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September 2011

New Directions

What Are “Mutations” And What Do They Mean for Cancer Treatment?

Cancer is a group of diseases in which cells grow out of control. As we learn more about the way cells work and the biology of cancer, how it is defined and treated is changing. Treatment is becoming more personalized, based on testing cancer tissue for genetic characteristics unique to the person and the cancer.

Cells are made up of DNA, a unique “blueprint” which tells the cell what to do. Inside each cell are stretches of DNA, called genes, that indicate which proteins to make and exactly how much of each is needed. The proteins control the necessary functions for life, including making cells grow, divide, and specialize. Sometimes errors, called mutations, occur in the DNA. When this happens, the mutated DNA can create proteins that may drive the development of cancer. Researchers have identified many such mutated genes and proteins in lung cancer. Targeted therapies, which target the mutated cancer cells but not healthy cells, have been developed. Today, much of the focus is on identifying patients who are most likely to respond to specific targeted therapies. This is done by testing cancer cells to find out what mutations exist. Doctors then use the information to help decide which treatment is best for the patient.

This *New Directions Newsletter* focuses on updates from studies reported in 2011, many of which are exploring targeted treatments in patients that have been found to have lung cancer with specific mutations. Continued success in studies like these will one day lead to the goal of personalized medicine—the right medicine for the right patient at the right time. ■

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2011 Research Highlights

If you see an asterisk (*) you can refer to the glossary located in the margins of page 2 and 3.

Screening and Early Detection

Screening High Risk Populations with Low Dose CT Scans Improves Lung Cancer Survival

The death rate from lung cancer is due, in part, to the fact that often a diagnosis is made after the cancer has already spread beyond the lung where it began. Screening for cancer can find it earlier but unlike breast, prostate, colon, and cervical cancers, there has not been an agreed upon way to screen for lung cancer. Both chest x-rays and chest CT scans have been considered, but a randomized* controlled* trial (the “gold standard” in clinical trials) was needed to show that CT screening can decrease deaths. In 2002, the National Cancer Institute (NCI) and American College of Radiology Imaging Network (ACRIN) began the National Lung Screening Trial (NLST). Over 50,000 current and former smokers, aged 55-74 years old, with at least a 30 pack year* smoking history were enrolled in the trial. Half of the participants had yearly chest x-rays and half had yearly low dose spiral CT scans over a three year period. There were 20% fewer deaths from lung cancer in the group screened with CT

scans compared with those who received chest x-rays. These findings show that CT scans caught more lung cancer early and that doing so saves lives. There have been major improvements to CT scanning technology since the trial started, which means the benefit from CT screening is likely to be higher than 20%. Other trials that may build more support for CT screening are going on worldwide and many hospitals and cancer centers across the US are deciding how to start lung cancer screening programs. For more information on screening, please visit www.screenforlungcancer.org.

Advanced Stage Non-Small Cell Lung Cancer (NSCLC)

Maintenance Therapy with Pemetrexed (Alimta®) May Improve PFS* in Advanced Non-Squamous NSCLC Patients

Maintenance therapy is treatment given or continued after the first treatment has ended, with the goal of keeping cancer stable or the patient

continued on page 2

Definitions

Pack year

A measure of the amount of cigarettes a person has smoked over an extended period.

Endpoint

A measurement that tells how well a treatment works in cancer clinical trials:

OS (Overall Survival)

The percentage of people in a study or treatment group who are alive for a certain period of time after they were diagnosed with or treated for a disease.

PFS (Progression-Free Survival)

The length of time during and after treatment in which the cancer does not get worse (progress).

ORR

(Overall Response Rate)

The number of patients whose cancer shrinks or disappears due to treatment.

DCR

(Disease Control Rate)

The number of patients who show complete response (CR), partial response (PR), or stable disease (SD).

- **CR (complete response)**
disappearance of visible tumors
- **PR (partial response)**
significant decrease in tumor size
- **SD (stable disease)**
no significant increase or decrease in tumor size

cancer-free. PARAMOUNT was a phase III* trial in patients with stage IIIB/IV non-squamous type NSCLC who had not yet received treatment. They were given cisplatin and pemetrexed (Alimta®). Those whose cancer did not grow or spread at the end of four cycles of treatment were randomized* into two groups: one stayed on pemetrexed as maintenance and the other did not receive further treatment but was monitored to see if the cancer grew or spread. Those on maintenance pemetrexed had significantly longer PFS*, regardless of age, stage, gender, smoking history, and response to initial treatment. DCR* was also better in the group continuing pemetrexed. The effects of maintenance pemetrexed on OS* will be reported when those data have been collected.

Erlotinib (Tarceva®) Shows Promise in First-Line Treatment for Stage IIIB and IV Patients with EGFR Mutations

Erlotinib (Tarceva®) is a drug that treats lung cancer by targeting a mutation in a receptor called EGFR. Erlotinib is currently approved to treat advanced NSCLC in patients who did not respond to platinum-based chemotherapy (e.g. cisplatin or carboplatin) and for maintenance therapy in NSCLC that was stable after four cycles of chemotherapy. The EURTAC study tested if erlotinib is effective when used as the first treatment a patient receives after diagnosis. 174 patients with stage IIIB or IV NSCLC who tested positive for the EGFR mutation and had not received any other treatment for their cancer were placed in two groups: one received standard platinum-based chemotherapy and the other received erlotinib. PFS* was significantly better in the group treated with erlotinib. As a result, it may be best to give erlotinib first instead of chemotherapy for those patients who test positive for the EGFR mutation.

MetMab with Erlotinib (Tarceva®) Benefits Patients with Tumors that Have High Levels of Met Protein

Cancer is the result of abnormal cell behavior. This behavior is controlled by a protein on the cell surface called a receptor. If the receptor is not working properly (mutated), cancer can develop. Met is a receptor that, when mutated, can cause cancers which do not respond well to treatment. This randomized*, double-blind*, phase II* study explored if MetMab, a drug that blocks the behavior of Met, combined with erlotinib (Tarceva®), could improve treatment response in

patients whose cancer had high levels of the Met receptor. 137 patients who had previously treated NSCLC were randomized* into two groups: one receiving MetMab and erlotinib and the other receiving placebo* and erlotinib. All tumors were tested and were either Met-positive (high Met) or Met-negative (low Met). In the Met-positive group, those who received MetMab plus erlotinib had PFS* twice as long as those who received erlotinib alone. The MetMab and erlotinib group also had better OS*. The results support further study of MetMab as a possible treatment for patients with high Met tumors and a larger phase III* trial is planned for late 2011.

Ongoing Crizotinib Trial Reports on Progression Free Survival in ALK-Positive NSCLC Patients

About 3-5% of patients with NSCLC are ALK positive, which means their cancer has ALK and EML-4 genes that have joined together in a way known as "fusion." A phase I* trial showed that the oral drug crizotinib had a significant anti-cancer effect on tumors with the ALK fusion gene. 57% of participants showed a partial* or complete* response. In an ongoing phase I study investigators reported updated safety and response data as well as PFS* data from a group of ALK positive NSCLC patients. Most of these patients were never or former smokers and had received a number of other treatments for their NSCLC. The results showed that when treated with crizotinib in 28-day cycles, the median PFS* was 10 months, and importantly there were no serious adverse events associated with the treatment. The investigators noted that the response to crizotinib was "robust and rapid." These results may mean a new standard of care for patients with the ALK fusion gene.

A New Generation of EGFR Inhibitor, BIBW 2992 (Afatinib), Shows Promise for NSCLC Patients who have Become Resistant to First-Generation EGFR Inhibitors

When tumor cells have overactive receptors (proteins found on the outside of cells that tell it how to behave) or make too many copies of receptors such as EGFR and HER2, the cancer tends to spread and outcomes are usually worse. First-generation targeted drugs were developed to block the activity of these receptors with the goal of stopping cancer growth. Even when cancer responds to these drugs, eventually the drug stops working and the cancer grows. BIBW 2992 (afatinib) targets both the EGFR and HER2 receptors and may work after

To learn about open clinical trials for which you qualify, call 800-698-0931. It may also be useful to take any studies of interest to your doctor to discuss.

the cancer has stopped responding to the first-generation drugs. In this study, patients whose cancer had stopped responding to other targeted treatments were given BIBW 2992 with increasing doses of cetuximab (Erbix®). Although it was a small study, more than 90% of patients showed partial response* or stable disease* from the drug combination without serious side effects. BIBW 2992's effectiveness will continue to be researched in a larger study.

The Lung Cancer Mutation Consortium (LCMC): A Study to Identify Common Mutations in NSCLC and Deliver the Best Personalized Treatments

The goal of the LCMC was to find key mutations common in lung cancer and identify targeted therapies that are most effective in treating them. Tumors from 1,000 patients with stage IV adenocarcinoma were tested for 10 different mutations that drive the cancer to grow. 54% of the tumors tested had a mutation for which a targeted drug has already been developed. Patients whose cancer had a mutation were offered the opportunity to participate in clinical trials using these drugs that target the mutations. The LCMC offers mutation testing to lung cancer patients at no cost. To participate, patients must be diagnosed with stage IIIB/IV lung adenocarcinoma and have enough tumor tissue to test. Currently there are 14 cancer centers around the country participating in the program (www.golcmc.com). This exciting approach to a more personalized diagnosis and treatment plan will continue to develop as other mutations are identified and treatments to target them are found.

TG01 (Apricoxib) Slows Time-to-Progression and Overall Survival* in Biomarker-Selected NSCLC Patients

TG01 (apricoxib) is an oral anti-inflammatory medication that targets how cancer cells communicate and function. This randomized*, double-blind*, controlled*, phase II* clinical trial found patients with high levels of a specific protein that indicates a potential response to a drug (biomarker) and treated

them with a combination of erlotinib (Tarceva®) and TG01 or erlotinib and placebo*. Patients under 65 years of age who got erlotinib and TG01 did better than those in the same age group who got erlotinib and placebo*. Those on TG01 had a 71% improvement in DCR*, a 93% improvement in PFS*, and a 205% improvement in median OS*. In addition, 52% of those taking TG01 and erlotinib were alive after one year, compared to 22% for those taking erlotinib and placebo*. Importantly, this study showed that testing for a biomarker can find patients who might benefit most from TG01. A larger phase III* study is planned. TG01 combined with chemotherapy is also being studied in another phase II* trial as second-line therapy for NSCLC.

Small Cell Lung Cancer (SCLC)

Amrubicin May Offer Another Treatment Option for Second-Line Treatment of Extensive SCLC

Extensive stage SCLC is hard to treat, especially if it does not respond to chemotherapy or if it comes back soon after treatment. In 2008, a trial comparing topotecan (Hycamtin®, which is the current standard for second-line treatment of extensive stage SCLC) to amrubicin showed that the group receiving amrubicin had better OS* than the group receiving topotecan. While recent phase III* trial results did not show the same difference in survival, the group that received amrubicin showed some benefits. In the ACT-1 trial, 637 patients were divided into two groups: one received topotecan and the other received amrubicin. The results showed improved OS* for patients whose cancer did not respond to prior treatment or responded at first but then stopped. All who received amrubicin had better ORR* and PFS* with fewer chemotherapy related side effects (such as fewer infections and need for transfusions). Amrubicin also requires less time to give than topotecan. While this trial did not show significantly improved outcomes for all, the improved OS* for some patients along with better symptom and side effect control make amrubicin an interesting drug for further study. ■

When to Search:

It is important to know about clinical trials you may be eligible for even before you have a biopsy. We also encourage you to search for trials before you begin treatment and whenever you need to make a new treatment decision.

Whether you decide on the recommended current standard of care or a clinical trial, it is important to know all of your options.

Definitions

Placebo

An inactive substance or treatment that looks the same and is given the same way as an active drug or treatment being tested. The effects of the active drug or treatment are compared to the effects of the placebo.

Randomized Trial

Trial design in which participants are assigned by chance to a treatment group.

Double-Blind Study

A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug.

Controlled Trials for Cancer

One group of participants is given standard of care (i.e., the control group), while another group is given a standard treatment plus an experimental drug or therapy.

Primary Research Goals in Clinical Trials:

Phase I - Evaluate the safety and dosage of a new drug or treatment.

Phase II - Continue to test the safety of the drug, and begin to evaluate how well the new drug works.

Phase III - Confirm the effectiveness of the study drug or treatment and compare it to the current standard of care.



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On The Horizon—Early Stage Non-Small Cell Lung Cancer (NSCLC)

When NSCLC is found early, surgery (with or without chemotherapy and radiation) is the standard treatment. Exciting advances in surgical techniques, radiation, and vaccines may offer other options for care.

Minimally invasive lung surgeries, such as VATS (video-assisted thoracic surgery), involve smaller surgical openings, generally require shorter hospital stays, and have faster recovery times and fewer side effects than traditional lung cancer surgery (thoracotomy). Research is testing how successful these techniques may be, and which patients will benefit most.

SBRT (Stereotactic Body Radiation Therapy) is a type of highly targeted, focused radiation. Many studies have shown promising results using SBRT to treat early stage NSCLC in patients who are not eligible for surgery. SBRTs

ability to control small, isolated cancers and improve survival appears similar to surgery. SBRT may allow patients who could not have surgery to avoid chemotherapy. Randomized* controlled* trials to compare SBRT to surgery continue to study differences in survival and the ability to control the cancer. Unfortunately, recruitment for these trials is slow and results may not be available for some time.

Another area to watch is immunotherapy, also called vaccine therapy. MAGRIT is a phase III* trial testing whether an anti-cancer vaccine given after a patient has had surgery can prevent the cancer from returning. The specific cancer marker that the vaccine is targeting must be present in the tumor sample for the patient to be eligible for the trial. The trial sponsors hope to recruit all participants by the end of 2011 and results should be available sometime in 2013. ■