Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

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A MESSAGE FROM ASCO’S PRESIDENT

The past few years have been incredibly exciting in cancer research and care. Some of the advances highlighted in Clinical Cancer Advances 2016 are already improving the lives of patients today, and many others provide direction for further research.

Compared with when I started my career in oncology, today we do the unthinkable. We no longer treat cancer simply by its type or stage. In the era of precision medicine, we select— and rule out— treatments based on the genomic profile of each patient and the tumor. We manage once-debilitating adverse effects to the point that many, if not most, patients can continue their daily activities during treatment.

No recent advance has been more transformative than the rise of immunotherapy, particularly over this past year, making immunotherapy the American Society of Clinical Oncology’s (ASCO’s) Advance of the Year.

The immunotherapy concept is simple: unleash the body’s immune system to attack cancer. It has proven extremely difficult, however, to develop treatments that deliver real, consistent results. Decades of bold ideas, dedication, and financial investment in research have been required to prove immunotherapy’s worth as a treatment for people with an array of different cancers.

Until the US Food and Drug Administration approved the first immune checkpoint blocker to treat advanced melanoma in 2011, life expectancy for patients with that disease was usually measured in months. But new immunotherapies have extended that time to years—and melanoma was just the tip of the iceberg. In 2015, clinical trials showed that the approach holds promise for patients with other hard-to-treat cancers, including advanced lung, kidney, bladder, and head and neck cancers and Hodgkin lymphoma.

Of course, immunotherapy is not the only area of recent progress—for it from. We also continue to make tremendous advances in surgery, chemotherapy, radiation therapy, and targeted therapy, and we are learning to deploy these approaches in far better ways.

These advances are proof of the importance of our nation’s investments in cancer research. In fact, more than 30% of the studies featured in this report were made possible by federal funding.

Congress has taken an important step forward in recognizing the vital importance of federal research by increasing fiscal year 2016 funding for the National Institutes of Health (NIH) and the National Cancer Institute (NCI). This hard-fought victory came after a decade-long decline in NIH funding and significant advocacy effort by ASCO and the larger biomedical research community.

ASCO calls on Congress to build on this year’s investment and provide robust funding for the federal research enterprise moving forward. We believe that is what it will take to achieve more of the kinds of advances highlighted in this report.

Although research funding is a key component, it is not the only factor affecting future progress against cancer. We also need to better harness technologic opportunities, including big data analytics. Several big data initiatives are currently under way, including ASCO’s CancerLinQ. By assembling and analyzing data from millions of electronic health records and other sources, CancerLinQ will allow us to learn from every individual treated for cancer—not just the fewest than 5% of patients who currently participate in clinical trials.

We also need to make sure that the care we provide offers real value to our patients. In June 2015, ASCO took an important step by publishing a conceptual framework for assessing the value of new cancer treatments on the basis of clinical benefits, adverse effects, and cost. This framework is a big advance forward in the needed effort to improve the value of medical care, and ASCO will remain heavily engaged in this issue.

Clinical Cancer Advances 2016 represents and acknowledges the collective wisdom that has made progress against cancer possible. I hope these achievements will inspire all of us to do our part to further accelerate the pace of research and discovery to help the millions of people who are living with cancer and the millions more who will face a cancer diagnosis in their lifetime.

Julie M. Vose, FASCO
President
American Society of Clinical Oncology

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In 2015, approximately 1.7 million Americans received a cancer diagnosis. In 2030, this number will rise to nearly 2.3 million. Today, approximately two of three Americans will live at least 5 years after being diagnosed with an invasive cancer.

In addition, with care that aims to balance effectiveness of treatment alongside the importance of quality of life, more patients than ever are not just living longer but able to lead full lives. Yet, cancer remains a leading cause of death in the United States, claiming approximately 600,000 lives in 2015.

On a global level, cancer is now one of the world’s most pressing health challenges. Seven of every 10 cancer deaths occur in Africa, Asia, and Central and South America. By the year 2030, these cancer deaths could increase globally by as much as 80%, according to WHO estimates.

The scientific community is working hard to avert this grim projection. Clinical research is the bedrock of progress against cancer, and discoveries are moving from bench to bedside faster than ever. The best example of this in recent years is the explosion of immunotherapy approaches for a variety of cancers.

Overall, research progress from one year to the next is incremental, and true breakthroughs are rare. Nevertheless, knowledge gathered from any single study can inform further research, and cumulative knowledge and progress result in tangible benefits for patients.

This report, “Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer,” reviews the recent top advances and emerging trends in clinical cancer research. These advances are based on discoveries in cancer biology that are leading to improved cancer treatments for patients. Now in its 11th year, this report also highlights policy issues and developments that will affect the future of cancer research in the United States and determine the pace of progress going forward.

Advance of the Year: Cancer Immunotherapy

Just 5 years ago, the immunotherapy drug ipilimumab was hailed as the first treatment to improve the survival of people with advanced melanoma. Today, newer immunotherapies directed against programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) proteins seem to be as or even more effective, while causing fewer adverse effects. Additional studies have suggested that combining immunotherapy agents from these two different classes of drugs may provide even more benefit, although the combined regimens can be more toxic.

Research reported in 2015 showed that immunotherapies can improve outcomes for other difficult-to-treat cancers. Within 3 months of approving the first PD-1 drug for melanoma, the US Food and Drug Administration (FDA) expanded its use to treatment of advanced lung cancer. This advance has major implications for cancer care, because lung cancer is the most common and most deadly malignancy worldwide.

Last year, early reports indicated that the immunotherapy drugs that block PD-1 or PD-L1 proteins may play a role in the treatment of other cancers, including those that begin in the bladder, kidney, liver, and head and neck. These findings revealed potential new options for patients with advanced disease, especially those who had exhausted all standard therapy options.

Exciting early signs of success have also been reported with experimental immunotherapy strategies for certain blood cancers (acute lymphoblastic leukemia [ALL] and diffuse large B-cell lymphoma [DLBCL]) and glioblastoma, the deadliest brain cancer in adults.

This continued wave of success with immunotherapies, which has extended beyond just a few tumor types, promises to transform cancer care, thus making it ASCO’s Advance of the Year. Just as important, these achievements are sparking more innovation, such as the development of approaches that pair immunotherapy with traditional cancer treatments—chemotherapy, targeted therapy, and radiation therapy. The first clinical studies of such combinations are already under way.

Treatment-Resistant Cancers: Precision Medicine Pushes Ahead

Drug resistance is a notorious and far too common problem in cancer therapy. Each time a cancer recurs or worsens, it becomes even more difficult to treat. Although most advanced-stage cancers cannot be cured, having more treatment options to choose from can improve both the length and quality of life.

Precision medicine approaches have been making steady gains against cancers that are resistant to traditional cancer therapy. The ever-expanding understanding of tumor biology provides direction for the development of new therapies. Treatments like targeted therapy are increasingly being tailored to the key genetic mutations that drive the growth of particular cancers.

In 2015, researchers reported marked gains in overcoming treatment resistance in several difficult-to-treat forms of blood, ovarian, lung, and breast cancers. New targeted treatments have been shown to keep cancer growth at bay for months to years. In each case, the success of newer treatments has stemmed from discoveries of the molecular underpinnings of cancer in general and of the mechanisms of drug resistance in particular.

Improving Quality of Life

Maintaining or improving quality of life for patients throughout the cancer continuum is an important component of overall cancer care. It is now recognized that maintaining or improving quality of life is particularly important for patients with advanced-stage disease; therefore, it is especially important to consider the balance of potential benefits and harms of various treatment options.

Accumulating clinical trial evidence supports the long-held belief that proper selection of treatment for an individual patient on the basis of his or her circumstances can help maximize quality of life. For example, recent research has shown that whole-brain irradiation for some patients with brain metastases exacerbates cognitive decline without extending survival. Meanwhile, another study identified a group of patients who nonetheless may benefit from this therapy.

Patients Gain Access to New Cancer Therapies

Between October 2014 and October 2015, the FDA approved 10 new cancer treatments and expanded use for 12 previously approved...
This report features examples of notable research successes achieved thanks to funding from the US National Institutes of Health (NIH), including:

- A large, nationwide analysis that found remarkable improvements in long-term childhood cancer survival rates over three decades.
- A large clinical trial that revealed an additional hormone treatment option to reduce the risk of new or recurrent breast cancer after ductal carcinoma in situ (DCIS).
- An early clinical trial that showed that a combination of two novel targeted drugs may slow the growth of a difficult-to-treat form of ovarian cancer.
- A clinical trial that demonstrated that avoiding whole-brain irradiation for limited brain metastases helps preserve patient quality of life.
- New evidence confirming that early palliative care not only extends patients' lives but can also benefit caregivers.

Despite the progress made in improving the care of patients with cancer, federal funding for cancer research had remained flat for more than a decade and, in fact, had decreased when adjusted for inflation. In inflation-adjusted dollars, the NIH budget was 24% lower in 2015 than it was in 2003 (Fig 1).

Federal Funds Support Critical Research

Clinical cancer research in the United States is made possible through funding from both the public and private sectors. Federal funding for cancer research has led to significant advances in cancer prevention, detection, diagnosis, treatment, and quality of life over the last half century.

When it comes to high-risk, pioneering research, federal funding is indispensable. Federally funded research also helps answer critical patient care questions that private industry research is unlikely to address. More than 14.5 million cancer survivors are alive in the United States today, largely because of the nation's commitment to cancer research.

“One of my proudest accomplishments as a member of Congress is helping to double NIH’s funding. That happened over a decade ago and since then the NIH’s purchasing power has declined significantly. Now we must reignite our nation’s investment in medical research. Congress must not preclude scientists from doing lifesaving research.”

—Representative Rosa DeLauro (D-CT)
Sustained robust federal funding is critical to continued progress.

**FISCAL YEAR 2016 BUDGET**

- NIH: $32B
  - 6.6% increase over FY 2015
- NCI: $5.2B
  - 5.34% increase over FY 2015

*20% funding decrease when adjusted for inflation.

**Funding cuts harm us all, especially people living with cancer and their families**

**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 of support to local economies is lost.

ASCO is calling on lawmakers to build on this year’s NIH and NCI investment to ensure tomorrow’s cures.

For more information visit asco.org/nihfunding

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Fig 1. Sustained robust federal funding critical to cancer progress.
In December 2015, Congress took an important step forward in recognizing the vital importance of federal research funding. The fiscal year 2016 budget contained a 6.6% increase for the National Institutes of Health (NIH) bringing their total budget to $32.1 billion, including $5.2 billion for the National Cancer Institute (NCI).

### Call to Action

ASCO is calling on lawmakers to build on this year’s NIH and NCI investment to ensure tomorrow’s cures.

Sustained funding of the NIH and the NCI is critical to maintaining the pace of scientific discovery, continued progress against cancer, and the development and delivery of new cancer therapies for millions of patients, now and into the future.

### About Clinical Cancer Advances

ASCO developed this annual report, now in its 11th year, to document the important progress being made in clinical cancer research and highlight emerging trends in the field. As a whole, this document attests to the current state of the science and envisions future directions of cancer research.

ASCO is supported by its affiliate organization, the Conquer Cancer Foundation, which funds groundbreaking research and programs that make a tangible difference in the lives of people with cancer. For ASCO information and resources, visit www.asco.org. Patient-oriented cancer information is available at www.cancer.net. The content of Clinical Cancer Advances was developed under the direction of an 18-person editorial board comprising experts in a wide range of oncology subspecialties. The editors reviewed research reports published in peer-reviewed scientific and medical journals or presented at major scientific meetings over a 1-year period (October 2014 to October 2015).

To be selected for inclusion in Clinical Cancer Advances, a study must improve meaningful outcomes for patients, such as overall survival or quality of life, and also have a substantial scientific impact on the field of clinical oncology. The advances featured in this report cover the full range of clinical research disciplines: prevention, treatment, patient care, and tumor biology.

### ADVANCE OF THE YEAR: CANCER IMMUNOTHERAPY

Although all research achievements highlighted in this report are remarkable, one area clearly stands out from the rest: cancer immunotherapy, ASCO’s Advance of the Year. In just a few short years, researchers and regulators have moved several different immunotherapy strategies from bench to bedside.

From the first astounding successes in advanced melanoma, there is now evidence that immunotherapy works against a range of cancers. Even for patients who have exhausted all traditional treatments, immunotherapy is able to halt cancer growth, often with only mild adverse effects.

Scientists first conceived the idea of manipulating the body’s immune system to attack cancer more than a century ago. However, the task proved to be fraught with challenges and setbacks. It would take a deeper understanding of both cancer biology and the immune system to realize the potential of immunotherapy.

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

Over 30 years, more than $90 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 who are 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.

Several of the studies featured in this year’s Clinical Cancer Advances report were led by past Conquer Cancer Foundation grant recipients who have continued their careers in oncology research.

### About the American Society of Clinical Oncology

Founded in 1964, ASCO is the world’s leading professional organization representing physicians who care for people with cancer. With nearly 40,000 members, ASCO is committed to conquering cancer through research, education, and promotion of the highest quality patient care.

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system before safe and effective immunotherapy could be delivered to patients.

As fundamental research on cancer immunotherapy intensified, clinical trials of promising approaches followed in quick succession. Two main strategies are now being explored, both achieving major success over the past year. The first involves unleashing the body's natural immune response to cancer, and the second helps the immune system find and destroy cancer cells.

**Immune Checkpoint Inhibitors: Enhancing the Immune Response to Cancer**

An overactive immune system can lead to excessive inflammation and development of autoimmune disorders. The body uses molecules known as immune checkpoints to control the strength and duration of immune responses, minimizing damage to healthy tissue. Some tumors produce these same molecules and thereby suppress the immune response to the tumor.

Immune checkpoint inhibitors release these tumor-induced brakes on the immune system, unleashing it to attack malignant tumors and stop their growth. These treatments are showing promising results in many types of cancer, including melanoma and lung cancer.

The first FDA-approved immune checkpoint inhibitor, ipilimumab, blocks the CTLA-4 molecule on T cells, which leads to a broad enhancement of immune responses, including attacks on cancer cells. A range of newer drugs targets a different immune checkpoint protein known as PD-1. Those treatments work by preventing cancer cells from attaching to the PD-1 protein on immune cells, which leads to an increased antitumor immune response and generally fewer adverse effects (Fig 2).

**Melanoma Immunotherapy Moves Ahead: Comparing and Combining Treatments**

By the end of 2014, three life-extending checkpoint inhibitor immunotherapies were FDA approved for the treatment of advanced melanoma: ipilimumab, nivolumab, and pembrolizumab. Overall, these new drugs have surpassed the efficacy of traditional melanoma treatments. Nevertheless, advanced melanoma remains incurable, although prolonged remissions induced by these immunotherapies extend life for multiple years for certain patients. In 2015, new studies explored how these three treatments stack up against one another and how to maximize their overall benefit—as stand-alone therapies and as combination regimens.

Ipilimumab, a CTLA-4 immune checkpoint inhibitor, was the first treatment to extend the lives of patients with advanced melanoma. Yet, recent evidence suggests that nivolumab and pembrolizumab, both PD-1 checkpoint inhibitors, may be more effective than ipilimumab. For example, in a recent phase III study, the 1-year survival rates were 68% and 74% for patients treated with pembrolizumab (depending on treatment schedule), compared with 58% for those who received ipilimumab. In addition, pembrolizumab was associated with a lower rate of severe adverse effects, such as fatigue, diarrhea, rash, and colitis.

Patients with advanced melanoma that worsens after ipilimumab or ipilimumab and a BRAF inhibitor (for patients with BRAF-mutated melanoma) gained a new treatment option in 2014. The FDA granted accelerated approval to the PD-1 checkpoint inhibitor nivolumab on the basis of preliminary findings from a phase III trial. In this clinical trial, tumors shrunk in 32% of patients treated with nivolumab and only in 11% of those who received standard...
chemotherapy. Longer follow-up will be needed to determine if nivolumab extends survival of patients with advanced melanoma.

Severe adverse effects of nivolumab included increased pancreatic and liver enzymes (lipase, ALT, AST), anemia, and fatigue, whereas chemotherapy was associated with more hematologic toxicity, including lower WBC counts (neutropenia, thrombocytopenia) and anemia. Severe treatment-related adverse effects occurred less frequently with nivolumab than with chemotherapy.

More broadly, these findings imply that patients whose tumors stopped responding to one type of immune checkpoint inhibitor may still benefit from a different checkpoint inhibitor. In fact, some experts believe that combining immunotherapies may be the most promising strategy for patients with advanced melanoma.

An early-stage clinical trial of an immune checkpoint inhibitor combination showed encouraging results. Tumor shrinkage rates were nearly six-fold higher (61% v 11%) among patients with untreated advanced melanoma who received ipilimumab and nivolumab than among those who received ipilimumab and placebo. The combination treatment controlled tumor growth longer than ipilimumab alone, but the rates of severe adverse effects, colitis, diarrhea, and elevated liver enzyme (ALT) levels were higher with the immunotherapy combination (54% v 24%). On the basis of these findings, the FDA granted accelerated approval to nivolumab in combination with ipilimumab for the treatment of patients with advanced melanoma without the BRAF V600 genetic mutation.

Meanwhile, results from a larger phase III trial of the same immunotherapy combination were also reported in 2015. The trial included nearly 1,000 patients with advanced melanoma who had not previously received cancer treatment. The median time before the disease worsened was 11.5 months with ipilimumab and nivolumab, 7 months with nivolumab alone, and 3 months with ipilimumab alone.

The rates of adverse effects were consistent with prior studies and were the highest among patients who received the immunotherapy combination. Given that the combination treatment was associated with the highest rate of severe adverse effects, the researchers also sought to determine whether there would be a particular group of patients who could benefit from this treatment.

They found that patients with higher levels of the PD-L1 protein in their tumors seemed to do as well with nivolumab alone as with the combination, with a median period of 14 months before the disease became worse. In contrast, patients with low PD-L1 levels in their tumors benefited much more from the combination than from nivolumab alone. If validated, these findings would provide clinically relevant information for appropriate selection of patients who are most likely to benefit, while sparing patients in whom toxicities would not be justified.

**New Treatment Paradigm for Lung Cancer**

The role of immunotherapy reached beyond melanoma to include patients with lung cancer in 2015. Highly promising clinical trials explored the role of immunotherapy using agents directed toward the PD-1 or PD-L1 immune checkpoint proteins. In addition, physicians gained new insight into which patients may benefit most from these drugs.

Lung cancer is the most common malignancy worldwide and the leading cause of cancer-related death, taking 1.6 million lives each year (according to WHO 2012 estimates). Although advanced lung cancer remains incurable, targeted therapies, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma receptor tyrosine kinase (ALK) inhibitors, may help control tumor growth. However, only a small proportion of patients with tumors that harbor specific genetic abnormalities can benefit from targeted therapies at this time.

Non–small-cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 85% of all cases. With modern platinum-based chemotherapy, the median life expectancy is only approximately 10 months. For patients whose disease worsens after initial treatment, docetaxel chemotherapy offers only a modest improvement in survival.

Moreover, the adverse effects of chemotherapy are too difficult for many patients to bear. Growing research evidence suggests that immunotherapy may be able to control advanced lung cancer longer, with fewer adverse effects.

In March 2015, the FDA approved nivolumab for the treatment of squamous lung cancer that worsens after platinum-based doublet chemotherapy. The approval was given on the basis of findings from a randomized clinical trial of patients with advanced, squamous NSCLC. The clinical trial reported that compared with standard second-line chemotherapy, nivolumab significantly improved the median overall survival (9 months v 6 months), nearly doubling the 1-year survival rate (42% v 24%).

Another randomized trial showed that nivolumab can provide a similar benefit to patients with advanced nonsquamous NSCLC, the predominant form of the disease. Compared with standard chemotherapy, the median survival was prolonged with nivolumab (12.2 months v 9.4 months). This clinical trial also suggested that patients who had tumors with high PD-L1 levels experienced more benefit from nivolumab.

Generally, nivolumab was easier for patients to tolerate than docetaxel, causing fewer adverse effects. No new toxicities were reported with nivolumab in the treatment of NSCLC. However, rare but serious inflammation involving the lungs (pneumonitis), colon (colitis), and kidneys (nephritis) was also reported in this trial. In October 2015, the FDA expanded the approved use of nivolumab to treat patients with nonsquamous NSCLC whose disease worsened during or after platinum-based chemotherapy.

Perhaps even more promising than the finding that immune checkpoint inhibitors are active for patients with lung cancer are...
the early results showing that these responses are quite durable. For example, in one early clinical trial that included patients with advanced, squamous, or nonsquamous NSCLC, the 2- and 3-year survival rates were 42% and 27%, respectively, at the dose chosen for further development.

Treatment with the PD-1 blocking immunotherapy pembrolizumab was associated with a median survival of 12 months in another early study of patients with advanced, previously treated NSCLC. Overall, tumors shrank in approximately one in five patients, but the rate was again much greater in those with high PD-L1 levels, of whom nearly half experienced tumor shrinkage. This group of patients also lived longer before the cancer worsened. No new safety concerns were reported.

In September 2015, the FDA granted accelerated approval to pembrolizumab as a treatment of patients with advanced, PD-L1-positive NSCLC that worsens after other treatments. Early reports from ongoing studies have suggested that nivolumab and pembrolizumab may also be effective as initial therapies for patients with advanced NSCLC.

A new immune checkpoint inhibitor, atezolizumab, has also shown promising results in the treatment of advanced NSCLC. Atezolizumab unleashes the immune response to cancer by blocking the PD-L1 protein on tumor cells. In an early study, the median survival among patients who received atezolizumab was 12.6 months, compared with 9.7 months among those treated with docetaxel chemotherapy.

As in the other studies, patients with the highest levels of PD-L1 in their tumors and immune cells benefited even more. In this group, the median survival was 15.5 months with immunotherapy, compared with 11.1 months with docetaxel. In contrast, among patients with low PD-L1 levels, atezolizumab did not extend survival compared with docetaxel.

Fewer patients experienced severe treatment-related adverse effects in the atezolizumab group compared with the docetaxel group. The most common severe adverse effects related to atezolizumab were pneumonia and increased AST levels.

In February 2015, the FDA granted atezolizumab a breakthrough therapy designation for the treatment of PD-L1–positive NSCLC that worsens after platinum chemotherapy, and a randomized phase III trial for this indication is under way (ClinicalTrials.gov identifier: NCT02486718). Other ongoing phase III clinical trials are exploring atezolizumab in combination with chemotherapy.

The therapeutic mechanism of immune checkpoint inhibitors—unleashing immune response to cancer—is profoundly different from that of standard treatments for NSCLC. This may explain the longer duration of benefit some patients experience from immunotherapy compared with chemotherapy or targeted therapy. Unlike other therapies, the effects of immunotherapy can persist long after the patient stops treatment. Future research directions for lung cancer immunotherapy include evaluating combinations of PD-1 or PD-L1 inhibitors with chemotherapy, targeted therapy, and other types of immunotherapy.

### Broadening the Possibilities for Checkpoint Inhibitors

The past year brought early reports suggesting that immune checkpoint inhibitors targeting PD-1 and PD-L1 are effective across a range of different cancer types, beyond melanoma and lung cancer. A particularly encouraging finding was that immunotherapy was effective against many tumors that were resistant to traditional treatments.

**Bladder cancer.** In the last three decades, there has been little progress in the treatment of advanced bladder cancer. Most patients with advanced bladder cancer are older (the median age of diagnosis is 73 years), and many suffer from kidney impairment. As a result, many patients forgo chemotherapy to avoid its difficult adverse effects. Outcomes are poor for patients who cannot tolerate chemotherapy or whose cancer worsens after initial chemotherapy.

Findings from an early clinical trial of patients with advanced urothelial bladder cancer bring new hope. The PD-L1 immune checkpoint inhibitor atezolizumab shrank tumors rapidly—within weeks of starting treatment in many study participants. Again, atezolizumab was particularly effective for patients who had high PD-L1 levels in their tumors and immune cells, with approximately half of these patients experiencing tumor shrinkage. The median duration of response was much longer than that typical for chemotherapy.

The most commonly reported treatment-related adverse effects were decreased appetite and fatigue. Severe adverse effects, such as weakness (asthenia) and hematologic abnormalities (thrombocytopenia and decreased blood phosphorus), occurred in 4% of patients. On the basis of these findings, the FDA granted atezolizumab a breakthrough therapy designation for the treatment of PD-L1–positive, advanced bladder cancer in 2014. An ongoing phase III trial seeks to compare atezolizumab with standard chemotherapy in patients with advanced bladder cancer (ClinicalTrials.gov identifier: NCT02302807).

**Kidney cancer.** Advanced kidney cancer is another malignancy in dire need of better treatments. The most common type of kidney cancer in adults is called renal cell carcinoma (RCC). At the time of diagnosis, nearly one third of patients with RCC already have metastatic disease, which is difficult to treat.

The last major advance in kidney cancer care occurred a decade ago, with the introduction of targeted therapies for metastatic RCC. Vascular endothelial growth factor (VEGF)–directed therapies and inhibitors of the mammalian target of rapamycin (mTOR) extended the median survival of patients with this disease from 1 year to nearly 3 years.

Yet, new drugs are needed to further extend survival when kidney cancers worsen despite VEGF- and mTOR-targeted therapies. Recent research has suggested that PD-1–directed immunotherapy may improve the outlook for at least some of these patients.

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**Breakthrough Therapy Designation**

The US Food and Drug Administration (FDA) Breakthrough Therapy Designation serves to expedite the development and review of drugs for treating serious or life-threatening illnesses where preliminary clinical data suggest the drug may provide a substantial improvement in patient outcomes. The designation helps ensure patients gain faster access to promising new treatments through FDA approval.
In a randomized phase II trial, nivolumab shrank tumors in approximately 20% of patients with metastatic clear cell RCC who were previously treated with a VEGF inhibitor. One striking result was related to the durability of these responses, which lasted more than 22 months in some patients. The median overall survival extended up to 25 months, roughly 1 year longer than is typically achieved with targeted therapies, as reported in prior clinical trials of patients with advanced RCC. Fatigue was the most common treatment-related adverse effect.

Meanwhile, larger ongoing trials are exploring additional uses of PD-1–directed therapies for metastatic RCC. In a phase III study of patients with advanced RCC who were previously treated with VEGF inhibitors, nivolumab improved outcomes compared with the mTOR inhibitor everolimus. The median survival was 25 months with nivolumab versus 19.6 months with everolimus. The toxicity profile of nivolumab was consistent with prior reports. However, compared with everolimus, there were fewer severe treatment-related adverse events reported.

Furthermore, although tumors shrank in 25% of patients treated with nivolumab, only 5% of those treated with everolimus experienced tumor shrinkage. Interestingly, however, everolimus delayed tumor growth for a similar length of time as nivolumab, approximately 4 months.

Another ongoing phase III trial is investigating the combination of nivolumab and ipilimumab as an initial treatment of advanced kidney cancer (ClinicalTrials.gov identifier: NCT02231749). The FDA approved nivolumab for the treatment of RCC in November 2015.

Liver cancer. Liver cancer is the second most common cause of death resulting from cancer worldwide, claiming approximately 750,000 lives each year. The most common type of liver cancer is hepatocellular carcinoma (HCC). The only FDA-approved treatment of advanced HCC, sorafenib, extends survival by merely 3 months.

Last year, researchers reported preliminary findings showing a promising role for nivolumab in the treatment of metastatic HCC. In the small study, nearly 20% of patients who had marked tumor shrinkage in response to nivolumab, Tumors completely disappeared in two patients. The responses were durable, lasting 9 months or longer in nearly all patients who responded. At 1 year, 62% of patients treated with nivolumab were still alive. This is a dramatic improvement when compared with the historical tumor response rate for sorafenib of only 2% to 3% and 1-year survival rate of 30%. Again, no new safety signals were reported. Of note, severe adverse effects of nivolumab included elevated ALT, AST, and lipase levels.

These early findings suggest that immunotherapy may be an effective treatment of some patients with advanced liver cancer. An expansion phase of this study, which seeks to recruit 400 patients, is projected to be completed in 2018 (ClinicalTrials.gov identifier: NCT01658878).

Head and neck cancer (HNC). People with recurrent or metastatic HNC have a poor prognosis. With existing treatments—chemotherapy and the targeted drug cetuximab—survival ranges from 10 to 12 months, on average. Overall, few patients respond to these treatments, and adverse effects are significant.

Early findings suggest PD-1 immune checkpoint inhibitors are active in patients with HNC. In one small trial, approximately 25% of patients who received the PD-1 immune checkpoint inhibitor pembrolizumab experienced tumor shrinkage. In contrast, the reported response rate to cetuximab was less than 13% in prior clinical trials. Although the toxicity profile of pembrolizumab in this population was similar to that in other trials, only 10% of patients experienced severe adverse effects, such as swelling of the face and lung inflammation (pneumonitis).

Perhaps as important, these agents might be active regardless of whether HNC is associated with human papillomavirus (HPV). It is well known that a subgroup of HNCs is HPV-positive disease, and that these tumors respond better to standard treatment than those that are HPV negative. Yet, in the clinical trial discussed here, pembrolizumab was active across a wide range of patients, including those with HPV-positive and HPV-negative tumors.

Although these early data are encouraging, larger studies are needed to determine if pembrolizumab can prolong patient survival. Two phase III trials evaluating pembrolizumab versus standard treatment in patients with recurrent or metastatic HNC are already under way (ClinicalTrials.gov identifiers: NCT02358031 and NCT02252042).

Blood cancer: Hodgkin lymphoma. Hodgkin lymphoma is a cancer of the lymphatic system, and it is most common in two age groups: age 15 to 40 years (particularly young adults in their 20s) and older than age 55 years. With existing initial treatments, four of five patients survive 5 years after a Hodgkin lymphoma diagnosis. People with the disease seldom experience recurrence if a complete response is achieved with initial treatment. When Hodgkin lymphoma does come back, however, it is more difficult to treat. At that time, patients are typically offered additional chemotherapy, radiation therapy, or stem-cell transplantation.

Emerging research data suggest that immunotherapy, specifically PD-1 blockade, may play a role in the treatment of recurrent Hodgkin lymphoma. Moreover, it has been speculated that a certain genetic abnormality makes Hodgkin lymphoma particularly vulnerable to PD-1 blockade. Findings from a small clinical trial of adult patients with recurrent Hodgkin lymphoma support this hypothesis (this study was funded in part by a grant from the NIH).

Nearly all the patients in the trial had previously received three or more treatments, including stem-cell transplantation and a targeted drug. Remarkably, the great majority (20 of 23 patients) responded to nivolumab, with cancer completely disappearing in 17%. By 6 months, only 14% of patients experienced disease progression.

The most common treatment-related adverse effects were rash and decreased platelet count (thrombocytopenia). Severe treatment-related adverse effects were rare.

Genetic abnormality tied to better response to PD-1 immunotherapy. Tumors with a high number of genetic mutations are likely to trigger a strong immune response, because they make more proteins (antigens) that the immune system recognizes as foreign. Melanoma, bladder cancer, and lung cancer are among the cancers with the most mutations.

In some patients with other types of cancers, the tumors have large numbers of mutations as a result of a genetic abnormality called mismatch repair deficiency, which undermines the ability of a cell to repair DNA damage. Scientists have speculated that tumors
with this abnormality may be susceptible to immune checkpoint blockade.

Mismatch repair deficiency occurs in approximately 15% of colorectal cancers. It is also found less frequently in other types of cancer, such as stomach, small bowel, endometrial, prostate, and ovarian cancers. The abnormality is sometimes inherited from parents, as is the case for patients with Lynch syndrome, but more often, mismatch repair deficiency develops at random during a person’s life.

One small trial reported last year provided the first evidence that mismatch repair–deficient tumors are susceptible to PD-1 blockade (this study was funded in part by a grant from the NIH). Mismatch repair deficient colorectal cancer responded to treatment with the immune checkpoint inhibitor pembrolizumab (the median progression-free and overall survival were not reached). In contrast, none of the eight patients with colorectal cancers that were not mismatch repair deficient experienced tumor shrinkage; the median progression-free survival was 2.2 months.

Furthermore, the researchers found that pembrolizumab was active against other types of cancer with mismatch repair deficiency, such as endometrial, ampullary, duodenal, and stomach cancers. Five of seven patients responded to pembrolizumab, and the median time to disease progression was 5.4 months.

The toxicity profile of pembrolizumab was similar to that in other trial reports. Severe adverse effects, such as low serum protein levels (hypoalbuminemia), low blood cell counts (anemia and lymphopenia), and bowel obstruction, occurred in 41% of patients.

Although this study was small, it opens the possibility of a new treatment option for patients with advanced cancer who have tumors with mismatch repair deficiency. More broadly, it shows that evaluation of the tumor genome can help identify patients who benefit from immunotherapy, regardless of the type of tumor they have. It is already suspected that cancers with other DNA repair deficiencies might also be sensitive to PD-1 blockade.

**Novel Immunotherapy Approaches Boost the Immune System**

*T-cell therapies promising for blood cancers.* In addition to immune checkpoint inhibitors, researchers are exploring other immunotherapy approaches, all of which are centered on T cells. A unique new immunotherapy, the antibody blinatumomab, attaches to two different proteins on WBCs: CD19 on B cells and CD3 on T cells. By doing so, the antibody brings the cancer-killing T cells into contact with the malignant B-cell leukemia cells.

In an early-stage trial, nearly one third of patients with relapsed or treatment-resistant ALL had no evidence of cancer (complete remission) after receiving blinatumomab. The responses were durable, lasting more than 6 months in many patients.

The study participants had an uncommon but aggressive type of ALL known as Philadelphia chromosome-negative precursor B-cell ALL, a rapidly growing cancer in which the bone marrow makes too many immature WBCs. On the basis of these results, in December 2014, the FDA approved blinatumomab to treat this difficult disease.

Although more research is needed to determine whether blinatumomab can improve survival compared with standard chemotherapy, it seems that immunotherapy will play a role in the treatment of ALL. Future directions include exploring use of blinatumomab earlier in the course of the disease and in combination with other therapies.

Another unique new strategy is the so-called chimeric antigen receptor (CAR) T-cell therapy. This approach involves collecting T cells from a patient, genetically reprogramming them in the laboratory, and infusing them back into the patient. The reprogrammed T cells make specific proteins that enable them to find and attack cancer cells throughout the body.

Earlier reports have suggested that patients with various difficult-to-treat blood cancers might benefit from CAR T-cell therapy. For example, CD19-directed CAR T cells are programmed to attack malignant B cells that have the CD19 molecule on their surface.

In a study of adults and children with relapsed ALL, 27 of 30 patients achieved complete remission after receiving this novel therapy, and for some (19 of 30), the remissions were durable, lasting as long as 2 years (this study was funded in part by a grant from the NIH). Overall, 78% of patients were alive 6 months after receiving CAR T cells.
In another early study, 12 of 15 patients with chemotherapy-resistant DLBCL and other blood cancers responded to CD-19 directed CAR T cells, with cancer completely disappearing in eight of the patients (this study was funded in part by a grant from the NIH).33

Although these findings are promising and support further research, the studies were small and limited to patients with hard-to-treat cancers. It is not yet clear if CAR T-cell therapy will have broader use in the future. In addition, because CAR T-cell therapy can cause considerable toxicities, such as fever (pyrexia), low blood pressure (hypotension), delirium, and neurologic adverse effects, it is administered only in specialized clinical centers at this time.

Cancer vaccines: A potential new treatment option for brain cancer. Glioblastoma is an aggressive and incurable form of brain cancer. Most patients are diagnosed when the disease is already at an advanced stage. Although surgery and chemotherapy can be effective initially, the cancer inevitably worsens over time. After a relapse, few treatment options remain, and the average survival duration is only 1.5 years.

Researchers have been exploring several new avenues for treating brain cancer, including immunotherapy strategies, such as vaccines, which deliver substances that trigger a specific immune response. Unlike prevention vaccines such as the HPV vaccine, the goal of therapeutic cancer vaccines is not to prevent cancer but to help the immune system find and attack it.

Preliminary findings from a phase II trial indicate that therapeutic cancer vaccines can improve outcomes for patients with relapsed glioblastoma.34 The rindopepimut vaccine works against glioblastoma tumors with a specific genetic mutation known as EGFRvIII, which contributes to uncontrolled growth of brain tumors. The mutation occurs in approximately one in four glioblastomas. It does not occur in healthy brain tissue.

In the study, patients with recurrent glioblastoma who received the vaccine along with the targeted drug bevacizumab developed an immune response to the cancer. Compared with patients who received bevacizumab alone, those who also received the vaccine experienced greater tumor shrinkage and a longer time before disease worsening. The median survival in the vaccine group was 12 months compared with 8.8 months in the bevacizumab-alone group. The most common toxicity of rindopepimut was a mild injection site reaction.

In early 2015, the FDA granted rindopepimut breakthrough therapy designation for EGFRvIII-positive glioblastoma. A phase III trial of rindopepimut in patients newly diagnosed with this type of glioblastoma is under way (ClinicalTrials.gov identifier: NCT01480479). Meanwhile, several ongoing, early-stage clinical trials are exploring other vaccines for glioblastoma. Cancer vaccines are also being explored as treatments for a range of other cancers, including breast, lung, bladder, cervical, kidney, pancreatic, prostate, and blood cancers.

“The 21st Century Cures is the promise of the future. This initiative will provide the next generation of doctors with powerful tools that will alleviate human suffering—and fight cancer—on a scale never before known.”

—Representative Michael C. Burgess, MD (R-TX)

Continuing Immunotherapy Research

Altogether, the rapid succession of immunotherapy research advances heralds a new pillar of cancer treatment beyond the traditional staples of chemotherapy, radiation therapy, and surgery. Compared with chemotherapy and targeted therapy, immunotherapy has the potential to control tumor growth much longer and often with fewer adverse effects.

It seems reasonable that harnessing a patient’s own immune system to fight cancer would be universally effective. In many studies thus far, however, only a minority of patients have benefited from immunotherapy approaches. With initial immunotherapies proving effective for some patients, researchers are now exploring ways to improve outcomes for more patients. These include combining different immunotherapies, using immunotherapy in combination with other traditional treatments, and starting immunotherapy earlier in the course of the disease.

Researchers are also studying ways to reliably predict response to immunotherapy, so patients can be spared the adverse effects and costs of treatments that may not help them. In addition, longer follow-up of patients who have received immunotherapies in clinical trials will help assess the true clinical benefit of these approaches.

Policy Focus

21st Century Cures Act

After more than a year of hearings, roundtables, and discussion drafts that included active engagement and comments from ASCO, the US House of Representatives passed the 21st Century Cures Act (H.R. 6) with a strong bipartisan vote. If passed by the Senate and signed into law, the bill will accelerate the discovery, development, and delivery of promising new treatments to people living with cancer.

The 21st Century Cures Act advances big data and precision medicine by encouraging the interoperability of electronic health records and prohibiting practices that prevent data sharing, which is key for optimal patient care. The bill also strengthens the National Institutes of Health and US Food and Drug Administration by increasing funding for federal research that has been and will continue to be crucial for making progress against cancer.

From genes to lifestyle and environment, many different factors can lead to the development of cancer. Worldwide, chronic infections cause approximately 2 million new cancer cases each year.53 Among the four main cancer-causing pathogens is HPV, the virus that causes nearly all cervical cancers. The same virus is also associated with other genital cancers in both men and women, as well as a rising number of HNGs.
According to the Centers for Disease Control and Prevention (CDC), genital HPV is the most common sexually transmitted virus in the United States, affecting 79 million people. In most cases, the immune system fights off the virus within a couple of years. However, if HPV persists, it can cause tissue damage that may lead to cervical cancer, as well as other cancers. Although there are more than 150 different types of HPV, only approximately 15 are associated with increased cancer risk.

Preventive vaccines can reduce the risk of HPV infection and development of HPV-related cancers. Two of the high-risk types of HPV (HPV-16 and HPV-18) cause approximately 70% of cervical cancers, and vaccines for these two strains have been available for nearly a decade. In 2015, a new preventive vaccine was introduced that protects against additional cancer-causing HPV strains, and new research confirmed the positive impact widespread HPV vaccination could have on the rates of HPV cancers.

**Global Opportunity and Challenge**

Cervical cancer is the second most common type of cancer in women worldwide. Routine screening through Pap smears and, more recently, HPV DNA tests has dramatically reduced cervical cancer rates in Western countries. In low-resource countries, however, large-scale routine cervical cancer screening is not feasible, and access to treatment is limited. According to the CDC, nine of 10 deaths resulting from cervical cancer occur in less developed regions of the world.

HPV vaccination may be the best strategy for reducing the global burden of cervical cancer. To realize the full potential of HPV vaccines, more eligible persons need to be vaccinated. Cultural, educational, and socioeconomic barriers to vaccination will first need to be overcome. In addition, worldwide implementation will require more cost-effective vaccines in the future.

**Promise of HPV Vaccines**

To date, the FDA has approved three different HPV vaccines for the prevention of cervical cancer: Gardasil, Cervarix and Gardasil 9. Gardasil, introduced in 2006, protects against high-risk HPV-16 and HPV-18 and two types of low-risk HPV that cause 90% of genital warts. Cervarix, approved in 2009, also protects against HPV-16 and HPV-18. Either vaccine can prevent up to 70% of cervical cancers.

In late 2014, the FDA approved Gardasil 9, which protects against nine high-risk HPV types, including five that are not addressed by Gardasil or Cervarix.36 By covering these additional HPV types, researchers estimate that Gardasil 9 could potentially prevent 90% of cervical cancers worldwide.37

Furthermore, a major study published in 2015 found that widespread HPV vaccination with Gardasil or Cervarix could prevent as many as 25,000 HPV-related cancers per year in the United States alone.38 These include the majority of invasive cervical, anal, oropharyngeal, and vaginal cancers, as well as some other genital cancers. The Gardasil 9 vaccine could prevent an additional 4,000 cancer cases per year. These estimates, made using US cancer registry data and detection rates of HPV types in tumor tissue, will help evaluate the effectiveness of future HPV vaccines.

A 2014 immunization survey found that 60% of US adolescent girls and 42% of teen boys have started the three-dose HPV vaccine series.38 However, the survey data also indicate that the rates of series completion are poor; only 40% of girls and 22% of boys who began HPV vaccination received the recommended three doses.

The CDC recommends that all boys and girls age 11 to 12 years receive an HPV vaccine. Although the HPV vaccine has been available for a decade, and vaccination coverage is improving, HPV vaccination rates in the United States lag behind those of other developed countries. Furthermore, HPV vaccination rates are significantly lower than the rates of other vaccinations recommended for adolescents (eg, pertussis and meningococcal disease vaccines).39

**Remaining Questions**

Given that none of the available vaccines protect against all high-risk HPV types, routine cervical cancer screening is still recommended after HPV vaccination. It is not yet known how long the initial series of HPV vaccinations will last or whether booster vaccinations might be necessary to maintain ongoing protection.

Longer follow-up of people who received a vaccine in clinical trials will provide important information about the need for reimmunization. It will likely take several more years to determine the impact of vaccination on overall incidence of and death rates from HPV-related cancers. Appendix Table A1 (online only) lists additional notable advances in cancer prevention.

Research continues to deliver new and improved treatment options for thousands of people living with cancer. Between October 1, 2014, and October 15, 2015, the FDA approved 10 new cancer treatments and a new cancer prevention vaccine (Table 1). These new approvals include three immunotherapies (blinatumomab, nivolumab, and dinutuximab) and five novel targeted drugs (olaparib, palbociclib, lenvatinib, panobinostat, and sonidegib).

In addition, the FDA expanded the use of 12 previously approved cancer therapies and one device. Altogether, the approvals have broadened treatment options for the most common cancers, including lung, breast, colorectal, and skin cancers, as well as less common but difficult-to-treat illnesses, such as ovarian cancer, multiple myeloma, ALL, and brain cancer.

Besides tremendous success with immunotherapy (as described in Advance of the Year: Cancer Immunotherapy), 2015 marked significant advances in using well-established approaches to treat cancer: hormone therapy, chemotherapy, and surgery. Such advances will help improve outcomes for patients with breast cancer, HNC, rectal cancer, and stomach cancer, as well as sarcoma. Researchers have also reported encouraging results using a unique new, noninvasive device to treat the most deadly type of brain cancer.

Precision medicine is shaping up to become a mainstream treatment approach for many types of cancer. Our understanding of tumor biology and the molecules that make tumors grow and spread is rapidly expanding. Building on this knowledge, promising new, targeted therapies have emerged for several hard-to-treat forms of blood, ovarian, breast, and kidney cancers.
Novel Treatment Device for Brain Cancer

Glioblastoma is one of the most common and deadliest forms of brain cancer in adults. Fewer than 10% of patients survive 5 years after initial diagnosis. Despite initial remission, the tumor often grows back and spreads quickly to other areas of the brain. Preliminary findings from a large clinical trial point to a new possibility to improve outcomes for glioblastoma. The approach is unlike other treatments for brain or other cancers, using so-called tumor-treating fields (TTFs) to stop the growth of rapidly dividing tumor cells. TTFs are low-intensity electrical fields that are delivered through the skin from a device patients wear on their head.

In the trial of patients with newly diagnosed glioblastoma who underwent surgery, adding TTFs to standard radiation therapy and chemotherapy delayed disease progression by a median duration of 3 months. The 2-year survival rate was 43% in the TTF group versus 29% in the standard therapy group (brain surgery followed by radiation therapy and chemotherapy).

The TTF device was previously approved by the FDA for the treatment of recurrent glioblastoma, and in 2015, the FDA expanded its use to treat patients with newly diagnosed glioblastoma. Yet, Preliminary findings from a large clinical trial point to a new possibility to improve outcomes for glioblastoma. The approach is unlike other treatments for brain or other cancers, using so-called tumor-treating fields (TTFs) to stop the growth of rapidly dividing tumor cells. TTFs are low-intensity electrical fields that are delivered through the skin from a device patients wear on their head.

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“Just about every person in this country has been touched by cancer and we want to make sure that we do in Congress helps bring better treatments and cures to the people who are fighting life-threatening diseases. Clinical cancer research has yielded tremendous gains and breakthroughs, but we can’t afford to stop this progress. Millions of Americans are counting on us.”

—Representative Gene Green (D-TX)
it is unclear how well this new therapy that disrupts cell division will be adopted in routine practice. The effect of the device on patient quality of life remains controversial, because some patients have reported that wearing the device was too onerous.

Averting Breast Cancer Recurrence

Ovarian suppression helps younger, high-risk patients. Initial treatment of estrogen receptor (ER)–positive breast cancer includes surgery followed by radiation therapy or chemotherapy. For premenopausal women, additional (adjuvant) treatment with the hormone drug tamoxifen is recommended to prevent recurrence—especially in women who are at higher risk. Knowing this type of breast cancer is fueled by estrogen, some experts surmised that blocking ovarian production of estrogen would further slow tumor growth and prolong the time to recurrence of the cancer. Ovarian function can be suppressed chemically, surgically, or by irradiation of the ovaries.

In 2015, the researchers’ hypothesis was confirmed when a phase III trial showed that ovarian suppression added to adjuvant hormone therapy improved outcomes for premenopausal women with a high risk of recurrence (this study was funded in part by a grant from the NIH).24 Compared with women with lower risk of recurrence, the study participants with higher risk tended to have larger, higher-grade tumors and cancer that had spread to the lymph nodes. All high-risk women had previously received chemotherapy. At 5 years, 78% of the high-risk women who received tamoxifen alone were cancer free. By comparison, 82% of those treated with ovarian suppression and tamoxifen and 86% of those treated with ovarian suppression and the aromatase inhibitor exemestane were cancer free at 5 years. As expected, the addition of ovarian suppression contributed to symptoms of menopause.

The added benefit of ovarian suppression was particularly prominent among patients younger than age 35 years, nearly all of whom had previously received chemotherapy. Among these patients, 5-year cancer-free rates improved from 68% with tamoxifen alone to 79% with tamoxifen and ovarian suppression and to 83% with exemestane and ovarian suppression. For women with a lower risk of recurrence who had not previously received chemotherapy, outcomes were similar regardless of the type of adjuvant treatment received, with more than 95% remaining cancer free at 5 years. These findings support the use of adjuvant ovarian suppression with hormone therapy as a standard of care for premenopausal women with hormone receptor–positive breast cancer, particularly if they have high-risk disease and have been treated with chemotherapy.

Aromatase inhibitors: An additional option for DCIS. Women with DCIS are at increased risk of developing invasive breast cancer. To reduce this risk, physicians recommend that women with ER-positive DCIS receive tamoxifen for 5 years after breast-conservation surgery (lumpectomy). A nationwide randomized trial reported that the aromatase inhibitor anastrazole may also yield excellent outcomes for postmenopausal women (this study was funded in part by a grant from the NIH).24 Ten-year breast cancer–free survival rates were higher in the anastrazole group than in the tamoxifen group (93% vs 89%).

This benefit was primarily seen in postmenopausal patients age younger than 60 years.

Both tamoxifen and aromatase inhibitors are already being used to prevent recurrences of more advanced forms of breast cancer. This is the first study to compare the two treatments in postmenopausal women with DCIS.

Importantly, the two hormonal drugs cause different adverse effects. The main adverse effect of anastrazole is hardening of the uterus, which increases the risk of bone fracture. Compared with those receiving tamoxifen, women receiving anastrazole are more likely to have joint pain but less likely to have hot flashes or blood clots in the veins. Tamoxifen is associated with slightly increased rates of uterine cancer, although this risk is low overall. Experts agree that both approaches carry their own risks and benefits and that patients should still consider the full range of options, including foregoing adjuvant treatment.

Targeted Therapy

Targeted therapy is designed to target molecules precisely in or on cancer cells or in the tissue surrounding a tumor. Genetic changes can cause cells to make too much of a certain protein or to produce abnormal proteins. Targeted therapy works by blocking or switching off such proteins that cause the cells to keep growing and dividing.

Precision medicine builds on the ever-expanding understanding of tumor biology. Several recent advances illustrate how specific molecular vulnerabilities in cancer can be exploited to develop powerful new treatments.

In 2015, researchers reported remarkable success with targeted therapy, with a range of new treatments that slow the growth of advanced cancers. In addition, early promising results were reported on drugs targeting a number of rare genetic abnormalities in lung tumors.

The FDA approved two first-in-class therapies, olaparib for the treatment of advanced ovarian cancer and palbociclib for the treatment of advanced breast cancer. Each of these drugs blocks a specific molecule that fuels the growth of that cancer.

Scientists also use information on the genetic makeup of different cancers to find new uses for existing drugs. For example, the targeted therapy ibrutinib, previously approved for chronic lymphocytic leukemia, was shown to work well against another type of blood cancer that shares the same genetic mutation, Waldenström’s macroglobulinemia (WM).

Similarly, another study confirmed that sorafenib, a drug used to treat liver, kidney, and thyroid cancers, is effective against acute myeloid leukemia (AML), as predicted by early research on key molecules implicated in this disease. Finally, a drug approved to treat thyroid cancer, cabozantinib, was found to delay worsening of advanced kidney cancer and NSCLC.

Tumor biology: Aiming at rare targets in lung cancer. Genetic mutations that cause cells to make abnormal proteins can lead to cancer. A landmark 2014 study found that two thirds of advanced lung adenocarcinomas harbor at least one such cancer-causing genetic change.45 This finding is important, because it suggests that most such patients may benefit from a targeted treatment that blocks the cancer-fueling protein. Nonetheless, only a minority of patients with lung cancer are candidates for targeted therapies at this time.
In the study, the most common genetic abnormalities were KRAS mutation (25%), sensitizing EGFR mutations (17%), ALK rearrangements (8%), other EGFR mutations (4%), ERBB2 mutations (3%), and BRAF mutations (2%). Several targeted drugs are already widely used to treat patients with EGFR mutations in the tumor: afatinib, erlotinib, and gefitinib. Crizotinib and ceritinib are recommended for tumors with ALK rearrangements. However, development of new options remains critical, because not all patients with ALK-positive NSCLC respond to these treatments, and some cannot tolerate them. Unfortunately, no treatments are yet available to target the most common genetic change: KRAS mutation.

Findings from a recent phase II trial point to a promising new treatment for patients with advanced ALK-positive NSCLC that is resistant to crizotinib. A novel ALK inhibitor, alectinib, shrunk tumors in half of the patients treated in the trial, with a median response duration exceeding 11 months.46 The treatment also shrunk brain metastases in close to 60% of patients. Serious treatment-related adverse effects, such as dyspnea and pulmonary embolism, occurred in 27% of patients.

In June 2013, the FDA granted alectinib a breakthrough therapy designation. In 2014, alectinib was approved in Japan for the treatment of advanced or recurrent ALK-positive NSCLC. In December 2015, the FDA granted accelerated approval to alectinib for the treatment of patients with metastatic ALK-positive NSCLC that has worsened after, or who could not tolerate, crizotinib.47 However, larger studies are needed to confirm the efficacy of alectinib. Meanwhile, many other ALK inhibitors that seem more potent than crizotinib or are active in crizotinib-resistant tumors are already in clinical trials.48 Emerging research findings suggest that patients with lung cancers driven by uncommon genetic abnormalities can also benefit from targeted therapies.

In another early clinical trial, crizotinib shrunk tumors of 72% of patients with ROS1 gene rearrangements (this study was funded in part by a grant from the NIH).49 The median duration of response was more than 17 months. ROS1 rearrangement is found in only 1% of tumors of patients with NSCLC. The most common treatment-related toxicities were visual impairment, diarrhea, and nausea. However, nearly all of the reported adverse effects were mild.

Approximately 28% of patients with similarly uncommon RET gene rearrangements responded to the targeted drug cabozantinib, which was previously approved by the FDA for the treatment of thyroid cancer.50 The median time to progression of advanced NSCLC was 7 months. Toxicities were mostly mild and included fatigue, diarrhea, hand-foot syndrome, and low platelets.

Preliminary results from a small trial suggest that the targeted drug dabrafenib is active against advanced NSCLCs harboring a specific mutation in the BRAF gene, V600E.51 The treatment shrunk tumors in 63% of the patients, and treatment-related adverse effects were mostly mild. The most common toxicities were fever, diarrhea, nausea, and vomiting. Dabrafenib is approved for the treatment of melanoma with the same mutation.

Finally, a large genomic profiling study identified a rare new subgroup of patients with NSCLC who could potentially respond to targeted MET inhibitors.52 Although ALK, ROS1, RET, and BRAF mutations are rare in frequency, given the high incidence of NSCLC, thousands of people may be candidates for the new targeted therapies. Further research is needed to determine the best way to screen patients for rare genetic changes. New technologies, such as next-generation sequencing and multiplex testing, may help more patients receive treatments targeting mutations in the tumor.

Zeroing in on a blood cancer’s weak spot. WM is a rare, slow-growing type of lymphoma. The disease can start almost anywhere in the body and may spread to almost any organ. In fact, when WM is diagnosed, it usually involves the blood and the bone marrow.

Patients with WM sometimes have thickened blood, which may cause symptoms such as headache, blurry vision, dizziness, and shortness of breath. Treatments include watchful waiting, chemotherapy, and monoclonal antibodies. This approach to treatment changed in 2015 with the approval of a new targeted drug that is effective in the vast majority of patients with WM.

In 2012, scientists first reported on a genetic mutation that occurs frequently in patients with WM. The abnormality leads to activation of the Bruton’s tyrosine kinase (BTK) protein, which drives tumor growth. Less than 3 years later, a small clinical study showed that blocking BTK with the targeted drug ibrutinib could be a promising new treatment strategy for WM.53 Overall, 90% of patients with previously treated WM responded to ibrutinib, and the 2-year survival rate exceeded 95%. These findings led to the FDA approval of ibrutinib for WM in
January 2015. Ibrutinib was previously approved for the treatment of other types of blood cancer.

Sorafenib targets AML. Sorafenib is a targeted drug that blocks a range of molecules that promote the growth of cancer cells and of the blood vessels to the tumor. It is has been FDA approved for the treatment of people with certain types of liver, kidney, and thyroid cancers.

Early research suggested that sorafenib may work against AML, because it blocks several key molecules implicated in this disease. Preliminary data from the first randomized trial of sorafenib in patients with newly diagnosed AML has now confirmed this.

At 3 years, 56% of patients who received sorafenib and standard chemotherapy and 38% of those treated with placebo and standard chemotherapy had not relapsed. The 3-year overall survival rates were 63% with sorafenib and chemotherapy and 56% with chemotherapy alone. The most common severe treatment-related toxicities included fever and bleeding events, both of which occurred more often with sorafenib.

The study was limited to adult patients younger than age 60 years. A prior study in older patients with AML showed no benefit of sorafenib. Larger trials are needed to fully assess the role of sorafenib in the treatment of people with AML.

Homologous DNA repair: A novel therapeutic target in ovarian cancer. In late 2014, the FDA approved olaparib for the treatment of advanced serous ovarian cancer with BRCA gene mutations. This approval marked the first major improvement in the treatment of high-grade serous ovarian cancer in 30 years. Serous ovarian cancer is the most common type of ovarian cancer, accounting for two thirds of ovarian cancer diagnoses.

Up to 15% of all ovarian cancers are linked to hereditary mutations in BRCA genes, which encode proteins that repair damaged DNA. Olaparib is the first of a new class of DNA repair blocking drugs called poly (ADP-ribose) polymerase (PARP) inhibitors. The year 2015 was marked by steady advances in research on PARP inhibitors, including new understanding of the populations they might benefit, as well as the development of other PARP-targeted drugs.

Cancer cells that already have a decreased ability to repair DNA damage because of mutations in BRCA1 or BRCA2 genes are particularly vulnerable to PARP inhibitors. These drugs completely disable the DNA repair mechanisms of BRCA-mutated cancer cells, leading to cell death. Approximately half of high-grade ovarian cancers have other defects in the DNA repair machinery of the cells, which may also make them susceptible to PARP inhibitors. Healthy cells that do not have an underlying defect in DNA repair are able to survive PARP blockade.

Approval of olaparib was given on the basis of a study of women with platinum-sensitive, recurrent, serous ovarian cancer. Preliminary findings showed that maintenance treatment with olaparib delayed disease progression by 7 months compared with placebo. Patients with BRCA mutations experienced the most benefit from olaparib, and longer patient follow-up is needed to determine if olaparib extends overall survival. Serious treatment-related adverse effects, such as fatigue and anemia, were reported in 18% of patients who received olaparib.

The most common adverse effects among patients treated with olaparib were fatigue and anemia. Serious adverse effects, such as small intestinal obstruction, were reported in 18% of patients who received olaparib and 9% of those who received placebo.

Other recent research has suggested that women who have tumors that become resistant to chemotherapy may also benefit from olaparib. One study showed that olaparib added to chemotherapy slowed cancer progression by roughly 3 months compared with chemotherapy alone. Again, the greatest clinical benefit was seen in patients with BRCA mutations. Phase III confirmatory trials of olaparib as a maintenance treatment for women with recurrent ovarian cancer are under way (ClinicalTrials.gov identifier: NCT01844986).

Ongoing research is also investigating how PARP inhibitors can be used more effectively. One study found that adding cediranib to olaparib delayed disease progression of recurrent serous ovarian cancer for 8 months longer than olaparib alone (this study was funded by a grant from the NIH). Women without inherited BRCA mutations particularly benefited from the combination. Cediranib is a targeted drug that blocks the growth of blood vessels to the tumor. In a previous clinical trial, cediranib administered as maintenance therapy improved survival of women with recurrent ovarian cancer.

Scientists are also working on ways to identify patients who are most likely to benefit from PARP inhibitors. For example, it seems that tumors with a mutation in the RAD51C gene, which is involved in homologous DNA repair, respond well to another PARP inhibitor, rucaparib. Like olaparib, rucaparib was active against ovarian tumors with BRCA mutations, with 66% of patients experiencing tumor shrinkage.

Importantly, however, rucaparib was also active against BRCA-negative tumors with homologous DNA repair deficiency leading to tumor genome-wide changes, known as loss of heterozygosity. Among women with recurrent ovarian cancer treated in a phase II study of rucaparib, the population of patients who had loss of heterozygosity also had a treatment response rate of 32%. The most common treatment-related adverse effects included GI symptoms, fatigue, anemia, and increased liver enzyme (ALT and AST) levels.

In 2015, the FDA granted rucaparib a breakthrough therapy designation to treat women with BRCA-positive advanced ovarian cancer. Pivotal studies of rucaparib in women with high-grade ovarian cancer are under way (ClinicalTrials.gov identifier: NCT01968213). The studies will also try to define a molecular signature that might be used to predict which patients might benefit from PARP-directed therapies.

Meanwhile, genomic analyses of tumor tissue are revealing additional molecular defects that could serve as therapeutic targets in the future. One such study has recently identified genes implicated in the resistance of ovarian cancer to chemotherapy.

Palbociclib sets a new standard of breast cancer care. The year 2015 brought an entirely novel treatment option for women with ER-positive breast cancer. This is the most common type of breast cancer, accounting for two thirds of cases. ER-positive breast tumors need estrogen to grow. Blocking estrogen production or its receptor is the cornerstone of ER-positive breast cancer therapy.

In recent years, scientists discovered that proteins called CDK4 and CDK6 also play a critical role in ER-positive breast cancer growth. Two large clinical studies subsequently showed that blocking CDK4 and CDK6 with the new oral drug palbociclib improved patient outcomes.

The first study compared standard hormone therapy letrozole with the combination of letrozole and palbociclib in postmenopausal...
women with advanced ER-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.63 The patients had not previously received any systemic treatment of the advanced disease.

The median time before the cancer worsened (progression-free survival) was 20 months with the palbociclib combination compared to 10 months with letrozole alone. Severe adverse effects, such as low WBC levels (neutropenia and leucopenia) and fatigue, were more frequently reported among patients who received palbociclib and letrozole.

Severe adverse effects related to the palbociclib and letrozole combination regimen included low WBC counts, fatigue, pulmonary embolism, back pain, and diarrhea. In February 2015, the FDA granted accelerated approval of palbociclib to be used with letrozole as initial therapy for women with ER-positive, HER2-negative breast cancer.64

After initial hormonal therapy stops working for women with advanced breast cancer, the next step is typically chemotherapy. Although chemotherapy can be effective, many women find the adverse effects too debilitating.

The second study assessed whether palbociclib could defer the need for chemotherapy.65 Women with advanced, ER-positive breast cancer that relapsed or worsened after prior hormone therapy received palbociclib with the hormone drug fulvestrant or fulvestrant with placebo. The median time before the disease worsened was markedly longer with the combination treatment (9.2 months) compared with fulvestrant alone (3.8 months). Both premenopausal and postmenopausal women benefited from palbociclib. Severe treatment-related adverse effects, such as low blood cell counts (neutropenia, leukopenia, and thrombocytopenia), anemia, and fatigue, were much more common in patients who received the combination of palbociclib and fulvestrant.

Together, the findings support the use of palbociclib as part of the standard therapy for ER-positive advanced breast cancer. More research is needed to determine the impact of palbociclib on overall survival and patient quality of life.

**Expanding treatment options for advanced kidney cancer.** Patients with advanced kidney cancer that worsens despite standard therapy are in urgent need of better treatment options. Research published in 2015 promises two potential new possibilities: an immunotherapy (Advance of the Year: Cancer Immunotherapy) and a targeted drug, both of which outperformed the standard second-line treatment, everolimus. The targeted drug everolimus blocks a protein called mTOR.

The targeted therapy cabozantinib blocks several different targets in cancer cells, including RET, MET, and VEGF receptor 2. The drug was previously approved for the treatment of advanced thyroid cancer.

In a large clinical trial of patients with previously treated metastatic kidney cancer, the median time before the disease worsened was 7.4 months with cabozantinib versus 3.8 months with everolimus.66 A preliminary analysis also showed a trend for improved overall survival with cabozantinib, but longer patient follow-up is needed to confirm this benefit.

The rates of adverse effects were similar with either drug, although the incidence of severe adverse effects was higher with cabozantinib. The most common severe adverse events related to cabozantinib were high blood pressure (hypertension), diarrhea, and fatigue, whereas anemia, fatigue, and high blood sugar (hyperglycemia) were most common with everolimus.

**Adjuvant Chemotherapy Extends Survival for Patients With Stomach Cancer**

Localized stomach cancer can potentially be cured with surgery, but recurrences are common. Approximately four in 10 patients experience a relapse within 2 years of surgery. After a relapse, treatment is much more difficult, and survival is shortened.

Recent research has demonstrated that outcomes can be improved if patients receive chemotherapy after surgery. A large randomized clinical trial compared postsurgery (adjuvant) capecitabine and oxaliplatin chemotherapy with observation.67 The patients had stage II to IIIB stomach cancer and had undergone surgical removal of parts of the stomach and nearby lymph nodes.

Adjuvant chemotherapy decreased the risk of cancer recurrence after surgery by 42%. The estimated 5-year survival rate was 78% in the chemotherapy group compared with 69% in the observation group.

**New Treatments for Soft Tissue Sarcoma**

Patients with advanced soft tissue sarcoma have poor outcomes, typically surviving 1 year or less. If the disease worsens after initial chemotherapy, there are few options available for further treatment. Early clinical trial findings point to promising new treatments for two common types of soft tissue sarcoma, liposarcomas (fatty tissue) and leiomyosarcoma (muscle tissue).

Among patients with treatment-resistant disease, eribulin chemotherapy extended the median survival from 11.5 to 13.5 months compared with the standard treatment dacarbazine.68 This was the first clinical trial in 20 years to show that a new drug improved survival in any type of sarcoma. For a disease where such few treatment options exist, even a 2-month improvement in survival represents progress. Nevertheless, the survival gain must be weighed against the burden of its adverse effects.

Eribulin belongs to a class of anticancer drugs known as microtubule inhibitors, which block cell division. The FDA approved eribulin for the treatment of advanced breast cancer in 2010.

Preliminary findings from another study suggest that the chemotherapy drug trabectedin can be effective against treatment-resistant soft tissue sarcoma.69 Compared with dacarbazine, trabectedin slowed liposarcoma and leiomyosarcoma progression by a median duration of 10 weeks. Longer follow-up is needed to determine if there is an improvement in overall survival.

The most common toxicities related to trabectedin were GI symptoms, fatigue, headache, and tissue swelling. Severe treatment-related adverse effects, including decreased WBC (neutrophil) levels and increased ALT levels, were more common with trabectedin than with dacarbazine.

The antitumor effects of trabectedin are multipronged: it blocks cell division, transcription of genes, and DNA repair. Recently, scientists discovered that trabectedin may also affect the tumor microenvironment. In October 2015, the FDA approved trabectedin to treat patients with chemotherapy-resistant liposarcoma or leiomyosarcoma that cannot be removed by surgery or is advanced.70

Although these survival gains could be construed as minimal, it is important to understand that improvements in survival
of patients with soft tissue sarcoma have not been achieved until now. The hope is that these incremental improvements will provide new opportunities for clinical research in this hard-to-treat cancer.

**Advances in Surgery**

For the vast majority of patients today, surgery remains a critical part of cancer care. Although it can be lifesaving, surgery also carries the risk of complications, which can impair a patient’s quality of life.

Research has delivered new insights that will help physicians and patients decide when it is most appropriate to undergo neck lymph node surgery. Until now, research evidence in this area was sorely lacking.

Another large clinical trial provided reassurance to patients with rectal cancer considering laparoscopic surgery. It showed that this less invasive procedure offers the same survival benefit with fewer risks compared with traditional surgery.

Each year, thousands of women with early-stage breast cancer undergo a lumpectomy. For such women, a new surgical technique that involves removing a little more tissue during lumpectomy may significantly reduce the need for additional surgery after an initial lumpectomy.

**Neck lymph node removal: When is it necessary?** Cancers that begin in the head or neck often spread to lymph nodes in the neck. Physicians commonly recommend preventive (elective or planned) neck lymph node surgery to reduce the risk of cancer recurrence and spread.

In addition to general risks of anesthesia and surgery, neck lymph node surgery may cause damage to the nerves of the lip and tongue, limited neck and shoulder movement, and problems talking and swallowing. To avoid such risks, some patients opt to delay lymph node removal until their cancer returns or worsens. Recent evidence from two large clinical trials will help physicians and patients decide when such surgery is the appropriate choice.

A phase III study conducted in India showed that elective neck lymph node surgery had a clear benefit for patients with early oral cancer. According to preliminary results, elective neck surgery halved the risk of relapse and increased 3-year survival rates by 12%. This new evidence will likely encourage greater use of elective lymph node surgery for patients with early oral cancer.

Another large clinical trial explored whether patients with more advanced HNC (stage III or IV) could forgo planned (elective) neck lymph node surgery after chemotherapy and radiation therapy and instead undergo active surveillance with positron emission tomography (PET)/computed tomography (CT). One group of patients with squamous cell HNC was assigned to undergo a planned neck surgery before or after chemotherapy and radiation therapy. A second group received chemotherapy and radiation therapy followed by active surveillance with PET/CT imaging. Those patients underwent neck surgery only if the PET/CT scan revealed abnormalities.

There was no difference in survival between the two patient groups, but the PET/CT group underwent fewer neck surgeries and experienced considerably fewer complications than the group who underwent the planned neck surgery. The findings suggest that after chemotherapy and radiation therapy, patients with advanced HNC can be safely observed using PET/CT. The surveillance approach was also more cost effective compared with immediate neck surgery.

**Rectal cancer: Laparoscopic surgery outperforms traditional surgery.** Patients with rectal cancer have two surgical options: laparoscopic surgery or traditional (open) surgery. Laparoscopic surgery is performed through several small incisions instead of one large incision. A video camera and thin instruments are placed through the incisions to allow access to the inside of the body. Laparoscopic procedures are as safe as traditional surgery, and recovery time is shorter.

A large clinical trial comparing traditional and laparoscopic rectal cancer surgery concluded that the laparoscopic procedure may improve outcomes for some patients. The rates of local recurrence did not differ between laparoscopy and traditional surgery. However, among patients with distal rectal cancer, local recurrences were less frequent after laparoscopy than after traditional surgery.

At 3 years, the rate of disease-free survival was 75% in the laparoscopy group and 71% in the traditional surgery group. For patients with stage III rectal cancer, however, laparoscopy provided a larger improvement in 3-year disease-free survival: the rates were 52% with traditional surgery and 65% with laparoscopy. Across disease stages, the two types of surgery resulted in similar overall survival rates at 3 years. These findings suggest that laparoscopic surgery, when performed by a highly trained colorectal surgeon, is not inferior to traditional surgery, at least for some types of rectal cancer.

**Lumpectomy: Getting it right the first time.** Many women diagnosed with early-stage breast cancer undergo a lumpectomy. During a lumpectomy, the surgeon removes the tumor and a small area of surrounding healthy tissue, which is known as a surgical margin. Specimens of the removed tissue are examined under a microscope. If cancer cells are seen at or close to the edge of the specimen, it is said to have positive margins. Margins that are free of cancer cells are called negative.

Up to 40% of women with early-stage breast cancer have positive margins after lumpectomy. In such cases, physicians often recommend a second surgery to remove more tissue, because any remaining cancer cells increase the risk of recurrence.

A recent study suggests that the need for such additional surgery could be reduced. The study explored a new technique called cavity shave, which involves removing additional tissue around the tumor during initial lumpectomy to improve the odds of achieving negative margins. The new technique decreased the rates of additional breast surgery by half (from 21% to 10%), and women perceived no difference in cosmetic outcomes with the new approach.

The findings of this study are immediately applicable to a large number of women with breast cancer. The new approach

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**Interesting Fact**

Eribulin and trabectedin are natural products derived from oceanic organisms: the sea sponge and the sea squirt, respectively.
will spare them the trauma of an additional procedure and allow them to start curative treatments sooner. It may also ultimately reduce the number of patients who opt for mastectomy instead of a re-excision surgery, as well as reduce overall cost of breast cancer care.

**Advances in Radiation Therapy for Early-Stage Breast Cancer**

Many women with early-stage breast cancer receive radiation therapy after breast-conserving surgery (lumpectomy) to reduce the risk of cancer recurrence in the breast and nearby tissue. In specific circumstances, such as having a larger tumor or cancer spread in many lymph nodes, radiation therapy may also be recommended after mastectomy.

After a lumpectomy, most women receive a type of radiation therapy known as whole-breast irradiation. Another type of radiation therapy, regional node irradiation, is only recommended to certain women, such as those with cancer that has spread to nearby lymph nodes or those who are deemed to be at a higher risk of recurrence. For such patients, regional node irradiation has been shown to reduce recurrence and improve survival.

Two large clinical trials published last year explored whether adding regional lymph node irradiation to whole-breast irradiation improved outcomes after surgery for women with early breast cancer. The findings of both studies suggest that the addition of regional lymph node irradiation offers no survival benefit but reduces the risk of recurrence.

The first trial included women with early-stage breast cancer that was either node positive or node negative with a high risk of recurrence (this study was funded in part by a grant from the NIH). After lumpectomy and systemic adjuvant therapy, the recurrence (this study was funded in part by a grant from the NIH). After lumpectomy and systemic adjuvant therapy, the recurrence (this study was funded in part by a grant from the NIH). After lumpectomy and systemic adjuvant therapy, the recurrence (this study was funded in part by a grant from the NIH).

The second clinical trial assessed adding regional node irradiation to either whole-breast or chest-wall irradiation for women who had undergone lumpectomy or mastectomy. At 10 years, the addition of regional node irradiation did not improve overall survival rates but did slightly increase disease-free survival rates (72.1% vs 69.1%). Breast cancer–related deaths were less frequent in the nodal irradiation group (14.4% vs 12.5%).

Regional nodal irradiation may increase the risk of treatment complications, such as lung inflammation, lymphedema (a condition in which extra lymph fluid builds up in tissues and causes swelling), heart disease, and second cancers. More research is needed to identify patients who might benefit the most from the combination of whole-breast and regional nodal irradiation therapy.

Appendix Table A1 lists additional notable advances in cancer treatment.

**Recent Clinical Practice Guidelines**

Each year, research yields new knowledge that helps inform all aspects of cancer care, including prevention, detection, diagnosis, treatment, and survivorship. Evidence-based clinical practice guidelines help to distill knowledge on a particular topic and provide recommended care options to assist clinicians in delivering the best treatment and care to each patient.

ASCO develops its clinical practice guidelines through a rigorous systematic review of relevant medical literature and clinical interpretation from a multidisciplinary panel of content experts and patient representatives. In 2015, ASCO issued new clinical practice guidelines, updates, and guideline endorsements on a variety of topics to help inform patient care (Table 2). The latest guidelines can be viewed at http://www.instituteforquality.org/recently-published-asco-guidelines.

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Physicians treating patients with cancer continuously strive not only to extend their patients’ lives but also to improve their well-being. In the case of childhood cancers, intensive therapies can eradicate the disease, but many survivors face risks of late effects, such as second cancers and heart disease. However, a major study in 2015 indicates that today, much fewer survivors are dying as a result of such complications compared with three decades ago.

Cancer care is also increasingly focused on the whole patient, which includes meeting the patient’s physical, emotional, psychological, and spiritual needs. This is achieved through improved communication between physicians and their patients, as well as collaboration across physician specialties and with nonphysician practitioners. For all patients, and particularly those with advanced or incurable cancer, it is important to ensure that the goals of treatment are aligned with patients’ preferences.

Multidisciplinary care teams are now common, and more patients are benefiting from palliative care services. New research has confirmed that the earlier patients with advanced cancer begin receiving palliative care, the longer they live. In addition, researchers found that family caregivers who themselves receive palliative care services early are better able to cope with caregiving. Research reported in 2015 has also provided valuable new insights into the risks and benefits of a type of radiation therapy for patients with cancer that has spread to the brain.

“We all worry about ourselves, family, friends being touched by cancer. When an oncologist walks into our offices, we want to hear what you have to say, what we can do to ensure high-quality, high-value care for all cancer patients. We can fight this fight together.”
—Representative Chuck Fleischmann (R-TN)

**Advances in Childhood Cancer Care**

*Childhood cancer survivors are living longer.* For decades, physicians have strived to avoid the paradox in which children survive cancer, only to become sick or die years later because of complications from the very treatment that cured them of cancer. Close monitoring of late effects has led to changes in therapy for the most common childhood cancers.

By carefully reducing treatment intensity, physicians have extended the lifespan of many childhood cancer survivors since the 1970s. Cancer cure rates have increased alongside a decrease in deaths resulting from complications of cancer treatment, such as second cancers and heart and lung diseases.

A recent analysis of roughly 34,000 childhood cancer survivors shows major gains in long-term survival achieved over three decades (this study was funded by a grant from the NIH). The study explored mortality rates among 5-year childhood cancer survivors diagnosed with cancer between 1970 and 1999.

The rate of death resulting from any cause within 15 years of a cancer diagnosis decreased from 12.4% among patients diagnosed in the 1970s to 6% among those diagnosed in the 1990s. This reduction in mortality was associated with changes in therapy that occurred during the same time period, such as decreased use of anthracyclines, alkylating agents, and cranial irradiation. This is promising news for the more than 370,000 childhood cancer survivors in the United States today.

**Transplantation options for children with ALL expanded.** Most children with ALL can be cured with chemotherapy, but those with high-risk disease require additional treatment. Hematopoietic stem-cell transplantation, also called bone marrow transplantation, is the standard of care for such high-risk patients.

It is estimated that only 20% to 25% of children who are candidates for stem-cell transplantation have matched sibling donors. A match is found when the HLA of one sibling’s bone marrow matches that of the other, and there is only a 25% chance that bone marrow HLA will match between siblings. Fortunately, the availability of unrelated volunteer donors has increased over recent decades.

A new study comparing matched sibling versus unrelated donor transplantation provides reassurance for continued use of unrelated donor stem cells. The survival of children with high-risk ALL was not affected by donor selection. The incidence of relapse was low in both groups of patients.

Furthermore, the rates of acute graft-versus-host disease, a serious complication of stem-cell transplantation, did not differ between sibling and unrelated donor use. Chronic graft-versus-host disease occurred more frequently after sibling donor transplantation. However, severe infections were more common among children who underwent unrelated-donor transplantation. These findings suggest that stem-cell transplantation using a well-matched unrelated donor could be a viable alternative for children with ALL who are at high risk of relapse but do not have a matched sibling donor.

**Reducing Disparities in the Care of Minorities**

Minorities have historically been underrepresented in clinical trials. Despite improvements in the two decades since Congress required that research funded by the NIH include minorities, only 10% of patients enrolled in clinical trial are minorities.

The participation of adult minorities in cancer clinical trials is still not proportional to the overall representation of minorities in the United States. This lack of diversity makes it difficult to generalize clinical trial findings to real-world populations.

Barriers to minority participation in clinical research are complex and multifaceted. The IMPaCT (Increasing Minority Participation in Clinical Trials) project was the first to use patient navigation to address such barriers (this study was funded by a grant from the NIH).

Between 2007 and 2014, more than 400 African American patients with cancer were referred to IMPaCT. Patient navigators matching the demographic characteristics of patients provided guidance to project participants.

Nearly 80% of the study participants who were eligible for a clinical trial enrolled. Patient navigation also improved retention in clinical trials. The trial completion rates were 74% for those who used patient navigation support while participating in a clinical trial, compared with 34% for those who did not have the support of a patient navigator.

**Selecting Care to Preserve Quality of Life**

Approximately one in four patients with cancer experiences brain metastases. Lung and breast cancers are the two cancers that...
Policy Focus

American Society of Clinical Oncology Continues to Call for Clinical Trial Coverage for Medicaid Patients

Medicaid is a major source of insurance coverage for racial and ethnic minorities who are underrepresented in clinical trials. Unfortunately, it is the only major insurer in which coverage of the routine costs associated with participation in a clinical trial is not mandated. Some states have statutes requiring coverage of costs of participation in clinical trials for Medicaid enrollees, but the vast majority of Medicaid programs do not require this coverage. ASCO strongly believes that patients with cancer who have Medicaid should not face insurance barriers to clinical trial participation. ASCO has issued a policy statement on Medicaid reform, with recommendations calling for clinical trial protections for patients with cancer with Medicaid coverage. In addition, ASCO has advocated on Capitol Hill on this issue and urged the Centers for Medicare & Medicaid Services to require the coverage of routine costs associated with participation in clinical trials for all Medicaid enrollees.

are most likely to spread to the brain. Generally, patients with brain metastases have a short life expectancy, but prognosis can vary significantly from patient to patient.

The initial treatment of most patients with limited brain metastases is stereotactic radiosurgery (SRS). SRS is a type of radiotherapy that aims beams precisely at the area of the brain tumor. After SRS, some patients also receive adjuvant whole-brain radiation therapy (WBRT).

The use of WBRT in patients with limited brain metastases has been controversial. Although WBRT does control tumor growth, it can have detrimental effects on quality of life. Preliminary findings from a federally funded study have provided new insights into the impact of adjuvant WBRT on cognition (this study was funded by a grant from the NIH).80

Patients with one to three small brain metastases who received WBRT after SRS were more likely to experience cognitive decline within the first 3 months than those who received SRS alone. Specifically, those who received WBRT had a greater decline in memory and verbal communication. There was no significant survival benefit from WBRT, compared with SRS alone.

The results strongly suggest it may be preferable to forgo WBRT in favor of SRS, because SRS can preserve a patient’s cognitive function as long as possible. Longer-term follow-up to assess late neurocognitive effects of WBRT is pending.

Nonetheless, WBRT decreases recurrence of brain metastases, and it is possible that it may prolong survival in certain patients. A smaller Japanese study identified one such patient group.81 Patients with NSCLC who had one to four brain metastases and a favorable prognosis lived 6 months longer when treated with SRS and WBRT compared with SRS alone. No such survival advantage was observed among patients with a poor prognosis. Larger prospective studies are needed to confirm these findings.

Palliative Care Benefits Extend Beyond the Patient

Palliative care is focused on the relief of suffering throughout the course of a patient’s illness, starting from the time of diagnosis. It is a partnership between the patient, medical specialists, and the patient’s family, with the goal of improving outcomes for both the patient and the family. Benefits of palliative care range from improved quality of life and treatment satisfaction to extended survival and reduced overall cost of care.

Unfortunately, many patients do not benefit from the full range of palliative care services, because palliative care is often introduced late in the course of cancer treatment. In 2012, ASCO recommended concurrent use of palliative care with cancer care early in the course of illness for any patient with metastatic cancer and/or high symptom burden.82

The randomized clinical trial Educate, Nurture, Advise, Before Life Ends (ENABLE) III has provided new evidence in favor of early palliative care. The study was one of the first to test concurrent palliative care interventions for patients and caregivers (this study was funded by a grant from the NIH).83

Researchers compared outcomes of patients with advanced cancer who received palliative care consults at the time of diagnosis of advanced cancer versus 3 months later. Although there were no differences in quality in life between the two groups, patients who received palliative care early lived longer. The 1-year survival rate for those who received early palliative care consults was 63%, compared with 48% for those who received delayed consults.

The same study also assessed a telephone-based palliative care intervention for the family caregivers of the patients who participated (this study was funded by a grant from the NIH).84

Because most study participants resided in rural areas, a telephone intervention improved access to palliative care services. The intervention began either shortly after the patient’s diagnosis or 3 months later. An early intervention was associated with lower caregiver depression compared with delayed intervention, and quality of life was comparable between the two groups.

Family caregivers are a crucial part of the patient care team. They provide daily assistance with symptom relief, emotional and spiritual support, personal care, transportation, and care coordination. Coupled with the emotional burden of their loved ones’ suffering, caregivers endure considerable strain that can affect their well-being. In fact, prior research has shown that a caregiver may experience psychological distress that is greater than the patient’s own.

Because the well-being of caregivers affects the well-being of patients, both parties benefit when caregivers receive palliative care. It is apparent that the earlier the palliative care services can be introduced to caregivers, the better they will be able to cope with their experience in the caregiving role. Future caregiver interventions should be tested in larger and more diverse populations.

The mounting evidence for the benefits of early palliative care has also spurred efforts to expand the availability of such services to all patients who need them. There are still many barriers to achieving this goal, from lack of trained personnel to insufficient funding.

Recent research points to one barrier to awareness and education that may be relatively easy to address (this study was...
funded by a grant from the NIH). The study found that some physicians are more likely to refer patients with cancer to end-of-life hospice care than others. That is, those physicians who had previously referred patients to hospice were approximately twice as likely to send other patients to hospice.

Moreover, the characteristics of the treating physicians were stronger predictors of hospice enrollment than the patients’ medical status, age, gender, or sex. The findings show that more effort is required to ensure that palliative care referrals are driven primarily by the alignment of patients’ needs and preferences with the assessment of the treating physicians.

Appendix Table A1 lists additional notable advances in patient care.

### LOOKING TO THE FUTURE

This report documents the incredible strides made in cancer research just in the last year; however, there is still much to do. This year, more than half a million people will die as a result of cancer in the United States alone, and the rate is much higher in low-resource countries. Substantially more research is needed for us to sustain this incredible progress and ensure that resulting advances are available to those who need it, both domestically and abroad.

ASCO has long-advocated for sustained investment in cancer research that can only happen with robust funding for the NIH and NCI, so we do not lose the momentum illustrated in this report. ASCO has also initiated a number of programs to deliver these advances to underserved populations in the United States and elsewhere.

### Cancer: A Growing Challenge

As the world’s population continues to grow, so will the incidence and prevalence of cancer. It is estimated that 22 million people will be diagnosed with cancer in 2030, up from 14 million in 2012. The greatest increase in cancer incidence will occur in low- and medium-resource countries, which are expected to experience the fastest population growth.

In the United States, the number of new cancer cases is projected to reach 2.3 million per year by 2030, a roughly 35% increase from 2015. This increase will be driven mainly by changing demographics. By 2030, the number of adults in the United States older than age 65 years is expected to increase to 72 million (up from 35 million in 2000) as the baby boomer generation continues to age. Risks for developing certain cancers and survival outcomes differ among racial and ethnic groups, and this will also affect cancer incidence and mortality rates as the US population continues to become more diverse.

### Focus on Prevention

The good news is that up to one third of deaths resulting from cancer could be avoided through simple lifestyle choices: maintaining a healthy body weight, increasing fruit and vegetable intake, increasing physical activity, and avoiding tobacco and alcohol use.

Quitting smoking is the single most important thing a person can do to lower his or her cancer risk. Tobacco is linked to 15 types of cancer and responsible for at least one fifth of all deaths resulting from cancer. In addition, smoking rates remain high in many parts of the world, despite decreasing in most high-resource countries.

Other forms of tobacco use include cigars or pipes, water-pipes, e-cigarettes, and smokeless tobacco, such as chewing tobacco and snuff. None of these choices is a safe substitute for cigarette smoking, because each can cause serious health problems, including cancer.

In addition to tobacco, alcohol is one of the few substances that research has consistently shown is linked to an increased risk of cancer. Drinking alcohol increases the risk of developing liver cancer, HNC, esophageal cancer, colorectal cancer, and stomach cancer.

In the near future, however, obesity is predicted to replace tobacco as the leading modifiable risk factor for cancer. Two thirds of US adults and up to 2.3 billion people worldwide are overweight. Endometrial, breast, colon, high-grade prostate, and esophageal cancers, along with many others, have been associated with being overweight and obesity. Obesity contributes to 20% of all deaths resulting from cancer.

Even after a cancer diagnosis, outcomes can be significantly improved if patients adopt healthy behaviors, such as stopping alcohol and tobacco use, engaging in physical activity, and achieving and maintaining a healthy body weight.

Another major opportunity for cancer prevention lies in broader use of cancer prevention vaccines, namely vaccines for two cancers that are most commonly caused by a virus—the hepatitis B virus and HPV. More than half of all liver cancers are caused by hepatitis B virus, and nearly all cervical cancers are attributed to HPV. Effective and affordable vaccination programs could prevent hundreds of thousands of deaths resulting from cancer worldwide.

### Changing Cancer Landscape

Some experts predict that demographic shifts in the United States will also affect the rates of specific cancers. Although breast, prostate, and lung cancers will remain the top three cancers diagnosed, thyroid cancer may replace colorectal cancer as the fourth most common cancer by 2030.

Furthermore, deaths resulting from pancreatic or liver cancer are expected to surpass those resulting from breast, prostate, or colorectal cancer, although lung cancer will remain the leading cause of death as a result of cancer. With 5-year survival rates of only 6% and 18%, patients with pancreatic and liver cancers are in urgent need of better treatments.

### Precision Oncology and Immunotherapy

For a growing number of patients with cancer, precision medicine is already part of routine care. Molecular characteristics of the tumor are often evaluated at the time of diagnosis, and whenever possible, therapy is tailored to the abnormality that drives the growth of a particular cancer.

Dozens of targeted drugs are already available, and new therapeutic targets are being discovered at a rapid pace. Novel clinical trial designs, such as basket and umbrella trials, allow for faster testing of new drugs against particular molecular targets. Clinical trials, such as ASCO’s TAPUR and NCI’S MATCH (Molecular Analysis for Therapy Choice), will help identify new
uses for existing targeted therapies by matching them to the genomic signature of the tumors of patients with advanced cancer.

Cancer immunotherapies have already proven effective for patients with a range of difficult-to-treat cancers, many of whom had exhausted all standard treatment options. Immunotherapy also has an added advantage: in many cases, it causes fewer serious adverse effects compared with standard therapy. Another unique advantage of immunotherapy is that it often continues controlling tumor growth long after a patient stops the treatment.

To see if patient outcomes could be improved further, researchers are now exploring combinations of immunotherapy treatments, as well as combinations of immunotherapies and other approaches, such as targeted therapy and chemotherapy. Other ongoing efforts in the field include finding biomarkers to predict response to immunotherapy; developing novel, more effective, and safer treatments; and expanding the range of cancer therapeutic vaccines. In the near future, cancer immunotherapy may become the fourth pillar of cancer treatment, along with chemotherapy, surgery, and radiation therapy.

Learning From Big Data

Emerging health information technologies promise to dramatically reshape the cancer care landscape, improving quality and efficiency in every cancer care setting. The technologies will use big data, such as electronic medical records and genomic test results, to guide personalized treatment decisions for each patient. They will also inform hypotheses for further research by aggregating and analyzing the massive body of cancer research data, practice experience, and practice guidelines. ASCO’s CancerLinQ is well on its way to delivering on this promise, as are other health information technology projects from other groups.

Improving Care for Patients, Survivors, and Caregivers

ASCO believes that every patient should receive high-quality, high-value care throughout his or her journey with cancer. Genomic technologies make it increasingly possible to match the right patients with the right therapy from the start, while sparing other patients the adverse effects and costs of ineffective treatments.

By targeting the unique characteristics of malignant cells, precision medicine approaches will help minimize collateral damage to healthy tissue. Refinements in treatment regimens will help reduce short- and long-term adverse effects of cancer therapies. In addition, advances in surgery will allow more patients to experience fewer risks and shorter recovery time, and blood tests for circulating tumor cells, cell-free DNA, and other tumor products may reduce the need for painful biopsies in the future.

In the coming years, researchers will continue to explore strategies for improving patient quality of life, beyond managing physical symptoms. Multidisciplinary care teams that focus on caring for the whole patient will likely become more common. Additionally, research will continue to identify ways to deliver palliative care services not only for patients but also for their caregivers, who share many of the burdens of cancer.

ASCO envisions a world where cancer is prevented or cured, and every survivor is healthy. Although the number of people living with cancer will continue to increase, the burden of cancer may actually lessen as treatments become more effective, adverse effects become fewer, and people with cancer are able to live longer, better, and more productive lives.

Cancer prevention strategies, from lifestyle changes to vaccination programs, could be deployed more widely. Other prospects are also within reach: harnessing the power of the immune system, expanding the possibilities of precision medicine, and integrating big data into cancer care. Increasing federal funding for research is critically important to continuing advances in these areas and to maintaining the pace of progress against cancer.


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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

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No relationship to disclose

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Speakers’ Bureau: Bayer HealthCare Pharmaceuticals, Eisai

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Stock or Other Ownership: Xenon Pharma (I), Intrinsic LifeSciences (I), Silarus Therapeutics (I), Merganser Biotech (I), TEVA Pharmaceuticals Industries, Novartis, Merck, Johnson & Johnson, Pfizer, GlaxoSmithKline, Abbott Laboratories
Consulting or Advisory Role: Keryx (I), Merganser Biotech (I), Silarus Therapeutics (I), InformedDNA
Research Funding: Keryx (I)
Patents, Royalties, Other Intellectual Property: Related to iron metabolism and the anemia of chronic disease (I); UpToDate royalties for section editor on survivorship
Travel, Accommodations, Expenses: Intrinsic LifeSciences (I), Keryx (I)

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Stock or Other Ownership: Express Scripts, Amgen, Merck (I), Amgen (I), Pfizer (I)
Honouraria: Jazz Pharmaceuticals, Sigma-Tau, Spectrum Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Co-inventor on US Patent No. 8,568,974 B2 identification of novel subgroups of high-risk pediatric precursor B acute lymphoblastic leukemia, outcome correlations, and diagnostic and therapeutic methods related to same (not licensed; no income)
Travel, Accommodations, Expenses: Amgen

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Research Funding: AbbVie (Inst), Novartis (Inst), Karyopharm Therapeutics (Inst), Genentech (Inst), Novocure (Inst), Aeterna Zentaris (Inst), Pfizer (Inst), Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals (Inst), Agens (Inst), GlaxoSmithKline (Inst), Stemline Therapeutics (Inst), Northwest Biotherapeutics (Inst), Plexxikon (Inst), Tocagen (Inst), Regeneron (Inst), VBL Therapeutics (Inst), e-Therapeutics (Inst), Novocure (Inst), Bristol-Myers Squibb (Inst), ImmunoCellular Therapeutics (Inst), Merck (Inst), Amgen (Inst), Celldex (Inst), Millennium Pharmaceuticals (Inst), MedImmune (Inst), Boehringer Ingelheim (Inst)
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Erica Mayer
Research Funding: Myriad Genetics (Inst), Pfizer (Inst), Eisai (Inst)

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Research Funding: Medivation

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No relationship to disclose

Richard Schilsky
No relationship to disclose

Gary K. Schwartz
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Consulting or Advisory Role: Novartis, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo
Patents, Royalties, Other Intellectual Property: Patent pending regarding development of PNA for targeted cancer therapy (new technology)
Travel, Accommodations, Expenses: Novartis, AstraZeneca (I), Boehringer Ingelheim, Daiichi Sankyo

David R. Spriggs
Patents, Royalties, Other Intellectual Property: Through my laboratory, we have discovered anti-MUC16 antibodies that MSKCC has filed patents about; these patents, if commercialized, could ultimately result in royalties paid to me (Inst)

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Research Funding: GlaxoSmithKline, Oncolytics Biotech

Gina Villani
No relationship to disclose

Gregory Masters
No relationship to disclose
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Appendix

Table A1. Additional Notable Advances From October 2014 to October 2015

<table>
<thead>
<tr>
<th>Area of Research</th>
<th>Study Title</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td>A randomized phase Ib/Ii study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human antiplatelet-derived growth factor α (PDGFRα) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS)</td>
<td>Tap WD, et al: J Clin Oncol 33, 2015 (suppl; abstr 10501)</td>
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<td>Final results of the multicenter randomized phase II PAZOGIST trial evaluating the efficacy of pazopanib (P) plus best supportive care (BSC) vs BSC alone in resistant unresectable metastatic and/or locally advanced GI stromal tumors (GIST)</td>
<td>Blay J-Y, et al: J Clin Oncol 33, 2015 (suppl; abstr 10506)</td>
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<td>Activity of regorafenib (RE) in leiomyosarcomas (LMS) and other types of soft-tissue sarcomas (OTS): Results of a double-blind, randomized placebo (PL) controlled phase II trial</td>
<td>Mir O, et al: J Clin Oncol 33, 2015 (suppl; abstr 10504)</td>
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<td>Docetaxel and/or zoledronic acid for hormone-naive prostate cancer: First overall survival results from STAMPEDE (NCT00268476)</td>
<td>James ND, et al: J Clin Oncol 33, 2015 (suppl; abstr 50001)</td>
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<td>RTOG 9802: Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma—Results by histologic subtype</td>
<td>Buckner JC, et al: Neuro Oncol 16:v11, 2014 (abstr AT-3)</td>
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<td>Patient care</td>
<td>Effect of low-intensity physical activity and moderate-to-high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial</td>
<td>Van Waart: J Clin Oncol 33:1918-1927, 2015</td>
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<td></td>
<td>Impact of the LIVESTRONG at the YMCA program on physical activity, fitness, and quality of life in cancer survivors</td>
<td>Irwin ML, et al: J Clin Oncol 33, 2015 (suppl; abstr 9508)</td>
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<td>T-lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value of end-induction minimal residual disease (MRD) in Children’s Oncology Group (COG) study AALL0434</td>
<td>Wood BL, et al: 56th ASH Annual Meeting and Exposition, San Francisco, CA, December 6-9, 2014</td>
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