Major Research Advances in Cancer Treatment, Prevention, and Screening

A REPORT FROM THE
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

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A MESSAGE FROM ASCO’S PRESIDENT

For the second consecutive year, the American Society of Clinical Oncology (ASCO) is publishing Clinical Cancer Advances: Major Research Advances in Cancer Treatment, Prevention, and Screening, an annual review of the most significant cancer research presented or published over the past year.

ASCO developed this report to demonstrate the enormous progress being made on the front lines of cancer research today. The report is intended to give all those with an interest in cancer care—the general public, cancer patients and physicians, policymakers, oncologists, and other medical professionals—an accessible summary of the year’s most important cancer research advances.

These pages report on new targeted therapies that are improving survival and response rates in hard-to-treat cancers such as kidney cancer, HER-2-positive breast cancer, head and neck cancer, and chronic myelogenous leukemia; the FDA’s approval of the world’s first preventive vaccine for human papillomavirus (HPV), which has the potential to dramatically reduce the global burden of cervical cancer; and advances in the fast-growing field of personalized medicine, including a new lung cancer test that could help physicians better target treatments and predict prognosis.

These advances are only part of the landscape. Survival rates are on the rise, the number of cancer deaths in the United States began declining for the first time since 1930, and new research is showing that the rates of certain common cancers, such as those of the breast and colon, have stabilized, and may have even begun to decline.

However, cancer research still faces a number of major obstacles. At a time of extraordinary scientific potential, declining federal funding of cancer research threatens to stall or even reverse recent progress. Such funding cuts have already led to fewer clinical trials, fewer talented young physicians entering the field, and a growing bottleneck of basic science discoveries waiting to be “translated” into useful therapies and diagnostics. In addition to highlighting the major research advances over the past year, this report also identifies key barriers to accelerating the pace of cancer research and outlines ASCO’s recommendations for overcoming them.

Despite these and other challenges, there is much good news on the front lines of cancer research. This report demonstrates the essential role of clinical cancer research in finding new and better ways to treat, diagnose, and prevent a group of diseases that strike half of men and one-third of women in the United States. I want to thank the Editorial Board members, the Specialty Editors, and the ASCO Cancer Communications Committee and Cancer Research Committee for their dedicated work to develop this report. I hope you find it useful.

Sincerely,

Gabriel N. Hortobagyi, MD, FACP
President
American Society of Clinical Oncology (ASCO)
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Clinical Cancer Advances is an independent annual review of the top advances in cancer treatment, prevention, and screening across all cancer types, conducted by the American Society of Clinical Oncology (ASCO).

Over the last three decades, investment in clinical cancer research, prevention, and screening has reduced cancer incidence and death rates, increased survival rates, and significantly reduced the symptoms and side effects of cancer and its treatment. The number of U.S. cancer deaths dropped slightly in 2003, the first such decline since 1930, and today, there are nearly 10 million cancer survivors in the United States.

This report documents the most significant advances on the front lines of cancer research. This year, major research advances can be grouped in three categories:

- **Prevention**: The approval of the world’s first preventive vaccine for human papillomavirus (HPV), a virus strongly associated with cervical cancer

- **Targeted Therapies**: Effective new targeted therapies for hard-to-treat cancers such as kidney cancer, HER-2-positive breast cancer, chronic myelogenous leukemia resistant to the current standard treatment, and head and neck cancer

- **Genetic Profiling**: The creation of a novel gene profiling test to predict lung cancer prognosis.

While much progress has been made, cancer still takes a tremendous toll, and new, more effective prevention and treatment strategies are urgently needed. With extraordinary recent advances in the understanding of the human genome and the inner workings of cancer cells, researchers have never been in a better position to accelerate progress against cancer. Yet significant obstacles stand in the way of realizing this potential. In addition to identifying the major clinical research advances of the year, this report outlines some of the most significant barriers to accelerating the pace of cancer research, and ASCO’s recommendations for overcoming them.

**SUMMARY OF FINDINGS**

Following is a summary of the major clinical research advances in 2006.

**FDA APPROVES FIRST VACCINE TO PREVENT HPV INFECTION**

The most significant advance over the past year in both gynecologic oncology and in cancer prevention was the U.S. Food and Drug Administration (FDA) approval of the first vaccine to prevent infection with human papillomavirus (HPV), a virus present in virtually all cervical cancers. The vaccine has the potential to profoundly reduce the burden of cervical cancer, which is diagnosed in nearly 500,000 women each year globally, including nearly 10,000 women in the United States.

The vaccine, known as Gardasil, was shown to be 100% effective in preventing HPV 16- and 18-related cervical precancers in women who were not previously exposed to these strains of the virus. These strains together account for approximately 70% of cervical cancer cases worldwide. In addition, an analysis of three large international studies suggests that the vaccine may also be very effective in preventing HPV-related vaginal and vulvar precancers.

The approval of the HPV vaccine is a major advance for cancer prevention. Critical to the success of the vaccine will be ensuring that women in the world’s poorest countries—where cervical cancer is most common—have rapid and affordable access to this life-saving new tool. (See p. 14)
TARGETED THERAPIES EFFECTIVE IN HARD-TO-TREAT CANCERS

Several studies stand out as advances that will change the standard of care for a number of hard-to-treat cancers. These include studies demonstrating improved survival and response rates in kidney cancer, HER-2-positive breast cancer, and chronic myelogenous leukemia, as well as a study showing that an existing targeted therapy can improve survival in head and neck cancers—the first new treatment for this disease in 45 years.

New Therapies Prove Effective in Kidney Cancer –
Treatment regimens for kidney cancer have not changed in more than two decades. By improving survival rates, the therapies tested in the following two studies represent major advances in the treatment of this disease. (See p. 12)

- Temsirolimus in Advanced, High-Risk Kidney Cancer – A large international randomized phase III trial showed that patients receiving the investigational drug temsirolimus (CCI-779) as a first-line treatment for advanced, high-risk kidney cancer lived longer than patients receiving the standard treatment, interferon-α, or therapy that combined interferon-α and temsirolimus. Temsirolimus is a targeted inhibitor of mTOR, a protein that regulates cell growth and angiogenesis (the growth of blood vessels that feed tumors).

- Sunitinib in Advanced Kidney Cancer – A large phase III study of patients with advanced renal cell carcinoma showed that sunitinib (Sutent) improved progression-free survival and response rates when compared with the standard treatment, interferon-α. Sunitinib was approved by the FDA in January 2006 as a second-line treatment for advanced renal cell cancer in patients whose cancer had progressed following treatment with immune therapies. This study was the first to assess the drug in previously untreated patients.

Lapatinib Improves Treatment of Advanced Breast Cancer – An international phase III trial showed for the first time that giving the targeted therapy lapatinib (Tykerb) with capecitabine (Xeloda) controlled cancer growth more effectively than capecitabine alone in women with advanced HER-2-positive breast cancer that grew despite prior treatment with the drug trastuzumab (Herceptin). The research indicates that lapatinib could be an additional tool for fighting breast cancer that overexpresses the HER-2/neu protein, which accounts for 20% to 25% of all breast cancer cases, and is particularly aggressive and difficult to treat. The FDA is currently reviewing an application for the approval of lapatinib for the treatment of advanced HER-2 breast cancer patients who did not respond to previous therapy, including trastuzumab. (See p. 8)
Dasatinib Effective in Leukemia Patients Resistant to Imatinib – A phase I clinical trial of the new targeted therapy dasatinib (Sprycel) in patients with chronic myelogenous leukemia (CML) who could not tolerate or had become resistant to the drug imatinib (Gleevec) showed that 92.5% of these poor prognosis patients had no evidence of disease after receiving dasatinib. In addition, 70% of patients with a more advanced form of leukemia experienced a significant decrease in the number of abnormal blood cells after receiving dasatinib. Following publication of this study, the FDA approved dasatinib for CML in June 2006. (See p. 7)

Cetuximab Provides First New Treatment For Head and Neck Cancer in 45 Years – A multinational study found that adding the targeted therapy cetuximab (Erbitux) to standard high-dose radiation therapy in patients with locally advanced head and neck cancer slowed cancer growth and prolonged survival, compared with patients who received radiation therapy alone. Patients on cetuximab lived an average of 49 months, compared with 29.3 months for patients who received radiation therapy alone. Following publication of this study, the FDA approved cetuximab to treat head and neck cancer, making it the first drug to be approved for this disease in 45 years. (See p. 16)
**RESEARCHERS CREATE GENETIC TEST TO PREDICT LUNG CANCER PROGNOSIS**

The most significant advance in lung cancer over the past year occurred in the fast-growing field of personalized medicine—the development of new ways to predict the effectiveness or side effects of therapy based on an individual’s genetic profile. As scientists learn more about the human genome and each individual’s particular genetic make-up, the creation of diagnostic tests and targeted therapies specific to the individual will allow oncologists to better target treatments and predict prognosis.

One of the most significant advances in this area over the past year was the creation of a novel gene profiling test that can predict which patients with early-stage non-small cell lung cancer (NSCLC) are most likely to be cured, as well as those that are most likely to experience a relapse of their disease. The test—called the “lung metagene model”—was 72% to 79% accurate in predicting recurrence, a rate more accurate than considering clinical characteristics, such as tumor size, alone. The test was especially helpful in identifying patients with stage “IA” lung cancer for whom chemotherapy after surgery might be appropriate. Current standard treatment for stage IA NSCLC is surgical removal of the tumor, but up to 25% of patients treated with surgery alone experience a recurrence of their disease.

Additional studies are planned to confirm the accuracy of this model. If confirmed accurate, the tool could provide an effective means of estimating a patient’s risk of recurrence, enabling physicians and patients to make more informed decisions about the use of chemotherapy for early-stage lung cancer. A similar test has been developed and is in clinical use in breast cancer, and a large randomized phase III trial launched in 2006 will examine its ability to select breast cancer patients most likely to benefit from chemotherapy.

**RECOMMENDATIONS: ACCELERATING CANCER RESEARCH**

As this report demonstrates, significant progress has been made in the understanding and management of cancer. Cancer mortality rates are dropping, the incidence of common cancers such as those of the breast and colon are stabilizing, and a growing number of highly-targeted therapies are proving effective in a variety of diseases. Much of the rapid progress in recent years can be attributed to a better understanding of basic biology and the role of genes in the origin and progression of disease.

However, much more needs to be done to ensure that such discoveries move rapidly through the cancer research process. A growing backlog of basic science discoveries are waiting to be studied to determine if they can be “translated” into potentially useful therapies for cancer patients. This problem is compounded by the fact that federal funding of clinical and translational research has been flat for the last several years, and additional budget cuts are possible for fiscal year 2007.

To accelerate the pace of cancer research, ASCO recommends two key action steps over the coming year:

1. **Increase Funding of Cancer Research.** Congress’ doubling of the National Institutes of Health (NIH) budget between 1998 and 2003 yielded major new discoveries in all areas of biomedical research, including cancer. However, flat funding since 2003—and possible cuts in 2007—threaten to derail this progress. To avoid losing critical ground in cancer research, ASCO supports annual minimum funding increases of 5% for NIH, beginning in fiscal year 2007.

2. **Advance Research From the Lab to the Clinic: Increasing Access to Biospecimens.** Human biospecimens—samples of tissue and blood taken from patients during surgeries, biopsies, or routine tests—play a critical role in the translation of basic science discoveries into clinical applications by allowing researchers to study the molecular characteristics of cancer cells.
However, ready access to biospecimens for use in cancer research has become a major challenge. Following are ASCO’s recommendations for improving access to human biospecimens:

a. **Standardized Collection and Storage of Biospecimens:** There are no common procedures for collecting and storing biospecimens, and no consistent quality-control measures. ASCO recommends the development of national guidelines to standardize procedures for collection, storage, and use of biospecimens, and the development of a national database linking National Cancer Institute (NCI)-supported repositories to allow for the sharing of information and expertise across institutions.

b. **Impact of Privacy Laws on Cancer Research:** Under the Health Insurance Portability and Accountability Act (HIPAA), in order to use biospecimens, researchers are required to get authorization from every patient for each research project. While ASCO agrees that preserving a patient’s right to privacy is important, variations in the interpretation of such privacy regulations have inadvertently made it much more difficult to conduct cancer research. Because the extent of HIPAA’s impact is unclear, ASCO recommends that an independent body, such as the Institute of Medicine, conduct a rigorous review of the law’s effect on cancer research, and calls on the U.S. Department of Health and Human Services to issue clear guidance on the implementation of HIPAA provisions across research settings.

c. **Intellectual Property Rights:** Debate over intellectual property rights—including who owns human biospecimen samples, and who owns the right to any discoveries made using the samples—has also limited access to biospecimens. ASCO recommends the creation of a centralized database for biospecimens, which could greatly speed scientific discovery in cancer research. In addition, ASCO calls for a new collaborative effort involving cancer institutions, industry, government, and patient groups to identify ways such information could be shared for the benefit of all parties in cancer research, while maintaining appropriate protection for intellectual property.
CANCER TYPES

CANCERS OF THE BLOOD AND LYMPHATIC SYSTEM

Cancers of the blood and lymphatic system (also called “hematologic” cancers) include leukemias, lymphomas, multiple myeloma, and myelodysplastic syndromes. A number of promising advances involving novel targeted therapies for hematologic cancers were made in the last year, including a particularly important advance in the treatment of leukemias resistant to imatinib (Gleevec). In addition, the FDA approved two new therapies for hematologic malignancies: dasatinib (Sprycel) for chronic myelogenous leukemia and lenalidomide (Revlimid) for myelodysplastic disorders and multiple myeloma.

MAJOR ADVANCE

DASATINIB EFFECTIVE IN MANY PATIENTS WITH LEUKEMIA RESISTANT TO IMATINIB

A phase I clinical trial to determine the optimal dose of a new targeted therapy called dasatinib (Sprycel) in patients with chronic myelogenous leukemia (CML) who could not tolerate or had become resistant to the drug imatinib showed that 92.5% of these poor prognosis patients had no evidence of disease after receiving dasatinib. In addition, 70% of patients with a more advanced form of leukemia experienced a significant decrease in the number of abnormal blood cells after receiving dasatinib. The duration of benefit was dependent on the phase of the disease when the patient was treated.1

Imatinib was approved by the FDA in 2001 and proved highly effective for the treatment of CML. The oral drug blocks an enzyme produced by a mutation in the BCR-ABL gene, which is involved in the development of certain forms of leukemia. However, some patients develop additional mutations in this gene, causing their cancers to become resistant to the drug. Dasatinib targets these secondary mutations. Following publication of this study, the FDA approved dasatinib in June 2006. Physicians believe that optimal treatment of diseases like CML may involve the combination or sequencing of targeted drugs, or the selection of drugs based on the particular BCR-ABL mutation in the leukemia cells.

OTHER NOTABLE RESEARCH

MAINTENANCE RITUXIMAB EXTENDS SURVIVAL IN ADVANCED FOLLICULAR LYMPHOMA

For the first time, a phase III, multicenter trial has shown that two years of maintenance therapy with the monoclonal antibody rituximab (Rituxan)—which blocks a specific protein on B-lymphocytes—after completion of conventional chemotherapy improved survival and slowed disease progression in patients with advanced follicular lymphoma. Maintenance therapy is extended drug therapy, usually at a diminished dose, administered after a disease has been brought under control. Four years after beginning treatment, 56% of patients who received maintenance rituximab showed no evidence of cancer growth, compared with 33% of patients who were observed following chemotherapy. Moreover, 88% of the rituximab group was still alive after four years, compared with 72% of the observation group.2

REFERENCES

BREAST CANCER

Over the past few decades, improvements in early detection and the development of more effective treatments have led to significant declines in breast cancer deaths and improved prognosis for women living with the disease. According to the 2006 Annual Report to the Nation on the Status of Cancer, the number of new breast cancer cases in the United States began stabilizing in 2001, and there are signs that it may be declining. In addition, major strides have been made in the treatment of more aggressive forms of breast cancer, such as HER-2 breast cancer with the targeted therapy trastuzumab (Herceptin).

Now, new research has identified an additional tool for treating advanced HER-2 breast cancer that is resistant to trastuzumab, while other research is resulting in important confirmatory evidence that trastuzumab can reduce the risk of breast cancer recurrence in women with early-stage HER-2-positive breast cancer. In addition, an NCI-sponsored study from seven institutions underscores the importance of regular screening for breast cancer, showing that both mammograms and adjuvant therapy (chemotherapy following surgery) have played a key role in declining breast cancer mortality over the last decade.

MAJOR ADVANCE
LAPATINIB IMPROVES TREATMENT OF ADVANCED BREAST CANCER

A phase III international multicenter trial demonstrated for the first time that giving the targeted therapy lapatinib (Tykerb) with capecitabine (Xeloda) controlled cancer growth more effectively than capecitabine alone in women with advanced HER-2/neu-positive breast cancer that grew despite prior therapy with the drug trastuzumab. The HER-2/neu receptor, located on the surface of cells, is present in abnormally high levels in approximately 20% to 25% of breast cancer patients, and is associated with a more aggressive form of the disease. Trastuzumab, a first-line treatment for patients with HER-2-positive breast cancer, blocks the activity of the HER-2/neu receptor by binding to the part of the receptor located outside of the cell. Lapatinib was developed to block HER-2/neu activity by inhibiting the receptor inside the cell.

In this study, researchers compared the time it took for cancers to grow and spread (time to progression) in 160 women randomly assigned to receive lapatinib plus capecitabine, and 161 women who received capecitabine alone. Time to progression was almost twice as long in the lapatinib/capecitabine group: 36.9 weeks vs. 19.7 weeks. Side effects were generally similar between the two groups, although women in the lapatinib group were somewhat more likely to experience mild to moderate diarrhea and rash.

OTHER NOTABLE RESEARCH
STUDIES CONFIRM EFFECTIVENESS OF TRASTUZUMAB IN EARLY BREAST CANCER; SUGGEST SHORTER COURSE MAY BE POSSIBLE

New findings from three large breast cancer trials provide additional evidence that trastuzumab can reduce the risk of cancer recurrence and improve survival in women with HER-2-positive early-stage breast cancer.

- The Breast Cancer International Research Group (BCIRG) 006 Trial—the fourth large clinical trial to show such a result—enrolled 3,222 women with early-stage breast cancer to determine the most effective way to use trastuzumab following breast cancer surgery. Patients were randomized to receive one of three treatment regimens: standard therapy with doxorubicin and cyclophosphamide followed by docetaxel (Taxotere) (ACT); an experimental regimen of ACT and one year of trastuzumab (ACTH); or an experimental
regimen of docetaxel and carboplatin and one year of trastuzumab (TCH). Patients on the two trastuzumab regimens were less likely to have their cancer recur than those receiving standard chemotherapy. However, the study also confirmed previous findings showing that trastuzumab, particularly after therapy with doxorubicin, increases the risk of cardiac problems.²

In the second study, the interim results of the Finland Herceptin (FinHer) trial, 232 women with early-stage HER-2 breast cancer who participated in the trial were given chemotherapy alone or chemotherapy with only nine weeks of trastuzumab, a shorter course than the previously reported studies, which all gave trastuzumab for one year. Women in the trastuzumab group were significantly less likely to experience a recurrence (10% vs. 23% of those on chemotherapy alone). The study also found that the shorter regimen of trastuzumab caused fewer cardiac side effects than previous studies of the drug—findings which, if confirmed with longer follow-up, suggest that patients may be able to safely take a shorter course of the therapy, limiting the cost of the drug and the risk of serious side effects, without reducing efficacy.³

A third study—the updated results of the European Herceptin Adjuvant (HERA) trial—showed that the addition of trastuzumab to chemotherapy after surgery for early-stage breast cancer significantly improved survival of patients with HER-2-positive breast cancer. The trial, which last year reported data showing that trastuzumab can reduce the risk of breast cancer recurrence by 46% among these women, now also demonstrates a 34% reduction in the risk of dying of breast cancer after one year of treatment.⁴

MAMMOGRAMS AND ADJUVANT THERAPY PLAYED KEY ROLE IN DECLINING BREAST CANCER MORTALITY

A study investigating the causes of declining breast cancer deaths indicates that mammograms accounted for 28% to 65% of the decline in deaths over the last several decades, with the remainder due to improvements in chemotherapy treatment after surgery (“adjuvant therapy”). The study, sponsored by the NCI, was designed to assess the effect of mammography and adjuvant treatment on the reduction in breast cancer mortality in the United States from 1975 to 2000. The death rate was nearly flat from 1975 to 1990, before dropping nearly 24% between 1990 and 2000.

In the study, a consortium of investigators from seven different institutions developed independent statistical models of breast cancer incidence and mortality to assess the effect of mammography and adjuvant treatment on the reduction in breast cancer mortality. Despite differences in methodology, all seven groups concluded that screening and treatment have contributed to the observed decline in the rate of death from breast cancer and that the decline can be explained by a combination of screening and adjuvant therapy and not by either one alone.⁵

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4. Smith IE on behalf of the HERA Study Team. Scientific Special Session: Trastuzumab following adjuvant chemotherapy in HER2-positive early breast cancer (HERA trial): disease-free and overall survival after 2 year median follow-up. Presented at: American Society of Clinical Oncology Annual Meeting, June 2-6, 2006; Atlanta, Georgia.
Primary brain tumors represent a unique clinical challenge. While clinical trials over the last 25 years have evaluated a variety of drugs and treatment delivery systems, the prognosis for people with brain tumors has remained largely unchanged. In 2006, two studies in patients with a type of brain tumor called oligodendroglioma demonstrated that certain molecular characteristics of the tumor may be associated with a better prognosis—a finding that could eventually help physicians select treatment based on the specific genetic profile of the tumor.

**NOTABLE RESEARCH**

**TUMOR CHARACTERISTICS MAY HELP PREDICT PROGNOSIS IN PATIENTS WITH OLIGODENDROGLIOMA**

Two phase III studies in patients with anaplastic oligodendroglioma comparing chemotherapy and radiotherapy vs. radiotherapy alone found that a subset of patients with a particular genetic profile experienced better overall survival, regardless of what treatment they received. Oligodendroglioma is a type of glioma normally found in the cerebrum, particularly in the frontal or temporal lobes. The tumor is most common in adults, and occurs more often in men than in women.

The trials, which were designed to assess overall survival between the two treatments, found that patients receiving chemotherapy plus radiotherapy did not live significantly longer than patients who received radiotherapy alone. However, in a secondary finding, researchers discovered that patients whose tumors lacked the 1p and 19q alleles lived longer, indicating that tumors with this genetic profile may be less aggressive, more responsive to therapy, or both. (An allele is an alternative form of a gene.) These trials are the first large phase III studies to validate a link between 1p/19q deletions and patient outcome.

- In the first study, median survival times were similar between the two treatment groups (4.9 years for patients receiving chemotherapy plus radiotherapy vs. 4.7 years for those receiving radiotherapy alone). However, patients with tumors lacking the 1p and 19q alleles (46% of patients) had significantly longer median survival times than those with these alleles (7.0 vs. 2.8 years, respectively).¹

- In the second study, after a median follow-up time of 60 months, researchers found that the addition of chemotherapy after radiotherapy did not prolong overall survival, but did increase the length of time before the cancer progressed. Of the 25% of patients in the trial that had both 1p and 19q deletions, approximately 74% were still alive after 60 months—regardless of which treatment regimen they received. By comparison, among patients whose tumors did not have the combined 1p/19q deletions, approximately one-quarter to one-third were alive, depending on the treatment received.²

**REFERENCES**

GASTROINTESTINAL CANCERS

Gastrointestinal cancers include those of the esophagus, stomach, liver, pancreas, biliary tract, colon, rectum, and anus. The ability to effectively treat these cancers varies significantly. For example, while many colorectal cancers can be diagnosed in their early, more curable stages using colonoscopy, no such screening tests exist for less common cancers of the digestive tract—such as those of the pancreas—which are often diagnosed when they are advanced and difficult to treat effectively. While there were no practice-changing studies in 2006, several studies provided information about the most effective treatments for pancreatic cancer and gastrointestinal stromal tumor (GIST).

NOTABLE RESEARCH

NO ADVANTAGE TO ADDING OXALIPLATIN TO GEMCITABINE FOR PANCREATIC CANCER

A phase III, multicenter trial showed that two investigational pancreatic cancer treatments—fixed dose-rate gemcitabine and gemcitabine plus oxaliplatin (GEMOX)—did not improve survival when compared with the current standard of care, a 30-minute infusion of gemcitabine, in patients with advanced, inoperable pancreatic cancer. Because gemcitabine, the standard therapy for pancreatic cancer, offers only a modest survival advantage over no treatment, researchers have been studying a number of new approaches, alone or in combination with gemcitabine, to determine better ways of fighting the disease.

The trial, conducted by the Eastern Cooperative Oncology Group (ECOG), involved 833 patients who were randomized to receive one of the three regimens. None of the patients had previously received chemotherapy, and the primary endpoint of the trial was overall survival. Researchers found that the median overall survival for the three arms was 5 months for standard gemcitabine regimen, 6 months for fixed dose-rate gemcitabine, and 6.5 months for GEMOX. The differences were not statistically significant, however. This study adds to several previous studies showing that adding another chemotherapy agent to gemcitabine does not provide any advantage over gemcitabine alone.¹

ACTIVITY OF SUNITINIB IN PATIENTS WITH GIST LINKED TO MUTATION STATUS

A new study examining the relationship between the genetic profile of a tumor and the activity of sunitinib (Sutent) in patients with imatinib-resistant GIST found that response to sunitinib is associated with the presence of mutations in the KIT and PDGFRA genes. Imatinib (Gleevec) is a first-line treatment for patients with GIST, but it does not work for all patients, and many develop resistance to the drug over time. Sunitinib, which inhibits enzymes called kinases that play a role in angiogenesis (the growth of blood vessels that feed the tumor), has been shown to improve survival in patients whose tumors don’t respond to imatinib, and in January 2006 was approved by the FDA for this indication.

The trial involved tumor specimens from 97 patients with advanced imatinib-resistant GIST who were taking sunitinib during phase I/II trials. Tumor specimens were collected prior to and following imatinib therapy and analyzed for KIT and PDGFRA mutations. Researchers found that while all patients benefited from the drug, the benefit was significantly influenced by the type of mutation a patient had. Progression-free survival and overall survival were significantly longer for patients with a primary KIT exon 9 mutation or those lacking KIT or PDGFRA mutations. (An exon is the segment of a gene that contains instructions for making a protein.)²

REFERENCES

GENITOURINARY CANCERS

Genitourinary cancers include cancers of the prostate, kidney, testicles, and bladder/urethra. The most significant research findings this year were in the treatment of kidney cancer. Patients with advanced kidney cancer or kidney cancer not cured by surgery have historically had few treatment options, with just 15% responding to the standard therapies interferon-a or interleukin-2.

In December 2005, the FDA approved the targeted therapy sorafenib tosylate (Nexavar) for the treatment of advanced kidney cancer, after studies indicated that the drug slowed disease progression and improved survival. Now, new research is demonstrating that two additional targeted therapies can improve survival and response rates in kidney cancer, providing additional hope for patients living with the disease. In addition, a study in patients with germ cell tumors (primarily testis cancers) provides additional information regarding the risks and benefits of high-dose chemotherapy.

MAJOR ADVANCES

TEMSIROLIMUS IMPROVES SURVIVAL IN ADVANCED, HIGH-RISK KIDNEY CANCER

An international, multicenter phase III trial found that administration of the experimental drug temsirolimus as a first-line treatment for high-risk patients with advanced kidney cancer was more effective than both the standard treatment, interferon-a, and therapy that combined interferon-a and temsirolimus. Temsirolimus is a targeted inhibitor of mTOR, a protein that regulates cell growth and angiogenesis (the growth of blood vessels that feed the tumor).

The study had three treatment arms—207 patients received interferon-a, 209 received temsirolimus, and 210 received a combination of the two drugs. Median overall survival for the three groups was 7.3 months, 10.9 months, and 8.4 months, respectively. Progression-free survival was 1.9 months, 3.7 months, and 3.7 months, respectively. The most common side effect in all groups was asthenia (weakness and fatigue), which was lower in the temsirolimus group.

Temsirolimus had other mild side effects which were easily controlled. The relatively mild toxicity associated with the drug suggests it has the potential to be combined with other agents in future studies.¹

SUNITINIB IMPROVES PROGRESSION-FREE SURVIVAL IN ADVANCED KIDNEY CANCER

A phase III international trial involving 750 patients with advanced renal cell carcinoma showed that sunitinib (Sutent) improved progression-free survival and response rates when compared with standard treatment, interferon-a. Sunitinib was approved by the FDA in January 2006 as a second-line treatment for advanced renal cell cancer in patients whose cancer had progressed following treatment with immune therapies. This study was the first to assess the drug in previously untreated patients.

In the trial, none of the patients had received previous chemotherapy, although most had undergone surgery to remove the affected kidney. Half were given sunitinib and half were given interferon-a. Progression-free survival was 47.3 weeks for the sunitinib group, compared with 24.9 weeks for the interferon-a group. Response rates were 24.8% for sunitinib, compared with 4.9% for interferon-a. Researchers will continue to follow the patients in the study to determine the difference in overall survival between the two treatments.²

OTHER NOTABLE RESEARCH

HIGH-DOSE CHEMOTHERAPY IS NOT SUPERIOR TO CONVENTIONAL CHEMOTHERAPY IN TESTIS CANCER

A randomized, phase III trial comparing high-dose chemotherapy with conventional-dose chemotherapy found that the addition of high-dose therapy did not improve survival or response rates for patients with metastatic germ cell tumors (primarily testis cancer). The study adds to a growing body of evidence showing that high-dose chemotherapy is not superior to conventional dose therapy in a number of cancer types, and may be associated with significant risks and additional side effects.
In this study, 219 patients were randomized to conventional chemotherapy followed by high-dose chemotherapy or conventional chemotherapy alone. At one year, 52% of patients on the high-dose regimen had a complete response, compared with 48% of patients who received conventional-dose chemotherapy only. At a median follow-up of 51 months, there was no difference in survival between the two groups. Patients on the high-dose regimen experienced more side effects than those who received conventional chemotherapy; however, these side effects could be managed and were not associated with increased mortality.

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GYNECOLOGIC CANCERS

Gynecologic cancers include cancers of the cervix, uterus, ovaries, fallopian tubes, vulva, and vagina. Ovarian and cervical cancers are two of the most common types of gynecologic cancers in the United States. Cervical cancer, which is closely associated with the human papillomavirus (HPV), is even more prevalent in the developing world, where screening with the Pap test is not widely available, and many pre-cancerous lesions go unnoticed and untreated. Ovarian cancer is difficult to detect in its early stages and, as a result, the majority of women are diagnosed during advanced stages of disease.

One of the most significant advances in gynecologic cancer over the past year was the FDA’s approval of the world’s first vaccine to prevent HPV infection. The implications for the prevention of cervical cancer among women are significant, both in the United States and abroad.

MAJOR ADVANCE
FDA APPROVES FIRST VACCINE TO PREVENT HPV INFECTION

The most significant advance in both gynecologic oncology and cancer prevention in the last year was the June 2006 FDA approval of the first vaccine to prevent HPV infection. The vaccine, known as Gardasil, was shown to be 100% effective in preventing HPV 16- and 18-related cervical precancers in women who were not previously exposed to these strains of the virus. These strains together account for approximately 70% of cervical cancer cases worldwide.1

The Gardasil findings resulted from four phase II and phase III clinical trials, which together evaluated more than 20,000 women between the ages of 16 and 26 from a number of different countries, for up to five years. The studies showed that Gardasil prevented all HPV 16- and 18-related cervical precancers: no cases occurred among 8,487 women who received Gardasil, compared with 53 cases among 8,460 women who received a placebo. Gardasil was also shown to be 99% effective in preventing cases of genital warts caused by HPV type 6 or 11.

Vaccine May Also Protect Against Most Vaginal and Vulvar Cancers

A separate study showed that Gardasil prevented 100% of HPV-related vaginal and vulvar precancers after two years. Such cancers are becoming increasingly common among young women. The study, known as FUTURE II, combined data from three clinical trials evaluating the HPV vaccine in 18,150 women from North and South America, Europe, and Asia who were randomly assigned to receive the vaccine or a placebo. After two years, researchers found that none of the women who received the vaccine developed HPV-related vaginal or vulvar precancers, compared with 24 women in the placebo group.2
In addition, a candidate vaccine known as Cervarix—which targets HPV strains 16 and 18—has shown promise in clinical trials, and is expected to be considered for approval by the FDA in early 2007.

**OTHER NOTABLE RESEARCH**

**CHEMOTHERAPY DELIVERED INTO THE ABDOMEN EXTENDS SURVIVAL FOR WOMEN WITH ADVANCED OVARIAN CANCER**

A new study found that delivering chemotherapy directly into the abdomen ("intraperitoneal" chemotherapy), in addition to intravenous chemotherapy, significantly extended survival in women with advanced ovarian cancer. The phase III trial included 415 patients with advanced ovarian cancer. Researchers found that the addition of intraperitoneal therapy extended median survival by more than one year (49.7 months vs. 65.6 months) compared with intravenous chemotherapy alone. In response to the findings, the NCI issued an announcement recommending that providers consider the combination of the two chemotherapy methods for women with advanced ovarian cancer.

However, women in the study who received intraperitoneal therapy experienced more toxic side effects—including some that were life-threatening—and were more likely to report poorer quality of life, compared with women who received only intravenous therapy. Only 42% of women in the combined chemotherapy group were able to complete all six cycles of therapy, compared with 83% of those who received intravenous chemotherapy alone. Such toxicity has limited the widespread use of intraperitoneal therapy. Researchers noted that subsequent studies should examine the effect of delivering lower doses or other agents through intraperitoneal administration.

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**REFERENCES**

HEAD AND NECK CANCER

Cancers of the head and neck—those affecting the nose, mouth, tongue, throat, and larynx—are usually treated with a combination of surgery, chemotherapy, and/or radiation therapy. In the past year, several studies identified new treatment regimens that could slow the growth of head and neck cancers and improve survival for these patients, without causing significant additional side effects. Head and neck cancers have traditionally been very difficult to treat, and these studies represent some of the most significant advances in the management of head and neck cancer in decades.

MAJOR ADVANCE
CETUXIMAB PLUS RADIOTHERAPY IMPROVES SURVIVAL FOR HEAD AND NECK CANCER PATIENTS

A multinational study found that adding the drug cetuximab (Erbitux) to high-dose radiotherapy in patients with locally advanced head and neck cancer slowed cancer growth and prolonged survival, compared with patients who received radiotherapy alone. Cetuximab is a monoclonal antibody that targets the epidermal growth factor receptor in cancer cells, which stimulates cancer cell growth and repair. The time it took for cancer to progress was significantly longer in the cetuximab group: 24.4 vs. 14.9 months. Patients in the cetuximab group also lived longer: 49 vs. 29.3 months. Moreover, the addition of cetuximab produced relatively mild side effects, including an acne-like rash and local reactions to the drug infusion.1

Cetuximab was approved for the treatment of metastatic colorectal cancer in combination with chemotherapy in 2004. Following publication of this study, the FDA this year approved the drug for use in combination with radiation therapy to treat squamous cell cancer of the head and neck, making it the first drug to be approved for this disease in 45 years. Additional studies are now underway to compare a regimen of cetuximab, platinum-based chemotherapy, and radiation vs. radiation and chemotherapy alone (another commonly-used treatment regimen for this group of patients).

OTHER NOTABLE RESEARCH
ADDING DOCETAXEL TO STANDARD TREATMENT FOR ADVANCED HEAD AND NECK CANCER PROLONGS SURVIVAL

An international, multicenter phase III study showed that patients with locally advanced head and neck cancer who received initial (“induction”) chemotherapy that included docetaxel (Taxotere) were 30% less likely to die than patients who received the standard induction therapy (cisplatin and 5-fluorouracil, or PF). All patients in the study had squamous cell carcinomas, which represent about 90% of head and neck cancers. The tumors were all advanced and were located in the larynx, pharynx, or oral cavity.

In the study, 538 patients were randomized between the two treatments. Induction therapy was followed by ongoing chemotherapy and radiation, and for some patients, surgery. Patients were followed for an average of 41.9 months. Researchers found that overall survival for the group at three years was 62.1%, compared with 48.1% for the control group. The majority of late side effects were related to
radiation therapy. This trial represents the first large multicenter effort to show that the addition of docetaxel to induction therapy, when followed by chemoradiotherapy, improves survival.²

CHEMOTHERAPY AND “RE-IRRADIATION” AFTER SALVAGE SURGERY SLOWS CANCER GROWTH

This study showed that giving the chemotherapy drugs 5-fluorouracil and hydroxyurea with additional radiation therapy to patients who underwent “salvage” surgery for second head and neck cancers or head and neck cancers that had returned extended the time it took for their cancers to grow by 60%, compared with patients who had no treatment after salvage surgery. “Salvage” surgery is the term used to describe surgery to remove cancerous tissue after a tumor has returned, or a new cancer has developed in an area previously treated for cancer. All of the patients had previously received radiation therapy for head and neck cancer. Overall survival did not significantly differ between the two groups.³

These data are the first to compare the effectiveness of such “re-irradiation” and chemotherapy in patients with head and neck cancer following salvage surgery. The additional treatment was not associated with significant side effects.

REFERENCES

LUNG CANCER

Lung cancer incidence and mortality have begun declining in recent years, due to a decrease in smoking rates over the last several decades, particularly among men. However, the disease remains the leading cancer killer in the United States, with an estimated 162,460 deaths expected in 2006.

There has also been recent progress in treating the disease. Some targeted therapies are proving effective against lung cancer, and research has shown that giving chemotherapy after surgery for more advanced lung cancer can prolong survival. At the same time, not all patients with lung cancer are benefiting from these advances. Researchers are learning that specific characteristics of an individual’s tumor may help predict prognosis and response to treatment.

In the last year, several studies have pinpointed specific genetic alterations that suggest whether a patient is likely to respond to a given drug. In addition, researchers have developed a test to identify patients whose cancers are likely to have been cured after surgery, and those that have a high risk of recurrence—individuals who could potentially benefit from chemotherapy following surgery.

MAJOR ADVANCE
RESEARCHERS CREATE GENETIC TEST TO PREDICT LUNG CANCER PROGNOSIS

New research from Duke University has produced a novel gene profiling test that could one day help physicians predict which early-stage non-small cell lung cancer (NSCLC) patients are most likely to have their cancer return. In the study, researchers combined data from two American multicenter trials and examined the genes of 89 patients to develop genetic profiles that could predict the risk of cancer recurrence. This “lung metagene model” was 72% to 79% accurate in predicting recurrence, a rate more accurate than when considering clinical characteristics alone. The test was especially helpful in identifying patients with stage “IA” lung cancer for whom chemotherapy after surgery might be appropriate. Current standard treatment for stage IA NSCLC is surgical removal of the tumor, but up to 25% of patients treated with surgery alone experience a recurrence of their cancer.

Additional studies are planned to confirm the accuracy of this model. If confirmed accurate, the tool could provide an effective means of estimating a patient’s risk of recurrence, enabling physicians and patients to make more informed decisions about the use of chemotherapy for early-stage lung cancer.

OTHER NOTABLE RESEARCH
LUNG CANCERS CONTAINING THE ERCC1 PROTEIN ARE MORE LIKELY TO RESPOND TO CISPLATIN

Researchers with the International Lung Cancer Trial found that patients with NSCLC whose tumors did not contain the enzyme ERCC1—which plays an essential role in DNA repair, including DNA damaged by chemotherapy agents—responded well to the anti-cancer drug cisplatin after surgery. Patients with ERCC1-negative cancers who received cisplatin lived 33% longer than patients with ERCC1-negative tumors who did not receive chemotherapy. However, among patients whose tumors contained ERCC1, there was no difference in survival between the cisplatin and observation groups.

While previous studies have shown that chemotherapy after surgery can help some patients with NSCLC, until now there has been no way to predict which patients are most likely to benefit. This study suggests that ERCC1 could be an important predictive marker, and if confirmed in prospective, randomized trials, could one day help oncologists better identify patients most likely to benefit from cisplatin-based chemotherapy after surgery.

STUDIES CONFIRM ERLOTINIB AND GEFITINIB ACTIVE IN LUNG CANCERS WITH EGFR MUTATIONS

For the first time, four prospective studies indicate that erlotinib (Tarceva) and gefitinib (Iressa) may be particularly effective in lung cancer patients whose tumors have mutations in the EGFR gene. Previous studies have shown that response to these therapies is just 8% to 10% among lung cancer patients without mutations in
the EGFR gene. Both drugs, called tyrosine kinase inhibitors, inhibit an enzyme called the epidermal growth factor receptor (EGFR) tyrosine kinase, on the surface of many tumor cells—including some lung cancers—and may control the growth of the tumor.

Although past research indicated that these drugs might be effective in treating non-small cell lung cancers with EGFR mutations, only retrospective studies supported this claim. The following four prospective studies demonstrate that erlotinib and gefitinib are active in non-small cell lung cancers that contain mutations in the EGFR gene, particularly those with deletions in exons 19 and 21. (An exon is the segment of a gene that contains instructions for making a protein.)

- The first study, a phase II trial by the Spanish Lung Cancer Group involving nearly 300 patients, showed that erlotinib was very active in patients with previously untreated NSCLC who had EGFR mutations, demonstrating an overall response rate of 90%, and a 100% response rate (complete or partial tumor shrinkage) among patients whose tumors had a mutation in exon 19 of the EGFR gene.

- A second study, the phase II ONCOBELL trial involving 28 patients to date, showed that 54% of patients with advanced NSCLC who had EGFR mutations responded to gefitinib.

- The third study, a phase II trial by Memorial Sloan-Kettering Cancer Center involving 20 patients, found that 50% of patients with early-stage lung cancer who received gefitinib before surgery and had deletions in exons 19 and 21 of the EGFR gene experienced tumor shrinkage, compared with 20% of patients with normal EGFR.

- The fourth study, in patients with bronchioloalveolar cell carcinoma, helps to explain why there has been considerable variation in both response to therapy and prognosis among lung cancer patients, even among patients with this distinctive type of lung cancer. In this study of 102 patients at four institutions, researchers showed that the presence of exon 19 and 21 EGFR mutations, the number of copies of the EGFR gene, and the presence of EGFR protein could more precisely predict sensitivity to erlotinib and survival.

REFERENCES

PEDIATRIC CANCERS

Significant progress has been made over the past several decades in treating childhood cancer, with overall five-year survival now at nearly 80%, compared with 58% 30 years ago. An estimated 12,500 new cases of cancer are expected to occur among infants, children, and adolescents under the age of 21 in 2006. An estimated 2,760 cancer-related deaths are expected among children this year, with approximately one-third of these deaths due to leukemia.

The most significant developments this year were the FDA’s approval of two drugs for the treatment of pediatric hematologic cancers.

NOTABLE RESEARCH

FDA APPROVES PEGASPARGASE FOR NEWLY-DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA

In July 2006, the FDA approved pegaspargase (Oncaspar) to treat children newly diagnosed with acute lymphoblastic leukemia (ALL), the most common cancer diagnosed in children.

The FDA approval of the drug for use among children was based on a randomized, multicenter trial of 118 pediatric patients, which demonstrated that pegaspargase could be safely used as an alternative to the previous standard of care, L-asparaginase, as part of a multi-drug regimen for ALL. Pegaspargase is a modified form of L-asparaginase, a naturally occurring enzyme. The major advantage of pegaspargase is that it requires significantly fewer injections than L-asparaginase—three injections over a 20-week period, compared with 21 injections for the standard regimen.

FDA APPROVES NELARABINE FOR RARE LEUKEMIA AND LYMPHOMA

In October 2005, the FDA approved nelarabine (Arranon) for the treatment of children with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), whose cancer has not responded to or has returned following two chemotherapy regimens. In a study of 39 pediatric patients with resistant or recurrent T-ALL/T-LBL, 23% experienced complete remission of disease, which lasted from 3.3 to 9.3 weeks. Nelarabine is the first drug to treat this limited population of patients, and was approved under the FDA’s accelerated approval program, which allows the agency to approve products for life-threatening illnesses based on early evidence of a drug’s effectiveness. As a condition of accelerated approval, the trial sponsor is completing additional studies to confirm the drug’s clinical benefit.

REFERENCES

SKIN CANCER

More than one million cases of skin cancer are diagnosed in the United States every year. While the vast majority of these are basal cell or squamous cell skin cancers, which are relatively easy to treat, there has been a steady increase in the incidence of melanoma in the last several decades. Though less common, melanoma is significantly more invasive, can spread quickly, and is more likely to be life-threatening than other types of skin cancers. Most skin cancers are caused by exposure to ultraviolet radiation from the sun, though other risk factors for melanoma have been identified recently, such as family history, suggesting that the development of melanoma may involve interactions among a variety of factors.

Several studies in the last year identified clinical and genetic factors that contribute to our understanding of the biology of melanoma, which is key to identifying more effective approaches to both treat and prevent the disease. In addition, researchers have developed a new tool to help physicians assess an individual's risk of developing melanoma and plan for potential interventions.

NOTABLE RESEARCH

SENTINEL-NODE BIOPSY HELPS REDUCE RISK OF MELANOMA RECURRENCE, PREDICTS SURVIVAL

The largest clinical trial to evaluate sentinel node biopsy in the staging of melanoma indicates that the procedure can help determine a patient's prognosis, and reduce the risk of melanoma recurrence. Sentinel-node biopsy involves surgical assessment of a lymph node in the area where cancer cells from a tumor are most likely to spread. If that node contains cancer cells, other lymph nodes around it are removed and analyzed as well. If the node is cancer-free, no other nodes are removed, and the patient is spared further surgery.

The study involved 1,269 patients with intermediate-thickness melanoma (1.2 to 3.5 mm) who were randomly assigned to one of two treatment strategies: surgery to remove the tumor, followed by sentinel-node biopsy in the nearby lymph nodes, with immediate removal of surrounding lymph nodes if cancer cells were found in the sentinel node; or surgery to remove the tumor, followed by observation, with immediate removal of the lymph nodes if cancer was found in the lymph nodes, as determined by physical examination.¹

Cancer cells in the lymph nodes were found a median of 16 months earlier by sentinel-node biopsy than by physical examination. In addition, the presence of cancer cells in the sentinel node was the most significant factor predicting a patient's survival. Overall, patients with melanoma who underwent sentinel-node biopsy had a significantly lower rate of cancer recurrence five years after diagnosis (21.7%) than patients whose lymph nodes were monitored after surgery by physical examination (26.9%). The rate of death from melanoma after five years, however, was similar between the two groups (87.1% vs. 86.6%, respectively). These findings support the use of sentinel-node biopsy as standard practice for the staging of cancer in patients with intermediate-thickness melanoma.
STUDIES SUGGEST MELANOMAS ARISE THROUGH DISTINCT PATHWAYS

Two new studies in melanoma suggest that the disease arises through distinct genetic pathways. In the first study, Australian researchers collected data from more than 300 melanoma patients, finding that melanomas of the head and neck are associated with chronic patterns of sun exposure, while those of the trunk are more closely linked to intermittent patterns of sun exposure.\(^2\)

The second study, an international multicenter investigation, found that genetic alterations in melanoma tumors differed according to where on the body the melanomas developed and the patients’ level of sun exposure. Researchers found that 81% of melanomas in parts of the body not damaged by the sun had mutations in the \(\text{BRAF}\) and \(\text{N-RAS}\) genes, while melanomas in parts of the body heavily exposed to the sun did not have these mutations. In addition, melanomas with normal \(\text{BRAF}\) and \(\text{N-RAS}\) genes frequently had more copies of the genes for two enzymes called \(\text{CDK4}\) and \(\text{CCND1}\). The researchers concluded that these findings indicate that melanomas can develop through different genetic pathways.\(^3\)

NEW TOOL DEVELOPED TO IDENTIFY PEOPLE AT HIGH RISK FOR MELANOMA

In this multicenter study led by the NCI, researchers used data from over 1,600 melanoma patients to develop a tool to estimate an individual’s risk of developing melanoma over the next five years. Based on data from more than 1,600 non-Hispanic whites with the disease, the model computes this risk by using information on an individual’s skin complexion, sun exposure, and results of a physical examination of the back and shoulders (including the number of dysplastic nevi—moles with the greatest potential of becoming cancerous).\(^4\)

The authors noted that the results of the tool can be used by health professionals to identify people with an increased risk of melanoma and to help them plan for potential interventions, such as reducing sun exposure, having regular skin exams, and participating in clinical trials of new agents to prevent the disease.

REFERENCES

CANCER PREVENTION

Cancer prevention research involves studying lifestyle changes to reduce the risk of cancer, such as smoking cessation, exercising, or following a balanced diet and maintaining a healthy weight, as well as researching certain drugs, vaccines, and dietary supplements that may lower the risk of developing cancer, often called “chemoprevention.” It may also involve research on interventions to eliminate environmental causes of cancer.

The most significant advances in cancer prevention in the last year were in the field of chemoprevention, including the FDA approval of a vaccine to prevent HPV infection, and the findings of the first head-to-head comparison of tamoxifen and raloxifene to reduce the risk of developing breast cancer.

MAJOR ADVANCE
FDA APPROVES FIRST VACCINE TO PREVENT HPV INFECTION
The most significant advance in cancer prevention in the last year was the June 2006 FDA approval of the first vaccine to prevent HPV infection. The vaccine, known as Gardasil, was shown to be 100% effective in preventing HPV 16- and 18-related cervical precancers in women who were not previously exposed to these strains of the virus. These strains together account for approximately 70% of cervical cancer cases worldwide. The vaccine was also found to be 99% effective in preventing genital warts, which are caused largely by HPV types 6 and 11. The implications for the prevention of cervical cancer among women are widespread, both in the United States and abroad. In addition, an analysis of three large international studies suggests that the vaccine may also be highly effective in preventing HPV-related vaginal and vulvar precancers. (See Gynecologic Cancers, p. 14)

OTHER NOTABLE RESEARCH
TAMOXIFEN AND RALOXIFENE EQUALLY EFFECTIVE IN PREVENTING INVASIVE BREAST CANCER, BUT DIFFERENCES SEEN FOR NON-INVASIVE BREAST CANCER, SIDE EFFECTS
Findings from one of the largest breast cancer prevention trials ever conducted—the Study of Tamoxifen and Raloxifene (STAR)—showed that tamoxifen and raloxifene were equally effective in preventing invasive breast cancer in women at high risk for the disease, reducing risk by about 50%. The study also found that raloxifene was not as effective as tamoxifen in the reduction of non-invasive breast cancer, but that tamoxifen caused more uterine cancers and blood clots than raloxifene. The findings underscore the need for women and their physicians to consider a woman’s medical history, current symptoms, and personal preferences when choosing between therapies.

Tamoxifen is approved by the FDA for three purposes—to treat metastatic breast cancer, to reduce the risk of breast cancer recurrence, and to reduce the risk of developing the disease in both pre- and post-menopausal women at high risk for breast cancer. Raloxifene is approved to prevent osteoporosis, and has also been shown in previous clinical trials to reduce breast cancer risk in postmenopausal women.

The STAR trial, conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), included 19,747 postmenopausal women at increased risk of breast cancer at more than 500 centers in the United States and Canada. Starting in July 1999, participants were randomly assigned to receive 60 mg of raloxifene or 20 mg of tamoxifen once daily for five years. After a median follow-up of four years, researchers found no significant difference in the number of invasive breast cancers between the tamoxifen group (163 cases) and the raloxifene group (167 cases). However, there were fewer non-invasive breast cancers, such as ductal carcinoma in situ or lobular carcinoma in situ, in the tamoxifen group (57 cases), compared with the raloxifene group (81 cases).

The number of uterine cancers was greater among women on tamoxifen (36) than in those who received raloxifene (23). Although both drugs are known to increase the risk of blood clots, the risk was 29% lower in the raloxifene group compared with the tamoxifen group. Rates of heart problems, stroke, bone fracture, or death were similar in both arms of the study. The women are continuing to be followed, and women in the tamoxifen group were given the option to switch to raloxifene.

REFERENCES

CANCER SURVIVORSHIP

According to the NCI, there are now more than 10 million cancer survivors living in the United States. The current five-year relative survival rate for all cancers diagnosed between 1995 and 2001 is 65%, up from 50% in 1974-1976. This marked improvement in survival has been fueled by a growing knowledge of the inner workings of cancer cells, which has brought about improved treatments and diagnostic techniques.

However, with progress in treating cancer comes an emerging challenge—ensuring the long-term health and quality of life of the growing number of cancer survivors. The effects of cancer, and cancer treatment, can last for years after the completion of therapy. Continued advances in cancer research, coupled with a growing and aging population, suggests that both the number of cancer survivors and the needs of this population will continue to increase.

Breast cancer survivors represent the largest group of cancer survivors in the United States. One of the most common side effects of breast cancer treatment is fatigue, and past research has indicated that such fatigue can persist up to five years after diagnosis and treatment. This year, a study of breast cancer patients found that fatigue can continue as much as ten years after diagnosis.

NOTABLE RESEARCH
MORE THAN ONE-THIRD OF BREAST CANCER SURVIVORS REPORT ELEVATED LEVELS OF FATIGUE 5 TO 10 YEARS AFTER DIAGNOSIS

The first large-scale study of fatigue in long-term breast cancer survivors found that more than one-third of women reported elevated levels of fatigue 5 to 10 years after diagnosis.

Between 1994 and 1997, researchers recruited 1,957 women who had been diagnosed with early-stage breast cancer one to five years earlier, were free of disease, and had completed all cancer therapies other than tamoxifen (which is often taken for five years following initial therapy to reduce the risk of recurrence). In 1998, the researchers re-contacted women who were at least five years post-diagnosis, and distributed questionnaires to those who expressed interest in participating in the follow-up survey. Seven hundred and sixty-three women completed questionnaires during both study periods. Researchers compared levels of fatigue during two periods: 1 to 5 years and 5 to 10 years after diagnosis.

Using a standardized survey, women provided information on three general areas of health-related quality of life: physical, emotional, and social well-being. This study focused on reported levels of vitality and physical pain. Researchers found that a similar percentage of women scored in the fatigued range in both the 1-to-5 year (35%) and 5-to-10 year (34%) periods. Among women classified as fatigued in the first assessment, 63% continued to score in the fatigued range at the second assessment. Overall, approximately 21% of women reported being fatigued during both assessment periods, suggesting that persistent fatigue may be a common issue for breast cancer survivors.¹

REFERENCES

As this report demonstrates, significant progress has been made across every area of cancer research—treatment, prevention, survivorship, and quality of life. Much of the progress seen in recent years can be attributed to a far greater understanding of basic biology and the role of genes and proteins in the origin and progression of disease. Such advances in basic science have been particularly important in understanding the genetic characteristics that lead to cancer growth, development, metastasis, recurrence, and responsiveness to treatment, and are critical for progress in the development of personalized therapy for cancer patients.

However, much more needs to be done to ensure that such discoveries move rapidly through the cancer research process. Cancer research faces a number of obstacles, including a growing bottleneck of basic science discoveries waiting to be “translated” into useful therapies and diagnostics, and declining federal funding of translational and clinical cancer research.

Another critical issue hampering cancer research is the increasingly limited access to “biospecimens” (samples of tissue and blood taken from patients during surgeries, biopsies, or routine tests). Such samples are central to most cancer research and vital to development of therapeutic clinical trials.

To accelerate the pace of cancer research, ASCO recommends action steps in two key areas over the coming year:

1. Increase funding for cancer research
2. Improve access to and quality of human biospecimens

1. INCREASE FUNDING FOR CANCER RESEARCH
Congress’ doubling of the NIH budget between 1998 and 2003 yielded major new discoveries in all areas of biomedical research, including cancer. However, flat funding for NIH since 2003, and a possible cut in fiscal year 2007, threatens to derail the translation of those basic scientific discoveries into treatments that will benefit humans. Such cuts would be particularly harmful for cancer research, which, in addition to shrinking federal grants, is suffering from program cuts and a limited supply of young investigators.

In addition, using the biologic “keys” discovered in the lab to unlock the door for cancer treatment will require additional funding for clinical trials, and the participation of many thousands of patients. Although hundreds of clinical trials are taking place at any one time, researchers estimate that today it takes as long as ten years between the identification of a target for cancer therapy and the availability of that therapy for patients, depending on the type of cancer being studied and the endpoints being measured. In order to take full advantage of new knowledge about the biology of cancer, we must accelerate the pace of clinical research and shorten this time frame. But without adequate funding, that timeline could become even longer and some promising new therapies might never be studied at all.

Recommendation:
- To avoid losing ground in cancer research, ASCO supports annual minimum funding increases of 5% for NIH, beginning in fiscal year 2007. Consistent funding levels—with 5% as the predictable floor—are the minimum required to keep pace with inflation. More aggressive increases are vital to speed research from the laboratory to the patient’s bedside and should be pursued if the current momentum in cancer research is to continue.
2. ADVANCE RESEARCH FROM THE LAB TO THE CLINIC: INCREASING ACCESS TO BIOSPECIMENS

While cancer research is dependent on a host of factors—scientific, financial, and human—biospecimens play a critical role in “translating” basic science discoveries into clinical applications. Using biospecimens, researchers can study the development and progression of cancer, develop drugs that target features of cancer cells, and test those drugs on tumor samples before human testing in clinical trials. But today, cancer researchers report that ready access to biospecimens is a major challenge. Below is a summary of the key issues regarding use of biospecimens in cancer research, and ASCO’s recommendations to overcome these obstacles.

Standardized Collection and Storage of Biospecimens

To conduct a single study, researchers must obtain a large number of high-quality biospecimen samples with accompanying clinical information about the patient’s disease, prior treatment, and other health problems. While many existing repositories in the United States house millions of biospecimens, there are no common procedures for collecting and storing specimens, and no consistent quality-control measures. Samples are often stored under varying conditions and may not have accompanying clinical information about the patient, making it difficult for researchers to pool, share, or compare results. In addition, many of these samples do not have appropriate authorization from the donor for use in research studies, and retroactive authorization is costly and difficult to obtain.

Recommendations:

There is an urgent need for national guidelines to standardize procedures for the collection, storage, and use of biospecimens and their accompanying data.

- New guidelines being developed by the NCI on the establishment and maintenance of NCI-supported biorepositories are an important first step, and should be rapidly implemented, but additional guidance will be needed beyond these basic requirements, as well as funding to support their implementation.

- A nationally-available database linking NCI-supported biorepositories should be created, so that cancer researchers can share information and expertise across institutions.

Impact of Privacy Laws on Cancer Research

The Health Insurance Portability and Accountability Act (HIPAA), enacted by Congress in 1996, established new protections for the use and disclosure of patient health information. While ASCO supports the overall principles of HIPAA and agrees that preserving a patient’s right to privacy is important, variations in the implementation and interpretation of such privacy regulations have inadvertently made it much more difficult to conduct critical cancer research. For example, researchers report that these regulations have led to delayed or limited access to human biospecimens needed for large-scale studies.

Under HIPAA, in order to use human biospecimens, researchers are required to get authorization from every patient for each research project. Scientists report that this requirement has made research significantly more complex than it was before HIPAA was enacted. Some examples from a recent Institute of Medicine (IOM) report include:

- Researchers report that their work has become significantly more expensive and time-consuming
- Community hospitals have reported terminating their participation in research efforts because of concerns about liability
- Researchers have reported that they are losing a large proportion of research participants because of confusion about regulations and heavy paperwork
- Cancer registries—which document information about cancer cases to identify demographic patterns and disease characteristics—are reporting sharp declines in patient participation, with some registries reporting only 15% enrollment today, compared with 100% enrollment before HIPAA was enacted.
In addition, important rules governing research—FDA regulations, the Common Rule, and HIPAA—often diverge.* These discrepancies have caused confusion and widely variable implementation across research institutions and settings. Such variation—in large part the product of institutions’ concern about liability—has added to delays and barriers mentioned above.

**Recommendations:**

- Because the extent of HIPAA’s impact on cancer research specifically is not clear, ASCO recommends that an independent body—such as the IOM—conduct a rigorous review of the law’s effect on cancer research, and identify what changes, if any, are necessary to improve access to biospecimens. Congress and the Administration should use recommendations from such a study to make appropriate regulatory or statutory changes.

- The Secretary of Health and Human Services (HHS) should make it a priority to harmonize HIPAA and relevant FDA regulations with those contained in the Common Rule.

- Clear standards and guidance, aimed at standardizing implementation of HIPAA provisions across research settings, should be issued by HHS.

**Tissue Ownership and Intellectual Property Rights**

Debate over tissue ownership and intellectual property rights has also limited access to biospecimens. Controversy exists over who owns samples—the repository or the patient who donated the sample—as well as who owns the right to any discoveries made using the samples. Such debates have also made it difficult for researchers to pool samples or to compare the results across institutions. As researchers and industry sponsors have sharply increased their demand for biospecimens, some institutions have begun asserting control over biospecimens, associated data, and research findings.

**Recommendation:**

- The creation of a centralized database for biospecimens could greatly speed scientific discovery in cancer research. ASCO calls for a new collaborative effort involving leaders from cancer institutions, government, industry, and patient groups to identify ways that such information could be shared for the benefit of all parties in cancer research, while maintaining appropriate protection for intellectual property.

* The Common Rule is the 1991 federal regulation that provides basic procedures and principles that are to be followed in the conduct of human subject research sponsored by federal agencies. It requires a review of proposed research by an Institutional Review Board (IRB), the informed consent of research subjects, and institutional assurances of compliance with regulations.
### Cancer Incidence, Mortality, And Survival Rates

#### Cancer Incidence & Mortality, 2006

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated Deaths</th>
<th>Estimated New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>564,830</td>
<td>1,399,790</td>
</tr>
<tr>
<td>Lung</td>
<td>162,460</td>
<td>174,470</td>
</tr>
<tr>
<td>Colorectal</td>
<td>55,170</td>
<td>148,610</td>
</tr>
<tr>
<td>Breast</td>
<td>41,430</td>
<td>214,640</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32,300</td>
<td>33,730</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,350</td>
<td>234,460</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>18,840</td>
<td>58,870</td>
</tr>
<tr>
<td>Liver</td>
<td>16,200</td>
<td>18,510</td>
</tr>
<tr>
<td>Ovary</td>
<td>15,310</td>
<td>20,180</td>
</tr>
<tr>
<td>Esophagus</td>
<td>13,770</td>
<td>14,550</td>
</tr>
<tr>
<td>Bladder</td>
<td>13,060</td>
<td>61,420</td>
</tr>
<tr>
<td>Kidney</td>
<td>12,840</td>
<td>38,890</td>
</tr>
<tr>
<td>Brain</td>
<td>12,820</td>
<td>18,820</td>
</tr>
<tr>
<td>Stomach</td>
<td>11,430</td>
<td>22,280</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>11,310</td>
<td>16,570</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>9,040</td>
<td>11,930</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7,910</td>
<td>62,190</td>
</tr>
<tr>
<td>Endometrial</td>
<td>7,350</td>
<td>41,200</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>4,660</td>
<td>10,020</td>
</tr>
<tr>
<td>Larynx</td>
<td>3,740</td>
<td>9,510</td>
</tr>
<tr>
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<td>9,710</td>
</tr>
<tr>
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<tr>
<td>Gallbladder</td>
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<td>8,570</td>
</tr>
<tr>
<td>Pharynx</td>
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<td>8,950</td>
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<tr>
<td>Mouth</td>
<td>1,870</td>
<td>10,230</td>
</tr>
<tr>
<td>Tongue</td>
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<tr>
<td>Other oral cavity</td>
<td>1,670</td>
<td>2,770</td>
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<tr>
<td>Childhood cancers(^1)</td>
<td>1,560</td>
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<tr>
<td>Thyroid</td>
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<td>Hodgkin lymphoma</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Bones &amp; joints</td>
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<tr>
<td>Small intestine</td>
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<td>6,170</td>
</tr>
<tr>
<td>Vulva</td>
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<tr>
<td>Vagina</td>
<td>820</td>
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</tr>
<tr>
<td>Ureter</td>
<td>770</td>
<td>2,430</td>
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<tr>
<td>Anus</td>
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<td>4,660</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>600</td>
<td>4,500</td>
</tr>
<tr>
<td>Testis</td>
<td>370</td>
<td>8,250</td>
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<tr>
<td>Penis</td>
<td>280</td>
<td>1,530</td>
</tr>
<tr>
<td>Eye</td>
<td>230</td>
<td>2,360</td>
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</table>

#### Five-Year Survival Rates, 1974-2000 (Select Cancers)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All Cancers</td>
<td>50%</td>
<td>53%</td>
<td>65%</td>
</tr>
<tr>
<td>Prostate</td>
<td>67%</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>92%</td>
<td>94%</td>
<td>97%</td>
</tr>
<tr>
<td>Testis</td>
<td>79%</td>
<td>91%</td>
<td>96%</td>
</tr>
<tr>
<td>Melanoma(^2)</td>
<td>80%</td>
<td>85%</td>
<td>92%</td>
</tr>
<tr>
<td>Breast</td>
<td>75%</td>
<td>78%</td>
<td>88%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>71%</td>
<td>79%</td>
<td>85%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>88%</td>
<td>83%</td>
<td>84%</td>
</tr>
<tr>
<td>Bladder</td>
<td>73%</td>
<td>78%</td>
<td>82%</td>
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<tr>
<td>Cervical</td>
<td>69%</td>
<td>69%</td>
<td>73%</td>
</tr>
<tr>
<td>Larynx</td>
<td>66%</td>
<td>67%</td>
<td>66%</td>
</tr>
<tr>
<td>Kidney</td>
<td>52%</td>
<td>56%</td>
<td>65%</td>
</tr>
<tr>
<td>Rectum</td>
<td>49%</td>
<td>55%</td>
<td>65%</td>
</tr>
<tr>
<td>Colon</td>
<td>50%</td>
<td>58%</td>
<td>64%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>47%</td>
<td>54%</td>
<td>60%</td>
</tr>
<tr>
<td>Oral(^3)</td>
<td>54%</td>
<td>53%</td>
<td>59%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34%</td>
<td>41%</td>
<td>48%</td>
</tr>
<tr>
<td>Ovary</td>
<td>37%</td>
<td>41%</td>
<td>45%</td>
</tr>
<tr>
<td>Brain</td>
<td>22%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>24%</td>
<td>28%</td>
<td>32%</td>
</tr>
<tr>
<td>Stomach</td>
<td>15%</td>
<td>17%</td>
<td>23%</td>
</tr>
<tr>
<td>Lung</td>
<td>13%</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5%</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Liver</td>
<td>4%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>

### Notes

1. Incidence and mortality figures for all sites include cancers not listed in table, including nonepithelial skin cancers; other digestive, respiratory, oral, and endocrine cancers; other types of leukemia; and unspecified primary sites.
3. Other skin cancers—including squamous cell and basal cell skin cancers—are diagnosed in more than 1 million people in the U.S. each year, and are not included in this table.
4. Oral cancers include those of the nose, mouth, tongue, throat, and pharynx.

CANCER MORTALITY TRENDS

Cancer Death Rates*, for Men, US, 1930-2002

Cancer Death Rates*, for Women, US, 1930-2002

*Age-adjusted to the 2000 US standard population.
National Center for Health Statistics, Centers for Disease Control and Prevention, 2005.

FDA APPROVALS OF ANTI-CANCER AGENTS
NOVEMBER 2005-OCTOBER 2006

NEWLY APPROVED AGENTS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Indication(s)</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>sorafenib tosylate</td>
<td>Nexavar</td>
<td>Advanced renal cell carcinoma</td>
<td>12/20/2005</td>
</tr>
<tr>
<td>lenalidomide</td>
<td>Revlimid</td>
<td>Transfusion-dependent anemia due to myelodysplastic syndromes (MDS)</td>
<td>12/27/2005</td>
</tr>
<tr>
<td>sunitinib</td>
<td>Sutent</td>
<td>Gastrointestinal stromal tumors (GIST) and advanced renal cell carcinoma (RCC)</td>
<td>1/26/2006</td>
</tr>
<tr>
<td>decitabine</td>
<td>Dacogen</td>
<td>Myelodysplastic syndromes (MDS)</td>
<td>5/2/2006</td>
</tr>
<tr>
<td>Quadrivalent HPV Recombinant Vaccine</td>
<td>Gardasil</td>
<td>Inoculation against human papillomavirus (Types 6, 11, 16, 18) among females 9-26 years of age</td>
<td>6/8/2006</td>
</tr>
<tr>
<td>dasatinib</td>
<td>Sprycel</td>
<td>Chronic myelogenous leukemia (CML)</td>
<td>6/28/2006</td>
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<tr>
<td>panitumumab</td>
<td>Vectibix</td>
<td>EGFR-expressing metastatic colorectal cancer</td>
<td>9/27/2006</td>
</tr>
<tr>
<td>voninostat</td>
<td>Zolinza</td>
<td>Progressive or recurrent cutaneous T-cell lymphoma (CTCL)</td>
<td>10/6/2006</td>
</tr>
</tbody>
</table>

EXPANDED INDICATIONS FOR EXISTING AGENTS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Indication(s)</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>erlotinib</td>
<td>Tarceva</td>
<td>First-line treatment of locally advanced, inoperable, or metastatic pancreatic cancer (in combination with gemcitabine)</td>
<td>11/2/2005</td>
</tr>
<tr>
<td>rituximab</td>
<td>Rituxan</td>
<td>First-line treatment of diffuse large B-cell (DLBCL) non-Hodgkin lymphoma (in combination with chemotherapy)²</td>
<td>2/10/2006</td>
</tr>
<tr>
<td>cetuximab</td>
<td>Erbitux</td>
<td>Advanced, unresectable squamous cell carcinoma of the head and neck (in combination with radiation therapy)</td>
<td>3/1/2006</td>
</tr>
<tr>
<td>topotecan hydrochloride</td>
<td>Hycamtin</td>
<td>Late-stage cervical cancer (in combination with cisplatin)</td>
<td>6/14/2006</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>Second-line therapy for metastatic colorectal cancer (in combination with chemotherapy)</td>
<td>6/20/2006</td>
</tr>
<tr>
<td>lenalidomide</td>
<td>Revlimid</td>
<td>Multiple myeloma among patients who have received at least one prior therapy (in combination with dexamethasone)</td>
<td>6/29/2006</td>
</tr>
<tr>
<td>gemcitabine hydrochloride</td>
<td>Gemzar</td>
<td>Recurrent ovarian cancer³</td>
<td>7/16/2006</td>
</tr>
<tr>
<td>pegasparagase</td>
<td>Oncaspar</td>
<td>Acute lymphoblastic leukemia (ALL)⁴</td>
<td>7/24/2006</td>
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<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>Unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (NSCLC) (in combination with chemotherapy)</td>
<td>10/11/2006</td>
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<tr>
<td>docetaxel</td>
<td>Taxotere</td>
<td>Inoperable, locally advanced squamous cell carcinoma of the head and neck (SCCHN)</td>
<td>10/17/2006</td>
</tr>
</tbody>
</table>

REFERENCES

1. Approved for use in adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy.
2. Approved for use in the first-line treatment of patients with diffuse large B-cell, CD20-positive, non-Hodgkin lymphoma, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens. Rituxan was previously approved as a single agent for use in relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma.
3. Approved for advanced ovarian cancer that has relapsed at least six months after initial therapy.
4. FDA previously approved Oncaspar in 1994 only for patients with ALL unable to receive L-asparaginase due to allergy.