It has been forty years since President Richard Nixon signed the National Cancer Act of 1971, which many view as the nation’s declaration of the “War on Cancer.” The bill has led to major investments in cancer research and significant increases in cancer survival. Today, two-thirds of patients survive at least five years after being diagnosed with cancer compared with just half of all diagnosed patients surviving five years after diagnosis in 1975.

The research advances detailed in this year’s Clinical Cancer Advances demonstrate that improvements in cancer screening, treatment, and prevention save and improve lives. But although much progress has been made, cancer remains one of the world’s most serious health problems. In the United States, the disease is expected to become the nation’s leading cause of death in the years ahead as our population ages.

I believe we can accelerate the pace of progress, provided that everyone involved in cancer care works together to achieve this goal. It is this viewpoint that has shaped the theme for my presidential term: Collaborating to Conquer Cancer. In practice, this means that physicians and researchers must learn from every patient’s experience, ensure greater collaboration between members of a patient’s medical team, and involve more patients in the search for cures through clinical trials. Cancer advocates, insurers, and government agencies also have important roles to play.

Today, we have an incredible opportunity to improve the quality of cancer care by drawing lessons from the real-world experiences of patients. The American Society of Clinical Oncology (ASCO) is taking the lead in this area, in part through innovative use of health information technology. In addition to our existing quality initiatives, ASCO is working with partners to develop a comprehensive rapid-learning system for cancer care. When complete, this system will provide physicians with personalized, real-time information that can inform the care of every patient with cancer as well as connect patients with their entire medical teams. The rapid learning system will form a continuous cycle of learning: securely capturing data from every patient at the point of care, drawing on evidence-based guidelines, and evaluating quality of care against those standards and the outcomes of other patients.

Clinical trials are another area in which collaboration is critical. Increasing clinical trial participation will require commitment across the cancer community from physicians, patients, insurers, hospitals, and industry. A 2010 report by the Institute of Medicine described challenges to participation in trials by both physicians and patients and provided recommendations for revitalizing clinical trials conducted through the National Cancer Institute’s Cooperative Group Program. ASCO has pledged its support for the full implementation of these recommendations.

More broadly, ASCO recently outlined a bold vision for translational and clinical cancer research for the next decade and made recommendations to achieve that vision. Accelerating Progress Against Cancer: ASCO’s Blueprint for Transforming Clinical and Translational Research, released in November, calls for a research system that takes full advantage of today’s scientific and technologic opportunities and sets a high-level agenda for policymakers, regulators, and advocates.

Cancer research has transformed cancer care in the past forty years, and this year’s Clinical Cancer Advances illustrates how far we have come in the past year alone. We now have a tremendous opportunity to use today’s knowledge and collaborate across all facets of cancer care to conquer this deadly disease.

Michael P. Link, MD
President
American Society of Clinical Oncology

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EXECUTIVE SUMMARY

Each year, the American Society of Clinical Oncology (ASCO) conducts an independent review of advances in clinical cancer research to identify those that have the greatest potential impact on patients’ lives. This year, Clinical Cancer Advances features 54 significant studies, including 12 that the editors consider major advances.

This year’s Clinical Cancer Advances also recaps the year’s most important cancer policy developments and ASCO policy initiatives that are likely to influence cancer care in the coming years. These include developments that could accelerate the pace of clinical cancer research progress and ensure access to quality cancer care for patients.

Summary of Findings

Screening and prevention. With cancer, the ultimate goal is to avoid the disease altogether. Smoking cessation efforts, lifestyle changes, and other biomedical interventions have successfully prevented thousands of cancers in the past decades. At the same time, researchers seek better ways to detect cancers early, when they are most curable. Screening advances are credited with improving survival rates for a range of cancers. Advances in cancer screening and prevention that occurred this year include:

- Low-dose computed tomography (CT) scanning reduces the lung cancer death rate in people at high risk: A national screening trial of more than 50,000 current and former heavy smokers found that three annual low-dose CT scans reduced the risk of dying from lung cancer by 20% compared with those who were screened with three annual chest x-rays. This landmark trial was the first to identify a screening regimen for patients at high risk for lung cancer, despite decades of attempts. Guidance on how to apply these findings is expected in the coming year.

- Exemestane reduces the risk of invasive breast cancer in high-risk, postmenopausal women: A phase III trial showed that exemestane (Aromasin; Pfizer, New York, NY), a member of a family of drugs called aromatase inhibitors, reduced the risk of developing breast cancer compared with placebo in high-risk, postmenopausal women. This is the first conclusive evidence, to our knowledge, that an aromatase inhibitor reduced the risk of a first breast cancer, making exemestane an option for postmenopausal women who are at high risk for the disease. Two other drugs, tamoxifen and raloxifene, are already approved for this purpose, but they carry with them concern over adverse effects that deter many women who could benefit from such treatment.

- Bevacizumab delays progression in recurrent ovarian cancers: A phase III trial showed that bevacizumab (Avastin; Genentech), a monoclonal antibody that inhibits blood vessel growth and development in tumors, together with standard chemotherapy helped women with recurrent ovarian cancer live significantly longer without disease progression than those treated with the same chemotherapy alone. In the Ovarian Cancer Evaluation of Avastin and Safety (OCEANS) trial, patients treated with bevacizumab lived a median of 4 months longer without disease progression than those who received chemotherapy alone—a 52% reduction in the risk of disease progression. In the second trial, data suggested that adding bevacizumab to standard carboplatin and paclitaxel chemotherapy for treatment of newly diagnosed ovarian cancer helps women live longer than with treatment with chemotherapy alone, particularly for patients with more aggressive forms of the disease. By extending the time patients can live without disease progression, and without additional treatment with chemotherapy, these results suggest that, increasingly, ovarian cancer may be treated as a longer-term, chronic disease. Researchers await longer-term data from both studies to get a clearer picture of how these regimens improve survival and which women benefit most.

- New high-dose chemotherapy regimen improves survival in children with high-risk neuroblastoma: A phase III trial showed that a new combination of chemotherapy drugs improved survival for children with high-risk, metastatic neuroblastoma. After 3 years, the event-free survival for patients treated with an intense dose of chemotherapy drugs busulphan-melphan was 49% compared with 33% for the three standard chemotherapy drugs (carboplatin, etoposide, and melphanal). These findings establish a new standard of care for high-risk neuroblastoma and, together with other recent treatment advances for the disease, are likely to lead to survival gains for patients.

Reducing cancer recurrence. Although many cancers can be treated successfully at first, preventing disease from returning is often difficult, particularly when the disease is diagnosed at advanced stages. When a cancer recurs, it is usually more resistant to therapy and may not be curable. This year, several studies marked important advances in preventing the recurrence of a form of GI cancer, a type of leukemia in children and young adults, and breast cancer.

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Newly approved agents

<table>
<thead>
<tr>
<th>Anticancer Agent</th>
<th>Trade Name</th>
<th>Indication</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Xgeva (Amgen, Thousand Oaks, CA)</td>
<td>For prevention of skeletal-related events in patients with bone metastases from solid tumors</td>
<td>November 18, 2010</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Yervoy (Bristol-Myers Squibb, New York, NY)</td>
<td>For treatment of unresectable or metastatic melanoma</td>
<td>March 25, 2011</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Vandetanib (AstraZeneca; Wilmington, DE)</td>
<td>For treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease</td>
<td>April 6, 2011</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>Zytiga (Janssen Biotech, Horsham, PA)</td>
<td>For use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel</td>
<td>April 28, 2011</td>
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<tr>
<td>Vemurafenib</td>
<td>Zelboraf (Genentech, South San Francisco, CA)</td>
<td>For treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation as detected by an FDA-approved test</td>
<td>August 17, 2011</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>Adcetris (Seattle Genetics, Bothell, WA)</td>
<td>For treatment of patients with Hodgkin’s lymphoma after failure of ASCT or after failure of at least two prior multagent chemotherapy regimens in patients who are not ASCT candidates; for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multagent chemotherapy regimen (accelerated approval)</td>
<td>August 19, 2011</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Xalkori (Pfizer; New York, NY)</td>
<td>For treatment of patients with locally advanced or metastatic non-small-cell lung cancer that is ALK positive as detected by an FDA-approved test: Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular,Abbott Park, IL)</td>
<td>August 26, 2011</td>
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Expanded indications for existing agents

<table>
<thead>
<tr>
<th>Anticancer Agent</th>
<th>Trade Name</th>
<th>Indication</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Herceptin (Genentech)</td>
<td>For patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with cisplatin and a fluoropyrimidine (capecitabine or fluorouracil)</td>
<td>October 20, 2010</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Sprycel (Bristol-Myers Squibb)</td>
<td>For newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase</td>
<td>October 28, 2010</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan (Genentech; Biogen Idec, Westton, MA)</td>
<td>For maintenance therapy for patients with previously untreated follicular, CD20-positive, B-cell non-Hodgkin’s lymphoma</td>
<td>January 28, 2011</td>
</tr>
<tr>
<td>Peginterferon alfa-2b</td>
<td>Sylatron (Merck, Whitehouse Station, NJ)</td>
<td>For patients with melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection, including complete lymphadenectomy</td>
<td>March 29, 2011</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Afinitor (Novartis, Summit, NJ)</td>
<td>For progressive neuroendocrine tumors of pancreatic origin in patients with unresectable, locally advanced or metastatic disease</td>
<td>May 5, 2011</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Sutent capsules (Pfizer)</td>
<td>For progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable, locally advanced, or metastatic disease</td>
<td>May 20, 2011</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Prolia (Amgen)</td>
<td>For increasing bone mass in patients at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer</td>
<td>September 16, 2011</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Soliris (Alexion Pharmaceuticals, Cheshire, CT)</td>
<td>For pediatric and adult patients with atypical hemolytic uremic syndrome</td>
<td>September 23, 2011</td>
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Abbreviations: ALK, anaplastic lymphoma kinase; ASCT, autologous stem-cell transplantation; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization.

- Three years of imatinib therapy improves survival for high-risk GI stromal tumors (GIST): A phase III trial showed that 3 years of treatment with the targeted kinase inhibitor imatinib (Gleevec; Novartis, Summit, NJ) after surgery in patients with high-risk GIST significantly improved overall and recurrence-free survival compared with 1 year of treatment. The findings could result in the 3-year course of therapy becoming the new standard of care for those patients who are at risk for relapse.

- New chemotherapy regimen boosts event-free survival for children and young adults with acute lymphoblastic leukemia (ALL): A phase III Children’s Oncology Group trial of nearly 2,500 children and young adults with ALL showed that giving the common chemotherapy drug methotrexate in large, consistent doses—rather than in the gradually increasing doses of the standard regimen—was more effective in preventing relapses and extending survival. These findings set a new standard of care and pushed cure rates for pediatric patients with ALL to more than 80%. This disease was once considered one of the most deadly pediatric cancers, but today, it is seen as one of the most curable.

- Adding regional nodal irradiation decreases recurrences in women with early-stage breast cancer: An analysis of a randomized phase III trial found that adding radiation to the regional lymph nodes reduces the risk of cancer recurrences both near the tumor and in other parts of the body in women with early-stage breast cancer who have one to three cancer-positive lymph nodes (or high-risk node-negative breast cancer). The findings are important because women with breast cancer that has spread to the lymph nodes are typically treated with breast-conserving surgery and surgery to remove many of the lymph nodes under the arm, which are then followed by radiation to the entire breast to reduce the likelihood of recurrence. The usefulness of expanding the traditional radiation field around the breast in this population of patients had previously been unclear.
New drug approvals. In addition to the approval of vemurafenib for melanoma, new treatment options were approved by the FDA for lung cancer and prostate cancer.

FDA approves crizotinib for lung cancer: The FDA approved a new drug, crizotinib (Xalkori; Pfizer), in August for patients with advanced non–small-cell lung cancer whose tumors harbor a specific type of alteration in the anaplastic lymphoma kinase (ALK) gene. The drug improved survival by 31% after 2 years. The approval of crizotinib is the latest example of a successful personalized medicine approach in treating patients with lung cancer.

Abiraterone acetate is approved for patients with prostate cancer: In April, the FDA approved the oral agent abiraterone acetate (Zytiga; Janssen Biotech, Horsham, PA) in combination with prednisone for patients with metastatic hormone-refractory prostate cancer who have received prior treatment with the chemotherapy drug docetaxel. Abiraterone works by blocking the production of male sex hormones (such as testosterone), which fuel the growth of prostate tumors. Given that only one other agent, cabazitaxel (Jevtana; sanofi-aventis, Bridgewater, NJ), an intravenous chemotherapy drug, has been shown to prolong survival in patients who no longer respond to treatment with docetaxel. This approval represents a much-needed new option for patients.

Special Update: US Panel Recommends Against Routine Use of Prostate-Specific Antigen for Prostate Cancer Screening

In October 2011, the US Preventive Services Task Force recommended against routine screening for prostate cancer by using the prostate-specific antigen (PSA) test, citing a lack of evidence that the test saves lives and stating that it can lead to unnecessary testing and treatment.

ASCOR 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. Patient-oriented cancer information is available at www.cancer.net.

Clinical Cancer Advances strives to fill a gap in cancer literature by publishing the major advances in clinical cancer research and care each year. ASCO developed this annual report, now in its seventh year, to document the important progress made in cancer research and to highlight emerging trends in the field.

The report was developed under the direction of an 18-person editorial board comprising prominent oncologists, and only studies that significantly altered the way a cancer is understood or that had a direct effect on patient care were included. The editors—including specialty editors for each of the disease- and issue-specific sections—reviewed research presented at major scientific meetings and studies published in peer-reviewed scientific journals during a 1-year period (October 2010-September 2011).

Although important research is underway in all cancer types, advances that met the above criteria were not demonstrated in all types of cancer in the past year. Studies included in this year’s report are grouped as follows:
to standard therapies. Brentuximab consists of an antibody directed against the CD30 protein that is chemically linked to a chemotherapy drug, monomethyl auristatin E. Monomethyl auristatin E has previously been tried alone but was found to be extremely toxic. The drug combination, termed a “conjugate,” is designed to bind and deliver the chemotherapy directly to cells with the CD30 protein, which is present only on the cancer cell. This approach concentrates chemotherapy on the cancer cells and spares healthy cells.

On the basis of phase II trial results, the FDA granted accelerated approval in August 2011 for brentuximab vedotin for patients with refractory Hodgkin’s lymphoma and ALCL. Brentuximab vedotin is the first drug ever approved specifically for ALCL and the first new drug approved by the FDA for Hodgkin’s lymphoma in more than 30 years. Briefly, the studies found the following:

- In a phase I multicenter trial, researchers tested the effectiveness of brentuximab in 45 patients with relapsed or refractory CD30-positive hematologic cancers, mostly Hodgkin’s lymphoma and ALCL. Tumors regressed in 36 (86%) of 42 evaluable patients.
- In one of two phase II trials, 102 patients with relapsed or refractory Hodgkin’s lymphoma were treated with brentuximab, with 75% of patients having tumors shrink to at least half of original size.
- In a phase II trial of 58 patients with ALCL, 87% of patients had tumors shrink to at least half of original size, with 57% of patients experiencing complete remission.
- Diarrhea, fatigue, nausea, and peripheral neuropathy were among the most common adverse effects of the drug combination.

**JAK inhibitor improves response rate for patients with high-risk MF.**

MF, a disorder characterized by scar tissue buildup in the bone marrow, is extremely difficult to treat. It causes anemia and a variety of debilitating symptoms (such as fatigue, night sweats, weight loss, bone pain, and an enlarged spleen) and leads to acute myeloid leukemia and bone marrow failure in more than a quarter of patients. Although bone marrow transplantation remains the only potential cure, relapse or postessential thrombocythemia MF. In the study, 219 patients with intermediate or high-risk disease were randomly assigned to either ruxolitinib (n = 146) or to the best available therapy (n = 73), with responses measured in terms of a reduction in spleen size of ≥ 35%. After 48 weeks, researchers found this reduction in spleen size in 28.5% of patients receiving the drug compared with 0% in those who did not receive the drug.

In the COMFORT I trial, treatment with ruxolitinib was compared with placebo in 309 patients with the same three types of MF. After treatment for a median follow-up of 32 weeks, 42% of those who received the drug had a 35% reduction in spleen size after 24 weeks compared with 1% of patients receiving placebo. The majority of patients receiving ruxolitinib in both studies saw improvement in fatigue, night sweats, weight loss, and bone pain.

**In recent years, there have been profound changes for women with breast cancer—the most common cancer among women in the United States—as those diagnosed with the disease live longer, healthier lives. New insights into breast cancer development on a molecular level are helping researchers understand and treat the disease as never before.

Important advances this year come from a study showing a new potential role for aromatase inhibitors to reduce the risk of developing breast cancer and a trial demonstrating the benefit of expanding radiation treatment to the lymph nodes after lumpectomy. Two trials showed the value of combining targeted drugs with chemotherapy in women with stage II and III human epidermal growth factor receptor 2 (HER2)–positive breast cancers. Additionally, a randomized trial of a poly (ADP-ribose) polymerase (PARP) inhibitor proved ineffective in metastatic triple-negative disease, an extremely aggressive form of breast cancer, despite earlier favorable results.

**Major Advances**

- Exemestane significantly reduces the risk of invasive breast cancer in high-risk, postmenopausal women. Although the antiestrogen drugs tamoxifen and raloxifene are FDA-approved for breast cancer prevention in women at high risk, only 4% of the approximately 2 million women in the United States who could benefit from them actually take either drug, because of concerns about the increased risk of developing endometrial cancers and blood clots.

- Over the past year, a phase III trial showed that exemestane (Aromasin), a member of a family of drugs called aromatase inhibitors, greatly reduces the risk of developing breast cancer in high-risk, postmenopausal women. This is the first evidence that an aromatase inhibitor reduces the risk of a first breast cancer, and it opens the door for exemestane to become an option for postmenopausal women who are at high risk for breast cancer.

- Aromatase inhibitors, which work differently than tamoxifen by preventing estrogen synthesis, have proven superior to tamoxifen in preventing recurrences in postmenopausal patients with early-stage breast cancer. The current study, known as MAP.3 (Mammary Prevention Trial.3), included 4,560 postmenopausal women who were age 60 years or older and who were considered at high risk for breast cancer. After a median follow-up of 3 years, the group receiving exemestane had a 65% reduction in invasive cancers. There was also a 60% reduction of invasive breast cancer and preinvasive ductal carcinoma in situ—the earliest form of breast cancer—in the exemestane group, and fewer precancerous conditions were seen.

- Adding regional nodal irradiation decreases recurrences in women with early-stage breast cancer. Women with breast cancer that has
spread to the lymph nodes are typically treated with breast-conserving surgery (also known as lumpectomy) and surgery to remove many of the lymph nodes under the arm, which are followed by radiation to the entire breast (whole breast irradiation [WBI]) to reduce the likelihood of recurrence. If a woman’s cancer is considered high-risk for recurrence (such as in the cases of larger tumor or of a tumor that has spread to more than three underarm or axillary lymph nodes), radiation is frequently administered to the entire region (regional node irradiation [RNI]) as well. The region consists of the lymph node basins under the arm, above the collar bone (supraclavicular), and beneath the sternum (internal mammary). However, for women with one to three cancer-positive nodes, the benefit of adding RNI has been unclear.

A randomized phase III trial showed that, in women with early-stage breast cancer with one to three positive lymph nodes (or high-risk, node-negative breast cancer), additional radiation treatment to the regional lymph nodes reduces cancer recurrences both near the tumor site and in other parts of the body. The study enrolled 1,832 women; most of the women (85%) had one to three positive lymph nodes, and a smaller proportion of the women (10%) had high-risk, node-negative breast cancer. All women had been treated with breast-conserving surgery and adjuvant chemotherapy or hormone therapy. The participants were randomly assigned to receive WBI alone or WBI plus RNI.

After five years, 90% of women in the RNI group experienced no recurrences compared with 84% of women in the WBI group. The RNI group also had a lower rate of recurrence nearer the tumor site (3% v 6%) and a lower rate of cancer recurrences in other parts of the body (8% at 5 years compared with 13% in the other group). These results should encourage radiation oncologists to discuss with their patients a more extended radiotherapy field to reduce the risk of recurrence.

**Notable Advances**

Targeting HER2 with drug combinations more effective than single agents. Although the monoclonal antibody trastuzumab (Herceptin; Genentech) is effective in treating many patients with breast cancer tumors that are positive for the HER2 protein, a significant number of tumors either do not respond to this drug or become resistant to it. Clinicians have recently begun conducting trials exploring dual targeting of HER2, adding one or multiple HER2-targeted breast cancer drugs to trastuzumab in an attempt to improve or extend treatment response. This strategy proved effective in two trials this year, and larger, longer-term trials (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation [ALTO] and Neo-ALTO) are currently evaluating whether this approach ultimately extends survival when given after surgery.

In the phase II Chemotherapy, Herceptin and Lapatinib in Operable Breast Cancer (CHER-LOB) trial, researchers found that women with stage II or III breast cancer who received chemotherapy before surgery responded better to treatment with a combination of trastuzumab and the tyrosine kinase inhibitor lapatinib (Tykerb; GlaxoSmithKline, Philadelphia, PA) than to treatment with either lapatinib or trastuzumab alone with chemotherapy. Investigators measured the complete disappearance of invasive tumor in the breast and axillary lymph nodes in the 121 patients who participated in the study. They found a pathologic complete response of 28% in the trastuzumab-only arm, 32% in lapatinib-only arm, and 48% in the combination arm.

A second study, the randomized phase II Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (Neosphere), showed that a combination of the chemotherapy drug docetaxel and the monoclonal antibodies pertuzumab (Omnitarg; Genentech, South San Francisco, CA) and trastuzumab is more effective against HER2-positive breast cancer than chemotherapy with either antibody alone. In the trial, investigators randomly assigned 417 women with either stage II or stage III HER2-positive breast cancer to four arms to test the effectiveness of the two HER2 antibodies with or without the chemotherapy drug docetaxel before surgery. They found that treatment with pertuzumab, trastuzumab, and docetaxel resulted in a 46% pathologic complete response rate compared with 24% with trastuzumab/docetaxel, 29% with trastuzumab/docetaxel (the standard therapy), and 18% with trastuzumab/pertuzumab.

**PARP inhibitor trial shows no improvement in survival in metastatic triple-negative breast cancer.** PARP inhibitors are a class of drugs that target a key enzyme involved in DNA repair, especially in the repair of tumor cells. Although early-stage trials involving PARP inhibitors have shown promise in breast, ovarian, and others cancers, no PARP inhibitors have been approved for cancer therapy as yet.

In an earlier randomized phase II study, the addition of the PARP inhibitor iniparib to the chemotherapy drugs gemcitabine and carboplatin improved response rates, progression-free survival, and overall survival in 123 women with metastatic triple-negative breast cancer, a particularly aggressive and difficult-to-treat cancer in which tumors lack estrogen and progesterone receptors and do not over express the HER2 protein. Overall survival increased from 8 months with gemcitabine/carboplatin to 12 months with the addition of iniparib.

However, in the past year, a larger phase III trial of gemcitabine and carboplatin along with iniparib in triple-negative breast cancer did not support the results seen in the phase II trial. In the phase III study, investigators randomly assigned 519 women with stage IV triple-negative breast cancer to gemcitabine/carboplatin or to gemcitabine/carboplatin/iniparib. The researchers found that the addition of iniparib did not improve survival.

The contrasting results between the first, smaller randomized phase II trial and the larger randomized phase III trial underscore the need to conduct carefully controlled, adequately powered studies to clarify promising results in a preliminary study. Additional research is needed to better understand the potential use of PARP inhibitors in this type of breast cancer, including identifying a biologic subset of breast cancers most likely to benefit.

Cancers of the CNS include those of the brain and spine. This year, a report showed that a gene may serve as a prognostic biomarker in newly diagnosed glioblastoma, and a companion study also provided evidence of the predictive value of four biomarkers for glioblastoma outcome. A third report showed the importance of the lack of a certain gene in glioblastoma development and as a potential drug target. Lastly, scientists identified a host of genetic alterations in a childhood brain cancer that may ultimately guide drug development and therapy.
Notable Advances

Study shows genetic biomarker predicts glioblastoma survival. Glioblastoma is the most common and deadly type of brain tumor. For patients with newly diagnosed glioblastoma, the outlook can be poor. Patients usually survive fewer than 6 months after diagnosis without treatment; after surgery, tumors often regrow rapidly, and standard treatment with radiation and chemotherapy extend median survival to approximately 18 months.

Still, it has been difficult to predict which patients with glioblastoma will do well with radiation therapy and adjuvant chemotherapy with the drug temozolomide. Some studies have indicated that patients whose glioblastoma carries a silenced methyl guanine methyl transferase (MGMT) gene have better survival and that intense temozolomide treatment can reduce levels of the MGMT enzyme in the blood and perhaps the tumor. The MGMT enzyme is an important factor in chemotherapy resistance to glioblastoma.

However, a randomized phase III trial led by the Radiation Therapy Oncology Group, a National Cancer Institute (NCI) –supported clinical trials group, showed that giving intense temozolomide with standard radiation did not help patients with newly diagnosed glioblastoma to live longer than with the usual dose. Although the study did not find survival differences among two treatment groups, the investigators found that MGMT status predicted overall survival, confirming the prognostic value of the MGMT gene. When they analyzed tumor tissue for MGMT, they found that patients whose tumors had silenced MGMT had better overall survival than those whose tumors did not (21 months vs 14).

In a companion study using the tumor samples from the same trial, researchers retrospectively evaluated four biomarkers or groups of biomarkers, showing that they could predict clinical outcome in glioblastoma. The authors proposed that the use of these biomarkers could improve the way glioblastomas are categorized by risk and could lead to the development of personalized therapies. Lack of gene linked to poor glioblastoma survival. Studies have shown that nearly all glioblastomas, the most common adult brain cancer, have alterations in the epidermal growth factor receptor (EGFR) gene, including overactive EGFR proteins or mutations in the gene itself. Yet, targeting this pathway with drugs has not been effective. A new study showed that the deletion of NFKBIA, a gene that inhibits the EGFR signaling pathway, also affects tumor formation, increases chemotherapy resistance and worsens survival; this may provide another target for treatment.

Researchers have previously found that glioblastomas with low NFKBIA expression were resistant to treatment with the chemotherapy drug temozolomide. In the current study, investigators analyzed 790 tumor samples collected from patients with glioblastoma between 1989 and 2009 and compared the results with outcomes of 570 current patients with glioblastoma. They found NFKBIA deletions in a high proportion of the samples (nearly 25%). They also confirmed earlier findings about EGFR, identifying alterations in the gene in about one-third of these samples. Defects in NFKBIA have been found in other cancers, but this is the first study to our knowledge to implicate the deletion of NFKBIA as contributing to glioblastoma. The authors suggest that discovery of the role of NFKBIA deletion in glioblastoma, and its effect on survival, could potentially improve the ability to predict a patient’s prognosis and, in turn, may play a role in choosing the most effective treatment.

Molecular characterization of medulloblastoma reveals new mutation patterns and may lead to personalized therapies. Brain tumors are the leading cause of childhood cancer deaths, and medulloblastoma is the most common malignant brain tumor in children, accounting for as many as 25% of pediatric brain tumors. Although approximately two-thirds of patients can be effectively treated, the therapies (including radiation therapy) can have long-term effects on learning and cognition.

In a new study, researchers characterized the most common genetic alterations in medulloblastoma, making it the first pediatric solid tumor to be genetically sequenced. Characterizing commonly affected genes in medulloblastoma and other pediatric cancers may allow for more accurate molecular classification of the disease and better prognosis, in addition to identifying molecular drug targets and leading to more personalized cancer care. This would be especially critical for pediatric brain tumors, in which some current therapies, particularly radiation, can be extremely toxic. The study found mutations in two predominant genes (MLL2 and MLL3) that are likely involved in the cancer’s development. They also found that, overall, medulloblastoma had fewer mutations than other forms of solid tumors. The results of these studies will likely guide development of drugs that target these key genes. Eventually, the results may be used to personalize care by using the genetic profile of patients’ tumors to select the most appropriate type and intensity of therapy.

GI cancers include those of the esophagus, stomach, liver, pancreas, biliary tract, colon, rectum, and anus. This year, researchers provided new evidence supporting extended use of a key drug for GIST. In addition, the FDA approved three new drugs that extend survival for GI cancers, including two drugs for locally advanced and metastatic neuroendocrine pancreatic cancer and one for advanced gastric cancer.

Major Advance

Three years of imatinib therapy improves survival for high-risk GIST. The use of the targeted kinase inhibitor imatinib (Gleevec) has greatly improved survival in patients with GISTs. GISTs usually begin in the stomach or intestine. Imatinib targets two abnormal proteins involved in the development and growth of GIST. Although there is evidence that giving imatinib to patients for 1 year after surgical removal of the tumor reduces the likelihood of recurrence, whether 1 year is the most effective length of treatment has been questioned.

This year, a phase III trial answered that question, showing that 3 years of treatment with imatinib after surgery in patients with high-risk GISTs significantly improved both overall and recurrence-free survival compared with 1 year of treatment. In the study, 400 patients with GISTs who were at high risk for recurrence were randomly assigned to either 1 or 3 years of imatinib after surgery. After a median follow-up time of 54 months, the investigators found that 5-year recurrence-free survival was higher in the 3-year group (66%) compared with the 1-year group (48%). Similarly, the 5-year overall survival for the 3-year group was higher (92%) compared with the 1-year group (82%).
Notable Advances

Trastuzumab approved for metastatic gastric cancer. In late 2010, the FDA approved trastuzumab (Herceptin), in combination with the chemotherapy drugs cisplatin and either capecitabine or fluorouracil, for the treatment of patients with gastric cancer whose tumors express high levels of the HER2 protein. The approval was based on results of the phase III ToGA (Trastuzumab for Gastric Cancer) trial, in which 594 patients with advanced HER2-overexpressing gastric cancers were randomly assigned to receive chemotherapy alone or in combination with trastuzumab. Patients treated with trastuzumab and chemotherapy lived longer than patients who received chemotherapy alone (median: 14 vs 11 months). ToGA is the first trial of a therapy for patients with these cancers that resulted in a median survival of more than 1 year.

Sunitinib, everolimus approved for rare type of pancreatic cancer. The FDA approved two drugs in May 2011 for the treatment of advanced pancreatic neuroendocrine tumors that cannot be surgically removed or that have spread to other parts of the body. Both were shown to more than double the time it took for cancer to progress compared with treatment with a placebo. The approval of these two new drugs increases treatment options for the disease, which previously consisted of only interferon and chemotherapy.

- Everolimus (Afinitor; Novartis) targets an important signaling molecule in tumor cells called mammalian target of rapamycin (mTOR). Its approval was based on a clinical trial of 410 patients with metastatic or locally advanced disease who received either everolimus or placebo. Patients treated with everolimus lived more than twice as long—a median of 11 months without the cancer worsening—compared with a median progression-free survival of 5 months in patients who received placebo.

- Sunitinib (Sutent; Pfizer) inhibits the vascular endothelial growth factor (VEGF) receptor (VEGFR), which is involved in the development of cancer growth–fueling blood vessels. The drug’s approval was based on data from a randomized study of 171 patients with metastatic or locally advanced pancreatic neuroendocrine tumors who received sunitinib or placebo. Patients treated with sunitinib lived more than twice as long without their disease progressing (median, 11 months) compared with those who received placebo (5 months).

Major Advance

Abiraterone acetate approved for patients with advanced hormone-refractory prostate cancer. In April 2011, the FDA approved abiraterone acetate (Zytiga), in combination with the drug prednisone, to treat patients with metastatic hormone-refractory prostate cancer who have received prior treatment with docetaxel. Abiraterone blocks the production of male sex hormones (such as testosterone) and androgens, which fuel the growth of prostate tumors. Prostate cancer is considered hormone-resistant when the drugs or surgery used to reduce testosterone production or block its effects no longer work and the cancer continues to grow. Hormone-refractory (or castration-resistant) prostate cancer has been extremely difficult to treat. This drug will help many patients who, until recently, had few options.

The drug’s approval was based on results from a study of 1,195 patients with hormone-refractory prostate cancer in which patients received either abiraterone in combination with prednisone or a placebo with prednisone. Patients who received the abiraterone-prednisone combination had a median overall survival of 15 months compared with 11 months for patients receiving the placebo-prednisone combination. This oral drug had an excellent safety profile. Only one other agent, cabazitaxel (Jevtana), an intravenous chemotherapy drug with a high rate of adverse effects, has been shown to prolong survival in patients who no longer respond to docetaxel.

Notable Advances

Multitargeted agent cabozantinib shows clinical activity against advanced prostate cancer and reverses bone metastases and pain. A phase II trial showed that cabozantinib, which inhibits MET and VEGFR2 (protein kinases involved in the development and progression of prostate cancer), reversed or slowed tumor growth in patients with advanced prostate cancer. The trial was designed as a randomized discontinuation trial, in which those who had partial responses stayed on the drug for 12 weeks; those with stable disease were randomly assigned to cabozantinib or placebo; and those with progressive disease were removed from the trial.

Of 168 patients enrolled onto the study, 100 were evaluable with progressive, metastatic hormone-refractory prostate cancer. Overall, the disease control rate (partial response and stable disease) at week 12 was 71% for patients treated with cabozantinib. Tumor shrinkage occurred in 84% of patients. The objective response rate (partial tumor shrinkage and complete disappearance of tumor) at week 12 was 5%.

Researchers reported, in addition to evidence of controlling prostate cancer progression, that 56 (86%) of 65 patients with bone metastases treated with cabozantinib experienced either partial or complete disappearance of bone metastases according to bone scans, often with a decrease in the blood tests indicative of bone damage and with significant pain relief. Among the 28 patients who required narcotics for severe bone pain at the beginning of the trial, 64% reported improved pain, and 46% either decreased use of or stopped taking narcotics.
Early-stage trial shows novel multitypered agent cabozantinib has significant effect on melanoma and several other advanced cancers. A phase II trial showed that treatment with cabozantinib resulted in either tumor shrinkage or slowed tumor growth in patients with various advanced cancers. Cabozantinib targets MET, VEGFR2, RET, and KIT, a group of protein kinases involved in the development and progression of many cancers. The drug was particularly active in advanced prostate, ovarian, and liver cancers, which are historically resistant to available therapies, as well as some types of melanoma including ocular. The drug also fully or partially suppressed bone metastases in patients with prostate and breast as well as other cancers.

The trial was designed as a discontinuation trial, in which all patients received the drug for 12 weeks. After 12 weeks, those who experienced responses continued to receive cabozantinib. Patients with stable disease (ie, the cancer did not grow or progress) were randomly assigned to continue to receive cabozantinib or placebo; patients with progressive disease were removed from the trial. This novel type of clinical trial design more quickly evaluates the disease-stabilizing activity of agents like cabozantinib compared with the traditional model of randomly assigning all patients to either the experimental arm or placebo.

This study evaluated patients after the initial 12 weeks of treatment with cabozantinib. Among 398 evaluable patients of 483 patients enrolled with the nine different types of cancer included in the trial, the response rate (percentage of patients with measurable tumor shrinkage) was 9% (34 of 398 patients). The overall disease control rate was 54% (264 of 483 patients) at week 12. The highest disease control rates (ie, partial response and stable disease) at week 12 (before random assignment) were 76% for liver cancer (22 of 29 patients), 71% for prostate cancer (71 of 100 patients), and 58% for ovarian cancer (32 of 51 patients). At least 11 of 60 patients remained on study with a 25- to 80-week follow-up at the time the study was reported.

Of 65 patients with melanoma who were evaluable at 12 weeks, 60% showed some tumor shrinkage with a 47% disease control rate at 12 weeks. Such responses were seen in patients with both ocular and skin melanoma subtypes. For those patients with melanoma who experienced a reduction in bone metastases, many also experienced significant pain relief and improved quality of life. At the time of the analysis, at least 17% of patients were still on study with stable disease after 25 to 80 weeks of follow-up and continued to receive cabozantinib.

Cabozantinib seems to be the first agent with significant activity in suppressing the activity of prostate and other cancers as seen by using bone scans, and in treating ocular melanoma, which represents a small proportion of patients with melanoma. In addition, cabozantinib seems to be active in a range of melanoma subtypes, unlike the targeted drug vemurafenib, which is effective only in patients with melanoma with tumors carrying a mutation in the BRAF gene.

Study identifies most effective second-line targeted therapy for advanced kidney cancer. Metastatic renal cell carcinoma is extremely difficult to treat, and fewer than 10% of patients live more than 5 years after diagnosis. Although several drugs have been approved by the FDA for metastatic renal cell carcinoma, and physicians understand which agents to use first on the basis of an individual’s risk profile, the most effective sequence for using these agents as second-line therapy and beyond has been debated.

A new study—the first phase III trial of a second-line therapy for metastatic disease to our knowledge—showed that axitinib, which inhibits VEGFR, helped patients with metastatic renal cell cancer live significantly longer without their disease worsening compared with the similar targeted therapy sorafenib (Nexavar; Bayer Pharmaceuticals, Berlin, Germany; Onyx Pharmaceuticals, South San Francisco, CA). In the study, 723 patients with clear-cell metastatic renal cell carcinoma who had completed initial therapy were randomly assigned to receive second-line therapy with either axitinib or sorafenib. Researchers found that patients treated with axitinib lived longer without disease progression (median, 7 months) than those receiving sorafenib (median, 5 months). Of the patients in the axitinib group, 19% had some tumor shrinkage compared with only 9% for patients who received sorafenib.

Denosumab approved to prevent cancer-related bone problems in patients with prostate and other advanced cancers. The FDA approved denosumab (Xgeva; Amgen, Thousand Oaks, CA) in November 2010 to help prevent skeletal-related events in patients with prostate, breast, and other cancers that have metastasized and damaged the bone. Denosumab is a monoclonal antibody that targets a protein involved in cancer-related bone destruction, the receptor activator of nuclear factor kappa B ligand. It is one of three FDA-approved drugs for skeletal-related events. In men with prostate cancer, the median time to a skeletal-related event was 21 months with denosumab compared with 17 months with zoledronic acid.

Gynecologic cancers include cancers of the cervix, uterus, ovaries, fallopian tubes, peritoneum, vagina, and vulva. This year brought several advances in ovarian cancer, highlighting new progress in identifying the underlying genetic drivers of the disease and therapies that target them. Researchers reported data on two targeted drugs: bevacizumab (a drug designed to interfere with growth of the blood vessels that fuel tumor growth) and olaparib (a drug designed to interfere with DNA repair in cancer cells). Two studies involving these drugs reported data about a relatively new strategy called maintenance therapy or longer-term drug therapy after standard chemotherapy. Lastly, researchers from the Cancer Genome Atlas project unveiled new clues about the inner workings of ovarian cancer cells, which will guide ongoing research efforts and new drug development.

Major Advances

Bevacizumab delays cancer progression in recurrent ovarian, peritoneal, and fallopian tube cancers. Ovarian cancer is often difficult to treat, because it is usually diagnosed in an advanced stage and, despite initial surgery and chemotherapy, most cancers recur and require additional courses of chemotherapy. However, results from a randomized trial showed that women with recurrent ovarian cancer who received a combination of bevacizumab and platinum-based chemotherapy lived significantly longer without disease progression than those treated with the standard course of platinum-based chemotherapy alone. By extending the time patients can live without disease progression and without additional treatment with chemotherapy, the results suggest that, increasingly, ovarian cancer may be treated as a chronic disease. In this case, bevacizumab is used as maintenance therapy.
In the phase III multicenter OCEANS trial, 484 patients were randomly assigned to receive bevacizumab, an anti-VEGF monoclonal antibody, and chemotherapy (carboplatin and gemcitabine) or a placebo with the same chemotherapy regimen. Bevacizumab or placebo was continued after the completion of chemotherapy until the cancer progressed. After a median follow-up of 24 months, median progression-free survival was 12 months for patients in the bevacizumab group compared with 8 months for patients treated with chemotherapy alone, a 52% reduction in the risk of disease progression. In addition, researchers found that 79% of women treated with bevacizumab experienced significant tumor shrinkage compared with 57% of women treated with chemotherapy alone. The tumor shrinkage also lasted longer in the bevacizumab group (10 vs 7 months).

The investigators said the next step is to evaluate the role of bevacizumab in combination with chemotherapy for patients in whom chemotherapy has stopped working and to combine bevacizumab with other emerging therapies such as PARP inhibitors.

**Bevacizumab extends progression-free survival for some patients with newly diagnosed ovarian cancer.** Interim data from a large, randomized phase III trial suggest that adding bevacizumab to standard carboplatin and paclitaxel chemotherapy for treatment of newly diagnosed ovarian cancer may offer a survival benefit over treatment with chemotherapy alone, particularly for patients with more aggressive disease.27

In the Seventh International Collaborative Ovarian Neoplasm (ICON7) study, 1,528 women with newly diagnosed high-risk or advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer were randomly assigned to receive either chemotherapy alone or chemotherapy concurrently with bevacizumab followed by maintenance bevacizumab for a total duration of 12 months. An interim analysis of overall survival requested by regulatory authorities found that there were fewer deaths in the bevacizumab group than in the standard therapy group (178 vs 200, respectively). This represents a 15% overall reduction in risk of death but was not considered significant. However, when investigators conducted additional analysis of the results in patients at highest risk, they found a significant benefit in the bevacizumab group. Specifically, among women with stage III ovarian cancer whose tumors were larger than 1 cm after surgery and all patients with stage IV disease, the risk of death was 36% lower in the bevacizumab arm (79 vs 109 deaths in the standard therapy group).

**Notable Advances**

**Cancer Genome Atlas provides molecular details and potential drug targets for ovarian cancer.** The majority of deaths in ovarian cancer (approximately 70%) occur in patients who are diagnosed with advanced high-grade ovarian cancer or serous adenocarcinoma. Although surgery and chemotherapy can be effective, most patients experience recurrences. The overall 5-year survival is approximately 31%, making the search for new drug targets and improved therapies a priority for cancer researchers. A major hurdle for research efforts has been the fact that the genes involved in high-grade serous tumors tend to be more complex than many other forms of cancer. But using more powerful genomic technologies, the Cancer Genome Atlas research project shared results this year from the first comprehensive effort to our knowledge to map the genome of ovarian cancer, pinpointing several common molecular features.28

Specifically, researchers analyzed 489 high-grade serous ovarian adenocarcinomas and DNA sequences from 316 of these tumors. They discovered mutations in the TP53 gene, which helps suppress tumors, in nearly all tumors (96%) and BRCA mutations in 22% of tumors. In addition, approximately 50% of tumors were found to have defects that interfere with DNA repair; drugs targeting this specific molecular feature (called PARP inhibitors) are being evaluated in late-stage clinical trials. These findings reinforce the promise of ongoing research on PARP inhibitors and will inform the development of future drugs with the ultimate goal of enabling physicians to tailor patient therapy to the specific genetic abnormalities in individual tumors.

**Randomized study shows that maintenance therapy and PARP inhibitors could play important roles in the treatment of relapsed ovarian cancer.** PARP inhibitors are a new class of molecularly targeted agents that inhibit the enzyme PARP, which is involved in DNA repair. Tumors in up to half of women with high-grade serous ovarian cancer, the most common type of ovarian cancer, may have a DNA repair deficiency that makes them more susceptible to treatment with PARP inhibitors.

A randomized trial showed that maintenance therapy with the PARP inhibitor olaparib significantly improved progression-free survival in patients with ovarian cancer with relapsed disease.29 The multicenter, international study randomly assigned 265 women with relapsed high-grade serous ovarian cancer to either olaparib or placebo after standard chemotherapy. Researchers found that progression-free survival was significantly longer in the group receiving olaparib than in the placebo group (median, 8 vs 5 months).

Several PARP inhibitors are being tested in phase I and phase II clinical trials, either alone or in combination with chemotherapies and radiation. Previous studies have shown that some patients with abnormal BRCA genes, a feature that increases the risk of developing breast and ovarian cancers, are most likely to benefit from treatment with PARP inhibitors.

Larger trials of PARP inhibitors are underway, and if these results are confirmed, olaparib could become an important treatment for women with advanced or high-risk ovarian cancer. The findings also add to the body of research on maintenance therapies as an additional option to prevent or delay recurrences after standard chemotherapy.

**LUNG CANCERS**

Lung cancers account for 28% of cancer deaths in men and 26% in women. Although death rates in men have been decreasing since 1990, they have only recently begun to decrease in women, paralleling the more recent increase in smoking cessation among women, although not all lung cancers are caused by smoking.

Important new studies in the past year focused on screening to improve early detection of lung cancer, new personalized approaches to treatment that target specific lung cancer mutations, and long-term maintenance therapy to improve survival among patients with advanced lung cancer.

**Major Advances**

**Large study shows low-dose CT scanning reduces lung cancer death rate.** Lung cancer is usually detected at an advanced stage when cures with surgery are far more difficult to achieve, highlighting the need for earlier detection strategies. Until now, potential screening approaches have had little impact on reducing the risk of dying as a
result of the disease. However, results published this year from a large national screening trial of more than 50,000 current and former heavy smokers found that annual low-dose CT scans reduced the death rate from lung cancer by 20% compared with screening with annual chest x-rays.30

In the study, 53,454 individuals ages 55 to 74 years at high risk for lung cancer—they smoked the equivalent of a pack of cigarettes a day for 30 years—were randomly assigned to receive three annual screenings with either low-dose CT or single-view chest x-ray and were observed for a median 6.5 years. The study was halted after 8 years when researchers saw a clear benefit with routine CT scanning.

The rate of positive screenings was 24% in the low-dose CT group and 7% in the chest x-ray group over the three screening rounds. The false-positive rates were high (approximately 95%) in both groups, which likely resulted from chronic inflammation in the lungs associated with smoking, suggesting a need to carefully select patients for screening. Overall, there were 1,060 cancers diagnosed in the low-dose CT group compared with 941 in the chest x-ray group and 356 and 443 for the low-dose CT and chest x-ray groups, respectively, with 94 cancers in the low-dose CT group identified as false positives.

Notable Advances

New consortium improves treatment outcome by matching tumor mutations to drug selection. The ability to detect mutations and other genetic alterations that drive the development of lung cancer and subsequently target them with specific drugs (as are the cases for alterations in the epidermal growth factor receptor [EGFR] and the ALK genes) has changed the management of the disease.

In a prospective study this year, the 14-member Lung Cancer Mutation Consortium (LCMC) has identified at least one of 10 recognized genetic driver mutations in tumors in nearly two-thirds of patients with lung adenocarcinomas.31 Investigators suggest that the LCMC program is an important molecular profiling model showing that patients’ tumors may be analyzed for mutations at diagnosis in a systematic way and such information can be given to physicians to help guide treatment selection and encourage participation in clinical trials.

The LCMC enrolled more than 1,000 patients with advanced-stage (IIIB/IV) lung cancers to test lung tumors for 10 driver mutations including K R A S, EGFR, HER2, BRAF, PIK3CA, AKT1, MEKI, and NRAS as well as for ALK rearrangements and MET amplifications. Many of these genetic mutations can be targeted by drugs currently approved for lung cancer and other forms of cancer, and some can be targeted by drugs being tested in clinical trials.

Earlier this year, ASCO issued a provisional clinical opinion advocating for routine mutation testing for the EGFR gene in certain patients with advanced lung cancers to help decide the most effective treatment. Physicians in this study used these mutation test results to choose the appropriate drug to match the mutation or gene abnormality. Just as the way drugs such as trastuzumab (Herceptin) and lapatinib (Tykerb) target the HER2 protein in breast cancers, crizotinib (Xalkori) may be used for patients with lung cancer who carry alterations in the ALK gene. Patients with other types of driver mutations that lack specific drugs are offered participation in trials open at the LCMC institutions that test agents aimed at the particular mutations identified.

As a result of the LCMC program, such multiplex testing for many tumor mutations at the same time is now routine at several LCMC sites. Although this consortium focuses on patients with advanced lung cancer, some cancer centers already routinely analyze all tumors for mutations. The same tumor mutation identification process can be used for other subtypes of lung cancer and is applicable for other cancers.

Additional pemetrexed treatment extends survival in patients with advanced lung cancer. Although the combination of the chemotherapy drugs cisplatin and pemetrexed (Alimenta; Eli Lilly, Indianapolis, IN) is often effective in bringing patients with advanced non–small-cell lung cancer into remission, it eventually loses its effectiveness.

A phase III randomized trial showed that maintenance therapy with pemetrexed reduced the risk of disease progression in patients with advanced lung cancers who also received pemetrexed as part of their initial chemotherapy regimen compared with placebo or best supportive care.34 This is the first large trial to demonstrate that using longer-term maintenance therapy with one of the same drugs included in initial treatment (termed “continuation maintenance”) can improve outcomes. The study provides physicians with a new treatment option after first-line therapy with pemetrexed.

In the study, 939 patients were given the standard four courses of first-line treatment with pemetrexed and cisplatin. Of those patients, 539 individuals whose cancer did not progress during this treatment were randomly assigned to maintenance pemetrexed and best supportive care (n = 359) or placebo and best supportive care (n = 180) until the cancer progressed. Best supportive care entails nonanticancer therapy, including treatment for pain and infections and to stimulate appetite. The investigators found that pemetrexed maintenance resulted in a 38% reduction in the risk of disease progression. The median progression-free survival was 4 months for those in the pemetrexed group compared with 3 months in the placebo group. The trial will continue to observe these patients to see whether those given pemetrexed maintenance will have improved survival.
Advanced melanoma is one of the most deadly forms of cancer. In the past three decades, melanoma incidence has increased faster than any other cancer type. In recent years, scientists have identified several important genetic mutations in melanoma cells that have led to the development of new therapies that target these specific molecular defects. At the same time, new insights into the immune system have helped in the development of novel therapies that mobilize a patient's immune system to fight the disease.

This year, researchers reported data on the first-ever, to our knowledge, molecularly targeted therapy to improve survival for patients with advanced melanoma, which led to the drug's approval shortly thereafter. A second study reported continued positive results on an immune therapy—findings that will open major avenues of research on combining this therapy with other effective drugs. Finally, an early-stage study found that combining oral targeted therapies had promising clinical activity against advanced melanoma.

**Major Advances**

**Phase III results show BRAF inhibitor improves survival in advanced melanoma, leading to FDA approval.** Results from a trial reported this year showed that the drug vemurafenib (Zelboraf), which targets a common mutation in melanoma, improved overall survival when compared with dacarbazine in patients with advanced melanoma. Vemurafenib, which received FDA approval in August 2011, could become a new standard treatment for patients with melanoma who have the V600E BRAF gene mutation. Approximately half of patients have tumors that carry this mutation, which makes this drug an important step toward tailoring patient care in melanoma.

A phase III trial compared treatment using vemurafenib with treatment using the standard drug dacarbazine in 675 patients with previously untreated, inoperable stage IIIIC or stage IV metastatic melanoma that carries a V600E BRAF gene mutation. The researchers found that 48% of patients receiving vemurafenib experienced tumor shrinkage compared with 5% in the dacarbazine group. Vemurafenib reduced the risk of disease progression by 74% as compared with dacarbazine. Those who received vemurafenib had an overall survival rate of 84% at 6 months compared with 64% for those in the dacarbazine group. The FDA approval of vemurafenib, which was based on these results, is only for patients with late-stage melanoma who have a V600E gene mutation.

Although few patients who received vemurafenib experienced problems with toxicity, approximately 20% developed a low-grade skin cancer, squamous cell carcinoma, which was treatable. The researchers plan to next test vemurafenib in combination with the monoclonal antibody ipilimumab (Yervoy).

*First-line ipilimumab plus chemotherapy improves overall survival in metastatic melanoma.* For years, investigators have tried to harness the body's immune system to fight melanoma with relatively little success. However, in 2010, investigators announced results from the first phase III trial to our knowledge that shows that ipilimumab, an immune therapy, improved survival in patients with advanced melanoma when used alone. This trial resulted in the FDA approval of ipilimumab in March 2011. Ipilimumab is a monoclonal antibody that represents a new class of drugs that allows the immune system's T cells to seek and destroy melanoma cells. This year, a phase III study found that treatment with ipilimumab, combined with dacarbazine, improved overall survival in patients with metastatic melanoma compared with patients treated with dacarbazine alone. In this study, 502 patients with metastatic melanoma were randomly assigned to ipilimumab plus dacarbazine (n = 250) or placebo and dacarbazine (n = 252). The overall survival rate for the combination after 1 year was 47% compared with 36% for dacarbazine alone and, at 3 years, 21% for the combination versus 12% for chemotherapy alone.Investigators also found that the median overall survival was better for those who received the combination (11 v 9 months for those given only dacarbazine).

**Notable Advance**

**Combining oral targeted therapies shows early antitumor activity for advanced melanoma.** Normally, a phase I trial, the first step in the clinical drug evaluation process, primarily focuses on the safety and toxicity of an experimental agent; it is rare to see any clear signs of treatment effectiveness. However, a phase I trial this year showed that a combination of two oral targeted therapies (GSK1120212 [GlaxoSmithKline, Middlesex, United Kingdom], an agent that inhibits the MEK protein, and GSK2118436 [GlaxoSmithKline], a BRAF protein inhibitor) appears to have substantial antitumor activity in patients with advanced melanoma. The trial results are important because they show promising synergistic anticancer activity for two therapies that target common genetic abnormalities in advanced melanoma.

The phase I/II trial included 43 patients with advanced melanoma. Of 16 evaluable patients, 13 experienced partial tumor shrinkage, and three experienced no additional tumor growth for an overall response rate of 81%. This trial suggests that targeting both the BRAF protein (as was done with vemurafenib) and another protein in the same pathway (MEK) may improve outcomes for patients.

### SARCOMAS

There are more than 70 types of sarcomas and more than 50 subtypes of soft-tissue sarcomas, which can arise in fat, muscle, and nerve tissue. Although treatment with surgery, chemotherapy, and radiation is standard for many patients, researchers are beginning to see the results of phase II and III trials that show the effectiveness of targeted therapies for soft-tissue sarcomas. At the same time, study results are helping investigators to unravel the molecular nuances of sarcomas, in turn enabling the development of better treatment strategies including prognostic and predictive markers and ways to personalize therapies for individual patients.

This year, significant progress has been made in the use of drugs that target various biologic pathways involved in sarcoma development and progression. A randomized trial found an effective treatment for metastatic soft-tissue sarcoma that progressed despite standard therapy, and another study showed that a drug that blocks the activity of a key cell growth–promoting protein improved progression-free survival among various types of advanced soft-tissue sarcomas.

**Notable Advances**

**Second-line treatment with antiangiogenic pazopanib improves progression-free survival in metastatic soft-tissue sarcoma.** Pazopanib

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(Votrient; GlaxoSmithKline), which is approved by the FDA for advanced kidney cancer, blocks cancer cell pathways that are associated with tumor growth and blood vessel formation. Preliminary research showed that pazopanib had activity in leiomyosarcoma, synovial sarcoma, and types of soft-tissue sarcoma. This year, a phase III trial found that pazopanib significantly extended the time it took for these tumors to progress (progression-free survival) in patients whose disease advanced despite previous treatment. The Pazopanib Explored in Soft-Tissue Sarcoma (PAL-ETTE) trial, 369 patients with metastatic soft-tissue sarcoma were randomly assigned to receive either pazopanib (n = 246) or placebo (n = 123). Researchers observed patients for a median of 15 months. The median progression-free survival was 5 months in patients treated with pazopanib compared with 2 months for patients given a placebo. Overall survival for the pazopanib group was also slightly longer, although the difference was not significant. Because pazopanib slowed down cancer growth, the results suggest that pazopanib blocks certain biologic pathways that help cancer to progress. Future efforts to break down the molecular makeup of these soft-tissue sarcoma subtypes may aid physicians in determining which patients are likely to benefit most from pazopanib. The study results are important because, for now, pazopanib has shown promising clinical activity as a second-line agent in difficult-to-treat metastatic disease. Angiogenesis agent brivanib delays disease progression in advanced soft-tissue sarcoma. An international, phase II randomized discontinuation trial showed that treatment with a single agent (brivanib) significantly improved progression-free survival compared with placebo in patients with advanced soft-tissue sarcoma who received previous chemotherapy. Brivanib is a novel agent that blocks two pathways (VEGF and fibroblast growth factor) instead of only one, which most widely used agents target. VEGF and fibroblast growth factor play roles in blood vessel growth and development. In the study, patients with inoperable soft-tissue sarcoma and no other treatment options received brivanib for 12 weeks. The trial was designed as a discontinuation trial in which those who had partial responses stayed on the drug; those with stable disease were randomly assigned to brivanib or placebo; and patients with progressive disease were removed from the trial. Of 251 patients enrolled, 76 were randomly assigned to continue to receive either brivanib or placebo beyond the original 12 weeks. Researchers found that patients who received brivanib after week 12 lived a median of 3 months without their cancer progressing compared with 1 month with placebo. In those 76 patients, they found a disease control rate (a combination of complete tumor disappearance, partial tumor shrinkage, and stable disease) of 30% overall. The drug also worked well in leiomyosarcoma, liposarcoma, angiosarcoma, and other types of sarcoma. The results provide a new treatment option for a group of patients who have historically been difficult to treat.

**ADVANCED CANCER CARE**

Although treatment advances have significantly increased cancer survival rates, thousands of patients in the United States face a diagnosis of metastatic cancer every year. For these patients, the priority is to provide both the most effective treatment for their cancer and palliative and other services to maximize quality of life. Palliative and/or hospice care specialize in helping patients manage pain and adverse effects and maintain a better quality of life, but research has long shown that many doctors and patients do not take advantage of these options. Earlier this year, ASCO published a statement recommending steps to ensure that all physicians initiate candid discussions about a patient’s illness and prognosis soon after diagnosis to help the patient and his family make informed decisions about treatment options. In addition, several studies this year provided insight into key areas in which advanced cancer care can be improved. One study found that both patients and caregivers benefit from receiving end-of-life care in a hospice compared with a hospital. Additionally, a major report explored the use of hospice care among Medicare recipients, identifying several specific areas for improvement. Finally, a survey showed that patient awareness of terminal illness did not adversely affect survival, and another study confirmed that hospice patients are less likely to have aggressive end-of-life care than those not in hospice.

**Notable Advances**

Where patients die affects both the patients and their caregivers. A study of patients with advanced cancer and their caregivers showed that individuals who died in a hospital or intensive care unit (ICU) had a worse quality of life at the end of their lives compared with those patients who died at home with hospice services. In addition, their caregivers were more likely to develop grief-related psychiatric illness. Researchers studied 342 patients with advanced cancer and their caregivers. Patients were observed from the time of study enrollment until death (median, 5 months). They assessed patient quality of life within two weeks of death. The researchers also evaluated caregiver mental health at the beginning of participation and six months after a patient’s death.

The investigators found that the type of care that patients received near the end of life mattered a great deal to both patients and their caregivers. Patients who died of cancer in an ICU or hospital reported more physical and emotional distress and worse quality of life than those who died at home with hospice. The study also found that caregivers of patients with cancer who died in ICUs had a fivefold greater risk of developing post-traumatic stress disorder compared with caregivers of patients who died at home with hospice services. Twenty-one percent (4 of 19) of caregivers of patients who died in the ICU or hospital developed post-traumatic stress disorder compared with 4% (6 of 137) of caregivers of those who died at home with hospice.

The researchers expected to find differences in patient quality of life on the basis of where the patient died, but they were surprised to find such striking differences in caregiver mental health during the grieving process. The authors emphasized that efforts aimed at reducing hospitalizations at the end of life or increasing the use of hospice services could have a substantial effect on the well-being of patients and their caregivers.

One-third of patients with poor prognosis spend the end of life in hospital, and many enter hospice late. The Dartmouth Atlas Project issued a report examining the care of Medicare patients older than age 65 years who were diagnosed with cancer with a poor prognosis, finding that care at the end of life varied across regions and academic medical centers. The report shows that many patients with advanced cancer spend significant time at the end of life in the hospital and do
not consistently receive hospice care that is aimed at maximizing quality of life. The report’s key findings include:

- In many regions and centers across the United States, patients with advanced cancer receive care at the end of life in hospice or some other palliative care setting. However, overall, more than one-third of patients with cancer with a poor prognosis spend their last days in the hospital or ICU. Approximately 60% of patients with cancer were hospitalized at least once during the last months of life.
- In at least 50 academic medical centers, less than half of patients with advanced cancer received hospice services during the last month of life. Many patients were enrolled within days of death, and patients and families seemed to benefit little from such care.

The authors suggest that conversations between health care providers and patients about end-of-life preferences should occur more consistently and sooner—in some cases within months or even weeks after diagnosis. They also point to research showing that palliative and hospice care may prolong life even as they improve its quality.

Awareness of terminal illness and entry into hospice or ICU does not cause physical or psychological harm to patients. Clinicians are often concerned about discussing a poor prognosis and palliative care/hospice options with patients, because they are afraid that it will take away hope for some individuals and affect their survival. However, a survey of terminally ill patients with cancer has shown that patients’ awareness that they are dying and whether they choose to enter either a hospice or ICU do not affect their survival.

In the Study to Understand Risks, Priority, and Issues at End-of-Life (SURPRISE), 44,619 patients were given questionnaires shortly after receiving a terminal cancer diagnosis from their physicians and observed throughout the course of their care. In a follow-up of 483 of these patients, the investigators showed that neither patient’s awareness of terminal illness nor use of palliative care services negatively affected survival. They found that patients who were aware of their terminal illness were more likely to use palliative care (71%) and less likely to enter an ICU (50%). The study showed that disclosing patients’ prognoses was not harmful and in fact helped them to make choices regarding their care.

Study shows that patients with terminal cancer not enrolled in hospice are more likely to receive diagnostic and testing procedures at the end of life. A large study of more than 14,000 men with terminal prostate cancer found that those enrolled in hospice care were less likely to have aggressive care at the end of life. 45

Of the more than 28,000 American men who die of prostate cancer annually, only one-third receive hospice care. Investigators examined Surveillance, epidemiology, and End Results (SEER)—Medicare data to measure hospice use and intensity of medical care in 14,521 men age 66 years or older who died of prostate cancer between 1992 and 2005. They wanted to characterize hospice use in this patient population and compare high-intensity care—including diagnostic and testing procedures—in the last 6 months of life and hospital care between those patients who did and did not enroll in hospice.

Patients who were not enrolled in hospice were more likely to receive diagnostic and testing procedures in the last 6 months of life and more likely to be admitted to the emergency room, hospital, or ICU. However, they noted that the proportion of patients using hospice before death increased over time as did the proportion of patients dying within 7 days of enrollment. The authors concluded that the study provides additional evidence that timely discussions regarding goals of care and referral to hospice can help prevent futile care at the end of life that actually lessens quality of life.

There has been remarkable progress in reducing cancer death rates in the last two decades thanks to improvements in screening, detection, and treatment. Yet, not all racial and ethnic groups in the United States have benefitted equally. New research in recent years has uncovered important differences in biology and cancer susceptibilities among various groups that could play a role in cancer-related disparities. At the same time, researchers continue to pay special attention to the effects of several factors, such as levels of income and education and access to care, that have a substantial effect on cancer outcomes. Better understanding of the causes of cancer disparities is needed to develop specific interventions aimed at reducing them.

To address some of these issues, ASCO recently published a policy statement advocating for policies and outlining specific strategies to ensure access to cancer care for the underserved including insurance reform, a reduction of economic barriers to quality health care, prevention and wellness, and research in health care disparities.

This year, researchers gained new insights into the effects of socioeconomic and educational differences on disparities in such areas as access to surgical and palliative care and their impact on minority and ethnic groups. In a large population-based study, investigators found racial and socioeconomic differences in hospice services among elderly insured patients with lung cancer, and a study of the New York City public hospital system found similar differences in access to ovarian cancer surgery. A special section of a large annual report described the connection between differences in educational levels and survival among various groups. Lastly, a study pointed to differences in survival improvements among blacks and whites with multiple myeloma.

Notable Advances

Hospice use among elderly patients with lung cancer differs by racial and socioeconomic levels. Hospice care provides compassionate care for individuals in the last phases of cancer. Previous studies have shown greater use of hospice among whites, individuals with higher educational level, and those who live in urban areas. But it has not been clear whether there are racial disparities in hospice use among ethnic minorities in urban versus rural areas and within socioeconomic levels.

Researchers examined hospice use in the last six months of life between 1991 and 2005 among 117,894 patients age 66 and older with advanced non–small-cell lung cancer on the basis of information from the SEER-Medicare database. Patients with advanced lung cancer account for approximately 34% of all hospice patients with cancer in the United States. The investigators found that, in urban areas and overall, patients with lung cancer who were black were 21% less likely to receive hospice services within the last six months of life compared with white patients; Asian/Pacific Islanders were 58% less likely, and Hispanic patients were 19% less likely. In rural areas, blacks were 21% less likely to receive hospice services than whites. 37

Overall, patients in the poorest socioeconomic levels were less likely to receive hospice care. When stratified by socioeconomic levels, blacks and Asians/Pacific Islanders obtained less hospice services compared with whites in each of the four socioeconomic level quarters.
Within the lowest socioeconomic group, Asian/Pacific Islanders were the least likely to receive services (70% less compared with whites within the poorest group). These findings point to the need to identify barriers, enhance support, and improve patient education for these populations about the benefits of hospice. This study is one of the first to examine cancer care of Asian/Pacific Islanders and suggests that this population is not sharing in the benefits of hospice care, which have been made broadly available with the advent of the hospice care movement begun nearly 40 years ago in Great Britain.

Ovarian cancer care differs between public and private hospitals. For women with ovarian cancer, in which approximately 75% of patients have advanced disease at diagnosis, appropriate surgical staging—including the removal of the ovaries, fallopian tubes, and uterus and the examination of various tissues in the abdominal cavity—is critical to determining how far the disease has spread and prognosis. In addition, comprehensive surgery to remove as much of the cancer as possible is closely linked to improved survival.

Although studies have shown that patients who receive their care from a gynecologic oncologist are more likely to undergo adequate surgery and have a higher survival than those who are treated by a gynecologist or general surgeon; only 40% of women with ovarian cancer are treated by gynecologic oncologists. Other studies have also found better outcomes for women treated by surgeons who are considered “high-volume,” meaning they more frequently perform ovarian cancer surgery. Additional studies have shown that blacks and Hispanics are less likely to receive standard ovarian cancer surgery.

In one of the first studies to describe the surgical management of patients with ovarian cancer in a large urban hospital system, investigators compared the care provided in New York City public hospital system with that provided in private hospitals in New York City between 2001 and 2006. The public hospital system provides care for patients without regard to insurance status and largely serves minority patients and recent immigrants.

Hospitals were stratified according to the availability of gynecologic oncologists, and surgeons were stratified by subspecialty training and volume of patients with ovarian cancer. Researchers found that patients treated in public hospitals were less likely to have their surgery performed by a gynecologic cancer surgeon than patients in private hospitals (57% v 74%) and less likely to be operated on by a high-volume surgeon (21% v 47%).

Because only 5% of ovarian cancer surgeries were conducted in public hospitals, these findings suggest that patients may benefit from being referred to hospitals that have the highest volume of ovarian cancer cases or have high-volume surgeons who practice at both public and private hospitals. The physician who conducted this research was a recipient of the Young Investigator Award given by ASCO’s Conquer Cancer Foundation.

New insight into link between cancer death rates and education level. Whereas overall cancer death rates have fallen by 22% for men and 14% for women between 1990 and 2007, death rates for individuals with lower socioeconomic status (defined by education, occupation, and other factors) showed little or no decrease, according to the American Cancer Society’s “Cancer Facts and Figures 2011 Special Section: Cancer Disparities and Premature Deaths.”

Many consider an individual’s education level a marker of socioeconomic status, and this report indicates that the gap in death rates between those with high and low education levels progressively grew during that 17-year period. In both black and white men between the ages of 25 and 64 years, the cancer death rate was twice as high in the least educated compared with the most educated patients in 1993. By 2007, there was nearly a threefold difference. The largest educational differences overall were seen in lung cancer, in which the death rate for men was five times higher for the least educated than for the most educated patients.

Many of the disparities in cancer outcomes among racial and ethnic minorities, the authors suggest, reflect low education levels and income, recent immigrant status, and lack of health insurance, which in turn are linked to access to and use of health care services. Educational levels are associated with certain behaviors that increase cancer risk, such as smoking and obesity, as well as lower rates of screening for colorectal and breast cancers.

To measure the impact of educational level on cancer disparities, the authors calculated potential cancer deaths that could have been prevented. In 2007, about 24,500 blacks ages 25 to 64 died of cancer. If death rates were adjusted to the rates observed for the most educated blacks, more than 10,000 potential deaths (40%) would have been avoided. In contrast, if all blacks were to have the same death rates as their white counterparts with the same level of education, only about 5,000 potential deaths (20%) would be avoided. The authors contend that reducing socioeconomic disparities among blacks could potentially prevent twice as many deaths as eliminating racial differences. Targeted intervention programs emphasizing health promotion as well as early detection are urgently needed to reduce cancer disparities.

Study finds key racial differences in multiple myeloma survival over three decades. Multiple myeloma is the most common blood cancer among blacks in the United States, but there is little data on racial disparities in incidence and survival. In the first large-scale, population-based study, to our knowledge, to assess differences in incidence and survival in multiple myeloma among blacks and whites in the United States, investigators found that the incidence of multiple myeloma was twice that in blacks as whites spanning three decades but that blacks had a higher disease-specific survival than whites.

Using information from the NCI’s SEER database, researchers analyzed data from 5,798 black and 28,939 white patients diagnosed with multiple myeloma between 1973 and 2005 and observed through 2006. They found that blacks have a younger age of onset (mean age at diagnosis, 66 years) than whites (mean age at diagnosis, 70 years). Despite the greater disease-specific and relative survival in blacks over the entire study period, improvements in relative survival were small (relative survival measures the reduced survival associated with a diagnosis of myeloma compared with the expected survival of the general age-matched population). However, for white patients, there were significant improvements in 5-year relative survival over the study period, including periods before and after 1994 and 1999 when important treatments such as stem-cell transplantation and the drug thalidomide were introduced. The fact that blacks tended to develop multiple myeloma at a younger age and had better survival compared with whites may suggest a different disease biology and susceptibility. However, lower improvements in relative survival during the study period raise the possibility of disparities in access and/or responsiveness to newer therapies.

The field of developmental therapeutics focuses on translating discoveries in the laboratory into drugs that improve the quality of life and...
survival of patients. The first step in clinical drug development is the phase I clinical trial, which evaluates the safety of new therapeutic agents or combinations of cancer therapies. A key study this year from researchers at The University of Texas MD Anderson Cancer Center showed the benefits of matching gene alterations in tumors with specific drugs for patients participating in phase I clinical trials.

**Notable Advance**

Innovative model shows that matching targeted drugs to tumor alterations in patients with advanced cancer can improve outcomes, even in phase I trials. One of the overarching goals of modern cancer medicine is to target cancer treatments to each patient’s cancer on the basis of the precise genetics of their tumor.

This year, investigators at The University of Texas MD Anderson Cancer Center reported that matching patients with advanced cancer in phase I clinical trials with targeted drugs on the basis of tumor makeup was feasible, resulted in longer survival, and caused stronger, longer-lasting treatment benefit compared with patients treated without such matching. The findings could lead to a new model for conducting phase I clinical trials, which could ultimately speed the development of therapies for specific subsets of patients with cancer on the basis of their tumor biomarkers.

In the study, investigators analyzed tumors of 1,144 patients with advanced cancer who had a median of four previous therapies; they identified one or more gene alterations in 460 patients. Such alterations included those in genes such as PIK3CA, mTOR, BRAF, MEK, KIT, EGFR, and RET. Researchers found that, when patients could be treated with targeted drugs that matched one of their tumor gene alterations, they had better survival than patients who were not matched to targeted therapies.

Median survival was 13 months for patients with a genetic change who were treated with a matched therapy compared with 9 months for those patients who did not receive a matched therapy. They also showed that patients with one known genetic alteration who received a matched therapy experienced a longer-lasting benefit from treatment than those who received unmatched therapy: the median time to a matched therapy showed that patients with one known genetic alteration who received a matched therapy experienced a longer-lasting benefit from treatment than those who did not receive matched therapy.

Researchers have taken tremendous strides in understanding the biology of cancer and are translating this progress into increasingly personalized cancer treatments. At the same time, research is leading to new ways to improve supportive care and quality of life for patients with cancer. An important study this year centered on the evaluation of markers for predicting risk of experiencing a key adverse effect of certain cancer treatments.

**Notable Advance**

Genetic biomarker predicts taxane-induced neuropathy. Peripheral neuropathy is a potentially severe complication of a commonly used class of chemotherapy drugs called taxanes (docetaxel and paclitaxel), and it affects about one-third of patients with cancer receiving such treatment. The condition results from damage to nerves that causes pain and numbness in the hands and feet. In some cases, this adverse effect limits the dose of chemotherapy a patient can receive.

Currently, only a few factors seem to predict which patients are likely to get peripheral neuropathy. Now, investigators have identified the first genetic biomarkers for peripheral neuropathy brought on by taxane chemotherapy, potentially explaining why the adverse effect occurs in some patients but not in others. The finding may eventually lead to the development of a blood test to determine whether a patient is at high risk for neuropathy and, in turn, allow physicians to choose alternative treatments or treatment schedules and better counsel patients about their risks.

Investigators conducted a genomewide association study on 2,204 patients who received taxane-based chemotherapy as part of a clinical trial conducted by the Eastern Cooperative Oncology Group. In the genomewide association study, researchers search the genome (all of an individual’s genes) for small variations that occur more often in people with a particular disease than in those without the disease. This study looked for variations in DNA called single nucleotide polymorphisms (SNPs). With a median follow-up of 15 months, the study identified subgroups of patients with certain differences in their genes that made them much more likely to develop peripheral neuropathy.

Those who carried two normal nucleotides in a specific type of gene had a 27% chance of experiencing neuropathy. But those who carried one normal nucleotide and one SNP had a 40% chance, and those who carried two SNPs had a 60% chance.

The large decreases in childhood cancer death rates in the past several decades have been some of the great achievements in cancer care. Long-term survival rates for childhood cancer increased more than 20% between 1975 and 2006, approaching 80% overall. Pediatric oncologists have begun to focus not only on refining traditional chemotherapy approaches but on moving in other new directions as well. Targeted therapies that seek out specific genes or enzymes within the cancer cell have been developed, and new immunotherapies are using novel delivery systems to attack only cancer cells. Personalized therapies are being explored that take advantage of specific genetic variations that exist within a tumor and using that information to increase the number of cancer cells killed. At the same time, researchers are seeking to develop less toxic therapies and improve the quality of life of long-term survivors, who face increased risks of developing new cancers, heart failure, lung damage, learning disorders, and other health problems.

This year, results from two trials transformed therapy for two forms of childhood cancer. In one, researchers found that a new combination of chemotherapy drugs used before stem-cell transplant in highly aggressive neuroblastoma significantly improved survival for children with this often deadly disease. In the second, investigators showed that a new, high-dose chemotherapy regimen significantly improved the cure rate for children with ALL, pushing the cure rate to more than 80%.

**Major Advances**

New high-dose chemotherapy regimen improves survival in children with hard-to-treat neuroblastoma. Neuroblastoma is the most common cancer for patients in the first year of life and accounts for approximately 15% of childhood cancer deaths. Approximately 40% of patients are considered high-risk, meaning they are likely to recur or progress despite therapy. This year, results from a phase III trial...
showed that a new combination of chemotherapy drugs improved survival for children with high-risk disease, establishing a new standard of care.53 The typical therapy for children with high-risk neuroblastoma includes intense chemotherapy to bring about remission followed by surgery, radiotherapy, and myeloablative therapy to kill the remaining cancer cells combined with stem-cell transplantation. This may be followed with additional treatment, including immunotherapy, to eliminate any remaining cancer cells.

The High-Risk Neuroblastoma-1 (HR-NLB1) trial compared the effectiveness of two high-dose myeloablative chemotherapy treatments. Myeloablative chemotherapy is high-dose chemotherapy aimed at killing cancer cells before stem-cell or bone marrow transplant. In the trial, 563 children (median age, 3 years) with stage IV, high-risk disease with distant metastases or local disease were randomly assigned to receive either a combination of the chemotherapy drugs busulphan and melphalan (\(n = 281\)) or the standard regimen of three chemotherapy drugs (carboplatin, etoposide and melphalan [CEM]; \(n = 282\)). After 3 years, the event-free survival for patients treated with busulphan-melphalan was 49% compared with 33% for the CEM group. Overall survival after 3 years was 60% for those who received busulphan-melphalan compared with 48% in the CEM group. The busulphan-melphalan group also had lower rates of relapse (47% vs 60%). On the basis of these strong early results, the random assignment was stopped, and all patients enrolled onto the trial were given busulphan-melphalan therapy.

*New chemotherapy regimen boosts event-free survival for children and young adults with ALL.* ALL is the most common leukemia in children. Patients are treated with a chemotherapy regimen to bring the cancer into remission followed by a course of interim maintenance therapy to keep the disease in remission. For many years, the standard interim maintenance therapy has consisted of treatment with the common chemotherapy drug methotrexate on an escalating schedule, giving the drug in gradually increasing amounts, followed by a second chemotherapy drug called asparaginase. However, the most effective dosages and treatment schedules have not been well-established, and relapses continue to be a problem.

The phase III Children’s Oncology Group trial of nearly 2,500 children and young adults with ALL showed that giving methotrexate in large, consistent doses rather than in gradually increasing doses was more effective in preventing relapses and extending survival.54 Investigators divided 2,426 patients age 30 and younger with newly diagnosed ALL into two groups. After initial treatment with chemotherapy to bring the disease into remission, patients in one group were treated with the standard escalating methotrexate plus asparaginase, whereas the other group received high-dose methotrexate at 50 times the starting dose of the escalating regimen. At a planned interim analysis, the 5-year event-free survival for patients who received high-dose methotrexate was 82% compared with 75% for patients on the escalating methotrexate regimen. There were significantly fewer bone marrow and CNS relapses in the high-dose group. On the basis of these results, the standard of care for patients with high-risk ALL now includes high-dose methotrexate rather than lower-dose methotrexate during the interim maintenance phase of therapy.

**PREVENTION AND SCREENING**

For many cancers, effective methods of detecting disease at an earlier, more treatable stage remain elusive. Screening for some cancers—most notably breast, colon, and cervix—has been tremendously successful at reducing cancer-related deaths. Similar progress in other cancers—such as lung, ovarian, and pancreatic—has proven frustratingly difficult, however. At the same time, researchers continue to seek new ways to reduce the risk of cancer ever developing.

This year, a special federal panel recommended against routine screening for prostate cancer by using a PSA test. Earlier, the results of a landmark national trial found that routine screening with a CT scan greatly reduces the risk of lung cancer—related death among current and former smokers (see Lung Cancer Major Advances). In another study, researchers reported a novel PSA testing strategy that can identify men at highest risk of dying as a result of prostate cancer and those that could minimize PSA testing for most men. Another large study provided new insights into the use of both human papillomavirus (HPV) and Papanicolaou (Pap) testing for cervical cancer screening. Finally, an important study showed that aromatase inhibitors could lower the risk of developing breast cancer (see Breast Cancer Major Advances).

**Special News Feature**

**US panel recommends against routine use of PSA for prostate cancer screening.** In October 2011, the US Preventive Services Task Force recommended against routine screening for prostate cancer by using the PSA test. The recommendation, on the basis of the results of five randomized clinical trials and other studies, said that healthy men should no longer receive PSA screening, because there is no evidence that its use saves lives overall despite a reduction in prostate cancer deaths in some of the trials, and it frequently leads to false-positive results, resulting in excessive testing, overdiagnosis, and unnecessary treatments. This report remains controversial with some representatives from the urology community citing flaws in the design of the trials and claiming that the potential reduction in prostate cancer deaths should not be completely ignored.

The US Preventive Services Task Force already recommends against routine PSA screening in men older than 75 years. The review also noted that treatment for prostate cancer, such as prostatectomy and radiation, is associated with risks for several adverse effects, such as urinary incontinence, impotence and bowel dysfunction.


**Major Advances**

**Study shows low-dose CT scanning reduces lung cancer deaths.** Until now, screening has had little impact on reducing the risk of dying as a result of lung cancer. However, results published this year from a large national screening trial of more than 50,000 current and former heavy smokers found that three annual low-dose CT scans reduced the death rate from lung cancer by 20% compared with screening with three annual chest x-rays.

In the study, 53,454 individuals from age 55 to 74 years at high risk for lung cancer—they smoked the equivalent of a pack of cigarettes a day for 30 years—were enrolled between 2002 and 2004 at 33 medical centers in the United States. They were randomly assigned to receive three annual screenings with either low-dose CT (\(n = 26,722\)) or single-view chest x-ray (\(n = 26,732\)) and were observed for a median 6.5 years. The study was halted after 8 years when researchers saw a clear benefit with routine CT scanning.
The rate of positive screenings was 24% in the low-dose CT group and 7% in the chest x-ray group over the three screening rounds. The false-positive results likely resulted from chronic inflammation in the lungs associated with smoking, suggesting a need to carefully select patients for screening. Overall, there were 1,060 cancers diagnosed in the low-dose CT group compared with 941 in the chest x-ray group and 356 and 443 deaths from lung cancer, respectively, equating to a 20% reduction in lung cancer–related death in the CT-screened population. This is the first randomized trial to our knowledge to find a definitive reduction in lung cancer deaths with a screening regimen.

On the basis of these results, ASCO is developing a clinical practice guideline on lung cancer screening in conjunction with the National Comprehensive Cancer Network, the American Cancer Society, and the American College of Chest Physicians.

Exemestane significantly reduces risk of invasive breast cancer in high-risk, postmenopausal women. Although the antiestrogen drugs tamoxifen and raloxifene are FDA-approved for breast cancer prevention in women at high risk, only 4% of the approximately 2 million women at high risk in the United States who could benefit from tamoxifen actually take it because of concerns over the increased risk of developing endometrial cancers and blood clots with available treatments.

A phase III trial showed that exemestane, an aromatase inhibitor, greatly reduces the risk of developing breast cancer compared with placebo in high-risk, postmenopausal women. To our knowledge, this is the first evidence that an aromatase inhibitor is effective in reducing the risk of a first breast cancer, and it opens the door for exemestane to become an option for postmenopausal women who are at high risk for breast cancer.

Aromatase inhibitors, which work differently than tamoxifen by preventing estrogen synthesis, have been proven superior to tamoxifen in preventing recurrences in postmenopausal patients with early-stage breast cancer. The MAP.3 study included 4,560 postmenopausal women who were age 60 years or older and who were considered at high risk for breast cancer. After a median follow-up of 3 years, the group receiving exemestane had a 65% reduction in invasive cancers. There was also a 60% reduction of invasive breast cancer and preinvasive ductal carcinoma in situ (the earliest form of breast cancer) in the exemestane group and fewer precancerous conditions.

**Notable Advances**

**Novel screening approach suggests PSA levels among men age 44 to 50 years may predict long-term risk of metastatic prostate cancer or death.** Doctors and patients have long sought an effective way to distinguish men at high risk for prostate cancer who need more vigilant monitoring from those at low risk. A major concern, which led to the recent public health recommendation against PSA screening use, has been that PSA screening in the general community has not been proven to lower death rates from prostate cancer and is associated with overtreatment of nonlife-threatening cancers. The test identifies conditions that are not cancer, and it misses some actual prostate cancers.

This year, a large retrospective, case-control study of previously unscreened Swedish men showed that PSA levels on initial screening among men age 44 to 50 years can accurately predict the risk that a man will die of prostate cancer or develop metastatic prostate cancer up to 30 years later.66 This predictability included men with the highest PSA levels and who were at the highest risk of death years later as well as men with the lowest PSA levels and who were at the lowest risk of death many years later. The authors suggest that an initial PSA test, provided that levels are low in this age group, could enable approximately 50% of men to undergo just three PSA tests in their lifetime.

Researchers analyzed PSA levels in stored blood samples from 12,090 men provided between 1974 and 1986 and nearly 5,000 repeat samples collected 6 years later as part of the Swedish Malmo Preventive Project. Using these samples, the investigators assessed the median PSA levels for men in three age groups: ages 44 to 50 years, ages 51 to 55 years, and 60 years. These median levels at baseline served as the baseline to distinguish men at high or low risk of dying as a result of prostate cancer or developing metastatic prostate cancer. As men aged, if their PSA level remained below the median for the population in their age group, the risk of death as a result of metastatic prostate cancer progressively declined. They found that 28% of metastases or deaths resulting from prostate cancer in the next 27 years occurred in men ages 44 to 50 years who had a PSA below the median in the population (0.7 ng/mL). For men ages 51 to 55 years with a PSA less than the median (0.8 ng/mL), the relative risk of metastatic prostate cancer or death was even lower at only 18%. At age 60, only 0.5% of deaths or metastases occurred in men with a PSA less than median for that age (1.1 ng/mL).

The researchers concluded that men with PSAs below the median in the population in each age group remain at progressively lower risk for dying as a result of prostate cancer as they age and that three tests between ages 44 and 60 years could be enough for 50% of men. The findings could have important implications in deciding who should be screened with increased frequency. The study also found that 44% of prostate cancer deaths occurred in men who had the top 10% of PSA levels when they were tested between the ages of 44 and 50 years. As a result, the authors say, nearly half of all prostate cancer deaths could potentially be prevented by intense surveillance of this small group of men.

*Large study finds that most women can safely extend cervical cancer screening to 3 years; HPV testing also appears to be superior to Pap testing.* Cervical cancer is caused by infection with HPV, a common sexually transmitted infection that can be detected by performing DNA testing on a sample of cervical cells. HPV infection is almost always cleared by the body, but if it is not, cancer may develop, typically decades after initial infection. Immunization can prevent HPV infection in both men and women, lowering the risk of future cervical and other cancers. Although Pap testing has dramatically reduced cervical cancer rates, screening guidelines from medical and health organizations such as the American College of Obstetricians and Gynecologists and the American Cancer Society have endorsed the use of routine HPV testing together with Pap tests as a safe alternative to routine Pap testing alone for women age 30 years and older, recommending cotesting every 3 years for women who are negative for HPV and have a normal Pap test. However, cotesting has not been widely adopted by physicians and women, many of whom are unsure about the safety of extending testing intervals for more than one year.

This year, the first large-scale study of cotesting in routine clinical practice showed that women can safely be tested every 3 years instead of every year.56 The study also found that a single HPV test may be more accurate than a conventional Pap test in determining cervical cancer risk.

Researchers observed 331,818 women ages 30 years and older who enrolled onto Kaiser Permanente Northern California’s cotesting program for five years. They found that the 5-year cancer risk for
women who had both a normal Pap test and tested negative for HPV was low (3.2 per 100,000 women per year). Looking at each test individually, women negative for HPV had half the cancer risk of women with a normal Pap test (3.8 per 100,000 women per year compared with 7.5 per 100,000 women per year), suggesting that HPV testing alone is more accurate than Pap testing alone. The study also showed that the cancer risk with a negative HPV test alone was similarly low compared with HPV and Pap testing together (3.8 v 3.2 per 100,000 women per year). According to the authors, these findings serve as a formal confirmation that cotesting every 3 years is a safe and highly effective cervical cancer screening strategy for most women over age 30 years.

YEAR IN REVIEW: CANCER POLICY DEVELOPMENTS IN 2011

Continued Progress Depends on Access to Clinical Trials and Quality Care

Forty years after the National Cancer Act of 1971, the advances described in this report represent the continued legacy of that landmark legislation, which led to major improvements in the care of people with cancer. Cancer survival rates in the United States are increasing thanks to better detection and new treatments together with advances in cancer prevention. Yet, much remains to be done. More than half a million Americans will die of cancer this year in the United States alone, and the disease is projected to become the nation’s leading cause of death as the population ages.

Continued progress requires accelerating the pace of clinical cancer research while expanding access to quality cancer care for patients. In many cases, action by policy makers will be crucial to our success. This section of Clinical Cancer Advances describes key cancer policy developments and ASCO policy initiatives from the past year that are likely to influence cancer care in the coming years.

New ASCO Report Recommends Steps to Transform Clinical Cancer Research

Clinical cancer research is the engine that drives progress against the disease. With our rapidly growing understanding of the biology of cancer, cancer science is rapidly moving into a genomic era in which each patient’s cancer can be understood and treated on the basis of its unique molecular features. Yet the nation’s clinical research system has not kept pace with recent scientific advances.

In a comprehensive report, ASCO lays out a vision for a clinical research system that takes full advantage of today's scientific and technological opportunities. The report makes recommendations in three areas:

- Establishing an approach to the development of new treatments on the basis of a more thorough understanding of cancer’s biology
- Designing faster and smarter clinical trials appropriate for the era of molecularly targeted therapies
- Harnessing information technology to seamlessly integrate clinical research and patient care

In the next 3 years, ASCO will be working with other stakeholders throughout the cancer community to help make the report's vision a reality.

Progress Made in Revitalizing Federally Funded Clinical Trials

In 2010, a report by the Institute of Medicine (IOM) made recommendations to modernize and strengthen one key component of the nation’s cancer research system: the NCI’s Cooperative Group Program. Because a strong, federally funded clinical trials system is essential to progress against cancer, ASCO supports the full implementation of the IOM’s recommendations. In the past year, the IOM, ASCO, and many others have provided input into NCI’s efforts to implement key elements of the report. For example, a joint ASCO/IOM workshop this past March brought together clinical trials stakeholders, ASCO members, and federal agency representatives to discuss the need for increased efficiencies and greater prioritization of trials as well as sustained resources to move this federally supported system into the future.

Analysis Examines Potential Impact of Health Care Reform on Cancer Disparities

Although survival rates have improved steadily in the United States, not all patients have benefitted equally. For many Americans, racial and economic disparities limit their opportunities to receive the best possible cancer care. To examine how the 2010 Patient Protection and Affordable Care Act might alleviate these disparities, ASCO conducted a thorough assessment of the legislation and issued a policy statement outlining specific provisions that may address disparities. ASCO also made specific recommendations to ensure that these provisions of the law are carried out effectively and urged additional steps to address systemic issues:

- Adopting patient-centered quality improvement initiatives
- Attracting more minority physicians and improving the training of the oncology workforce to meet the needs of racially and ethnically diverse patients with cancer
- Improving data collection on cancer disparities and determining what must be done to make meaningful medical evaluations
- Ensuring access to cancer specialists for all patients who seek treatment at federally qualified community health centers
- Allowing for cancer-centered services to be at the direction of oncology professionals in community health centers and medical homes where many seek medical care

Severe Cancer Drug Shortages Gain Attention From Media and Congress

Patient access to cancer therapy has been severely impacted in recent years by the growing problem of oncology drug shortages. The effected treatments include many mainstays of chemotherapy treatment for both adults and children with cancer. Shortages have become more widespread and frequent in the past year and have received much-needed attention from media and policy makers. ASCO is a leading voice advancing legislative and regulatory strategies to promote both short- and long-term solutions to this health care crisis. For example, in November 2010, ASCO joined with other societies and stakeholders to hold a summit on drug shortages that resulted in 21 recommendations for short- and long-term solutions. In addition, ASCO has been working with members of Congress on legislation that has been introduced in both the Senate and the House of Representatives to address the shortage. Most recently, ASCO testified at a congressional hearing and at a meeting convened by the FDA and is in
ongoing discussions with the Department of Health and Human Services to advance solutions at the highest levels.

**ASCO Takes Steps to Improve Advanced Cancer Care Planning**

For patients with advanced cancer, quality care involves considering the full range of treatments for their cancer and palliative care options to maximize their quality of life. However, research from the Dartmouth Atlas Project, highlighted in this report, found that many patients do not fully benefit from available palliative care services. To improve patient quality of life, ASCO issued a comprehensive statement calling for a new approach in which all available treatment options are discussed as soon as possible after a patient’s diagnosis with advanced cancer and patient needs and preferences are addressed throughout the course of treatment. ASCO also called on policymakers and insurers to ensure appropriate coverage for time devoted to these difficult but essential discussions with patients and their loved ones.

**Research Highlights Potential Solutions for Oncology Workforce Shortages**

With the incidence of cancer projected to grow as the US population ages and the number of survivors of cancer increases, the demand for oncology services is projected to soon exceed the capacity of available oncologists. If not addressed, these workforce shortages could have a major impact on access to high-quality cancer care for patients in the years ahead. To address this critical issue, ASCO commissioned a study supported by the Susan G. Komen Foundation for the Cure, which found that increasing the role of nurse practitioners and physician assistants can effectively help practices manage the increasing demand for care. This national survey of 226 practices, 33 of which provided additional in-depth data, found high levels of patient satisfaction and improved efficiency in practices in which all nurse practitioners and physician assistants collaborate with physicians and see a wide variety of patients.

**United Nations Summit Addresses Cancer Crisis in Developing Countries**

Although significant progress has been made against cancer in recent decades, cancer deaths around the globe are projected to surpass 11 million per year by 2030. Cancer mortality is most severe in low- and middle-income countries, where access to modern cancer care is limited or even nonexistent. In September, the cancer crisis in developing countries received unprecedented new attention at a United Nations high-level meeting to address noncommunicable diseases and a mechanism for measuring progress toward agreed to establish specific targets by 2012 for combating noncommunicable diseases and a mechanism for measuring progress toward those targets. ASCO and other medical societies advised on the development of key recommendations put forth at the meeting.

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