

advances

Volume 1, Issue 1

SPRING 2015

IN THIS ISSUE

More Treatment Options for People with Squamous Cell Lung Cancer [page 1](#)

Overcoming Resistance to Targeted Therapies [page 1](#)

Empowering Our Own Immune Systems to Fight Lung Cancer [page 3](#)

Advances in Early Detection—Lung Cancer microRNA and Metabolite Biomarkers [page 4](#)

For the most up-to-date information about our current research program, please visit: LUNGEVITY.org/research-we-fund



The screenshot shows the LUNGEVITY website with a navigation bar including 'ABOUT LUNG CANCER', 'THE RESEARCH WE FUND', 'SUPPORT & SURVIVORSHIP', 'EVENTS', 'ABOUT US', and 'DONATE'. Below the navigation is a search bar and a 'DONATE NOW' button. The main content area features a banner for 'THE RESEARCH WE FUND' with a microscope image. Below the banner is a section titled 'IN THIS SECTION' with a sub-section 'The Research We Fund' containing text about research funding and a 'DONATE NOW' button.



LUNGEVITY Foundation is firmly committed to making an immediate impact on increasing quality of life and survivorship of people with lung cancer by accelerating research into early detection and more effective treatments, as well as by providing community, support, and education for all those affected by the disease.

More Treatment Options for People with Squamous Cell Lung Cancer

Squamous cell lung cancer represents 25%-30% of all lung cancer diagnoses in the United States, affecting about 60,000 people each year.

Yet, until recently, progress for this patient population was extremely slow, with just three approved treatment options: surgery, chemotherapy, and radiation therapy. Now, within four months, two new types of treatment have been approved for this large group of lung cancer patients: an immunotherapy drug and an angiogenesis inhibitor.

Immunotherapy is the big lung cancer story of 2015 to date, with approval of the first drug in this class for lung cancer in March. Nivolumab (brand name: Opdivo®) was approved specifically for the treatment of patients with metastatic squamous non-small cell lung cancer. While Opdivo and other immunotherapies *continued on page 2*

Overcoming Resistance to Targeted Therapies

The past decade has seen a revolution in the treatment of a subset of non-small cell lung cancers that are altered in growth-promoting genes such as EGFR or ALK.



Dr. Leicia Sequist and her team are studying drug resistance.

Targeted therapies that block the function of aberrant proteins in the lung cancer cells cause regression of the tumors. Unfortunately, after initial response, many patients relapse because the cancer becomes resistant to the original drug treatment and reappears.

continued on page 2

More Treatment Options *continued from page 1*

continue to be studied in clinical trials for all types and stages of lung cancer, having a first approval in squamous cell lung cancer sends a powerful message of hope to this group of patients.

Angiogenesis inhibitors stop tumors from making new blood vessels, cutting off the tumors' blood supply, the source of the oxygen and nutrients they need. They do this by blocking the cancer cells' vascular endothelial growth factor (VEGF) receptors. Approved by the FDA in December, ramucirumab (brand name: Cyramza®) is considered a VEGF receptor 2 antibody, which works differently from bevacizumab (brand name: Avastin®), the first angiogenesis inhibitor approved for lung cancer. Avastin is not approved for use in squamous cell lung cancer, but Cyramza is approved for treatment of patients with all types of metastatic non-small cell lung cancer (NSCLC), including squamous. Both drugs are approved for use in combination with chemotherapy.

In addition, a third major class of treatment—**targeted therapies**—is being studied in a **groundbreaking clinical trial known as Lung-MAP**. The Cancer Genome Atlas, with a team of more than 300 scientists and leadership by former

LUNGEvity awardee Dr. Matthew Meyerson, published its groundbreaking work on molecular mutations in squamous cell lung cancer in 2012. More than half of squamous tumors were found to have mutations for which drugs were already in development or could be developed. Building on this knowledge, Lung-MAP is focused on patients with recurrent Stage IIIB-IV squamous cell lung cancer. This first-of-its-kind clinical trial uses a targeted screening method to match patients with studies of multiple new treatments, including immunotherapy and targeted therapies. Lung-MAP treatments are being studied as second-line or later therapy. More information can be found at www.lung-map.org. Drugs targeting other genetic mutations seen in squamous cell lung cancer are being studied in other clinical trials as well.

In addition, numerous **clinical trials** are **studying how best to maintain quality of life and length of response**, including by combining chemotherapy agents with radiation therapy, surgery, immunotherapy, or targeted cancer therapy and by giving the chemotherapy nab-paclitaxel (brand name: Abraxane®) as maintenance therapy in patients with advanced squamous cell lung cancer to keep the cancer from coming back.

Targeted Therapies *continued from page 1*

Several LUNGEvity-funded researchers are trying to develop better treatment approaches for patients with these types of tumors by researching how the tumors acquire resistance. They are working to identify and study the genetic alterations that allow the cancer cells to bypass the inhibition by the EGFR or ALK inhibitor therapy.



With a Career Development Award from LUNGEvity, **Dr. Christine Lovly of Vanderbilt-Ingram Cancer Center** studies the changes that enable lung cancer cells to acquire **resistance to the ALK inhibitor crizotinib**. In an article recently published in the high-impact journal *Nature Medicine*, Dr. Lovly and her mentor, Dr. William Pao, reported another set of changes that leads to the growth of lung cancer cells through the activation of ALK. They found that growth of these cells could be repressed by using an inhibitor of a protein called IGF-1R. Lung tumors from patients whose cancer had progressed on the ALK inhibitor crizotinib exhibited signs of activation of the IGF-1R pathway. **Using a dual targeting strategy, they provide proof that targeting both ALK and IGF-1R simultaneously results in better control of this type of lung cancer.** In addition to her laboratory-based studies, Dr. Lovly is a member of the NIH/NCI teams that are planning the NCI MATCH trial and the NCI ALK Master Protocol trial.

Drs. Lecia Sequist and Jeffrey Engelman of Massachusetts General Hospital developed a program to identify the changes in tumors from lung cancer patients who, after an initial response, had **relapsed on targeted therapy directed against EGFR or ALK**. They obtained repeat biopsies from patients and used the latest deep-sequencing technology to identify genetic changes that occurred in the tumor cells. By testing the sensitivity of the cells to a panel of targeted drugs, they were able to identify which molecular pathways the cells were depending on for growth.



Dr. Lecia Sequist

In a breakthrough study recently published in Science magazine, the team reported that this approach was successful in identifying drug combinations active against different tumor-derived cells. This multiplex strategy could benefit individual patients by helping to choose targeted combination therapies against their specific tumor cells.

With new technologies available to test for several mutations and drug combinations at the same time with just a small piece of tumor tissue, the molecular testing of the cancer tissue in real time is a distinct possibility. This approach provides a leg-up in the race to outwit the evolving cancer cells with effective drug combinations.



Dr. Jeffrey Engelman

Empowering Our Own Immune Systems to Fight Lung Cancer

We usually think of our immune system in terms of its role in fighting infections such as flu and other viruses. Equally important, however, is the role of the immune system in preventing the development of cancer. Recent important breakthroughs in cancer research have led to the approval of new drug treatments for prostate cancer and melanoma that work by stimulating the immune system to attack cancer cells.

This March, the first immunotherapy in lung cancer was approved for use in patients with advanced squamous cell lung cancer. This drug, nivolumab (brand name: Opdivo®), belongs to the group of drugs known as immune checkpoint inhibitors or anti-PD-1 antibodies. They work by releasing the “brakes” on the human immune system and allowing it to attack cancer cells.

Given the promising results seen so far, many additional immunotherapies are in clinical development, and the FDA has given many of these treatments special standing for expedited development and review to help bring them to patients more quickly. Importantly, immunotherapy of all kinds is being studied in all types and stages of lung cancer and in combination with each other and with other kinds of treatment, like surgery, radiation therapy, chemotherapy, and targeted therapy.



Dr. Patrick Forde

Recent LUNGeVity awardee **Dr. Patrick Forde of Johns Hopkins Kimmel Cancer Center** is studying nivolumab for patients with **earlier stage lung cancer**. While some early-stage lung cancers may be cured by surgery and chemotherapy, cancer may recur for many patients, and effective treatments that reduce the risk of this happening are urgently needed. His Phase I clinical trial examines the role of nivolumab given before surgery for earlier-stage lung cancer. Patients who have newly diagnosed stage IB, II, or IIIA non-small-cell lung cancer may be candidates for this trial.

The study will also examine how anti-PD-1 affects the immune system in patients with lung cancer. The overall aim of the study is to move anti-PD-1 forward as

a treatment for earlier stage lung cancer. This research will provide us with important new insights into how the immune system deals with lung cancer and will allow us to plan additional studies of immunotherapy to directly benefit patients.



Dr. Lucia Beatrice Jilaveanu

In a new collaborative effort, LUNGeVity has joined together with the Melanoma Research Alliance and Lung Cancer Research Foundation to support the work of **Dr. Lucia Beatrice Jilaveanu of Yale University**.

Brain metastases are extremely common in both NSCLC and melanoma patients. Two new immunity-boosting drugs are showing promise against both of these kinds of cancer. However, little is known about immune cells in the brain and whether the immune system can be stimulated to reject cancer cells. Dr. Jilaveanu will study patients with brain metastases treated with the new drugs in a clinical trial to find biomarkers that could predict which patients are most likely to benefit from this type of therapy.

Drs. Alberto Chiappori and Scott Antonia of H. Lee Moffitt Cancer Center & Research Institute are leading a study on the effect of **combining the PD-L1 inhibitor, MEDI3746, with an immune-boosting drug that works by a different**



Dr. Alberto Chiappori

mechanism than the PD-L1 inhibitor. They expect the combination immunotherapy to provide patients with a stronger anti-tumor response and improved outcomes.

Dr. Julien Sage of Stanford University is studying immunotherapy for **small cell lung cancer (SCLC)**. He is examining a type of immunotherapy that boosts macrophages, the immune cells that can engulf and digest tumor cells. In collaboration with the group of Dr. Irving Weissman, Dr. Sage has found that SCLC cells express at their surface a “don’t-eat-me” protein signal that inhibits the activity of macrophages. Using a dual strategy, he will block this signal to enhance the activity



Dr. Julien Sage

of macrophages and recruit macrophages to the proximity of the tumor cells. If successful, this novel immunotherapeutic approach may be rapidly applicable to small cell lung cancer patients in the clinic.

Advances in Early Detection

Lung Cancer microRNA and Metabolite Biomarkers

A major challenge for lung cancer treatment is that the disease is most often diagnosed at a late stage. Like mammograms for breast cancer and colonoscopies for colon cancer, a safe and sensitive blood or spit test for lung cancer could catch the disease at an early stage and allow treatment to begin when the cancer is still contained. An easily accessible, widely used early detection test would allow more effective treatment and help save thousands of lives. LUNGeivity has made early detection a priority area of research and has funded several projects that aim to discover good biomarkers to reliably and accurately detect early disease, as well as to more accurately predict the stage of lung cancer.

In the search for candidates that could be useful predictors of the disease stage, researchers are studying several types of biomarkers that can be detected in the blood of patients with early-stage disease. These include proteins, antibodies, genes, bits of RNA called microRNAs, and chemicals produced by the metabolic activity of cancer cells.

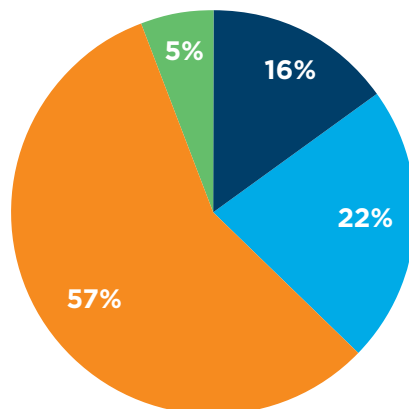
Dr. Suzanne Miyamoto and her colleagues Drs. Oliver Fiehn and Karen Kelly at UC Davis in Sacramento received a LUNGeivity Early Detection Award to study chemical biomarkers in tumor and normal lung tissue, along with blood samples from cancer patients, healthy individuals, and patients with benign lung nodules. In one of the largest studies on lung cancer tissues to date, **the group has recently defined a set of chemicals that are produced by energy use in cells (metabolic activity) that differ between early stage adenocarcinoma tissue and the normal tissue counterpart.** These studies provide new chemical biomarkers that may serve in the detection of early-stage lung cancer.

Dr. Steven Dubinett of UCLA has gathered a substantial database of proteins and microRNAs detected in the blood of lung cancer patients. With support from a LUNGeivity award in 2010, his group continues to study which of these may be secreted from tumor cells and be useful biomarkers that reflect tumor growth. Dr. Dubinett believes that **cells from early stages of lung cancer must have increased growth and movement**, and he studies telltale signs of cancer cell movement. He has discovered a microRNA called mir125 that regulates this process. **Reduced levels of mir125 were correlated with enhanced tumor growth and malignancy.** Further studies are underway to confirm these findings in early-stage lung cancer patient samples.



Dr. Steven Dubinett

Percent of Lung Cancer Diagnosis by Stage



- Localized: Confined to primary site
- Regionalized: Spread to regional lymph nodes
- Distant: Cancer has metastasized
- Unknown: Unstaged