer Screening

Although long-standing availability of Pap testing has dramatically reduced cervical cancer diagnoses and death rates in the Western world, researchers have continued to explore other approaches. Knowing that HPV infection causes nearly all cervical cancers, researchers suspected that detecting HPV in the cervix could serve as an early warning sign for possible development of cervical cancer. They found that combining the Pap test with a test to detect HPV provides the most accurate results. In 2003, an FDA panel recommended that Pap tests and HPV tests be used longer-term studies suggested these approaches also offer important benefits for caregivers.

Drawing on this research, in 2012 ASCO issued provisional guidelines recommending that palliative care be offered along with standard cancer care early in the course of illness for any patient with metastatic cancer and/or high symptom burden.53
together when screening for cervical cancer in women older than age 29 years. In 2011, a study of more than 300,000 patients showed that adding a test for HPV to Pap testing every 3 years is safe and produces highly accurate results. This study provided important reassurance to many women and physicians who were skeptical of this alternative to routine, annual Pap testing. In 2012, ASCO and the USPSTF updated their guidelines on cervical cancer screening.

For parts of the world where Pap and HPV tests are not widely available, and where cervical cancer remains one of the most common and deadly women’s cancers, another major cervical cancer screening study brought new hope. The study showed that a simple screening strategy called visual inspection with acetic acid (vinegar), delivered by local public health workers, is both highly effective and easy to implement in low-resource parts of the world. Researchers concluded this approach could reduce cervical cancer deaths in India by one third and save the lives of more than 70,000 women worldwide every year.

**Cancer Prevention Vaccine**

Much like traditional vaccines for communicable diseases, cancer prevention vaccines trigger immune system defenses against a virus that causes the disease, thus preventing the development of cancer in the first place. For example, infection with HPV is known to cause almost all cases of cervical cancer. Like traditional vaccines, cancer prevention vaccines must be given before a person is infected with a virus to provide protection. The two approved cervical cancer vaccines, Gardasil and Cervarix, have the potential to prevent approximately 70% of cervical cancers and some other HPV-associated cancers, such as throat and anal cancers. The hepatitis B vaccine, originally developed to protect against liver disease, also has the potential to prevent some forms of liver cancer and was the first cancer prevention vaccine approved by the FDA (in 1981).

**Refining Breast and Prostate Cancer Screening Approaches**

A succession of large clinical trials over the past 10 years has helped highlight both the benefits and risks of routine prostate-specific antigen (PSA) testing and breast cancer screening and which patients will benefit most.

The use of PSA testing—once a standard screening test for prostate cancer—has seen a shift in recent years, driven by a series of large clinical trials that clarified its benefits and risks. Although the trials found no reduction in overall mortality from routine PSA screening, the evidence was less clear in healthy men with life expectancies of more than 10 years. Over the last several years, several public health and medical organizations have updated screening recommendations based on these findings. In 2012, ASCO’s provisional recommendations encouraged physicians to discuss the benefits and risks of PSA testing only with asymptomatic men with life expectancies of more than 10 years. For all other men, ASCO emphasized that the risks—such as overdiagnosis, unnecessary biopsy, and treatment for low-risk cancers—outweigh the benefits.

Similarly, in breast cancer, another set of studies drove debate over the most appropriate age and frequency of mammography screening. Although routine mammography is still widely recommended, especially for women older than age 50 years, the findings underscored the need for greater patient and physician communication about individual risk factors and screening benefits and risks.

Meanwhile, for women who have an increased breast cancer risk—because of family history, genetics, or other factors—research evidence validated breast magnetic resonance imaging (MRI) as a powerful tool for detecting new cancers that may have gone unnoticed by mammogram or clinical examination alone. Based on findings from two large clinical studies, in 2007 ASCO issued recommendations supporting routine MRI screening for certain women at high risk of breast cancer.

**Common Medications May Reduce Cancer Risk**

Large clinical trials have suggested that some commonly used drugs can have important effects on cancer prevention. For example, an analysis of data from almost 50 epidemiologic studies revealed that oral contraceptives lower ovarian cancer risk by 20% for every 5 years that the pill is taken. This reduction in risk persists up to 30 years after oral contraceptive use ceases. Based on these findings, researchers estimated that oral contraceptives have prevented as many as 200,000 ovarian cancer cases and 100,000 deaths; they also predicted that they will prevent upward of 30,000 new cases annually in the coming decades.

Additional studies identified benefits of daily aspirin for reducing colorectal cancer, as well as cancer risk overall. Although regular use of aspirin is not recommended as a cancer prevention tool—because of risks such as stomach bleeding—research continues to explore the benefits of anti-inflammatory drugs in cancer prevention and treatment.
The 10-Year Horizon

We have seen remarkable progress in clinical cancer research during the last decade, but what does the future hold? Recent developments in fundamental and translational cancer research give us a glimpse into promising areas that may start affecting patient care as early as in the next 10 years.

CANCER STEM CELLS: THE BANE OF CANCER THERAPY RESISTANCE

The cancer stem-cell theory postulates that among all cancerous cells in a given patient, only a small subset, termed cancer stem cells, is responsible for initiating and maintaining a tumor and triggering its spread to distant sites in the body (metastasis). Researchers think that cancer stem cells are biologically different from so-called regular cancer cells in that they have the ability to self-renew and generate different cancer cell types, just like normal stem cells generate different organs and tissues.

The theory also suggests that cancer stem cells are more resistant to chemotherapy because they have specialized proteins that expel and repair DNA damage. It is thought that this may be why some tumors grow back after initially shrinking. Therefore, treatments that specifically attack cancer stem cells are needed to reduce relapses, prevent metastasis, and treat the most aggressive cancers.

New insights into cancer stem-cell biology are offering leads for development of such approaches in the near future. Researchers are exploring several strategies for eradication of cancer stem cells, such as targeting specific molecular pathways (eg, Notch, Hedgehog), proteins on the surface of cancer stem cells, and the tumor microenvironment.

FASTER, CHEAPER, AND MORE SOPHISTICATED GENOMICS TECHNOLOGY

Advanced genomic profiling technologies known as next-generation sequencing (NGS) are poised to revolutionize personalized medicine. NGS allows for much faster and drastically less expensive testing compared with older technologies. For example, the Human Genome Project took 13 years to complete at a cost of roughly $13 billion a decade ago, but with the new technologies, a person's whole genome can be sequenced in a couple of days at a cost of only $5,000. Another advantage of NGS is that it can find certain types of cancer-related genetic changes that are not detectable with any other technology. It can even be used to conduct molecular analyses of individual cells. This has provided unique new insights into types of genetic changes that occur during cancer development and progression.

NGS also holds tremendous promise as a diagnostic tool and a way of tailoring treatments to individual patients. Smaller NGS machines are already available for use in hospital laboratories. However, there are many technologic, regulatory, ethical, and cost concerns that have to be resolved before these technologies become broadly implemented.

LIQUID BIOPSIES

Although cancers are thought to originate from a single
rogue cell, distinct subgroups of cells emerge over time, which can differ in the specific genetic changes they carry. This phenomenon has important ramifications for cancer treatment success, particularly in approaches that rely on tissue biopsy to determine whether a patient is a candidate for a particular targeted drug. For example, physicians typically do molecular tests on tiny slivers of cancer tissue collected through biopsy. That tissue sliver may or may not represent all the mutations present in the different areas of the tumor or even in the majority of tumor cells. This explains why some patients who test positive for specific mutations turn out to be resistant to therapies targeting those mutations. A new approach, however, may be able to address this challenge.

Uncovering Clues From Tumor Cells in the Blood
Unlike the potentially painful and risky tissue biopsy, the new approach—a liquid biopsy—only involves the collection of a few drops of blood. Advanced technologies are used to count and extract the rare CTCs from the blood sample. As tumors shed a variety of cells into the bloodstream, this approach potentially provides a more complete molecular picture than can be obtained from a traditional biopsy of a single area of a tumor. Patients with larger and faster-growing cancers generally have higher levels of CTCs in the blood, and physicians can use the CTC level as a yardstick for real-time, noninvasive monitoring of the patient’s response to therapy, so that ineffective treatments can be stopped. However, recent research has called into question whether changing treatment in the face of rising CTC counts improves outcomes. Other recent studies have suggested that analyzing genetic changes in CTCs could help match patients to suitable targeted drugs, optimizing outcomes.

Circulating Tumor DNA and RNA May Help Guide Treatment Decisions
More recently, the liquid biopsy concept has extended to detecting, capturing, and analyzing circulating tumor DNA (ctDNA) and tumor microRNA, miniscule pieces of the cancer cell’s genetic material that float freely in the bloodstream. Recent studies show that ctDNA testing could be applied to all stages of patient care—from detection and diagnosis to selection of treatments and monitoring of disease progression. Simple measurement of ctDNA levels in the blood may also be used to quickly estimate how advanced the cancer is and the patient’s survival chances, because higher levels of ctDNA are strongly associated with shorter survival. Analysis of ctDNA could also be used for real-time monitoring of new mutations that arise during tumor progression and therapy and to select the most suitable treatments.

Approximately a decade ago, researchers discovered that abnormalities in microRNAs—molecules that prevent cells from making specific proteins—are associated with cancer development and progression. Subsequent research has shown that microRNA analysis is a promising and cost-effective way to identify what type of cancer a patient has, estimate how fast a cancer is growing, monitor response to therapy, and detect relapse.

Although all these avenues are under intensive research, confirmation in large-scale clinical trials is needed before liquid biopsies become routine and widely available in the clinic.

POWER OF THE SMALL: NANOMEDICINE
Nanotechnology refers to the use of materials on a nanometer scale. For reference, the DNA double helix is 2 nanometers wide, a flu virus is approximately 100 nanometers long, and a red blood cell is approximately 6,000 nanometers in diameter. Nanometer-sized objects are so tiny that they cannot even be seen through a regular light microscope.

First Cancer Nanodrugs
Nanotechnology has come a long way in the past couple of decades, and it holds tremendous promise for cancer therapy. The first nanoparticle-based cancer treatment, paclitaxel, was approved by the FDA in 2005 for the treatment of breast cancer and has recently received
approval for the treatment of lung and pancreatic cancers. Several nanotechnology-based therapies are being tested in clinical trials, including the first nanoparticle-delivered gene therapy for cancer.

Broad Potential for Improving Cancer Treatments

Scientists can now make nanoparticles in different shapes (balls, rods, shells) and sizes, using a variety of materials that are suitable for medical use, including gold, carbon, and even viruses. Cancer drugs can be loaded into the nanoparticles, and the surface of the nanoparticle can be coated with molecules such as antibodies that help guide and attach the nanoparticle to tumor cells.

Nanoparticles can also be chemically programmed to release their payload only on docking to or entering the cancer cell. This targeted and timed release concentrates the drug inside the tumor. For a patient, this means fewer adverse effects and less medication required. Coating nanoparticles with a chemical called PEG prevents the nanoparticle from attacks by the immune system, extending its lifespan in the blood. Some nanoparticles can be injected directly into the tumor. They can then be activated by magnetic fields, x-rays, or light to produce heat and destroy cancer cells locally.

Nanotechnology Enhances Cancer Detection

Nanoparticles are also being studied for early detection and diagnosis of cancer. Gold nanorods coated with antibodies that attach to cancer-specific biomarkers in the blood have proven to be an inexpensive and sensitive method of detecting cancer, even at early stages. Targeted delivery of specific nanoparticles into tumors can force the cancer cells to ramp up production and release biomarkers. As a result, rising biomarker levels in the blood potentially allow for earlier detection of cancer. Cancer-directed iron-oxide nanoparticles have magnetic properties that make them suitable for use as imaging agents. They can precisely pinpoint the cancerous areas on MRI scans, which surgeons rely on to plan for surgical removal of the tumor.

THE UNTAPPED POSSIBILITIES OF HEALTH IT IN CANCER CARE

Recent advances in health IT offer powerful possibilities for improving the quality of cancer care and outcomes for patients over the next decade.

Today, nearly every aspect of cancer care is based on information gleaned from the roughly 3% of patients who participate in clinical trials. But new health technologies in development offer the ability to learn from every patient. These big data tools make it possible to aggregate, analyze, and learn from a wide range of medical data—electronic health records, genetic test results, and more—while protecting the security and confidentiality of a patient’s individual data. In addition, these technologies promise to help cut through the massive—and constantly growing—web of cancer research data and guidelines to feed cancer care insights to physicians that are personalized to the unique characteristics of each patient and his or her tumor.

Projects that deliver on this promise are already under development—including ASCO’s own CancerLinQ™. As these technologies are rolled out over the next decade, they could dramatically reshape the cancer care landscape, improving quality and efficiency in every cancer care setting and generating new, more informed research hypotheses than ever—drawing on a body of cancer data of previously unseen size and scope.
# Appendix

## TABLE A1. ADDITIONAL NOTABLE ADVANCES (OCTOBER 2013—OCTOBER 2014)

<table>
<thead>
<tr>
<th>Prevention and Screening</th>
<th>Preventive and Screening Studies</th>
</tr>
</thead>
</table>

## Tumor Biology: Cancer Genetics

<table>
<thead>
<tr>
<th>Tumor Biology: Cancer Genetics</th>
<th>Genetic Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Supreme Court Decision: Association for Molecular Pathology et al v. Myriad Genetics, Inc., et al</td>
<td><a href="http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf">www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf</a></td>
</tr>
</tbody>
</table>

## Tumor Biology: Biomarkers

<table>
<thead>
<tr>
<th>Tumor Biology: Biomarkers</th>
<th>Biomarker Studies</th>
</tr>
</thead>
</table>

## Tumor Biology: New Therapeutic Targets

<table>
<thead>
<tr>
<th>Tumor Biology: New Therapeutic Targets</th>
<th>Therapeutic Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer</td>
<td>Camidge DR et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 8001)</td>
</tr>
<tr>
<td>Targeting FGFR1-amplified lung squamous cell carcinoma with the selective pan-FGFR inhibitor BGJ398</td>
<td>Nogova L et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 8034)</td>
</tr>
<tr>
<td>A phase Ib open-label multicenter study of AZD4547 in patients with advanced squamous cell lung cancers: Preliminary antitumor activity and pharmacodynamics data</td>
<td>Paik PK et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 8035)</td>
</tr>
<tr>
<td>Phase I/II dose-escalation study of daratumumab in patients with relapsed or refractory multiple myeloma</td>
<td>Lokhorst HM et al: J Clin Oncol 31, 2013 (suppl 15s; abstr 8512)</td>
</tr>
<tr>
<td>SAR650984, a CD38 monoclonal antibody in patients with selected CD38+ hematological malignancies: Data from a dose-escalation phase I study</td>
<td>Martin TG et al: Blood 122, 2013 (abstr 284)</td>
</tr>
<tr>
<td>A phase Ib dose escalation trial of SAR650984 (anti-CD-38 mAb) in combination with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma</td>
<td>Martin TG et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 8512)</td>
</tr>
</tbody>
</table>

## Treatment: Targeted Therapy

<table>
<thead>
<tr>
<th>Treatment: Targeted Therapy</th>
<th>Therapeutic Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>First results from the phase III ALTTO trial (BIG 2-06; NCT01 AlliancenoG33) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC)</td>
<td>Piccart-Gebhart MJ et al: J Clin Oncol 32, 2014 (suppl 15s; abstr LBA4)</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; CT, computed tomography; EGFR, epidermal growth factor receptor; FU, fluorouracil; GIST, GI stromal tumor; HER2, human epidermal growth factor receptor 2; HPV, human papillomavirus; PD-1, programmed death-1; PD-L1, programmed death-1 ligand.
<table>
<thead>
<tr>
<th><strong>TREATMENT: TARGETED THERAPY</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC)</td>
<td>Tolaney SM et al: San Antonio Breast Cancer Symposium, December 10-14, 2013 (abstr SI-04)</td>
</tr>
<tr>
<td>Overall survival in patients with advanced non-small cell lung cancer harboring common (del19/L858R) epidermal growth factor receptor mutations: pooled analysis of two large open-label phase III studies (LUX-Lung 3 and LUX-Lung 6) comparing afatinib with chemotherapy</td>
<td>Yang JCH et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 8004)</td>
</tr>
<tr>
<td>First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients with advanced ALK-positive non-squamous non-small cell lung cancer: Results of a phase III study (PROFILE 1014)</td>
<td>Mok T et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 8002)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TREATMENT: IMMUNOTHERAPY</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL)</td>
<td>Sznol M et al: J Clin Oncol 32, 2014 (suppl 15s; abstr LBA9003)</td>
</tr>
<tr>
<td>Combined KIT and CTLA-4 blockade in patients with refractory GiST and other advanced sarcomas</td>
<td>Shoushtari AN et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 10521)</td>
</tr>
<tr>
<td>Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL)</td>
<td>Ribas A et al: J Clin Oncol 32, 2014 (suppl 15s; abstr LBA9000)</td>
</tr>
<tr>
<td>Nivolumab for metastatic renal cell carcinoma (mRCC): Results of a randomized, dose-ranging phase II trial</td>
<td>Motzer RJ et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 5009)</td>
</tr>
<tr>
<td>HPV-targeted tumor-infiltrating lymphocytes for cervical cancer</td>
<td>Hinrichs CS et al: J Clin Oncol 32, 2014 (suppl 15s; abstr LBA3008)</td>
</tr>
<tr>
<td>Inhibition of PD-L1 by MPDL3280A and clinical activity in pts with metastatic urothelial bladder cancer (UBC)</td>
<td>Powles T et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 5011)</td>
</tr>
<tr>
<td>Primary overall survival (OS) from OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma</td>
<td>Kaufman HL et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 9008a)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TREATMENT: CHEMOTHERAPY</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of a multicenter, randomized, double-blind, phase III study of TAS-102 versus placebo, with best supportive care (BSC), in patients with metastatic colorectal cancer (mCRC) refractory to standard therapies (RECURSE)</td>
<td>Yoshino T et al: ESMO World Congress on GI Cancer, Barcelona, Spain, June 25-28, 2014</td>
</tr>
<tr>
<td>NAPOLI-1: Randomized phase 3 study of MM-398, with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer progressed on or following gemcitabine-based therapy</td>
<td>Wang-Gillam A et al: ESMO World Congress on GI Cancer, Barcelona, Spain, June 25-28, 2014</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TREATMENT: HORMONAL THERAPY</strong></th>
<th></th>
</tr>
</thead>
</table>
### TREATMENT: COMBINATION THERAPY

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin or oxaliplatin/5-FU/leucovorin with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum</td>
<td>Venook AP et al: J Clin Oncol 32, 2014 (suppl 15s; abstr LBA3)</td>
</tr>
<tr>
<td>COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAF(^{V600E/K}) mutation-positive cutaneous melanoma</td>
<td>Long GV et al: J Clin Oncol 32, 2014 (suppl 15s; abstr 9011)</td>
</tr>
</tbody>
</table>

### PATIENT CARE

<table>
<thead>
<tr>
<th>Intervention Description</th>
<th>Reference</th>
</tr>
</thead>
</table>

### DISPARITIES IN CARE

<table>
<thead>
<tr>
<th>Disparities Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Health Disparities Report</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
</tbody>
</table>

### SURVIVOR CARE

<table>
<thead>
<tr>
<th>Survivor Care Description</th>
<th>Reference</th>
</tr>
</thead>
</table>

### QUALITY OF CARE

<table>
<thead>
<tr>
<th>Quality of Care Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons for failure to deliver National Comprehensive Cancer Network (NCCN)-adherent care in the treatment of epithelial ovarian cancer at an NCCN cancer center</td>
<td>Erickson BK et al: Gynecol Oncol 133:142-146, 2014</td>
</tr>
</tbody>
</table>
References


**Adenocarcinoma:** Cancer that begins in cells that line certain internal organs and that have gland-like (secretory) properties.

**Adjuvant therapy:** Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

**Angiogenesis:** Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This process is caused by the release of chemicals by the tumor and by host cells near the tumor.

**ALK gene:** A gene that makes a protein called anaplastic lymphoma kinase (ALK), which may be involved in cell growth. Mutated (changed) forms of the ALK gene and protein have been found in some types of cancer, including neuroblastoma, non-small cell lung cancer, and anaplastic large cell lymphoma. These changes may increase the growth of cancer cells. Checking for changes in the ALK gene in tumor tissue may help to plan cancer treatment. Also called anaplastic lymphoma kinase gene.

**Androgen deprivation therapy:** Treatment to suppress or block the production or action of male hormones. This is done by having the testicles removed, by taking female sex hormones, or by taking drugs called antiandrogens. Also called androgen ablation and androgen suppression.

**Aromatase inhibitor:** A drug that prevents the formation of estradiol, a female hormone, by interfering with an aromatase enzyme. Aromatase inhibitors are used as a type of hormone therapy for postmenopausal women who have hormone-dependent breast cancer.

**Biomarker:** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.

**Biopsy:** The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue. There are many different types of biopsy procedures.

**CT scan:** A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs.

**DNA:** The molecules inside cells that carry genetic information and pass it from one generation to the next. Also called deoxyribonucleic acid.

**DNA sequencing:** A laboratory process used to learn the exact sequence (order) of the four building blocks, or bases, that make up DNA. Information is stored in DNA in a code made by arranging the four bases (identified by the letters A, C, G, and T) in different orders. DNA sequencing can be used to find DNA mutations (changes) that may cause diseases, such as cancer.

**EGFR:** The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called epidermal growth factor receptor, ErbB1, and HER1.

**Epigenetic alteration:** A heritable change that does not affect the DNA sequence but results in a change in gene expression. Examples include promoter methylation and histone modifications. These changes can affect a person's risk of disease and may be passed from parents to their children.

**False-positive finding:** A test result that indicates that a person has a specific disease or condition when the person actually does not have the disease or condition.

**Gene expression:** The process by which a gene gets turned on in a cell to make RNA and proteins. Gene expression may be measured by looking at the RNA, or the protein made from the RNA, or what the protein does in a cell.
**Gene transcript**: An RNA copy of a sequence of DNA that is a gene.

**Genomic profile**: Information about all the genes in an organism, including variations, gene expression, and the way those genes interact with each other and with the environment. A genomic profile may be used to discover why some people get certain diseases while other people do not, or why people respond differently to the same drug.

**HER2-positive**: Describes cancer cells that have too much of a protein called HER2 on their surface. In normal cells, HER2 helps to control cell growth. When it is made in larger than normal amounts by cancer cells, the cells may grow more quickly and be more likely to spread to other parts of the body. Checking to see if a cancer is HER2 positive may help plan treatment, which may include drugs that kill HER2 positive cancer cells.

**Hormone therapy**: Treatment that adds, blocks, or removes hormones. To slow or stop the growth of certain cancers (such as prostate and breast cancer), synthetic hormones or other drugs may be given to block the body’s natural hormones.

**Incidence**: The number of new cases of a disease diagnosed each year.

**Kinase**: A type of enzyme (a protein that speeds up chemical reactions in the body) that adds chemicals called phosphates to other molecules, such as sugars or proteins. This may cause other molecules in the cell to become either active or inactive. Kinases are a part of many cell processes. Some cancer treatments target certain kinases that are linked to cancer.

**KRAS gene**: A gene that may cause cancer when it is mutated (changed). The KRAS gene makes the KRAS protein, which is involved in cell signaling pathways, cell growth, and apoptosis (cell death). Agents that block the activity of the mutated KRAS gene or its protein may stop the growth of cancer.

**Metastatic**: Having to do with metastasis, which is the spread of cancer from the primary site (place where it started) to other places in the body.

**Molecular pathway**: A series of actions among molecules in a cell that leads to a certain end point or cell function.

**Mortality**: Mortality refers to the death rate, or the number of deaths in a certain group of people in a certain period of time.

**Mutation**: Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

**Nanotechnology**: The field of research that deals with the engineering and creation of things from materials that are less than 100 nanometers (one-billionth of a meter) in size, especially single atoms or molecules. Nanotechnology is being studied in the detection, diagnosis, and treatment of cancer.

**Overall survival**: The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works.

**Overall survival rate**: The percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease, such as cancer. The overall survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after their diagnosis or the start of treatment. Also called survival rate.
**Palliative care:** Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of palliative care is to prevent or treat as early as possible the symptoms of a disease, adverse effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, supportive care, and symptom management.

**Progression free survival:** The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works. Also called PFS.

**Prostate-specific antigen (PSA):** A protein made by the prostate gland and found in the blood. PSA blood levels may be higher than normal in men who have prostate cancer, benign prostatic hyperplasia (BPH), or infection or inflammation of the prostate gland. Also called prostate-specific antigen.

**Proteomics:** The study of the structure and function of proteins, including the way they work and interact with each other inside cells.

**Response:** In medicine, an improvement related to treatment.

**Resistant cancer:** Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant during treatment. Also called refractory cancer.

**RNA:** One of two types of nucleic acid made by cells. RNA contains information that has been copied from DNA (the other type of nucleic acid). Cells make several different forms of RNA, and each form has a specific job in the cell. Many forms of RNA have functions related to making proteins.

**Quality of life:** The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual’s sense of well-being and ability to carry out various activities.

**Radioiodine:** A radioactive form of iodine, often used for imaging tests or to treat an overactive thyroid, thyroid cancer, and certain other cancers. To treat thyroid cancer, the patient takes a large dose of radioactive iodine, which kills thyroid cells.

**Randomization:** When referring to an experiment or clinical trial, the process by which animal or human subjects are assigned by chance to separate groups that compare different treatments or other interventions. Randomization gives each participant an equal chance of being assigned to any of the groups.

**Receptor:** A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific effect in the cell.

**Screening:** Checking for disease when there are no symptoms.

**Stem cell:** A cell from which other types of cells develop. For example, blood cells develop from blood-forming stem cells.

**Supportive care:** Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, adverse effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, palliative care, and symptom management.

**Targeted therapy:** A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer adverse effects than other types of cancer treatments.

**Tyrosine kinase inhibitor (TKI):** A drug that interferes with cell communication and growth and may prevent tumor growth. Some tyrosine kinase inhibitors are used to treat cancer.
ASCO Resources

CancerProgress.Net
www.cancerprogress.net
Progress timeline of milestones for nearly 20 cancers and all types of patient care

ASCO Guidelines
www.asco.org/guidelines
Information on ASCO clinical practice guidelines, Provisional Clinical Opinions and guideline endorsements

Cancer.Net
www.cancer.net
Comprehensive information on more than 120 cancer types and cancer-related syndromes

ASCO in Action
ascoaction.asco.org
News, advocacy, and analysis on cancer policy from ASCO

State of Cancer Care Report
www.asco.org/stateofcancercare
ASCO’s annual report on the state of the cancer care delivery system in the United States

Conquer Cancer Foundation
www.conquercancerfoundation.org
An organization working to create a world free from the fear of cancer by funding breakthrough research, sharing leading-edge knowledge, and improving the quality of care and access to care