Clinical Trials and Emerging Therapies for Lung Cancer

Emily Duffield, MPH, MSN, ANP-BC

Introduction

Clinical research is being carried out to develop novel lung cancer treatments. Several new treatments are now commercially available, and others are available only to patients who participate in clinical trials. Traditional chemotherapy attacks any rapidly dividing cells, but targeted therapy concentrates on specific abnormalities unique to cancer cells, resulting in fewer side effects and potential for improved cancer control. Targeted therapies can pinpoint specific molecular alterations to prevent tumor cells from growing and dividing out of control. Targeted therapies may be used alone or in combination with other treatments to improve overall care. However, targeted therapies often apply to a select group of patients who have tumors with unique mutations, and these therapies are not appropriate for all patients. Research and clinical trials continue to evaluate the best use of these newer targeted agents in an effort to improve the quality of life and longevity of patients.

Additional new treatments for lung cancer include immunotherapy and vaccines. Researchers and clinicians are hopeful that these therapies will improve outcomes for patients diagnosed with lung cancer. Despite these new treatments, chemotherapy remains an important treatment option, and researchers continue to evaluate newer chemotherapy agents and combinations to treat lung cancers. Other areas of research include targeted agents and chemotherapy for lung cancer maintenance (prevention of relapse) and medications to prevent lung cancer (chemoprevention) in patients at high risk for developing this disease.
Clinical Trials

Drug development begins with the identification of new substances that show anti-cancer activity in research laboratories. Following extensive laboratory testing, clinical trials are done to establish whether or not these substances are effective at fighting cancer in people. The purpose of clinical trials is to identify new agents that will improve survival or quality of life more than other currently available treatment options.

Clinical trials of new drugs are done in a series of phases, each with a specific purpose. If the drug is safe and provides benefit in an early phase trial, it is further tested in subsequent phases:

- **Phase 1**: the drug is tested for the first time in people to establish safety, tolerability, dosage, and treatment schedule for subsequent studies.
- **Phase 2**: the drug is tested in more people to determine efficacy, safety, and side effects.
- **Phase 3**: the drug is tested in a larger group of people to determine whether or not the new drug is more effective than existing treatments. Side effects and safety also are monitored.
- **Phase 4**: after approval by the United States Food and Drug Administration (FDA), the drug is available for treatment in the general population and further monitored for safety, efficacy, and long-term side effects.

During phases 1 to 3, the drugs are available only to patients who participate in the clinical trial. In phase 4, the drugs are commercially available through drug stores and specialty pharmacies. Clinical trials are available at major medical centers, but are increasingly becoming available at smaller community medical centers due to the expansion of hospital networks. A list of all clinical trials available for lung cancer patients is provided on the Internet site of the National Cancer Institute [http://www.cancer.gov/clinicaltrials/search](http://www.cancer.gov/clinicaltrials/search). The treating oncologist may recommend trials that are available locally as well as at regional medical centers.

Sometimes new drugs that demonstrate a major increase in efficacy compared with older therapies are granted FDA Fast Track Status, and the FDA expedites the availability of these new treatments to patients who have limited options. Drugs with Fast Track Status are available only in clinical trials but may move through the clinical trial process and become widely available more quickly. Certain targeted therapies have shown such great efficacy and tolerability that they have moved from the phase 1 “first in human trials” to FDA approval in four years or less.
Targeted Therapy

Chemotherapy drugs are effective because they kill cancer cells that multiply rapidly. However, many normal cells also multiply rapidly, such as cells of the digestive tract, hair follicles, and blood. When these normal cells are affected by chemotherapy drugs, undesirable side effects occur. Targeted therapy includes newer drugs that interfere with specific aspects of cancer cells, avoiding damage to normal cells. Targeted therapy consists of either monoclonal antibodies (names ending in “-ab”) that target the outside surface of the cancer cell or small molecules (names ending in “-ib”) that target the inside of the cancer cell.

As genetic research advances, great strides are being taken to better understand the molecular make-up of tumors, and to determine the mechanisms which drive tumor growth, development, and spread to other organs. The wider availability of full genome sequencing of tumor DNA is opening up the opportunity for truly personalized medicine, in which therapies are targeted to the specific genetic make-up of an individual’s tumor. Genome sequencing offers the opportunity to identify rare mutations and then design a treatment plan to block the exact mechanism that is making the cancer grow. Examples of well-studied mutations that are common in lung cancer are EGFR mutation, EML4-ALK rearrangement and KRAS mutation. Newer targets being researched in lung cancer include ROS1, BRAF, HER2, MET, PIK3CA and RET. Several drugs used to target these mutations have been approved by the FDA for either lung cancer or other types of cancer, while many of the novel agents listed below are available only through clinical trials.

Monoclonal antibodies are proteins that attach to receptors on the cell surface. The cell surface receptors may be stimulated by proteins, and this may start a controlled series of reactions inside the cell that may increase cellular growth and development. The normal cellular controls are absent in malignant cells, and cellular replication proceeds uncontrolled. Antibodies are normally produced by the immune system to fight infections caused by bacteria or viruses, and the body produces specific antibodies for each type of infectious agent (antigen) to which the body is exposed. Identification of tumor specific antigens allows novel drugs to use the immune response to recognize and fight cancer cells. The class of drugs known as monoclonal antibodies are produced in a laboratory and are designed to bind with a very specific target, such as a cell surface receptor or other defect unique to cancer cells.

**Monoclonal antibodies can fight cancer cells by:**
- Turning off the series of reactions in the cells by blocking the receptors,
- Targeting specific defects in the cancer cells or labeling the cancer cells, making them more vulnerable to destruction by the body’s own immune system, or delivering other drugs or substances directly to the cancer cells.
Trastuzumab is a monoclonal antibody that targets HER2 overexpression. It has been used in HER2 positive breast cancer (received FDA approval for this application in 1998), and is now being evaluated in lung cancers with the same mutation. Common side effects include nausea, vomiting, loss of appetite, fatigue and muscle or joint aches. Cardiac toxicity can be a serious complication, and warrants close monitoring. Allergic reactions may occur during the infusion of this drug. If used in combination with chemotherapy it may contribute to decreased white blood cell count and increased risk of infection.

Cetuximab is a monoclonal antibody that binds to and blocks signaling of the EGFR receptor. Although not yet FDA approved for use in lung cancer, it is currently approved for use in certain head and neck as well as colorectal cancers. Side effects include potential for allergic reactions during infusion, as well as rash, fatigue, diarrhea, and electrolyte imbalances. If used in combination with other EGFR targeted therapies significant rash and/or diarrhea may occur.

Seribantumab (MM-121) is a monoclonal antibody designed to target ErBb3 in heregulin positive NSCLC. Heregulin positive cancers tend to evade the effects of anti-cancer therapies and progress more quickly than heregulin negative cancers. Up to half of lung cancers are heregulin positive. Seribantumab was granted fast track status by the FDA in July 2016 for heregulin positive lung cancer that has progressed on immunotherapy. Efficacy and side effects are being evaluated in combination with standard of care chemotherapy through the SHERLOC trial.

Small molecule drugs enter the cell and block the sequence of reactions that cause cellular proliferation. By blocking this sequence of reactions in cancer cells, the small molecule drugs kill the cancer cells and slow or stop tumor growth. In normal cells, tyrosine kinase enzymes activate a phosphorylation cascade that regulates signals sent to the cell nucleus and governs the timing of cellular proliferation, differentiation, and programmed cell death (apoptosis). In malignant cells, this communication cascade may be switched on permanently, resulting in unregulated cellular proliferation and tumor growth. Tyrosine kinase inhibitors are small molecule drugs that interfere with this sequence of reactions, stopping cell proliferation and causing cell death. New tyrosine kinase inhibitors continue to be studied for use in lung cancer, and several are now commercially available for patients with specific, targetable mutations in tumor DNA. During treatment with small molecules the cancer cells may develop additional mutations that confer resistance to first line therapy. Identification of second and third-line therapies that continue to exploit the underlying driver mutation but also block resistance mutations has become increasingly important. EGFR and ALK are two well established therapeutic targets for small molecule inhibitors. However, multiple newer targets continue to be identified, offering patients a chance at treating their disease while maintaining better quality of life with fewer side effects than they might have with chemotherapy.
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**EGFR inhibitors**

ASP8273 is a third generation Epidermal Growth Factor Receptor (EGFR) pathway inhibitor with activity against the T790m resistance mutation. Over 60% of patients with EGFR mutation will develop a T790m resistance mutation contributing to failure of first-line EGFR inhibitor therapy. ASP8273 selectively inhibits mutant forms of EGFR, which means it may be better tolerated than other non-selective agents. Common side effects included diarrhea, nausea, vomiting, decreased platelet count and rash. Safety and efficacy continue to be evaluated in clinical trials, however, early data suggest response in up to 80% of treated patients.5

EGF816 is a third generation EGFR inhibitor with activity against exon 19 deletion, L858R and T790m mutations. Common side effects included rash, diarrhea, itching, mouth soreness, and fatigue. Response rate in the Phase 1 trial was 44%, with median response lasting 9.2 months.6 Currently this drug is available only through clinical trials.

Olmotinib (BI 1482694), a third-generation small molecule is being evaluated for use in patients with an EGFR mutation who have developed the T790m mutation following initial EGFR TKI therapy. Over half of patients (54%) responded to therapy in early trials, and their response lasted for approximately 8.3 months.7-8 Because Olmutinib spares normal EGFR, the drug is well tolerated with fewer side effects compared to first and second generation EGFR targeted therapies. Currently it is approved in South Korea, but is available in the US only through clinical trials.

PF-06747775 is a third generation EGFR inhibitor targeted against the T790m resistance mutation. It selects for mutant EGFR rather than wild type, so the side effect profile is more tolerable than with non-selective EGFR inhibitors. Safety and efficacy continue to be evaluated through phase 2 clinical trials.9

**ALK inhibitors**

Brigatinib (AP-26113) is an ALK inhibitor that is being evaluated for use both in the first line as well as second line settings for patients whose tumors harbor an EML4-ALK rearrangement. Phase 1/2 data were promising, with a greater than 70% response rate.10 Like several other second and third generation ALK inhibitors it also showed anti-cancer activity in the brain, which was exciting as ALK+ NSCLC tends to spread to the brain. Respiratory changes were seen in a small percentage of patients within the first 7 days of dosing, additional research is being done to further evaluate this phenomenon. This compound is tolerated quite well, with mild side effects including diarrhea, nausea, vomiting, and fatigue. Brigatinib has now moved into phase 3 testing, and remains available only through clinical trials.
Lorlatinib is a selective ALK-inhibitor that has shown activity against both initial and resistance mechanisms. In Phase 1 trials it demonstrated a 40% response rate, including activity in patients who had developed resistance mutations to prior ALK targeted therapies. In addition, it was effective in treating brain lesions. Common side effects included elevated cholesterol levels and peripheral neuropathy. It continues to be studied in Phase 2 clinical trials, and is only available through enrollment into a clinical trial.

Entrectinib is a targeted therapy with activity against ALK, ROS1 and NTRK. In the phase 1 trial 57% of ALK positive patients responded to treatment, and showed activity in the brain. Common side effects were mild, and included fatigue, taste changes, constipation, diarrhea, dizziness, paresthesia, myalgia and weight gain. It continues to be studied in phase 2 clinical trials, and is only available through enrollment into a clinical trial.

X-396 is a potent ALK inhibitor with anti-cancer activity against both treatment naïve and tumors that developed resistance to first line therapy with Crizotinib. In the phase 1 trial over 80% of patients responded to therapy, with observed activity in the brain. Response lasted for a median duration of more than 20 weeks with some responses lasting for over 50 weeks. Common side effects included rash, fatigue, nausea, vomiting and swelling. X-396 continues to be studied in phase 2 clinical trials, and is only available through enrollment into a clinical trial.

TSR-011 is an ALK inhibitor with activity against TRK as well. Data from the phase 1 trial shows that it has activity, but overall response rates were difficult to estimate due to small sample size of dose cohorts. Common side effects include fatigue, diarrhea, heart rhythm changes, headache, decreased appetite, vomiting and constipation. The safety and efficacy of TSR-011 continue to be evaluated in phase 2 clinical trials.

**ROS-1 Inhibitors**

Cabozantinib is a multi-kinase inhibitor with activity against several cell signaling targets including ROS-1 rearrangement. It is being evaluated in lung cancer following progression on Crizotinib. In particular, it has shown efficacy against the G2032R and L2026M resistance mutations found in ROS-1 rearranged tumors. Safety and efficacy of Cabozantinib continue to be evaluated in lung cancer, but common side effects when used in other types of cancer included nausea, diarrhea, fatigue, mouth sores, and hand-foot syndrome (redness, pain, tingling and numbness to hands and feet).

Ceritinib has been shown to have activity in pre-clinical studies for lung cancer tumors with ROS-1 rearrangement. Case studies are available that show response in a small number of patients. The available pre-clinical data also supports its use in patients who have progressed on Crizotinib. Particularly if they have developed the G2032R resistance mutation. Although efficacy data continues to be collected through phase 2 clinical trials, safety data can be conferred from its use in patients with an ALK rearrangement. Common
side effects include diarrhea, nausea, vomiting, increased liver function enzymes and low phosphate levels.\textsuperscript{18}

The ROS1 target is conformationally quite similar to that of ALK, thus in addition to Ceritinib both Lorlatinib and Entrectinib are also being evaluated for efficacy against ROS1 in phase 2 trials.

**BRAF Inhibitors**

Dabrafenib both as a single agent and with the addition of Trametinib is being evaluated for a subset of BRAF mutant lung cancer patients with the V600E BRAF mutation. The V600E mutation is present in approximately half of all BRAF mutant lung cancers.\textsuperscript{19} Trametinib is a MEK inhibitor which interferes with the cell signaling cascade. These drugs first showed promise in metastatic melanoma patients with the same mutation. The combination showed increased efficacy 33\% response rate with Dabrafenib alone, and 63\% response rate with Dabrafenib and Trametinib together.\textsuperscript{20} Common side effects included fever, fatigue, low white blood cell count, anemia, and low salt level.\textsuperscript{21} An unusual side effect that is unique to BRAF inhibition is the development of eruptive squamous cell carcinomas.\textsuperscript{22} Thus, patients should be evaluated by a dermatologist in the event of any skin changes or new lesions. Dabrafenib and Trametinib continue to be studied, and remain available through Phase 2 clinical trials.

Vemurafenib has also demonstrated activity in BRAF V600E mutation positive lung cancer patients. In phase 1 testing 42\% of patients responded, and preliminary 12 month survival was 66\%.\textsuperscript{23} Side effects included rash, fatigue and arthralgia. Vemurafenib continues to be studied in clinical trials as both a single agent and in combination with other agents.\textsuperscript{24}

LGX818 is a new BRAF inhibitor that is being evaluated both as monotherapy in an open-label, and in combination with the MEK inhibitor MEK162. A triplet therapy with MEK162 and LEE011 is also being considered in early phase clinical trials.\textsuperscript{25} Because these compounds are in early stages of clinical trial evaluation little safety, efficacy and response data are available. However, pre-clinical data shows that these agents and combinations show promising activity in the BRAF mutant lung cancer patient population.\textsuperscript{26}

**MEK inhibitor**

Selumetinib is a small molecule drug that has been studied in early phase clinical trials. It inhibits the mitogen-activated protein kinases MEK-1 and MEK-2. The MEK pathway is thought to be a potential therapeutic target for KRAS positive NSCLC, which are often resistant to standard chemotherapy. It stops cellular proliferation and induces apoptosis in some cell lines.\textsuperscript{27} Common side effects include rash, diarrhea, nausea, vomiting, hypertension, visual disturbance, and decreased liver function. It has been evaluated in combination with chemotherapy as well as other EGFR targeted therapies and unfortunately has not shown significant benefit in terms of progression free or overall survival benefit.
compared to standard chemotherapy. However, it continues to be evaluated in combination with immunotherapy in ongoing clinical trials.

Trametinib is being evaluated both as a single agent and in combination with other targeted therapies as well as combined with traditional standard of care chemotherapies. It showed similar efficacy to docetaxel in the second line treatment setting. Common side effects include rash, diarrhea, and retinal changes. It continues to be studied in phase 2 clinical trials, and remains available through clinical trials only.

Bimetinib (MEK162) is being evaluated in combination with other therapeutic agents for lung cancer, including standard of care chemotherapy agents as well as other targeted therapies. Common side effects include diarrhea, fatigue, elevated lipase levels, and rash. It continues to be evaluated in phase 1 clinical trials, and remains available through clinical trials only.

**Additional Small Molecule Inhibitors**

Multiple other targets continue to be discovered for NSCLC. These include HER2, RET, NTRK-1, PI3Ca, and MAP2K1. Numerous drugs are currently being investigated that show activity against one or more of these targets, including Cabozantinib, Alectinib, Apatinib, Vandetanib, Ponatinib, Lenvatinib, Selumetinib, Cobimetinib. Interestingly, many of these drugs have more than one intra-cellular target, and are being evaluated for application in different types of cancer as well as potentially being useful for multiple different tumor mutations. As the science of tumor genetic sequencing progresses more drug-gene targets will be established in an effort to truly personalize treatment to the genetic fingerprint of an individual patient’s cancer, with continued improvement in treatment options and therapeutic outcomes for lung cancer patients.

**Immunotherapy**

Cancers develop and spread in part because they evade detection by the immune system. The goal of immunotherapy is to make cancer cells recognized as abnormal or “non-self” by the immune system, enabling natural immune defense mechanisms to eliminate the cancer. With immunotherapy, side effects are typically mild because the drugs affect only certain types of cells, and they use the body’s own defenses (not cytotoxic drugs) to kill cancer cells. However, in some cases the immune system may be over-engaged, creating auto-immune inflammatory side effects. These can be severe, and may require immune suppressant medications to control.

Several antibodies are currently being evaluated that target certain immune checkpoints that have been shown to play a role in cell signaling and driving cancer growth. Some of the most promising developments in treating lung cancer have been seen in trials evaluating the Programmed Death 1 (PD-1) receptor pathway, including Opdivo (Nivolumab), Keytruda (Pembrolizumab, formerly Lambrolizumab), Atezolizumab (MPDL3280A), and Durvalumab...
Currently both Nivolumab and Pembrolizumab are approved for second line treatment of NSCLC. Pembrolizumab has also demonstrated efficacy in the first line setting. Although it is not yet FDA approved for first line treatment, it is being reviewed by the FDA for this additional indication. Atezolizumab and Durvalumab continue to be evaluated in NSCLC and show potential similar to the two currently approved drugs.

Immunotherapy is a type of targeted therapy that utilizes key receptors in the immune recognition process. The PD-1 receptor is found on immune cells (T cells), and when activated, it can suppress the ability of the immune system to recognize and attack cancer cells. Similarly, PD-L1 is the ligand to which PD-1 binds on the surface of the tumor cell. By blocking these receptor sites with targeted Anti-PD-1 or Anti-PD-L1 antibodies, it is possible to increase the body’s own defenses against cancer. This change to cell signaling enhances the immune system so that it can recognize and attack cancer cells. Data on efficacy of these drugs continues to emerge, but they appear to be effective in 20% or more of patients, in some cases offering complete response and eradicating evidence of the cancer. At this time it appears that expression of PD1 marker on the cell surface is correlated with higher response rates. These drugs have a very different side effect profile than traditional chemotherapy drugs, and are typically well tolerated. However, because these medications increase the activity of the immune system, it is possible for the immune system to attack healthy cells along with cancer cells. Side effects are remarkably mild, but rare severe drug toxicities have occurred. Adverse effects commonly manifest as a result of an inflammatory response, and can occur nearly anywhere in the body – skin (rash), eyes (iritis/uveitis), colon (colitis/diarrhea), lungs (pneumonitis), liver (hepatitis), and kidneys (nephritis). Due to the inflammatory nature of the side effects, steroids are used to control and reverse these inflammatory-mediated reactions. At this time administration of these drugs to people with auto-immune conditions is prohibited, as the reaction of the compromised immune system is unclear and such exposure poses undue risk to patients.

Ipilimumab and Tremelimumab are monoclonal antibodies that inhibit the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway. Although these have been used extensively in the treatment of melanoma, they are now being evaluated in NSCLC, typically in combination with the Anti-PD1 class of drugs. They have a similar side effect profile to the Anti-PD1 antibodies, including rash, diarrhea/colitis, hepatitis, iritis/uveitis, hormonal changes and pneumonitis. However, side effects tend to be more common with Anti-CTLA-4 drugs compared to Anti PD-1 and Anti-PD-L1 compounds.

Vaccines

Vaccines are also being used to treat lung cancer and as maintenance therapy with the goal of decreasing or preventing the risk of recurrence. Analogous to vaccines that may prevent the spread of viruses, cancer vaccines stimulate the immune system to identify and attack cancer cells without damaging normal cells.
Belagenpumatucel-L (Lucanix®) currently is being studied for people with stage III and IV NSCLC. It is given as a series of monthly injections for 12 months. Although a positive effect was seen in early studies, ultimately the vaccine did not provide survival benefit over placebo. However, the data suggested a survival benefit if the vaccine was started within 12 weeks of conclusion of chemotherapy, and if the patient had received prior radiation. Common side effects include injection site reaction and flu-like symptoms.41

Tecemotide (Stimuvax®) was studied in patients with inoperable stage III and IV NSCLC. It targets the Mucin 1 (MUC1) protein on the surface of cancer cells. The MUC1 protein is a good target because overexpression of this protein in cancer cells may cause decreased apoptosis, decreased immune function, and increased resistance to chemotherapeutic agents. Final analysis of a large phase 3 trial did not yield overall survival benefit, but there was an over 10 month improvement in survival in the subset of patients treated with concurrent chemotherapy and radiation, compared to those who received their therapies sequentially.42 Common side effects include injection site reaction, nausea, vomiting, diarrhea, and flu-like symptoms.

TG4010 is targeted immunotherapy based on a pox virus (the Modified Vaccinia Ankara virus) that codes for the MUC1 tumor-associated antigen and interleukin-2. TG4010 has been assessed in combination with first-line chemotherapy in advanced NSCLC and has shown an improvement in progression-free survival.43 Common side effects include injection site reaction and flu-like symptoms.44 TG4010 continues to be evaluated in phase 3 clinical trials.45

BI 1361849 (CV9202) is a vaccine that is made up of six mRNAs that code for six different NSCLC-associated antigens. A phase 1 trial demonstrated safety and tolerability of the compound, as well as an enhanced anti-tumor effect when combined with radiation.46 Collection of survival data remains ongoing. The most common side effects were injection site reactions and mild to moderate flu-like symptoms. As it is thought that this compound may increase tumor infiltrating lymphocytes, a trial combining it with an immunotherapeutic agent targeting Anti-PD-1 is currently enrolling patients.

Chemotherapy

Although much research is focusing on new approaches to lung cancer treatment, research also is being done to develop new drugs for chemotherapy or improve existing chemotherapy regimens. Combination therapy has long been the hallmark of cancer treatment. As promising new agents are identified, they are evaluated in clinical trials in an effort to identify novel treatment modalities that will improve quality of life and prolong survival. Multiple trials evaluating the addition of small molecules, monoclonal antibodies, as well as immunotherapy are currently underway.

Amrubicin is approved by the FDA for use in treating breast cancer, and has been investigated for use in treating both small cell and non-small cell lung cancer.47 It did not
provide survival benefit when compared to topotecan in second line treatment for small cell lung cancer.\textsuperscript{48} It is an anthracycline, a highly effective class of chemotherapy drugs that has a high risk of cardiac toxicity (damage to the heart). However, amrubicin does not cause the same amount of cardiac toxicity observed with other anthracyclines, even at high doses.\textsuperscript{49} Common side effects include decreased bone marrow function (anemia, neutropenia, and low platelet counts).

**Maintenance Therapy**

Maintenance therapy can be given to patients in remission, or to prevent relapse of cancer. Erlotinib (Tarceva\textsuperscript{®}) was approved by the FDA in 2010 as a maintenance therapy for NSCLC patients who completed at least four cycles of platinum-based therapy, and who have disease that has not progressed.\textsuperscript{50} Pemetrexed (Alimta\textsuperscript{®}) was approved by the FDA in 2008 as a maintenance therapy for patients with non-squamous NSCLC who completed at least four cycles of platinum-based therapy, and who have disease that has not progressed. Bevacizumab (Avastin\textsuperscript{®}) has not been approved by the FDA for maintenance treatment in NSCLC, but it frequently is continued as a single agent after being used in combination with other chemotherapy drugs in the initial or induction treatment.

**Chemoprevention**

Multiple studies have been conducted in an effort to identify compounds that might prevent the development of lung cancer. Unfortunately, to date none have been identified that have demonstrated a dramatic decrease in cancer rates.\textsuperscript{51} Antioxidants and anti-inflammatory drugs like COX-2 inhibitors did not ultimately show a decreased cancer incidence, but aspirin seemed to slightly decrease risk in several studies, particularly in those at highest risk for developing lung cancer.\textsuperscript{52} A better understanding of features of pre-malignant lesions continues to develop, and a personalized “cocktail” may ultimately offer the best protection against developing lung cancer in high risk individuals.\textsuperscript{53}

Pioglitazone hydrochloride (Actos\textsuperscript{®}), a drug used in treating type 2 diabetes mellitus, is being evaluated as a drug that may slow or prevent the growth of tumors in patients with NSCLC. Currently it is being evaluated in patients with a smoking history who are at risk for developing lung cancer. A trial considering it in patients with stage IA through IIIA NSCLC was terminated early due to low enrollment. However, Pioglitazone is not without side effects. Cardiotoxicity has been noted, as well as the potential risk for developing bladder cancer.\textsuperscript{54} Additional information is needed to better understand the risks and benefits of potential long term use as a protective agent.

**Lung Cancer Screening Programs**

Because 1 in 9 smokers will go on to develop lung cancer\textsuperscript{55}, avoiding exposure to tobacco smoke and smoking cessation remain the best defense against lung cancer. See Chapter 11,
How to Quit Smoking Confidently and Successfully. However, novel screening algorithms are being developed for use of low-dose screening CT scans in order to identify both those individuals at highest risk for lung cancer, as well as to identify cancers in an early, asymptomatic, surgically resectable and thus more treatable stage. The best lung cancer screening programs are comprehensive, and include the services of pulmonary experts, as well as oncologists and counselors who can educate patients regarding their risk of developing cancer as well as interpret and appropriately act on any screening test results.

Conclusion

Lung cancer is a devastating diagnosis, but research is improving the options for treatment of this disease. Chemotherapy is the mainstay of treatment for most advanced lung cancers. New targeted therapies and immunotherapies are changing the treatment landscape for lung cancer, with several new drugs demonstrating remarkable improvement in patient outcomes in terms of both progression free and overall survival. Additional novel agents used both alone and in combination with existing agents are being studied in clinical trials, with the goal of further improving patient outcomes and survival. More therapies will become available in the near future. With advances in lung cancer treatment, patients will benefit with improved tolerance and response to therapy, such that lung cancer may well evolve to a chronic disease such that even if it remains incurable, it may be treated and managed for many years.

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