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# CLINICAL CANCER ADVANCES 2012

ASCO's Annual Report on Progress Against Cancer

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I am delighted to present you with “Clinical Cancer Advances 2012: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology.” The American Society of Clinical Oncology (ASCO) uses this opportunity each year to share the steady progress occurring in our understanding and treatment of cancer. For 2012, we offer again an inspiring perspective on clinical cancer advances over the past year, but with a cautionary note: if current threats to federal funding materialize, future progress in cancer research will be seriously undermined.

Continued Progress Against Cancer

As you read the following pages of this report, I hope you will share my unabashed enthusiasm—and pride—in how far we have come. To appreciate what this progress has meant to the millions of people who receive a cancer diagnosis each year, consider the following: (1) two of three people in the United States live at least 5 years after a cancer diagnosis (up from roughly one of two in the 1970s); (2) the nation’s cancer death rate has dropped 18% since the early 1990s, reversing decades of increases; and (3) individuals with cancer are increasingly able to live active, fulfilling lives because of better management of symptoms and treatments with fewer adverse effects.

Importance of Clinical Cancer Trials

These dramatic trends—and the advances highlighted in this report—would have been unthinkable without the engine that drives life-saving cancer treatment: clinical cancer research. Advances in technology and in our knowledge of how patient-specific molecular characteristics of the tumor and its environment fuel the growth of cancer have brought new hope to patients. Clinical trials are the key to translating cutting-edge laboratory discoveries into treatments that extend and improve the lives of those with cancer.

But progress is only part of the story. Cancer remains a challenge, with many cancers undetected until their latest stages and others resisting most attempts at treatment. Tragically, cancer still kills more than 500,000 people in the United States every year, and its global burden is growing rapidly.

Bridges to Better Care

To conquer cancer, we need to build bridges to the future—bridges that will get scientific advances to the patient’s bedside quicker, bridges that will enable us to share information and learn what works in real time, and bridges that will improve care for all patients around the world.

At ASCO, we recognize the unique role that oncologists must play. ASCO’s “Accelerating Progress Against Cancer: Blueprint for Transforming Clinical and Translational Cancer Research,” published last year, presents our vision and recommendations to make cancer research and patient care vastly more targeted, more efficient, and more effective. We have also launched a groundbreaking initiative, CancerLinQ, that aims to improve cancer care and speed research by drawing insights from the vast pool of data on patients in real-world settings.

Renewing a national commitment to cancer research. We are on the threshold of major advances in cancer prevention, detection, and treatment— but only if, as a nation, we remain committed to this critical endeavor.

The federally funded cancer research system is currently under threat by larger federal budget concerns. Clearly, Congress faces a complex budget environment, but now is not the time to retreat from our nation’s commitment to conquering a disease that affects nearly all of us. Bold action must be taken to ensure that we can take full advantage of today’s scientific and technologic opportunities.

Please join me in celebrating our nation’s progress against cancer and in recommitting ourselves to supporting cancer research. Millions of lives depend on it.

Sandra M. Swain, MD
President
American Society of Clinical Oncology
Executive Summary

Background
Each year, the American Society of Clinical Oncology (ASCO) conducts an independent review of advances in clinical cancer research that have the greatest potential impact on patients' lives. This year's Report, “Clinical Cancer Advances 2012: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology,” features 87 studies, 17 of which the Report's editors have designated as major advances.

Although cancer-related deaths have declined tremendously since the early 1990s, cancer remains a leading cause of death worldwide. An estimated 577,000 Americans will lose their lives to cancer in 2012. The large number of advances featured in the Report affirms that clinical cancer research yields remarkable improvements in survival and quality of life for patients with cancer. Many studies highlighted this year capitalized on the growing knowledge about the complexity of cancer to develop sophisticated treatment approaches, such as combining targeted drugs for difficult-to-treat cancers and expanding the use of targeted drugs to multiple forms of cancer that share the same genetic alteration. Major advances over the past year were achieved in the areas of overcoming treatment resistance, personalized medicine, and screening.

It takes years of research effort to achieve advances that extend patients’ lives. This progress would not be possible without patient volunteers, dedicated investigators, and substantial public and private research investment. In the United States, the federally funded clinical trials system is essential to progress against cancer. The Clinical Trials Cooperative Group program, sponsored by the National Cancer Institute (NCI), involves approximately 3,100 institutions and places more than 25,000 patients into large clinical trials of promising treatments each year. Many of the significant developments presented in this document were a direct result of clinical research conducted by these cooperative groups. Despite difficult economic times, preserving our nation's investment in cancer research is absolutely necessary to keep the momentum that brings better treatments to the growing number of people with cancer.

This year’s Report includes two new sections, Tumor Biology and Quality Cancer Care, which feature studies reflecting the rapid pace of progress in those specialized areas. The Report also highlights the year’s most important cancer policy developments and cancer care guidelines that are likely to influence cancer care over the coming years.

Overcoming Treatment Resistance
Some cancers, such as sarcoma, ovarian cancer, and neuroblastoma, are notoriously difficult to treat, and many patients succumb to the disease shortly after diagnosis. A variety of factors contribute to treatment resistance. Some tumors are located in parts of the body that may not be readily accessi-
able to some drugs. Tumors acquire genomic changes, some of which enable them to evade or counter the effects of the treatment. Research results reported this year demonstrate how our understanding of the complex biology of cancer is leading the way to overcoming treatment resistance.

A potentially useful strategy for conquering resistant tumors is to attack more than one target in a molecular pathway that is critical for tumor survival and growth. This can be achieved through use of multitargeted drugs, such as the new agents regorafenib, which has benefited patients with treatment-resistant G1 stromal tumors (GISTs) and metastatic colorectal cancer; crizotinib, which has shown promising activity against neuroblastoma and anaplastic large-cell lymphoma (ALCL) in children; and cabozantinib, which seems to slow progression of medullary thyroid carcinoma. An alternative approach is to treat patients with two or more drugs that target the same pathway. There were three reports of improved outcomes for patients with breast cancer using such a strategy (combining two anti-human epidermal growth factor receptor 2 (HER2) agents and combining an aromatase inhibitor with a mammalian target of rapamycin [mTOR] inhibitor) this year. Early trial results showed that combining drugs that target mTOR and insulin-like growth factor receptor (IGF-R) delays progression of metastatic sarcoma resistant to standard treatments.

In addition, novel targeted agents in the class of drugs known as tyrosine kinase inhibitors (TKIs) showed promising activity against treatment-resistant forms of leukemia (ponatinib and ibrutinib), soft tissue sarcoma (pazopanib), and breast cancer (lapatinib).

**No Two Tumors Are the Same: The Promise of Precision Medicine**

Oncology is rapidly transitioning to an era of precision medicine, where patients receive treatments tailored to the genetic makeup and biology of their tumors. Just as no two patients are the same, it is becoming increasingly clear that no two tumors are exactly the same. In some situations, the genetic variations are not critical to the behavior of a tumor, but in others, these variations may guide specific treatment approaches. This year, an important study revealed that there are also dramatic variations in the genomic landscape within a single tumor and among primary and distant tumors (metastases) in the same patient. Researchers now know that even subtle genetic differences can make one tumor responsive and another resistant to the same drug.

Two large-scale genomic profiling studies captured genomic snapshots of more than 1,000 different cancer cell lines, representing much of the tissue-type and genetic diversities of human cancers, and assessed how each of them responded to dozens of different anticancer drugs. This information will enhance rational drug development and speed the discovery
of new personalized treatments. New results stemming from The Cancer Genome Atlas Project identify potential new drug targets in colorectal cancer, a prospective trial that identified key factors affecting chemotherapy adverse effects in elderly patients, and a study showing promising activity of a new targeted drug in patients with a chemotherapy-resistant form of sarcoma.

The mission of the Conquer Cancer Foundation is to conquer cancer worldwide by funding breakthrough research and sharing cutting-edge knowledge. Over nearly 30 years, the Foundation’s Grants and Awards Program has provided more than $77 million in funding to support clinical and translational scientists at all levels of their careers, working around the globe. The grants reflect the commitment of the Foundation to address the full spectrum of oncology—focusing on every moment in which cancer touches people’s lives—from prevention to end-of-life care, for nearly every cancer type, and funding research in virtually all cancers, including rare ones.

New Insights Into Risks and Benefits of Cancer Screening

It is estimated that approximately one third of all cancer cases could be prevented. The main opportunities for cancer prevention include lifestyle and dietary changes and early detection through screening.

Although routine screening has dramatically reduced the incidence and death rates for some cancers, such as cervical cancer, the value of screening for many other cancers remains uncertain. In fact, in some instances, risks of screening, such as false-positive findings leading to unnecessary treatments, have been shown to be greater than potential benefits.

For example, this year, a study found that flexible sigmoidoscopy, a technique used to examine the rectum and lower part of the bowel, reduces colorectal cancer incidence and death rates. These findings support wider use of flexible sigmoidoscopy in colorectal cancer screening, but more research is needed to determine how its performance compares with that of colonoscopy. On the other hand, another large study showed that yearly chest x-ray examinations do not reduce lung cancer death rates in the general population.

New Drug Approvals

Between October 2011 and October 2012, on the basis of encouraging results from large clinical trials, the US Food and Drug Administration (FDA) approved seven new anticancer drugs and expanded indications for five existing agents to provide new treatment options for patients with certain forms of myeloma (carfilzomib), leukemia (liposomal vincristine), breast cancer (pertuzumab and everolimus), skin cancer (vismodegib), prostate cancer (enzalutamide), GISTs (imatinib mesylate), colorectal cancer (cetuximab, ziv-aflibercept, and regorafenib), kidney cancer (axitinib), and soft tissue sarcoma (pazopanib).

Almost all of the newly approved drugs are targeted agents, meaning that they are designed to block the activity of specific proteins involved in tumor growth. One agent, vismodegib, marks the first FDA approval of a drug that targets the hedgehog signaling pathway, which plays an important role in tissue growth and repair. The drug is also being tested in clinical trials for colorectal, stomach, and pancreatic cancers.
About Clinical Cancer Advances

ASCO developed this Annual Report, now in its eighth year, to document the important progress being made in clinical cancer research and to highlight emerging trends in the field. The Report serves to outline to the public progress achieved against cancer by reviewing the major advances in clinical cancer research and care each year.

This report was developed under the direction of a 21-person editorial board composed of prominent oncologists with expertise in areas pertinent to each section of the Report. The editors reviewed research published in peer-reviewed scientific or medical journals and presented at major scientific meetings over a 1-year period (October 2011 to September 2012).

The advances included in this Report are categorized as major and notable. Major advances are considered practice changing and had to have been published in a peer-reviewed journal and/or report on a treatment that received FDA approval in the past year. Notable advances are promising clinical research results that are not immediately applicable to practice, either because a drug is not yet FDA approved or because the information is only available in abstract form (i.e., has not yet appeared in a peer-reviewed publication).

The research reviewed in this Report covers the full range of clinical research disciplines: epidemiology, prevention, screening, early detection, treatment (including surgery, chemotherapy, radiation, targeted therapy, immunotherapy, and personalized therapy), patient and survivor care (including end-of-life care and elderly patient care), biomarkers, tumor biology, and cancer disparities.

This Report is intended for anyone with an interest in cancer care, including the general public, news media, patients, caregivers, oncologists and other medical professionals, policymakers, and cancer advocacy organizations.

About ASCO

ASCO is the world’s leading professional organization representing physicians who care for people with cancer. With more than 30,000 members, ASCO is committed to improving cancer care through scientific meetings, educational programs, and peer-reviewed journals. For ASCO information and resources, visit www.asco.org. Cancer information for the lay public is available at www.cancer.net.
New Therapies

FDA APPROVALS OF ANTICANCER AGENTS, OCTOBER 2011 – OCTOBER 2012

Newly Approved Agents

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<th>Date of Approval</th>
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<tr>
<td>Axitinib</td>
<td>Inlyta</td>
<td>For treatment patients with advanced kidney cancer (renal cell carcinoma) who have not responded to other treatments for this type of cancer</td>
<td>January 27, 2012</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Erivedge</td>
<td>For use in patients with locally advanced basal cell cancer who are not candidates for surgery or radiation and for patients whose cancer has metastasized.</td>
<td>January 30, 2012</td>
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<tr>
<td>Pertuzumab</td>
<td>Perjeta</td>
<td>For use in combination with trastuzumab and docetaxel as a first-line treatment for patients with HER2-positive metastatic breast cancer</td>
<td>June 8, 2012</td>
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<tr>
<td>Carfilzomib</td>
<td>Kyprolis</td>
<td>For treatment of patients with multiple myeloma whose disease progressed despite at least two prior therapies, including bortezomib and an immunomodulatory agent</td>
<td>July 20, 2012</td>
</tr>
<tr>
<td>Ziv-Aflibercept</td>
<td>Zaltrap</td>
<td>For use in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin containing regimen</td>
<td>August 3, 2012</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Xtandi</td>
<td>For treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel</td>
<td>August 31, 2012</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Stivarga</td>
<td>For treatment of patients with metastatic colorectal cancer that has progressed despite standard treatments</td>
<td>September 27, 2012</td>
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Expanded Indications for Existing Agents

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<td>Imatinib mesylate</td>
<td>Gleevec</td>
<td>For the adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive gastrointestinal stromal tumors (GIST)</td>
<td>January 31, 2012</td>
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<tr>
<td>Pazopanib</td>
<td>Votrient</td>
<td>For treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy.</td>
<td>April 26, 2012</td>
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<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>For use in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) chemotherapy for first-line treatment of patients with KRAS mutation-negative, epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer</td>
<td>July 6, 2012</td>
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<td>Everolimus</td>
<td>Afinitor</td>
<td>For use in combination with exemestane to treat certain postmenopausal women with advanced hormone-receptor positive, HER2-negative breast cancer</td>
<td>July 20, 2012</td>
</tr>
<tr>
<td>Vincristine sulfate liposome injection</td>
<td>Marquibo</td>
<td>For treatment of adult patients with Ph- acute lymphocytic leukemia in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies</td>
<td>August 9, 2012</td>
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“An increasing number of targeted therapies are being evaluated in clinical trials and are becoming available for our patients. Clinicians will need to select therapeutic approaches using these novel agents, standard chemotherapeutic regimens, and combinations of the two based on their knowledge of their patients and the specific features of their diseases.”

– HARRY P. ERBA, MD, PHD

BLOOD AND LYMPHATIC CANCERS

SPECIALTY EDITOR: HARRY P. ERBA, MD, PHD
Cancers of the blood and lymphatic system include leukemia, lymphoma, and multiple myeloma. The most common blood cancer, leukemia, includes several distinct diseases: acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML).

This year, investigators reported encouraging results in clinical trials that tested new chemotherapies, targeted drugs, antibodies, and antibody-drug combinations. One trial resurrected interest in a previously withdrawn AML drug, proposing a new dosing scheme that seems safer for patients yet still effective. Long-term results of a large trial confirmed that a new antibody-chemotherapy drug combination is more effective and better tolerated than the standard antibody-chemotherapy combination in mantle-cell and indolent lymphomas. And finally, results of three early-phase trials point to promising new therapies for treatment-resistant CML, ALL, and CLL.

**Major Advances**

**Lenalidomide maintenance therapy delays multiple myeloma relapse after stem-cell transplantation**

Since the introduction of high-dose chemotherapy, outcomes have improved considerably for patients with multiple myeloma. However, in most of those patients, cancer returns within 10 years of receiving high-dose chemotherapy and stem-cell transplantation because chemotherapy typically fails to eradicate all myeloma cells. Several treatments for controlling growth of residual myeloma cells after transplantation (maintenance of remission) have been explored, but their use has thus far been hindered by inconsistent effectiveness and harmful adverse effects.

However, results of two placebo-controlled phase III trials reported this year indicate that lenalidomide may be able to delay relapses in patients with multiple myeloma after stem-cell transplantation. In the first study, 615 patients age younger than 65 years were randomly assigned to maintenance treatment with either lenalidomide or placebo until relapse. On average, the disease returned after 41 months with lenalidomide therapy versus 23 months with placebo (Fig 1). After 4 years of follow-up, more than 70% of patients were alive in
both groups. In the second study, 460 patients with multiple myeloma age younger than 71 years were randomly assigned to receive lenalidomide or placebo. The median time to disease progression was 46 months in the lenalidomide group and 27 months in the placebo group. Lenalidomide also increased overall survival; a total of 35 deaths occurred in the lenalidomide group compared with 53 deaths in the placebo group. In both studies, the benefit of lenalidomide was seen among all patient subgroups and was independent of patient age, prior use of lenalidomide, and disease stage. However, lenalidomide was also associated with more adverse effects and higher incidence of second cancers compared with placebo (7% to 8% vs 3% to 4%). These results provide compelling evidence of improved progression-free survival with lenalidomide maintenance therapy. But given the uncertainty of the overall survival benefit and considerable risks associated with the treatment, including myelodysplastic syndrome and AML, the risks and benefits should be carefully assessed to maximize both survival and patients' quality of life. The association of lenalidomide with second malignancies in patients with myeloma continues to be evaluated.

**Notable Advances**

**Gemtuzumab ozogamicin added to standard chemotherapy improves survival of older patients with AML**

Gemtuzumab ozogamicin was widely used to treat AML from 2000 until 2010, when it was withdrawn from the market based on concerns that it does not provide enough benefit compared with standard therapy to justify its associated serious risks, including death. Gemtuzumab ozogamicin consists of an antitumor antibiotic calicheamicin that is chemically linked to an antibody that targets CD33, a protein found on the surface of most immature AML white blood cells (blasts) and myeloid precursor cells.

This year, investigators reported data from a phase III trial that sought to determine if the addition of gemtuzumab ozogamicin to standard induction (initial) and consolidation chemotherapy could improve outcomes of older patients with AML. Consolidation therapy is used to kill any cancer cells left in the body after initial therapy.

In the study, 280 patients between ages 50 and 70 years with newly diagnosed with AML were randomly assigned to treatment with chemotherapy alone or chemotherapy plus gemtuzumab ozogamicin. Gemtuzumab ozogamicin was administered on a novel dosing schedule during induction; fewer doses were administered during consolidation. At 2 years, the proportion of patients who remained free of disease was twice as high in the gemtuzumab ozogamicin group of patients, an estimated 40.8% vs 17.1% (Fig 2). Overall and recurrence-free survival rates were also significantly improved in the gemtuzumab ozogamicin group (53.2% vs 41.9% and 50.3% vs 22.7%). However, this benefit was not observed in patients with high-risk subtypes of the disease.

Although the addition of gemtuzumab ozogamicin increased the hematologic toxicity associated with chemotherapy, unlike previous studies, this trial found there was no increase in induction mortality or death in remission. This study, along with three other European trials reported at the 53rd Annual Meeting of the American Society of Hematology in December 2011, shows the addition of gemtuzumab ozogamicin to chemotherapy seems to improve outcomes and even
prolong the survival of older patients with AML. Gemtuzumab ozogamicin is currently only available as an investigational agent. Pfizer is considering its next steps with this important antibody-drug conjugate for older adults with AML.

**New chemotherapy-antibody combination delays disease progression in lymphoma**

Mantle-cell lymphoma is a rare but difficult-to-treat form of lymphoma. Even with treatment, patients live a median time of just 3 to 6 years after diagnosis. A chemotherapy drug called bendamustine has previously been used in combination with the antibody rituximab to treat relapsed and recurrent mantle-cell lymphoma and indolent (slow growing) lymphoma, but the efficacy of this combination in previously untreated patients has been unclear.

Long-term results of a phase III trial that explored the efficacy of bendamustine plus rituximab (B-R) versus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy plus rituximab (CHOP-R) in 514 patients with indolent and mantle-cell lymphomas were reported this year. The median patient age was 64 years. Investigators found that B-R extended the median time to disease progression by more than 3 years (69.5 months with B-R v 31.2 months with CHOP-R) and was better tolerated than CHOP-R. Overall survival did not differ between the two treatment groups, partly because nearly half of the CHOP-R patients whose disease continued to progress were permitted to receive B-R, and partly because survival for indolent lymphomas tends to be long (10 to 15 years).

This study demonstrates that B-R is superior to the standard treatment (ie, CHOP-R) for patients with previously untreated indolent lymphoma and elderly patients with mantle-cell lymphoma. Once the final report of this trial is published, the results are expected to change clinical practice, especially in the United States, where the CHOP-R regimen has been widely used.

**Ponatinib is active in treatment-resistant CML and ALL**

Introduction of BCR/ABL TKI drugs revolutionized the treatment of patients with CML and Philadelphia chromosome (Ph)-positive ALL. However, patients harboring a specific alteration in the BCR/ABL protein T315I are resistant to the TKI drugs. But results from an ongoing phase II study showed that a new, rationally designed TKI drug, ponatinib (Fig 3), is active in this group of patients.

In the study, nearly all of the 449 patients enrolled had experienced failure of two or more previous treatments with BCR/ABL TKIs. Remissions occurred in 65% of patients with chronic-phase CML with the T315I alteration, and hematologic responses (recovery of healthy blood cell counts) were observed in 37% of patients with Ph-positive ALL with T315I. These results suggest that ponatinib is an active agent for these two populations of patients.

**Small trial reveals a potential new initial treatment for elderly patients with CLL**

The standard therapy for CLL, fludarabine, is effective in elderly patients, but it carries significant risk of adverse effects, including treatment-related death. Therefore, older patients with CLL are in great need of new effective but less toxic treatments. Interim results of a phase I/II study suggest that
a new drug candidate may fulfill this unmet clinical need. In the study, 31 patients were treated with the investigational drug ibrutinib, which targets Bruton’s tyrosine kinase and thereby blocks cancer cell division and spreading. The study assessed two different doses of ibrutinib both in relapsed and treatment-resistant patients with CLL as well as in patients who had no prior treatment. The median patient age was 71 years, and three quarters of patients were older than age 70 years. At the lower dose, patients were observed for a median time of 10.7 months, and during that time, 19 (73%) of 26 patients experienced tumor shrinkage, and 8% of those had complete remissions. The higher dose was not more active compared with the lower dose. These findings indicate that ibrutinib should be explored further as the first treatment for elderly patients with CLL either alone or in combination with other therapies such as monoclonal antibodies.

Immunotherapy drug leads to complete remissions in relapsed/resistant ALL

B-precursor ALL is the most common subtype of ALL. Relapsed and resistant B-precursor ALL has a dismal prognosis in older adults, with fewer than 10% of patients older than age 60 years surviving long term. New effective therapies are urgently needed. Results from a small phase II clinical trial assessing the safety and efficacy of a promising new agent called blinatumomab for this group of patients were reported this year. Blinatumomab is an antibody that directs the patient’s own white blood cells—T cells—to attack the CD19-positive tumor cells. In the study, 17 (68%) of 25 patients treated experienced complete remissions. Among the first 18 patients treated, responses lasted 7.1 months, and six patients relapsed. On the basis of these exceptionally high remission rates and the favorable safety profile documented in this study, researchers have launched a larger, global study to confirm the results.

FDA approves targeted drug for patients with treatment-resistant multiple myeloma

The FDA approved a new proteosome inhibitor, carfilzomib, in July for the treatment of patients with multiple myeloma whose disease had progressed despite at least two prior therapies, including bortezomib and an immunomodulatory agent.

FDA approves liposomal vincristine for the treatment of patients with Ph–negative ALL

In August, the FDA approved vincristine sulfate liposome injection for the treatment of adult patients with Ph-negative ALL in second or greater relapse or whose disease had progressed after two or more antileukemia therapies. This is an important milestone, because there are no other approved standard treatment options for this group of patients.
On average, the disease returned after 41 months with lenalidomide therapy versus 23 months with placebo.

REFERENCES


8. US Food and Drug Administration: FDA approves Kyprolis for some patients with multiple myeloma. [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312920.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312920.htm)

“Advances in breast cancer research over the past year were especially exciting. They provided evidence that several new targeted therapies benefit patients with metastatic breast cancer. The studies also allowed a glimpse into the future, in which the power of genomic technologies is used to define the molecular underpinnings of breast cancer, opening avenues for better understanding of drug resistance and the discovery of new therapeutic targets.”

– SYLVIA ADAMS, MD
The overall breast cancer death rate has dropped steadily over the last decade. However, breast cancer remains the second-leading cause of cancer-related deaths in American women, and advanced and metastatic breast cancers are particularly difficult to treat.

This year, three trials brought important treatment advances for metastatic breast cancer. Two trials reported significantly improved outcomes with new targeted therapy combinations for patients with HER2-positive breast cancer. Another trial showed the benefits of combining hormone therapy with targeted therapy to treat hormone receptor-positive advanced breast cancer and supported the FDA approval of a new targeted agent. The success of these targeted drugs underscores the value of studying the underlying biology of tumors and translating these results to the clinic.

Additionally, there have been notable advances stemming from genomic analysis of breast tumor tissue. Three large-scale genomic studies identified new breast cancer subtypes and potential treatment targets as well as genetic alterations involved in resistance to aromatase inhibitors. The studies provide insight into the genetic diversity of breast cancers, opening the door for the discovery of new targets and determinants of responsiveness to therapy.

**Major Advances**

**New armed antibody improves survival in HER2-positive metastatic breast cancer**

Results of an international randomized phase III trial indicate that an experimental drug outperforms the only current standard therapy for HER2-positive metastatic breast cancer that does not respond to trastuzumab. The drug, called T-DM1, consists of two chemically linked anticancer drugs: trastuzumab, an antibody against HER2, and the chemotherapy drug DM1 (emtansine) (Fig 4). T-DM1 wages a two-pronged attack against cancer cells. The antibody, which in itself works against HER2-positive breast cancer cells, also selectively delivers DM1 to those cells, minimizing toxic adverse effects to healthy tissues. On entry into cells, DM1 is cleaved from trastuzumab and disrupts cancer cell division.

The present trial compared the effectiveness of T-DM1 versus capecitabine and lapatinib (XL) in 991 women with HER2-positive locally advanced or metastatic breast cancer that worsened despite standard trastuzumab therapy. TDM-1 delayed the median time to disease progression compared with XL (9.6 v 6.4 months). Furthermore, 2 years after treatment, the median survival rates for T-DM1 were also higher than for XL (65.4% v 47.5%) (Fig 5). At interim analysis, the
median survival times for T-DM1 and XL were 30.9 versus 25.1 months. The study suggests that T-DM1 may provide an additional and potent treatment option for HER2-positive breast cancer; the drug is currently under FDA review for treatment of patients with HER2-positive metastatic breast cancer. Phase III studies evaluating T-DM1 both for newly diagnosed and previously treated HER2-positive breast cancer are under way.

**Trial finds two HER2-targeted drugs are better than one in first-line therapy, leading to new drug approval**

Although trastuzumab improves outcomes in HER2-positive breast cancer, most patients with advanced disease eventually become resistant to the drug. But results of a phase III trial reported this year indicate that combining trastuzumab and chemotherapy (docetaxel) with pertuzumab, another anti-HER2 antibody, in previously untreated patients may overcome or delay this resistance.

The combination treatment significantly delayed metastatic breast cancer progression compared with standard therapy, consisting of trastuzumab and docetaxel. In the trial, 808 patients were randomly assigned to receive docetaxel and either placebo plus trastuzumab (control group) or pertuzumab plus trastuzumab as initial (first-line) treatment. The median time to disease progression was 12.4 months for the control group versus 18.5 months in the pertuzumab group (Fig 6). There was no substantial added toxicity from pertuzumab. On the basis of the trial results, on June 8, 2012, the FDA approved pertuzumab in combination with trastuzumab and docetaxel as a first-line treatment for patients with HER2-positive metastatic breast cancer.

**Adding targeted therapy to aromatase inhibitor delays disease progression in postmenopausal hormone receptor–positive advanced breast cancer**

Aromatase inhibitors, drugs that block estrogen production in the body, are used to treat advanced cancers that are fueled by estrogen (hormone receptor-positive disease). Unfortunately, in most patients with breast cancer, the disease eventually progresses despite such therapy. With the recent discovery of the key molecular player responsible for resistance to aromatase inhibitors—mTOR—researchers surmised that blocking mTOR may be a way to overcome the resistance.

Exploring this hypothesis, a randomized phase III trial compared the effectiveness of combination therapy with the aromatase inhibitor exemestane plus the mTOR inhibitor everolimus with exemestane plus placebo in 724 patients with hormone receptor-positive advanced breast cancer whose disease had progressed despite aromatase inhibitor therapy. Investigators found that the combination more than doubled the time until cancer progressed: the median time to disease progression was 10.6 months in women who received everolimus plus exemestane versus only 4.1 months in those who...
received exemestane plus placebo. However, the addition of everolimus increased the overall toxicity of the treatment, and therefore, careful observation of treated patients is important.

On the basis of these trial results, on July 20, 2012, the FDA approved everolimus for use in combination with exemestane to treat certain postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer.5

**Notable Advances**

**Two-pronged attack on HER2-positive tumors outperforms single-agent therapy even in early-stage breast cancer**

Another phase III study this year reported improved efficacy from combining two anti-HER2 agents in patients with early-stage breast cancer, in this case trastuzumab and the TKI lapatinib (Fig 8), before surgery [neoadjuvant therapy].6 Currently, the standard treatment in this setting is chemotherapy combined with one anti-HER2 agent (trastuzumab). In this pivotal trial, 455 women with HER2-positive primary breast cancer were randomly assigned to receive paclitaxel plus either single-agent trastuzumab or lapatinib, or the combination (trastuzumab plus lapatinib). Remission (pathologic complete response) rates were much higher among patients treated with the combination treatment (51%) compared with those treated with trastuzumab alone (29%) or lapatinib alone (25%) (Fig 7). Certain adverse effects, including severe diarrhea, occurred more frequently in the lapatinib and combination treatment groups than in the trastuzumab-alone group. The findings show that dual inhibition of HER2 is a promising new preoperative treatment strategy for patients with HER2-positive breast cancer. A clinical trial testing the combination of trastuzumab and lapatinib in the postoperative (adjuvant) setting recently completed accrual, and results are awaited.

**Study uncovers genomic changes that make some breast tumors resistant to common treatments**

Patients with estrogen receptor-positive breast cancer have highly variable treatment outcomes. This year, results of a whole-genome analysis study were reported, helping to characterize the genomic landscape and identify factors linked to treatment success, specifically response to aromatase inhibitor.7 Researchers analyzed 77 pretreatment tumor samples collected from clinical trial participants with estrogen receptor-positive breast cancer who were treated with aromatase inhibitors before surgery. Significant alterations were found in 18 genes, including five genes previously linked to five blood disorders.

Further analysis pinpointed the pathways of DNA replication and repair that seem to facilitate aromatase inhibitor treatment resistance. For example, more than one third of resistant tumors had alterations in the TP53 signaling path-
way. On the other hand, alterations in the MAP3K1 gene were associated with favorable outcomes after aromatase inhibitor therapy. The study represents an important step in the effort to link mutations in the tumor genome to clinical outcomes. Ultimately, this work could support the use of genetic studies to guide treatment for individual patients.

Probing breast tumor genomes and transcriptomes reveals novel clinical subgroups
Results of a recent study point to a novel way of categorizing patients with breast cancer that is based on gene copy number and expression changes in their tumors. Investigators analyzed genetic alterations and gene expression patterns in approximately 2,000 primary breast tumors (all known subtypes included) and examined associated long-term clinical follow-up data. New subgroups with distinct clinical outcomes emerged from the analysis, such as a new high-risk, estrogen receptor-positive subgroup, along with several genes that seem to be involved in breast cancer development. This study is important because it provides a more precise framework for understanding how gene copy number abnormalities affect gene expression in breast cancer and identifies new patient subgroups to be explored in future research studies.

Six technologies unveil a comprehensive molecular portrait of breast cancer
Results of a new study from The Cancer Genome Atlas (TCGA), which combined six technologies to systematically analyze genes, gene transcripts, and proteins in more than 800 breast tumor samples, confirm that there are four main molecular subtypes of breast cancer; each subtype harbors a distinct set of genetic and epigenetic abnormalities. Integration of these complementary and highly interdependent layers has led to a deeper understanding of the dysregulated processes that contribute to tumor development and progression, which would have not been possible using more traditional approaches. The data generated by the TCGA comprise an extraordinary and valuable resource expected to fuel discoveries of candidate biomarkers and therapeutic targets. For example, the finding that basal-like breast cancers share marked genomic similarities with ovarian cancers may be harnessed in optimizing therapies for both cancers.

Fig 8. Targeted therapies for HER2+ breast cancer: Trastuzumab, Lapatinib, and TDM-1
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This year, three trials brought important treatment advances for metastatic breast cancer.
“We are moving into an era of streamlined clinical trial designs that incorporate molecular markers with the idea of rapidly identifying cancer subtypes that are most likely to respond to treatment, allowing personalized treatment approaches for each patient.”

– MARK GILBERT, MD
Cancers of the central nervous system (CNS) include those of the brain and spinal cord. This year brought progress in the arena of identifying predictive molecular markers that enhance physicians’ ability to tailor therapies to individual patients with certain brain cancers. First, two phase III trials explored chromosome abnormalities that predict response to chemotherapy in a subset of patients with glioma. Another study examined the role of a molecular marker called O6-methylguanine DNA-methyltransferase (MGMT) in predicting response to radiation therapy versus chemotherapy in elderly patients with high-grade astrocytoma, the most common form of glioma.

Other notable findings hint at the next era of smarter clinical cancer research, in which clinical trials could be smaller, faster, and more efficient—enabling new treatments to reach patients sooner.

**Notable Advances**

**Genetic markers linked to better treatment response, longer survival in patients with oligodendroglioma**

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

In the first study, patients with AOD were randomly assigned to receive PCV (procarbazine, lomustine, and vincristine) immediately followed by radiation therapy (148 patients) or radiation therapy alone (143 patients). After a median follow-up of 11.3 years, the combination therapy was associated with a longer time to disease progression compared with radiation therapy alone (2.5 v 1.7 years), but overall median survival was comparable between the two groups. However, an analysis of the subgroup of patients with the 1p/19q codele-
The current standard treatment for older patients with astrocytoma and glioblastoma is surgery or biopsy followed by radiation therapy. It has not been clear if those patients might also benefit from chemotherapy.

Results of a clinical trial reported this year suggest that temozolomide chemotherapy may be as effective as, and in some cases better than, radiation therapy and that this benefit could be predicted on the basis of a molecular marker. In the study, patients with glioblastoma (n = 373) and anaplastic astrocytoma (n = 39), all older than age 65 years, were treated with either radiation therapy or temozolomide. Although median overall survival did not differ between the two treatment groups, further analysis showed that patients who had a specific alteration of the MGMT gene (promoter methylation) in their tumor survived longer; those treated with temozolomide survived longer than those who received radiation therapy. In contrast, patients who did not have the MGMT alteration survived longer if treated with radiation therapy.

These results suggest that MGMT alteration status can be used to determine which treatment (radiation therapy or chemotherapy) would be best for individual elderly patients with glioblastoma and high-grade astrocytoma.

Novel clinical trial designs speed pace of discovery for rare diseases

This year brought important validation for two novel clinical trial designs that are increasingly being used in CNS cancer research. The new designs allow trials to be completed with fewer patients, saving time and resources and, most importantly, helping patients benefit from new treatments faster.

The first, called the Bayesian-based trial design, uses accumulating study data in real time to guide the course of the trial. This flexibility increases the probability that patients will be assigned to treatment cohorts that show evidence of benefit.

Genetic marker helps inform choice between radiation therapy or chemotherapy in elderly patients

Recent epidemiologic data suggest that an increasing proportion of glioblastomas will occur in elderly patients. The findings of these studies suggest that MGMT alteration status can be used to determine which treatment (radiation therapy or chemotherapy) would be best for individual elderly patients with glioblastoma and high-grade astrocytoma.
efficacy. To determine if Bayesian-based design would require fewer patients to answer a scientific question (eg, whether an experimental drug is better than placebo) than a traditional trial design, researchers retrospectively applied adaptive randomization to patient data from four phase II trials in patients with recurrent glioblastoma. They determined that if Bayesian design had been used in those studies, 30 fewer patients (approximately one third) in each trial would have been needed to achieve the same scientific results.

The second novel clinical trial design, termed factorial design, was also found to be useful in efficiently testing new drug combinations (including combinations of targeted drugs) as well as the impact of individual drugs in these combinations. Factorial design was successfully applied in a recent phase II study that sought to determine if the addition of certain drugs to temozolomide improved patient outcomes. In this study, 175 newly diagnosed patients with glioblastoma were randomly assigned to receive one of eight different temozolomide combination regimens. The factorial design allowed researchers to determine the impact of each agent on outcome; four treatment arms contained the agent, and four arms did not. Furthermore, the impact of three- versus two-drug combinations could be determined. Although none of the agents provided benefit over temozolomide alone, the findings indicate that adding the anticancer drug isotretinoin to temozolomide leads to worse outcomes than treatment with temozolomide alone. This study demonstrated that factorial design is suitable for testing drug combinations and that the statistical design requires approximately 50% fewer patients when compared with traditional randomized phase II studies.

These early reports demonstrating the feasibility of the adaptive randomized and factorial clinical trial designs strongly suggest that the field will be at the cutting edge of testing and developing new treatments for malignant brain tumors.

In summary, the highlighted studies provide a clear demonstration that brain tumor studies are moving into an era that recognizes that there are distinct varieties of brain tumors even within defined histologic subtypes. Furthermore, establishment of a predictive marker for anaplastic oligodendroglioma has led to a new marker-based standard of care. Similarly, an established prognostic marker, MGMT alteration, may be helpful in choosing the optimal treatment in elderly patients with glioblastoma. Looking toward the future, novel clinical trial designs will be needed to efficiently integrate molecular markers with the evaluation of the rapidly expanding portfolio of targeted agents.

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“There is a change in the way we think about cancer drug usage. Recent trials have shown benefit from keeping bevacizumab, a component of a first line of therapy for metastatic colorectal cancer, in the second line of therapy, but changing the companion drug. This approach can transform a growing number of cancers from a deadly disease to a chronic illness, though at a skyrocketing cost. There is a growing need to develop biologic drugs such as bevacizumab at a cheaper cost, with emphasis on shifting compensation based on outcome rather than services provided.”

– FADI BRAITEH, MD
Major Advances

Preoperative chemotherapy and radiation therapy double overall survival for esophageal and gastroesophageal junction cancers

Esophageal cancer is one of the most deadly cancers, causing more than 400,000 deaths per year worldwide. Although a cure is possible for patients whose tumors can be removed completely during surgery, this is not possible for approximately one quarter of patients and leads to poorer outcomes. On the basis of positive results from an early-phase clinical trial, researchers launched a phase III clinical trial to determine if treatment with chemotherapy and radiation therapy before surgery would improve the success of surgery and extend patient survival. In the trial, patients with adenocarcinoma, squamous cell carcinoma, and large-cell undifferentiated carcinoma of the esophagus or gastroesophageal junction were randomly assigned to chemotherapy (carboplatin and paclitaxel) plus radiation therapy followed by surgery (178 patients) or surgery alone (188 patients). This year, researchers reported that preoperative treatment yielded substantial benefits: 29% of patients experienced complete remissions; median overall survival was longer (49 v 24 months) (Fig 11), and the death rate was 35% lower in patients who underwent
preoperative treatment compared with those who had surgery alone. Toxicities from this additional therapy were minor. These findings will likely change the standard of care for most patients with esophageal and gastroesophageal junction cancers, offering the possibility of cure for many.

**Regorafenib prolongs overall survival in patients with metastatic colorectal cancer**

Regorafenib is a multitargeted experimental drug that blocks the growth of tumor cells and blood vessels. The drug has shown promising antitumor effects in preclinical studies and is currently being tested in clinical trials for various cancer types (Sarcoma).

This year, researchers reported results of a phase III clinical trial that sought to determine if regorafenib would extend overall survival in patients with metastatic colorectal cancer whose disease had progressed after all approved standard therapies. This international clinical trial (CORRECT) randomly assigned patients to receive regorafenib plus best supportive care (505 patients) or placebo plus best supportive care (255 patients). Results of an interim analysis of trial data show a notable improvement in median overall survival for regorafenib versus placebo (6.4 v 5.0 months). On the basis of these encouraging results, the study was unblinded to allow patients who had been receiving placebo to switch to regorafenib. In September this year, the FDA approved regorafenib to treat patients with metastatic colorectal cancer whose disease had progressed despite standard treatments.

**Notable Advances**

**Second-line treatment with bevacizumab extends overall survival in patients with metastatic colorectal cancer**

Bevacizumab added to chemotherapy is a standard first-line treatment for metastatic colorectal cancer. Bevacizumab is also used as a second-line treatment for patients who had not been treated with the drug previously. But before this year, it was unclear if it was beneficial to administer bevacizumab as a second-line treatment to patients whose disease had progressed after first-line bevacizumab plus chemotherapy.

To answer this question, researchers conducted a clinical trial in patients with inoperable metastatic colorectal cancer whose disease had worsened within 3 months of stopping initial treatment with bevacizumab and chemotherapy. In the study, patients were randomly assigned to receive bevacizumab plus chemotherapy (409 patients) or chemotherapy alone (411 patients). This year, investigators reported the first trial results, finding that the median overall survival was longer with combination treatment compared with chemotherapy alone (11.2 v 9.8 months). The combination treatment also delayed time to disease progression. The results of this randomized study support a rationale for continuing bevacizumab in patients whose disease worsens after first-line treatment with bevacizumab plus chemotherapy. It remains to be proven if this so-called recycling of bevacizumab after first-line therapy is a cost-effective strategy that prolongs survival, with expected differences in application in Europe versus North America.

**Adding cetuximab to standard adjuvant chemotherapy does not improve outcomes in stage III colon cancer**

Approximately half of patients with stage III colon cancer (cancer that has spread to the lymph nodes surrounding the colon but not to other parts of the body) are cured by surgery and postoperative (adjuvant) chemotherapy, and efforts are ongoing to elevate such cure rates. Postoperative FOLFOX (leucovorin, fluorouracil, and oxaliplatin) chemotherapy has been shown to reduce recurrence rates and improve overall survival in those patients.

This year, researchers reported results of a phase III study...
evaluating whether adding the targeted drug cetuximab to FOLFOX improves outcomes for those patients. Cetuximab was previously approved to treat patients with metastatic colon cancer who do not carry alterations in the KRAS gene as a single agent or in combination with irinotecan in previously treated patients with metastatic disease. In July 2012, the FDA granted its approval in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) as a first-line treatment for patients with metastatic disease without KRAS alterations as well. This trial—involving 2,686 patients with stage III colon cancer—found that survival rates for FOLFOX alone were 74.6% versus 71.5% for FOLFOX plus cetuximab in patients without KRAS alterations and 67% versus 65% in those with KRAS alterations. The results suggest that cetuximab should not be used in patients with stage III colon cancer after surgery and underscore the need for a better understanding of the distinct tumor biology in advanced colon cancers.

FDA approves cetuximab in combination with FOLFIRI chemotherapy for patients with metastatic colorectal cancer

In July, the FDA approved cetuximab for use in combination with FOLFIRI chemotherapy for first-line treatment of patients with KRAS mutation-negative, epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer. Adding cetuximab to chemotherapy results in improved overall and progression-free survival for this group of patients.

FDA approves ziv-aflibercept injection in combination with FOLFIRI chemotherapy for patients with metastatic colorectal cancer

In August, the FDA approved the biologic ziv-aflibercept injection for use in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen. This new targeted treatment offers the possibility of slowing disease progression in this subset of patients.

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“Results from recently presented Phase III studies of androgen/androgen receptor targeted therapies have validated the driver biology in castration resistant prostate cancer and immediately improved the prognosis for this population. Meanwhile, investigational therapies targeting the tumor micro-environment, including novel radiopharmaceuticals and growth factor targeted therapies, are promising to improve patient outcomes in the near future.”

– DANIEL GEORGE, MD
Major Advances
Enzalutamide improves survival benefit and becomes new standard treatment option for men with chemotherapy-treated prostate cancer

Androgens fuel the growth of prostate tumors. To exert their action, they must bind to a protein called the androgen receptor inside cancer cells. Past studies of agents that block the activity of the androgen receptor have demonstrated clinical activity, but not a survival benefit, in men with prostate cancer.

This year, a multinational phase III trial of the targeted drug enzalutamide achieved this goal and established a new standard treatment for men with metastatic disease that had progressed despite initial chemotherapy. Enzalutamide blocks androgen binding and translocation of the androgen receptor into the nucleus as well as its attachment to DNA. The trial enrolled 1,199 men with castration-resistant prostate cancer who were previously treated with docetaxel.1 Median overall survival for men treated with enzalutamide was 18.4 months compared with 13.6 months for men who received placebo (Fig 12). At interim analysis, patients receiving enzalutamide had a 37% lower rate of death compared with those receiving placebo. On the basis of these remarkable results, the study was unblinded, and patients who had been receiving place-
bo were offered enzalutamide. In August, the FDA approved enzalutamide for the treatment of men with metastatic castration-resistant prostate cancer previously treated with docetaxel chemotherapy.2

Notable Advances
Abiraterone acetate delays cancer progression in men with metastatic castration-resistant prostate cancer not previously treated with chemotherapy
In 2011, the FDA approved abiraterone acetate in combination with prednisone for the treatment of men with castration-resistant prostate cancer previously treated with docetaxel, based on an observed prolongation of survival compared with prednisone alone. However, many men with castration-resistant prostate cancer are never treated with docetaxel-based chemotherapy. Results of a phase III multinational study, released this year, indicate that the combination of abiraterone acetate and prednisone may also benefit men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer who have not received prior chemotherapy.3 In the study, 1,088 patients were randomly assigned to receive abiraterone acetate and prednisone or prednisone and placebo. Interim analysis after a 22-month follow-up period revealed that abiraterone acetate improved progression-free survival (time to prostate-specific antigen progression was 11.1 months v 5.6 months for abiraterone and placebo, respectively) and showed a strong trend toward prolonged overall survival. Compared with patients receiving placebo, patients receiving abiraterone also had delayed onset of cancer-related pain and functional decline, and initiation of chemotherapy was postponed. On the basis of these compelling results, the study was unblinded, and patients who had received placebo were offered abiraterone acetate. This is the first randomized trial to our knowledge showing both overall survival and progression-free survival benefits in patients with metastatic castration-resistant prostate cancer who had not received prior chemotherapy.

New insight into efficacy of intermittent androgen-deprivation therapy for certain patients with prostate cancer
Continuous (long-term) androgen-deprivation therapy is associated with a variety of adverse effects, such as hot flashes, loss of libido, fatigue, and depression, which diminish patients’ quality of life. In addition, almost all patients eventually become resistant to androgen-deprivation therapy. Preclinical studies had suggested that androgen-deprivation therapy administered intermittently could delay the onset of androgen resistance (also called castration resistance). Intermittent therapy improves patients’ quality of life by reducing adverse effects. A large international phase III trial was undertaken in 3,040 patients with metastatic prostate cancer not previously treated with hormone therapy to determine if intermittent androgen-deprivation therapy was comparable to continuous therapy in terms of survival outcomes. After 9 years of follow-up, intermittent androgen-deprivation therapy resulted in a median overall survival of 5.1 years compared with 5.8 years for continuous therapy, indicating that intermittent androgen-deprivation therapy is not more effective than continuous therapy for patients with hormone-sensitive prostate cancer.4 A subanalysis showed that among men with minimal disease spread (no spread beyond the spine, pelvis, or lymph nodes), the median overall survival was 7.1 years for those who received continuous therapy versus 5.2 years for those who received intermittent therapy, indicating that intermittent therapy is not more effective than continuous therapy for patients with hormone-sensitive prostate cancer.4 A subanalysis showed that among men with minimal disease spread (no spread beyond the spine, pelvis, or lymph nodes), the median overall survival was 7.1 years for those who received continuous therapy versus 5.2 years for those who received intermittent therapy, indicating that continuous therapy may be a better option for those patients. Among men with more extensive disease spread, median overall survival was similar with both treatments (4.4 years
for the continuous therapy group vs 5 years for the intermittent therapy group).

However, another recently published study revealed no significant difference in overall survival between intermittent and continuous hormonal therapy after radiation therapy for localized prostate cancer (minimal disease spread), with a median follow-up of nearly 7 years. Taken together, these findings affirm the standard treatment approach—continuous androgen deprivation for patients with metastatic disease—because to date, no clinical trial in metastatic disease has shown improved efficacy with intermittent therapy. In the case of minimal disease spread, physicians should discuss both treatment options with patients, because intermittent therapy may not be as beneficial in terms of extending survival as continuous therapy. The decision to administer intermittent androgen-deprivation therapy should be individualized and be based at least in part on the stage of the cancer.

Radium-223 improves overall survival in castration-resistant prostate cancer metastasized to the bone

Prostate cancer most commonly metastasizes to the bones, where it can frequently result in skeletal complications including pain, fracture, and nerve compression. Recently, researchers investigated the use of a first-in-class alpha-emitting radiopharmaceutical, radium-223 (223Ra), which has the potential to deliver radiotherapy specifically to sites where calcium is deposited in the bone. 223Ra belongs to a class of drugs called alpha pharmaceuticals because they emit a form of radiation, called high-energy alpha particles. Because the range of radioactive alpha particles is short (roughly 100 microns), penetration is limited to five- to 10-cell diameters, so damage to surrounding tissue is minimal. 223Ra is particularly suitable for bone metastases because radium is deposited in bone, mimicking calcium deposition. Excess 223Ra is cleared through the GI tract, differing from beta-emitting radiopharmaceuticals, which are cleared through the urinary system; this may benefit some patients with decreased kidney function.

A phase III trial randomized trial compared the efficacy of 223Ra (615 patients) versus placebo (307 patients) in men with castration-resistant prostate cancer with two or more bone metastases. Median overall survival was 14.9 months in the 223Ra group and 11.3 months in the placebo group. Only minor adverse effects were observed in patients receiving 223Ra. An updated analysis of the trial data showed that compared with placebo, 223Ra reduced the risk of death by 30.5%, delayed the onset of skeletal complications by 6 months, and improved patients’ quality of life. These results indicate that 223Ra may become the first alpha-emitting radiopharmaceutical and a new standard option for patients with castration-resistant prostate cancer and bone metastases.

FDA approves axitinib for patients with treatment-resistant advanced kidney cancer

In January, the FDA approved axitinib to treat patients with advanced kidney cancer (renal cell carcinoma) who have not responded to other treatments for this type of cancer. This approval offers a new treatment option for the disease.

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“Germline (hereditary) mutations in BRCA1 and BRCA2 genes are found in up to 23% of women with high grade serous ovarian cancer. Thus, genetic counseling is important for all women diagnosed with high grade serous ovarian cancer.”

– CAROL AGHAJANIAN, MD
Major Advances
Chemotherapy plus bevacizumab is more effective than chemotherapy alone in platinum-resistant recurrent ovarian cancer

Platinum-resistant ovarian cancer is defined as progression of disease within 6 months from completion of platinum-based chemotherapy. Treatment options for women with platinum-resistant ovarian cancer are limited. Options include pegylated liposomal doxorubicin, topotecan, and weekly paclitaxel. These treatments result in relatively low response rates (compared with those seen in untreated or platinum-sensitive patient groups) and short durations of response. Furthermore, randomized phase III trials have failed to show superiority of any agent over another. Combination regimens likewise have failed to improve efficacy as compared with single-agent therapy.

Three recent clinical trials demonstrated that adding bevacizumab—a drug that blocks the growth of tumor blood vessels—to platinum-based chemotherapy extends time to disease progression in patients with newly diagnosed and first platinum-sensitive recurrent ovarian cancer. This year, results of a phase III trial, AURELIA, indicate that adding bevacizumab to standard chemotherapy also offers benefits for women with recurrent ovarian cancer resistant to platinum-based...
In the trial, 361 women, who had received up to two prior treatment regimens, were randomly assigned to receive selected standard chemotherapy (pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel) alone or chemotherapy plus bevacizumab. The median time to disease progression was 6.7 months for chemotherapy plus bevacizumab versus 3.4 months for chemotherapy alone (Fig 13). Patients in the chemotherapy-only arm were allowed to cross over (on study) to bevacizumab monotherapy at progression. This is the first phase III trial to our knowledge showing improved outcome with a combination of targeted therapy and chemotherapy in platinum-resistant ovarian cancer.

**Notable Advances**

**BRCA1 and BRCA2 mutations associated with longer survival and better treatment response**

Epithelial ovarian cancer is a general term for tumors that arise from Mullerian tissues, including the fallopian tubes, ovaries, endometriosis, and the peritoneal cavity. There are several distinct histologic types of epithelial ovarian cancer, including high-grade serous, low-grade serous, clear cell, mucinous, endometrioid, and carcinosarcoma. Over 75% of patients with advanced epithelial ovarian cancer have the high-grade serous type. High-grade serous cancers are characterized by alterations in a cancer-related gene called p53.4 High-grade serous ovarian cancers are also associated with BRCA1 and BRCA2 mutations. Alterations in BRCA1 and BRCA2 genes are associated with an overall increased risk of developing ovarian cancer. Two studies reported this year demonstrated these mutations are also associated with improved prognosis in patients with ovarian cancer.

A pooled analysis of 26 observational studies involving patients with epithelial ovarian cancer with BRCA1 (909 women) and BRCA2 mutations (304 women) and 2,666 women who did not carry mutations in either of the two genes found that women with ovarian cancer who carried BRCA1 and BRCA2 mutations survived longer than noncarriers.5 The 5-year overall survival rates were 36% for noncarriers, 44% for BRCA1 mutation carriers, and 52% for BRCA2 mutation carriers (Fig 14).

Another study assessed the impact of BRCA1 and BRCA2 mutations on survival outcomes as well as responses to multiple lines of chemotherapy.6 This Australian population-based, case-control study enrolled 1,000 women, who were screened for alterations in BRCA1 and BRCA2 genes. Germline (hereditary) mutations were found in 14% of patients overall, including 23% of patients with high-grade serous ovarian cancer. Investigators documented responses to initial therapy and responses to treatment for relapsed disease, finding consistently better response rates in BRCA mutation carriers than in noncarriers with relapsed disease, regardless of the type of chemotherapy used. Compared with noncarriers, BRCA1 and BRCA2 mutation carriers also had improved progression-free and overall survival rates.7

Taken together, results of these two studies indicate that these mutations are an important prognostic factor, associated with both better response to treatment and longer survival. Future clinical trials in high-grade serous ovarian cancer will need to consider BRCA mutation status as an additional stratification factor.

**Carboplatin plus paclitaxel is as effective as but safer than cisplatin-based combinations for endometrial and cervical cancers**

Investigators are continuously working on ways to improve the efficacy of cancer treatments, reduce adverse effects, and improve patients’ overall quality of life. Two large studies showed that less-toxic regimens can be used for endometrial and cervical cancers without sacrificing efficacy.

An interim analysis of data from a large international phase III study, performed by the Gynecologic Oncology Group, an
NCI-funded cooperative group, showed that treatment with a combination of carboplatin and paclitaxel (TC) is comparable in terms of overall survival and delaying of disease progression to the standard combination of cisplatin, doxorubicin, and paclitaxel (TAP) and is generally easier for patients to tolerate.\(^7\) In the study, 1,381 women with metastatic or recurrent endometrial cancer were randomly assigned to treatment with TC or TAP. The median time to disease progression (13.3 v 13.5 months) and median overall survival (36.5 v 40.3 months) for TC and TAP, respectively, were similar in both arms. These results suggest that TC is an acceptable chemotherapy regimen for use in future trials, particularly those exploring combinations of chemotherapy with new targeted drugs.

Another study compared the effectiveness of TC with that of paclitaxel plus cisplatin (TP), the current standard therapy for stage IVB or recurrent cervical cancer, in 253 women with stage IVB, persistent, or recurrent cervical cancer.\(^8\) In this phase III randomized trial, the median overall survival was similar for both regimens (18.3 months with TP v 17.5 months with TC). The median times to disease progression were also comparable: 6.9 months for TP and 6.2 months for TC. TC was associated with a favorable toxicity profile. On the basis of these results, TC is a reasonable treatment option for stage IVB or recurrent cervical cancer.

**REFERENCES**

“Research in thyroid cancer has been proceeding at a rapid pace since the discovery that kinase inhibitors have strong clinical activity in this disease, while advances in other head and neck cancers continue to improve care through the identification of specific subgroups that benefit from targeted approaches.”

– MARCIA BROSE, MD, PhD

HEA AND NECK CANCERS

SPECIALTY EDITOR: MARCIA BROSE, MD, PhD
Cancer.net

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

Thyroid cancer forms in the thyroid gland, a small organ at the base of the throat that makes hormones that help control heart rate, blood pressure, body temperature, weight, and calcium levels. Although also rare, the overall incidence of thyroid cancer in the United States has increased over the past two decades, and it has the fastest increasing incidence of all cancers, occurring more frequently in women than in men.

In a pivotal trial this year, researchers reported encouraging responses to a new targeted drug for patients with medullary thyroid carcinoma (MTC), a notoriously treatment-resistant form of thyroid cancer. Other notable research included a pilot study that identified another targeted drug that has the ability to increase radioactive iodine uptake in a subset of patients with thyroid cancer resistant to radioiodine (RAI) therapy. Additionally, a large trial showed that a drug targeting EGFR protein was active against HPV-negative but not HPV-positive head and neck cancers. And finally, results of a small gene therapy study revealed a potential new treatment option for late-stage oral cancer.

Major Advances

Cabozantinib significantly delays MTC progression

MTC is the third most common form of thyroid cancer, accounting for 5% to 8% of cases. MTC is not treatable by standard thyroid cancer therapy, which primarily relies on RAI therapy, and has much lower cure rates compared with other thyroid cancer types. Currently, there is just one treatment available for these patients: vandetanib; however, the cancer progresses despite this therapy after an average of 23 months.

Results of a phase III trial reported this year point to a potential new treatment option for advanced or metastatic MTC. In the study, 330 patients with progressive, inoperable, locally advanced, or metastatic MTC were randomly assigned to receive the investigational drug cabozantinib or placebo. Unlike previous trials, this trial specifically targeted tumors...
Selumetinib blocks a protein called mitogen-activated protein
kinase (MEK) 1/2, involved in uptake of RAI by tumor cells.
In this study, pretreatment with selumetinib increased RAI
uptake in 12 of 20 patients, seven of whom had enough of an
increase that they could be treated subsequently with RAI
therapy. Overall, the combination treatment led to tumor
shrinkage in five patients and disease stabilization in two. The
adverse effects of selumetinib were minimal.

These findings indicate that selumetinib can increase RAI
uptake to clinically meaningful levels in more than one third
of metastatic DTC cases. Additional studies on the clinical
significance of these studies are clearly warranted. Further
genetic analysis of patients’ tumors suggested that the treat-
ment may be particularly effective in patients harboring RAS
gene alterations.

Panitumumab improves survival for patients with
HPV-negative squamous cell carcinomas of the head and neck
HPV infection is an important risk factor for head and neck
cancers. In the United States, the incidence of HPV-positive
oropharyngeal cancers (those that affect the middle part of
the throat) has increased, particularly in men. Previous stud-
ies have suggested that patients with HPV-positive head and
neck cancers have a better prognosis compared with those
with HPV-negative tumors.

However, results of a large phase III trial published this year
reveal a promising new treatment option—called panitumum-
ab—for HPV-negative tumors, although it did not improve out-
comes for patients with HPV-positive tumors. Panitumumab
is an antibody that targets the EGFR and is already approved
to treat metastatic colorectal cancer. The study enrolled 99
patients with recurrent or metastatic oropharyngeal cancer
with HPV-positive tumors and 344 with HPV-negative tumors;
that were actively growing. Cabozantinib blocks growth of tu-
mor blood vessels and metastases by inhibiting three different
proteins involved in these processes: MET, vascular endothelial
growth factor receptor 2, and RET. Approximately half of the
trial participants had RET gene alterations in their tumors. The
multitargeted drug prolonged time to disease progression by
more than 7 months compared with placebo (11.2 v 4 months)
(Fig 15). Tumor shrinkage occurred in 28% of patients receiv-
ing cabozantinib and in none of those receiving placebo, with
responses lasting a median of 14.6 months. On the basis of
these results, the manufacturer has applied for FDA approval
of the drug for patients with inoperable, advanced, or meta-
static MTC. The drug is also being explored in other cancer
types that frequently harbor the proteins targeted by caboza-
tinib, including differentiated thyroid cancer (DTC), melanoma,
and breast, kidney, liver, and prostate cancers.

Notable Advances
Small study identifies promising salvage drug for
RAI-resistant metastatic thyroid cancer
Ninety percent of patients with thyroid cancers have DTC,
which start in follicular cells of the thyroid; patients with DTC
are generally able to be cured with a combination of surgery
and RAI therapy. However, because of genomic changes in
patients with metastatic disease, RAI uptake into tumor cells
becomes impaired in up to two thirds of patients with recur-
rent or metastatic DTC, resulting in treatment resistance and
disease worsening. Unfortunately, current treatments for
these patients are not consistently effective, and only 50% of
patients with metastatic, RAI-resistant tumors live longer than
3 years.

Results from a promising early clinical trial published
this year indicate that the targeted drug selumetinib might
reverse RAI resistance in a subset of patients with DTC. Selumetinib blocks a protein called mitogen-activated protein
kinase (MEK) 1/2, involved in uptake of RAI by tumor cells.
In this study, pretreatment with selumetinib increased RAI
uptake in 12 of 20 patients, seven of whom had enough of an
increase that they could be treated subsequently with RAI
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comes for patients with HPV-positive tumors. Panitumumab
is an antibody that targets the EGFR and is already approved
to treat metastatic colorectal cancer. The study enrolled 99
patients with recurrent or metastatic oropharyngeal cancer
with HPV-positive tumors and 344 with HPV-negative tumors;
all patients had a common subtype of the disease called squamous cell carcinoma. Squamous cell carcinoma, which begins in squamous cells that line moist surfaces inside the head and neck, is the most common form of head and neck cancer. The patients were randomly assigned to receive panitumumab with platinum-based chemotherapy or chemotherapy alone.

Patients with HPV-negative tumors in the panitumumab group had an improvement in overall survival compared with those who received chemotherapy alone (11.7 v 8.6 months). However, the combination treatment did not significantly prolong survival in HPV-positive patients (11.0 v 12.6 months).

**Adding gene therapy to chemotherapy dramatically increases overall survival in late-stage oral cancer**

A majority of mouth (oral) cancers are diagnosed at a late stage, when long-term survival rates are only 45%. Those patients are typically treated with irradiation, chemotherapy, and/or targeted therapy. In recent years, gene therapy has emerged as a potential new treatment for advanced head and neck cancers.

Results of a phase II trial released this year show high rates of tumor shrinkage for late-stage oral cancers treated with gene therapy and standard chemotherapy. The goal of gene therapy in this study was to restore the function of a gene called \( p53 \) that had been inactivated in patients’ tumors. The \( p53 \) gene is a tumor suppressor, meaning it triggers cell death for cancerous or otherwise defective cells.

In this study, 99 patients with advanced oral cancer were randomly assigned to receive gene therapy plus chemotherapy (group I), gene therapy alone (group II), or chemotherapy alone (group III). The chemotherapy regimen consisted of the drugs oxaliplatin, bleomycin, methotrexate, and cyclophosphamide. Researchers found that the combination of gene therapy plus chemotherapy was far more effective than the other two approaches. Tumor shrinkage rates were 88.6%, 54.5%, and 51.6% for groups I, II, and III, respectively, and the 3-year overall survival rates were 82.9%, 60.6%, and 58.1%, respectively. Further investigation is warranted to verify whether \( p53 \) gene therapy represents a viable addition to standard treatment for late-stage oral cancer.

**REFERENCES**


“Our understanding of the molecular basis of lung cancer has increased exponentially in recent years. These discoveries are bringing effective, and well tolerated, therapies to our patients. The transition of drugs like crizotinib from bench to bedside is unprecedented in the history of lung cancer therapy.”

– JYOTI PATEL, MD

LUNG CANCER
SPECIALTY EDITOR: JYOTI PATEL, MD
Major Advances
Combination chemotherapy extends survival in certain patients with advanced NSCLC

Performance score, a measure of how well a patient is able to perform ordinary tasks and daily activities, is used to determine whether a patient can safely undergo chemotherapy. Current guidelines recommend that patients with a performance status of 2 (capable of self-care but no work activities) be treated with just one chemotherapy drug to slow the progression of their disease but help maintain their quality of life.

Results of a phase III trial reported this year indicate that patients with a performance score of 2 may live longer if treated with carboplatin and pemetrexed combination chemotherapy. In the study, patients with advanced NSCLC who had received no prior therapy were randomly assigned to receive pemetrexed (102 patients) or carboplatin and pemetrexed (103 patients). Tumor shrinkage was observed in 10% of patients receiving pemetrexed and 24% of patients receiving the two-drug treatment. The median overall survival was 5.6 months with carboplatin and 9.1 months with carboplatin and pemetrexed (Fig 16). The findings of this study represent a paradigm shift in the standard care for advanced NSCLC, indicating that...
patients with NSCLC with a performance score of 2 can tolerate and benefit from combination chemotherapy, underscoring the importance of not undertreating this patient population.

**Notable Advances**

**Study uncovers the first promising targeted therapy for a common subtype of NSCLC**

Alterations in the *KRAS* gene are the most common molecular markers in NSCLC, found in 20% to 30% of patients. However, there are no effective targeted therapies for this subset of patients with NSCLC. This year, a phase II trial reported important data on the efficacy of an investigational drug called selumetinib in this population of patients with advanced cancer. Selumetinib, which blocks MEK, a key protein in the *KRAS* signaling pathway, is being explored in clinical trials for the treatment of various types of cancer harboring *KRAS* mutations (Head and Neck Cancers).

In this international phase II study, patients were randomly assigned to receive selumetinib plus standard docetaxel chemotherapy (44 patients) or placebo plus docetaxel (43 patients) as a second-line treatment for advanced NSCLC. Overall survival was substantially longer in the selumetinib arm compared with the placebo arm (9.4 v 5.2 months), as was the time to disease progression (5.3 v 2.1 months).

This is the first prospective study to our knowledge showing a clinical benefit from targeted therapy for patients with any type of *KRAS*-mutated cancer. The findings of this study may influence standard treatment of not only NSCLC but also all other cancers with *KRAS* alterations.

**Molecular testing identified new therapeutic targets in squamous cell lung cancer**

Squamous cell carcinoma accounts for approximately 40% of lung cancer cases. The development of targeted drugs for squamous cell lung carcinoma has been slow compared with development of drugs for other cancers, because few druggable targets (ie, those that are presumed to be accessible and amenable to attaching to drug molecules) have been discovered. However, recently, researchers have identified alterations in three genes, *FGFR1, DDR2, and PI3K/PTEN*, which together occur in 50% of squamous cell lung carcinomas. The Squamous Cell Lung Cancer Mutation Analysis Program (SQ-MAP) was established at the Memorial Sloan-Kettering Cancer Center (New York, NY) to screen lung tumor samples for the presence of those three targets as well as 80 other genes implicated in lung cancer development overall. SQ-MAP is also being used to identify patients who are eligible to participate in clinical trials of drugs targeting *FGFR1* and *PI3K*. This year, SQ-MAP uncovered potential new drug targets in lung cancer (this study was funded in part by a 2012 Conquer Cancer Foundation of ASCO Career Development Award to Paul Paik).3 Forty specimens from patients with squamous cell lung cancer have been processed through SQ-MAP to date. Druggable targets, such as alterations in *PI3KCA, FGFR1, and PTEN* genes, have been identified in 60% of specimens, but there are currently no drugs available for those targets. In the future, SQ-MAP may become an important platform that will guide drug development and personalized treatment planning.

**Small study suggests crizotinib may benefit additional rare lung cancer subtypes and confirms ROS1 as a therapeutic target in cancer**

A recent study found that a small subset of patients with NSCLC (approximately 2%) carries alterations in a gene called ROS1, which encodes a protein involved in cell growth and development. Crizotinib is a multitargeted drug that blocks
the ROS1, MEK, and ALK proteins, approved by the FDA in 2011 for advanced or metastatic, ALK-positive NSCLC.

Results of an ongoing phase I trial show that crizotinib may also be effective in patients with ROS1-altered NSCLC. In the study, 13 patients with NSCLC adenocarcinoma were treated with crizotinib for an average of 20 weeks. Seven of 13 patients experienced tumor shrinkage, most in the first 8 weeks, and 12 patients continue treatment on the study.

This study provides the first clinical validation to our knowledge of ROS1 as a therapeutic target in cancer and identifies a potential new treatment option for a subset of patients with advanced, difficult-to-treat NSCLC. Although only a small percentage of all lung adenocarcinomas harbor the ROS1 genomic marker, because lung cancer is such a common disease, this finding could eventually translate into an important new treatment option for 3,000 to 4,000 new patients diagnosed annually with ROS1-altered NSCLC in the United States alone.

Positive results of a phase III trial using combination chemotherapy in advanced NSCLC patients may lead to a new standard of care for certain patients.

REFERENCES


“Many cancers are treated like a chronic illness where one takes pills to prevent relapse. It’s an expensive strategy but it doubles or triples life expectancy. The future hope is to produce lasting remissions that do not require maintenance therapy. And that’s where the antibodies to PD-1 and PD-L1 come in.”

– WOLFRAM E. SAMLOWSKI, MD
**Major Advances**

**Blocking the hedgehog pathway stops growth of basal-cell carcinomas**

Basal-cell carcinoma is the most common form of skin cancer. A rare, inherited condition called basal-cell nevus syndrome can cause development of hundreds to thousands of basal-cell carcinomas in a single patient. There are currently no consistently efficacious therapies for the syndrome. Given that the syndrome is associated with an overactive hedgehog pathway resulting from alteration in the patched 1 (PTCH1) gene, investigators hypothesized that blocking the pathway may be an efficient treatment strategy. Results of a phase II trial reported this year indicate that the new hedgehog inhibitor, vismodegib, is effective in this setting.1

In the study, 41 patients were randomly assigned to receive vismodegib or placebo. During the 8-month follow-up, the drug significantly reduced basal-cell carcinoma tumor burden and blocked the growth of new tumors. No tumors progressed during treatment with vismodegib, and in some patients, all basal-cell carcinomas regressed. However, more than half of treated patients had to stop vismodegib because of adverse effects of the treatment (eg, loss of taste, muscle cramps, weight loss, and hair loss); similar adverse effects...
have been observed in previous trials with vismodegib and other hedgehog inhibitors.

These findings confirm the critical role of the hedgehog pathway in basal-cell carcinomas and indicate that vismodegib is effective in both preventing and treating basal-cell carcinomas in patients with basal-cell nevus syndrome. The drug was approved by the FDA this year for use in patients with locally advanced basal-cell cancer who are not candidates for surgery or radiation therapy and for patients whose cancer has metastasized. More broadly, this study shows the potential of using targeted drugs for cancer prevention.

**Notable Advances**

**Two months of biochemotherapy provide significant survival advantage over 1 year of high-dose interferon therapy**

One year of high-dose interferon alfa-2b is a standard postoperative (adjuvant) treatment for high-risk melanoma. However, currently, it is estimated that fewer than one third of eligible patients receive adjuvant therapy for melanoma because of concerns about the adverse effects of interferon and its low benefit. Results of a phase III trial, released this year, point to a shorter and potentially more effective alternative treatment regimen for these patients. The treatment—termed biochemotherapy, because it combines chemotherapeutic (cisplatin, vinblastine, and dacarbazine) and biologic drugs (interleukin-2 and interferon alfa)—extended recurrence-free survival in 432 patients with advanced melanoma by a median of 2.1 years compared with high-dose interferon. This is the best survival outcome ever reported in patients with stage III high-risk melanoma. Furthermore, only 2 months of biochemotherapy resulted in the same overall survival (56%) at 5 years as 1 year of high-dose interferon. The rates of serious adverse effects were similar between the two treatment arms. These trial results indicate, for the first time to our knowledge, that a treatment other than high-dose interferon could be used as an effective adjuvant therapy for those with high-risk melanoma. These findings will likely make many oncologists rethink the way they are treating these patients.

**Promising treatment options for patients with advanced or metastatic melanoma carrying BRAF mutations**

Approximately half of melanoma tumors harbor a V600E mutation in the BRAF gene. In those patients, the MEK signaling pathway is also highly active. Blocking the activity of the BRAF protein with a drug called dabrafenib produced significant tumor responses in early-phase clinical trials in patients with melanoma harboring this mutation, including melanoma metastasized to the brain. Three clinical trials reported this year confirmed that blocking BRAF and/or MEK pathways also offers improved survival for patients harboring BRAF mutations in their tumors. The first study, a phase III trial, compared the activity of dabrafenib with that of the standard chemotherapy drug dacarbazine and a doublet regimen of dabrafenib and trametinib. The second study compared dabrafenib and trametinib with dacarbazine and placebo. The third study compared dabrafenib alone with dacarbazine and placebo. All three trials showed significantly improved survival for patients treated with the BRAF inhibition regimens compared with those treated with the standard chemotherapy regimen.
Vismodegib is effective in both preventing and treating basal-cell carcinomas in patients with basal-cell nevus syndrome.

dacarbazine in 250 patients with previously untreated, inoperable late-stage melanoma. They found that patients treated with dabrafenib were more likely to respond to treatment and survive longer without their disease worsening. Tumor shrinkage occurred in 53% of patients treated with dabrafenib compared with only 19% treated with dacarbazine, and median progression-free survival was 5.1 and 2.7 months (Fig 17), respectively.

A second trial, the METRIC phase III study, compared the efficacy of the MEK inhibitor trametinib alone with chemotherapy in 322 patients with BRAF-mutated advanced or metastatic melanoma. It took only 1.5 months for the disease to progress in patients receiving chemotherapy and 4.8 months in those who received trametinib. Tumor shrinkage occurred in 24% of patients receiving trametinib and only in 7% of patients receiving chemotherapy. These results affirm trametinib as the first MEK inhibitor to significantly extend survival in patients with BRAF-mutated metastatic melanoma.

Preclinical studies have shown that combinations of BRAF inhibitors such as dabrafenib with MEK inhibitors have stronger activity against BRAF-mutated melanoma compared with either drug alone. Results of a phase I/II clinical trial reported this year in 162 patients with BRAF-mutated metastatic melanoma seem to confirm these findings. Patients who were treated with a combination of the BRAF inhibitor dabrafenib and MEK inhibitor trametinib had lower incidence of skin rash and lesions compared with patients treated with either drug alone (7% v 19%). Tumor shrinkage was observed
Fig 19. Anti-PD-L1 antibody BMS-936559 shrinks melanoma metastases in patient’s lungs

in 76% of patients receiving combination therapy compared with 54% of those receiving single-agent therapy (Fig 18). The median times to disease progression with combination and single-agent therapy were 9.4 and 5.8 months, respectively, comparable to what was observed in past single-agent studies with the current standard BRAF-targeted drug, vemurafenib (6.8 months). Skin lesions, a well-known adverse effect of vemurafenib, occurring in up to 25% of patients, were far less common with the dabrafenib plus trametinib combination; just 2% of patients in the trial developed squamous cell carcinomas, and another 2% developed small premalignant lesions. The clinical activity of the drug combination will be investigated further in a phase III trial comparing dabrafenib plus trametinib with vemurafenib.

Immunotherapy for melanoma: Targeting the programmed death-1/programmed death-1 ligand pathway

The programmed death-1 (PD-1)/programmed death-1 ligand 1 (PD-L1) pathway plays an essential role in the body’s immune response to cancer [Tumor Biology]. Two clinical trials this year showed promising results with drugs targeting PD-1/PD-L1 in a number of tumor types. Results of the first clinical study of an anti-PD-L1 antibody, BMS-936559 (Fig 19), in patients with solid tumors, including 55 patients with melanoma, indicate that the drug is active and generally well tolerated. Tumor shrinkage was observed in 17% of patients with melanoma; responses lasted a median of 11 weeks, and several patients continued to benefit from the drug for more than 1 year.

Another clinical trial explored the activity and safety of a second antibody, BMS-936558, that blocks the activity of PD-1. Tumor shrinkage was observed in 26 of 94 (28%) patients with advanced melanoma, and 12 patients continued to experience benefit from the drug for more than 1 year.

The results from these studies indicate that antibody-based therapies can produce lasting responses in a subset of patients with melanoma comparable to, and possibly better than, current immunotherapies for late-stage melanoma, perhaps with fewer adverse effects. Unfortunately, researchers are not yet able to predict which patients with melanoma will respond to anti-PD-1 or anti-PD-L1 antibodies. Ongoing larger trials testing these and similar agents may help answer this question.
This trial’s results indicate, for the first time, that a treatment other than high-dose interferon could be used as an effective adjuvant therapy for high-risk melanoma patients.

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“The recognition of the long term negative health effects of routine CT imaging has led to a fresh look at surveillance programs following the completion of therapy. The demonstration that less intensive radiologic follow-up is needed is a significant advance for the health of survivors of childhood cancer.”

– ERIC LARSEN, MD

PEDiatric CANCERS

SPECIALTY EDITOR: ERIC LARSEN, MD
In the United States, childhood cancer is a rare disease; on average, only one or two children develop cancer each year among every 10,000 children, but it is nonetheless the leading cause of disease-related death in children younger than age 14 years.

Long-term survival rates for childhood cancer have increased dramatically. In the 1950s, less than 10% of patients were cured, but today, cure rates are approaching 80%. This progress is a culmination of research efforts that have led to new and improved treatments as well as better ways of identifying the causes of childhood cancers, understanding tumor biology, reducing treatment adverse effects, and improving quality of life for childhood cancer survivors.

This year, investigators reported encouraging results regarding treatment for some of the most common forms of childhood cancers. Early results from a small study show remarkable remission rates in patients with neuroblastoma who were treated with the new targeted drug crizotinib. Three more studies reported progress in improving treatments and prognosis prediction for children and adolescents suffering from B-precursor acute lymphoblastic leukemia (ALL). And finally, results of a long-term follow-up study suggest that computed tomography (CT) imaging surveillance should not be routinely used to screen for relapse in children with Hodgkin lymphoma.

**Notable Advances**

**New targeted drug shows encouraging early results in children with neuroblastoma and anaplastic large cell lymphoma (ALCL)**

Abnormalities in the anaplastic lymphoma kinase (ALK) gene are present in the majority of ALCL cases and 14% of high-risk neuroblastomas, a common form of solid cancer in children. Crizotinib, a drug that blocks the activity of the abnormal ALK protein, was recently approved by the FDA to treat certain lung tumors in adults that harbor ALK abnormalities. Crizotinib impedes several other proteins involved in cancer cell growth (Lung Cancer).

Results of a phase I study published this year suggest that crizotinib may be an effective new treatment for children with aggressive neuroblastoma or ALCL whose tumors carry such ALK abnormalities and persist despite all other standard treatment options. In these patients, crizotinib seems to stall tumor growth and, in some cases, eradicate all signs of cancer. Among patients with ALCL, 88% (seven of eight children)
The findings from this largest cohort of AYA patients with ALL studied to date demonstrate that high cure rates can be achieved when AYAs are treated on pediatric regimens.

experienced complete responses, having no detectable disease after crizotinib treatment. Two of 27 patients with neuroblastoma had complete responses, and another eight experienced no disease progression after treatment. Those responses were long lasting, and treatment-related adverse effects were minimal. Larger studies with more patients are being planned to confirm these results, particularly those for neuroblastoma.

Adding bortezomib to chemotherapy results in high remission rates for certain aggressive childhood leukemias

ALL is the most common form of cancer in children. Although long-term survival rates are high with current treatments (> 85% live longer than 5 years), approximately one in five patients experiences a relapse. Available therapies for relapsed acute lymphoblastic leukemia are not as effective; childhood acute lymphoblastic leukemia represents an area where more effective therapies are urgently awaited.

Recent early clinical results indicate that bortezomib, a drug that inhibits the protein breakdown machinery of the cell and is effective in multiple myeloma, may be active against treatment-resistant ALL when added to standard chemotherapy—a regimen that includes the drugs vincristine, dexamethasone, asparaginase, and doxorubicin.² Twenty-two patients with relapsed ALL—20 patients with B-precursor ALL and two with T-cell ALL—whose disease worsened despite treatment with two or three previous regimens were enrolled onto the study. Patients’ ages ranged from 1 to 22 years. Responses occurred in 73% of patients overall, with 14 patients experiencing complete remissions. However, the two patients with T-cell ALL did not respond to the treatment. These findings suggest that the combination of bortezomib plus chemotherapy may be an effective treatment for many children with relapsed B-precursor ALL. Larger studies are planned to confirm these results.

Routine CT surveillance imaging does not improve Hodgkin lymphoma survival

CT imaging is routinely performed to screen for relapse for 5 years after Hodgkin lymphoma treatment. Given the high cost and harms of radiation exposure, researchers have been concerned about its overall clinical benefit.

Findings of a study published this year indicate that CT screening detects far fewer Hodgkin lymphoma relapses in the first year compared with conventional clinical and laboratory assessments.³ In the study, 216 patients with Hodgkin lymphoma younger than age 22 years were observed for a median of 7.4 years. During the first year of follow-up, 12% of patients (25 patients) overall experienced relapses, 76% (19 patients) of which were detected based on symptoms and laboratory or physical examinations; only 8% of relapses were identified through CT surveillance imaging. Six deaths occurred among patients whose relapses occurred during the first year after therapy. In the subsequent 4 years of follow-up, only four patients had their relapses detected exclusively through CT, and none of those patients has died.

These results indicate that most childhood Hodgkin lymphoma relapses are detected through clinical examinations and laboratory testing, and annual surveillance by CT imaging does not significantly improve overall survival. Given the considerable harms from radiation and high cost, the investigators concluded that CT imaging should not be used for surveillance, particularly after the first year after treatment.

Adolescent and young adult patients with ALL have lower overall survival rates and higher relapse rates than younger patients

Historically, outcomes in patients with high-risk older than age 16 years’ have been worse than those in younger patients. This trend is attributed to higher relapse rates and more treatment-related adverse effects in the adolescent and young adult (AYA) population.

But encouraging results from a phase III trial reported this year point to a promising new treatment regimen for this age group.⁴ In the study, 2,574 patients age 1 to 30 years (501 AYAs) with newly diagnosed B-precursor high-risk ALL were randomly assigned to receive either dexamethasone or prednisone as initial chemotherapy and high-dose methotrexate or escalating Capizzi methotrexate as the maintenance regimen. The overall survival rates were 80% for AYAs compared with 88% for children. The 5-year incidence of relapse was 21% for AYAs versus 13% for children. Fewer AYA patients than younger patients experienced remissions. Although it has been previously suggested that AYA patients with high-risk ALL have inferior outcomes compared with younger patients, until this study, there had not been a trial with substantial numbers of patients who received the same treatment to make a direct
comparison. The findings from this largest cohort of AYA patients with ALL studied to date demonstrate that high cure rates can be achieved when AYAs are treated with pediatric regimens. However, survival rates among AYA patients were not as high as among younger patients. As a result of this study, the Children's Oncology Group is considering several options to both enhance leukemia control and reduce the toxicity of treatment. It is hoped that future strategies will continue to improve the outcome for AYA patients with high-risk ALL.

Genome analysis reveals new markers of poor survival outcome in childhood ALL

High levels of CRLF2 protein are present in the majority of patients with standard- and high-risk ALL; CRLF2 is virtually absent in patients with low- and very high-risk disease. However, the prognostic significance of alterations in CRLF2 and associated genes in childhood B-precursor ALL has been unclear. Although an initial study in children with high-risk ALL revealed an association between high levels of CRFL2 transcript and poor outcome, a larger study reported this year offered more specific insight.

A genomic analysis of tumor samples from 562 children with standard- and intermediate-risk ALL and 499 with high-risk ALL, published this year, uncovered molecular signatures that predict relapse-free survival. Elevated levels of the CRLF2 gene transcript and alterations in the IKZF1 gene, which is frequently associated with CRLF2 activity, were linked to higher rates of relapse among patients with high-risk ALL. The relapse-free survival rates were 42.6% and 72.8% for patients with and without CRLF2 alterations and 42.4% and 70.9% for those with and without IKZF1 alterations, respectively (Fig 20). These gene alterations do not play a role in standard-risk ALL. The results indicate that screening for CRLF2 gene alterations could be useful in identifying patients who are at risk of poor outcome and might benefit from experimental treatments targeting the relevant genomic alterations.

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“The advent of targeted drug therapy has now arrived for patients with sarcomas. As the molecular biology advances and new “druggable” genes and mutations are identified, patients with sarcoma will be able to benefit from the latest advances in cancer therapeutics based on the biology of their disease.”

– GARY K. SCHWARTZ, MD
Sarcoma is a collective name for approximately 50 different cancers that arise from cartilage, muscle, fat, blood vessels, or other connective or supportive tissues. The disease is especially complex because each of these sarcoma subtypes is biologically and molecularly distinct, and these tumors are generally resistant to chemotherapy. Some forms of sarcoma are among the deadliest cancers with no curative treatment options.

Because it is a rare disease—accounting for just 1% of cancers in adults—research funding for new sarcoma treatments is rather limited, and progress has been challenging. However, since the identification of c-Kit gene alterations in patients with GISTs and the success of the c-Kit inhibitor imatinib in the treatment of this disease, it has been clear that identification of discrete molecular events that drive sarcoma growth could result in the successful development of new targeted agents. This same approach is now being applied to other sarcoma subtypes. This has resulted in the identification of new druggable targets. On the basis of these laboratory studies, clinical trials of experimental drugs that block these targets are now being explored.

This strategic approach to drug development for patients with drug-resistant sarcoma was evident in research presented over the past year. First, findings from a phase III study are soon likely to offer a new line of therapy for patients with GISTs whose disease has progressed despite standard therapies. And results of a smaller, phase II trial suggest that a drug targeting a common gene alteration in liposarcoma may also offer improved survival. Both drugs are targeting a family of proteins known as kinases. Also, a large study testing a combination of drugs that target both IGF-1R and mTOR found signs of clinical benefit.

**Major Advances**

**Pazopanib delays cancer progression in patients with chemotherapy-resistant metastatic soft tissue sarcoma**

This year, results of a multi-institutional, international, phase III study led to the first FDA new drug approval for advanced soft tissue sarcoma in decades. In the study, 369 patients with advanced soft tissue sarcoma (except those considered to arise from fat cells), whose disease had worsened despite standard chemotherapy, were randomly assigned (at a ratio of two to one) to receive a targeted drug called pazopanib or placebo. Patients whose...
were allowed to switch to regorafenib treatment if their disease worsened; in all, 85% of patients were able to cross over to receive regorafenib. Regorafenib was well tolerated, with manageable adverse effects. The results of this trial point to the first effective treatment option for patients with advanced GISTs resistant to treatment with imatinib and sunitinib.

Targeted drug shows promising effects in a subset of patients with liposarcoma Liposarcoma is the most common soft tissue sarcoma in adults. Chemotherapy is not effective in those with advanced liposarcoma, so alternative treatments, including targeted therapies, are sorely needed. An experimental drug called PD0332991 (PD) blocks the protein CDK4, which is overproduced in approximately 90% of patients with certain forms of liposarcoma (well-differentiated and de-differentiated liposarcoma). This year, researchers reported the results of a phase II trial that evaluated the efficacy and safety of PD in advanced liposarcomas that overproduce the CDK4 protein and carry the retinoblastoma protein, which is critical for the effect of the drug (this study was funded in part by a 2011 Conquer Cancer Foundation of ASCO Career Development Award to Mark Dickson). All patients had cancers that had worsened despite at least one prior regimen. After 12 weeks of treatment with PD, 70% of patients had no disease progression, which exceeded what was anticipated from historical controls. The median progression-free survival was 18 weeks. Serious adverse effects included anemia, low platelet counts, and low neutrophil counts. On the basis of these encouraging results, a randomized phase III trial is planned.

Two-pronged targeted treatment approach may help patients with metastatic sarcoma Building on promising antitumor effects observed in preclini-
This year, results of a multi-institutional, international, phase III study led to the first FDA new drug approval for advanced soft tissue sarcoma in decades.

cal studies, researchers launched a clinical trial to determine if blocking two proteins, mTOR and IGF-1R, would increase progression-free survival in bone and soft tissue sarcomas resistant to chemotherapy. On the basis of historical data, treatment was considered nonpromising if the cancer did not progress in fewer than 20% of patients at 12 weeks of treatment. A total of 174 patients were enrolled and treated at 19 cancer centers, making this the largest NCI-supported clinical trial in sarcoma in the United States. The study results, announced this year, show that combination therapy with drugs targeting mTOR (temsirolimus) and IGF-1R (cixutumumab) delays cancer progression in patients (progression-free survival rates at 12 weeks ranged from 32% to 43%); the study met its primary end point in patients with metastatic bone and soft tissue sarcoma who were either IGF-1R-positive or IGF-1R-negative. Further clinical development of this treatment strategy for bone and soft tissue sarcoma is planned. These results represent the culmination of years of intensive laboratory research translated into promising new clinical developments for the treatment of sarcomas, which are among the most chemotherapy-resistant tumors.

FDA approves imatinib mesylate as a postoperative treatment for GIST

In January, the FDA granted full approval for imatinib mesylate tablets for the adjuvant treatment of adult patients after complete gross resection of Kit (CD117)-positive GISTS. The decision to grant full approval was based on new data presented at the 47th ASCO Annual Meeting indicating improvement in relapse-free and overall survival with prolonged (3 years) postoperative imatinib therapy for patients with GISTs who were considered at high risk for recurrence.

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“We must move beyond the approach that “one size fits all” for patients with tumors from a common origin, and identify the appropriate driver genetic alterations so that we can develop and use the best therapy(s) to target these pathways.”

– LEE M. ELLIS, MD

TUMOR BIOLOGY AND DEVELOPMENTAL THERAPEUTICS

SPECIALTY EDITOR: LEE M. ELLIS, MD

DNA microarrays are used in genomic profiling.
Our understanding of tumor biology is continuously evolving. Rapid progress in collecting and interpreting genomic data has led to important new insights into factors that predict response to systemic therapies and alterations that drive or sustain tumor growth and spread (metastasis). New insights into the field of tumor biology help investigators discover potential new drug targets and understand why tumors become resistant to targeted therapies and why the same drug is effective in one tumor and not another. Studies of tumor biology also reveal new molecular subsets of cancer, enabling selection of appropriate therapies for individual patients.

However, we have also learned that for most tumors, the complexities of genetic alterations will require a much more concerted and complex therapeutic approach, because few tumors are driven by a single dominant cancer-related gene. This year, there have been more than a dozen groundbreaking research studies in the field of tumor biology that have the potential to lead to improved treatment strategies for patients with cancer.

Cancer Treatment Progress in the Era of “Omics”

Modern technology is facilitating the accumulation of massive amounts of data on the comprehensive genetic and protein makeup (genome and proteome, respectively) of dozens of cancer types. Despite tremendous progress in understanding the molecular underpinnings of cancer over the past two decades, it remains a challenge to determine which patients will respond to a particular treatment. Research is making it increasingly clear that even subtle genetic differences can make one tumor sensitive and another resistant to the same drug, and investigators continue to seek reliable markers that predict patient response.

This year, two research teams demonstrated the power of large-scale genomic profiling in systematic discovery of new markers of drug response. In addition, a set of guidelines issued by the Institute of Medicine (IOM) will help enhance discovery and development of new omics-based tests intended for clinical use, while ensuring that these tests are grounded in scientific practice and appropriately validated.
Large-scale genomic profiling uncovers new markers for response to anticancer drugs

Working independently, two research teams compiled large collections of cancer cell lines to systematically uncover genomic clues as to how and why cancer cells respond to drugs. The first collection, termed the Cancer Cell Line Encyclopedia, included 947 cell lines that represent much of the tissue-type and genetic diversity of human cancers.¹ The investigators collected genomic information on all the cell lines and screened 479 of them for sensitivity to 24 different anticancer agents. A second team conducted a similar analysis using 639 cancer cell lines and 130 drugs.² Both studies identified new genetic and gene-expression markers, some of which are associated with sensitivity to a broad range of anticancer agents. This new information and future genomic profiling of cancer cell lines will enhance rational drug development in the laboratory as well as clinical trial design, potentially resulting in faster discovery of personalized treatment regimens.

IOM report provides guidance on quality standards for genomics-based tests

The complexity of omics technologies and the enormous size of associated data sets also bring new challenges, including how to rigorously evaluate new clinical genomic data. In the wake of the discovery of a series of flawed or misinterpreted genomics-based tests, this year, the IOM provided recommendations to enhance omics-based test development and validation and prevent problems with moving new omics-based tests from discovery to routine clinical use.³ On the basis of these recommendations, investigators are urged to consult the FDA before beginning a clinical trial that uses an omics test to guide decisions about patient care, such as choice of chemotherapy.

Research Provides New Clarity on Genetic Differences Within a Patient’s Tumor: Implications for Personalized Cancer Treatment

Although cancers start from a single aberrant cell, researchers have recently discovered that genetically distinct subpopulations of cancer cells emerge as the tumor grows. This phenomenon, known as intratumor heterogeneity, may hamper personalized approaches that rely on a single biopsy to determine the genetic makeup of a tumor, because a single sample is not representative of all mutations present in different areas of the tumor. Intratumor heterogeneity also enables tumors to adapt to therapy, resulting in drug resistance and ultimately treatment failure.

This year, investigators published results of the first study to our knowledge that systematically characterized heterogeneity within primary human tumors and associated metastases (distant tumors) using multiple samples from four different patients with advanced kidney cancer.⁴ Mutational profiling was performed on multiple samples taken from different areas of the patients’ primary tumors and associated metastases. The investigators categorized mutations as ubiquitous (ie, present in all regions of a primary tumor and shared by metastatic tumors), shared by primary-tumor regions, shared by metastatic sites, or unique to a region. Overall, only 34% of all detected mutations were ubiquitous. Some regions of the same tumor had signatures of a favorable prognosis, whereas others had unfavorable prognosis markers. In some cases, the same gene was altered in different ways in various parts of the tumor. Taken together, these findings demonstrate that taking a biopsy sample from a single region of a patient’s tumor may not correctly predict outcome. Development of more meaningful prognostic
biomarkers and more effective personalized treatments will have to rely on identifying ubiquitous mutations and genes.

**Cancer Genome Atlas Advances Our Understanding of the Molecular Drivers of Cancer**

Identifying genomic changes and understanding how those changes drive the development and growth of various forms of cancer make up the foundation of personalized cancer treatments. Since its launch in 2009, the Cancer Genome Atlas (TCGA) project has been at the forefront of using genome/proteome analysis to develop improved ways to diagnose, treat, and prevent cancer. More than 150 TCGA investigators nationwide are charting genomic changes in over 20 forms of cancer and making their data readily available to the worldwide research community, enabling faster and more appropriate development of new targeted therapies aimed at specific pathways in a certain cancer type or subtype.

This year, the TCGA research network published the results of its comprehensive molecular characterization of human colorectal cancer. Other major TCGA findings this year include two studies that explored sophisticated new ways of predicting chemotherapy response in ovarian cancer and a study that identified gene activations that determine cancer cell survival.

**Study offers detailed landscape of molecular alterations in colon and rectal cancers**

This study systematically analyzed DNA sequence alterations, gene expression patterns, chromosome number changes, and gene activation status in 224 tissue samples from patients with colorectal cancer and matched normal tissue samples. Investigators found that approximately 16% of the tumor samples were hypermutated, having roughly 50% more alterations than the other samples, and that these types of tumors most commonly occurred in the right ascending colon. Furthermore, among nonhypermuted samples, colon and rectal tumors had very similar patterns of genomic change. This was a surprising finding, because many researchers suspected that the two tumor types were biologically different. The analysis also identified 32 genes that were frequently mutated in both hypermutated and nonhypermuted tumors, including three genes—FAM123B, ARID1A, and SOX9—that had not been previously associated with colorectal cancer. Further analysis of the genomic data revealed that most tumors had activation of the WNT pathway and inactivation of the transforming growth factor beta pathway. This study also identified several potential drug targets, including proteins in the WNT, beta-catenin, RAS, and PI3K signaling pathways.

**Two studies report improved ways of predicting chemotherapy response in ovarian cancer**

Ovarian cancer is the leading cause of death resulting from gynecologic cancer. A majority of patients are diagnosed with advanced disease, for which the standard treatment is surgery followed by platinum-based chemotherapy. Unfortunately, approximately 30% of patients do not benefit from chemotherapy, and more than 75% of those who initially respond to chemotherapy relapse within a few years. Therefore, it is of utmost importance to identify chemotherapy-resistant patients early, so they can be directed to alternate treatments that may be more efficacious. Using large TCGA data sets and repositories, two studies published this year developed and validated new tests that are able to predict response to platinum chemotherapy in patients with advanced ovarian cancer.

In the first study, investigators developed two different profiling approaches that could be used to distinguish between
This year, there have been more than a dozen groundbreaking research studies in the field of tumor biology that have the potential to lead to improved treatment strategies for patients with cancer.

patients with favorable and unfavorable prognoses—a 227-gene expression signature and a morphologic signature, based on profiling the size and shape of tumor cell nuclei. The gene expression signature, derived from analysis of 740 samples, was able to correctly classify chemotherapy-sensitive and chemotherapy-resistant tumors with 85% accuracy. Investigators also explored more than 250 tumor samples under a microscope to establish a morphologic signature that was strongly associated with chemotherapy response. The tumor imaging approach classified cell nuclei according to size and 15 different shape features, such as roundness. Integration of gene expression and tumor imaging profiling provides new insights into the molecular mechanisms that enable tumors to become resistant to chemotherapy.

The second study zeroed in on expression of genes involved in repairing DNA damage caused by platinum-based chemotherapy, proposing a new scoring system that helps predict outcomes after first-line chemotherapy for advanced epithelial ovarian cancer. Analysis of data from 511 patients identified 23 DNA repair genes that were associated with overall survival after first-line platinum chemotherapy, and a molecular score was devised based on their expression. High scores were associated with substantially improved overall survival at 5 years after treatment completion compared with low scores (40% vs 17%). The molecular score was also predictive of tumor shrinkage and recurrence-free (lasting cancer remission after chemotherapy) and progression-free survival. These findings suggest that a DNA repair gene-focused score may become a powerful prognostic tool for patients with advanced-stage ovarian cancer, facilitating decisions regarding treatment with first-line platinum-based chemotherapy. Additional prospective validation in clinical trials is necessary before these powerful new tools are incorporated in routine clinical practice.

Researchers discover that reversible gene alterations play a key role in cancer: Potential for novel anticancer therapies

Epigenetic regulation fine tunes gene expression by attaching and removing methyl groups from the DNA backbone, a process called methylation. Previous research showed that epigenetic processes play a key role in cancer. A study revealed this year that abnormal epigenetic regulation of specific genes is critical for cancer cell survival. In the study, investigators mapped all genetic and epigenetic alterations in a set of prostate cancer samples. Using both experimental and bioinformatics approaches, they identified genes that had to be deactivated through methylation to maintain cancer cell survival. These findings may improve current epigenetic therapies (eg, azacitidine and entinostat), which are nonspecific, and boost development of next-generation epigenetic therapies that would specifically target those deactivated genes.

Insight Into Drug Resistance Mechanisms Brings New Opportunities for Targeted Therapy Approaches

Conceptually, targeted therapies represent an effective and personalized way of treating cancer. However, tumors are continuously changing, and they frequently develop resistance to targeted drugs. The molecular processes that bring about this resistance are not well understood. Results of two studies published this year reveal how colorectal tumors acquire resistance to certain targeted drugs and propose alternative strategies for resistant patients.

Emergence of new KRAS mutations may trigger secondary resistance to cetuximab

Mutations in the KRAS gene lead to activation of MEK and EGFR pathways, both of which drive cancer cell growth. Anti-EGFR antibody drugs cetuximab and panitumumab are used to treat patients with metastatic colorectal cancer who do not carry mutations in the KRAS gene, but the drugs are not effective in those who do carry KRAS mutations. Unfortunately, patients invariably become resistant to these drugs, even after an initial response.

This year, investigators discovered KRAS gene mutations in metastases samples from six patients who developed such resistance to cetuximab and whose primary tumors initially had no mutations in KRAS. Despite being resistant to cetuximab, those tumors remained sensitive to experimental drugs targeting MEK. These findings indicate that previously undetected new KRAS alterations drive the development of cetuximab resistance in patients with metastatic colorectal cancer. Furthermore, KRAS mutations were detected in the blood of those patients, as early as 10 months before drug resistance and disease progression were documented, suggesting that finding these alterations early in the course of treatment would prompt earlier redirection of those patients to alternative targeted drugs, such as MEK inhibitors. Several MEK inhibitors are being tested in clinical trials for patients with metastatic colorectal cancer.
Study uncovers why targeted drug is effective against melanoma tumors but not colorectal cancers harboring the same mutation

There are no effective targeted treatment options for approximately 10% of patients with colorectal cancer who harbor a specific alteration in the **BRAF** gene known as V600E. Scientists have been puzzled about why the drug vemurafenib, which effectively blocks mutated BRAF protein in patients with melanoma, is rarely effective in patients with metastatic colorectal cancer. However, research results published this year provide a plausible explanation.\(^\text{10}\)

The investigators discovered that in colorectal cancer cells, the use of vemurafenib to block BRAF triggers compensatory activation of EGFR, which continues fueling cancer cell growth. The same compensatory response occurs in melanoma, but it does not lead to drug resistance because the levels of EGFR are too low to offset the BRAF blockade. These findings suggest that patients with colorectal cancer with BRAF (V600E) alterations may benefit from a regimen that combines drugs targeting BRAF and EGFR.

**T-Cell–Directed Cancer Immunotherapy Holds New Promise**

Tumors resist immune system attacks by blocking activation of tumor-specific T cells (white blood cells that help fight infection and cancer). This is achieved through the interaction of specific proteins, called ligands, on the surface of cancer cells and receptors on the surface of T cells. PD-1 is one such receptor on T cells, and its ligand, PD-L1, is expressed in various forms of cancer cells. Two phase I studies published this year reported encouraging results using strategies that disrupt interaction between PD-1 and PD-L1.

In the first study, 207 patients with advanced solid tumors were treated with the anti-PD-L1 antibody BMS-936559.\(^\text{10}\) Tumor shrinkage was observed in patients with melanoma (17.3% of patients), kidney cancer (11.8%), lung cancer (10.2%), and ovarian cancer (5.9%). Responses lasted for more than 1 year in eight of the 16 patients who responded to the treatment. The drug was well tolerated, with serious adverse effects occurring in 9% of patients overall.

The second trial assessed the activity of BMS-936558, an antibody directed against PD-1, in 296 patients with advanced solid tumors. Tumor shrinkage was seen in approximately 18% to 27% of patients with NSCLC, melanoma, or kidney cancer \(^\text{10}\). The responses lasted more than 1 year in 20 of the 31 patients who responded to the therapy. The treatment was not effective in colorectal or prostate cancer.

These findings indicate that the PD-1/PD-L1 pathway is an important pathway to target therapeutically, particularly for some forms of cancer. Additional studies are planned to determine which patients are most likely to respond and to define the full spectrum of tumors that can be effectively treated with these new agents.

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“A major study showed that sigmoidoscopy was an effective approach to decreasing colorectal cancer incidence and mortality but left open the question of where this test fits in the screening paradigm. Other research in the past year highlighted still unresolved questions regarding the application of specific screening and prevention approaches to the at risk population and the relative magnitude of their benefits and risks.”

– PETER B. BACH, MD, MAPP
Major Advances

Screening with flexible sigmoidoscopy reduces deaths resulting from certain colorectal cancers

Flexible sigmoidoscopy is a minimally invasive technique physicians use to look inside the rectum and lower part of the bowel called the sigmoid colon. Although flexible sigmoidoscopy examines only part of the intestine, it covers those areas that are most frequently affected by colorectal cancer. The procedure is also easier and faster to perform than colonoscopy, which examines the entire large bowel.

A large study found that screening with flexible sigmoidoscopy significantly decreases colorectal cancer incidence and the number of deaths resulting from the disease.1 In the study, more than 154,000 participants age 55 to 74 years were randomly assigned to the intervention group—involving initial flexible sigmoidoscopy screening and up to two repeat screenings at 3 or 5 years—or usual care. During a median follow-up time of 11.9 years, flexible sigmoidoscopy, as compared with usual care, was associated with a 26% reduction in overall colorectal cancer mortality and a 21% reduction in colorectal cancer incidence. Mortality related to distal colorectal cancer (affecting the lowest part of the bowel) was reduced by 50%, and its incidence was reduced by 29%. On the other
hand, the incidence of proximal colorectal cancer (affecting upper portions of the bowel) was reduced by only 14%, and there was no significant reduction in mortality. Taken together, these results provide strong evidence that flexible sigmoidoscopy substantially reduces colorectal cancer incidence and death rates, supporting wider use of this screening strategy. These results affirm that flexible sigmoidoscopy offers clear survival benefits, but more research is needed to determine how the performance of this screening strategy compares with that of colonoscopy, which is more costly but offers a comprehensive view of the colon.

**Notable Advances**

**Yearly chest x-rays do not reduce lung cancer mortality**

Lung cancer is the most common cause of cancer death in the United States, in part because the disease is often diagnosed at a late stage. Annual chest x-ray examinations had once been a common lung cancer screening strategy, particularly for smokers and former smokers, and some continue to recommend it for asymptomatic patients. A handful of past studies failed to find a benefit of chest x-ray screening, but they were too small to be definitive.

This year, researchers reported data from a large-scale study on the effect of chest x-ray screening on lung cancer mortality, finding that this screening approach provided no advantage compared with usual care. In the study, 77,455 men and women were randomly assigned to annual chest x-ray screenings for 4 years (intervention group) and 77,456 to usual care. In the intervention group, participants underwent follow-up diagnostic testing if suspicious lesions were found in the x-ray examination. Participants in the usual care group were observed but offered no screenings or interventions during the trial. Lung cancer incidence and mortality rates were similar in both groups, providing solid evidence that annual lung cancer screening using chest x-ray examinations does not provide a benefit, and it should not be performed.

An evidence-based clinical practice guideline published this year recommends using low-dose CT screening instead of chest x-ray or no screening for individuals who are at increased risk of developing lung cancer as a result of smoking. However, uncertainty remains over the potential harms of this screening.

Analysis of 51 randomized trials points to short-term benefits of daily aspirin in cancer prevention

Research studies have linked long-term daily intake of aspirin (for 10 years or so) to reduction of risk of dying as a result of cancer. However, this year, an analysis of patient data from 51
randomized trials that evaluated daily aspirin use for the prevention of heart attack and stroke revealed anticancer benefits of aspirin use over as few as 3 years. Overall, in 31 trials, there were 15% fewer cancer deaths among patients taking daily aspirin compared with those who did not take aspirin. The mortality reduction was even higher (37%) among those who took aspirin for more than 5 years. And in six primary prevention trials, daily low-dose aspirin for 3 years reduced cancer incidence by 25% in women and 22% in men. The findings of this review provide further support for the role of daily aspirin in cancer prevention.

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“As advances are being made in cancer treatment, it is critical to expand our knowledge of patient and survivor care that will minimize risk of treatment side effects and improve quality of life.”

– LESLIE ROBISON, PHD

PATIENT AND SURVIVOR CARE

SPECIALTY EDITORS: JAMIE VON ROENN, MD, LESLIE ROBISON, PhD, and STUART M. LICHTMAN, MD
Research in patient and survivor care helps address a wide range of challenges facing those who care for patients with cancer, including optimal treatment selection, assessment of short- and long-term risks of treatments, pain control, and improvement of the quality of life of patients and survivors.

Two important studies this year identified drugs that are effective in treating chemotherapy-induced neuropathy and breakthrough nausea and vomiting, both of which are common adverse effects of many anticancer treatments. Another study revealed the molecular underpinnings of increased risk of cardiomyopathy (heart muscle disease) in childhood cancer survivors treated with a class of drugs called anthracyclines. Two notable studies described effective interventions for improving the quality of life of patients with advanced cancer: a video support tool on cardiopulmonary resuscitation (CPR) and a new approach for incorporating palliative care early in the course of disease. Finally, a survey of oncologists reported this year highlights barriers to improving knowledge, attitudes, and practices in cancer pain management. Advances related to elderly patient care are covered in a separate subsection.

**Major Advances**

**Study shows antipsychotic drug olanzapine may control breakthrough chemotherapy-induced nausea and vomiting**

Patients with cancer rank nausea and vomiting among the worst and most feared adverse effects of treatment. Over the past 20 years, development of new drugs that prevent chemotherapy-induced nausea and vomiting (CINV) has dramatically reduced its incidence and severity, but those drugs are not always sufficient, and a condition called breakthrough CINV continues to occur. Breakthrough CINV is a serious problem because it lowers patients' quality of life and may necessitate reductions in chemotherapy doses, possibly diminishing the overall effectiveness of the treatment.

A phase III trial this year provided the first systematic evidence to our knowledge that olanzapine, an antipsychotic medication, may be helpful in controlling breakthrough CINV! The study enrolled patients receiving highly emetogenic (nausea-triggering) chemotherapy (cisplatin, doxorubicin, and/or cyclophosphamide) who were treated with recommended drugs to prevent CINV before starting chemotherapy. Those patients (80 of 205) who developed breakthrough CINV were randomly assigned to receive either daily olanzapine...
or daily metoclopramide, a conventional antinausea drug, for 3 days. During the observation period, 71% of patients receiving olanzapine had no vomiting versus 32% of patients receiving metoclopramide. Nausea did not occur in 67% and 24% of patients receiving olanzapine and metoclopramide, respectively (Fig 22). These results indicate that olanzapine significantly outperforms metoclopramide for the treatment of breakthrough CINV, addressing an important unmet need for patients who experience such adverse effects despite routine preventive treatment.

**Antidepressant drug duloxetine relieves pain from chemotherapy-induced peripheral neuropathy**

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common reasons patients stop chemotherapy early. Approximately one in three patients with cancer experiences CIPN, the symptoms of which range from tingling and numbness to stabbing pain primarily in the hands and feet. Although the causes of CIPN are not fully understood on a molecular level, it is known that certain types of chemotherapy drugs, such as platinum-based drugs and taxanes, damage cells in the peripheral nervous system. To date, no drugs have been able to fully alleviate CIPN-related pain.

This year, researchers reported results from a phase III trial showing the efficacy of duloxetine for the treatment of painful CIPN related to taxane- or platinum-based chemotherapy. Duloxetine is currently approved to treat depression among adults. The drug helps prevent pain signals from reaching the brain, and it has also been widely used to treat pain associated with diabetes, fibromyalgia, and arthritis.

In the study, 231 patients with CIPN caused by prior treatment with oxaliplatin or paclitaxel were randomly assigned to receive duloxetine followed by placebo or placebo followed by duloxetine. Patients who received duloxetine over the initial treatment period had a greater average decrease in their pain score (-1.09) compared with those who received placebo (-0.33) in the initial period. Duloxetine was well tolerated, with the most common adverse effect being mild fatigue. Although researchers cautioned that the drug did not alleviate pain in all patients, these findings indicate that duloxetine may be a useful new treatment option for patients with cancer suffering from CIPN.

**Notable Advances**

**Study reveals genetic basis of anthracycline-related heart disease risk in childhood cancer survivors**

Anthracyclines are included in more than half of all therapies for childhood cancers. Although effective against the cancer, these drugs can also cause long-term damage to the heart (cardiomyopathy). Although there are certain known risk factors, such as higher cumulative dose, for developing anthracycline-related cardiomyopathy, it is not fully understood why some patients develop such adverse effects while others do no not.
Results reported this year by the Children’s Oncology Group shed new light on the matter. The study found that alterations in two carbonyl reductase genes, CBR1 and CBR3, increased the risk of cardiomyopathy in childhood cancer survivors treated with low and moderate anthracycline doses. In particular, individuals harboring the CBR3 variant V244M had an increased cardiomyopathy risk even at relatively low anthracycline doses. High anthracycline dose increased the risk of cardiomyopathy regardless of CBR1 and CBR3 alteration status. These findings, which confirm those from an earlier pilot study, will be helpful in the efforts to individualize therapy and evaluate strategies for enhanced surveillance and prevention of cardiac dysfunction among childhood survivors exposed to anthracyclines.

Electronic tool helps patients with advanced cancer make more informed decisions regarding CPR

For patients with advanced, incurable cancer, a central priority of care is to ensure that they remain comfortable and that their care carefully reflects their personal preferences. Whenever possible, patients should have the opportunity to make informed decisions about their end-of-life care, and to communicate their preferences to physicians and family, well in advance. For many patients, establishing preferences regarding CPR is an important part of this process.

Although CPR can save lives in otherwise healthy people, its benefits may be limited for patients with cancer who are nearing the end of their lives. Among these patients, the heart and lungs often fail again soon afterward, or the procedure may be just partially successful, leaving patients with complications such as brain damage or in need of a ventilator indefinitely.

Physician-patient discussions about CPR are traditionally limited to verbal descriptions. Previous research has suggested that visual representations would be helpful in improving patients’ understanding of the procedure, its value, and its limitations. To explore this hypothesis, investigators conducted a clinical trial involving 150 patients with advanced cancer and a life expectancy of less than 1 year. Patients were randomly assigned to either listen to a standard verbal narrative of CPR or watch a video with both a verbal narrative and visual depiction of CPR, including its success rates among patients with advanced cancer. After this explanation, the mean CPR knowledge score (measure of comprehension based on follow-up questions) was significantly higher in the video group than in the verbal narrative group. Nearly all participants reported that the video was helpful and comfortable to view and that they would recommend it to others. Among patients who watched the video, 20% stated that they would prefer to have CPR attempted. Among those in the verbal narrative group, the figure was 47%.

These results suggest that supplementing verbal descriptions with video support tools may increase patients’ understanding of the CPR procedure and associated risks and benefits, enhancing their ability to make informed decisions.
regarding their end-of-life care. This and similar tools are an important part of the ongoing efforts to ensure that patients receive care consistent with their goals and wishes.

**Early palliative care intervention improves satisfaction with care, quality of life, and symptom control**

Palliative care has traditionally been offered to patients late in the course of the disease, typically after all therapeutic treatment options have been exhausted. However, recent research has suggested that offering palliative care services earlier in the course of the disease leads to meaningful improvements in patients’ quality of life and, in some cases, extends survival.

These findings were validated through an important randomized study reported this year. The study assessed the impact of early palliative care on quality of life (physical, social, emotional, functional, and spiritual well-being), symptom severity, and satisfaction with care in 461 patients with metastatic cancer with an estimated survival of 6 months to 2 years. Survey data were collected at baseline and monthly for 4 months. Patients were randomly assigned to either the intervention group (received initial and follow-up care by a palliative care team, in addition to standard cancer care) or the control group (standard cancer care alone). Compared with patients in the control group, patients in the intervention group had a marked improvement in quality of life and slight decrease in symptom severity at 4 months and reported consistently higher satisfaction with their care.

These findings offer important affirmation that early administration of palliative care offers many benefits to patients with metastatic cancer and should be routinely implemented.

**Survey reveals challenges in cancer pain management**

Pain management is an important component of care for patients with cancer and an ongoing concern for patients. Results of a survey of approximately 600 oncologists published this year reveal barriers to pain treatment and gaps in pain-related knowledge and practice among US oncologists. Although physicians overall rated their specialty highly with regard to ability to manage pain, they stated that inaccurate pain assessment and patient reluctance to take opioids or report pain were the most important barriers to pain management. Physicians also identified the need for better pain management training during medical school and residency and perception of excessive regulation regarding pain medication prescribing. Increasing knowledge about pain management among oncology fellows, practicing oncologists, and patients is needed to improve this important aspect of care for patients with cancer.
Ideally, a comprehensive geriatric assessment should be performed before starting anticancer treatment in an elderly patient, and although most oncologists agree that geriatric assessment is worthwhile, the procedure is time consuming and consequently not commonly performed in practice. Given such constraints, investigators conducted a study to determine what measures are most important for helping physicians select appropriate treatments for their elderly patients as well as the risk of fatality after initiation of chemotherapy. A baseline abbreviated comprehensive geriatric assessment was performed for 348 patients age older than 70 years who were scheduled for initial chemotherapy for various types of cancer. Investigators found that advanced disease, low nutritional assessment score, and poor mobility predicted early death (in less than 6 months) after beginning chemotherapy treatment. These findings suggest that pretreatment mobility and nutritional assessments are particularly important factors when determining whether patients older than 70 years of age will benefit from chemotherapy.

CARE OF ELDERLY PATIENTS WITH CANCER

Cancer is predominantly a disease of older age. As the developed nations age, the number and proportion of elderly patients with cancer will increase significantly. Management of elderly patients with cancer entails unique challenges and considerations. For example, having chronic disorders other than cancer (comorbidities) poses an increased risk of treatment-related complications. In frail patients, the risks of chemotherapy may actually outweigh the benefits. Therefore, patients’ physical, emotional, and mental states should be thoroughly assessed to arrive on optimal, individualized treatment regimens that avoid significant harms and maintain patients’ quality of life. This year, researchers reported results of three studies focused on specific challenges related to care of elderly patients with cancer.

Major Advances

Study identifies factors affecting whether elderly patients can safely undergo chemotherapy

Deciding whether to treat elderly patients with cancer and what treatment to administer is difficult, given that few trials have been conducted among this population specifically. Elderly patients have characteristics that affect prognosis, including comorbid conditions such as heart disease and diabetes, which can complicate delivery and tolerability of cancer treatment. Ideally, a comprehensive geriatric assessment should be performed before starting anticancer treatment in an elderly patient, and although most oncologists agree that geriatric assessment is worthwhile, the procedure is time consuming and consequently not commonly performed in practice.

Given such constraints, investigators conducted a study to determine what measures are most important for helping physicians select appropriate treatments for their elderly patients as well as the risk of fatality after initiation of chemotherapy. A baseline abbreviated comprehensive geriatric assessment was performed for 348 patients age older than 70 years who were scheduled for initial chemotherapy for various types of cancer. Investigators found that advanced disease, low nutritional assessment score, and poor mobility predicted early death (in less than 6 months) after beginning chemotherapy treatment. These findings suggest that pretreatment mobility and nutritional assessments are particularly important factors when determining whether patients older than 70 years of age will benefit from chemotherapy.

Prospective trial reveals factors that predict risk for chemotherapy side effects in older adults

Older patients with cancer are generally more vulnerable to harmful adverse effects of chemotherapy, but there are no
objective factors to determine which elderly patients are at
elevated risk. A study published this year proposes a predic-
tive model to address this concern (this study was funded in
part by a 2005 Conquer Cancer Foundation of ASCO Career
Development Award to Arti Hurria). A total of 500 patients
(age 65 to 91 years) with stage I to IV lung, GI, gynecologic,
breast, genitourinary, and other cancers were enrolled onto
the observational study. An assessment that captured demo-
graphics, tumor and treatment characteristics, laboratory test
results, and geriatric status (function, comorbidity, cognition,
physiologic state, social activity/support, and nutritional
statuses) was carried out before treatment, and patients were
observed through one round of chemotherapy. On the basis of
pretreatment assessments and observed toxicities, research-
ers developed a scoring system and risk stratification model
that identifies older adults at low, intermediate, and high risk
of chemotherapy adverse effects.

This study is important because it provides a sorely need-
ed tool to inform chemotherapy decision making for elderly
patients with any type and stage of cancer. If the utility of
this tool is subsequently validated in other cancer popu-
lations, it will not only serve an important clinical role but
also provide the basis for designing future interventions to
decrease the risk of chemotherapy adverse effects for
the elderly.

Notable Advances
Retrospective study proposes a prognostic scoring
system for elderly patients with cancer
Little is known about elderly patients with cancer in Asia,
because of the dearth of research in geriatric oncology in the
region. However, results of a study released this year provide
important new insights to help local physicians determine
which patients will benefit most from cancer treatment.Investigators retrospectively analyzed data collected from
249 patients with cancer age 70 years or older to identify
significant prognostic factors. The following factors were
found to be predictive of survival: age, abnormal albumin
level, poor Eastern Cooperative Oncology Group perfor-
manence status score (standard measure of patient’s general
well-being and daily activities), abnormal geriatric depression
scale status, high malnutrition risk, and advanced disease. On
the basis of these findings, researchers developed a scoring
system for prediction of overall survival. The scoring system
predicted 1-, 2-, and 3-year overall survival with relatively
high accuracy. Once validated, the prognostic model devel-
oped in this study may be applicable to elderly populations in
other regions.
This study is important as it provides a sorely needed tool to inform chemotherapy decision-making for elderly patients with any type and stage of cancer.

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“Improving the value of care is now a fundamental responsibility for all of us who care for patients with cancer. Success depends upon focusing on patient needs, a firm commitment to accurate measurement of meaningful outcomes of care, and the relentless pursuit of unwarranted variation in care processes.”

– JOSEPH JACOBSON, MD
Ensuring that all patients with cancer receive the highest quality care is a central priority for the oncology community. Achieving this goal requires improving access to timely cancer detection, maximizing adherence to evidence-based treatment guidelines, appropriate supportive care and survivor care, counseling about clinical trial participation, and other important priorities. Many initiatives and research projects are under way that together promise to improve the quality of patient care and provide a clearer picture of the areas where changes are still needed.

This year, five studies brought new ideas about strategies for improving adherence to quality standards, predicting patient outcome, improving end-of-life care for patients with cancer, and assessing the impact of hospital spending on patient outcomes.

**Notable Advances**

**Collaborative practice networks may improve cancer care in outpatient practices**

One barrier to achieving consistent, high-quality cancer care delivery is inconsistent adherence to practice guidelines and quality standards. Results of a Michigan study published this year show that although overall adherence to key quality processes for breast and colorectal cancer care is high among practitioners, significant improvement is needed in certain aspects of patient care. The study was conducted in a consortium of 36 outpatient oncology practices in Michigan that participate in the ASCO Quality Oncology Practice Initiative (QOPI). QOPI measures adherence of practices to a comprehensive set of quality processes in areas including disease-specific care, supportive care, pain and symptom management, and care for patients at the end of life. It is assumed that adherence to good care processes leads to improved short- and long-term outcomes. The overall guideline adherence rate for quality care processes was 85%, higher than previously reported. However, the rates for end-of-life care processes and symptom management were lower, at 73% and 56%, respectively. The largest quality variations were found in management of cancer pain.
To address these gaps, researchers developed interventions to improve adherence to treatment guidelines, improve pain management, and incorporate palliative care into oncology practice. Another intervention is aimed at improving provision of primary palliative care and referrals to secondary palliative care. Researchers will assess the impact of these efforts through ongoing QOPI data collections.

Patients’ self-reporting of symptoms contributes to a more accurate survival prediction

Clinicians evaluate and report patient symptoms in clinical trials using a standardized scoring system. The scores are typically incorporated into a model for prediction of overall survival, which helps physicians select the most appropriate treatments. Results of a retrospective study released this year suggest that adding patient-reported symptom scores to the traditional physician-based scoring system may result in a more accurate prediction of survival.2

In the study, investigators analyzed pooled data on 2,279 patients who had participated in 14 different clinical trials. Physician and patient scoring on six cancer quality-of-life symptoms (pain, fatigue, vomiting, nausea, diarrhea, and constipation) had been recorded at study entry. Researchers found notable differences between clinician- and patient-reported scores, particularly in the case of fatigue (on a scale of 1 to 4, the patient- and clinician-reported scores were 2.10 and 1.36, respectively). For each of the six symptoms, both clinician and patient scoring separately improved the accuracy of the survival prediction model. These results suggest that patients’ subjective assessment of symptom severity should be incorporated into decision making involving their care. In addition, the findings lend strong support for the Patient Centered Outcomes Research Institute (www.pcori.org), which was recently authorized by Congress to broadly develop, test, and implement patient-reported outcome measures across the disciplines of medicine.

High composite scores associated with favorable outcomes after colorectal surgery

The quality of care in hospital settings can be assessed through measures called process indicators, which show whether steps proven to benefit patients are followed correctly. They measure whether an action, such as administering a drug, was completed. Process indicators are sometimes combined into composite measures of quality, which provide a summarized picture of quality care and can be used to make quality comparisons between hospitals. Few studies have demonstrated a link between processes of care and outcomes.

A study published this year explored the association between composite measures (based on process indicators) and morbidity and mortality after colon and rectal cancer surgeries.3 In this study, investigators looked at more than 6,000 patients with colon or rectal cancer treated at 85 Dutch hospitals and found that at the hospital level, a high score on composite quality measures was consistent with
Advancing Quality Care through Clinical Guidelines

Clinical practice guidelines are a cornerstone of high-quality cancer care, helping doctors to provide the most effective and efficient care possible for each patient. Over the past two decades, ASCO has published close to 40 guidelines, with a goal of providing timely and relevant clinical advice to practicing oncologists in areas where clinical science has evolved quickly or where there are urgent clinical questions that need to be addressed.

Development of ASCO guidelines has typically relied on a systematic, objective review of medical literature conducted by a panel of experts. This rigorous and time-intensive approach is utilized in the majority of ASCO’s existing guidelines and is considered the gold-standard for clinical guidance by the Institute of Medicine and others.

To address the growing need for rapid guidance on a larger number of topics, ASCO has also introduced other guidance tools to support clinicians, including the official endorsement of other organizations’ guidelines and development of ASCO Provisional Clinical Opinions (PCOs). PCOs offer more rapid clinical direction to physicians than traditional guidelines following the publication or presentation of potentially practice-changing data, and are subject to updates as new data becomes available.

Over the past year, ASCO has issued guidance on several key topics, including:

- **Integration of Palliative Care into Standard Oncology Care**: This PCO recommends that all patients with metastatic non-small cell lung cancer be offered palliative care along with standard cancer therapy, beginning at the time of diagnosis. The guidance is based on evidence that this approach not only improves patients’ quality of life but also, in some cases, can extend their lives. While available evidence is strongest for metastatic lung cancer, the guidance recommends that palliative care be considered early in the course of care for all patients with metastatic cancer, and for those with a high burden of cancer-related symptoms.

- **Appropriate chemotherapy dosing for obese adult patients with cancer**: ASCO’s guideline recommends that physicians use an obese patient’s actual body weight, rather than an ideal body weight or other estimate, to calculate the appropriate dose of nearly all chemotherapy drugs. The recommendation addresses a range of provider concerns regarding this approach, pointing to clear evidence that weight-based dosing maximizes the effectiveness of treatment for obese patients without raising the risk of side effects.

- **CT screening for lung cancer in clinical practice**: A joint guideline developed by ASCO and the American College of Chest Physicians recommends yearly screening with a low-dose CT scan for individuals aged 55 to 74 who have smoked for 30 pack years or more or who have quit within the past 15 years. Such screening is not recommended for other populations including those who have smoked for less than 30 pack years or who quit smoking more than 15 years ago.

- **Sentinel lymph node biopsy for melanoma**: A joint guideline from ASCO and the Society of Surgical Oncology provides the first evidence-based guidance on the use of sentinel lymph node biopsy for staging – or determining extent of cancer spread – in patients with newly diagnosed melanoma. These recommendations clarify which patients should receive the procedure and undergo complete lymph node dissection.

- **Screening for prostate cancer with prostate-specific antigen (PSA) testing**: This PCO recommends that physicians discuss the benefits and risks of PSA testing with asymptomatic men who have life expectancies of greater than 10 years. For men with shorter life expectancies, the PCO states that the risks – such as over-diagnosis and unnecessary treatment and side effects – outweigh the potential benefits. ASCO’s guidance differs from recommendations issued in May 2012 by the U.S. Preventive Services Task Force, which concluded that routine PSA testing is not recommended for any asymptomatic men.
lower hospital-wide morbidity (adverse effects of disease or treatment) and mortality rates for rectal cancer and lower hospital-wide morbidity rates for colon cancer. However, at the individual patient level, higher composite measures were not associated with better short-term morbidity and mortality, potentially because individual patient factors (e.g., comorbidity) may have had a greater influence on outcome than location where the surgery is performed. These results demonstrate that composite measures based on process indicators are able to predict clinically significant outcomes of colorectal surgery at the hospital level.

Intensity of end-of-life cancer care varies widely among hospitals
In their final weeks of life, many patients with cancer receive intensive hospital care, often with limited benefits in terms of improved survival or quality of life. This care is often more aggressive than patients would prefer; surveys have shown that more than 80% of patients say they wish to avoid hospitalization and intensive care during the last stages of their illness.

Results of a study released this year reveal that the intensity of end-of-life care in the United States varies up to two-fold from hospital to hospital, even among hospitals with similar characteristics (e.g., for-profit status, hospital size, cancer center designation, community hospital, academic center). The study looked at end-of-life care measures, such as hospice use, intensive care unit use, and hospitalization, among 215,311 poor-prognosis, elderly patients with cancer in their last 6 months of life. Billing codes were used to document use of chemotherapy and uncomfortable procedures (e.g., placement of feeding or breathing tubes) in the last 14 days of life.

Overall, there was a tendency toward administering intensive care in the last months of life, and patients in larger and medium-sized hospitals received more care than those in smaller hospitals. Compared with patients treated at National Comprehensive Cancer Network hospitals, patients treated at community hospitals were more likely to have late initiation of hospice care, spend more time in the intensive care unit in the last month of life, and receive chemotherapy in the last 14 days of life, all of which are in disagreement with quality care standards set by the National Quality Forum.

These findings point to the need for a broad re-examination of end-of-life care in terms of quality and alignment with patients’ needs and wants.

Higher hospital spending is associated with higher quality of care and better patient outcomes
One might expect that hospitals that spend more provide higher quality of care, but until now, research has not been able to fully support this hypothesis. In 2012, investigators reported results of a large Canadian study showing that higher-spending hospitals had better outcomes for patients with certain acute diseases, including cancer, compared with lower-spending hospitals.

The study tracked costs for patients admitted to 129
These findings point to the need for a broad re-examination of end-of-life care in terms of quality and alignment with as well as patients’ needs and wants.

Ontario hospitals for acute heart attack (179,139 patients), congestive heart failure (92,377 patients), hip fracture (90,046 patients), and colon cancer (26,125 patients) over the course of 1 year. Hospital spending was calculated as the mean adjusted spending on hospital, emergency department, and physician services provided to patients. Adjusted spending varied by as much as two-fold across the highest and lowest-spending hospitals. Higher-spending hospitals had more inpatient nursing and critical care staff, and their patients received more inpatient medical specialist visits and preoperative specialty care. The highest-spending hospitals had lower rates of all adverse outcomes compared with the lowest-spending hospitals. For example, among patients with colon cancer, 30-day mortality rates and hospital readmission rates were 3.3% and 10.3% in the highest-spending hospitals, compared with 3.9% and 13.1% in the lowest spending hospitals, respectively. Although the findings may not be fully applicable to other countries, they suggest that higher spending on acute care services can provide meaningful benefits to patients.

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“Well into the 21st century, significant disparities based on age at cancer diagnosis and financial means keep key segments of our society from fully engaging in the best cancer therapy and clinical trials, in particular. There is a pressing need to increase clinical trial participation and improve access and quality of care in key groups including, but not limited to, financially deprived, elderly and adolescent/young adult populations.”

– DAVID QUINN, MD
Although cancer care has improved tremendously in recent decades, not all patients have benefited equally from advances in cancer prevention, screening and diagnosis, and treatment. Certain patient groups also have persistently lower rates of participation in cancer clinical trials—a fact that limits the ability to generalize research findings to all patients with cancer and slows the discovery of effective new therapies for these populations. This year, research provides new insight into certain socioeconomic disparities in clinical trial participation and the unique needs of vulnerable populations, namely AYAs and the elderly.

**Notable Advances**

**Survey identifies socioeconomic barriers to clinical trial participation**

An important study presented this year by SWOG, one of the largest clinical trial cooperative groups, explored how socioeconomic status shapes a patient’s decision to participate in a clinical trial. Researchers assessed how income and education as well as demographic factors (age, sex, race) correlate with clinical trial participation decisions. The study surveyed 5,499 patients who were newly diagnosed with breast, lung, colorectal, or prostate cancer. Overall, they found clinical trial participation differed by age, income, and education, with higher participation rates for younger, wealthier, and more educated patients. Regardless of age, lower-income patients were much less likely to participate in clinical trials, and the trend persisted even among patients who were universally covered by Medicare. Patients who reported an annual income less than $50,000 were approximately 30% less likely to participate in a clinical trial than those reporting a higher income. Looking at lower income levels, patients who made less than $20,000 per year were 44% less likely to participate in a clinical trial than patients who made more than $20,000.

A better understanding of why income is a barrier may
identify ways to increase clinical trial participation to all patients, enabling generalization of research results across all socioeconomic levels.

New insights into challenges facing progress against cancer among AYAs with cancer

In the United States, approximately 70,000 AYAs are diagnosed with cancer each year. The most common cancers diagnosed in this age group are lymphoma, leukemia, germ cell tumors (including testicular cancer), melanoma, CNS tumors, sarcomas, and breast, cervical, liver, thyroid, and colorectal cancers. Over the past 35 years, there have been astounding increases in survival rates of childhood and older adult patients with cancer. However, among AYAs, survival rates have not improved nearly as much, and cancer remains the leading cause of death. This is driven by a range of factors, including limited access to care and lack of health insurance, delayed diagnosis of primary cancer, low participation in clinical trials, and unique psychosocial and supportive care needs of AYAs with cancer. This year, three studies contributed new insight into some of these challenges.

Clinical trials are the crucial link between discoveries in the laboratory and new treatments that extend and improve patients’ lives, but enrollment is low among AYAs, particularly those treated at adult oncology centers. To address this challenge, the University of Pittsburgh Cancer Institute, an adult medical oncology center, and the Children’s Hospital of Pittsburgh established a joint AYA oncology program. Investigators reported that this novel program led to much higher enrollment of newly diagnosed AYA patients with cancer onto clinical trials. Over a 4-year period, participation in clinical trials among AYA patients rose from 3% to 33% at the University of Pittsburgh Cancer Institute. This is important because there is evidence that increased clinical trial participation leads to increased survival and cure rates and access to promising investigational treatments. Higher enrollment rates would also enable faster completion of clinical trials, bringing more new treatments to AYAs with cancer. This study offers an important model for improving collaboration between pediatric and adult oncologists, which can ultimately bring better care for AYA patients with cancer.

Maintaining career and educational goals is an important concern for AYAs, affecting quality of life as well as patient income, health insurance coverage, and access to high-quality health care. A second important study explored factors affecting return to work and education among 463 AYA patients with germ cell cancer, lymphoma, sarcoma, or ALL. The study found that although most AYA patients with cancer returned to work or school 15 to 35 months after diagnosis, patients who were uninsured before diagnosis and those who quit work or school directly after diagnosis had a much lower likelihood of resuming their professional or academic pursuits. They also found that AYAs who underwent intensive treatments were more likely to believe that cancer negatively affected work or educational outcomes. These findings help identify vulnerable subgroups of patients and underscore the need to develop best practices for transitioning AYA cancer survivors to the workplace or school after treatment.

A third study examined the long-term health status of AYA cancer survivors using data from the Behavioral Risk Factor Surveillance System. Data were collected from 4,054 AYA cancer survivors (diagnosed with cancer between the ages of 15 and 29 years) and 345,592 individuals older than 18 years with no history of cancer. Compared with this control group, AYA cancer survivors reported higher prevalences of current health conditions.
smoking (26% v 18%), obesity (31% v 27%), cardiovascular disease (14% v 7%), hypertension (35% v 29%), asthma (15% v 8%), disability (36% v 18%), poor mental health (20% v 10%), poor physical health (24% v 10%), and reduced use of medical care because of high cost (24% v 15%) (Fig 23). These results show that AYA cancer survivors have important long-term medical and psychosocial needs that are not yet being adequately addressed.

Researchers join forces to address gaps in geriatric oncology research

Cancer is primarily a disease of the elderly, with incidence rates being 11-fold higher in people older than age 65 years compared with those younger than 65 years and climbing. Elderly patients with cancer have unique care needs and challenges, such as other illnesses (comorbidities), frail physical status, and mental decline. Because of low participation of elderly patients with cancer in clinical trials, there are often few data to guide treatment for those patients.

In September 2010, investigators in the fields of aging and cancer organized a joint, interdisciplinary conference to identify and address these challenges.5 A summary of the proceedings and recommendations of the meeting was published this year, highlighting current levels of research evidence in geriatric oncology, major research gaps (particularly lack of tools to measure success of cancer therapy in older patients), and complementary strategies that would address these deficits over the next decade. This conference laid the foundation for future collaborations and changes to clinical trial designs that will enhance clinical trials in elderly patients with cancer. In upcoming conferences, organizers plan to highlight research designs and collaborations that will enhance therapeutic and intervention trials in older adults with cancer, leading to improved cancer care for the elderly.

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The advances highlighted in this year’s Clinical Cancer Advances Report provide evidence that clinical cancer research is continuing to lengthen and improve the lives of patients with cancer. As we continue to learn more through research about the biology of cancer, discoveries in one type of cancer are now leading to important advances in treatment for other types of cancer as well. The collective progress being made against cancer is a direct result of the nation’s investment in cancer research as a whole.

More importantly, future progress is critically dependent on continued national investment in research conducted through the National Institutes of Health (NIH). A newly emerging understanding of cancer at the most basic molecular level, including the ability to identify features unique to different cancer types and individual patients, is generating enormous insight into the diseases we collectively call cancer. Harnessing these discoveries to improve patient care will require increasingly sophisticated research to capture, store, and analyze huge amounts of this omics-based information and ultimately link these to patient treatment and outcome data. Acceleration of clinical cancer research will be essential to maximizing scientific opportunities going forward.

In addition to the need to accelerate cancer research, other policy and practice issues have affected patient care and progress against cancer in 2012, including a growing emphasis on quality and value in cancer care and serious shortages of important cancer drugs. This section of the Report outlines these major developments that have affected oncology over the past year and highlights related ASCO initiatives aimed at creating an environment where faster progress can be made against cancer.

**Funding for Clinical Cancer Research Jeopardized**

Over the past year, the NCI, a component of the NIH, continued the revitalization and renewal of the NCI Cooperative Group System with launch of requests for applications for the newly created National Clinical Trials Network. This process began in 2010 based on recommendations made in a major IOM report: “A National Cancer Clinical Trials System for the 21st Century.” Although the changes that the cooperative groups and the NCI have undergone are significant, they are not sufficient to sustain this nation’s vital cancer research system; continued financial investment is vital to preserving our nation’s ability to translate laboratory findings into meaningful results for patients.

In 2010, ASCO called for full implementation of the recommendations in the IOM report—including a significant increase in funding by 2015. Federal funding for the NIH has remained essentially flat for the past decade, and when the biomedical inflation rate is factored in, the NIH has actually lost more than 20% of its purchasing power to continue to fund import-
ant research. In fact, the current purchasing power of the NCI is less than it was in 2001. As this Report went to press, public funding for cancer research was also threatened with enormous cuts because of sequestration, the automatic federal budget cuts set to go into effect on January 2, 2013, as part of the 2011 debt ceiling agreement. Unless Congress acts to stop these cuts, the NIH will lose an additional 8% of its funding. NCI Director Harold Varmus, MD, has said the automatic cut would result in the NIH being unable to fund up to 40% of new grants in fiscal year 2013.

As of this writing, ASCO continues to use all means and channels possible to implore Congress to avert the disastrous impact of sequestration on current and future patients with cancer. ASCO has also joined with One Voice Against Cancer to advocate for the most robust funding possible in this challenging economic climate.

Initial Steps Toward a Rapid Learning System for Cancer Care

Although cancer science and information technology are advancing rapidly, the way we currently care for patients cannot fully capitalize on those advances. Today, we still know little about most patients with cancer—from the molecular characteristics of their tumors to the outcomes of their treatments—because we are only beginning to use genomic analysis that will give us these details. In addition, we are not enabling a majority of patients the opportunity to participate in cancer research and provide their information in a way that can improve cancer outcomes. This is because we keep cancer treatment and outcome data locked away in unconnected electronic and paper records, and we have not incorporated tools to routinely collect patient feedback in research. This is true across all of medicine. In 2012, the IOM issued a report calling for the development of a rapid learning system that would use real-time knowledge to improve outcomes, engage patients and family members, and create a continuous cycle of learning and improvement. The report, “Best Care at Lower Cost: The Path to Continuously Learning Health Care in America,” includes a number of recommendations designed to double the output of innovative new medicines in the next 10 to 15 years. The recommendations lay the groundwork for incorporating a rapid learning system into the research to develop new cancer prevention, detection, and treatment.

As part of its long-standing focus on quality improvement—from clinical practice guidelines to the QOPI—ASCO embarked in 2012 on a multiphase initiative to build a rapid learning system for oncology. The new system, known as CancerLinQ, promises to change the way cancer is understood and treated. CancerLinQ will harness technologic advances to connect oncology practices, measure quality and performance, and provide physicians with decision support in real time. A CancerLinQ prototype was unveiled at the inaugural ASCO Quality Cancer Care Symposium held in November 2012.

Action to Address Shortages of Oncology Drugs

The critical issue of drug shortages, which began in 2010, carried over into 2012, with oncology practices experiencing an unprecedented number of shortages of important, life-extending cancer drugs over a 2-year period. Although drug shortages have affected a number of different medical specialties, the problem is especially acute in oncology, because there are often no equivalent substitutions for the standard agents that have been shown to improve patient outcomes.

In response to the severe shortages, ASCO worked with the American Society of Health-System Pharmacists and several other organizations to heighten awareness of this life-threatening issue. As part of this effort, ASCO worked directly with
top news media to specifically bring national attention to the crisis in oncology. As legislators worked to address the shortages in 2012, ASCO issued three key recommendations for addressing the national crisis:

- Require manufacturers to give the FDA confidential notification for market withdrawals or manufacturing interruptions 6 months in advance.
- Provide economic incentives for companies to develop shortage contingency plans.
- Establish FDA user fees for generic drugs as part of the regulatory approval process.

The ASCO recommendations to establish user fees for generic drugs and require early notification for manufacturers were included in the final version of the Food and Drug Safety and Innovation Act. President Obama signed the legislation into law on July 9, 2012. As of this writing, the FDA is building the infrastructure to carry out these requirements.

Quality and Value in Cancer Care Emphasized

This past year saw a heightened national focus on improving the quality and value of medical care in the United States, driven in part by continued increases in health care costs in this country. As part of this focus, the American Board of Internal Medicine Foundation launched a campaign to identify common, and sometimes costly, procedures in medical practice that have little or no proven benefit to patients.

ASCO was one of nine initial specialty societies that joined the Choosing Wisely campaign in 2012. Each society developed a list of the top five tests and treatments that are routinely performed in their specialty despite a lack of supporting medical evidence.

The top five list for oncology represents some of the most significant opportunities to improve quality—and value—in cancer care today. ASCO defines value as maximization of patient benefits achieved for each dollar spent. The top five list in oncology included the following recommendations:

1. For patients with advanced solid-tumor cancers who are unlikely to benefit, do not provide unnecessary anticancer therapy, such as chemotherapy, but instead focus on symptom relief and palliative care.

2. Do not use positron emission tomography, CT, or radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.

3. Do not use positron emission tomography, CT, or radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.

4. For individuals who have completed curative breast cancer treatment and have no physical symptoms of cancer recurrence, routine blood tests for biomarkers and advanced
imaging tests should not be used to screen for cancer recurrences.

5. Avoid administering colony-stimulating factors to patients undergoing chemotherapy who have less than a 20% risk for febrile neutropenia.

The goal of the top five list in oncology is to help spark conversations about the benefits and potential harms of these interventions, so together, physicians and patients can rely on evidence-based medicine to make informed decisions that consistently yield high-quality—and high-value—care.

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

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

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

Antibody therapy: Treatment with an antibody, a substance that can directly kill specific tumor cells or stimulate the immune system to kill tumor cells.

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

Biologic drug: A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines. Also called biologic agent and biological agent.

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

Cell line: A perpetuating strain of cells grown in laboratory culture.

Chromosome: Discrete physical structures inside a cell nucleus that consist of proteins and DNA organized into genes

Colonoscopy: Examination of the inside of the colon using a colonoscope, inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing.

Epidemiology: The study of the patterns, causes, and control of disease in groups of people.

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

Estrogen: A type of hormone made by the body that helps develop and maintain female sex characteristics and the growth of long bones.
**Estrogen receptor-positive:** Describes cells that have a receptor protein that binds the hormone estrogen. Cancer cells that are estrogen receptor positive may need estrogen to grow, and may stop growing or die when treated with substances that block the binding and actions of estrogen. Also called ER+.

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

**Flexible Sigmoidoscopy:** Examination of the lower colon using a sigmoidoscope, inserted into the rectum. A sigmoidoscope is a thin, tube-like instrument with a light and a lens for viewing.

**Gastroesophageal junction:** The place where the esophagus is connected to the stomach.

**Gene therapy:** A type of experimental treatment in which foreign genetic material (DNA or RNA) is inserted into a person’s cells to prevent or fight disease. Gene therapy is being studied in the treatment of certain types of cancer.

**Gene copy number:** Refers to the genetic trait involving the number of copies of a particular gene present in the genome of an individual. Copy number variants account for a significant proportion of the genetic variation between individuals.

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

**Gene transcript:** An RNA copy of a sequence of DNA that is a gene.

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

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

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

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

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

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

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

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

**mTOR:** A protein that helps control several cell functions, including cell division and survival, and binds to rapamycin and other drugs. mTOR may be more active in some types of cancer cells than it is in normal cells. Blocking mTOR may cause the cancer cells to die. It is a type of serine/threonine protein kinase. Also called mammalian target of rapamycin.

**Neoadjuvant therapy:** Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.

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

**Overall survival rate:** The percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease, such as cancer. The overall survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after their diagnosis or the start of treatment.

**Personalized Medicine:** A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. Also called precision medicine.

**Platinum:** A metal that is an important component of some anticancer drugs, such as cisplatin and carboplatin.

**Progression free survival:** The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works. Also called PFS.
Prostate-specific antigen (PSA): A protein made by the prostate gland and found in the blood. PSA blood levels may be higher than normal in men who have prostate cancer, benign prostatic hyperplasia (BPH), or infection or inflammation of the prostate gland. Also called prostate-specific antigen.

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

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

Radiopharmaceutical: A drug that contains a radioactive substance and is used to diagnose or treat disease, including cancer. Also called radioactive drug.

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

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

Screening: Checking for disease when there are no symptoms.

Squamous cell carcinoma: Cancer that begins in squamous cells, which are thin, flat cells that look like fish scales. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts.

Stem cell transplantation: A method of replacing immature blood-forming cells in the bone marrow that have been destroyed by drugs, radiation, or disease.

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

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

**Additional Resources**

Oncologist-approved cancer information from the American Society of Clinical Oncology

**Basic Cancer Information**

[www.cancer.net/cancertypes](http://www.cancer.net/cancertypes)

Comprehensive information on more than 120 cancer types and cancer-related syndromes

- Risk factors
- Staging
- Diagnosis
- Questions to ask the doctor
- Treatment
- Symptoms
- Spanish language section

**Coping Resources**

[www.cancer.net/coping](http://www.cancer.net/coping)

Resources to help people with cancer and those who care for them

- Caregiving
- Sexuality
- Personal stories
- End-of-life care
- Relationships
- Mental health

**Survivorship**

[www.cancer.net/survivorship](http://www.cancer.net/survivorship)

Information and resources for cancer survivors and their families and friends

- About survivorship
- The booklet, *Cancer Survivorship: Next Steps for Patients and Their Families*
- Late effects
- Childhood cancer survivorship
- Treatment summaries and follow-up care plans
- Survivor stories and artwork
- Rehabilitation
Guidelines
www.asco.org/guidelines
Information on ASCO guidelines, provisional clinical opinions (PCOs), and guideline endorsements

ASCO Connection
connection.asco.org
The professional networking site for ASCO’s worldwide oncology community

Conquer Cancer Foundation
www.conquercancerfoundation.org
A not-for-profit organization working to create a world free from the fear of cancer by funding breakthrough research and sharing cutting-edge knowledge worldwide
• Apply for grants and awards
• Donate in support of the Foundation’s mission
• See the latest progress Foundation funded researchers are making
Cancer Progress

www.cancerprogress.net

A dynamic history of progress against cancer, with stories of cancer survivors, advocates, and physicians, and expert perspective on challenges we face to continue making progress. Watch videos, click around the interactive Timeline, and download statistics, reports and other useful materials.

ASCO in Action

ascoaction.asco.org

Public policy news and information from ASCO

ASCO Progress Reports

cancerprogress.net/cca

Clinical Cancer Advances: ASCO’s Annual Report on Progress Against Cancer (2005-present)