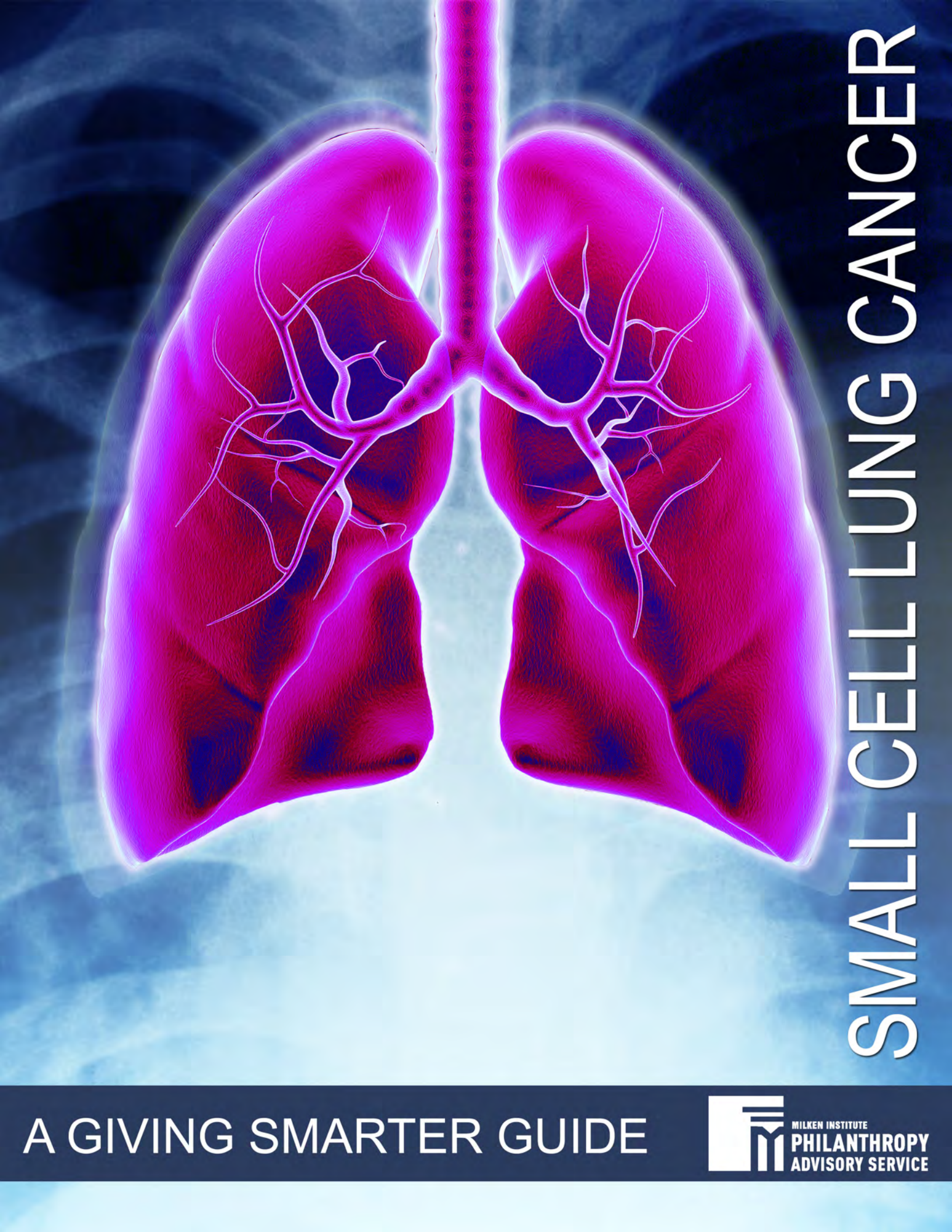

SMALL CELL LUNG CANCER

A GIVING SMARTER GUIDE

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EXECUTIVE SUMMARY

Lung cancer is the deadliest cancer in the United States, claiming the lives of about 160,000 Americans each year – more than breast, prostate, and colon cancer combined. The survival outlook is dismal, with 17.4 percent of patients surviving five years after being diagnosed. With a 1 in 14 lifetime chance of being diagnosed with lung cancer, it is clear that progress is desperately needed to combat this disease. Additionally, the economic burden of lung cancer care is staggering, as the estimated annual cost of $12.1 billion is projected to increase by at least 25 percent over the next five years.

There are two major types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). While the majority of lung cancer patients have the NSCLC subtype, SCLC patients suffer from the more aggressive of the two, with a much lower five-year survival rate.

In contrast to SCLC, a plethora of new life saving treatment options have become available for NSCLC patients, while the standard of care for SCLC patients has remained unchanged for more than 30 years. This delay in progress is largely due to:

- Poor understanding of SCLC disease biology and lack of funding to support research
- Lack of access to SCLC biospecimens to identify biomarkers and new therapeutic targets
- Inefficient clinical trial enrollment processes and data sharing

As a result, SCLC patients and their families are still waiting for innovative medical solutions that could dramatically improve and or save the lives of SCLC patients.

Overall, this is an exciting time for cancer research, as physician scientists have found a number of ways to leverage personalized medicine tools and employ a patient's own immune system to kill tumors. These new breakthroughs have resulted in dramatic responses in patient populations with aggressive cancers, such as melanoma, which typically have poor prognostic outlooks.

SCLC is poised to benefit from these breakthroughs; however, strategic investment in research tools, infrastructure, and discovery science is essential. While there has been some recent attention by Congress on the need to dedicate more resources to SCLC, through the Recalcitrant Cancer Act of 2012, the mandate is currently unfunded and, according to experts, likely to be underfunded given the scope of unmet needs in SCLC research. Thus there is an immense opportunity for strategic philanthropy to fill the gap in order to elevate SCLC research so that patients are presented with new treatment options soon.

The Milken Institute Philanthropy Advisory Service has developed this Giving Smarter Guide for Small Cell Lung Cancer with the express purpose of empowering patients, supporters, and stakeholders to make strategic and informed decisions when directing their philanthropic investments and energy into research and development efforts. Readers will be able to use this guide to pinpoint research solutions aligned with their interests. This guide will help to answer the following questions:

- *Why should I invest in SCLC research?*
- *What is the current standard of care?*
- *What are the barriers preventing development of new therapeutics?*
- *What key things should I know about this disease?*
- *What is the current state of SCLC research efforts?*
- *How can philanthropy expand infrastructure to support SCLC research and advance new therapies?*

OVERVIEW

More than 400,000 Americans are currently suffering with lung cancer, with over 200,000 new cases estimated to be diagnosed this year alone. Approximately 15 percent of people diagnosed with lung cancer are told that they have one of the most aggressive forms of the disease – small cell lung cancer (SCLC). SCLC is a particularly dismal disease, having a five-year survival rate of less than 7 percent if caught early in the limited disease (LD) stage; however, most SCLC cases are detected at the extensive disease (ED) stage, where the five-year survival rate is less than 2 percent – representing an urgent need to make progress in this disease space.

Given these alarming statistics, SCLC has been named a *recalcitrant cancer* and has become the focus of a new bill recently signed into law – the Recalcitrant Cancer Research Act (RCRA, H.R. 733). The bill defines a cancer as recalcitrant if it has a five-year relative survival rate of less than 50 percent. The RCRA was developed to chart the way forward to accelerate cancer research for particularly intractable cancers.

SCLC IS A RECALCITRANT CANCER

The National Cancer Institute (NCI) was tasked with selecting two recalcitrant cancers with a five-year relative survival rate of less than 20 percent and that are estimated to cause at least 30,000 deaths in the United States per year to pilot the RCRA. This directive led NCI to prioritize SCLC, along with pancreatic cancer, as cancers in desperate need of additional and focused resources to accelerate treatment science in order to mitigate suffering among the thousands of patients diagnosed with these aggressive cancers each year.

For both cancers, Congress mandated the NCI to develop a comprehensive scientific plan that would address key resource and knowledge gaps that are currently impeding the advancement of the science. The SCLC Working Group, consisting of over 50 scientists, physicians, and patient advocates, was formed to accomplish this. The most urgent recommendations put forth in the Scientific Framework for Small Cell Lung Cancer were:

1. Develop Better Research Tools for the Study of SCLC
2. Perform Comprehensive Genomic Profiling of Tumors from SCLC Patients
3. Develop New Diagnostic Approaches
4. Enhance Therapeutic Development Efforts
5. Elucidate Mechanisms Underlying Both Initial Rate of Response and the Rapid Emergence of Drug and Radiation Resistance

Currently, the ***RCRA is an unfunded mandate***, meaning that there has been no Congressional funding put forth to actualize any of these recommendations. This ***further underscores the need for philanthropic investment into this space*** to make research progress and pave the way for therapeutic advances that have not been seen for SCLC for over three decades.

CHARACTERISTICS OF SMALL CELL LUNG CANCER

Cancer cells are characterized by uncontrollable growth and invasion of nearby tissues. Abnormal cell division and growth are caused by genetic mutations that either turn on oncogenes (genes that speed up cell division) or silence tumor suppressor genes (genes that protect against cancer by slowing down cell growth and controlling cell

death). The accumulation of this type of genetic damage over time can lead to the progressive transformation and survival of abnormal cell populations that can form benign or malignant tumors.

Lung cancers start in the lung tissue or cells lining the airways of the respiratory tract that allow air to flow into the lungs (also known as the bronchi). ***There are two primary types of lung cancer, Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC)***, which can be distinguished from one another by their cellular characteristics.

A key difference between SCLC and NSCLC malignancies is that SCLC cells have neuroendocrine characteristics, meaning that SCLC cells can receive signals from neurons and release hormones into the blood; NSCLC cells cannot as they are non-neuroendocrine. Each of these cancers can be further categorized into subtypes as outlined in Figure 1.

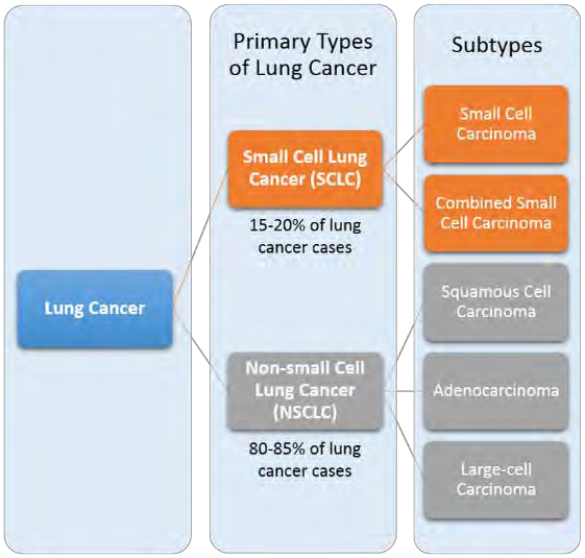


Figure 1: Primary Types of Lung Cancer
The illustration depicts the two primary types of lung cancer and their respective subtypes.

SCLC is significantly more aggressive than NSCLC. SCLC tumors grow rapidly and spread (metastasize) quickly. The most commons sites of SCLC metastasis are the brain, bones, and gastrointestinal tract, all of which are very difficult sites to perform surgical resection of tumors, thereby further complicating the disease.

Given the aggressive nature and complexity of SCLC compared to NSCLC and the lack of treatment options, there are significant unmet needs for patients suffering with this disease. The primary aim of this report is to highlight these unmet needs and concomitant solutions that can potentially address these unmet needs.

RISK FACTORS AND PREVENTION

There are several risk factors associated with an increased likelihood of developing SCLC:

- Current or past history of smoking tobacco products (e.g., cigarettes, cigars, or pipes)
- Exposure to secondhand smoke
- Using beta carotene supplements while being a heavy smoker
- Family history of lung cancer
- Exposure to asbestos, nickel, chromium, arsenic, soot, tar, or radon gas
- Being infected with HIV
- Residing in areas with high air pollutant levels

SMOKING IS THE LEADING CAUSE OF SMALL CELL LUNG CANCER; HOWEVER 4% OF PATIENTS WITH THIS DISEASE HAVE NEVER SMOKED.

It is important to note that having one or several of the risk factors listed above does not guarantee development of SCLC.

While there is a small percentage of SCLC patients who are “never-smokers,” it is clear that the most frequent cause of SCLC is smoking. Currently the best known preventative measure against SCLC is to abstain from smoking. Importantly, smokers can significantly lower their risk for SCLC within as little as two years of smoking cessation. Living a healthy lifestyle, including a balanced diet and physical activity, has also been reported to decrease the risk of SCLC.

DIAGNOSIS AND TREATMENT

DETECTION

SCLC, as with other types of lung cancer, is usually first detected using imaging methods that help to identify the presence of masses or lesions in the lung region. The most commonly used imaging methods for this purpose are outlined below:

- Chest x-ray – This is usually the first test that a physician will perform to detect spots on the lungs. If any masses are detected, then further imaging and diagnostic tests will be performed.

- Computer Tomography scan (CT scan) – This scan provides information about the size, shape, and position of lung masses and can detect enlarged lymph nodes that may contain cancer cells that have spread, or metastasized, from the lung. This scan uses computer processing to create cross-sectional images from a series of x-ray images of one's bones and tissues taken from several different angles.

- Magnetic Resonance Imaging (MRI) – If lung cancer is suspected, a physician may perform an MRI brain scan as this is a common site of SCLC metastasis. This scan uses a strong magnetic field to induce one's organs to emit radio waves that are processed into an image.

- Positron Emission Tomography (PET) – This imaging test requires intravenous administration of a radioactive tracer, which will accumulate in the patient's organs and allow for 3D imaging of the radioactively traced organs, including the lungs. The PET scan is often used in combination with other imaging tests (e.g., PET/CT). For SCLC cases, PET scans are often used for detection and staging of SCLC, tracking metastasis, and monitoring response to treatment.

DIAGNOSIS

It is important to note that while detection methods provide visual evidence of potentially cancerous lesions arising from SCLC, a formal diagnosis of SCLC can only be made after lung cells and/or tissue are microscopically examined by a pathologist. Cells can be obtained from lung secretions (i.e., mucus), fluid surrounding the lung, or pieces of lung tissue. To accurately diagnose SCLC, physicians can obtain lung specimens using one of the following procedures:

- Sputum cytological exam – During this exam, sputum (mucus) secretions from the lung are examined for presence of cancer cells. Sputum samples can be obtained by the patient coughing up mucus or during a bronchoscopy (described below).

- Bronchoscopy – A bronchoscope (lighted, flexible fiber-optic tube) is fed through the mouth or nose and down into the windpipe and bronchi. Lung tissue samples and/or sputum can then be removed for further examination under a microscope.

- Thoracentesis – If there is excess fluid buildup in the space between the lining of the lungs and the chest wall (pleural space), the physician will use a needle to remove and collect that fluid (pleural effusion). Conditions such as lung infection, heart failure, or lung cancer can cause fluid buildup in the pleural space. Therefore, to determine that the cause of fluid buildup is due to lung cancer, the fluid is then examined under the microscope for the presence of cancer cells.

- Needle biopsy – During this exam, a hollow needle is used to remove a sample of tissue from the suspicious mass identified in an imaging scan for further examination under the microscope.

STAGES OF DISEASE

Cancer staging terminology is used to describe the characteristics of tumors with respect to size and the extent to which the tumor(s) has spread to other organs. The PET scan (described above) is important for accurately staging SCLC. Treatment options, disease prognosis, and eligibility for clinical trials are largely determined by cancer stage.

There is a two-stage system that is used for the staging of SCLC:

Limited disease (LD) stage: This stage describes SCLC that is confined to one side of the chest – meaning SCLC that is found in one lung and lymph nodes on the same side of the chest (see Figure 2). Lymph nodes play an important role in maintaining proper function of the immune system by filtering out foreign particles from fluid that circulates through the lymphatic system, which clears the body of toxins and waste. According to the American Cancer Society, only one out of every three people present with LD at time of SCLC diagnosis.

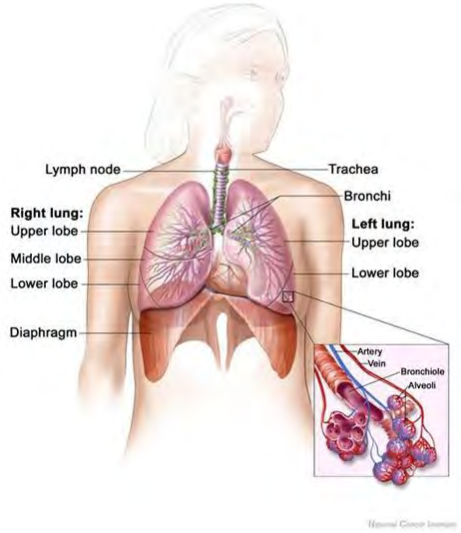


Figure 2: Anatomy of the Respiratory System
Oxygen inhaled through the nose or mouth passes through the trachea (windpipe), bronchi (airways of the lungs), and into the lungs. Oxygen then passes through the alveoli and into the bloodstream (see inset). Lymph nodes and diaphragm are also shown above. By National Cancer Institute [Public Domain], via Wikipedia Commons.

Extensive disease (ED) stage: This stage describes SCLC that has spread to both sides of the chest – meaning SCLC that is found in both lungs, lymph nodes on both sides of the chest and/or SCLC that has spread to distant organs. Due to poor detection methods, **nearly 70 percent of SCLC patients present with ED at diagnosis**, resulting in limited treatment options and low survival rates.

TREATMENT OPTIONS

There are several categories of treatment options for SCLC:

- Surgery – Surgical removal of an SCLC lesion can be performed if detected at the LD stage and confined to a localized region in the lung. This treatment option is rarely used since SCLC patients usually present with extensive disease.

- Chemotherapy – Chemotherapy agents exploit the implicit nature of cancer cells to divide rapidly. These drugs interfere with the process of cell division and can somewhat target cancer cells because they divide more frequently than normal cells; however, these effects are not exclusive to cancer cells and can cause unwanted side effects (e.g., nausea, vomiting, hair loss). Due to the aggressive nature of the disease, the standard of care for SCLC involves the combination of two chemotherapeutic agents that are administered in multiple cycles (phases). In many SCLC cases, the tumor(s) will often respond well to the first-line (initial) chemotherapy regimen, but in many cases will return requiring a second-line and/or third-line of chemotherapy. Currently, there are three Food and Drug Administration (FDA)-approved chemotherapeutic agents for the treatment of SCLC (see Table 1).

- Radiation Therapy (RT) – This is a localized treatment that uses focused, high energy rays (such as x-rays) to kill cancer cells. External beam radiation therapy (EBRT) is used most often to treat SCLC.

- Prophylactic Cranial Irradiation (PCI) – This form of radiation therapy is utilized to irradiate the whole brain. The brain is a common site for metastatic SCLC lesions, thus this procedure is sometimes conducted as a preventative measure even when there are no detectable metastatic lesions in the brain. This treatment option is usually administered shortly after first-line treatment with chemotherapy and/or radiation. Recently, there has been debate in the thoracic oncology community concerning the benefit of PCI for SCLC patients. New data suggest that PCI may not clinically benefit LD or ED-stage SCLC patients, although studies addressing this question are still ongoing.

- Targeted Therapy – This form of therapy uses agents that inhibit specific molecular targets involved in cell signaling pathways, which are cascades of biochemical events that regulate cellular development and behavior. Biochemical molecules that are central to these pathways that behave abnormally are suspected as key drivers to the development, progression, and/or survival of cancer cells. While there are few targeted therapies being tested in SCLC clinical trials, ***there are currently no approved targeted therapies for SCLC patients.***

- Immunotherapy – This form of therapy uses agents that activate the immune system to recognize and kill cancer cells. There are various types of immunotherapy strategies, as outlined in the "Cancer Immunotherapy Strategies" section below. Recently, a new cancer immunotherapy strategy known as immune checkpoint inhibition has shown success in NSCLC clinical trials, culminating in the May 2015 FDA approval of Nivolumab, an immune checkpoint inhibitor, for NSCLC. There are several more of these drugs in clinical trials, and there are few being tested in the SCLC patient population. However, ***there are currently no approved immunotherapies for SCLC patients.***

It is important to note that a treatment plan for SCLC may include one or more of these treatment options and is highly dependent on the stage of disease progression, previous treatments, patient health, and treatment tolerance.

Table 1: FDA-approved agents for SCLC

Generic Name	Brand Name, Manufacturer	Type of agent	Method of Action	Phase of treatment	Stage of Disease Treated
Cisplatin	Platinol®, Bristol-Myers Squibb	Chemotherapy	Inhibits DNA synthesis and repair, which causes programmed cell death	First-line	LD & ED
Carboplatin	Paraplatin®, Bristol-Myers Squibb	Chemotherapy	Inhibits DNA synthesis and repair, which causes programmed cell death	First-line	LD & ED
Etoposide	Toposar®, Teva Pharmaceuticals; VePesid®, Bristol-Myers Squibb; Etopophos®, Bristol-Myers Squibb	Chemotherapy	Forms complex with DNA and a DNA-unwinding enzyme, which halts DNA synthesis and leads to programmed cell death	First-line	LD & ED
Topotecan	Hycamtin®, GlaxoSmithKline	Chemotherapy	Inserts into DNA and inhibits the activity of a DNA unwinding enzyme, which causes programmed cell death	Second-line	ED

TREATMENT BY STAGE

Treatment options vary by stage of SCLC:

- **Limited disease**: Concurrent chemotherapy (cisplatin or carboplatin + etoposide) and radiation therapy followed by prophylactic cranial irradiation in some patients, as deemed appropriate by the physician.

- **Extensive disease**: Chemotherapy alone (cisplatin or carboplatin + etoposide) followed by prophylactic cranial irradiation in some patients, as deemed appropriate by the physician.

TREATMENT RESPONSE AND PROGNOSIS

Approximately 60 to 80 percent of SCLC patients respond well to first-line therapy; however, the majority of SCLC tumors develop resistance to chemotherapy, leading to disease progression. SCLC that comes back after first-line treatment is known as recurrent SCLC. Recurrent SCLC is much less responsive to treatment than the initial primary disease. Patients with recurrent SCLC are stratified based on how quickly their cancer returns following first-line treatment:

- **Sensitive patients**: those patients who remain responsive to first-line treatment for at least three months.

- **Refractory patients**: those patients who are either not responsive to first-line treatment or remain responsive for less than 3 months.

DISEASE BIOLOGY

There are a number of genetic mutations that are thought to contribute (directly or indirectly) to the development of SCLC. As is the case with many cancers, many of these mutations affect how cells grow and divide.

Human cells grow and divide through a highly ordered process called the cell cycle. Several genes that control the progression of the cell cycle are often mutated in cancer. There are two broad categories of genes relevant to this discussion:

- **Tumor suppressor genes** suppress cell division to prevent rapid and uncontrolled cell division. If a cell begins to divide out of control, these genes can initiate a signal that will prompt the cell to die. ***These genes suppress tumor growth.***
- **Oncogenes** override a cell death signal and allow a cell to grow uncontrollably and evade death from tumor suppressor gene signals. ***These genes promote tumor growth*.**

When a cell is in a cancerous state, tumor suppressor genes are usually inactivated (turned off) and oncogenes are usually activated (turned on).

INACTIVE TUMOR SUPPRESSOR GENES IN SCLC TUMORS

The following tumor suppressor genes are commonly found inactivated (switched off) in SCLC tumors. This creates an ideal environment for unregulated cell growth in a manner that is consistent with the aggressive cell division that is commonly observed in these types of tumors.

Tumor protein P53 (TP53) – The *TP53* gene encodes for the p53 protein that plays a key role in protecting cells from genetic instability such that damaged DNA is not passed onto new cells during cell division. Research studies show that approximately 90 percent of SCLC tumors have a mutated form of *TP53*, which renders the gene inactive. Tumors produce high levels of mutant p53, which has prompted researchers to exploit the mutant form to specifically target tumor cells. This has led to the development of mutant p53-targeting vaccines, which are currently being evaluated in clinical trials (NCT00049218 ; NCT00617409). For more general information on the treatment vaccine strategy, please see the Cancer Vaccines section below.

Retinoblastoma (RB) – The activation and inactivation of the *RB* gene at appropriate times is essential for regulating normal cell division. More than 90 percent of SCLC tumors do not express the *RB* gene or express a mutant form of the gene. Both outcomes result in unregulated cell growth, enabling the SCLC tumors to divide rapidly without being targeted for cell death.

ACTIVATED MYC ONCOGENE MAY BE A KEY BIOMARKER FOR TARGETING SCLC

MYC – *MYC* genes code for MYC proteins that regulate cell cycle progression and cellular transformation. MYC proteins are transcription factors, which are proteins that directly control whether other genes are turned on or off. Abnormally high levels of this gene (also known as overexpression) can give rise to uncontrolled cell division.

Studies show that MYC is overexpressed in 18 to 36 percent of SCLC tumors and cell lines. Researchers have attempted to target MYC proteins by designing drugs that can inhibit their function; however, this effort is challenging because of the nature of transcription factors, which typically lack binding sites for small molecules on

the surface of their molecular structure. Also, in many cases several different transcription factors can play redundant roles within the cells; thus, targeting one transcription factor, like MYC, may not result in a halt to uncontrolled cell division since there are other transcription factors that can perform similar functions. Another key challenge is that the location of transcription factors within the cell and transient expression patterns make it difficult for pharmaceutical agents to access these types of proteins.

Despite these challenges, researchers are developing new ways to therapeutically target SCLC cells that overexpress MYC. Research has shown that molecules that inhibit another protein that controls cell division, Aurora kinase, can kill cells that overexpress MYC. By using MYC as a biomarker, researchers are able to identify subsets of SCLC cells that express high levels of the protein and thus may respond to Aurora kinase inhibitors. Based on preliminary data in cell lines and mice, the FDA approved testing of an Aurora kinase inhibitor in SCLC patients in a clinical trial (NCT02038647).

CLINICAL TRIALS AND INVESTIGATIONAL THERAPIES

CLINICAL TRIALS - OVERVIEW

Clinical research (also referred to as clinical development) is a branch of biomedical research involving human subjects. The goal of clinical research is to evaluate safety and efficacy of drugs, medical devices, or diagnostics intended for use in human patients.

Clinical trials are an important component of clinical research since they are used to evaluate the safety and efficacy of an experimental drug or therapy in human subjects. They can also be used to collect specimens from human subjects for further research. Importantly, information on potential side effects are gathered during the clinical trial period and weighed against the potential therapeutic benefit of the treatment under investigation.

The research and development (R&D) process – the process by which a laboratory discovery is developed into a commercial therapeutic, diagnostic, or device –is very costly and time-intensive.

Clinical research is divided into four key phases. Each phase is described in Table 2 below.

Table 2: Phases of Clinical Development

Clinical Phase	Description	Number of Patients
Phase I	Tests the safety of the new experimental drug or therapy in a very small group of healthy volunteers or patients afflicted with a specific disease for the first time. Appropriate dose ranges and side effects are identified during this phase as well.	20-80
Phase II	Evaluates the safety and efficacy of the new experimental drug or therapy at a pre-determined dose compared to the standard of care for the particular disease being treated.	100-300
Phase III	Evaluates the new experimental drug or therapy compared to the standard of care in a larger diverse population to determine broader efficacy and develop usage guidelines.	1,000-3,000
Phase IV	Evaluates the long-term effects of the new experimental drug or therapy following FDA approval for public use.	All patients prescribed the drug by a treating physician

LUNG CANCER CLINICAL TRIALS AND AGENTS IN DEVELOPMENT

As of September 2015, there are 78 active, interventional clinical trials for SCLC and 35 distinct agents in clinical development for SCLC. The majority of clinical trials are in Phases I and II, and only two agents in Phase III. Figure 3 illustrates the distribution of clinical trials (left) and experimental agents (right) by phase of clinical development. In contrast, the pipeline is robust for NSCLC, as there are several experimental agents being tested in Phase II and III clinical trials and there are a high volume of clinical trials being performed. SCLC pales in comparison to NSCLC in terms of number of active clinical trials being performed and number of experimental agents in the pipeline. ***SCLC's lean pipeline is indicative of the need for strategic philanthropic investment into the development of new therapies.***

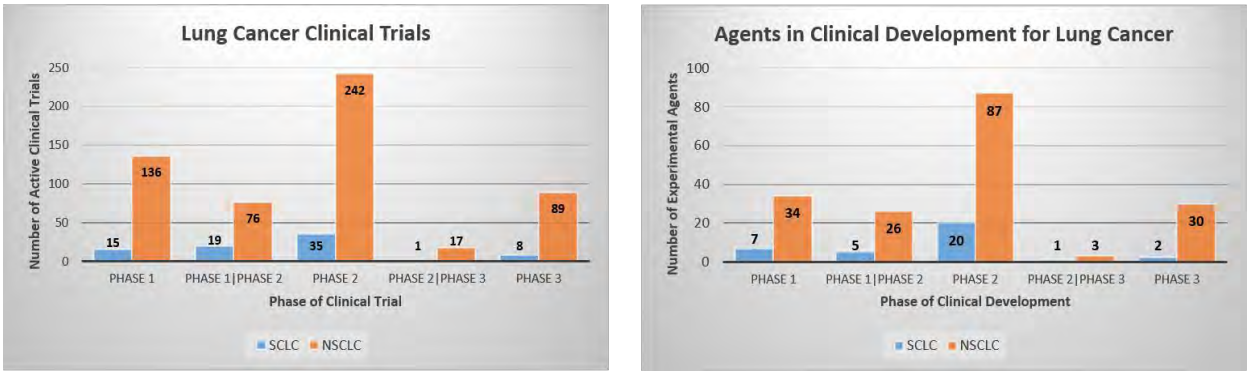


Figure 3: Lung Cancer Clinical Trials and Experimental Agents in Development Pipeline
(Left) The number of active, interventional clinical trials for SCLC and NSCLC, broken down by phase, currently registered at clinicaltrials.gov.
(Right) The number of experimental agents in clinical development for SCLC and NSCLC at each phase of development.

In the sections below, we discuss key therapeutic strategies that are currently in clinical development for SCLC as well as those that have achieved tremendous success in other indications, such as NSCLC, and thus will likely be considered for testing in SCLC patients in the near future.

TARGETED THERAPY STRATEGIES

Development of targeted therapies is currently a major focus in lung cancer drug development. As mentioned previously, targeted therapies differ from chemotherapies in that these agents specifically engage certain biochemical molecules (molecular targets) shown to be critical to the development, progression, or survival of tumor cells. As a result, to pursue this particular drug approach, the identification of key molecular targets to engage is imperative – and this cannot be done without human biospecimens, which are scarce in SCLC clinical research.

While NSCLC treatment options have improved significantly as a result of advances in targeted therapies, SCLC needs progress in this therapeutic arena, as there are no targeted therapies available for SCLC to date. There are a few promising agents currently in early-stage trials; however, the data are not yet mature, and general conclusions from the data cannot yet be drawn.

The rate-limiting step to expanding the cadre of targeted therapies for SCLC has been a poor understanding of key genetic mutations and molecular targets that drive the development, progression, and aggressiveness of SCLC (as outlined in "Identification of SCLC Biomarkers" later in this guide). Since key molecular targets for SCLC are lacking, promising strategies that target key properties unique to SCLC are currently under development, such as:

- DNA-repair pathway targeting therapies
- Cell-cell connection targeting therapies

DNA REPAIR PATHWAY TARGETING THERAPIES

DNA repair pathways maintain the genomic integrity of our cells and are often referred to as the "spell checkers" of the genetic alphabet. Defects in DNA repair pathways lead to an accumulation of mutations within a cell, and there are several cancers that exhibit this behavior, including SCLC. It is hypothesized that a cancer with a high mutational load, such as SCLC, develops dependency on one or a few DNA repair pathways in order to survive.

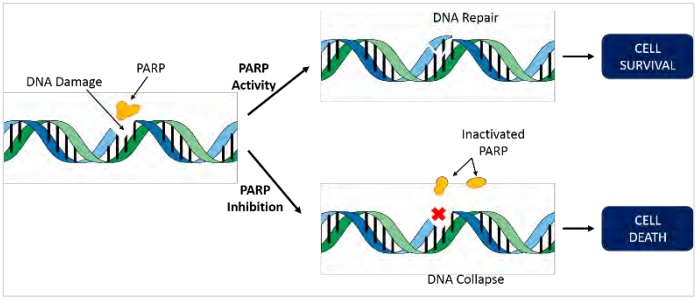


Figure 4: How PARP inhibitors work
In the presence of PARP-1, DNA repair is able to proceed successfully, thus leading to cell survival. Tumor cells that are dependent on DNA repair pathways are able to survive despite having several gene mutations. When PARP-1 is inhibited, DNA repair is unable to proceed, thus leading to apoptosis, a programmed cell death pathway.

Research shows that PARP-1, an important molecule in a DNA repair pathway, is important for the survival of SCLC cells. Thus in an effort to induce death of SCLC cells, PARP-1 inhibition (see Figure 4) using small molecule drugs is emerging as a promising therapy for SCLC (NCT01642251) and is an area of active investigation for other cancers as well. This therapeutic approach in combination with traditional DNA-damaging agents (chemotherapy) may be a useful strategy for SCLC.

CELL-CELL CONNECTION TARGETING THERAPIES

Unlike NSCLC and many other cancers, portions of SCLC tumors can circulate in the blood stream as small clumps. Additional study of the cell to cell adhesion properties that enable these tumor cells to aggregate and travel throughout the blood may potentially elucidate new ways to target SCLC. As such, targeting the molecules or signaling pathways that drive cell-cell connections are a promising approach that is currently in early clinical development for SCLC.

CANCER IMMUNOTHERAPY STRATEGIES

Cancer immunotherapy, also known as immuno-oncology, has been successful in NSCLC and other cancers such as melanoma and renal cancer in recent years. These new therapeutic strategies stimulate the immune response to identify and destroy tumor cells, which are inherently masterful at disguising themselves as normal cells to evade the immune system.

OVERVIEW

The immune system is made up of several specialized cells that actively monitor the body to detect and destroy foreign agents (e.g., bacteria) and transformed cells. Transformed cells are distinguished from normal cells by their antigens, which are cellular proteins that cause the immune system to make antibodies against it. While the immune system should be able to detect and destroy tumor cells, many tumors can develop evasion mechanisms where they can change the display of their antigens to resemble non-transformed cells (called immune editing) or they can effectively turn off immune cells by engaging with inhibitors on the immune cell surface (known as immune checkpoints).

Cancer immunotherapy strategies work to dismantle the tumor cell's ability to evade immune cells. The relevant strategies discussed below are:

- **Cancer vaccines –** this strategy works by programming T cells (a type of immune cell) to attack tumor cells expressing an antigen that is either not expressed by normal cells or is selectively over-expressed by tumors.
- **Immune checkpoint inhibitors –** this strategy works by blocking the tumor cell's ability to engage with T cell inhibitors (known as immune checkpoints), thereby releasing the inhibitory signal on the T cell and allowing it to attack tumor cells.

While immunotherapy has been successful in the treatment of NSCLC, challenges remain for use of immunotherapy for SCLC patients. Identification of specific SCLC antigens for vaccine-based approaches are lacking, and thus **investment in comprehensive genomic profiling could have a significant impact on this area** as outlined in the "Lack of Access to SCLC Biospecimens" section.

Additionally, timing of immunotherapy administration remains a challenge, as mounting an immune response requires time that ED-SCLC patients may not have. Therefore **investment in early detection methods and clinical trials focused on cancer immunotherapy and combination with other types of therapy (e.g., chemotherapy) may also have a significant impact on improving therapeutic options for SCLC patients.**

The following sections will discuss each of these immune-oncology strategies in more detail as well as provide information on specific immune-oncology agents in clinical development for SCLC.

CANCER VACCINES

This strategy is used to treat an existing cancer by promoting an immune response directed to the cancer, as illustrated in Figure 5. There are two key components of a vaccine:

- Adjuvant – this component is used to activate resting immune cells. The agents used for this purpose vary depending on the vaccine.
- Antigen – this component is a target RNA or protein that is expected to be

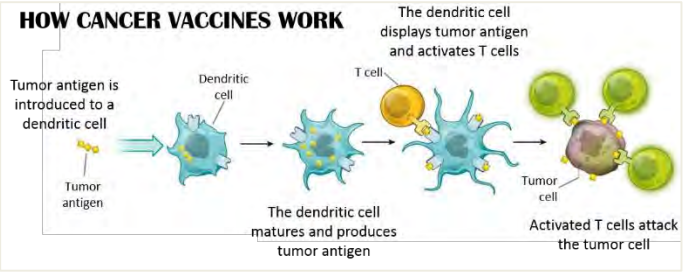


Figure 5: How cancer vaccines work
As depicted above, dendritic cells (a type of immune cell) mature and present antigen to T cells (another type of immune cell), which causes T cell activation. The T cell will then attack tumor cells that display a particular antigen. Adapted by permission from Macmillan Publishers Ltd: Nature, 2011.

expressed solely by the tumor cells and not the normal cells, or expected to be selectively over-expressed by the tumor cells.

The antigen is introduced to dendritic cells (another type of immune cell), which will then activate T cells and cause them to attack tumor cells displaying that particular antigen. There are active clinical trials investigating this approach for the treatment of both SCLC and NSCLC.

IMMUNE CHECKPOINT INHIBITORS

Cytotoxic T cells, also known as killer T cells, are responsible for destroying foreign cells, in this case tumor cells. To control the killing capacity of these cells, there is a "braking system" in place to minimize killing of normal cells. This "braking system" is commonly referred to as immune checkpoints, which are molecules that deactivate the killing mechanism of killer T cells. Tumors are able to evade destruction by displaying molecules that resemble that of a normal cell, which upon engaging with the immune checkpoint on the killer T cell, activates the braking system.

Immune checkpoint inhibitors are molecules that are able to block the tumor cell from activating immune checkpoints, and thus allow the T cell to attack and kill the tumor. The immune checkpoint molecules that have been most actively studied are cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1).

Most Actively Studied Immune Checkpoint Molecules:

CTLA-4
PD-1
PD-L1

The blockbuster success of immune checkpoint inhibitors took center stage at the 2015 American Society of Clinical Oncology (ASCO) meeting. This approach has fundamentally revolutionized the way that cancer is treated, and is actively being tested as a new treatment option for lung cancer. As recent advances have been made in the treatment of NSCLC using immune checkpoint inhibitors, there is interest in whether this new approach could be applied to SCLC patients. While there are challenges to address, such as the amount of time it takes to mount an immune response – time which SCLC patients usually do not have – the lung cancer community remains optimistic considering the success of these agents in the NSCLC patient population.

There are a number of immune checkpoint inhibitors in various stages of clinical development for several different cancers. The profiles for three checkpoint inhibitors currently in clinical trials for SCLC are provided below.

YERVOY® (IPILIMUMAB)

Ipilimumab was the first checkpoint inhibitor to be approved by the FDA for the treatment of melanoma. It is now being tested in clinical trials for the treatment of lung cancer.

Under normal circumstances, B7 is expressed by immune cells that present antigen to T cells (also called antigen presenting cells). Antigen presenting cells "turn off" T cells by binding to CTLA-4 on the T cell surface to prevent over-activation of the immune system. Tumor cells can co-opt this mechanism and evade detection by the immune system by expressing B7 and subsequently binding to CTLA-4 on T cells (as depicted in Figure 6).

Clinical Development Stage for SCLC: Phase II and III

Clinical Development Stage for Other Therapeutic Areas: NSCLC (Phase II); Melanoma (Marketed); Pancreatic cancer (Phase III); Prostate cancer (Phase III); Solid Tumors (Phase II)

The field is eagerly awaiting the results of the three ongoing trials listed below testing ipilimumab in SCLC patients:

- Randomized, Multicenter, Double-Blind, Phase 3 Trial Comparing the Efficacy of Ipilimumab Plus Etoposide/Platinum Versus Etoposide/Platinum in Subjects With Newly Diagnosed Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC); ClinicalTrials.gov Identifier: NCT01450761

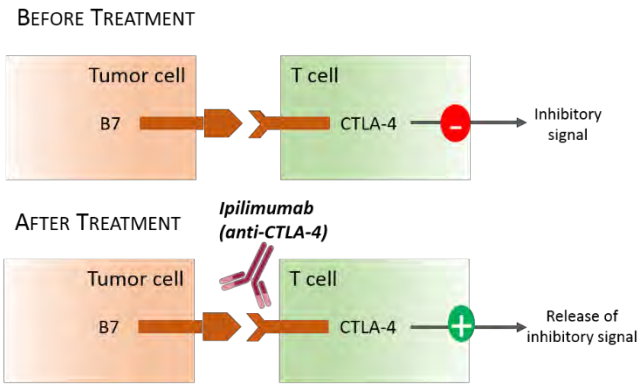


Figure 6: How Ipilimumab works
Ipilimumab works by binding CLTA-4, which blocks B7 from binding, and thus releases the T cell inhibitory signal allowing the T cell to attack and kill tumors.

- A Phase II Trial of the Addition of Ipilimumab to Carboplatin and Etoposide Chemotherapy for the First Line Treatment of Extensive Stage Small Cell Lung Cancer (ICE); ClinicalTrials.gov Identifier: NCT01331525
- A Randomized Open-label Phase II Trial of Consolidation Ipilimumab in Limited-stage SCLC After Chemo-radiotherapy (STIMULI); ClinicalTrials.gov Identifier: NCT02046733

OPDIVO® (NIVOLUMAB)

Nivolumab was approved for the treatment of NSCLC in May 2015. This new immunotherapy has been hailed as a game changer for the treatment of lung cancer. Nivolumab is currently being investigated for the treatment of SCLC as both a monotherapy or in combination with ipilimumab.

Under normal circumstances, PD-L1 is expressed by antigen presenting cells. Antigen presenting cells "turn off" T cells by binding to PD-1 on the T cell surface to prevent over-activation of the immune system. Tumor cells can co-opt this mechanism and evade detection by the immune system by expressing PD-L1 and subsequently binding to PD-1 on T cells (as depicted in Figure 7).

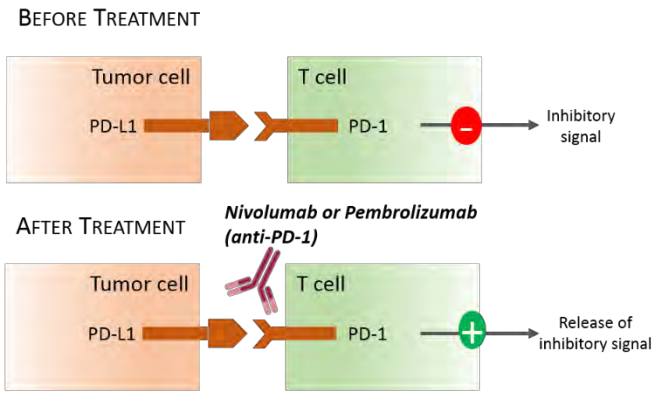


Figure 7: How Nivolumab and Pembrolizumab work
Nivolumab and Pembrolizumab work by binding PD-1, which blocks PD-L1 from binding, and thus releases the T cell inhibitory signal allowing the T cell to attack and kill tumors.

Clinical Development Stage for SCLC: Phase I/II

Clinical Development Stage for Other Therapeutic Areas: NSCLC (***Marketed - approved in 2015***); Melanoma (Marketed); Brain cancer (Phase III); Renal cancer (Phase III); Esophageal cancer (Phase II); Hodgkin's lymphoma (Phase II); Liver cancer (Phase I/II); Solid tumors (Phase I/II); Hematologic malignancies (Phase I); Non-Hodgkin's lymphoma (Phase I); Hepatitis C virus (Phase I)

Key Clinical Data: Impressive response rates were reported at ASCO 2015 for SCLC patients on the Phase I/II CheckMate 032 clinical trial (NCT01928394) testing nivolumab alone or nivolumab in combination with ipilimumab. Results indicated that both monotherapy and combination therapy showed durable responses in SCLC patients whose disease progressed after at least one prior therapy. Additionally, median overall survival was 4.4 months on nivolumab monotherapy and 8.2 months on nivolumab + ipilimumab.

KEYTRUDA® (PEMBROLIZUMAB)

Pembrolizumab is another PD-1 inhibitor, like nivolumab (see Figure 7).

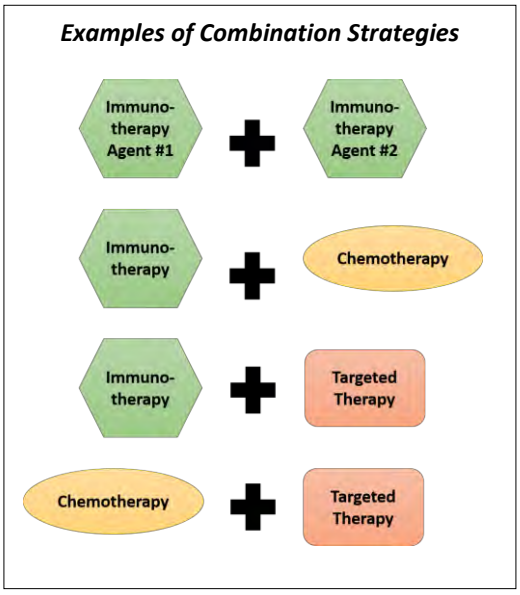
Clinical Development Stage for SCLC: Phase I/II

Clinical Development Stage for Other Therapeutic Areas: NSCLC (***Registration***); Melanoma (Marketed); Brain cancer (Phase I/II); Breast cancer (Phase I/II); Pancreatic cancer (Phase I/II); Renal cancer (Phase III); Solid tumors (Phase I/II); Bladder cancer (Phase I); Gastric cancer (Phase I); Head and neck cancer (Phase I); Lymphoma (Phase I)

Key Clinical Data: Encouraging results were presented at ASCO 2015 from the KEYNOTE-28 clinical trial (NCT02054806) for heavily pre-treated PD-L1 positive ED-SCLC patients. Researchers reported an overall response rate of 35 percent, with patients experiencing durable responses and five of seven patients seeing a reduction in tumor size. The median time to response was 8.6 weeks, and the median duration of response was 29.1 weeks, a significant increase for this patient population.

COMBINATION THERAPY STRATEGIES

Identifying synergistic therapies is a hot area in cancer treatment. Specifically, researchers and clinicians look to target multiple molecules or pathways by combining multiple treatment approaches, such as targeted therapy + immunotherapy, or combining different therapeutic agents within a strategy, such as immunotherapy agent 1 + immunotherapy agent 2. Encouraging data were presented at ASCO 2015 for SCLC patients on the Phase I/II CheckMate 032 clinical trial (NCT01928394), showing early evidence of therapeutic benefit when using a combination of two immunotherapy agents, nivolumab and ipilimumab, targeting two different immune checkpoints, PD-1 and CTLA-4, respectively (discussed above). Mean overall survival for patients on the combination therapy was 8.2 months versus 4.4 months on nivolumab alone.



Since SCLC is a disease characterized by such a high mutational load and rapid resistance to chemotherapy, it is hypothesized that multiple pathways will need to be therapeutically targeted to see durable responses and possibly overcome resistance to therapy. It is the hope that these positive results will soon pave the way for more combination clinical trials for SCLC patients.

BARRIERS TO SCLC RESEARCH PROGRESS AND KEY PHILANTHROPIC OPPORTUNITIES

There are a number of challenges and unmet needs that stand in the way of desperately needed progress in SCLC research and treatment science. In May 2015, the Milken Institute Philanthropy Advisory Service convened world-renowned SCLC experts from academia and industry as well as lung cancer patient advocates to discuss the state of science relevant to SCLC and the challenges currently impeding research progress (see Small Cell Lung Cancer Action Plan Meeting Participants). The primary goal of the retreat was to identify high-impact research opportunities where philanthropic investment could accelerate progress in SCLC. This effort was both timely and necessary because:

- SCLC-specific funding is scarce, as it is often overshadowed by the more common form of lung cancer – non-small cell lung cancer (NSCLC).
- SCLC patients have very few treatment options.
- As treatment options for NSCLC patients have recently increased, the SCLC community should capitalize on that momentum and use these recent successes as a model to pave a way forward.
- Key biological underpinnings of SCLC are poorly understood.

Below we present the key issues that were prioritized by the group and recommendations to address these challenges with strategic philanthropic investment. The key issues identified are as follows:

1. ***Funding***
2. ***Lack of access to SCLC biospecimens***
3. ***Lack of efficiency in clinical trial enrollment and data sharing***

It is import to note that the list below is not an exhaustive list, and the philanthropic opportunities presented here should be considered carefully with respect to your philanthropic goals and discussed with a philanthropic advisor.

LOW FUNDING LEVELS

THE PROBLEM:

SCLC-specific funding is scarce, which is underscored by the fact that there is currently only one active NIH R01-level funded grant for SCLC. Although SCLC has been declared as a recalcitrant cancer under the RCRA, this is currently an unfunded mandate in which no additional federal funds have been specifically allocated towards the research framework put forth by the SCLC Working Group. Overall, this lack of funding not only restricts ongoing research programs, but also discourages young talent from the field, thereby confounding limits on progress in both the near and long-term future.

POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE:

- *Incentivize researchers to study SCLC* – Low funding levels deter scientists from pursing certain areas of research. A focused effort to encourage investigators to study the basic biology of SCLC is needed.

- *Incentivize young scientists to enter the SCLC field* - Encouraging young investigators to enter this field would help secure continuity of research programs and eventually lead to new discoveries that are necessary for therapeutic development.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES:

- Fund an SCLC mentor-mentee program to support young investigators
- Fund SCLC-specific Request for Proposals (RFPs) to administer grants to labs investigating:
    - Basic biology of SCLC
    - SCLC cells of origin
    - Mutational variation in the never-smoker patient population to uncover unique molecular signatures that could be potential targets for therapy

LACK OF ACCESS TO SCLC BIOSPECIMENS

There is a great unmet need to improve researcher access to clinically-annotated human SCLC biospecimens. The current lack of access negatively impacts the following:

- ***Basic biology*** studies to better understand SCLC,
- ***Preclinical modeling*** of SCLC, and the
- ***Identification of biomarkers*** that can help diagnose and monitor disease and/or treatment response as well as potentially give rise to new therapeutic targets.

The need for human SCLC biospecimens is a key underpinning of the barriers to research progress in this space. Efforts to address this challenge would greatly aid therapeutic development for SCLC.

BASIC BIOLOGY

THE PROBLEM:

Large-scale deep sequencing efforts can shed light on the complex genomics of SCLC with the aim of answering the loss of function question as well as many others related to molecular features critical to the development and progression of SCLC tumors; however, a large number of biospecimens (including blood, saliva, urine, and tissue) are necessary in order to power the data such that findings are soundly supported by statistical analysis.

Key points that support the statement above are as follows:

- The genome of SCLC is highly complex. As a result, it is very difficult to identify driving mutations and molecular vulnerabilities.
- While researchers do sequence tumors, this is not being done in aggregate, which limits the depth of information that can be gleaned from the data.

- Lack of tissue is a key contributor to this problem. Thus there was consensus amongst the group of SCLC experts that the field would greatly benefit by pooling tissues currently housed in the biobanks of each individual academic institution and conducting standardized genomics on the samples.
- Most SCLC cases are treated in the community and not academic centers. Therefore, there should be a concerted effort to coordinate the collection and sequencing of SCLC biospecimens from community hospitals and practices.

POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE:

- *Incentivize community points of care* – The majority of SCLC cases are seen and treated at the community level and, as such, most samples exist in the community and not academic centers. A focused effort to ease biospecimen collection from the community would help to mitigate this issue.
- *Centralized biobanking* – Pooling SCLC tissues will help to increase the number of SCLC biospecimens available to researchers regardless of their location.
- *Collecting SCLC tumors from autopsies* – In practice, most SCLC patients do not undergo surgery to remove their tumors as they are usually diagnosed at the extensive disease stage, which contributes to the lack of tissue. Previously inaccessible tumors can be collected from recently deceased SCLC patients if proper warm autopsy protocols are in place.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES:

- Fund the development of a centralized biobank with the following features:
  - Multi-institutional access to biospecimens
  - Centralized administration
  - Oversight committee comprised of SCLC experts
- Subsidize biopsy costs to alleviate financial burden on the patient and facilitate tissue collection at community hospitals and referral centers. This should also include repeat biopsies in order to gather metastatic tissue samples.
- Fund the creation and/or expansion of biospecimen processing core facilities to support community hospitals and/or clusters.
  - Fund the hiring of laboratory management personnel to run processing cores and standardize a biospecimen sharing protocol at the community level.
  - Fund the hiring of dedicated IT professionals to set up and run software management systems needed to track the chain of custody of biospecimens acquired at community hospitals.

PRECLINICAL MODELING

THE PROBLEM:

Improved access to clinically annotated human SCLC biospecimens would enhance SCLC preclinical models, particularly those that utilize human samples to more closely replicate human SCLC pathology, namely, patient-derived xenografts (requires tissue) and circulating tumor cell-derived xenografts (requires blood).

- While preclinical models have improved dramatically in recent years, these models still face key limitations with respect to elucidating key biological underpinnings of SCLC as well as the drivers of tumor initiation, progression, and resistance to therapy. Thus it is essential for the field to use SCLC human biospecimens as complementary tools to the current cadre of preclinical modeling systems.

POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE:

- Centralize banking of the aforementioned preclinical models.
- Develop models that account for the tumor microenvironment, an aspect that is lacking in the currently available models.
- Optimize the CTC capture process from SCLC patients in order to create cell lines and CDX preclinical models.
- Develop a broad set of carefully annotated SCLC cell lines derived from human tissue and CTCs in order to capture the genetic diversity of SCLC.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES:

- Fund the expansion of the SCLC cell line bank at the American Type Culture Collection (ATCC).
- Fund the central banking of PDX and CDX mouse models at research animal vendors.
- Fund a multi-disciplinary team (including bioengineers, cancer biologists, biophysicists, etc.) to optimize and standardize the CTC capture and stabilization process to streamline CDX model creation.

IDENTIFICATION OF SCLC BIOMARKERS

THE PROBLEM:

The lack of clinically annotated human SCLC biospecimens limits biomarker discovery. For NSCLC, researchers have been able to identify mutations that are directly causal to the disease (referred to as driver mutations), which has led to improved treatment options for patients. On the contrary, the same level of progress has not been achieved for SCLC. To date, there are no clearly defined biomarkers for SCLC, and biomarkers cannot be identified without biospecimens. Multi-platform analysis of biospecimens is necessary to uncover key molecular drivers of disease amid the mutational noise inherent in SCLC. While ideal, large amounts of tissue are difficult to obtain due to anatomical location and patient condition at time of biopsy; however, blood is much easier to obtain. Table 3 features some blood-based technologies that may be able to provide clinically relevant diagnostic and prognostic information.

Table 3: Blood-based Technologies

Technology	Key Features
Circulating tumor cell (CTC) analysis	• High CTC count is a key attribute of SCLC, thus may be an appropriate substrate for molecular analysis • Technique may allow for the serial tracking of SCLC patients to examine tumor evolution and resistance mechanisms and can also be used to establish xenograft models (CDX)
Anti-tumor autoantibodies	• Detection of these antibodies may be an indicator that the patient is able to mount an immune response
Cell-free DNA (cfDNA)	• May allow for serial characterization of SCLC

POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE:

- Centralized biobanking.
- Focused effort on full genomic, proteomic, and microRNA characterization of resected SCLC tumors and blood samples.
- Genomic analysis of the SCLC never-smoker population (4 percent of all SCLC patients) to identify unique mutations that may inform drug discovery efforts.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES:

- Fund the collection of 250 SCLC samples with matched clinical data, with particular attention to never-smokers, and run intensive multi-platform "-omics" analysis (including genomics, transcriptomics, proteomics, methylomics, epigenomics, secretomics, etc.).

LACK OF EFFICIENCY IN CLINICAL TRIAL ENROLLMENT AND DATA SHARING

CLINICAL TRIAL ENROLLMENT

THE PROBLEM:

There is a high administrative burden to enroll patients in clinical trials, which has effects on patient accrual, data collection, and dissemination. In addition, incompatible institutional review board (IRB) policies from multiple institutions often introduce barriers to enrolling patients in multi-institutional studies, thereby hampering collaboration. Further, accessing the small SCLC patient population that is spread all over the world is quite a daunting task given the poor overlap between clinical trial enrollment centers and patient location.

- While a master protocol may decrease that burden, the SCLC field is too young for a master protocol since there are a lack of validated targets to make such an effort work.
- The Genomics of Young Lung Cancer Study clinical trial (NCT02273336) was discussed by the group as a case study.

- This trial has successfully mitigated those barriers by utilizing an ***online consent form,*** facilitated by a third-party (Addario Lung Cancer Medical Institute), thereby making the location issue obsolete, increasing the likelihood of patient accrual.
- Patients were empowered to facilitate the collection of their own biospecimens by taking the study-provided collection kit to their physicians. The patient-driven nature of this trial has contributed to rapid patient accrual and sample acquisition.
- While a tissue collection trial and not a treatment trial, this study demonstrated the willingness of patients to join a study and submit samples despite not undergoing an experimental treatment.

*Employing methods to increase SCLC patient accrual in clinical trials provides investigators with the valuable patient resource from which to gather biospecimens that are **desperately** needed to make progress.*

POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE:

- Utilize a third party to facilitate patient consent and, if possible, a remote study platform, to increase the SCLC patient pool from which to obtain biospecimen samples.
- Shorten the timetable for clinical trials approval through cooperative groups.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES:

- Fund a third party to facilitate and administer online informed consent.
- Fund a third party to manage data collection and processing through a remote study platform.
- Sponsor a central coordinating office to work with cooperative groups.

DATA SHARING

THE PROBLEM:

Clinical trial data silos can lead to duplicative efforts and ultimately limit target discovery. By allowing access to data, researchers from around the world can interrogate the data, compare findings, and tailor future clinical investigations accordingly, thus increasing the likelihood of discovery.

POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE:

- Aggregate and clean patient data from multiple institutions for future analysis.
- Develop a set of standard operating procedures (SOPs) with clear guidelines for data sharing before the start of a trial.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES:

- Fund a contract research organization (CRO) to aggregate and clean clinical trial data from multiple institutions. Consider making the data open-source to encourage data mining and analysis by researchers worldwide.

KEY STAKEHOLDERS IN THE LUNG CANCER COMMUNITY

RESEARCH GRANT-MAKING ORGANIZATIONS

There are several nonprofit organizations specifically focused on charitable giving to support lung cancer. The majority of these organizations are focused on improving awareness, providing patient support, and/or aiding research for cures. We identified national organizations with annual revenues greater than $1 million that provide direct support for lung cancer research. Financial information for these organizations from fiscal year 2012 is provided in Table 4 below. Additional information regarding their mission, key research funding mechanisms, and clinical trials support activities is also provided below.

Table 4: Charitable organizations supporting lung cancer research with annual revenues greater than $1 million

Organization	Revenue	Research Support	Research/Expense Ratio
American Lung Association	$42,808,235	$5,698,592	13%
LUNGevity Foundation	$4,925,022	$1,813,793	38%
Free to Breathe	$3,906,236	$1,051,081	30%
CHEST Foundation	$2,802,619	$450,365	30%
Bonnie J. Addario Lung Cancer Foundation	$2,491,499	$1,405,280	51%
Lung Cancer Research Foundation	$1,336,690	$800,000	52%

AMERICAN LUNG ASSOCIATION

MISSION

The mission of the American Lung Association (ALA) is to save lives by improving lung health and preventing lung disease. Mission goals include reducing lung cancer deaths, serving as the premier resource for lung health, cutting adult and youth smoking rates, increasing research funding, and increasing volunteer engagement.

RESEARCH FUNDING MECHANISMS

ALA funds independent investigator and training awards (listed below) ranging from $21,000 to $100,000/year for up to two years. For more information about these and other awards, please visit its website.

- Lung Cancer Discovery Award
- Biomedical Research Grant
- Clinical Patient Cancer Research Grant
- Social-Behavioral Research Grant
- Lung Health Dissertation Grant
- Senior Research Training Fellowship

PROGRAM ALIGNMENT WITH UNMET NEEDS

The funding mechanisms listed above address research funding gaps across all levels of research (basic to clinical) and research experience (pre-doctoral to independent investigator). The funding provided also aims to support investigators who seek to understand basic lung disease biology, and improve traditional clinical studies and patient care.

LUNGEVITY FOUNDATION

MISSION

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 providing community, support, and education for all those affected by the disease.

RESEARCH FUNDING MECHANISMS

LUNGevity Foundation funds multi-year translational research awards (listed below) ranging from $100,000 to $600,000. For more information about these and other awards, please visit its website.

- Career Development Awards
- Early Detection Awards
- Targeted Therapeutics Awards

PROGRAM ALIGNMENT WITH UNMET NEEDS

LUNGevity Foundation supports collaboration by funding teams of scientists, which will also have positive effects on data sharing. Their grants address research funding gaps for independent investigators and prioritize the search for targeted therapeutics, which are lacking for the SCLC community.

FREE TO BREATHE

MISSION

The mission of Free to Breathe is to ensure surviving lung cancer is the expectation, not the exception. Its vision is to double lung cancer survival by 2022. Free to Breathe focuses on funding research with the greatest potential to save lives, increasing the number of lung cancer patients participating in clinical trials, and building and empowering the lung cancer community.

RESEARCH FUNDING MECHANISMS

Free to Breathe funds multi-year translational and clinical research awards (listed below) ranging from $100,000 to $600,000. For more information about these and other awards, please visit its website.

- Metastasis Research Grant
- Accelerate Clinical Trials Grant

- Clinical Trials Innovation Prize

PROGRAM ALIGNMENT WITH UNMET NEEDS

Free to Breathe funds projects that seek to understand, prevent, and/ or halt lung cancer progression. This line of research may uncover mechanisms of resistance and how to overcome their onset. They also support increased clinical trials participation, which could have widespread effects such as accruing more SCLC patients, thereby increasing potential for biospecimen collection and powering clinical trials to be able to make clear conclusions from the data.

CHEST FOUNDATION

MISSION

The CHEST Foundation's mission is to develop resources to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

RESEARCH FUNDING MECHANISMS

The CHEST Foundation has given nearly $7 million for clinical research and $2 million for community care research since the start of its research granting program to support several chest ailments, including lung cancer. Its award focus changes yearly. However, it generally funds clinical research and community care-focused research. For more information about available awards, please visit its website.

PROGRAM ALIGNMENT WITH UNMET NEEDS

The CHEST Foundation has directed giving at the community level, which is where the majority of lung cancer patients are seen and treated. Providing funding to innovate healthcare practices at the community level provides an avenue to reach patients for clinical trial participation, which is a critical area of unmet need in the lung cancer community.

BONNIE J. ADDARIO LUNG CANCER FOUNDATION

MISSION

The Bonnie J. Addario Lung Cancer Foundation (ALCF) is a patient-founded, patient-focused, and patient-driven philanthropy devoted exclusively to eradicating lung cancer through research, early detection, education, and treatment. The foundation's goal is to work with a diverse group of physicians, organizations, industry partners, individuals, patients, survivors, and their families to identify solutions and make timely and meaningful change and turn lung cancer into a chronically managed disease by 2023. It is the world's largest lung cancer nonprofit.

RESEARCH FUNDING MECHANISMS

ALCF funds a $500,000 multi-year, multi-disciplinary clinical research award led by teams of young investigators. For more information about this and other awards, please visit its website.

- Young Innovators Team Award
- Clinical Trials Innovation Prize
- ALCF-IASLC Joint Fellowship Award for the Early Detection of Lung Cancer
- ALCF-ALA Award to Study Gender Differences in Lung Cancer
- ALCF Lectureship Award
- Research Specialist Award

PROGRAM ALIGNMENT WITH UNMET NEEDS

ALCF promotes scientific collaboration by funding team science specifically to address treatment science. In addition, ALCF's current award seeks to address funding gaps specifically for young investigators with the aim of infusing the lung cancer research pipeline with bold, new, high-risk ideas.

LUNG CANCER RESEARCH FOUNDATION

MISSION

The Lung Cancer Research Foundation's (LCRF) mission is to improve and save lives by funding groundbreaking research for the prevention, diagnosis, treatment, and cure of lung cancer.

RESEARCH FUNDING MECHANISMS

LCRF funds a one-year, $75,000 research grant for investigators focused on basic, translational, or clinical research as well as supportive care. For more information about this and other awards, please visit its website.

- Lung Cancer Research Grant

PROGRAM ALIGNMENT WITH UNMET NEEDS

LCRF seeks to address research funding gaps across all levels of research and research experience, as well as all aspects of lung cancer research and treatment ranging from basic science to clinical care.

COLLABORATIVE INITIATIVES

GOVERNMENT-SPONSORED PROGRAMS

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORE)

SPOREs are a key part of the Translational Research Program at NCI. SPOREs are grants awarded to research scientists to support organ site-specific projects that will result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers. SPOREs are intended to facilitate a "bench-to-bedside" approach, meaning the application of basic scientific finding into a clinical setting. In fact, SPOREs are required to reach a human end-point within the five-year funding period of the grant. The lung is one of the 18 organ sites that is represented in the SPORE portfolio, and there are four active Lung Cancer SPORE Programs around the country:

- Johns Hopkins University
- University of Colorado Cancer Center
- University of Pittsburgh Cancer Center
- University of Texas Southwestern Medical Center/MD Anderson Cancer Center

Each institutional SPORE grant supports **multiple lung cancer research projects** overseen by a **Principal Investigator**, as well as **core facilities** that are available to all researchers working on a SPORE project in order to centralize certain administrative, biospecimen, and data processing procedures to facilitate research efficiency.

NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM (NCORP)

NCORP is a national network of investigators, cancer care providers, academic institutions, and other organizations. NCORP will conduct multi-site cancer clinical trials and studies in diverse populations in community-based healthcare systems across the United States and Puerto Rico.

NCORP consists of three major components:

- Research Bases: centralized centers with established infrastructure that design and conduct NCORP multi-center clinical trials.
- Community Sites: consortia of community hospitals, oncology practices, and integrated healthcare systems. These sites are for patient accrual to clinical trials conducted by NCORP Research Bases.
- Minority/Underserved Community Sites: these sites are also for patient accrual like Community Sites, but with patient populations comprised of at least 30 percent racial/ethnic minorities or rural residents.

There are only seven Research Bases located in five cities (Boston, MA; Philadelphia, PA; Portland, OR; Rochester, NY; and Winston-Salem, NC). Increasing the number of Research Bases around the country would make these NCORP facilities more accessible to lung cancer patients, and thus increase the likelihood of reaching more SCLC patients.

LUNG CANCER RESEARCH PROGRAM (LCRP)

The United States Department of Defense funds the LCRP through the office of the Congressionally Directed Medical Research Programs (CDMRP). Broadly, the CDMRP seeks to fund the best research to eliminate diseases, particularly those that affect military personnel. Research focus areas include development of non- or minimally invasive detection and screening tools, understanding basic lung cancer biology, progression of disease, and resistance to treatment, as well as investigating biomarkers to identify responders and non-responders.

CONSORTIA AND STRATEGIC PARTNERSHIPS

THE LUNG CANCER MUTATION CONSORTIUM (LCMC)

In collaboration with Free to Breathe, the LCMC offers genetic mutation testing for NSCLC patient tumors in an effort to match them with the best available therapies (NCT01014286). The LCMC is the largest national effort of its kind, comprised of 16 cancer centers around the country. With the support of philanthropic giving to address this unmet need in SCLC research and therapy, this initiative can serve as a model for SCLC.

DETECTING EARLY LUNG CANCER AMONG MILITARY PERSONNEL (DECAMP) CONSORTIUM

Funded by the United States Department of Defense Lung Cancer Research Program, the DECAMP clinical consortium represents the largest consortium of scientists researching and developing novel non-invasive tools for the early detection of lung cancer. This represents an important initiative, as military personnel experience higher smoking rates than civilians, and veterans are more likely to be diagnosed with lung cancer than non-veterans.

ADDARIO LUNG CANCER MEDICAL INSTITUTE (ALCMI)

ALCMI, the sister organization of ALCF, is an international, patient-centric research consortium that advances novel diagnostics and therapeutics that directly improve patient outcomes. ALCMI projects open up new channels of access for enrollment in clinical trials, making research and participation more accessible to lung cancer patients who have historically been grossly under-represented in clinical trials.

The research consortium directly facilitates and drives molecular testing, therapeutic discoveries, targeted treatments, and early detection. Leveraging its research infrastructure and team of investigators from more than 20 institutions, ALCMI has developed and implemented a portfolio of innovative translational research projects and clinical trials.

BONNIE J. ADDARIO LUNG CANCER FOUNDATION (ALCF) AND OPEN HEALTH NETWORK

ALCF and Open Health Network have jointly launched a health app to help lung cancer patients navigate care, diagnosis, and treatment options. This patient engagement technology tool will aid patients make more informed health decisions and play an active role in their care.

BONNIE J. ADDARIO LUNG CANCER FOUNDATION (ALCF) AND CANCER COMMONS

In an effort to make life-saving, expert-reviewed insight available to all lung cancer patients, ALCF and Cancer Commons have launched a personalized patient portal called MyCancerCommons. The goal is to have patients share their experiences and data in order to get personalized treatment guidance. As data are collected and analyzed from thousands of lung cancer patients, patterns in treatment choices, outcomes, side effects, and quality of life will begin to emerge and provide a rich source of patient-collated data for ALCF to consult.

LUNG CANCER RESEARCH FOUNDATION (LCRF) AND MOLECULARMATCH

LCRF and MolecularMatch have teamed up to make personalized medicine breakthroughs more accessible to lung cancer patients. Using the MolecularMatch portal, patients and their physicians are able to quickly find the most relevant targeted therapies and clinical trials matched to their tumor. This partnership seeks to facilitate clinical trial recruitment and enrollment by acting as a third party between clinicians and patients, providing a matching service, and facilitating patient consent.

MASTER PROTOCOL EFFORTS

Master protocols are being hailed as a game-changer with the potential to revolutionize oncologic clinical development. Lung cancer is leading the way with this new approach. Master protocols have the advantage of bringing flexibility to the traditional clinical trial model by allowing for the addition or removal of experimental drugs to treat the same patient population without changing the eligibility criteria. Also, each experimental group (known as an "arm") is independent of the others and thus allows for patient recruitment into different arms without affecting the ability of the other arms to proceed with testing. With less than 5 to 10 percent of Phase I lung cancer therapeutics successfully reaching the end of Phase III, a change in clinical trial approach was desperately needed, as this touches on a core unmet need in the lung cancer space.

The NSCLC patient population has benefitted greatly from the implementation of master protocols, as druggable molecular targets and key driver mutations have been identified for NSCLC. Eligibility criteria for these studies depend on a patient's cancer having a certain mutational signature in order to be assigned to various treatment arms of the clinical trial study. ***Since genomic characterization of SCLC lags far behind NSCLC***, SCLC experts have suggested that the SCLC field is too young for a master protocol for treatment purposes. However, as stated in the "Barriers to SCLC Research Progress and Key Philanthropic Opportunities" section above, ***the SCLC field could benefit greatly from a clinical trial dedicated solely to increasing the collection and banking of SCLC biospecimen for future research.***

LUNG CANCER MASTER PROTOCOL (LUNG-MAP)

LUNG-MAP is a multi-drug, multi-arm, biomarker-driven clinical trial for NSCLC patients (NCT02154490). This trial will stratify patients based on the genomic profile of their cancer and match patients to one of several experimental treatments. As mentioned previously, the identification of driver mutations in NSCLC has driven the success and advancement in treatment options for this form of lung cancer, and it is the hope that this approach will serve as a model for SCLC.

GENOMICS OF YOUNG LUNG CANCER STUDY (GOYLC)

This study aims to perform a focused, multi-institutional, prospective genomic analysis of primary lung cancer occurring in 60 patients diagnosed at age less than 40 years (NCT02273336). It is important to note that this is not a treatment study. Rather, this is a biospecimen collection study allowing for complete genomic analysis of the submitted samples to provide new insight into lung cancer biology, facilitate the identification of new genome-defined subtypes of lung cancer, accelerate delivery of targeted therapies, and lay the groundwork for further studies of lung cancer risk and inheritance. As mentioned in the "Lack of Efficiency in Clinical Trial Enrollment and Data Sharing" section, ***philanthropic investment could be used to fund a GoYLC-like study specifically for SCLC patients, as this study represents a successful model of obtaining biospecimens.***

COLLABORATIVE ADVANCED STAGE TISSUE LUNG CANCER (CASTLE) NETWORK

CASTLE is a repository for tissue and molecular data gathered from NSCLC and SCLC specimens to be used globally for lung cancer research (NCT01574300). The CASTLE network study will collect blood and tissue samples from lung cancer patients who donate their specimens to the study. The specimens and the associated clinical, biological, and molecular data will be banked at the Addario Lung Cancer Medical Institute (ALCMI). CASTLE is a joint initiative of 10 U.S. and international academic institutions and nine community hospitals. The goals of CASTLE are to encourage the application of known biomarkers to current lung cancer patients and to develop a clinically and biologically meaningful biobank that can be used for several projects, such as parallel clinical trials, correlative studies, and discovering new biomarkers for future diagnostic and therapeutic purposes.

As mentioned previously, the **scarcity of human SCLC tissue biopsies** is a major contributor to the unmet needs in SCLC. Programs such as the CASTLE Network aim to address this key unmet need by providing a clinically annotated repository of lung cancer samples for the scientific community to study. ***A focused effort to specifically increase the amount of SCLC samples would greatly benefit the research community.***

GLOSSARY

Adjuvant	Component in vaccines used to activate resting immune cells
Antibody	Protein used by the immune system to bind antigen. Antibodies can be used for therapy or research. Some common uses for antibodies are to neutralize a pathogen, identify and locate intracellular and extracellular proteins, or bind to a cellular molecule expressing a specific antigen.
Antigen	Molecule that serves as a target for antibodies or immune cell receptors
Antigen presenting cells	Cells that present antigen to T cells
Apoptosis	Programmed cell death
Benign	Abnormal growth of body tissue that is not cancerous
Biobanking	Type of repository that stores biological samples
Biomarker	Measurable substance or molecule whose presence is indicative of disease, infection, or environmental exposure
Biopsy	Tissue removed from a living body
Biospecimen	Samples of material from humans, such as urine, blood, saliva, tissue, and cells
Cell cycle	Series of events that takes place in a cell leading to its growth and division into two cells
Chemotherapy	Systemic treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic and other drugs
Clinical Research	Branch of biomedical research involving human subjects
Combination Therapy	Treatment in which a patient is given two or more therapeutic agents for a single disease
Cytotoxic T cell	A type of immune cell that destroys infected or cancerous cells. Also known as killer T cells.
Dendritic cell	A type of immune cell that processes antigen material and presents it on its cell surface to T cells. It is a type of antigen-presenting cell.
Disease prognosis	Medical prediction of the future course of a disease and the chance for recovery
DNA repair pathways	Collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome
Driver mutation	Mutations that are directly causal to, or "drive", the disease
Efficacy	Measure of the ability of the drug to treat whatever condition it is indicated for. It is not a statement about the drug's tolerability or ease of use.
Epigenomics	Study of the modifications in the DNA
Extensive Disease Stage	Stage of the disease where small cell lung cancer has spread to both sides of the chest
First-line therapy	Initial treatment regimen
Genetic mutation	Permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people
Genome	An organism's complete set of DNA
Genomics	Branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes
Genotype	Genetic constitution of an individual

Immune checkpoints	Inhibitory pathways hardwired into the immune system that are crucial for maintaining immune responses. Act as the "brakes" for the immune system.
Immuno-oncology	Use of the immune system to treat cancer
Immunotherapy	Prevention or treatment of disease with substances that stimulate the immune response
Institutional Review Board	Committee established to review and approve research involving human subjects
Intravenous	Existing or taking place within, or administered into, a vein or veins
Irradiation	Exposure to radiation
Ligand	Molecule that binds to another molecule to form a complex
Limited Disease Stage	Stage of the disease where small cell lung cancer is confined to one side of the chest
Malignant growth	Cellular growth that develops quickly and uncontrollably that has the ability to destroy tissues and/or travel to other parts of the body
Mechanism of action	Specific biochemical interaction through which a drug substance produces its pharmacological effect
Melanoma	Tumor of melanin-forming cells, typically a malignant tumor associated with skin cancer
Metastasize	Spread of cancer
Molecular signatures	Sets of genes, proteins, genetic variants, or other variables that can be used as markers for a particular characteristic
Molecular target	Biochemical molecule that is the target of a certain treatment
Monotherapy	Treatment of a disease with a single drug
Needle biopsy	A hollow needle is used to remove a sample of tissue
Neuroendocrine	Relating to or involving both nervous stimulation and endocrine (hormone) secretion. SCLC cells are neuroendocrine, so they can receive signals from neurons and release hormones into the blood
Non-Small Cell Lung Cancer (NSCLC)	One of two major types of lung cancer. Less aggressive than small cell lung cancer.
Oncogenes	Genes that speed up cell division
Overexpression	High levels of a gene
Pathologist	Physician who interprets and diagnoses the changes caused by disease in tissues and body fluids
Personalized medicine	Use of an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease
Preclinical model	Stage of research before clinical trials where feasibility and drug safety is collected
Proteome	An organism's complete set of proteins expressed by the genome
Proteomics	Branch of molecular biology concerned with the entire complement of proteins that is or can be expressed by a cell, tissue, or organism
Radiation therapy	Treatment of disease, especially cancer, using X-rays or similar forms of radiation
Recalcitrant cancer	Cancer with a five-year survival rate less than 50 percent
Receptor	A protein that responds specifically to a particular neurotransmitter, hormone, antigen, or other substance.
Refractory patients	Patients who are either not responsive to first line treatment or remain responsive for fewer than three months

Research and development (R&D) process	Process by which a laboratory discovery is developed into a commercial therapeutic, diagnostic, or device
Sensitive patients	Patients who remain responsive to first-line treatment for at least three months
Signaling pathway	Cascade of biochemical reactions inside the cell that eventually reach the target molecule or reaction
Small Cell Lung Cancer (SCLC)	Aggressive form of lung cancer where tumors grow rapidly and spread quickly
Sputum cytological exam	Examination of sputum (mucus) secretions from the lungs for presence of cancer cells
Surgical resection	Surgical removal of all or part of an organ, tissue, or structure
T cell	Type of immune cell that plays a central role in cell-mediated immunity. There are several subtypes of T cells.
Targeted therapy	Form of therapy that uses agents that specifically engage certain biochemical molecules
Transcription factor	Proteins that directly control whether genes are turned on or off
Tumor suppressor genes	Genes that slow down cell growth and control cell death
Unfunded mandate	Statute or regulation that requires a state or local government to perform certain actions, with no money provided for fulfilling the requirements

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