



Published in final edited form as:

Cancer. 2015 March 01; 121(5): 664–672. doi:10.1002/cncr.29098.

Small Cell Lung Cancer: Where Do We Go From Here?

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Abstract

Small cell lung cancer (SCLC) is an aggressive disease that accounts for approximately 14% of all lung cancers. In the United States, approximately 31,000 patients are diagnosed annually with SCLC. Despite numerous clinical trials, including at least 40 phase 3 trials since the 1970s, systemic treatment for patients with SCLC has not changed significantly in the past several decades. Consequently, the 5-year survival rate remains low at <7% overall, and most patients survive for only 1 year or less after diagnosis. Unlike nonsmall cell lung cancer (NSCLC), in which major advances have been made using targeted therapies, there are still no approved targeted drugs for SCLC. Significant barriers to progress in SCLC include 1) a lack of early detection modalities, 2) limited tumor tissue for translational research (eg, molecular profiling of DNA, RNA, and/or protein alterations) because of small diagnostic biopsies and the rare use of surgical resection in standard treatment, and 3) rapid disease progression with poor understanding of the mechanisms contributing to therapeutic resistance. In this report, the authors review the current state of SCLC treatment, recent advances in current understanding of the underlying disease biology, and opportunities to advance translational research and therapeutic approaches for patients with SCLC.

Keywords

small cell lung cancer; genomics; proteomics; translational research; novel therapies

INTRODUCTION

Where Are We Now?

Small cell lung cancer (SCLC) is the most aggressive form of lung cancer. In the United States, SCLC makes up 14% of lung cancers overall, with approximately 31,000 patients diagnosed annually.¹ In the vast majority of patients, the development of SCLC is associated with tobacco exposure.^{2,3} This, combined with frequent TP53 mutation (>75%–90% of

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CONFLICT OF INTEREST DISCLOSURES

Dr. Byers reports consulting fees from BioMarin and AbbVie outside the submitted work. Dr. Rudin reports consulting fees from AbbVie, Aveo/Biosesik, Boehringer Ingelheim, GlaxoSmithKline, and Merck outside the submitted work.

SCLCs),^{4–6} results in an aggressive, highly complex disease at the molecular level with a large number of mutations present in each tumor.^{7,8}

Lack of early detection methods—Compared with non—small cell lung cancers (NSCLC), SCLC is characterized by a rapid doubling time and early, widespread metastases. Consequently, most patients (60%–70%) will have extensive-stage (ES) disease at the time of diagnosis (defined as cancer that has spread beyond the ipsilateral lung and regional lymph nodes and cannot be included in a single radiation field). Recently, results from the National Lung Screening Trial highlighted the aggressive nature of SCLC and its propensity for characteristic early hematogenous spread.^{9,10} That study proved the value of screening high-risk patients with low-dose computed tomography (CT) imaging for the early detection of lung cancers overall. However, for patients who had SCLC identified (in contrast to those who had NSCLC), early detection did not reduce the number of patients who were diagnosed with ES disease, nor did it have an evident impact on survival for patients with SCLC. Specifically, 86% of the 125 patients who had SCLC identified through this early detection program had advanced disease at diagnosis. On the basis of these results, there are currently no methods with proven efficacy for the early detection of SCLC.

Current treatment standards for limited-stage SCLC—The vigorous response of SCLC to frontline chemotherapy (roughly 60%–70% response rates¹¹) and to radiation is starkly contrasted by its subsequent resistance to second-line and subsequent therapies after disease recurrence. In general, limited-stage (LS) SCLC (ie, cancer confined to the thorax in a single radiation field) is treated with concurrent chemoradiation, whereas ES-SCLC is treated with chemotherapy alone. The current state-of-the-art treatment for LS-SCLC has recently been reviewed in *Cancer* by Amini et al¹² and typically includes cisplatin-etoposide chemotherapy in combination with radiation therapy (RT). For LS-SCLC, clinical trials have established the superiority of hyperfractionated RT and the importance of beginning RT as early in the treatment course as possible (preferably during cycle 1 of chemotherapy).^{13–19} With these multimodality treatments, up to 20% of patients will have long-term disease control. However, a majority will recur despite definitive chemoradiation.^{20,21} Additional progress in the treatment of SCLC has included the use of prophylactic cranial irradiation in patients with ES-SCLC and LS-SCLC who have a response to their initial platinum-based chemotherapy.^{22,23}

Current treatment standards for ES-SCLC—For patients with ES-SCLC, front-line treatment is platinum-based chemotherapy. Most patients in the United States receive platinum-etoposide (EP) chemotherapy (with either carboplatin or cisplatin), and some patients receive platinum-irinotecan as an alternative, especially outside the United States.²⁴ After relapse, topotecan is the only second-line drug approved by the US Food and Drug Administration (FDA). However, despite its indication in this setting, topotecan has produced disappointing response rates. As with other second-line therapies, responses are typically higher in patients who experiences longer disease control after frontline, platinum-based therapy. For example, response rates may be as high as 25% in patients who relapse >3 months after the completion of EP, but the rates are only 3% to 6% if patients relapse <3 months after EP.²⁵ Other options after front-line therapy include taxanes, irinotecan,

vinorelbine, and gemcitabine. A more recent arrival to the second-line setting is temozolomide (TMZ), which is attractive for its oral dosing and activity in central nervous system lesions (a 38% response rate was observed in patients who had brain metastasis in a phase 2 study).²⁶ In the third-line setting, responses to chemotherapy are rare, and there is no consensus on treatment beyond first-line and second-line therapy.²⁵

Clinical trials for SCLC—Given the high rates of recurrence, rapid development of treatment-resistant disease, and limited activity of existing therapies after relapse, current National Comprehensive Cancer Network (NCCN) guidelines support the use of clinical trials in the second-line and later settings after disease progression or recurrence.²⁴ However, despite intensive efforts by clinical investigators, the list of unsuccessful drugs for SCLC is long. These include more than 40 failed phase 3 studies since the 1970s, including 3 studies that attempted to replicate results from the Japanese Cooperative Oncology Group which had suggested the superior activity of platinum-irinotecan^{27–30} and a platinum-pemetrexed study that was terminated early for inferiority relative to platinum-etoposide.³¹ Many more drugs did not make it far beyond the starting gates because of early negative data in phase 1 or 2 trials or limitations because of poor enrollment or early toxicity. These include imatinib, oblimersen, and bevacizumab (targeting c-Kit, B-cell leukemia 2 [Bcl2], and vascular endothelial growth factor [VEGF], respectively).^{32–34} To address these challenges and bring forward more effective drugs, the medical and scientific community will need to address existing barriers to SCLC research and leverage opportunities for progress in the field.

Few advances in therapeutic options—In the absence of effective approaches for early detection or prevention, effective treatments for patients diagnosed with SCLC become even more critical. However, as described above, therapeutic options have remained largely unchanged for over 3 decades.³⁵ This finding, combined with the relative resistance of recurrent SCLC to salvage chemotherapy, has resulted in persistently dismal patient outcomes. Less than 7% of patients diagnosed with SCLC are alive 5 years after diagnosis (all stages), and <5% of patients with ES disease survive for >2 years.³⁶

The lack of major therapeutic breakthroughs in SCLC is in stark contrast to nonsmall cell lung cancer (NSCLC), in which a growing number of mutations or gene fusions guide treatment selection for specific patient subsets. These include epidermal growth factor receptor (*EGFR*) and B-Raf proto-oncogene serine/threonine kinase (*BRAF*) mutations as well as anaplastic lymphoma kinase (*ALK*), v-ros avian UR2 sarcoma virus oncogene homolog 1 (*ROS1*), and ret proto-oncogene (*RET*) fusions.³⁷ Because of the success of targeted therapies in NSCLC, molecular profiling (primarily in nonsquamous cancers) has become standard in clinical practice. For example, the current NCCN guidelines for the treatment of metastatic NSCLC recommend that oncologists have adequate tissue for molecular testing to establish histologic subtype, with repeat biopsy if necessary that can then be used for standard-of-care mutation testing (eg, for *EGFR* and *ALK*) performed during multiplexed/next-generation sequencing.³⁷

By using Clinical Laboratory Improvement Amendments (CLIA)-certified, multiplexed platforms that test for DNA alterations in multiple genes simultaneously, like those in use at our institutions or others that are commercially available, it is possible to test for validated

targets (eg, *EGFR* mutation, *ALK* fusion) that are critical for initial treatment selection while also screening for the presence of additional potentially drug-gable targets. Although most of these additional targets are not currently used to select front-line therapy, this information can subsequently be used to match patients to clinical trials or other therapies at the time of relapse based on the best available clinical data. Online resources like www.mycancergenome.org allow medical professionals to explore the most recent data around specific gene alterations, including existing clinical data for a given target and ongoing clinical trials for drugs directed against the target (or associated pathway).³⁸

In addition to the genomic profiling that has been adopted into clinical practice, several research initiatives to catalog DNA, RNA, and protein profiles among lung squamous carcinomas and adenocarcinomas have accelerated the pace of discovery, such as The Cancer Genome Atlas (TCGA) (which includes >493 squamous carcinomas and 512 adenocarcinomas with molecular profiling to date).^{39–41} Unfortunately, similar efforts have not yet been possible in SCLC because of a lack of adequate tumor tissue (most patients are diagnosed with SCLC by fine-needle aspiration, and surgically resected specimens are relatively rare).

Overview—To improve outcomes for patients with SCLC, therapies are needed that 1) improve the durability of responses to front-line therapy (including an increased number of patients with LS-SCLC who have long-term survival) and 2) have activity after disease relapse. To achieve this, we need to apply an approach similar to what has been done in NSCLC and other cancers, including in-depth characterization of potential drug targets and activated pathways present in SCLC, followed by translation of the most promising drug targets into the clinic. Furthermore, beyond profiling of treatment-naïve tumors, there is an urgent need to better understand what drives therapeutic resistance in recurrent SCLC—because chemotherapy resistance to second-line and later treatments remains a key factor in poor patient outcomes.

To make progress in these areas, there are several barriers specific to SCLC that must be addressed. These include, first and foremost, a lack of adequate tissue for molecular profiling. This is the result of rare surgical resections in SCLC, small diagnostic biopsies, and the absence of a validated biomarker (for treatment selection) that would necessitate more substantial diagnostic biopsies (and rebiopsies at the time of progression). Furthermore, given the rapid pace of disease progression, translation of new targets into the clinic will require multidisciplinary teams that can expedite biopsies and profiling to minimize the time to treatment initiation. In this review, we discuss the current state of SCLC treatment, established hallmarks of SCLC biology, existing challenges in translational research, and opportunities for progress.

Recent Advances in SCLC Translational Research

Several recent advances in SCLC research have contributed to the understanding of SCLC biology, including the development of new animal models of SCLC to help facilitate translational studies.^{42–44} Some of these findings have led to the identification of new potential drug targets that are now being investigated in clinical trials. For example, among

127 interventional studies currently enrolling SCLC patients, novel drug targets under investigation include poly(ADP-ribose) polymerase 1 (PARP1), immune checkpoints, stem cell targets, and fibroblast growth factor receptor (FGFR).⁴⁵ In addition, novel bioinformatics approaches have opened new avenues for exploring existing data, including the identification of existing drugs that potentially could be repurposed for SCLC treatment (eg, tricyclic antidepressants).^{46,47} Other investigators have recently demonstrated the potential of “liquid biopsies”—obtaining SCLC cells from a patient’s circulation that can be propagated in mouse models for subsequent molecular profiling and drug sensitivity screening.⁴⁸

Molecular hallmarks of SCLC—and their clinical implications—The current classification system for lung cancers from the World Health Organization (WHO 2004) recognizes 3 high-grade lung cancers of neuroendocrine (NE) origin.⁴⁹ These include SCLC, combined SCLC (which contain areas of NSCLC), and large cell NE cancer (LCNEC) (a subset of NSCLC). It is noteworthy that previous studies have demonstrated similarities at the protein and messenger RNA (mRNA) levels between SCLC and LCNEC, suggesting a related underlying biology.^{50–52} SCLC and other high-grade NE lung cancers are distinct in their biology and clinical behavior from intermediate-grade and low-grade NE cancers like atypical and typical carcinoid.

SCLC is characterized by a nearly universal loss of tumor protein 53 (*TP53*) (75%–90% of patients)^{4–6} and retinoblastoma 1 (*RBI*) (approaching 100%)^{53,54} and by frequent 3p deletion.⁵⁵ Beyond these shared molecular features, increased expression of cKit,^{56,57} amplification *v-myc* avian myelocytomatosis viral oncogene homolog (*MYC*) family members (*MYC*, *MYC* lung carcinoma-derived homolog 1 [*MYCL1*], and *MYC* neuroblastoma-derived homolog [*MYCN*]),⁵⁸ and loss of phosphatase and tensin homolog (*PTEN*) have also been described in subsets of SCLC. These molecular hallmarks of SCLC (or SCLC subsets) were confirmed in 2 recent comprehensive genomic profiling studies of SCLC.^{7,8} Consistent with prior studies, loss of the tumor suppressors *TP53* and *RBI* were the 2 most common events identified by both groups. However, those studies also identified novel mutations (eg, those in epigenetic regulators) and driver mutations with well established roles in multiple cancer types (eg, *MYC* family genes, *BCL2*, *PTEN*, CREB binding protein [*CREBBP*], and *FGFR1*) (Fig. 1).

Myc alterations and targeting—Alterations in *MYC* family members were observed in approximately 20% of SCLC patient tumors. Unlike *TP53* and *RBI*, which are tumor suppressors, *MYC* family members represent frequent oncogenes in SCLC and other cancer types. Although Myc has been recognized as a potentially important target for many years, designing a drug to directly inhibit Myc activity has been challenging. However, *MYC* amplified or driven tumors may be more sensitive to certain emerging targeted drugs, such as Aurora kinase or bromodomain inhibitors.^{25,59,60}

In 1 recent example, a phase 2 clinical trial of single-agent alisertib (a highly selective Aurora kinase A inhibitor) produced response rates of 21% in 47 patients with recurrent or progressive SCLC.⁶¹ Among these, the highest response rates were observed in patients with platinum-refractory SCLC (defined as disease recurrence within 3 months of completing

front-line platinum-based therapy), typically the most drug-resistant population. Correlative studies from SCLC patients treated on this trial are pending; however, data from preclinical models of SCLC, as well as other cancer types, suggest that tumors with *Myc* alterations may be especially sensitive to Aurora kinase inhibitors.^{62,63} The mechanism through which *MYC*-amplified or *Myc*-overexpressing tumors are sensitized to inhibition of Aurora kinase is still incompletely understood. However, previous studies suggest that *Myc* plays an important role in transcriptional regulation of Aurora kinases A and B, which, in turn, may provide a growth advantage in the absence of p53.^{63–66} Because of the key role of Aurora kinase A in mitotic spindle assembly, these drugs may be especially active in combination with taxane chemotherapies.

If the activity of Aurora kinase inhibitors is validated in subsequent SCLC clinical trials (such as a new study of paclitaxel with or without alisertib in second-line SCLC; National Clinical Trial no. NCT02038647), then *Myc*-amplified SCLC could be the first genomically defined subgroup of SCLC with a specific targeted agent. In addition to the *MYC* amplifications mentioned above, others biomarkers and/or targets that may predict response in specific subsets of SCLC patients include those with mutations or amplification in *FGFR1*⁵⁹ or sex-determining region Y box 2 (*SOX2*)⁸ and alterations affecting epigenetic changes, such as O-6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation (associated with response to TMZ).²⁶

Overexpression of PARP1 protein and potential role of DNA repair inhibitors—

Beyond mutations and changes in DNA copy number, overexpression of certain proteins in SCLC tumors or changes at the epigenetic level may represent new and important therapeutic targets. For example, proteomic profiling of a large panel of SCLC cell lines led to the identification of several potentially novel therapeutic targets.⁵² These include the DNA repair proteins PARP1 and checkpoint kinase 1 (Chk1) as well as enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) (a chromatin modulator). Increased expression of these proteins appears to be independent of alterations at the DNA level (mutation, amplification) in their corresponding genes (*PARP1*, *CHEK1*, and *EZH2*), emphasizing the value of comprehensive molecular profiling—ie, examining not just tumor DNA but alterations that occur at the protein or pathway level.

On the basis of this observation, several PARP inhibitors (eg, olaparib, rucaparib, BMN-673) were then investigated in preclinical models of SCLC and exhibited single-agent activity in cell lines and/or animal models.^{52,67} Those results led to the investigation of PARP inhibitors (eg, BMN-673 and veliparib) in patients with SCLC in several clinical trials (eg, NCT01286987, NCT01642251, and NCT01638546). The first results of PARP inhibitors in SCLC patients were recently presented at the 2014 American Society of Clinical Oncology annual meeting and, among other findings, exhibited single-agent activity of the PARP inhibitor BMN-673 in a subset of SCLC patients.⁶⁸ Other ongoing studies are testing the combination of PARP inhibition with chemotherapy and include a TMZ/veliparib combination for second-line or third-line treatment (NCT01638546) and a first-line trial of veliparib with platinum-etoposide (Eastern Cooperative Oncology Group trial ECOG-E2511). Further studies are ongoing to identify biomarkers that may predict response to these drugs and include levels of PARP1 or other DNA repair proteins.⁶⁷

Immunotherapy and other promising targets—Several immunotherapy approaches have been investigated or are under current investigation in SCLC, including vaccine studies, interferon- α , and several clinical trials of immune checkpoint inhibitors (for review, see Spigel and Socinski⁶⁹). Immune checkpoint blockade, either alone or in combination with chemotherapy, represents a particularly promising approach to the treatment of this disease. For example, a randomized phase 2 study investigated the combination of ipilimumab (a monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) in combination with paclitaxel and carboplatin. One hundred thirty patients with treatment-naïve were randomized to 1 of 3 treatment arms: 1) concurrent ipilimumab (ipilimumab plus chemotherapy for 4 cycles followed by 2 cycles of chemotherapy plus placebo), 2) *phased* ipilimumab (chemotherapy plus placebo for 2 cycles followed by chemotherapy plus ipilimumab for 4 cycles), or 3) chemotherapy plus placebo. In the patients who received phased ipilimumab, an improvement was observed in progression-free survival based on immunerelated response criteria (hazard ratio, 0.64; P 5 .03), with a trend for improved overall survival (12.5 months vs 9.1 months).⁷⁰ Several trials of immunotherapy in the first-line and relapsed settings are now ongoing, such as the investigation of a programmed cell death protein 1 (PD-1) inhibitor (nivolumab) combined with ipilimumab (NCT01928394).

Another drug target with potential activity in SCLC is FGFR. Alterations (eg, amplification or mutation) in FGFR family members have been described in a small subset of SCLC tumors; and some, but not all, SCLC models with FGFR1 amplification have demonstrated sensitivity to FGFR inhibitors.⁵⁹ Drugs targeting FGFR family members that are currently in clinical investigation for SCLC include JNJ-42756493 (a pan-FGFR inhibitor) and BIBF1120 (a multitargeted drug that inhibits FGFR, vascular endothelial growth factor receptor [VEGFR], and platelet-derived growth factor receptor [PDGFR]; NCT01703481 and NCT01441297). However, the extent to which SCLC with mutations and/or amplifications in FGFR family member genes are dependent on the FGFR pathway is not yet known.

Current Barriers and Challenges in Translational SCLC Research

There are several barriers that have made translational research in SCLC particularly difficult. These include 1) limited tissue available for study, 2) the molecular complexity of SCLC, 3) a poor understanding of the mechanisms of chemotherapy resistance in recurrent disease (including unique molecular alterations that may be acquired after initial treatment), and 4) the rapid pace of disease progression. In addition, investment in SCLC research has been low in recent years (possibly because of some of the limitations noted above in contrast to NSCLC, in which research tools, including tissue and model systems, are more plentiful). For example, in fiscal Year 2012, the National Cancer Institute (NCI) research portfolio contained 745 projects that included lung cancer research, but only 17 (approximately 2%) of those had a focus on SCLC.⁷¹

Contribution of SCLC pathobiology to scarce tissue resources for research—SCLC cells are readily recognized by light microscopy because of their characteristic appearance as small blue cells, often with “crush” artifact (an effect of cell fixing). Thus, a diagnosis can be made based on the presence of as few as 3 to 10 cancer cells (Fig. 2). The

ability to establish a diagnosis of SCLC from a small number of malignant cells, combined with infrequent surgical resection and a lack of validated predictive biomarkers that would necessitate larger tissue biopsies, has significantly limited the availability of SCLC tissue for molecular profiling and other scientific studies. This is especially true for profiling technologies which currently work best on frozen tissue in adequate quantities, including in-depth whole genome sequencing of DNA and comprehensive expression analysis for RNA and protein.

To date, whole-exome sequencing data (ie, DNA sequencing of protein-coding regions of the genome) has only been published on 82 SCLC tumors.^{7,42} This is in stark contrast to NSCLC, for which data from more than 1000 NSCLC tumors have been published.^{9,35,39,41} This small number of profiled tumors is especially problematic in a disease like SCLC, which carries one of the highest rates of mutations per tumor⁴² because of long-term tobacco exposure and near universal loss of p53 function.⁴ On average, SCLC tumors have greater than 4 times the number of mutations observed in breast cancer and almost 10 times the number in prostate cancer.⁴² The vast majority of mutations observed in SCLC patient tumors are passengers (those that do not meaningfully contribute to disease behavior or progression). This makes it more difficult to definitively identify those mutations that are drivers of cancer growth and invasion (including those that may be druggable).

The challenge of discriminating driver mutations from passengers is even more critical for cases in which a driver may only be present in a subset of SCLC patients. We know that driver genes—even those identified in only a minority of patients—still may have incredible clinical importance. For instance, although *ALK* fusions are identified in only 7% of lung adenocarcinomas, testing for *ALK* fusions has become a standard of care in the metastatic setting, because we have highly effective, FDA-approved drugs targeting *ALK* (crizotinib and ceritinib) that provide substantial clinical benefit for a majority of *ALK*-positive patients.^{72–74} However, the genomic studies of SCLC to date have been insufficiently powered to reliably identify recurrent mutations present in <10% of patients.

This point was illustrated by 2 studies that reported the frequency of amplification events in SCLC patient tumors. Whereas one reported *FGFR1* amplifications in 6% of SCLC tumors,⁸ the other study did not identify any instances of *FGFR1* amplification.⁷ This example illustrates the finding that we are likely missing other potentially druggable driver genes in our existing analyses that have potential therapeutic relevance.

Opportunities and Tools for Advancing Progress Improved research tools for the study of SCLC

Recent progress in modeling SCLC has included the development of a cohort of patient-derived xenografts (PDXs) and several genetically engineered mouse models (GEMMs). These animal models can be extremely helpful in dissecting the biology of disease and providing a system in which to test new drugs. Furthermore, a new, potentially transformative tool for animal models (and for expanding SCLC patient tissue for profiling) was recently reported by Hodgkinson et al, who demonstrated the feasibility of using circulating tumor cells (CTCs) to establish animal models (CTC-derived xenografts; [CDXs]) to propagate patient-derived SCLC cells collected from blood.⁴⁸ This approach has

the potential to allow for longitudinal sampling of SCLC cells from patient blood at the time of initial diagnosis and at relapse.

In addition, there are several established resources supported by the NCI and other National Institutes of Health programs that can be leveraged for SCLC research. These include the large drug screening effort in SCLC described below as well as a collection of core facilities, consortia, and networks to support a broad range of research activities, including molecular profiling, animal studies, and early detection initiatives (available at: <http://resresources.nci.nih.gov>; accessed September 1, 2014).

Clinical strategies to promote progress in the treatment of SCLC—Ultimately, our goal is to improve patient survival and quality of life. To do this, translating research findings into clinical trials and, subsequently, into new standard-of-care therapies for SCLC must be achieved. Successful drug development will require a multidisciplinary, translational approach that incorporates discovery and prioritization of candidate drugs and/or targets in preclinical models, as well as well-designed correlative studies as part of each clinical trial to better define those patients most likely to benefit from specific therapeutic approaches.

Toward this goal, a major initiative to characterize drug sensitivity is ongoing at the NCI through the Developmental Therapeutics Program, which is investigating more than 400 targeted drugs and 100 FDA-approved oncology therapies in a panel of >60 SCLC cell lines. Results from this drug screen and other ongoing preclinical efforts—combined with an integrated analysis of the molecular profiles of these SCLC cell lines⁷⁵ (eg, mutations, amplifications, deletions, or alterations at the protein or pathway levels that correspond to drug sensitivity)—will provide important leads that can be validated in the laboratory and taken forward into clinical trials. As part of this, bioinformatics tools will allow us to mine these growing data sets for the new targets or biomarkers to maximize the value and use of a growing molecular resource/database in SCLC.⁴⁷

Remarkably, only approximately 100 interventional clinical trials in SCLC have been registered at www.clinicaltrials.gov since December 2007. This number is clearly inadequate to meet the needs/demand that exists for SCLC patients—particularly with the goal of making a meaningful advance in patient outcomes in the short term. Critical clinical components of a successful SCLC translational research framework must also include 1) biopsy and rebiopsy programs to obtain adequate issue for molecular profiling, 2) mechanisms to support the logistics and funding of patient tumor profiling to identify potential drug targets (such as cooperative group programs or other laboratory protocols), and 3) clinical trial options for all stages of disease that meet the needs of our patients and respond to emerging discoveries/targets identified by ongoing profiling efforts or other research (eg, clinical trial consortiums, basket studies, SCLC master protocols). Figure 3 is an illustration of the key elements to a successful translational approach for the advancement of SCLC treatment, in which CLIA-approved biomarker testing to guide therapeutic selection is occurring in parallel to potentially transformative exploratory analyses.

Furthermore, beyond SCLC of the lung, there is a similarly underserved group of patients with extrapulmonary small cell carcinoma. Partnerships of pulmonary and extrapulmonary

small cell efforts also potentially could advance our understanding of SCLC biology and opportunities for clinical trials of shared targets. Although the aggressiveness of SCLC introduces challenges to clinical research (such as the need for efficient decision making, biopsy completion, and initiation of therapy), previous studies, such as the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination 1 (BATTLE1) trial and, more recently, the BATTLE2 trial (both for metastatic, relapsed NSCLC), have demonstrated the feasibility of obtaining fresh biopsies in a population of patients with advanced, chemotherapy-resistant disease.⁷⁶

Summary

SCLC is an aggressive disease affecting >30,000 individuals per year in the United States. Most patients present with advanced disease and rapidly develop treatment resistance despite a high rate of responses to initial chemotherapy and radiation. Regardless of numerous clinical trials, treatment has not changed significantly for more than 30 years.

Progress in the treatment of SCLC has been limited by several factors, including limited tissue availability for translational research. Consequently, SCLC lags significantly behind NSCLC and other cancers in molecular profiling and the development of targeted therapies. Despite these challenges, there have been some notable recent discoveries that have led to clinical trials and have the potential to advance the field.

By using a multidisciplinary, collaborative, cross-institutional approach, we have the opportunity to meaningfully impact outcomes in the next 5 to 10 years. Important steps toward this goal will include a coordinated effort to collect adequate SCLC tumor tissue for research from treatment-naïve and treatment-refractory patients, support for a scientific community of SCLC investigators, and a framework for translating the most promising discoveries into clinical trials and, ultimately, clinical practice.

Acknowledgments

FUNDING SUPPORT

L.B. is supported, in part, by the R. Lee Clark Fellow Award (supported by the Jeane F. Shelby Scholarship Fund), the MDACC Physician Scientist Award, and the NCI Cancer Clinical Investigator Team Leadership Award.

We thank Dr. Neda Kalhor for providing the cytology image of small cell lung cancer for Figure 2.

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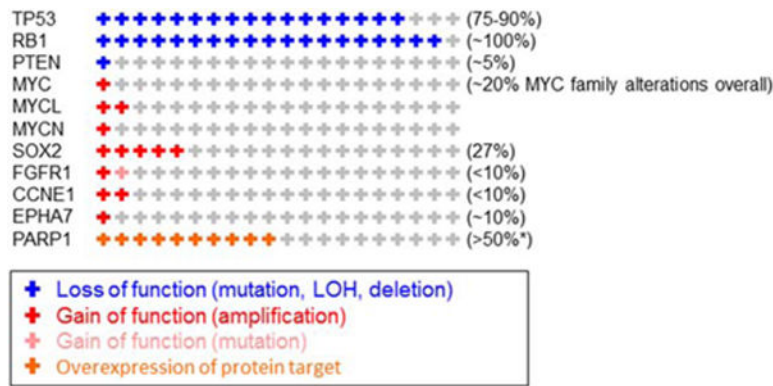


Figure 1.

The frequency of genomic alterations is illustrated according to percentage in small cell lung cancer (SCLC). This is a representative list of the more common and/or potentially targetable alterations. An asterisk indicates the percentage that was positive for poly(ADP-ribose) polymerase 1 (PARP1) protein expression based on the number of SCLC tumors that had an immunohistochemical staining score of 3 in 100% of tumor cells. TP53 indicates tumor protein 53; RB1, retinoblastoma 1; PTEN, phosphatase and tensin homolog; MYC, *v-myc* avian myelocytomatosis viral oncogene homolog; MYCL, *v-myc* avian myelocytomatosis viral oncogene lung carcinoma-derived homolog; MYCN, *v-myc* avian myelocytomatosis viral oncogene neuroblastoma-derived homolog; SOX2, sex-determining region Y box 2; FGFR1, fibroblast growth factor receptor 1; CCNE1, cyclin E1; EPHA7, ephrin receptor A7.

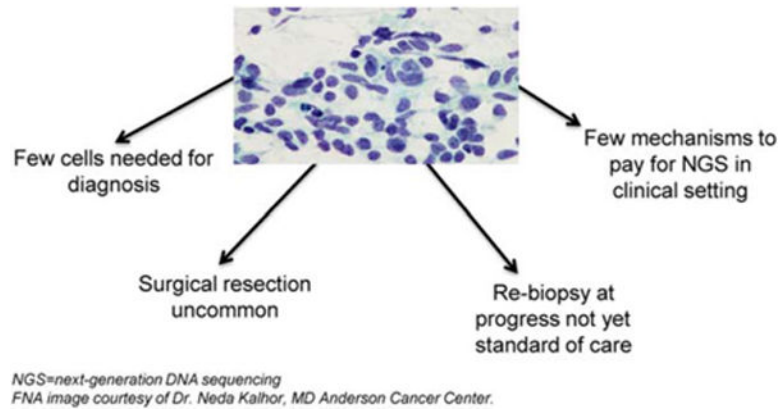


Figure 2. Tissue limitations in the study of small cell lung cancer are illustrated. NGS indicates next-generation DNA sequencing.

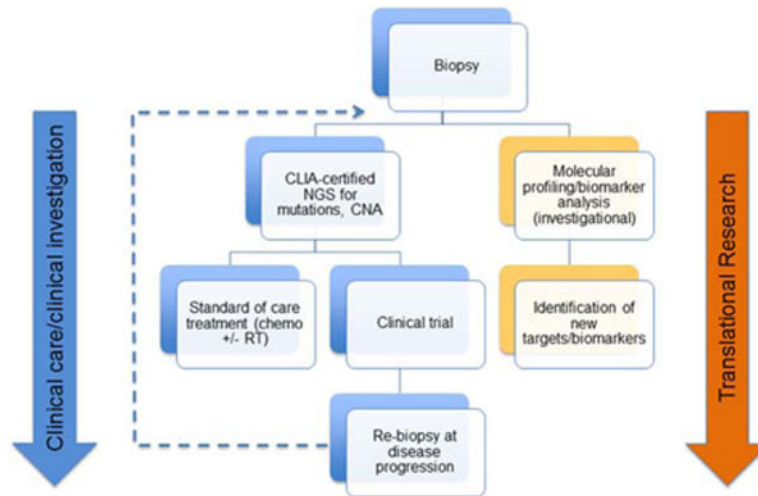


Figure 3.

The framework for clinical-translational research in small cell lung cancer (SCLC) is illustrated. Tissue biopsies (fine-needle aspiration and/or core-needle) are required that provide ample material for integrated molecular analysis 1) to guide clinical decision making (eg, marker-selected clinical trial) and 2) for translational/exploratory scientific analysis (eg, the identification of new targets and/or biomarkers). Patient rebiopsies at the time of progression are necessary to assess for potential new therapeutic targets and to characterize molecular features/alterations acquired in resistant disease. CLIA indicates Clinical Laboratory Improvement Amendments; NGS, next-generation DNA sequencing; CNA, copy number alterations; RT, radiotherapy.