CANCERCARE® CONNECT BOOKLET SERIES

Your Guide to the Latest Cancer Research and Treatments

Highlights From the 2015 Annual Meeting of the American Society of Clinical Oncology

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This special edition of the Cancer*Care* Connect Booklet Series highlights cutting-edge research presented at the 2015 Annual Meeting of the American Society of Clinical Oncology, which took place May 29 to June 2 in Chicago, Illinois.

The Cancer*Care* Connect Booklet Series offers up-to-date, easy-to-read information on the latest treatments, managing side effects and coping with cancer.

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Your Guide to the Latest Cancer Research and Treatments

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How to Use This Booklet

Each year, Cancer*Care*® publishes a special edition of the Cancer*Care* Connect Booklet Series that presents research highlights from the Annual Meeting of the American Society of Clinical Oncology. The information contained in these pages is intended for discussion with your doctor. He or she can tell you whether these advances in cancer treatment affect your treatment plan and whether a clinical trial is right for you.

Some of the treatments discussed in this booklet are still in the very early stages of research and may not be available to the general public outside of a clinical trial. The advances in treatment that have come about are because of the many people who have taken part in such studies. If current drugs or other types of cancer treatment no longer benefit you, you may wish to explore joining a clinical trial. The members of your health care team will help you fully understand the possible risks and benefits involved.

On page 65, you will find a list of resources, including websites where you can search for a clinical trial. If your particular type of cancer is not discussed in this booklet and you wish to take part in a study, these websites can help.

About the Editors

The content of this booklet was taken from Cancer*Care*'s two-part Connect Education Workshop 2015 ASCO Highlights series, during which the following leading experts presented:

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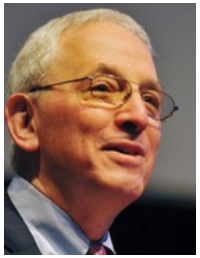

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Brain Cancer

Researchers reported a number of important findings in brain cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

An individualized heat shock protein peptide vaccine added to standard therapy after surgery might improve survival in glioblastoma. The vaccine can only be made for patients with glioblastomas that can be removed by surgery (page 6).

The addition of tumor treating fields (TTFs) to temozolomide maintenance therapy improved survival in patients with newly diagnosed glioblastoma in a large international study. TTFs are electric fields generated by a portable device worn by patients (page 8).

Combination treatment with a new vaccine rindopepimut plus bevacizumab appear to help patients with relapsed glioblastoma. A small study found that this combination provided a modest survival benefit over bevacizumab plus placebo (a look-alike containing no active ingredient) (page 9).

Individualized Heat Shock Protein Peptide Vaccine for Newly Diagnosed Glioblastoma

An individualized (autologous) heat shock protein peptide vaccine (HSPPC-96) added to standard therapy after surgery might improve survival in people with newly diagnosed glioblastoma, according to initial results from a small clinical trial. HSPPC-96 is a protein peptide complex consisting of a heat shock protein, gp96, and an array of gp96-associated cellular peptides. The vaccine is made by isolating HSPPC-96 from the patient's own resected tumor tissue. Thus, all 46 patients in this study had glioblastoma that could be surgically removed.

After surgery to remove the tumor, patients received chemoradiotherapy. During this period, laboratory technicians processed samples of from each patient's resected tumors to make the individualized HSPPC-96 vaccines. Within five weeks after the end of chemoradiotherapy, patients started weekly and then monthly vaccination until their vaccine ran out or their cancer progressed. Patients also received standard adjuvant temozolomide (Temodar). An adjuvant treatment is any type of therapy given after the main treatment used to treat or remove the cancer. The purpose of adjuvant treatment is to decrease the chance that a cancer will return.

The vaccine appeared to have some anti-cancer activity. Vaccinated patients experienced median progression-free survival of about 18 months and median overall survival of about 24 months (95% CI, 19.8-30.2). The vaccinations did not cause any serious side effects.

What Patients Need to Know

The study did not include a control group of patients not treated with the vaccine, so there is no way to know for sure whether the vaccine improved survival. An ongoing clinical trial is comparing HSPPC-96 plus bevacizumab (Avastin) versus bevacizumab alone in patients with recurrent glioblastoma that can be removed by surgery.

Tumor Treating Fields for Newly Diagnosed Glioblastoma

The addition of tumor treating fields (TTFs) to temozolomide maintenance therapy improved survival in patients with newly diagnosed glioblastoma in a large international study. TTFs are electrical fields generated by a portable device (Optune) worn by patients. The device sends low-intensity, alternating electrical fields into the brain that block cancer cell division. It is used for several weeks at a time, and is equipped with a battery power pack so that patients can continue with their daily activities.

The study included 700 patients. After patients completed chemoradiotherapy, they received either adjuvant maintenance therapy with temozolomide alone or temozolomide plus TTF. Patients treated with TTF experienced improved progression-free survival (7 versus 4 months), overall survival (19 versus 17 months), and two-year survival (43 percent versus 29 percent). The addition of TTF did not appear to cause any side effects or interfere with quality of life.

What Patients Need to Know

Results from the first 315 patients were published in the Journal of the American Medical Association in December 2015. These results paved the way for the U.S. Food and Drug Administration (FDA) to expand the indication of Optune to be used in combination with temozolomide to treat adults with newly diagnosed glioblastoma in October 2015 (it was initially approved in 2011 for use in glioblastoma patients following tumor recurrence.) For the TTF device to work, patients must have their heads shaved, as the device's transducer arrays stick to the shaved scalp. Patients are allowed to cover their head with hats, scarfs, and loose-knit wigs. The device should stay on for at least 18 hours a day, during which it must stay dry.

Rindopepimut Vaccine for Recurrent Glioblastoma

Combination treatment with a new vaccine rindopepimut (Rintega) plus bevacizumab appeared to modestly benefit patients with relapsed glioblastoma compared to bevacizumab plus placebo vaccination in a small study. Rindopepimut is a vaccine against EGFRvIII, a specific mutation in epidermal growth factor receptor (EGFR) that is present in some glioblastoma patients. The vaccine is injected into the skin along with granulocyte-macrophage colony-stimulating factor (GM-CSF), a medication that boosts the immune system's ability to fight infection.

The study included 72 patients with relapsed EGFRvIII-positive glioblastoma who had not previously received bevacizumab. Patients treated with bevacizumab plus rindopepimut experienced longer overall survival (12 versus 9 months) and better progression-free survival at six months (27 percent versus 11 percent) compared to patients treated with bevacizumab plus the placebo vaccine.

A mild injection site reaction was the most common side effect of the vaccine. The researchers have not yet published the final results of this study, although mature long-term survival data were presented at the Annual Scientific Meeting of the Society for Neuro-Oncology in November 2015.

What Patients Need to Know

Rindopepimut is an investigational vaccine only available through clinical trials. However, a phase 3 study of rindopepimut in glioblastoma was discontinued in March 2016 because it failed to provide a survival benefit; the future of this therapy is not clear.

Breast Cancer

Researchers reported a number of important findings in breast cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Anastrozole was slightly better than tamoxifen in decreasing cancer recurrences (the cancer returning) after surgical removal of ductal carcinoma in situ (DCIS). The trial included 3,000 post-menopausal women who were followed for 10 years (page 11).

Palbociclib added to fulvestrant improved survival in women with estrogen receptor-positive, HER2-negative metastatic breast cancer that had relapsed or progressed during hormone therapy. Patients treated with palbociclib experienced longer progression-free survival compared to placebo-treated patients, with only minor side effects (page 12).

Treatment with ado-trastuzumab emtansine (T-DM1) was as effective as trastuzumab plus a taxane in women with locally advanced or metastatic HER2-positive breast cancer. A study found no difference in progression-free survival between patients who received T-DM1 plus pertuzumab, T-DM1 plus placebo, and trastuzumab plus a taxane (page 13).

Preoperative T-DM1 appears to improve outcomes in patients with HER2-positive hormone receptor-positive early-stage breast cancer, according to preliminary results from a clinical trial. T-DM1 more effectively eliminated these cancers compared to trastuzumab (page 15).

Anastrozole for DCIS

Anastrozole (Arimidex) decreased recurrences after surgical removal of ductal carcinoma in situ (DCIS) at a slightly higher rate than tamoxifen, according to a large clinical trial that included 3,000 post-menopausal women with DCIS. The women underwent surgical removal (lumpectomy) of the DCIS, followed by radiation therapy. Then, half of the women took anastrozole for five years, while the other half took tamoxifen. After 10 years, the researchers counted how many patients were alive and had not experienced a "breast cancer event"—either a DCIS recurrence or the appearance of breast cancer. Compared to tamoxifen, anastrozole provided patients about a 4 percent absolute improvement with respect to not experiencing a breast cancer event during the 10-year period. This benefit was most commonly observed in post-menopausal women younger than 60 years, although the reasons for this are not known.

The researchers also found that the patients who received tamoxifen were more likely to develop cancers of the uterus and blood clots than those who received anastrozole, while patients in the anastrozole group experienced more bone fractures.

What Patients Need to Know

DCIS is a pre-invasive breast cancer that represents about 15 percent of the breast cancers that are diagnosed in the United States. DCIS is most commonly found by screening mammograms. Previous studies demonstrated that tamoxifen decreased the rate of breast cancer recurrence after surgical removal of DCIS surgery. The results of this trial suggest that anastrozole might be better than tamoxifen in reducing the rate of recurrence. Patients and their doctors should carefully weigh the risks and benefits when considering drug therapy after DCIS.

Palbociclib for Estrogen Receptor-Positive Invasive Breast Cancer

Palbociclib (Ibrance) added to fulvestrant (Faslodex) improved survival in women with estrogen receptor-positive, HER2-negative metastatic breast cancer that had relapsed or progressed during hormone therapy (also called endocrine therapy). Palbociclib is a cyclin-dependent kinase 4/6 inhibitor. In laboratory studies, palbociclib was shown to work together with hormone therapies, such as fulvestrant and letrozole (Femara), to limit breast cancer cell proliferation.

This study included 521 pre- and post-menopausal women. All patients received monthly intramuscular injections of fulvestrant. Every three out of four weeks, 174 patients took daily placebo pills and 347 took daily palbociclib pills.

Women who took both palbociclib and fulvestrant experienced longer progression-free survival (9 months versus 4 months) compared to women who took placebo and fulvestrant. Side effects associated with palbociclib included low white blood cells, low red blood cells (anemia), low platelets (blood cells that help in clotting), extreme tiredness (fatigue), and infection. Most of these side effects were minor, and very few patients stopped treatment because of side effects.

What Patients Need to Know

In February 2015, the FDA approved palbociclib combined with letrozole for women with estrogen receptor-positive, HER2-negative metastatic breast cancer not previously treated with endocrine therapy. Based on the results of this new study—which were published in the *New England Journal of Medicine* in June 2015—the FDA expanded the palbociclib indication: palbociclib is now also approved to be given with fulvestrant in women who experience their breast cancer advance after hormone therapy.

T-DM1 for Previously Untreated Metastatic HER2-Positive Invasive Breast Cancer

The results of a large trial indicated that ado-trastuzumab emtansine (T-DM1; Kadcyla) with or without pertuzumab (Perjeta) was as effective as trastuzumab (Herceptin) plus a taxane (docetaxel [Taxotere] or paclitaxel [Taxol]) in women with locally advanced or metastatic HER2-positive breast cancer. There are four FDA-approved drugs for patients with HER2-positive breast cancer: trastuzumab, pertuzumab, lapatinib (Tykerb), and T-DM1. Pertuzumab and trastuzumab are monoclonal antibodies that bind to different places on the HER2 molecule, while lapatinib blocks the chemical activity of HER2. T-DM1 consists of trastuzumab linked to the chemotherapy drug emtansine. The trastuzumab portion allows T-DM1 to bind to HER2 on breast cancer cells, and it then enters the cell to deliver the chemotherapy payload that kills it.

This study included 1,095 women who had not been treated for their metastatic recurrence. One-third of the women in the trial received T-DM1 plus placebo, one-third received T-DM1

plus pertuzumab, and one-third received the standard of care—a taxane plus trastuzumab.

After almost three years, no difference in progression-free survival was observed between the three patient groups: 15 months for T-DM1 plus pertuzumab, 14 months for T-DM1 plus placebo, and 14 months for a taxane plus trastuzumab.

Compared to patients who received a taxane with trastuzumab, patients treated with T-DM1 experienced fewer side effects, including neuropathy, diarrhea, and hair loss, and better health-related quality of life. However, patients treated with T-DM1 experienced more liver toxicity and decreased platelet counts.

What Patients Need to Know

T-DM1 is approved as a single agent to treat patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. The results of this trial suggest that T-DM1 works as well as trastuzumab plus chemotherapy in metastatic breast cancer, with fewer side effects.

Preoperative T-DM1 for HER2-Positive Early-Stage Breast Cancer

T-DM1 appears to improve outcomes in patients with HER2-positive, hormone receptor-positive early-stage breast cancer when it's given before surgery, according to preliminary results from a clinical trial. In this trial, 380 patients received 12 weeks of preoperative (called neoadjuvant) therapy. There were three treatment groups: one group received T-DM1 and hormone therapy, one group received T-DM1 alone, and the third group received trastuzumab plus hormone therapy. Hormone therapy consisted of tamoxifen for premenopausal women and an aromatase inhibitor for postmenopausal women. After the 12 weeks, patients underwent surgery to remove any remaining traces of cancer. Following surgery, all of the study participants received standard postoperative chemotherapy plus trastuzumab.

The results from the first 130 patients suggest that T-DM1 was more effective than trastuzumab in removing cancer. After the 12 weeks of treatment, 40 percent and 45 percent of patients in the two T-DM1 groups had pathologic complete responses, meaning that no evidence of cancer was found following therapy. In contrast, only 7 percent of patients in the trastuzumab group had complete responses.

What Patients Need to Know

Thus far, preoperative T-DM1 appears to work better than trastuzumab in eliminating early-stage breast cancer. However, this study is still ongoing, and these initial findings need to be verified among all of the study patients. If confirmed, these excellent response rates with preoperative T-DM1 suggest that some early-stage HER2-positive breast cancer patients may be able to avoid chemotherapy after surgical removal of their cancers.

Colorectal Cancer

Researchers reported a number of important findings in colorectal cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Past and new studies make it clear that exercise and a healthy diet reduce the risk of colon cancer recurrence after treatment. Researchers are investigating whether use of anti-inflammatory drugs such as aspirin may also help reduce colon cancer recurrence (page 16).

Metastatic colorectal cancer patients with high vitamin D blood levels have better outcomes following treatment than patients with low vitamin D levels. More research is needed to confirm these findings and to determine whether boosting people's vitamin D levels can improve the effectiveness of chemotherapy (page 19).

TAS-102 improved survival compared to placebo in patients with previously treated metastatic colorectal cancer. These results led to fast-track approval of TAS-102 by the FDA (page 20).

Patients with mismatch repair-deficient colorectal cancer appear to be more likely to benefit from pembrolizumab than patients with mismatch repair-proficient cancers. Patients with mismatch repair-deficient colorectal cancer experienced longer survival compared to patients with mismatch repair-proficient cancers (page 21).

Secondary Prevention for Colon Cancer

The 2015 meeting of the American Society of Clinical Oncology dedicated an entire session to the topic of cancer prevention. For colon cancer, researchers discussed how exercise, diet, and certain medications can lower the chance of cancer recurrence. Based on new and old information, three important recommendations were made.

First, **exercise** can definitely impact the likelihood of colon cancer recurrence, especially when done during treatment after upfront surgery. Studies have shown that people get the most benefit from exercise when they do moderate to strenuous activities several times per week. To verify this finding, researchers checked whether only patients who were fit enough to do vigorous exercise had a lower rate of cancer recurrence. The researchers found exercise had a positive impact even when patients were matched for lifestyle, diet, and body mass. These results suggest that exercise alone can reduce cancer recurrence. While the most effective level of activity is greater than a light stroll around the block, any level of exercise helps.

Second, **eating well** helps prevent cancer. Several large studies have suggested that people who eat a healthier diet have an improved likelihood of remaining cancer-free.

Third, **controlling inflammation** with medications might help prevent cancer. Over the years, several research studies have demonstrated that aspirin and other anti-inflammatory medications help not only in preventing colon cancer, but also in preventing colon cancer from recurring.

One of the main scientific presentations at the 2015 meeting looked retrospectively (meaning that it evaluated events that had occurred in the past) at data from a very large group of patients in Norway who had been diagnosed with stage I, II, or III colon cancer. Because at the time of the study Norway did not implement routine screening colonoscopies, most of the patients had been diagnosed after experiencing symptoms, such as bleeding. Of the 25,000 patients, 6,000 patients regularly took aspirin and 19,000 patients did not. The aspirin users tended to be older and male. Most of them were taking aspirin for another medical problem, such as a heart condition.

The researchers found that aspirin users had about a 25 percent significant improvement in survival compared to non-aspirin users. The analysis was adjusted to account for any differences in heart disease and other health problems

between the groups. Since this was a retrospective study, a prospective, or forward-looking, randomized study would help confirm the results.

What Patients Need to Know

An ongoing clinical study, called the CHALLENGE trial, is testing the effect of an exercise program in preventing cancer recurrence in people who have been treated for high-risk stage II or III colon cancer. The study will compare outcomes between people who participate in a physical activity program and receive general health education materials versus people who only receive the general health education materials. The CHALLENGE trial is recruiting patients in the United States, Canada, France, and South Korea.

An ongoing clinical trial, called CALGB 80702, is enrolling patients with surgically removed stage III colon cancer and will try to answer two questions: (1) How much chemotherapy is enough to prevent cancer recurrence? (2) Does use of an anti-inflammatory agent help prevent cancer recurrence? All of the patients will receive FOLFOX chemotherapy—a combination of folinic acid (leucovorin), fluorouracil, and oxaliplatin (Eloxatin). Half of the patients are being randomized to 6 cycles of chemotherapy and half to 12 cycles. Patients are also being randomized to take the anti-inflammatory medication celecoxib (Celebrex) or a placebo pill for 2 years. The results from this study will help determine whether anti-inflammatory drugs help prevent colon cancer recurrence.

Vitamin D Levels for Metastatic Colorectal Cancer

Patients with metastatic colorectal cancer who have high vitamin D blood levels had better outcomes following treatment than patients with low vitamin D levels, according to a retrospective analysis of data from a large clinical trial. The trial compared chemotherapy plus bevacizumab (Avastin) versus chemotherapy plus cetuximab (Erbitux) versus chemotherapy plus bevacizumab and cetuximab. The main results from the trial were presented at the 2015 American Society of Clinical Oncology Annual Meeting.

To study the effects of vitamin D levels in colorectal cancer, researchers evaluated data from the 1,000 patients in this study who had their blood drawn and vitamin D levels tested before they started treatment. These patients had vitamin D levels that ranged from very low (less than or equal to 8 milligrams per deciliter) to the high end of normal (at or above 27 milligrams per deciliter).

The researchers found that patients with high vitamin D levels had the best outcomes following chemotherapy. More studies are needed to confirm these findings and to determine whether boosting vitamin D levels can improve outcomes following colorectal cancer treatment.

How does vitamin D influence colorectal cancer? Vitamin D is absorbed through the intestinal tract. Healthy colon cells have proteins on their surface called vitamin D receptors that bind vitamin D to regulate how much vitamin D the body absorbs at any time. Colon cancer cells also have these vitamin D receptors. When vitamin D molecules bind to cancer cells, they divide at a slower rate. Vitamin D also helps decrease inflammation in and around the tumor. This triggers the cancer cells to die via an organized type of cell death called apoptosis.

What Patients Need to Know

Future results from clinical trials will help answer the question of what role, if any, vitamin D has in improving outcomes in patients undergoing treatment for colorectal cancer. For example, in an ongoing clinical trial in patients with stage IV colon cancer in which all patients are being treated with FOLFOX and bevacizumab, half of the patients are also receiving very high-dose vitamin D supplementation while half are taking a regular dose of vitamin D. These results may help determine whether vitamin D dose influences patient outcomes.

Trifluridine and Tipiracil for Metastatic Colorectal Cancer

The combination drug TAS-102 (Lonsurf) improved survival compared to placebo in patients with previously treated metastatic colorectal cancer in a large clinical trial. TAS-102 consists of two compounds: trifluridine and tipiracil. Trifluridine is a molecule that mimics one of the building blocks of DNA. Cancer cells incorporate trifluridine into their DNA, which prevents the DNA from functioning properly and eventually leads to cell death. The second component of TAS-102, tipiracil, blocks an enzyme that breaks down trifluridine, enabling it to be active for a longer time. In laboratory experiments, TAS-102 inhibited the growth of tumors from patients who have been treated with fluorouracil.

This study included 800 patients who had not responded to standard chemotherapy drugs or biologic medications. Some of the patients had also been treated with regorafenib (Stivarga), which was the newest drug approved for colorectal cancer at the time the study started. Two-thirds of the patients received TAS-102 while the other one-third received placebo. The TAS-102 group experienced about 32 percent longer survival compared to the placebo group. Responses to TAS-102 occurred even in patients who had not responded to regorafenib. The most common side effects of TAS-102 were low white blood cell counts (neutropenia and leukopenia). The results of this clinical trial–which were published in May 2015 in the *New England Journal of Medicine*—underwent fast-track review by the FDA.

What Patients Need to Know

In September 2015, the FDA approved TAS-102 to treat patients with metastatic colorectal cancer after prior chemotherapy containing a fluoropyrimidine, oxaliplatin, and irinotecan (Camptosar), and after biologic therapy with an anti-vascular endothelial growth factor (VEGF) medication (e.g., bevacizumab). TAS-102 is another example of how cancer researchers continue to make incremental improvement in the fight against colorectal cancer.

A Predictor of Response to Pembrolizumab for Colorectal Cancer

Patients with mismatch repair-deficient colorectal cancer appear to be more likely to benefit from pembrolizumab (Keytruda) than patients with mismatch repair-proficient cancers, according to results from a small study. Cancers that have proper DNA proofreading genes are said to be mismatch repair-proficient, while those that lack these genes are mismatch repair-deficient. Mismatch repair-deficient cancers contain large amounts of mutated (changed) DNA—called a "high mutational load." Pembrolizumab is a checkpoint inhibitor, a newer type of agent that triggers the immune system so that it can recognize and attack cancer cells.

This study included 41 patients with previously-treated, progressive metastatic cancers. Of these patients, 11 had mismatch repair-deficient colorectal cancer and 21 had mismatch repair-proficient colorectal cancer. All patients received pembrolizumab.

None of the patients with mismatch repair-proficient cancer experienced responses to pembrolizumab, while 62 percent of patients with mismatch repair-deficient cancers experienced tumor shrinkage. Among patients with colorectal cancer, those with mismatch repair-deficient disease experienced longer survival than those with mismatch repair-proficient cancers.

What Patients Need to Know

One of the highlights from ASCO this year was new and emerging immunotherapy agents. Immunotherapy is a type of cancer treatment that uses the body's immune system to fight cancer. Unfortunately, in colorectal cancer, immunotherapy has not yet resulted in the dramatic outcomes seen in other cancers such as melanoma and some lung cancers. However, this study suggests that immunotherapy may have an important role to play in colorectal cancer after all. Even though this study was small, the results suggest that immunotherapy drugs like pembrolizumab might help patients with mismatch repair-deficient cancers, particularly colorectal cancers. This is an ongoing area of intense research.

Gastrointestinal Stromal Tumor

Researchers reported a number of important findings in gastrointestinal stromal tumor treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Three years of imatinib provided more benefit than one year in patients with operable high-risk gastrointestinal stromal tumor (GIST). After seven and a half years, patients who received three years of treatment experienced longer recurrence-free survival and overall survival compared to patients who were only treated for one year (page 23).

Pazopanib added to best supportive care prolonged progression-free survival in patients with inoperable metastatic or locally advanced GIST. Four-month progression-free survival was better in patients who received pazopanib compared to best supportive care only (page 24).

It may be possible to detect tumor DNA in the blood of patients with GIST. The results of some small studies suggest that this technique might replace the need for biopsies for some patients (page 25).

Imatinib After Surgery for Operable Gastrointestinal Stromal Tumor (GIST)

Three years of imatinib (Gleevec) provided greater benefit than one year in patients with operable high-risk GIST, according to an updated analysis of a large clinical trial. In this study, 400 patients with high-risk GIST underwent surgery to remove their tumors. They were then randomized to receive either one year or three years of imatinib. The initial study analysis followed patients for four and a half years. Those results demonstrated a survival benefit for the three-year arm: patients who received imatinib for three years experienced longer recurrence-free survival and overall survival compared to patients who received the drug for only one year.

The current analysis followed patients for seven and a half years, and the results continued to show longer recurrence-free survival and overall survival in patients who received three years of treatment. These results highlight the need for ongoing research to further evaluate whether longer treatment durations might benefit patients with GIST.

What Patients Need to Know

Imatinib has several FDA-approved indications for various cancers. In GIST, imatinib is indicated for the treatment of patients with KIT (CD117)-positive unresectable (cannot be removed by surgery) and/or metastatic malignant GIST. Imatinib is also indicated for the adjuvant (post-surgery) treatment of adult patients following resection of KIT-positive GIST.

Pazopanib for Inoperable GIST

Pazopanib (Votrient) added to best supportive care prolonged progression-free survival in patients with inoperable metastatic or locally advanced GIST, according to the results of an ongoing study. The 81 patients in the study had received at least two previous drug treatments.

All of the patients received best supportive care, and they were randomized into two groups: patients in one group received pazopanib while patients in the other group did not receive any additional treatment. Four-month progression-free survival was better in the pazopanib group (45 percent versus 18 percent).

Patients who had undergone significant prior surgery on their stomach benefitted less from pazopanib than patients who had not undergone surgery; this is likely due to the fact that pazopanib enters the body through the stomach, so patients with less stomach tissue are expected to absorb less drug into their bodies. Researchers have made similar observations in other cancer types.

What Patients Need to Know

Pazopanib is an oral tyrosine kinase inhibitor that is FDA-approved for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma. The results from this study suggest that pazopanib may help patients with GIST. However, more studies are needed to confirm this finding.

Detection of GIST DNA in Blood Samples

The results of some small studies suggest that it might be possible to detect tumor DNA in the blood of patients with GIST, rather than requiring tumor tissue from a biopsy. In GIST, mutations in the gene that encodes the protein KIT cause excess amounts of excess KIT protein to be produced, which stimulates tumor growth. GIST patients have many different types of KIT mutations, which may respond differently to treatment. Therefore, doctors use information about KIT mutations to guide treatment decisions.

It is not always practical to perform biopsies—removal of a sample of tumor tissue—for all GIST patients to detect their specific mutations. Blood samples are much easier to collect than tissue samples. Thus, researchers are developing ways to identify mutations in the tumor DNA found in patients' blood—a so-called "liquid biopsy." Results from initial studies suggest that this is possible, but more studies are needed to test and improve the methods.

What Patients Need to Know

The ability to perform a reliable liquid biopsy in GIST patients is becoming increasingly possible. In the future, blood tumor DNA tests might help doctors monitor how well a drug is working.

Leukemia

Researchers reported a number of important findings in leukemia treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

CD19-targeted chimeric antigen receptor (CAR) T-cell therapy appeared to help patients with relapsed or refractory (cancer does not respond to treatment) acute lymphocytic leukemia (ALL). A small study reported an overall 91 percent complete response rate (page 27).

Erythrocyte encapsulated L-asparaginase seemed to be a good alternative to standard L-asparaginase for patients with relapsed ALL. It caused fewer allergic reactions and resulted in a higher complete response rate (page 28).

Gilteritinib, a new FLT3 inhibitor, appeared to be active in patients with relapsed or refractory chronic myeloid leukemia (CML). At the higher doses of gilteritinib tested, over half of patients experienced a response, and a few had complete remissions (page 29).

Ibrutinib added to bendamustine plus rituximab improved progression-free survival in patients with previously treated chronic lymphocytic leukemia (CLL). The addition of ibrutinib increased the percentage of patients who experienced complete remissions (page 30).

In two small studies, ponatinib and bosutinib showed long-term activity in patients with previously treated chronic-phase CML. Depending on the study, 40 to 50 percent of patients remained on treatment four to five years later (page 31).

CAR T-Cell Therapy for Acute Lymphocytic Leukemia (ALL)

CD19-targeted chimeric antigen receptor (CAR) T-cell therapy appeared to help patients with ALL, according to updated results from a small clinical trial of 33 patients with relapsed or refractory ALL. CD19 is a protein that is present on the surface of ALL cells. CD19-targeted CAR T-cell therapy is specifically developed for each individual patient. Doctors first collect T-cells from a patient's blood. Then, the T-cells are modified in the laboratory so that they recognize CD19 on ALL cells. The doctors then reinfuse the modified T-cells back into the patient, where they help launch an immune response against their targets, CD19-positive ALL cells.

In this trial, one-third of the patients had Philadelphia chromosome-positive disease and one-third had previously undergone bone marrow transplantation. Half of the patients had minimal ALL left, while the other half still had evidence of ALL in their bone marrow. Long-term follow-up after CD19-targeted CAR T-cell therapy revealed an overall complete response rate of 91 percent. This high response rate is consistent with the results of other CAR T-cell therapy clinical trials. Furthermore, 100 percent of patients who had low amounts of ALL (called minimal residual disease) at the beginning of the trial experienced complete remission. Most (82 percent) of the patients who responded to treatment had no remaining evidence of cancer.

Less than one-third of patients experienced cytokine release syndrome—a serious side effect that is treatable if identified early.

What Patients Need to Know

CAR T-cell therapy appears to be very promising for ALL as well as several other cancers. However, this experimental therapy is currently only available through clinical trials.

Erythrocyte Encapsulated L-Asparaginase in ALL

Erythrocyte encapsulated L-asparaginase may be a good alternative to standard L-asparaginase for patients with ALL, according to the results from a small study. L-asparaginase is a key drug in the treatment of patients with ALL. Unfortunately, some patients develop allergic reactions to it, called hypersensitivity. Some of the patients with hypersensitivity make antibodies that prevent L-asparaginase from functioning properly. To decrease this side effect, researchers enclosed the drug inside a protective red blood cell membrane, resulting in erythrocyte encapsulated L-asparaginase

The study included 80 patients with relapsed ALL: 28 patients received standard L-asparaginase and 52 were treated with the encapsulated drug. Half of the patients who took the encapsulated drug were allergic to L-asparaginase.

None of the non-allergic patients treated with encapsulated L-asparaginase experienced allergic reactions, compared to 42 percent in the group treated with the standard drug. More patients treated with the encapsulated drug experienced a complete response and subsequently underwent successful stem cell transplantation.

What Patients Need to Know

L-asparaginase is an important drug for ALL, but the development of allergies may prevent some patients of receiving it. Versions of L-asparaginase that decrease the risk of developing allergies, such as erythrocyte encapsulated L-asparaginase, are urgently needed. Currently, erythrocyte encapsulated L-asparaginase is only available through clinical trials—more studies are needed to confirm the results of this study, which are not yet final.

Gilteritinib for Acute Myeloid Leukemia (AML)

Gilteritinib (ASP2215), a new FLT3 inhibitor, appeared to be active in patients with relapsed or refractory AML in its first clinical trial. Mutations in FLT3 result in unregulated AML cell growth. Several drugs target the FLT3 signaling pathway in AML. Gilteritinib inhibits two types of FLT3 mutations, which together are observed in up to one-third of patients with AML.

This trial was conducted to find the optimal dose of gilteritinib—that is, the highest dose that does not cause dangerous side effects. The trial included a small group of patients who received different doses of gilteritinib and a larger group that received the highest dose. Some of the patients had AML with FLT3 mutations while others had AML with normal FLT3. At the higher doses of gilteritinib, over half of the patients with FLT3 mutations experienced a response, and a small number had complete remissions.

What Patients Need to Know

Gilteritinib is a promising new FLT3 inhibitor. Several ongoing clinical trials are evaluating it in combination with chemotherapy and other targeted drugs for AML. Late in 2015, the manufacturer started an FDA registration trial that is comparing gilteritinib to salvage chemotherapy in patients with relapsed or refractory AML.

Ibrutinib Added to Bendamustine Plus Rituximab for CLL

Ibrutinib (Imbruvica) added to bendamustine (Treanda) plus rituximab (Rituxan) improved progression-free survival in patients with previously treated CLL in a large clinical trial. Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK), an enzyme that is hyperactive and contributes to uncontrolled growth in many patients with CLL. This study included 578 patients with CLL or small lymphocytic lymphoma (SLL). All of the patients received bendamustine plus rituximab—a commonly used regimen for CLL. Half of the patients also received ibrutinib, while the other half received placebo. Progression-free survival at 18 months was 79 percent for ibrutinib and 24 percent for placebo.

The response rate was high in both treatment groups. Nevertheless, patients who received ibrutinib had a higher complete remission rate, and ibrutinib appeared to improve the clearance of any minimal residual disease, resulting in higher quality remissions and delayed relapses.

The two groups had the same rate of serious side effects, including low white blood cell counts (neutropenia) and low platelet counts (thrombocytopenia). Some patients treated with ibrutinib experienced bleeding and an irregular heart rhythm (atrial fibrillation). However, the addition of ibrutinib did not increase the frequency of side effects.

What Patients Need to Know

The results from this trial were published in February 2016 in the journal Lancet Oncology. This drug appears to be an important addition to the available medications for patients with CLL. Ibrutinib is approved for the treatment of patients with CLL and CLL with 17p deletion. An ongoing trial is comparing ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab (Gazyva) in previously untreated patients with CLL and SLL.

Ponatinib and Bosutinib for Chronic Myeloid Leukemia (CML)

In two small studies, ponatinib (Iclusig) and bosutinib (Bosulif) showed long-term activity in patients with previously treated chronic-phase CML. In the ponatinib clinical trial, 41 of the enrolled 81 patients were still taking ponatinib after 4 years. Only nine percent of patients had stopped treatment due to disease progression. About three-quarters of patients experienced a major remission, and two-thirds had a complete cytogenetic remission. More than half of the patients achieved a deep molecular remission. Ponatinib caused some side effects, including rash, fatigue, abdominal pain, and headache. About 30 percent of patients experienced a serious vascular side effect. Despite the risk of side effects, the study results suggest that ponatinib can help patients who received several prior treatments for CML.

Another study found that leukemia patients treated with ponatinib in different clinical trials often have high blood pressure before starting treatment. One of the known side effects of ponatinib is hypertension (increased blood pressure). However, the presence of hypertension rarely led to changes in how ponatinib therapy was given. These results suggest that doctors need to closely monitor hypertension when giving ponatinib and should help patients control their blood pressure.

In the bosutinib trial, about 40 percent of the initially enrolled 284 patients remained on treatment five years later. These patients had previously received imatinib. Of the patients who experienced a major cytogenetic response or complete cytogenetic response, three-quarters were able to maintain the response. Only four percent of patients experienced a transformation to advanced-phase or blast-phase CML. This is a remarkable result for patients who have received two or more previous treatments.

The most prominent late side effect of bosutinib was an elevation in creatinine, a metabolic waste product that is normally removed from the body by the kidneys; elevated levels indicate kidney dysfunction.

What Patients Need to Know

The FDA approved bosutinib to treat adult patients with chronic-, accelerated-, or blast-phase Philadelphia chromosome-positive CML with resistance or intolerance to prior therapy. Ponatinib is approved to treat adult patients with T315I-positive chronic-, accelerated-, or blast-phase CML.

Lung Cancer

Researchers reported a number of important findings in lung cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Immunotherapy drugs called checkpoint inhibitors helped patients with some lung cancers. Several studies showed that various checkpoint inhibitors were better than chemotherapy at shrinking cancers and lengthening survival (page 33).

New epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors—osimertinib, rociletinib, and EGF816—helped patients with non-small cell lung cancer (NSCLC). In different studies, these drugs appeared to be very effective in patients with tumors containing the EGFR T790M mutation (page 35).

Researchers have made some progress in identifying drugs that might decrease and treat the spread of NSCLC to the brain. In initial studies, the EGFR inhibitors AZD3759, PF-06463922, and erlotinib helped reduce the risk of lung cancer brain metastases (page 36).

Immunotherapy With Checkpoint Inhibitors for Lung Cancer

Checkpoint inhibitors improved survival of patients with some lung cancers, according to results from several clinical trials. It has been a dream of oncologists for over a century to find a way to harness our own immune system to fight cancer the same way that we fight infections. The new generation of immunotherapies that are currently being developed to fight lung cancer and other tumors are called checkpoint inhibitors.

Currently, there are two classes of checkpoint inhibitors. One class blocks molecules that prevent T-cells from proliferating. These molecules are cell death protein 1 (PD-1) and PD ligand 1 (PD-L1). Two drugs in this class—nivolumab (Opdivo) and

pembrolizumab (Keytruda)—are approved by the FDA to treat people with melanoma and lung cancer. Two other drugs in this class—atezolizumab (MPDL3280A) and durvalumab (MEDI4736)—are in clinical trials.

The other class of checkpoint inhibitors activate T-cells by blocking a molecule called cytotoxic T-lymphocyte antigen 4 (CTLA-4). CTLA-4 normally suppresses T-cell activity, so the net effect of blocking CTLA-4 is T-cell activation. Drugs in this class include ipilimumab (Yervoy), which is FDA-approved to the treatment of people with some types of melanoma, and the investigational agent tremelimumab.

In several studies presented at this meeting, PD-1 and PD-L1 inhibitors were compared to standard chemotherapy in patients who had received at least one round of previous treatment. Results of these studies indicated that the checkpoint inhibitors were better than chemotherapy at shrinking cancers and lengthening survival.

The anti–CTLA-4 drugs have been shown to be very beneficial in fighting malignant melanoma. Some early studies indicated that these drugs also help patients with lung cancer; ongoing clinical trials should provide more information in the future.

What Patients Need to Know

Thus far, checkpoint inhibitors, a new class of immunotherapy drugs, are helping people with several types of lung cancer, and are becoming part of standard care. These drugs are being studied in many clinical trials. It is likely that using two checkpoint inhibitors together (for example, ipilimumab plus nivolumab) will provide added benefit; this has already been observed in melanoma.

New Drugs That Target EGFR for NSCLC

New EGFR tyrosine kinase inhibitors—osimertinib (Tagrisso; previously called AZD9291), rociletinib (CO-1686), and EGF816—helped patients with NSCLC in several studies. These drugs worked in patients after they had been treated with the EGFR inhibitors afatinib (Gilotrif), gefitinib (Iressa), or erlotinib (Tarceva) and their cancers had developed a second mutation in EGFR called T790M. In fact, 60-70% of people with the T790M mutation experienced major tumor shrinkage in response to the new agents.

These drugs also seemed to be less harmful to the normal tissues of the body compared to older EGFR inhibitors. Fewer patients experienced side effects like diarrhea and rash, and people who had been previously treated with erlotinib or gefitinib said that the new EGFR inhibitors were easier to tolerate.

Results presented at the ASCO meeting suggest that these drugs may have the potential to replace afatinib, gefitinib, or erlotinib, as initial treatment for NSCLC.

What Patients Need to Know

In November 2015, the FDA granted accelerated approval for Tagrisso to treat patients with EGFR T790M mutation-positive metastatic NSCLC. This accelerated approval was based on response rate and duration of response data. This type of approval requires the manufacturer to conduct additional clinical trials to confirm the drug's benefits. The results from these trials should reveal whether or not osimertinib improves progression-free survival and overall survival.

EGFR Inhibitors for NSCLC Spread to the Brain

Many patients with NSCLC who initially have good results with EGFR inhibitors later develop brain metastases. In early studies, researchers have made some progress in identifying drugs that might decrease and treat the spread of NSCLC to the brain, including two new EGFR inhibitors, AZD3759 and PF-06463922. Clinical trials are ongoing.

Results from another clinical trial suggest that high-dose erlotinib might prevent the development of EGFR T790 mutations as well as NSCLC spread to the brain. This type of dosing is called pulse dosing.

What Patients Need to Know

New EGFR inhibitors and new ways to dose EGFR inhibitors (for example, pulse dosing) may help reduce the spread of NSCLC to the brain. However, it is important to note that these are very preliminary findings and that the studies have not been completed. Larger studies are needed to confirm these findings. However, these results do support the importance of molecular genetic testing for patients with NSCLC to determine EGFR mutation status, as these results may help doctors decide which drugs might work best for their patients.

Lymphoma

Researchers reported a number of important findings in lymphoma treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

The complete response rate at 30 months seemed to predict progression-free survival associated with first-line treatment of follicular lymphoma, according to results from the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) project. This promising surrogate marker might shorten the time it takes to find out how well new drugs work for this disease (page 37).

Regular aerobic exercise was linked to a better quality of life in aggressive non-Hodgkin lymphoma survivors. Three years after their initial diagnosis, survivors who regularly exercised reported a better quality of life than those who did not exercise regularly (page 39).

High complete response rates and more side effects than expected were seen when brentuximab vedotin was added to the AVD regimen for patients with early-stage Hodgkin lymphoma. More patients than expected had low blood counts and numbness/tingling of the fingers and toes (page 40).

Surrogate Markers for Follicular Lymphoma Treatments

The complete response rate at 30 months predicted progression-free survival associated with first-line treatment of follicular lymphoma, according to results from the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) project. Follicular lymphoma is the most common of the indolent (slower growing) lymphomas, and patients often require treatment for many years. There are several different treatments for follicular lymphoma, many of which work for a long period of time in many patients. When new treatments

are compared in clinical trials, it can take several years to get meaningful results with traditional outcome measures, such as median progression-free survival.

The FLASH project aims to identify surrogate markers for potential follicular lymphoma therapies. A surrogate marker is something that can be measured in the short term that is well correlated with long-term outcomes; such markers allow researchers to know whether a treatment is benefitting a patient sooner than waiting for long-term results. Results presented at ASCO from the FLASH project indicated that 30-month complete response rate appears to be a promising surrogate marker for follicular lymphoma.

For the FLASH project, researchers analyzed individual patient data from almost 4,000 patients who participated in 13 clinical trials over many years. The researchers found that the rate of complete response 30 months after therapy was a good predictor (surrogate marker) for progression-free survival. This means that if drug A is associated with a higher 30 month complete response rate than drug B, then it is very likely that drug A will also yield longer progression-free survival than drug B.

What Patients Need to Know

Once finalized and published, the FLASH project results could provide cancer researchers with a good tool to do shorter-term clinical trials of new treatments for follicular lymphoma. The FLASH project is also an important example of how the results of several clinical trials can be analyzed together to gain important insights.

Exercise and Quality of Life in Non-Hodgkin Lymphoma Survivors

Regular aerobic exercise was linked to a better quality of life in aggressive non-Hodgkin lymphomas survivors, according to a survey study. Three years after their initial diagnoses, 625 survivors completed a detailed survey about their exercise patterns and quality of life. The survey responders did not have active disease and had not been recently treated. Some of the survey questions asked about exercise patterns. Other questions asked about quality of life. Most of the study participants had diffuse large B-cell lymphoma (60 percent), mantle cell lymphoma (12 percent), or grade III follicular lymphoma (11 percent).

The survey results showed that 49 percent of survivors met the Centers for Disease Control (CDC) standard exercise recommendations of 30 minutes of moderate activity at least five days per week. Survivors who regularly exercised had a better quality of life than those who did not exercise regularly.

What Patients Need to Know

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma, and is relatively aggressive. However, as many patients with aggressive forms of non-Hodgkin lymphoma are cured with therapy, doctors and researchers are interested in finding ways to improve the quality of life of non-Hodgkin lymphoma survivors. The results of this study suggest that regular aerobic exercise positively impacted survivors' quality of life. However, it's important to note that because this was not a randomized clinical trial, a cause-and-effect relationship between exercise and quality life could not be established.

Brentuximab Vedotin for Early-Stage Hodgkin Lymphoma

High complete response rate and more side effects than expected were seen with brentuximab vedotin (Adcetris) added to AVD (Adriamycin [doxorubicin], vinblastine, and dacarbazine), according to a small study in patients with non-bulky stage I and II Hodgkin lymphoma. Brentuximab vedotin is an antibody-drug conjugate that targets CD30, a molecule that is present on the surface of many types of lymphoma cells. The typical treatment for early state Hodgkin lymphoma is ABVD chemotherapy (Adriamycin, bleomycin, vinblastine, and dacarbazine). Many studies are currently evaluating the substitution of brentuximab vedotin for one or more of the agents in the ABVD regimen.

The study included 34 patients who received four to six cycles of brentuximab plus AVD. By the end of treatment, 88 percent of patients experienced a complete response. The combination regimen was associated with more side effects than usually seen with AVD alone. More patients than expected had low blood cell counts as well as numbness and tingling of the fingers and toes (neuropathy). Many patients (38 percent) needed dose reductions because of side effects, especially neuropathy.

What Patients Need to Know

Brentuximab vedotin is currently FDA-approved as a single agent for the treatment of patients with Hodgkin lymphoma whose diagnosis remains after undergoing autologous stem cell transplantation (SCT) or at receiving least two prior chemotherapy regimens, and for patients with systemic anaplastic large cell lymphoma whose diagnosis remains after receiving at least one prior chemotherapy regimen. It is also approved for Hodgkin lymphoma patients who have a high risk of relapsing or progressing after undergoing autologous SCT. Current clinical trials are evaluating brentuximab vedotin in lymphoma patients at an earlier stage in combination with standard chemotherapy agents.

Melanoma

Researchers reported a number of important findings in melanoma treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Adding cobimetinib to vemurafenib improved survival and symptoms in patients with previously untreated, unresectable, locally advanced, or metastatic melanoma containing a BRAF V600 mutation. Patients treated with the combination had better outcomes than those treated with vemurafenib plus placebo (page 42).

Patients with advanced melanoma experienced better outcomes with pembrolizumab than with ipilimumab, according to a large clinical trial. Study participants had unresectable stage III or IV melanoma and no more than one previous treatment for advanced disease (page 43).

Nivolumab plus ipilimumab and nivolumab alone worked better than ipilimumab alone in patients with advanced melanoma. Patients in this study had previously untreated, unresectable, stage III or IV melanoma (page 44).

Vemurafenib and Cobimetinib Combination for Unresectable or Metastatic Melanoma

Adding cobimetinib (Cotellic) to vemurafenib (Zelboraf) improved survival and symptoms in patients with melanoma containing a BRAF V600 mutation, according to updated results from a large clinical trial. Cobimetinib blocks the activity of the enzymes MEK1 and MEK2, which along with BRAF (the target of vemurafenib) contribute to uncontrolled cancer cell growth.

The trial included 495 patients with previously untreated, locally advanced, or metastatic melanoma that could not be surgically removed. Half of the patients took vemurafenib plus cobimetinib and the other half took vemurafenib plus placebo. The initial results from this study were published in the *New England Journal of Medicine* in November 2014. The updated results presented at the 2015 American Society of Clinical Oncology meeting confirmed that patients treated with the combination experienced better outcomes than those who received vemurafenib plus placebo. The combination improved progression-free survival (12 months versus 7 months), the overall response rate (70 percent versus 50 percent), and symptoms like insomnia, fatigue, and pain.

What Patients Need to Know

This cobimetinib plus vemurafenib combination is a good example of how the increased understanding of the molecular nature of cancer is helping researchers make more effective drugs that target the abnormalities in cancer cells. This combination causes relatively rapid responses, and it is thought that it may particularly benefit patients with cancer-related symptoms or who need a bridge to another therapy, such as an immunotherapy. In 2011, the FDA approved vemurafenib to treat patients with unresectable or metastatic melanoma that contains BRAF V600E mutations. In November 2015, the FDA approved cobimetinib to be used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Note that neither drug is approved for patients with wild-type BRAF melanoma.

Pembrolizumab for Advanced Melanoma

Patients with advanced melanoma experienced better outcomes with pembrolizumab (Keytruda) than with ipilimumab (Yervoy), according to a large clinical trial that enrolled patients with unresectable stage III or IV melanoma who had received no more than one previous treatment for advanced disease. The study results were published online in the *New England Journal of Medicine* right before the American Society of Clinical Oncology 2015 meeting.

The study included 834 patients who were randomly divided into three groups. Two groups received different regimens of pembrolizumab: every two weeks or every three weeks; patients in the other group received ipilimumab. Patients in the two pembrolizumab groups experienced better six-month progression-free survival (46 percent and 47 percent versus 26 percent), 12-month survival (68 percent and 74 percent versus 58 percent), and overall response rate (33 percent and 34 percent versus 12 percent) compared to patients in the ipilimumab group. Patients in the pembrolizumab groups also experienced fewer severe treatment-related side effects.

What Patients Need to Know

The results of this study indicated that the PD-1 inhibitor pembrolizumab was more effective and tolerable than the CTLA-4 inhibitor ipilimumab as front-line treatment for patients with advanced melanoma.

Nivolumab Alone or With Ipilimumab for Advanced Melanoma

Nivolumab plus ipilimumab and nivolumab alone worked better than ipilimumab alone for patients with advanced melanoma, according to a large clinical trial. The 945 patients in the study had untreated, unresectable stage III or IV melanoma. The study results were published online in the *New England Journal of Medicine* during the 2015 American Society of Clinical Oncology meeting.

The researchers randomly divided the patients into three groups: nivolumab plus ipilimumab, nivolumab alone, and ipilimumab alone. Patients treated with nivolumab alone or in combination with ipilimumab experienced longer progression-free survival (6 months versus 12 months versus 3 months) and objective response rates (44 percent versus 58 percent versus 19 percent) compared to patients treated with ipilimumab alone.

The study researchers also looked at potential biomarkers that could help predict which patients would most likely benefit from the combination. They found that cancers with higher levels of the PD-L1 protein were more likely to respond to nivolumab alone compared to cancers without PD-L1 protein, suggesting that patients with high levels of PD-L1 may not need the addition of ipilimumab to nivolumab.

The study results also confirmed that, as with other drugs used to treat cancer, caution must be exercised when administering these immunotherapies. More than half of the patients experienced significant immune-related side effects.

What Patients Need to Know

The results of this study suggest that melanoma patients may benefit from nivolumab with or without ipilimumab depending on whether or not their cancers have high levels of PD-L1. Thus, some patients could avoid the additional side effects that the second drug contributes.

Oral and Head and Neck Cancer

Researchers reported a number of important findings in oral and head and neck treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Pembrolizumab helped patients with previously treated, recurrent, or metastatic squamous cell carcinoma of the neck. The overall response rate was high and side effects were manageable (page 45).

Chemoradiotherapy de-intensification might be possible for patients with low-risk human papillomavirus (HPV)-positive head and neck cancer. Most patients experienced a pathologic complete response (page 47).

Persistent HPV16 DNA detected in oral rinses was associated with worse disease-free survival in patients with head and neck cancer. Oral HPV16 DNA could be a useful biomarker to monitor patients after curative treatment for head and neck cancer (page 48).

Pembrolizumab for Squamous Cell Carcinoma of the Neck

Pembrolizumab (Keytruda) helped patients with recurrent or metastatic squamous cell carcinoma of the neck in a non-comparative clinical trial. The study included 132 patients who had received many previous treatments. All of the patients were treated with pembrolizumab. Testing for PD-L1 status was not required in this study.

The overall response rate was very encouraging. Both human papillomavirus (HPV)-positive and HPV-negative patients experienced long-lasting responses, although HPV-negative patients had a slightly better response rate.

The treatment was very well tolerated. Only 10 percent of the patients had serious side effects, including facial swelling and inflammation of the lung (pneumonitis). Other side effects included fatigue, low thyroid activity (hypothyroidism), decreased appetite, rash, joint pain (arthralgia), nausea, and weight loss. All of the side effects were manageable.

What Patients Need to Know

In the future, immunotherapy may become the backbone of treatment for head and neck cancers, with other treatments, such as chemotherapy and targeted therapy, added to this backbone. Researchers are currently working to determine the best way to dose these treatments and whether biomarkers can be used to optimize treatment for individual patients.

Chemoradiotherapy De-Intensification for HPV-Associated Head and Neck Cancer

Lower-dose chemoradiotherapy might be an option for patients with low-risk HPV-associated head and neck cancer, according to a phase II study. Chemoradiotherapy consisted of radiation given at a lower dose than usual along with low-dose cisplatin chemotherapy.

The study included 43 patients with oropharyngeal squamous cell carcinoma. Following chemoradiotherapy, any remaining tumor tissue (if present) and nearby lymph nodes were surgically removed and checked under a microscope for the presence of cancer cells. The results were excellent: most patients (86 percent) had a pathologic complete response, meaning that all traces of cancer had disappeared. As this study was done in a small group of patients who were followed only for a short time, a larger study is needed to confirm these encouraging results.

What Patients Need to Know

Patients with HPV-positive head and neck cancer tend to have significantly better outcomes than HPV-negative patients. A tremendous effort to develop new treatment strategies in which HPV-positive patients receive less treatment without decreasing efficacy is currently ongoing. Removal of lymph nodes—called lymph node dissection—to check for the presence of cancer cells could potentially be replaced by a positron emission tomography (PET) scan, a method for visualized the degree of tumor shrinkage after treatment. In the future, fewer patients with HPV-positive head and neck cancer many undergo surgery after definitive treatment.

HPV16 DNA Detection in Oral Rinses

Persistent HPV16 DNA detected in oral rinses was associated with worse cancer-free survival in patients with head and neck cancer in a clinical study. The study reported results from 124 patients with a history of oropharyngeal cancer treated with curative intent. Patients were asked to rinse their mouths and spit into a cup, and researchers then measured the amount of HPV 16 DNA in the sample. The patients gave samples at diagnosis (baseline) and then at 9, 12, 18, and 24 months after diagnosis. At baseline, more than half of the patients had HPV16 in their mouth rinse samples.

All of the patients had excellent responses to treatment and were in remission after two years. A small number of patients (6 percent) had HPV16 DNA in their mouth rinse samples after treatment. Some of these patients experienced a cancer recurrence, and patients with oral HPV16 DNA experienced worse cancer-free survival and overall survival than patients without oral HPV16 DNA. These results suggest that oral HPV16 DNA could be a useful biomarker for monitoring patients after curative treatment for head and neck cancer. However, more research is needed before this can become part of routine practice.

The results raise additional questions, such as whether the cancer recurrence was caused by a persistent HPV infection or by a new HPV infection, and whether the HPV DNA detected in the oral rinses was from viruses themselves or from viral DNA within infected tumor cells.

What Patients Need to Know

The development of a method to more easily detect persistent HPV16 infection could lead to better treatments. However, the data in this study should be validated by determining whether the patients' sexual partners have the same HPV infection. The results also need to be confirmed by other studies.

Ovarian Cancer

Researchers reported a number of important findings in ovarian cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Avelumab showed some activity and a good safety profile in patients with previously treated, recurrent, or refractory ovarian cancer. Avelumab is an investigational monoclonal antibody that targets PD-L1 (page 49).

The poly ADP-ribose polymerase (PARP) inhibitors—rucaparib, olaparib, and veliparib—appeared to be effective in women with ovarian cancers. PARP inhibitors seemed to be both active and safe drugs in clinical studies (page 50).

Avelumab for Recurrent or Refractory Ovarian Cancer

Avelumab, an investigational monoclonal antibody that targets PD-L1, had some activity and a good safety profile in patients with previously treated recurrent or refractory ovarian cancer, according to an initial study. This study included 75 patients who had been treated with a median of four prior treatment regimens. Patients stayed on treatment for an average of 10 weeks. Among the 23 patients evaluable for a response, 17 percent experienced partial responses and 48 percent had stable diagnosis. This is a good response rate considering these patients received a median of four prior therapies; stabilization is considered a success in such patients. Median progression-free survival was about 12 weeks.

Avelumab treatment was associated with mostly mild side effects. The most common side effects were fatigue, nausea, and diarrhea.

What Patients Need to Know

Avelumab showed promise in patients with previously treated ovarian cancer. Based on this and other studies, avelumab is being evaluated in larger clinical trials in patients with ovarian cancer and other types of tumors.

Rucaparib, Olaparib, and Veliparib for Ovarian Cancer

Three poly ADP-ribose polymerase (PARP) inhibitors—rucaparib, olaparib (Lynparza), and veliparib—appeared to be effective in patients with ovarian cancer, according to results from several small studies. PARP is an enzyme that cells need to repair damaged DNA. By preventing DNA repair, PARP inhibitors cause cancer cell death.

Rucaparib showed strong activity in women with ovarian, fallopian tube, and primary peritoneal cancer that contained BRCA mutations in a non-comparative study. This study included 35 patients who had received two to four prior therapies. The overall response rate was 65 percent.

The combination of olaparib plus carboplatin appeared to be active in low–genetic-risk women with heavily pretreated high-grade ovarian cancer in an initial study. The 30 women in the study had received a median of seven previous treatments. The researchers reported partial response and stable disease in 54 percent of patients. Most of the responders had platinum-sensitive cancer.

Veliparib was safely combined with bevacizumab (Avastin) and chemotherapy in women with ovarian, fallopian tube, or primary peritoneal cancers in an initial study. The 189 patients had newly diagnosed stage II to IV cancers. All of the patients received both veliparib and bevacizumab along with one of three different chemotherapy regimens for ovarian cancer. The first regimen included standard intravenous carboplatin and paclitaxel (Taxotere) every three weeks. The second regimen included carboplatin every three weeks and paclitaxel every week. The third regimen included intraperitoneal paclitaxel and cisplatin. The results of this dose-finding study showed that the combinations did not cause unexpected side effects, and that they were active against the cancer. These combinations will be tested in larger studies.

Researchers are looking for ways to give patients the best medications for their specific type of cancer. In one study that attempted to identify ovarian cancer patients who were most likely to respond to rucaparib, researchers used a next-generation sequencing method to look for specific genetic abnormalities. The study included 206 women with recurrent high-grade ovarian cancer that had previously responded to platinum therapy. The researchers found two groups of patients who were most likely to respond to rucaparib treatment: patients with BRCA mutations, and patients who had lost one copy of the BRCA gene. More research is needed to confirm these results.

What Patients Need to Know

PARP inhibitors appear to be active and relatively safe drugs, and researchers are currently studying how to use them in combination with traditional chemotherapy in ovarian cancer. Rucaparib and veliparib are only available through clinical trials, while the FDA approved olaparib in 2014 to treat women with BRCA-mutated advanced ovarian cancer treated with at least three prior lines of chemotherapy.

Pancreatic Cancer

Researchers reported a number of important findings in pancreatic cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

PEGPH20 added to gemcitabine and nab-paclitaxel was particularly effective in patients with newly diagnosed pancreatic cancer with high levels of hyaluronan. These results need to be finalized and confirmed in larger clinical trials (page 52).

CAR T-cell therapy against mesothelin seemed to be safe and showed initial signs of efficacy in patients with previously treated refractory metastatic pancreatic cancer. Only six patients received the therapy in this initial study (page 53).

Preoperative FOLFIRINOX—a fluorouracil, leucovorin, irinotecan, and oxaliplatin regimen—might improve surgical outcomes in patients with borderline resectable pancreatic cancer. In a small study, many patients underwent complete removal of their pancreatic cancer following FOLFIRINOX and chemoradiotherapy (page 55).

PEGPH20 Added to Chemotherapy for Untreated Pancreatic Cancer

PEGPH20 added to chemotherapy was particularly effective in patients with newly diagnosed pancreatic cancer with high levels of hyaluronan, according to early results from a small comparison study that included 146 patients. PEGPH20 targets the physical barrier (called matrix or stroma) that surrounds and nurtures pancreatic cancer cells. This barrier helps tumor growth, development, and spread (metastasis). This barrier is thought to be one of the reasons why pancreatic cancers are relatively drug resistant. The barrier is made up of different types of molecules—one of these is called hyaluronan. Researchers think that PEGPH20 works by breaking down this barrier and improving drug delivery into tumors.

All of the patients were treated with the standard chemotherapy regimen of gemcitabine (Gemzar) plus *nab*-paclitaxel (Abraxane). Half of the patients also received PEGPH20. The addition of PEGPH20 to chemotherapy improved the overall response rate and progression-free survival in patients with high tumor levels of hyaluronan.

After this trial was started in 2013, it was paused because more patients than expected experienced blood clots while on treatment. Researchers restarted the study with a revised protocol that included daily injections of low–molecular-weight heparin, intended to prevent blood clots. Following the protocol revision, fewer patients developed blood clots. This trial is still ongoing. If this finding is confirmed by the final results, researchers plan to start a larger randomized study in patients with high hyaluronan levels.

What Patients Need to Know

This study suggests that adding PEGPH20 to standard chemotherapy might improve responses and progression-free survival in people with pancreatic cancer. The results also indicated that some patients (those with tumors with high hyaluronan levels) are more likely to benefit from this drug. If confirmed in other studies, this type of approach could advance the treatment of people with pancreatic cancer.

CAR T-Cell Therapy for Pancreatic Cancer

CAR T-cell therapy appeared to be safe and showed initial signs of efficacy in patients with previously treated refractory metastatic pancreatic cancer in a very small early clinical trial. To make the CAR-T-cell therapy, the researchers collected a sample of T-cells from each patient and manipulated them in the laboratory so that they would recognize mesothelin—a protein that is on the surface of pancreatic cancer cells, some normal tissues, and other types of cancer. The modified T-cells were then returned to patients.

The study included 10 patients who experienced their cancer progress after at least one prior chemotherapy regimen. Only

six patients received the CAR T-cell therapy. This treatment appeared to be safe and to produce the desired immune response against the cancer. Two patients experienced disease stabilization, which lasted for longer than four months in one of the patients. These initial results suggest that this therapy might have potential in controlling pancreatic cancer, although the final results of the study have not yet been published.

What Patients Need to Know

For CAR T-cell therapy to be successful in pancreatic cancer patients, researchers need to answer many questions such as: What are the best targets in pancreatic cancer? What is the best way to improve immunity? How often does the therapy need to be given? How well does the therapy work? Studies are underway to try to answer these questions.

Neoadjuvant FOLFIRINOX in Borderline Resectable Pancreatic Cancer

Preoperative modified FOLFIRINOX might improve surgical outcomes in patients with borderline resectable pancreatic cancer, according to the initial results from a study. FOLFIRINOX is a multi-drug combination (folinic acid [leucovorin], 5-fluorouracil [5-FU], irinotecan [Camptosar], and oxaliplatin [Eloxatin]) that is widely used to treat patients with metastatic pancreatic cancer. About 15 percent of patients diagnosed with pancreatic cancer have borderline resectable cancer, meaning that the cancer has spread to nearby blood vessels, making it difficult for surgeons to completely remove the cancer. To try to shrink the tumor so that it can be surgically removed, patients are treated with chemotherapy and/or radiation before the surgery.

In this trial, patients were first treated with modified FOLFIRINOX, then chemoradiotherapy, and then surgery. Overall, 22 patients completed therapy with modified FOLFIRINOX, 21 finished chemoradiotherapy with an oral medication, and 15 underwent surgery. In most of the patients who underwent surgery, the pancreatic cancer was completely removed—called a margin negative (R0) surgical resection. However, almost half of the patients (46 percent) experienced serious but apparently manageable side effects during FOLFIRINOX treatment.

What Patients Need to Know

The initial results from this trial suggest that FOLFIRINOX can potentially be added to pre-surgery treatment. However, more research is needed to make sure that FOLFIRINOX improves patient outcomes without dangerous side effects.

Prostate Cancer

Researchers reported a number of important findings in prostate cancer treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Adding docetaxel to hormone therapy improved survival in men with metastatic prostate cancer. In early results from two large clinical trials, patients with bulky disease seem to benefit most from the added docetaxel (page 56).

Adding docetaxel plus prednisone to long-term hormone therapy and radiotherapy improved survival in men with localized, high-risk prostate cancer. These are preliminary results from a large study (page 57).

Docetaxel Added to Androgen Deprivation Therapy for Metastatic Prostate Cancer

The addition of docetaxel (Taxotere) to hormone therapy (androgen deprivation therapy [ADT]) improved survival in men with metastatic prostate cancer, according to results of a large clinical trial. The study randomized patients with metastatic prostate cancer to ADT alone, ADT plus docetaxel, ADT plus zoledronic acid, or ADT plus docetaxel plus zoledronic acid. Patients who received docetaxel had longer survival compared to patients treated with ADT alone or ADT plus zoledronic acid.

These results suggest that this regimen might be good for patients who can tolerate docetaxel; however, all patients might not benefit from the added chemotherapy.

What Patients Need to Know

Up to now, the standard of care for men with metastatic prostate cancer has been ADT. This is the first evidence that adding a chemotherapy agent such as docetaxel to ADT can improve survival. However, as these are preliminary results, final study data are required for confirmation.

Hormone Therapy Plus Chemotherapy After Radiotherapy for High-Risk Prostate Cancer

Adding docetaxel plus prednisone to long-term hormone therapy and radiotherapy improved survival in men with localized, high-risk prostate cancer, according to early results from a larger clinical trial. A total of 562 patients received hormone therapy for 24 months. Patients were randomized to receive either hormone therapy plus radiotherapy plus chemotherapy (chemotherapy group) or hormone therapy plus radiotherapy (no chemotherapy group).

At four years, more men in the chemotherapy group were alive versus the no chemotherapy group (93 percent versus 89 percent).

What Patients Need to Know

While promising, these are preliminary results. The final results will be published soon.

Sarcoma

Researchers reported a number of important findings in sarcoma treatment at the 2015 Annual Meeting of the American Society of Clinical Oncology:

Doxorubicin alone and gemcitabine plus docetaxel were equally effective in patients with untreated advanced unresectable or metastatic soft tissue sarcoma. In this large study, the gemcitabine plus docetaxel combination was associated with higher rates of many side effects (page 58).

Eribulin was superior to dacarbazine in patients with leiomyosarcoma and liposarcoma sarcoma. In a large clinical trial, patients treated with eribulin experienced longer median overall survival and more side effects (page 59).

Trabectedin was superior to dacarbazine in patients with previously treated advanced liposarcoma and leiomyosarcoma. In a large study, trabectedin-treated patients experienced higher progression-free survival rates at 3 months and 6 months, and similar rates of side effects as patients treated with dacarbazine (page 61).

Doxorubicin for Sarcoma

Doxorubicin alone and gemcitabine (Gemzar) plus docetaxel (Taxotere) were equally effective in patients with untreated advanced unresectable or metastatic soft tissue sarcoma, according to a large clinical trial. This study compared two of the most commonly used chemotherapy regimens in patients with advanced sarcoma. Past studies have shown that both regimens—doxorubicin alone and gemcitabine plus docetaxel—are active in sarcoma; however, they have never been directly compared to each other in a clinical trial.

The study included 257 patients with advanced soft tissue sarcoma. The trial confirmed that the two regimens had similar cancer-fighting activity. At 24 weeks, 46 percent of patients in each group had not experienced progression. The two regimens worked equally well in subgroups of patients with different types of sarcoma.

Patients treated with gemcitabine plus docetaxel experienced more side effects than patients who received doxorubicin alone. The final results from this study have not been published.

What Patients Need to Know

The results of this study suggest that both regimens are equally active against sarcomas, and that they are associated with different side effects. The availability of two effective regimens with different side effect profiles provides options for patients. For example, one regimen may be better for some patients based on their ability to tolerate certain side effects, while other patients may receive both regimens at different times during their treatment.

Eribulin for Leiomyosarcoma and Liposarcoma

A large clinical trial demonstrated that eribulin (Halaven) was superior to dacarbazine in patients with leiomyosarcoma and liposarcoma (adipocytic) sarcoma. Eribulin is a chemotherapy drug used in the treatment of breast cancer, whereas dacarbazine (also called DTIC) is a long-time standard treatment in sarcoma.

This study included 452 adults with advanced high- or intermediate-grade leiomyosarcoma or different variants of liposarcoma that were deemed incurable by surgery and radiotherapy. Enrolled patients had already received two or more lines of therapy. Patients were randomized to eribulin or dacarbazine treatment.

Patients treated with eribulin experienced longer median overall survival compared to dacarbazine-treated patients (14 months versus 11 months). The survival superiority of eribulin was most notable in patients with liposarcoma.

Patients treated with eribulin experienced more side effects, including low white blood cell counts (neutropenia) and low platelet counts (thrombocytopenia). Overall, the most common side effects were low blood cell counts, fatigue, nausea, hair loss (alopecia), and constipation.

What Patients Need to Know

When the study started, eribulin only had an FDA-approved indication for patients with previously treated metastatic breast cancer. Late in January 2016, the FDA also approved eribulin for the treatment of patients with unresectable or metastatic liposarcoma.

Trabectedin for Advanced Liposarcoma or Leiomyosarcoma

Trabectedin (Yondelis) was superior to dacarbazine in patients with previously treated advanced liposarcoma and leiomyosarcoma, according to a large clinical trial. Enrolled patients had to have previously received an anthracycline (e.g., doxorubicin) and at least one other systemic therapy. The study included 518 patients, most of whom had leiomyosarcoma. Two-thirds of the patients were randomized to trabectedin, and the other one-third received dacarbazine.

The trabectedin group had higher progression-free survival rates at 3 months (56 percent versus 34 percent, respectively) and 6 months (37 percent and 14 percent, respectively) compared to patients in the dacarbazine group. This progression-free survival benefit was observed in patients with all subtypes of sarcoma. The clinical benefit rate and time to next anticancer therapy were also higher in patients who received trabectedin.

The two groups experienced similar side effects. The most common side effects seen in trabectedin-treated patients were nausea, tiredness, low blood cell counts, and increased levels of the liver enzyme alanine aminotransferase, indicative of liver dysfunction.

What Patients Need to Know

In October 2015, the FDA approved trabectedin to treat patients with unresectable or metastatic liposarcoma and leiomyosarcoma, after chemotherapy with an anthracycline. Although in both the eribulin and trabectedin randomized trials the new drugs were better than dacarbazine, dacarbazine still showed activity. Thus, dacarbazine continues to be an option for some patients.

Notes

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Resources

CancerCare®
800-813-HOPE (4673)
www.cancercare.org

American Cancer Society
800-227-2345
www.cancer.org

Cancer.Net
888-651-3038
www.cancer.net

Cancer Support Community
888-793-9355
www.cancersupportcommunity.org

National Cancer Institute
800-422-6237
www.cancer.gov

National Comprehensive Cancer Network
215-690-0300
www.nccn.org

National Library of Medicine (MedlinePlus)
888-FIND-NLM (346-3656)
www.medlineplus.gov

CLINICAL TRIAL WEBSITES

Coalition of Cancer Cooperative Groups
877-227-8451
www.CancerTrialsHelp.org

EmergingMed
877-601-8601
www.emergingmed.com

National Cancer Institute
800-422-6237
www.cancer.gov/clinicaltrials

This booklet was supported by a grant from Genentech; Astellas US, LLC; Gilead; Takeda Oncology; an unrestricted educational grant from Incyte; and an educational donation provided by Amgen.

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