

Novel Agents for Castrate-Resistant Prostate Cancer Include Potent Androgen Blockers and Immunotherapies

By Joe Munch

Despite progress in screening and therapy, prostate cancer continues to be a leading cause of cancer death among men worldwide.

When discovered in its early stages, prostate cancer can be effectively treated with surgery or radiation therapy; however, these therapies are not always curative. Current therapies for patients with recurrent or metastatic disease, which include surgical or medical castration, are initially

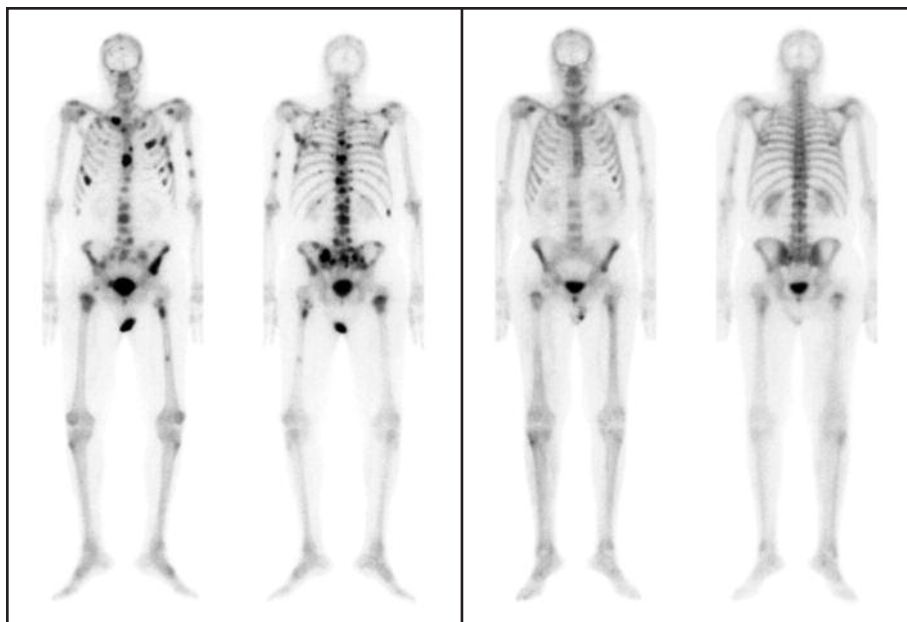
effective in controlling the disease but are not curative.

Fortunately, a spate of novel therapies for castrate-resistant advanced prostate cancer have recently been approved by the U.S. Food and Drug Administration (FDA), and others are showing promise in clinical trials. Some of these therapies build upon an improved understanding of the disease process and the molecular pathways that drive it; others take advantage of the body's inherent ability to fight cancer. All offer new hope to prostate cancer patients.

Standard hormone therapies

Treating patients in whom prostate cancer has spread or recurred typically involves suppressing the production

of testosterone, the main driver of most prostate cancers, to curb or prevent tumor growth. In the past, this was accomplished with orchiectomy. Today, most patients are treated with nonsurgical hormone therapies (aka medical castration) that either lower testosterone production itself (e.g., luteinizing hormone-releasing hormone [LHRH] agonists such as leuprolide or LHRH antagonists such as degarelix) or block the effect of testosterone in cancer cells (e.g., bicalutamide). Such therapies are also being given with increasing frequency as neoadjuvant therapy for locally advanced disease to



Bone scintiscans taken before (left) and after 6 weeks of treatment with cabozantinib, a novel tyrosine kinase inhibitor, show a reduction in skeletal metastases in a patient with metastatic prostate cancer.

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reduce the size of a prostate tumor prior to radiation therapy or prostatectomy with curative intent.

Hormone therapy can keep prostate cancer under control for years. But in many patients, it eventually fails. Such patients are said to have castrate-resistant prostate cancer—once called hormone-refractory or androgen-independent disease—which is defined as disease that persists despite therapies that lower serum testosterone to less than 50 ng/dL.

“Statistically, we know that most men, probably up to 90% of them, who initially present with androgen-dependent disease will initially respond to hormone therapy,” said Paul Corn, M.D., Ph.D., an assistant professor in the Department of Genitourinary Medical Oncology at The University of Texas MD Anderson Cancer Center. “However, if those men live long enough, a sizable proportion eventually develop castrate-resistant prostate cancer. And there’s extreme heterogeneity in how long a patient will benefit from hormone ablative therapy—it could be 6 months or 10 years.”

New hormone therapies

Fortunately, many cancers that become resistant or no longer responsive to therapies that block androgen signaling or reduce androgen levels can respond to other hormone therapies, according to Dr. Corn. “Even when patients have castrate levels of testosterone, their disease can stop responding to one hormone therapy but begin responding when another hormone therapy is started.”

For a time, it was unknown how these patients’ diseases could respond to additional therapies despite such low testosterone levels.

“When we measure testosterone levels in patients, we are measuring only serum testosterone, which is produced mostly by the testes and to a lesser extent in the adrenal glands. But a number of studies have demonstrated that one adaptation in advanced prostate cancers is that they make their



Dr. Padmanee Sharma and **Dr. Paul Corn** both serve as principal investigators in clinical studies of new treatments for castrate-resistant prostate cancer.

own testosterone. They become like an endocrine organ,” Dr. Corn said. “Now we understand that it’s the paracrine or autocrine production of androgen within the tumor that is likely driving tumor growth, and this production is not revealed in serum levels.”

In response to this finding, researchers are developing novel ways to block or suppress androgen production and thus tumor growth and progression. For example, abiraterone, which the FDA approved earlier this year for the treatment of metastatic prostate cancer, blocks androgen production not only in the testes but also in the adrenal glands and the prostate tumor itself by preventing steroid reactions involving two critical enzymes in the testosterone synthesis pathway. Another agent, MDV3100, which interferes with testosterone’s ability to interact with prostate cancer cells, is showing promise in clinical trials.

“New therapies like abiraterone are extremely potent—probably several orders of magnitude more potent than the androgen-ablative therapies we had before now,” Dr. Corn said. “But the important thing is that they block all sources of testosterone synthesis.”

New chemotherapy options

Docetaxel-based chemotherapy is usually offered after hormone therapy options have been exhausted in patients who are found to have castrate-resistant prostate cancer. At MD Anderson, outside of clinical trials, chemotherapy is typically given to avoid or treat symptoms related to advanced disease, including bone pain or obstruction of urine flow.

“For patients who have symptoms associated with their cancer, chemotherapy can significantly improve their quality of life,” Dr. Corn said. “They might go from ‘I can’t even walk’ to ‘I’m out golfing.’”

If tumor cells develop resistance to a chemotherapy drug, however, its positive effects become short-lived. Fortunately, other chemotherapy drugs can be offered after docetaxel. For example, another taxane derivative, cabazitaxel, was shown to prolong life in patients who had already received docetaxel and was approved as a second-line therapy for patients with castrate-resistant metastatic prostate cancer in 2010. At MD Anderson, Dr. Corn and other researchers are in the process of testing whether combining cabazitaxel with other chemotherapy

drugs will work better than cabazitaxel alone.

Even if a patient's tumor develops resistance to second-line chemotherapy, a different chemotherapy drug can be used. "We have experience with other third- and fourth-line chemotherapy combinations. We really try to keep going if at all possible and if the patient will benefit," Dr. Corn said. "There are a number of drugs that have not necessarily been tested for efficacy in a randomized phase III study, but we certainly use them in a serial manner to try to prolong life and preserve quality of life."

Given the advances of the past 5 years, tumors that may have once been routinely treated with chemotherapy are now studied to determine whether they will respond to more potent blockers of androgen signaling before chemotherapy is necessary.

"We're recognizing that we may be able to refine when we have to give chemotherapy by understanding the underlying biology of the tumor involved," Dr. Corn said.

New tyrosine kinase inhibitors

A number of new drugs block growth-promoting pathways important in the progression of prostate cancer and the development of skeletal metastases. Examples of drugs in this category—tyrosine kinase inhibitors—include dasatinib, cabozantinib, and dovitinib. Studies of these three agents are under way at MD Anderson.

"These drugs work quite differently from androgen-ablative agents and chemotherapies," Dr. Corn said. "We are still working out the exact mechanisms, but these drugs appear to interfere with the ability of prostate tumors to promote their own blood supply and remodel bone."

New immunotherapy options

Advances against prostate cancer have also been made in therapies that utilize the body's immune system to fight the disease. An improved understanding of T cell regulation and the tumor microenvironment in recent

years has enabled researchers to design therapies that spur the body's defense mechanisms to attack tumor cells.

"Immunotherapy for cancer has been explored for decades now, going all the way back to Coley's toxins in the 1890s. But only recently have we been able to show that immunotherapy can provide a survival benefit for patients with prostate cancer in randomized phase III trials," Padmanee Sharma, M.D., Ph.D., an associate professor in the Departments of Genitourinary Medical Oncology and Immunology, said.

One such agent, the sipuleucel-T (Provenge) vaccine, was approved for use in patients with advanced prostate cancer in 2010. Another agent, ipilimumab, an anti-cytotoxic T lymphocyte antigen (CTLA)-4 monoclonal antibody, has already been approved to treat melanoma and is now being investigated in patients with different stages of prostate cancer in several clinical trials at MD Anderson.

Therapeutic vaccine

Sipuleucel-T is an autologous cell-based immunotherapy. A patient's white blood cells are harvested via leukapheresis and incubated with a fusion protein containing prostatic acid phosphatase (PAP), an antigen expressed on prostate cancer cells, and granulocyte-macrophage colony-stimulating factor, an immune-modulating cytokine. The treated cells are then reinjected into the patient. The belief is that sipuleucel-T enables T cells to recognize PAP, thereby allowing them to attack PAP-expressing tumor cells in the body.

The way in which sipuleucel-T extends survival is, however, not yet fully understood. According to Dr. Corn, the survival benefit that sipuleucel-T offers has not been accompanied by the usual benchmarks researchers use to determine the effectiveness of a cancer therapy.

"Most of the time, when a drug prolongs survival, it prevents progression of the disease. While sipuleucel-T

prolongs disease-specific survival, it doesn't prolong progression-free survival, which is somewhat counterintuitive," Dr. Corn said. "And it doesn't consistently make prostate-specific antigen levels go down, shrink lymph nodes, or make bone scans appear better."

At MD Anderson, sipuleucel-T is typically given to patients with asymptomatic metastatic prostate cancer in whom androgen-ablative therapies are starting to fail but who have not yet received chemotherapy. In these patients, the disease is not rapidly progressing, and life expectancy is long enough to allow sipuleucel-T to work. Researchers are still trying to determine which patients will optimally benefit from sipuleucel-T.

Sipuleucel-T is an FDA-approved therapy option for patients with advanced prostate cancer, and other therapies available through clinical trials may be employed if sipuleucel-T fails.

"We never think of 'last options,'" Dr. Sharma said.

Anti-CTLA-4 therapy

Unlike sipuleucel-T, which enables T cells to target prostate tumor cells specifically, ipilimumab enhances a general T cell response against all tumor cells.

In short, T cells are activated when the T cell receptor and the CD28 molecule on T cells are both engaged by their respective ligands, which sends an "on" signal. Shortly after T cells are activated, a series of signals within the cells leads to the expression of the "off" switch, known as CTLA-4. CTLA-4 acts to limit T cell responses, which is necessary in normal settings to prevent damage to surrounding normal cells and tissues. But in the setting of bulky tumors, CTLA-4 may hinder the function of tumor-specific T cells.

"When you give ipilimumab, all you're doing is blocking the 'off' switch; you're allowing the 'on' switch to continue for a longer period of time," Dr. Sharma said.

Because anti-CTLA-4 therapy enhances T cell responses against

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tumors, Dr. Sharma said, it is potentially applicable to many tumor types. Ongoing studies are investigating ipilimumab's use in other cancer types including non-small cell lung cancer, breast cancer, and ovarian cancer.

Dr. Sharma and her colleagues are testing ipilimumab in patients with prostate cancer. In one study, patients with metastatic prostate cancer are given ipilimumab in addition to hormone therapy. Because hormone therapy enables tumor cell death, which in turn triggers an immune response, it is hypothesized that ipilimumab will enhance the immune response, possibly providing a greater benefit than hormone therapy alone.

In another study, patients whose prostate cancer has metastasized to the bone and for whom hormone therapy and chemotherapy have failed receive

ipilimumab after radiation therapy is given to bony lesions. Ipilimumab is given to potentially increase the immune response initiated by the radiation-induced cell death and subsequent release of antigens.

In a third study, patients with localized prostate cancer who are being considered for prostatectomy but have a very high risk of recurrence (lymph node involvement, high Gleason score, and/or high grade of disease) receive ipilimumab in combination with leuprolide acetate to potentially boost the immune response to the tumor. These patients then undergo surgery.

Although ipilimumab can shut down CTLA-4 in everyone (because CTLA-4 is present in every human), it does not elicit an antitumor response in everyone.

"Why some patients have an anti-

tumor response and others don't is still a mystery," Dr. Sharma said. "That's why we're investigating ipilimumab in patients with early-stage disease who will undergo prostate surgery. Obtaining some tissue specimens that we can study will help us understand the immune response that's being generated."

Toward that goal, researchers will continue to explore combinations of immunotherapies or combinations of immunotherapies and standard therapies.

"We think that the combination approach will allow the best clinical benefit," Dr. Sharma said. "But what those combinations are and how to give them still need to be explored." ■

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CLINICAL TRIALS: Prostate Cancer

A randomized, open-label, neoadjuvant prostate cancer trial of abiraterone acetate plus a luteinizing hormone-releasing hormone (LHRH) analogue versus LHRH analogue alone (2009-0322). Principal investigator (PI): Christopher Logothetis, M.D. The goal of this study is to find out how treatment with abiraterone acetate in combination with prednisone and an LHRH analogue affects the tumor's pathological stage at surgery compared with treatment with an LHRH analogue alone.

A phase II multicenter open-label study evaluating the safety and efficacy of TAK-700 in patients with nonmetastatic castration-resistant prostate cancer and a rising prostate-specific antigen (PSA) (2009-0754). PI: Paul Corn, M.D. The goal of this study is to learn if TAK-700, a novel androgen-ablative therapy, can decrease PSA levels in patients with nonmetastatic prostate cancer.

An observational study of TKI-258 in castration-resistant prostate cancer patients evaluating markers of

fibroblast growth factor (FGF) signaling in bone marrow plasma (2008-0510). PI: Dr. Corn. The main objective of this study is to learn if blockade of FGF using tyrosine kinase inhibitor TKI-258 (dovitinib) will be beneficial to men whose prostate cancer has spread to the bones.

Maximal androgen depletion followed by randomization of maximal androgen ablation with molecular targeted therapies (2010-0070). PI: Dr. Logothetis. The goal of this study is to learn if adding either sunitinib malate or dasatinib to the combination of abiraterone acetate and prednisone can help to control castrate-resistant metastatic prostate cancer.

A randomized, double-blind, phase III trial comparing ipilimumab versus placebo following radiotherapy in patients with castration-resistant prostate cancer that have received prior treatment with docetaxel (2009-0443). PI: Padmanee Sharma, M.D., Ph.D. The goal of this study is to compare radiation therapy followed by ipilimumab to radiation therapy followed

by a placebo to learn how long these treatments may help control castrate-resistant metastatic prostate cancer.

A neoadjuvant phase IIa study of ipilimumab (formerly known as MDX-010) plus hormone ablation in men with prostate cancer followed by radical prostatectomy (2009-0135). PI: Dr. Sharma. The aim of this study is to learn how ipilimumab in combination with leuprolide acetate affects the body's own immune system before surgery to remove prostate cancer.

A phase II study of ipilimumab plus androgen deprivation therapy in castration-sensitive prostate carcinoma (2009-0378). PI: Ana M. Aparicio, M.D. The goal of this study is to learn if ipilimumab in combination with leuprolide, goserelin, or degarelix can affect PSA levels in patients with metastatic prostate cancer. Researchers also want to learn if these drug combinations affect the body's immune system. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.



New Targeted Therapy Offers Hope in Relapsed Hodgkin and Anaplastic Large-Cell Lymphoma

By Bryan Tutt

The U.S. Food and Drug Administration (FDA) has approved the first new drug for Hodgkin lymphoma since 1977.

In August, the FDA granted accelerated approval for brentuximab vedotin to treat patients with Hodgkin lymphoma whose disease has recurred after stem cell transplantation and patients with relapsed or treatment-resistant systemic anaplastic large-cell lymphoma (ALCL).

Most patients with Hodgkin lymphoma can be cured with standard chemotherapy and/or radiation therapy, but those who cannot face a grim prognosis. “In all, 20%–30% of patients with Hodgkin lymphoma require second-line therapy, and this percentage may be a little higher for patients with ALCL,” said Anas Younes, M.D., a professor and the director of clinical and translational research in the Department of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center.

Autologous stem cell transplantation is effective as a second-line therapy in about half of those with Hodgkin lymphoma who do not attain a long-term remission with conventional therapy, but for patients whose disease relapses after transplantation, the overall survival rate is 55% at 2 years and only 32% at 5 years.

Patients with relapsed ALCL have a poor prognosis. They typically receive additional chemotherapy, and once a second remission is achieved, an autologous stem cell transplant is recommended. “Patients with ALCL have high rates of disease progression or relapse after front-line chemotherapy,” said Michelle Fanale, M.D., an assistant professor in the Department of Lymphoma and Myeloma. She added that patients whose tumors do not express the *ALK* gene have the highest rates of disease progression or relapse (40%–65%) after front-line chemotherapy. “Thus there has been a great need to develop effective targeted therapies for ALCL,” she said.

Pivotal studies

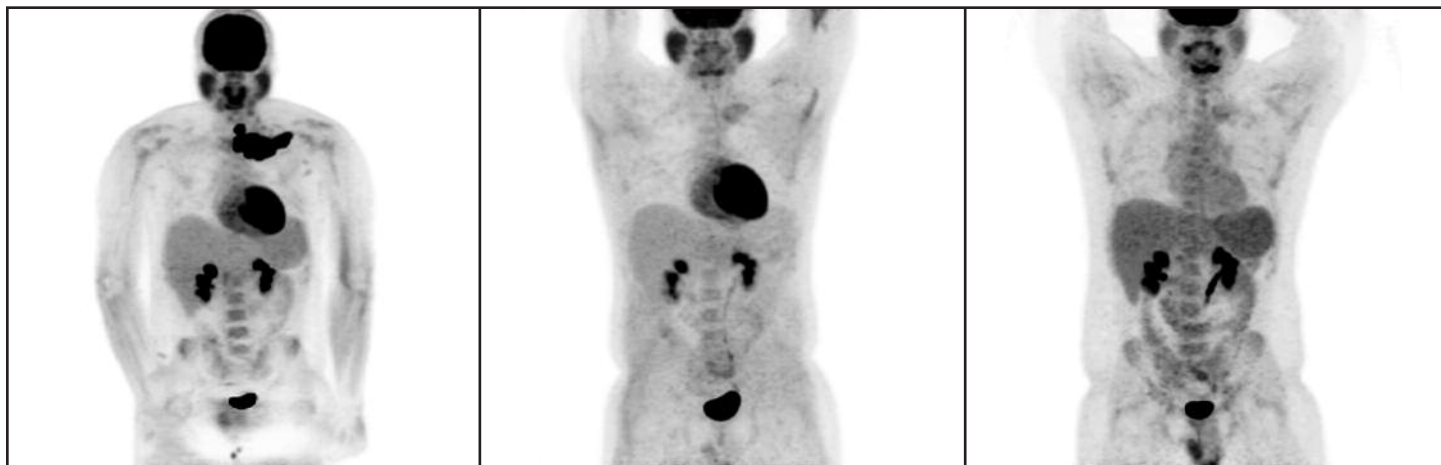
The recommendation for FDA approval of brentuximab vedotin was made on the basis of two pivotal studies—one in patients with Hodgkin lymphoma and the other in patients with

ALCL—conducted at MD Anderson and other institutions. In both studies, brentuximab vedotin was given as a single agent by 30-minute intravenous infusion every 3 weeks for up to 16 doses.

In the Hodgkin lymphoma trial, patients had undergone a median of four previous chemotherapy regimens; Dr. Younes, who served as MD Anderson’s principal investigator for the trial, said some had undergone as many as 13 previous regimens. In addition, all patients had undergone an autologous stem cell transplant that had failed. The objective rate of response to brentuximab vedotin was 75%, with approximately one-third of patients experiencing complete remissions.

In the ALCL study, brentuximab vedotin was given to 58 patients with relapsed or treatment-refractory ALCL. All patients had previously undergone one or more multi-agent chemotherapy regimens with curative intent. Most patients had not undergone stem cell transplantation. The objective response rate was 86%, with 57% of patients experiencing complete remission. Some of these patients went on to receive stem cell transplantation.

Dr. Fanale, MD Anderson’s princi-



Positron emission tomography scans taken before treatment (left), after two cycles of treatment with brentuximab vedotin (center), and after six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (right) show improvement in a patient with anaplastic large-cell lymphoma.

New Targeted Lymphoma Therapy

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pal investigator for the ALCL trial, said that patients whose tumors did not express the *ALK* gene—a group that typically does not respond well to chemotherapy—had the same response rate as those whose tumors did express *ALK*.

“I think this agent has had a profound impact on the lives of our patients with Hodgkin lymphoma and ALCL,” Dr. Fanale said. “We have seen significant positive responses to outpatient treatment with brentuximab vedotin, and our patients have been able to return to many of their normal daily activities at work, school, and home.”

Mechanism of action

Brentuximab vedotin targets the tumor necrosis factor receptor CD30, which is expressed on the surface of ALCL and Hodgkin lymphoma cells. Brentuximab vedotin comprises the CD30-specific monoclonal antibody cAC10 and the antitubulin agent monomethyl auristatin E, which are attached by a protease-cleavable linker.

The antibody-drug conjugate binds

to CD30 on the surface of lymphoma cells and is rapidly internalized. Inside the cell, the linker is selectively cleaved and the monomethyl auristatin E binds tubulin, prompting cell cycle arrest and apoptosis.

Ongoing research

Other types of lymphoma sometimes express CD30, although this expression occurs in fewer patients and at lower levels in other lymphomas than in Hodgkin lymphoma or ALCL. “Given the activity of brentuximab vedotin in Hodgkin lymphoma and ALCL, it’s reasonable for us to test it against other types of lymphoma,” said Yasuhiro Oki, M.D., an assistant professor in the Department of Lymphoma and Myeloma.

Dr. Oki will be the principal investigator at MD Anderson for a multi-institutional phase II trial of brentuximab vedotin in patients with CD30-positive non-Hodgkin lymphoma that has relapsed or is treatment-refractory. “We’re hoping this agent will provide another option for these patients,” he said. The trial is expected to begin

recruiting patients later this fall.

Even as studies of brentuximab vedotin in patients with treatment-resistant disease continue, Dr. Fanale, Dr. Younes, and other researchers are testing its use in front-line regimens for treatment-naïve patients.

Two of these trials are already under way at MD Anderson. In patients with Hodgkin lymphoma, brentuximab vedotin is being given with the standard chemotherapy regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine. In patients with ALCL, it is being given with the standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone.

Dr. Younes is optimistic about the addition of brentuximab vedotin to front-line therapy regimens. “Hopefully, we will change the standard of care and improve the cure rate for patients with these diseases,” he said. ■

FOR MORE INFORMATION

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Dr. Michelle Fanale.....713-792-2860

Dr. Anas Younes.....713-792-2860

CLINICAL TRIALS: Hodgkin or Anaplastic Large-Cell Lymphoma

A phase I study of brentuximab vedotin administered sequentially and concurrently with multi-agent chemotherapy as front-line treatment in patients with systemic anaplastic large-cell lymphoma (2010-0776).

Principal investigator (PI): Michelle A. Fanale, M.D. The goal of this study is to learn about the safety and effectiveness of brentuximab vedotin when given before and after standard cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy or when given simultaneously with and after cyclophosphamide, doxorubicin, and prednisone chemotherapy in patients with anaplastic large-cell lymphoma (ALCL).

A phase I dose-escalation safety study of brentuximab vedotin in combination with multi-agent

chemotherapy as front-line therapy in patients with Hodgkin lymphoma (2009-0801).

PI: Anas Younes, M.D. The objective of this study is to find the highest tolerable dose of brentuximab vedotin when given in combination with the chemotherapy regimen doxorubicin, bleomycin, vinblastine, and dacarbazine and when given in combination with the chemotherapy regimen doxorubicin, vinblastine, and dacarbazine to treatment-naïve patients with stage IIa bulky or stage IIb–IV Hodgkin lymphoma.

A randomized, double-blind, placebo-controlled phase III study of brentuximab vedotin and best supportive care versus placebo and best supportive care in the treatment of patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant (2009-0851).

PI: Paolo Anderlini, M.D. The goal of this study is to observe the effects of brentuximab vedotin on cancer in patients who have had an autologous stem cell transplant for Hodgkin lymphoma and are at high risk for the cancer to return.

Phase II trial of brentuximab vedotin at dose of 1.8 mg/kg intravenously every 3 weeks in patients with CD30-positive lymphoproliferative disorders (cutaneous ALCL), mycosis fungoides, and extensive lymphomatoid papulosis (2010-0914).

PI: Madeleine Duvic, M.D. The purpose of this study is to learn if brentuximab vedotin can help to control cutaneous ALCL, mycosis fungoides, or lymphomatoid papulosis. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.





Colorectal Cancer Screening

Risk factors determine who should be screened and how often

Regular colorectal cancer screening has long been considered one of the best ways to prevent colorectal cancer or to find the disease early, when it is most treatable.

More Americans than ever before are following recommendations for screening, and this has led to fewer deaths from colorectal cancer.

Yet a new report by the Centers for Disease Control and Prevention indicates that one in three Americans who should be screened for colorectal cancer is still not receiving the recommended screenings. If all people age 50 years and older were screened for colorectal cancer, the death rate from this disease would be cut in half, saving approximately 25,000 lives per year, the American Cancer Society reports.

Screening tests

After abnormal cells grow to become polyps on the inner wall of the colon or rectum, it usually takes 10–15 years before the polyps develop into colorectal cancer. Screening tests can detect these polyps, which, if found early, can be removed before they turn into cancer.

A variety of tests are used to screen for colorectal cancer and precancerous polyps in people who have no symptoms of the disease.

A **colonoscopy**, one of the most thorough tests, examines the rectum and entire colon with a lighted, flexible instrument called a colonoscope. Precancerous and cancerous growths found during the colonoscopy may be removed, or tissue samples may be taken for biopsy. Most patients receive some form of sedation before this test.

A **virtual colonoscopy** uses computed tomography (CT) or magnetic resonance imaging (MRI) to produce pictures of the colon and rectum that can show polyps and other abnormalities. No sedation is needed. If any polyps are detected, a standard colonoscopy

is performed to remove them.

Other screening tests include **sigmoidoscopy** and **double-contrast barium enema**. A sigmoidoscopy is similar to a colonoscopy, but only the rectum and lower colon are examined. A double-contrast barium enema test uses a series of x-ray scans to examine the entire colon and rectum after the patient is given an enema with a barium solution and air is introduced into the colon.

To prepare for any of these tests, the patient's colon and rectum must be empty. This usually means that the day before the test, the patient will consume only clear liquids and will take laxatives or enemas as prescribed by his or her doctor.

In another common screening procedure, the **fecal occult blood test**, tiny stool samples from the patient are tested to detect any blood in the stool. If the test is positive, a colonoscopy can determine the cause of the bleeding.

Screening guidelines

How often should these screening tests be done? That depends on a number of factors, including a patient's risk of getting colorectal cancer.

■ Average risk

For people at average risk for colorectal cancer, MD Anderson physicians recommend any one of the following beginning at age 50 years: a colonoscopy every 10 years, a virtual colonoscopy every 5 years, or a fecal occult blood test every year.

■ Increased risk

People are considered at increased risk for colorectal cancer if they have a personal or family history of colorectal cancer or polyps.

For those who have had one or two small precancerous polyps removed, MD Anderson recommends a colonoscopy every 5 years. If they've had

several polyps removed, they should be tested more often.

People with a first-degree relative (parent, brother, sister, daughter, or son) who had colorectal cancer or precancerous polyps before the age of 60 years—or two first-degree relatives who had these at any age—should have a colonoscopy every 5 years. These people can determine the age they should begin testing by subtracting 10 years from the relative's age at diagnosis. For instance, if your brother was 50 years old when he was diagnosed with colorectal cancer, you should begin screening at age 40 years.

People with a first-degree relative who had colorectal cancer or precancerous polyps at age 60 years or older—or two second-degree relatives (grandparents, aunts, uncles, or cousins) with colorectal cancer—should start colorectal screening at age 40 years. For these people, MD Anderson recommends a colonoscopy every 10 years, a virtual colonoscopy every 5 years, or a fecal occult blood test every year.

■ High risk

People at the highest risk for colorectal cancer include those with a personal history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Crohn disease, or chronic ulcerative colitis. For those in this risk category, MD Anderson recommends consulting a physician and undergoing screening every 1–2 years. ■

– K. Stuyck

FOR MORE INFORMATION

- Talk to your physician
- Call askMDAnderson at 877-632-6789
- For MD Anderson's annually updated screening guidelines for colorectal and other cancers, visit <http://utmsf01a.mdacc.tmc.edu/mda/cm/cwtguide.nsf/luhtml/sidebar1>

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IN BRIEF

Everolimus May Overcome Trastuzumab Resistance in HER2-Positive Breast Cancer Patients

Adding everolimus to trastuzumab in the treatment of HER2-positive metastatic breast cancer helps some women whose disease has been resistant to previous trastuzumab-based therapies, according to a study conducted at The University of Texas MD Anderson Cancer Center and other centers.

In the phase I/II study, 47 women with HER2-positive metastatic breast cancer that had progressed on trastuzumab-based therapy were given trastuzumab every 3 weeks and the mTOR (mammalian target of rapamycin) inhibitor everolimus daily.

The treatment was well tolerated, and side effects, which included fatigue, infection, and mouth sores, were manageable. The combination therapy resulted in partial responses in 15% of the patients and persistent stable disease in 19%.

“Even if HER2-positive metastatic breast cancer initially responds to trastuzumab, the disease usually eventually progresses,” said Phuong Khanh Morrow, M.D., an assistant professor in the Department of Breast Medical Oncology and a co-author of the study’s report, which was recently published in the *Journal of Clinical Oncology*.

Resistance to the monoclonal antibody trastuzumab has been linked to the activation of the PI3K (phosphoinositol 3-kinase) signaling pathway.

PTEN (phosphatase and tensin homolog), a tumor-suppressing protein, can negate the activity of PI3K, thus inhibiting the activation of the mTOR pathway. However, in the absence of PTEN, PI3K activity leads to the activation of the mTOR pathway, which causes trastuzumab resistance.

On the basis of preclinical data developed at MD Anderson, Dr. Morrow and her colleagues hypothesized that mTOR inhibition with everolimus would abrogate trastuzumab resistance in patients whose tumors had PTEN loss and/or mutations in the *PIK3CA* gene.

The study’s results showed that patients whose tumors had PTEN loss had lower rates of overall survival than did patients whose tumors had normal PTEN levels but that PTEN levels did not affect progression-free survival rates. *PIK3CA* mutations did not significantly affect progression-free survival or overall survival. Dr. Morrow and her colleagues believe that these findings suggest that the addition of everolimus may slow tumor progression through the inhibition of mTOR.

“This is a great example of translational research—applying a novel concept from bench to bedside to benefit our patients,” said Francisco J. Esteva, M.D., Ph.D., a professor in the Department of Breast Medical Oncology and the senior author of the study’s report. ■

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