

A Report From the American Society of Clinical Oncology 2007 Annual Meeting

Lung Cancer

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Lung cancer is one of the most common cancers in the world. In the United States, approximately 213,400 people are diagnosed with lung cancer each year. The two main types are **small cell lung cancer** and the much more common **non-small cell lung cancer**. These types are diagnosed based on how the cells look under a microscope. The rate of lung cancer cases appears to be dropping among white and African-American men in the United States, while it continues to rise among both white and African-American women.

Using Genes to Customize Treatment for Non-Small Cell Lung Cancer

MAGE-A3 GENE IS TARGET IN EARLY LUNG CANCER TREATMENT

A novel treatment for people with early non-small cell lung cancer may change the way this common form of lung cancer is treated in the future. MAGE-A3, named for the gene it targets, is a newer type of cancer treatment. Called immunotherapy, this treatment tries to stimulate a person's own immune system to identify and attack cancer cells.

About 35 percent of people with early non-small cell lung cancer **overexpress** the MAGE-A3 protein. That means their tumors contain a large amount of either the MAGE-A3 gene or a substance produced by this gene. Healthy cells do not express MAGE-A3, but cancer cells in many lung, bladder, and head and neck tumors overexpress this substance. For this reason, researchers thought that MAGE-A3 treatment might be effective.

In European clinical trials, researchers evaluated more than 1,000 people who had surgery for early lung cancer. Of the more than 350 people who overexpressed MAGE-A3, about 120 received this new treatment and 60 received a placebo (inactive substance). After a little more than two years, the cancer returned in only about 30 percent of those who received

What's New, What's Important

- An experimental treatment called MAGE-A3 may help people who had surgery for early non-small cell lung cancer live longer without the cancer returning.
- People with non-small cell lung cancer who have epidermal growth factor receptor mutations may be more likely than those without such gene mutations to respond to treatment with erlotinib (Tarceva) or gefitinib (Iressa).
- Researchers now know that a higher dose of pemetrexed (Alimta), a drug used to treat advanced non-small cell lung cancer, offers no advantage over a lower dose and may cause more side effects.
- Adding bevacizumab (Avastin) to standard chemotherapy may benefit patients with advanced non-small cell lung cancer.
- Adding cetuximab (Erbix) to standard chemotherapy may prolong the lives of people with advanced non-small cell lung cancer.

MAGE-A3 treatment compared with 43 percent of those who did not receive this treatment. Further studies of this encouraging treatment are planned.

EGFR MUTATIONS AND RESPONSE TO TREATMENT

A specific **genetic mutation** (change in the **DNA** structure of a gene) may help doctors predict whether people with non-small cell lung cancer will respond to **targeted treatment** and perhaps live longer. Substances known as **epidermal growth factor receptors (EGFRs)** may be the key to identifying which patients have the best chance of responding to the targeted drugs erlotinib (Tarceva) and gefitinib (Iressa).

Erlotinib and gefitinib block EGFRs, which reside on the surface of cells and take in messages ordering cells to grow and divide. Even though many healthy cells contain EGFRs, certain cancer

cells contain excess amounts of them. Sometimes erlotinib and gefitinib can slow the growth of cancer in people with EGFR mutations.

Researchers from Massachusetts General Hospital in Boston studied the use of gefitinib in about 100 people with advanced lung cancer. Thirty-one of these patients had EGFR mutations and received gefitinib. The tumor shrank in more than half of the patients with EGFR mutations who received gefitinib, and one year after treatment, their tumors still had not grown.

Clinical trials of this approach are ongoing. For example, in another study, the Spanish Lung Cancer Group reported that the presence of EGFR mutations may affect how people with lung cancer respond to treatment with erlotinib. The results of these two clinical trials suggest that we are potentially moving toward a time of personalized medicine for lung cancer which will benefit patients significantly. Researchers believe that the cost of performing such genetic studies may be less than the cost of giving unneeded chemotherapy.

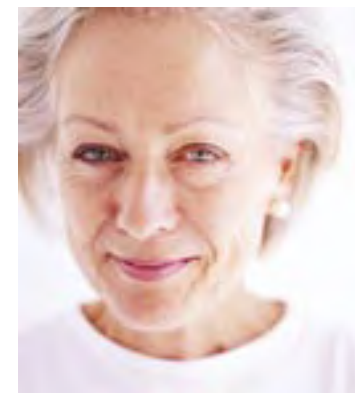
Chemotherapy and Advanced Non-Small Cell Lung Cancer

PEMETREXED (ALIMTA) AS SECOND-LINE TREATMENT

Doctors often prescribe a second course (also called **second-line**) of drug treatment for people whose non-small cell lung cancer comes back after the first course of chemotherapy. For instance, docetaxel (Taxotere) is often used for second-line treatment if it was not used in the first treatment plan. A newer drug called pemetrexed (Alimta) may also be used for second-line treatment of non-small cell lung cancer. Clinical trials seem to show that not only is pemetrexed as effective as docetaxel in fighting this type of lung cancer, but it also causes less serious side effects.

Researchers from Queen Elizabeth Hospital in Birmingham, England, thought that if pemetrexed was effective at the standard dose of 500 mg, it might be even more effective at

a higher dose. They studied almost 600 people with locally advanced or **metastatic** non-small cell lung cancer. In none of these people had a previous chemotherapy been successful. Half of these patients received pemetrexed at the standard dose, and the other half received it at a higher dose (900 mg). No difference was seen between the two groups in the rate of survival or amount that tumors shrank. However, people who received the higher dose had more side effects and were also in the hospital more often for treatment-related problems than the people who received the lower dose.



Researchers concluded that the higher dose of pemetrexed offers no advantage over the lower dose for people with advanced non-small cell lung cancer.

Combining Chemotherapy With Other Drugs to Treat Advanced Non-Small Cell Lung Cancer

CHEMOTHERAPY COMBINED WITH BEVACIZUMAB (AVASTIN)

Early research findings have shown that combining chemotherapy with the targeted treatment bevacizumab (Avastin) may prolong the lives of people with advanced non-small cell lung cancer. Bevacizumab seems to control the development of cancer by blocking vascular endothelial growth factor (VEGF)—a substance that plays a crucial role in the growth of blood vessels feeding cancerous tumors.

Because adding bevacizumab to chemotherapy holds promise, researchers from the Eastern Cooperative Oncology Group—one of the largest clinical cancer research

organizations in the United States—studied the combination in a large clinical trial of people with advanced non-small cell lung cancer. The patients, none of whom had received previous treatment for the cancer, were separated into three groups. One group of nearly 400 people received a standard dose of cisplatin/gemcitabine (Gemzar), a common chemotherapy combination used outside the United States, plus a low dose of bevacizumab. A second group of about 350 people received cisplatin/gemcitabine

plus a higher dose of bevacizumab. The third group of approximately 350 people received only the cisplatin/gemcitabine combination.

The cancer was slower to return in those who received either the high or low dose compared with patients who had not received bevacizumab. The response rate (a measure of a treatment's ability to slow or stop the growth

of a cancer) and how long the response lasted were also better in those who received bevacizumab.

None of the treatments led to many serious side effects. Further studies of such combinations are underway. At this time, most doctors consider bevacizumab combined with chemotherapy to be the best treatment option available for people with advanced non-small cell lung cancer.

CHEMOTHERAPY COMBINED WITH CETUXIMAB (ERBITUX)

Clinical trials have shown that the targeted treatment cetuximab (Erbix) can improve the effectiveness of other treatments. For instance, combining cetuximab with radiation for head and neck cancer, and with chemotherapy for

advanced colorectal cancer, has benefited patients. Recently, the combination of cetuximab and chemotherapy has been studied in people with advanced non-small cell lung cancer.

Researchers from several cancer centers in the United States and Canada tested this combination in a clinical trial of more than 130 people who had not been treated before for advanced lung cancer. The patients were separated into two groups. One group received cetuximab plus standard chemotherapy consisting of gemcitabine (Gemzar) and a platinum-containing drug (cisplatin [Platinol] or carboplatin [Paraplatin]). The other group received just standard chemotherapy without cetuximab.

Tumor growth stopped or slowed in almost 30 percent of those treated with cetuximab, compared with only about 20 percent of those who did not receive cetuximab. People treated with cetuximab lived longer than those who did not receive cetuximab (almost 12 months versus about nine months).

To learn more about the promising benefits of cetuximab in people with advanced non-small cell lung cancer, researchers have conducted two more clinical trials. Results of these studies are expected by the end of 2007.

CHEMOTHERAPY COMBINED WITH VANDETANIB (ZACTIMA)

Another encouraging combination treatment for people with advanced non-small cell lung cancer focuses on the use of a new drug called vandetanib (Zactima). Like the targeted treatment bevacizumab, vandetanib seems to control the development of cancer by blocking VEGF. It also blocks other such substances that control the growth of blood vessels.

Researchers from the United States and the United Kingdom studied more than 180 people with advanced lung cancer. Patients received one of three **first-line** treatments:

- vandetanib alone;



- vandetanib plus the chemotherapy combination of carboplatin (Paraplatin) and paclitaxel (Taxol);
- just carboplatin and paclitaxel.

More than 400 blood samples were taken from patients—at the start of the clinical trial and then 8, 22, and 43 days after treatment. About 35 substances in the plasma (the fluid part of the blood) were analyzed to see whether they could predict if a person would respond to cancer treatment.

Women seemed to benefit more from the addition of vandetanib to carboplatin and paclitaxel than did men, perhaps because lung tumors grow differently in women and men. Analyzing these substances—what researchers refer to as blood-based markers—may be more suitable and less expensive than using other methods such as tumor biopsy or imaging techniques. Researchers believe that further clinical trials would be worthwhile.

Advanced Lung Cancer and Brain Metastases

PREVENTIVE TREATMENT FOR THE SPREAD OF LUNG CANCER TO THE BRAIN

Small cell lung cancer makes up about 15 percent of all lung cancers. It is usually described as either limited **stage** (the cancer is located on one side of the chest) or extensive stage (the cancer has spread to others areas of the chest or outside the chest). People with extensive-stage disease are often treated with chemotherapy, but there is a high risk of the cancer spreading to the brain (**metastasis**). So researchers are studying ways to reduce the risk of brain metastasis and improve patients' response to treatment.

One possible solution is the use of preventive radiation to the brain, also called prophylactic cranial irradiation. This approach has significantly reduced the risk of brain metastasis in people

What's New, What's Important

- Women with advanced non-small cell lung cancer may benefit more from treatment with a new drug called vandetanib (Zactima) than men with advanced lung cancer, perhaps because these tumors grow differently in men and women.
- Preventive radiation treatment to the brain may help patients with advanced small cell lung cancer live longer and may reduce the risk of the cancer spreading to the brain.
- For people with lung cancer that has spread to the brain, the combination of radiation and a new drug called motexafin gadolinium seems to significantly lengthen the time until the cancer affects the brain's ability to function normally.
- A new vaccine, P53-DC, appears to help people with extensive-stage small cell lung cancer respond to chemotherapy, which may prolong their lives.

with limited-stage small cell lung cancer. Researchers thought it might also help patients with extensive-stage cancer.

At VU University Medical Center in Amsterdam, The Netherlands, researchers performed the first clinical trial of preventive radiation to the brain in people with extensive-stage lung cancer whose tumors shrank in response to chemotherapy. Half of the nearly 300 patients who took part in the clinical trial received the radiation treatment once a day for one to two weeks, and the other half received none.

After one year, only 15 percent of patients treated with radiation showed symptoms that cancer had spread to the brain, compared with 40 percent of the people who were not treated. Also, people who received the radiation treatment lived longer than those who received none.

In people with advanced lung cancer who responded to initial chemotherapy, preventive radiation treatment may now be a way to reduce the risk of cancer spreading to the brain.

MOTEXAFIN GADOLINIUM AND RADIATION FOR THE SPREAD OF LUNG CANCER TO THE BRAIN

For people with lung cancer that has already spread to the brain, the combined results of two clinical trials focus on a promising treatment. This approach seems to prolong the time it takes for the cancer to affect the nervous system. The treatment consists of radiation to the brain plus motexafin gadolinium. The U.S. Food and Drug Administration is currently considering this drug for the treatment of brain **metastases** from non-small cell lung cancer.

The use of radiation plus this new drug was compared with radiation alone in both clinical trials, which involved more than 800 people with lung cancer that had spread to the brain. About 80 percent of these people had multiple brain metastases that impaired their nerve function. Patients in both groups received treatment for 10 days.

People in both trials who were treated with motexafin gadolinium showed a longer delay in the time it took for the cancer to affect the nervous system compared with those not treated with the drug—15 months versus nine months. Combining the new drug with radiation also lengthened the time it took until the cancer affected the brain's ability to remember and function normally.

The most common side effect of treatment with motexafin gadolinium was a green discoloration of the skin which usually went away after 24 hours.

On the Horizon

P53-DC VACCINE FOR SMALL CELL LUNG CANCER

Small cell lung cancer accounts for about 15 percent of lung cancers in the United States. By the time doctors find it, small cell lung cancer has usually spread, at least in small amounts. When that is the case, it is called extensive-stage cancer. At first, small cell lung cancer responds to chemotherapy. But

many times these responses do not last, and the tumor returns, often resistant to chemotherapy. So researchers have been seeking better ways to help people fight this type of lung cancer.

One of the newer methods being studied is a **vaccine** that targets one specific substance. Approximately 90 percent of small cell lung cancers have an abnormal form of the p53 gene. Researchers think this gene mutation may be the reason small cell lung cancer can be difficult to treat. The p53-DC vaccine has been designed to try to make this tumor more responsive to chemotherapy.

Researchers have completed clinical trials of the p53-DC vaccine in more than 40 people with extensive-stage small cell lung cancer. After three **vaccination** doses, those whose cancer had not spread received another round of vaccinations. When the cancer started to spread, all patients were offered further chemotherapy. Researchers from H. Lee Moffitt Cancer Center in Tampa, Florida, and the Hospital de la Paz in Madrid, Spain, found that almost half of the patients who were treated with chemotherapy after the vaccine seemed better able to fight the cancer. The vaccine does appear to make this type of lung cancer sensitive to additional chemotherapy, which may help these people live longer.



Please note: Although the treatments discussed in this chapter are showing promise, most are still in clinical trials—some in earlier phases of research—and may not be available yet to the general public. Your doctor can help guide you as to which new medications could be right for you and whether you are eligible to take part in the clinical trials of these new treatments.