National Cancer Institute
Clinical Trials and Translational Research
Advisory Committee (CTAC)

Progress in Small Cell Lung Cancer (SCLC)
Research Working Group
(SCLC Progress Working Group)

Working Group Report
July 17, 2019

The report was accepted at the July 17, 2019 CTAC Meeting

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EXECUTIVE SUMMARY OF THE SCLC WORKING GROUP REPORT

The Recalcitrant Cancer Research Act (RCRA) of 2012[1] called upon the National Cancer Institute (NCI) to identify two or more recalcitrant cancers that have a five-year relative survival rate of less than 20 percent and cause more than 30,000 deaths per year in the United States and to develop scientific frameworks that will assist in making progress against these cancers. Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than seven percent and the loss of approximately 30,000 lives per year. The NCI's scientific framework for SCLC, which provided the background, rationale, and implementation plans for five initiatives proposed to expand SCLC research, was submitted to Congress in June 2014. The five initiatives were (1) Better Research Tools for the Study of SCLC, (2) Comprehensive Genomic Profiling of SCLC, (3) New Diagnostic Approaches for SCLC, (4) Therapeutic Development Efforts, and (5) Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance.

The NCI convened the Progress in SCLC Research Working Group (SCLC Progress WG), with a membership representing the broad clinical and translational research and advocacy communities. The SCLC Progress WG met on February 4, 2019 with the objective of assessing research progress and identifying new scientific opportunities related to the initiatives in the scientific framework for SCLC. The SCLC Progress WG members assessed the implementation of the various initiatives by the NCI and provided recommendations for continued or more concentrated efforts with regard to the initiatives. The deliberations, conclusions, and recommendations of the SCLC Progress WG are summarized below.

To address the five research initiatives, NCI released three Funding Opportunity Announcements for a new SCLC consortium in December 2015, with funding mechanisms to develop therapeutic and early detection strategies as well as to create a coordinating center for research sites in the Consortium[2]. The coordinating center grant was awarded in February 2017 and has a hub for models and molecular profiling, an extensive number of cell lines, and a clinical correlates database. Research sites focused on therapeutic development perform preclinical studies including new clinically annotated SCLC models, molecularly-defined subsets of SCLC, targeted drugs and therapeutic strategies, and immunotherapy. A total of seven such projects have been funded as of February 2019. Additional research sites have the objective of understanding the molecular changes that precede SCLC and identifying populations at risk, with projects including the molecular status of normal lung in SCLC, genetic risk factors, biomarker validation, and characterization of early events leading to disseminated disease. A total of six such projects have been funded.

The assessment of the SCLC Progress WG was that the research initiatives delineated in the 2014 SCLC Scientific Framework continue to be relevant and important to guide future research. The number of grants for SCLC research has increased approximately three-fold over the past five years, including projects within the SCLC Consortium, which address all five initiatives, as well as other research awards. The increased number of genomic studies, greater understanding of SCLC biology,

[1] Public Law 112-239, §1083.

[2] PAR-16-050, Coordinating Center (U24), PAR-16-049, Therapeutic Development and Mechanisms of Resistance (U01), and PAR-16-051, Innovative Approaches to the Prevention and Early Detection of Small Cell Lung Cancer (U01).

and emerging approaches to therapy, including targeted therapies and immunotherapy, have created new research opportunities. While the current set of initiatives remain important and multiple grants have been funded to address them, these projects are in early stages and it is not possible to report on specific progress yet.

Important advances in the field over the past five years include the recent approval by FDA of atezolizumab plus chemotherapy for first-line treatment of extensive-stage SCLC, the identification of SCLC subsets, the emergence of new animal and cell models for the study of SCLC, recognition of DLL3 as a potential therapeutic target and biomarker, and implication of SLFN11 and WNT signaling in resistance to therapy.

Recommendations for continued or more concentrated efforts with regards to the initiatives include:

- Coordinated mechanisms for sample acquisition, storage, and characterization beyond what is currently supported within the SCLC Consortium, including access to clinical trial specimens, mandating biopsies when practicable within SCLC trials, funding for rapid autopsy programs, and enhanced bioinformatics resources modeled on the Cancer Genome Atlas (TCGA)
- Increased sample collection for late stage disease, metastases, pre- and post-therapy, and exceptional responders
- Greater efforts to investigate the transcriptome, epigenome, metabolome, and microenvironment of SCLC
- Increased resources for the storage and sharing of cell and mouse models, including increased molecular characterization with clinical annotation
- Development of models for immunotherapy
- Continued efforts to develop blood-based and imaging approaches for screening and diagnosis
- New approaches to prevention.

Of critical importance is the need to continue to attract new and established investigators to study SCLC. The SCLC workshops sponsored by the International Association for the Study of Lung Cancer (IASLC) in 2015 and 2017 are examples of productive meetings that have led to fruitful collaborations that expanded and enhanced research efforts in SCLC. The SCLC Consortium held its inaugural annual meeting in 2018 on the NCI campus and will meet again as part of the IASLC SCLC workshop in 2019.

The inclusion of SCLC patient advocates in activities is important to help support research teams. Examples of areas needing advocate input include the development of a standard set of SCLC patient-reported outcomes and incorporation of more underserved and disadvantaged populations in SCLC studies to ensure research cohorts reflect real-world populations.

As previously noted, all original research initiatives remain relevant to future progress in SCLC. Although research in prevention of SCLC is a largely unmet need, the field is in its infancy and depends on greater understanding of early events in SCLC carcinogenesis. The SCLC Progress WG concluded that real progress has been made, but there is much more to be done to ultimately have a clinical impact.

NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)
PROGRESS IN SMALL CELL LUNG CANCER (SCLC) RESEARCH WORKING GROUP
(SCLC PROGRESS WORKING GROUP)

WORKING GROUP REPORT, July 2019

INTRODUCTION

On September 19, 2012, the 112th Congress amended the Public Health Service Act by enacting the Recalcitrant Cancer Research Act (RCRA) of 2012 (Public Law 112-239, §1083). The legislation called upon the National Cancer Institute (NCI) to identify two or more recalcitrant cancers that have a five-year relative survival rate of less than 20 percent and cause more than 30,000 deaths per year in the United States and to develop scientific frameworks that will assist in making progress against these cancers. Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than seven percent and the loss of approximately 30,000 lives per year[1]. The NCI's scientific framework for SCLC was submitted to Congress in June 2014 and posted on the NCI's website. The NCI convened the Progress in SCLC Research Working Group (SCLC Progress WG), co-chaired by Dr. Alex Adjei of the Mayo Clinic and Dr. Laurie Gaspar of the University of Colorado and Banner MD Anderson Cancer Center, to advise the NCI on the progress of the research initiatives outlined in the scientific framework. The SCLC Progress WG members represent the broad clinical and translational research and advocacy communities (Appendix 1).

This report summarizes the recommendations of the SCLC Progress WG. The SCLC Progress WG met on February 4, 2019 (Appendix 2) with the objective of assessing research progress and identifying new scientific opportunities related to the initiatives in the scientific framework for SCLC. Important scientific advances were identified in the areas of (a) Biology and Genetics (including tumor biology, genomics and other 'omic' characterization, epidemiology, and etiology), (b) Models (including cell and animal models of SCLC and preclinical testing), (c) Prevention, Screening, and Diagnosis, and (d) Treatment and Resistance. The SCLC Progress WG assessed the research landscape and the continued scientific relevance of the 2014 research initiatives. Implementation of the various initiatives by the NCI was also assessed and the SCLC Progress WG provided recommendations for continued or more concentrated efforts with regard to the initiatives.

INITIATIVES FOR SMALL CELL LUNG CANCER RESEARCH

The 2014 scientific framework for SCLC provides the background, rationale, and implementation plans for five initiatives proposed to expand SCLC research. These initiatives are summarized below:

1. **Better Research Tools for the Study of SCLC.** Build better research tools for the study of SCLC by (a) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC (from initial diagnosis to disease recurrence following radio-chemotherapy) and (b) developing new tumor models (e.g., cell lines, patient-derived xenografts, and genetically-engineered mouse models) that reflect the phases of SCLC found in the clinic.
2. **Comprehensive Genomic Profiling of SCLC.** Expand comprehensive genomic profiling studies of clinically-annotated SCLC specimens to improve the basic understanding of the frequency, distribution, and range of molecular abnormalities that exist both at diagnosis and following therapeutic relapse.
3. **New Diagnostic Approaches for SCLC.** Investigate new diagnostic approaches for populations at high risk of developing SCLC.
4. **Therapeutic Development Efforts.** Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC (tumor suppressor gene loss, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy).
5. **Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance.** Examine the mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following first-line treatment.

ASSESSMENT OF RESEARCH PROGRESS

Prior to the February SCLC Progress WG meeting, four planning groups consisting of SCLC Progress WG members and NCI staff met during a series of webinars, each focused on different areas of SCLC research. The subject areas were (a) Biology and Genetics, (b) Models, (c) Prevention, Screening, and Diagnosis, and (d) Treatment and Resistance. Each planning group discussion was structured around the identification of important, recent scientific advances in their designated subject area, the continued scientific relevance of the 2014 research initiatives, and current gaps and opportunities for SCLC research.

The NCI provided information on NCI-funded extramural grants with relevance to SCLC and NCI-supported clinical trials for SCLC (Appendix 3).

SUMMARY OF PROGRESS

SCLC CONSORTIUM AND OTHER EXTRAMURAL GRANTS

To address the five research initiatives, NCI released three Funding Opportunity Announcements (FOAs) for a new SCLC consortium, with funding mechanisms to develop therapeutic and early detection strategies as well as to create a coordinating center for research sites in the Consortium. The

coordinating center (PAR-16-050, Coordinating Center (U24)) has a hub at Memorial Sloan Kettering Cancer Center (MSKCC) for models and molecular profiling, extensive cell lines (University of Texas Southwestern, UTSW), a clinical correlates database (Vanderbilt), and other sites of expertise at the NCI, Case Western Reserve University, and Massachusetts General Hospital. The genomics and clinical database is the most comprehensive SCLC dataset in the world, with compiled genomic and clinically-annotated data that are accessible to the public. The SCLC Consortium has monthly conference calls and annual meetings that include in addition to Consortium members, associate members (principal investigators of NCI-funded SCLC grants that are outside of the consortium) and interactions with investigators in related fields.

A separate FOA (PAR-16-049, Therapeutic Development and Mechanisms of Resistance (U01)) encouraged preclinical studies with a preference for use of human specimens. Areas of research interest included new clinically-annotated SCLC models, molecularly-defined subsets of SCLC, targeted drugs and therapeutic strategies, and immunotherapy. There are currently seven grants funded under this FOA as of FY 2018. The third funding announcement (PAR-16-051, Innovative Approaches to the Prevention and Early Detection of Small Cell Lung Cancer (U01)) had the objective of understanding the molecular changes that precede SCLC and identifying populations at risk. Areas of research interest included the molecular status of normal lung in SCLC, genetic risk factors, biomarker validation, and characterization of early events leading to disseminated disease. There are six grants funded under this announcement, four in early SCLC biology and two in detection.

Of note, NCI funding for SCLC research has increased significantly over the past several years, with 47 active NCI grants in FY 2018 (details may be found in Appendix 4). Many of the non-consortium grantees participate within the consortium as associate members.

NCI Intramural Activities

Current studies in the NCI intramural clinical trials program are based on the observation that DNA replicative stress is a hallmark of SCLC and therefore DNA repair pathways may be a vulnerability that can be targeted therapeutically, via inhibition of cellular regulators such as WEE1, ATM, ATR, and PARP[2,3].

The intramural program hosts CellMinerCDB[4], a web-based tool that provides integrated access to cancer cell pharmacogenomic databases. An initiative is underway to develop a SCLC dataset within CellMinerCDB (SCLC-CellMinerCDB), which will include data on cell lines, genomic studies, and drugs.

Discussion

The SCLC Progress WG members agreed that the NCI has stimulated research and collaboration by the creation of the SCLC Consortium. The consortium makes a wealth of data widely available to the broader SCLC research community, including both human and mouse data. These data represent an important shared resource for investigators. An increased awareness of SCLC research is evident, not only in the responsiveness of applicants to the consortium funding announcements and the increased number of SCLC grants overall, but also in the higher profile of SCLC research at major scientific meetings, including

the recent international SCLC workshops held by the International Association for the Study of Lung Cancer (IASLC). Heightened interest from the pharmaceutical sector is also evident in the increased number of new agents and clinical trials for SCLC.

A detailed assessment of SCLC Consortium projects is not possible given their recent funding. Looking forward, it will be important to develop overall metrics of the impact of the research on the field. The SCLC Consortium was not designed to support clinical trials, but the results of consortium projects will likely provide the foundation for future clinical studies. The development of new models and biomarkers should be considered as interim landmarks of progress. In particular, research on the prevention and early detection of SCLC is only beginning: there were no grants in these areas in FY 20145 but now there are six such grants within the consortium. These fields are in their infancy and there is a need for greater biologic and mechanistic understanding of early SCLC biology to underpin future clinical studies.

Publications in SCLC have increased in recent years, especially since the first reports on SCLC genomes in 2012[6,7]. The development of the scientific framework and the SCLC research initiatives in 2014 coincided with an increase in the SCLC genome discovery. The increase in publications has continued apace and reflects an increased interest and level of activity in the field.

BIOLOGY AND GENETICS

ASSESSMENT

The Biology and Genetics planning group was charged with assessing recent scientific advances, the continued relevance of the 2014 research initiatives, and current gaps and opportunities for SCLC research in the areas of biology, genetics, genomics and other 'omic' technologies, etiology, and epidemiology (a summary of gaps and opportunities is provided in Appendix 5). The increased number of funded grants for SCLC research is an encouraging sign and many projects within the SCLC Consortium are directly responsive to the research initiatives delineated in the scientific framework for SCLC. Several of the initiatives were considered relevant to the Biology and Genetics planning group and progress overall in the field in the following areas was described.

A number of important scientific advances pertain to initiative #2 (Comprehensive Genomic Profiling of SCLC). Among these are the publication of genomic profiling studies of SCLC tumors and work by several groups identifying specific SCLC subsets with potential implications for patient selection for new treatments[6-11], including novel insights into the cell-of-origin of SCLC[12] and the biology of MYC-driven SCLC in tumors with low neuroendocrine characteristics[13]. Additional genomic profiling work contributed to initiative #5 (Mechanisms of Response and Resistance), implicating WNT signaling pathway aberrations in the emergence of recurrent SCLC[14]. Lastly, work in mice on pulmonary neuroendocrine cell (PNEC) development has provided new insights into the aggressive, metastatic nature of early SCLC[15].

Overall, the group thought that all of the research initiatives remained scientifically relevant. While there has been significant progress overall in the field of SCLC research, the group acknowledged that much more needs to be done. This sentiment was shared across all of the planning groups.

Research Gaps and Opportunities

- Tumor heterogeneity
- Microenvironment factors, including immune cells and inflammatory processes
- Role of transcription, epigenetics, and metabolomics in SCLC
- Mechanisms of metastasis
- Cell-of-origin studies

Discussion

Despite many interesting and important developments in the field, several areas remain as gaps in research or represent new opportunities based on recent findings. There remains a need for a greater number of patient tissue samples to enable ongoing research.

Key issues are related to tissue acquisition and centralized resources for storage, sharing, and characterization. A number of resources exist. For example, the NCI Navigator website provides a list of all samples obtained from within the NCI National Clinical Trials Network (NCTN) (the number of available SCLC samples is limited at the present time). Additional centralized resources could facilitate the development of genomic and protein-based assays. The integration of existing resources, or the development of new ones, could be facilitated by the establishment of a bioinformatics working group for SCLC. Longitudinal collections of both preclinical and patient samples, including high-quality RNA samples, to use for deep profiling remains an unmet need. The existence of a SCLC master protocol with required serial biopsies could be a means toward this end. Another potential source of tissue samples for research purposes are rapid autopsy programs, although funding for such programs remains challenging. The lung microbiome is relatively unstudied and should be investigated.

MODELS

Assessment

The Models planning group assessed scientific advances as well as current gaps and opportunities for research in SCLC models and preclinical testing. They also assessed the continued relevance of the 2014 research initiatives. Overall progress in the following areas was described.

Key advances pertaining to initiative #1 (Better Research Tools) include the use of circulating tumor cells (CTCs), which recapitulate the features of tumors at multiple stages of disease (e.g., at diagnosis, after initial treatment, at first progression, etc.) and are more easily accessible than tumor tissue, for genomic profiling and for the creation of CTC-derived xenograft (CDX) models[16,17]; the reprogramming of normal human epithelial cells to generate a novel model in mice for small cell tumors, including SCLC[18]; and the

development of PNECs from human embryonic cells that could be driven to develop SCLC-like tumors through genetic manipulation[19]. Also cited were the development of new genetically-engineered mouse models of MYC-driven SCLC[13], the role of nuclear factor I B (NFIB) in promoting metastasis[20,21], CD47 as a potential new target for immunotherapy for SCLC[22], and the role of CREB binding protein (CREBBP) in SCLC tumorigenicity and sensitivity to histone deacetylase (HDAC) inhibition[23]. Relevant to initiative #4 (Therapeutic Development Efforts) was a comprehensive screen of approved drugs and experimental agents in human SCLC cell lines that was accompanied with extensive characterization of gene expression[24].

The group thought that this research initiative, as well as the other initiatives, remained scientifically relevant.

Research Gaps and Opportunities

- Tissues and corresponding cell/PDX models for pre- and post-therapy and after relapse for evaluation (including immunotherapy, metastases, exceptional responders, and newly diagnosed and refractory patients)
- Models for testing of immunotherapy approaches
- Models for newly identified subsets of SCLC
- Newly derived cell lines
- Models for smoking-related damage to DNA and tissues.
- Models of conversion from adenocarcinoma to SCLC post-therapy
- Understanding the mechanisms of therapeutic resistance in cell lines, animal models and in humans

Discussion

There was some degree of concern that current models may not fully represent human disease. A way forward would be to do in-depth characterization of a subset of models that could serve as the standard in the field for researchers. Furthermore, there is a need to develop mechanisms for the uniform use of such models and to facilitate sharing across groups. A centralized resource for PDX models, similar to the American Type Culture Collection resource for cell lines, would be beneficial (the panel recognized the efforts to provide access to PDX models within the SCLC Consortium and the NCI PDX Model Repository (PDMR)). Funding is a limiting factor in all of these activities.

The group acknowledged that the SCLC cell lines in common use are quite old and new cell lines are needed. Where possible, cell lines derived from PDXs could be used to run parallel in vitro and in vivo experiments.

Although steps have been made in developing mouse models of *MYC* and *CREBBP*, further understanding of the roles of these genes is needed. Moreover, many other genes of interest have not yet been modeled in mice. Investigations into the order of mutations in early precursors of SCLC may prove useful.

PREVENTION, SCREENING, AND DIAGNOSIS

ASSESSMENT

The Prevention, Screening and Diagnosis planning group assessed scientific advances, primarily pertaining to the prevention and early detection funding opportunity. They assessed the continued relevance of this initiative and overall progress in this area of research.

SCLC is closely associated with tobacco use and the decrease in cigarette smoking in the US population is largely responsible for a concomitant decline in the incidence of SCLC[25,26]. Smoking cessation continues to be a critical primary prevention strategy. The impact of E-cigarettes on future incidence is not known. The results of the National Lung Cancer Screening Trial (NLST) suggest that Low Dose Computed Tomography (LDCT) imaging has no observable impact on SCLC outcome, in contrast to the benefit found for non-small cell lung cancer (NSCLC)[27,28].

The group acknowledged that this area of research is in its infancy and will likely build on progress being made in other diseases (particularly in new detection technologies) and on the results of the basic investigations supported by the SCLC Consortium. An important advance impacting initiative #3 (New Diagnostic Approaches) is the use of circulating tumor DNA for early detection of SCLC[29].

RESEARCH GAPS AND OPPORTUNITIES

- Although the NLST was negative for SCLC benefit, there may be opportunities to study the frequency of screening, potential technological improvements in CT with reduced radiation exposure and improved image quality, and other novel imaging approaches.
- Circulating tumor DNA (ctDNA) is a promising area to pursue to detect and/or monitor development of SCLC but the methods are not yet sensitive enough for clinical use.
- Another opportunity relates to the use of molecularly-targeted imaging agents for detection and/or response assessment.
- Little is known about pre-cancerous lesions and the field of injury from which SCLC may arise.

DISCUSSION

Despite the discouraging results of the NLST regarding SCLC, the potential to cure some patients with early stage SCLC warrants continued investigations of early detection and screening approaches, including CT. New CT technologies that may be investigated include spectral- and photon-counting approaches. Radiomics, the extraction of imaging features using together with advanced analytics such as machine learning, is a new area that may improve upon the utility of CT and other imaging approaches[30,31], and may play a role for SCLC in the future. Images generated in all NCI-funded studies should be collected and made available for further investigation. Circulating markers that are biologically linked with partner imaging markers could also provide advances in early detection.

There remains a need to investigate disparities in smoking-related and non-smoking related lung cancers, including among populations with high rates of tobacco-associated cancers[25].

Several newly funded projects address various approaches to the characterization and detection of early SCLC (see Appendix 4, projects 5U01CA213285-02, 5U01CA213330-02, 1U01CA224276-01A1, 1U01CA224293-01A1, 1U01CA224326-01, and 1U01CA231851-01). Development of novel early detection and preventive approaches requires a better understanding of early events in SCLC pathogenesis. An open question is whether there is sufficient ongoing research to address remaining gaps in this area. The need to continue emphasizing and funding smoking cessation programs was noted.

THERAPY AND RESISTANCE

ASSESSMENT

The Therapy and Resistance planning group identified a number of advances in research that impacted initiative #4 (Therapeutic Development Efforts). Among these were an increased understanding of the role of DNA repair pathway alterations[2,3,32], the identification of SCLC subtypes that are susceptible to Aurora Kinase inhibition and other targeted agents[9], the use of Schlafen family member 11 (SLFN11) as a potential biomarker of sensitivity to PARP inhibition[33] and of tumor mutational burden for sensitivity to immune checkpoint inhibition[34], and the recognition of delta-like protein 3 (DLL3) as a potential target for SCLC therapy[35] and for use as an imaging biomarker[36]. The recent approval of atezolizumab as frontline treatment of extensive-stage SCLC[37] is the most significant advance in SCLC treatment in many years and represents a proof-of-principle for the use of immune checkpoint inhibitors for this disease. The discovery of the role of SLFN11 in mediating resistance to therapy also contributed to initiative #5.

RESEARCH GAPS AND OPPORTUNITIES

- Studies focused on understanding the unique features of SCLC that could be used to develop new therapeutics
- A clearer understanding of the potential of immunotherapy in SCLC and the limitations thereof
- Elucidation of SCLC subsets of disease and development of biomarkers for clinical use.
- Identification of molecular vulnerabilities that could be used to develop targeted agents.
- Investigations into potential mechanisms of response and resistance including, but not limited to:
    - Elevated expression of DNA repair proteins
    - Elevated expression of ABC transporter proteins
    - Activation of the PI3K/AKT/mTOR pathway
    - Expression of stem cell markers
- Biopsies in patients who relapse to understand the underlying tumor progression
- New approaches to clinical trials for SCLC. For example:
    - Large basket trials which include early disease as well as patients with late stage disease
    - Carefully designed studies to ensure rapid accrual
- Preclinical models specific to therapeutic targets and development of resistance
- Studies that track and research the evolution of circulating tumor DNA (ctDNA) in patients before therapy and at the time of recurrence.

- A standard set of patient-reported outcomes (PROs) for SCLC trials
- Address the benefits and risks of prophylactic cranial irradiation (PCI)

Discussion

The focus in the 2014 scientific framework was on studying specific molecular vulnerabilities of SCLC, including lost or mutated tumor suppressor genes, unique genetic drivers and their pathways, nuclear transcription factors (e.g. achaete-scute family bHLH transcription factor 1 (ASCL1), MYC), Notch signaling pathways, neuronal characteristics, and immunotherapy. The planning group felt that the original initiatives are still relevant, and it is important to continue pursuing those goals. Effective treatment options remain a clear unmet clinical need in SCLC. Moreover, investigating issues related to access to care, including palliative care, is important. The members noted that in the last several years that there has been a slight improvement in median patient survival.

The group identified several key issues and needs. They stressed the need to learn from past failures of clinical trials for SCLC (i.e., agents that did not lead to improved patient outcomes) that may have failed due to the lack of an appropriate biomarker to identify disease subsets. A more effective approach to move from preclinical research to studies of patients in clinical trials is needed as are accrual difficulties related to patients being primarily treated in community settings, as opposed to academic centers. Future studies must optimize the information that can be gained from patients, requiring additional funding and resources for biopsies and tumor profiling, as well as additional correlative studies. Intensive characterization of available human samples would move the field forward.

CONCLUSIONS AND NEXT STEPS

The assessment of the SCLC Progress WG was that the research initiates delineated in the 2014 SCLC Scientific Framework continue to be relevant and important to guide future research. The number of grants for SCLC research has increased approximately three-fold over the past five years, including projects within the SCLC Consortium, which address all five initiatives, as well as other research awards. The increased number of genomic studies, greater understanding of SCLC biology, and emerging approaches to therapy, including targeted therapies (PARP, WEE1, DLL3, Aurora kinase) and immunotherapy, have created new research opportunities.

While the current set of initiatives remain important and multiple grants have been funded to address them, these projects are in early stages and it is not possible to report on specific progress yet.

Important advances in the field over the past five years include:

- The recent approval by FDA of atezolizumab plus chemotherapy for first-line treatment of extensive-stage SCLC
- Identification of SCLC subsets defined by lineage transcription factors (ASCL1, neuronal differentiation 1 (NEUROD1), POU class 2 homeobox 3 (POU2F3)) and MYC expression

- The emergence of new models for the study of SCLC, including CDX models, newer genetically engineered mouse models, and novel approaches in cell models (reprogrammed basal cells and embryonic stem cells).
- Recognition of DLL3 as a potential therapeutic target and biomarker
- Implication of SLFN11 and WNT signaling in resistance to therapy

Recommendations for continued or more concentrated efforts with regards to the initiatives include:

- Coordinated mechanisms for sample acquisition, storage, and characterization beyond what is currently supported within the SCLC Consortium, including access to clinical trial specimens, mandating biopsies when practicable within SCLC trials, funding for rapid autopsy programs, and enhanced bioinformatics resources modeled on TCGA
- Increased sample collection for late stage disease, metastases, pre- and post-therapy, and exceptional responders
- Greater efforts to investigate the transcriptome, epigenome, metabolome, and microenvironment of SCLC
- Increased resources for the storage and sharing of cell and mouse models, including increased molecular characterization with clinical annotation
- Development of models for immunotherapy
- Continued efforts to develop blood-based and imaging approaches for screening and diagnosis
- New approaches to prevention.

Of critical importance is the need to continue to attract new and established investigators to study SCLC. The IASLC-sponsored SCLC workshops in 2015[38] and 2017 are examples of productive meetings that have led to fruitful collaborations that expanded and enhanced research efforts in SCLC. The SCLC Consortium held its inaugural annual meeting in 2018 on the NCI campus and will meet again as part of the IASLC SCLC workshop in 2019.

The inclusion of SCLC patient advocates in many such activities is important, including to help support research teams, the development of a standard set of SCLC PROs, and incorporating more underserved and disadvantaged populations in SCLC studies to ensure research cohorts reflect real-world populations.

As previously noted, all original research initiatives remain relevant to future progress in SCLC. Although research in prevention of SCLC is a largely unmet need, the field is in its infancy and depends on greater understanding of early events in SCLC carcinogenesis. The SCLC Progress WG concluded that real progress has been made but there is much more to be done to ultimately have a clinical impact.

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APPENDICES – SUPPLEMENTAL RESOURCES

Appendix 1: Progress in Small Cell Lung Cancer (SCLC) Research Working Group (SCLC Progress WG) 2019 Roster

Appendix 2: Progress in Small Cell Lung Cancer (SCLC) Research Working Group (SCLC Progress WG) February 4, 2019 Meeting Agenda

Appendix 3: Open NCI-Supported SCLC Clinical Trials as of March 2019

Appendix 4: Funded Project Summary FY 2018

Appendix 5: Summary of Research Gaps and Opportunities

National Cancer Institute
Clinical Trials and Translational Research Advisory Committee (CTAC) Progress in Small Cell Lung Cancer Research Working Group (SCLC Progress WG)

ROSTER

Co- Chairs

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Appendix 1
SCLC Progress WG Roster

Eric Haura, M.D.
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Executive Secretary

Wolf Lindwasser, Ph.D.
Program Director
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Appendix 2
SCLC Progress WG Agenda

NCI CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) PROGRESS IN SMALL CELL LUNG CANCER RESEARCH WORKING GROUP (SCLC PROGRESS WG)

MEETING AGENDA
MONDAY, FEBRUARY 4, 2019
9:00 AM – 3:00 PM (ET)

NATIONAL CANCER INSTITUTE
SHADY GROVE – SEMINAR 110

09:00 AM – 09:05 AM	**I. WELCOME AND INTRODUCTIONS**	James Doroshow (NCI)
09:00 AM – 09:15 AM	**II. OVERVIEW AND CHARGE**	Alex Adjei (Mayo) Laurie Gaspar (Colorado)
09:15 AM – 10:30 AM	**III. SESSION 1: NCI UPDATES**	
09:15 AM – 09:25 AM	SCLC Consortium Overview	Peter Ujhazy (NCI)
09:25 AM – 09:35 AM	Therapy/Resistance U01 Projects	Suzanne Forry (NCI)
09:35 AM – 09:45 AM	Early Detection/Prevention U01 Projects	Eva Szabo (NCI)
09:45 AM – 09:55 AM	NCI Intramural Activities	Yves Pommier (NCI) Anish Thomas (NCI)
09:55 AM – 10:30 AM	Q/A Discussion	All
10:30 AM – 10:45 AM	**Break**	
10:45 AM – 03:30 PM	**IV. SESSIONS 2 – 5: HIGHLIGHTS FROM WEBINARS, SCIENTIFIC PROGRESS, GAPS/NEW OPPORTUNITIES** 2014 Scientific Initiatives ○ Are they still scientifically relevant? ○ Do they need to be modified? ○ Is the NCI on target in terms of research direction? New Opportunities	
SESSION 2	**Biology and Genetics**	
10:45 AM – 11:40 AM	**Moderator**	**Lauren Byers (MDACC)**
10:45 AM – 11:00 AM	Moderator Presentation	Lauren Byers
11:00 AM – 11:40 AM	Moderator-Led Discussion	
Panel	Alex Adjei, Ramaswamy Govindan, Eric Haura, Charles Rudin, Julien Sage	
SESSION 3	**Models**	
11:40 AM – 12:20 PM	**Moderator**	**Julien Sage (Stanford)**
11:40 AM – 11:55 AM	Moderator Presentation	Julien Sage
11:55 AM – 12:20 PM	Moderator-Led Discussion	
Panel	Alex Adjei, David Carbone, Charles Rudin, David Schrump	

Appendix 2
SCLC Progress WG Agenda

12:20 PM – 12:50 PM	**WORKING LUNCH**	
SESSION 4	**Prevention, Screening, and Diagnosis**	
12:50 PM – 01:30 PM	**Moderator**	**Laurie Gaspar (Colorado)**
12:50 PM – 01:05 PM	Moderator Presentation	Laurie Gaspar
01:05 PM – 01:30 PM	Moderator-Led Discussion	
Panel	Steven Dubinett, Janet Freeman-Daily, David Mankoff	
SESSION 5	**Therapy and Resistance**	
01:30 PM – 02:10 PM	**Moderator**	**Alex Adjei (Mayo**
01:30 PM – 01:45 PM	Moderator Presentation	Alex Adjei
01:45 PM – 02:10 PM	Moderator-Led Discussion	
Panel	Lauren Byers, David Carbone, Laurie Gaspar, Ramaswamy Govindan, Christine Hann, Roman Perez-Soler	
02:10 PM – 03:00 PM	**V. SESSION 6: CONCLUSIONS**	
02:10 PM – 03:00 PM	General Discussion,	Alex Adjei (Mayo)
	Additional Items Not Previously	Laurie Gaspar (Colorado)
	Discussed, Summary, Action Items	

2014 Scientific Initiatives

- Better Research Tools for the Study of SCLC
- Comprehensive Genomic Profiling
- New Diagnostic Approaches
- Therapeutic Development Efforts
- Mechanisms Underlying both High Initial Rate of Response and the Rapid Emergence of Drug and Radiation Resistance

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT00613626	Hoosier Oncology Group	Cisplatin or Carboplatin and Etoposide with or Without Vandetanib in Treating Patients with Previously Untreated Extensive Stage Small Cell Lung Cancer or High-Grade or Poorly Undifferentiated Neuroendocrine Cancer	II	TREATMENT	Complete
NCT00632853	Alliance for Clinical Trials in Oncology	Three Different Radiation Therapy Regimens in Treating Patients with Limited-Stage Small Cell Lung Cancer Receiving Cisplatin or Carboplatin and Etoposide	III	TREATMENT	Active
NCT00856037	University of Nebraska Medical Center	Topotecan Hydrochloride and Doxorubicin Hydrochloride in Treating Patients with Relapsed or Refractory Small Cell Lung Cancer	I	TREATMENT	Active
NCT01345539	UPMC-Shadyside Hospital	Stereotactic Radiosurgery in Treating Patients with Oligometastatic Disease	II	TREATMENT	Active
NCT01345552	UPMC-Shadyside Hospital	Stereotactic Radiosurgery in Treating Patients with Oligo-Recurrent Disease	II	TREATMENT	Active
NCT01587703	GlaxoSmithKline	A Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects With NUT Midline Carcinoma (NMC) and Other Cancers	I	TREATMENT	Closed to Accrual
NCT01631552	Immunomedics Inc	Phase I/II Study of IMMU-132 in Patients With Epithelial Cancers	I_II	TREATMENT	Closed to Accrual

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT01642251	ECOG-ACRIN Cancer Research Group	Cisplatin and Etoposide with or without Veliparib in Treating Patients with Extensive Stage Small Cell Lung Cancer or Metastatic Large Cell Neuroendocrine Non-Small Cell Lung Cancer	I_II	TREATMENT	Complete
NCT01737502	Mayo Clinic in Arizona	Sirolimus and Auranofin in Treating Patients With Advanced or Recurrent Non-Small Cell Lung Cancer or Small Cell Lung Cancer	I_II	TREATMENT	Active
NCT01941316	Cancer Research and Biostatistics	Study of Carfilzomib With Irinotecan in Irinotecan-Sensitive Malignancies and Small Cell Lung Cancer Patients	I_II	TREATMENT	Active
NCT02054104	National Cancer Institute	Adjuvant Tumor Lysate Vaccine and Iscomatrix With or Without Metronomic Oral Cyclophosphamide and Celecoxib in Patients With Malignancies Involving Lungs, Esophagus, Pleura, or Mediastinum	I_II	TREATMENT	Temporarily Closed to Accrual
NCT02157792	EMD Serono Research & Development Institute, Inc.	M6620 First in Human Study	I	TREATMENT	Active
NCT02200757	CytRx Corporation	Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects With Metastatic Small Cell Lung Cancer	II	TREATMENT	Active
NCT02223052	Celgene	Bioequivalence & Food Effect Study in Patients With Solid Tumor or Hematologic Malignancies	I	TREATMENT	Closed to Accrual

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02289690	Abbvie	Dose Escalation and Double-blind Study of Veliparib in Combination With Carboplatin and Etoposide in Treatment-naive Extensive Stage Disease Small Cell Lung Cancer	I_II	TREATMENT	Closed to Accrual
NCT02307630	Memorial Sloan Kettering Cancer Center	Iodine I 124 Monoclonal Antibody 3F8 PET/CT in Imaging Patients with Solid Tumor	NA	DIAGNOSTIC	Closed to Accrual
NCT02312622	Stanford Cancer Institute Palo Alto	Etirinotecan Pegol in Treating Patients with Refractory Brain Metastasis from Non-small Cell Lung Cancer or Small Cell Lung Cancer or Metastatic Breast Cancer	II	TREATMENT	Closed to Accrual
NCT02391480	Abbvie	A Study Evaluating the Safety and Pharmacokinetics of ABBV-075 in Subjects With Cancer	I	TREATMENT	Closed to Accrual
NCT02394548	Dana-Farber Harvard Cancer Center	Intensity-Modulated Radiation Therapy Using a Contralateral Esophagus-Sparing Technique in Treating Patients with Locally Advanced Non-small Cell Lung Cancer or Limited-Stage Small Cell Lung Cancer	I	TREATMENT	Closed to Accrual
NCT02402920	M D Anderson Cancer Center	Pembrolizumab and Concurrent Chemoradiotherapy or Radiation Therapy in Treating Patients with Small Cell Lung Cancer	I	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02414672	Baylor College of Medicine/Dan L Duncan Comprehensive Cancer Center	CareSTEPS in Improving Quality of Life in Caregivers and Participants with Stage IIIB-IV Non-small Cell Lung Cancer or Extensive Stage Small Cell Lung Cancer	NA	SUPPORTIVE_CARE	Active
	Baylor College of Medicine/Dan L Duncan Comprehensive Cancer Center	NextSTEPS in Improving Quality of Life in Participants with Stage IIIA, IIIB, or IV Non-small Cell Lung Cancer, Extensive Stage Small Cell Lung Cancer, Stage IVB-IVC Head and Neck Cancer, or Stage IV Gastrointestinal Cancer and Their Caregivers	NA	SUPPORTIVE_CARE	Active
NCT02446704	Dana-Farber Harvard Cancer Center	Olaparib and Temozolomide in Treating Patients with Recurrent Small Cell Lung Cancer	I_II	TREATMENT	Active
NCT02454972	PharmaMar SA	Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors	II	TREATMENT	Closed to Accrual
NCT02484404	National Cancer Institute	Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers	I_II	TREATMENT	Active
NCT02487095	National Cancer Institute	Trial of Topotecan With VX-970, an ATR Kinase Inhibitor, in Small Cell Cancers Amd Extrapulmonary Small Cell Cancers	I_II	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02498613	Yale University Cancer Center LAO	A Phase 2 Study of Cediranib in Combination with Olaparib in Advanced Solid Tumors	II	TREATMENT	Active
NCT02500914	Stemcentrx	SC-002 in Small Cell Lung Cancer and Large Cell Neuroendocrine Carcinoma	I	TREATMENT	Administratively Complete
NCT02511795	AstraZeneca Pharmaceuticals LP	AZD1775 Combined with Olaparib in Patients With Refractory Solid Tumors	I	TREATMENT	Closed to Accrual
NCT02514447	G1 Therapeutics, Inc.	Trilaciclib (G1T28), a CDK 4/6 Inhibitor, in Patients with Previously Treated Extensive Stage SCLC Receiving Topotecan Chemotherapy	I_II	TREATMENT	Closed to Accrual
NCT02528942	University of Colorado Hospital	4DCT Ventilation Imaging in Radiation Treatment Planning in Patients with Lung Cancer	NA	DIAGNOSTIC	Active
NCT02538666	Bristol-Myers Squibb	An Investigational Immuno-Therapy Study of Nivolumab, or Nivolumab in Combination with Ipilimumab, or Placebo in Patients With Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) After Completion of Platinum-based Chemotherapy	III	TREATMENT	Closed to Accrual
NCT02554812	Pfizer	A Study of Avelumab In Combination with other Cancer Immunotherapies in Advanced Malignancies (JAVELIN Medley)	II	TREATMENT	Active
NCT02561234	Aeglea Biotherapeutics	A Multiple Dose, Dose Escalation Trial of AEB1102 in Patients with Advanced Solid Tumors	I	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02566993	PharmaMar SA	Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) Versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer	III	TREATMENT	Closed to Accrual
NCT02579226	AstraZeneca Pharmaceuticals LP	A Phase I Study of Safety, Tolerability, and PK of AZD2811 in Patients with Advanced Solid Tumors.	I	TREATMENT	Active
NCT02589522	Mayo Clinic Cancer Center LAO	VX-970 and Whole Brain Radiation Therapy in Treating Patients with Brain Metastases from Non-small Cell Lung Cancer, Small Cell Lung Cancer, or Neuroendocrine Tumors	I	TREATMENT	Active
NCT02611024	PharmaMar SA	Pharmacokinetic Study of PM01183 in Combination with Irinotecan in Patients with Selected Solid Tumors	I	TREATMENT	Active
NCT02614456	Fox Chase Cancer Center	Interferon Gamma-1b and Nivolumab in Treating Patients with Metastatic Solid Tumors	I	TREATMENT	Complete
NCT02628067	Merck and Company Inc	Study of Pembrolizumab (MK-3475) in Participants with Advanced Solid Tumors (MK-3475-158/KEYNOTE-158)	II	TREATMENT	Active
NCT02635009	NRG Oncology	Whole-Brain Radiation Therapy with or without Hippocampal Avoidance in Treating Patients with Limited Stage or Extensive Stage Small Cell Lung Cancer	II_III	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02660034	BeiGene	The Safety, Pharmacokinetics and Antitumor Activity of BGB-A317 in Combination With BGB-290 in Subjects with Advanced Solid Tumors	I	TREATMENT	Active
NCT02701400	Emory University Hospital/Winship Cancer Institute	Tremelimumab and Durvalumab with or without Radiation Therapy in Treating Patients with Relapsed Small Cell Lung Cancer	II	TREATMENT	Active
NCT02712905	Incyte Corporation	An Open-Label, Dose-Escalation/Dose-Expansion Safety Study of INCB059872 in Subjects with Advanced Malignancies	I_II	TREATMENT	Active
NCT02734004	AstraZeneca Pharmaceuticals LP	A Phase I/II Study of MEDI4736 in Combination with Olaparib in Patients with Advanced Solid Tumors.	I_II	TREATMENT	Active
NCT02735980	Eli Lilly and Company	A Study of Prexasertib (LY2606368) in Participants with Extensive Stage Disease Small Cell Lung Cancer	II	TREATMENT	Closed to Accrual
NCT02763579	Hoffmann-La Roche	A Study of Carboplatin Plus Etoposide with or Without Atezolizumab in Participants With Untreated Extensive-Stage (ES) Small Cell Lung Cancer (SCLC)	III	TREATMENT	Closed to Accrual
NCT02769832	University of Iowa/Holden Comprehensive Cancer Center	Nab-Paclitaxel and Gemcitabine Hydrochloride in Treating Patients with Relapsed or Progressive Small Cell Lung Cancer after First-Line Therapy	II	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02769962	National Cancer Institute	Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People with Relapsed/Refractory Small Cell Lung Cancer	I_II	TREATMENT	Active
NCT02819999	Stemcentrx	A Study of Rovalpituzumab Tesirine (SC16LD6.5) in the Frontline Treatment of Patients with Delta-Like Protein 3-Expressing Extensive Stage Small Cell Lung Cancer	I	TREATMENT	Closed to Accrual
NCT02859415	National Cancer Institute	Continuous 24h Intravenous Infusion of Mithramycin, an Inhibitor of Cancer Stem Cell Signaling, in People with Primary Thoracic Malignancies or Carcinomas, Sarcomas or Germ Cell Neoplasms with Pleuropulmonary Metastases	I_II	TREATMENT	Temporarily Closed to Accrual
NCT02874664	Stemcentrx	A Study of Rovalpituzumab Tesirine to Study Cardiac Ventricular Repolarization in Subjects with Small Cell Lung Cancer	I	TREATMENT	Complete
NCT02899728	Laura and Isaac Perlmutter Cancer Center at NYU Langone EDDOP	Olaparib, Cediranib Maleate, and Standard Chemotherapy in Treating Patients with Small Cell Lung Cancer	II	TREATMENT	Temporarily Closed to Accrual
NCT02934503	Laura and Isaac Perlmutter Cancer Center at NYU Langone	Pembrolizumab in Treating Patients with Extensive-Stage Small Cell Lung Cancer	II	TREATMENT	Closed to Accrual

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT02936323	Tarveda Therapeutics	PEN-221 in Somatostatin Receptor 2 Expressing Advanced Cancers Including Neuroendocrine and Small Cell Lung Cancers	I_II	TREATMENT	Active
NCT02937402	Vanderbilt University/Ingram Cancer Center	Bronchoscopy with Bronchoalveolar Lavage in Identifying Biomarkers of Response to Immune Checkpoint Inhibitors in Patients with Non-small Cell or Small Cell Lung Cancer	NA	DIAGNOSTIC	Active
NCT02963090	Alliance Foundation Trials, LLC.	Pembrolizumab vs Topotecan in Patients with Small Cell Lung Cancer	II	TREATMENT	Closed to Accrual
NCT03000257	Abbvie	A Study of ABBV-181 in Participants with Advanced Solid Tumors	I	TREATMENT	Active
NCT03026166	Abbvie	A Study of Rovalpituzumab Tesirine Administered in Combination with Nivolumab and With or Without Ipilimumab for Adults with Extensive-Stage Small Cell Lung Cancer	I	TREATMENT	Closed to Accrual
NCT03033511	Abbvie	A Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First- Line Platinum-Based Chemotherapy in Participants with Extensive Stage Small Cell Lung Cancer (MERU)	III	TREATMENT	Active
NCT03041311	G1 Therapeutics, Inc.	Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28), a CDK 4/6 Inhibitor, in Extensive Stage Small Cell Lung Cancer (SCLC)	II	TREATMENT	Closed to Accrual

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03043599	Moffitt Cancer Center	Ipilimumab, Nivolumab, and Thoracic Radiation Therapy in Treating Patients with Extensive-Stage Small Cell Lung Cancer after Chemotherapy	I_II	TREATMENT	Temporarily Closed to Accrual
NCT03043872	AstraZeneca Pharmaceuticals LP	Durvalumab ± Tremelimumab in Combination with Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer (CASPIAN)	III	TREATMENT	Closed to Accrual
NCT03061812	Abbvie	Study Comparing Rovalpituzumab Tesirine Versus Topotecan in Subjects with Advanced or Metastatic Small Cell Lung Cancer with High Levels of Delta-like Protein 3 (DLL3) and Who Have First Disease Progression During or Following Front-line Platinum-based Chemotherapy (TAHOE)	III	TREATMENT	Closed to Accrual
NCT03066778	Merck and Company Inc	A Study of Pembrolizumab (MK-3475) in Combination with Etoposide/Platinum (Cisplatin or Carboplatin) for Participants with Extensive Stage Small Cell Lung Cancer (MK-3475-604/KEYNOTE-604)	III	TREATMENT	Closed to Accrual
NCT03076372	Merrimack Pharmaceuticals	A Study Evaluating MM-310 in Patients with Solid Tumors	I	TREATMENT	Active
NCT03085849	NYP/Columbia University Medical Center/Herbert Irving Comprehensive Cancer Center	Guadecitabine, Durvalumab, and Tremelimumab in Treating Patients with Extensive-Stage Small Cell Lung Cancer	I	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03088813	Ipsen	Study of Irinotecan Liposome Injection (ONIVYDE®) in Patients with Small Cell Lung Cancer	II_III	TREATMENT	Active
NCT03089125	Dana-Farber Harvard Cancer Center	Behavioral Intervention in Improving Breathlessness in Patients with Advanced Lung Cancer	NA	SUPPORTIVE_CARE	Active
NCT03098030	United Therapeutics	Dinutuximab and Irinotecan Versus Irinotecan to Treat Subjects with Relapsed or Refractory Small Cell Lung Cancer	II_III	TREATMENT	Closed to Accrual
NCT03107663	ImaginAb Inc	^{89}Zr-Df-IAB22M2C PET/CT in Patients with Selected Solid Malignancies or Hodgkin's Lymphoma	I	DIAGNOSTIC	Complete
NCT03121287	University of Michigan Comprehensive Cancer Center	Early Imaging Biomarkers in Predicting Radiation-Induced Cardiopulmonary Toxicity in Patients with Lung or Esophageal Cancer	NA	DIAGNOSTIC	Closed to Accrual
NCT03146117	Medical University of South Carolina	PET-DECT in Imaging for Staging and Treatment Planning in Patients with Small Cell or Non-small Cell Lung Cancer	NA	DIAGNOSTIC	Closed to Accrual
NCT03150810	BeiGene USA, Inc.	Study to Assess Safety, Tolerability and Clinical Activity of BGB-290 in Combination with Temozolomide (TMZ) in Subjects With Locally Advanced or Metastatic Solid Tumors	I_II	TREATMENT	Active
NCT03154190	Stanford Cancer Institute Palo Alto	Health Care Coach Support in Reducing Acute Care Use and Cost in Patients with Cancer	NA	HEALTH_SERVICES_RESEARCH	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03220100	Dana-Farber Harvard Cancer Center	Stepped Palliative Care in Improving Quality of Life in Patients with Advanced Lung Cancer	NA	SUPPORTIVE_CARE	Complete
NCT03228667	Altor BioScience	QUILT-3.055: A Study of ALT-803 in Combination With PD-1/PD-L1 Checkpoint Inhibitor in Patients with Advanced Cancer	II	TREATMENT	Active
NCT03297424	Plexxikon Inc	A Study of PLX2853 in Advanced Malignancies.	I_II	TREATMENT	Active
NCT03313778	Moderna Therapeutics	Safety, Tolerability, and Immunogenicity of mRNA-4157 Alone in Subjects with Resected Solid Tumors and in Combination With Pembrolizumab in Subjects With Unresectable Solid Tumors	I	TREATMENT	Active
NCT03315065	Duke University Medical Center	19F MRI in Assessing Lung Function in Patients with Lung Cancer Undergoing Radiotherapy	I	DIAGNOSTIC	Active
NCT03319459	Fate Therapeutics	FATE-NK100 as Monotherapy and in Combination with Monoclonal Antibody in Subjects With Advanced Solid Tumors	I	TREATMENT	Active
NCT03319940	Amgen, Inc.	Study Evaluating Safety, Tolerability and PK of AMG 757 in Adults with Small Cell Lung Cancer	I	TREATMENT	Active

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NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03325816	MedStar Georgetown University Hospital	Nivolumab and Lutetium Lu 177-DOTA-TATE in Treating Patients with Relapsed or Refractory Extensive-Stage Small Cell Lung Cancer or Grade I-II Lung Neuroendocrine Tumors That Are Advanced or Cannot Be Removed by Surgery	I_II	TREATMENT	Active
NCT03334487	Abbvie	Study Evaluating the Safety of Rovalpituzumab Tesirine for Third-Line and Later Treatment of Subjects With Relapsed or Refractory Small Cell Lung Cancer	III	TREATMENT	Withdrawn
NCT03337399	Dana-Farber Harvard Cancer Center	Stepped Palliative Care or Early Integrated Palliative Care in Improving Quality of Life in Patients with Advanced Lung Cancer	NA	SUPPORTIVE _CARE	Active
NCT03345485	Mundipharma-EDO GmbH	Study of the Safety, Pharmacokinetics and Efficacy of EDO-S101, in Patients with Advanced Solid Tumors	I_II	TREATMENT	Active
NCT03361228	Incyte Corporation	A Study to Evaluate the Safety, Tolerability, and Antitumor Activity of INCB001158 Plus Epacadostat, With or Without Pembrolizumab, in Advanced Solid Tumors	I_II	TREATMENT	Closed to Accrual
NCT03365791	Novartis Pharmaceuticals Corporation	PDR001 Plus LAG525 for Patients with Advanced Solid and Hematologic Malignancies	II	TREATMENT	Closed to Accrual
NCT03366103	JHU Sidney Kimmel Comprehensive Cancer Center LAO	Navitoclax and Vistusertib in Treating Patients with Relapsed Small Cell Lung Cancer and Other Solid Tumors	I_II	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03371979	Aeglea Biotherapeutics	Pegzilarginase and Pembrolizumab for Extensive Disease Small Cell Lung Cancer	I_II	TREATMENT	Active
NCT03382561	ECOG-ACRIN Cancer Research Group	Cisplatin/Carboplatin and Etoposide with or without Nivolumab in Treating Patients with Extensive Stage Small Cell Lung Cancer	II	TREATMENT	Closed to Accrual
NCT03391362	Dana-Farber Harvard Cancer Center	Stereotactic Radiosurgery in Treating Patients with Small Cell Cancer and 1-6 Brain Metastases	II	TREATMENT	Active
NCT03392064	Amgen, Inc.	A Phase 1 Study Evaluating the Safety, Tolerability and Efficacy of AMG 119 in Subjects with RR SCLC	I	TREATMENT	Active
NCT03406715	Moffitt Cancer Center	Ipilimumab, Nivolumab, and Ad.p53-DC in Treating Participants with Relapsed Small Cell Lung Cancer	II	TREATMENT	Active
NCT03416582	University of Miami Miller School of Medicine-Sylvester Cancer Center	Feasibility Study of a Nurse Intervention to Impact Mucositis Severity and Prevent Dehydration	NA	SUPPORTIVE_CARE	Active
NCT03460977	Pfizer	PF-06821497 Treatment of Relapsed/Refractory SCLC, Castration Resistant Prostate Cancer, and Follicular Lymphoma	I	TREATMENT	Active
NCT03488472	University of Alabama at Birmingham Cancer Center	Stereotactic Radiosurgery followed by Tumor Treating Fields Therapy in Treating Participants with Small Cell Lung Cancer with Brain Metastases	NA	TREATMENT	Active
NCT03508752	UT Southwestern/Simmons Cancer Center-Dallas	Stereotactic Radiosurgery in Treating Participants with Brain Metastases and Studying Their Neurocognitive Decline	I_II	TREATMENT	Active

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Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03509012	AstraZeneca Pharmaceuticals LP	Immunotherapy in Combination with Chemoradiation in Patients With Advanced Solid Tumors	I	TREATMENT	Active
NCT03532880	Memorial Sloan Kettering Cancer Center	Olaparib and Low Dose Radiation Therapy in Treating Patients with Extensive Stage Small Cell Lung Cancer	I	TREATMENT	Active
NCT03538028	Incyte Biosciences International Sàrl	A Safety and Tolerability Study of INCAGN02385 in Select Advanced Malignancies	I	TREATMENT	Active
NCT03554473	National Cancer Institute	M7824 and Topotecan or Temozolomide in Relapsed Small Cell Lung Cancers	I_II	TREATMENT	Active
NCT03568539	Innovent Biologics (Suzhou) Co. Ltd.	IBI308 in Subjects with Advanced/Metastatic Solid Malignancies	I_II	TREATMENT	Active
NCT03583086	Vanderbilt University/Ingram Cancer Center	Nivolumab and Vorolanib in Treating Participants with Non-Small Cell Lung Cancer and Refractory Thoracic Tumors	I_II	TREATMENT	Active
NCT03595059	Abbvie	A Study With ABBV-155 Alone and in Combination with Taxane Therapy in Adults with Relapsed and/or Refractory Solid Tumors	I	TREATMENT	Active
NCT03607682	Vanderbilt University/Ingram Cancer Center	Tumor-Treating Fields Therapy in Preventing Brain Tumors in Participants with Extensive-Stage Small Cell Lung Cancer	NA	PREVENTION	Active
NCT03639194	Abbvie	A Study of SC-011 Alone and in Combination With ABBV-181 in Subjects with Relapsed or Refractory Small Cell Lung Cancer	I	TREATMENT	Active

Appendix 3
Open NCI-Supported SCLC Clinical Trials as of March 2019

NCT Number	Lead Organization	Title	Phase	Primary Purpose	Current Trial Status
NCT03662074	Wake Forest University Health Sciences	Second Line Gemcitabine and Nivolumab in Treating Participants with Metastatic Small Cell Lung Cancer	II	TREATMENT	Active
NCT03672773	UCLA / Jonsson Comprehensive Cancer Center	Talazoparib and Low-Dose Temozolomide in Treating Participants with Relapsed or Refractory Extensive-Stage Small Cell Lung Cancer	II	TREATMENT	Active
NCT03694249	Vanderbilt University/Ingram Cancer Center	Ifetroban in Treating Patients with Malignant Solid Tumors at High Risk of Metastatic Recurrence	II	TREATMENT	Active
NCT03703297	AstraZeneca Pharmaceuticals LP	Study of Durvalumab + Tremelimumab, Durvalumab, and Placebo in Stage I-III Limited Disease Small-Cell Lung Cancer in Patients Who Have Not Progressed Following Concurrent Chemoradiation Therapy	III	TREATMENT	Active
NCT03728361	Ohio State University Comprehensive Cancer Center	Nivolumab and Temozolomide in Treating Patients with Recurrent or Refractory Small-Cell Lung Cancer or Advanced Neuroendocrine Cancer	II	TREATMENT	Active
NCT03750864	The University of Arizona Medical Center-University Campus	Acceptance and Commitment Therapy in Helping Patients with Lung Cancer Cope with Lung Cancer Stigma	NA	SUPPORTIVE_CARE	Active

Appendix 4
Funded Project Summary FY2018

Extramural Grants

Project Number	Principal Investigators	Title	Institution
1F30CA232475-01	GRUNBLATT, ELI	Role of MYC Family Members in Driving Chemoresistance in Small Cell Lung Cancer	UNIVERSITY OF WASHINGTON
5F31CA206346-03	CRISTEA, SANDRA	Investigating the Role of the Mek5-Erk5 Kinase Module in Small Cell Lung Cancer	STANFORD UNIVERSITY
1F31CA225119-01	KOYEN, ALLYSON	Elucidating and Targeting EZH2 in the DNA Damage Response in Small Cell Lung Cancer	EMORY UNIVERSITY
5F99CA223015-02	MOLLAOGLU, GURKAN	Identifying Genetic Drivers of the Immunosuppressive Tumor Microenvironment in Lung Cancer	UNIVERSITY OF UTAH
1F99CA234942-01	RUSSELL, SHONAGH	Understanding metabolic vulnerabilities in cancer and the impact the tumor microenvironment has on cancer progression.	UNIVERSITY OF SOUTH FLORIDA
5K08CA222657-02	OSER, MATTHEW GILBERT	New Therapeutic Targets in Small Cell Lung Cancer that are Epistatic or Synthetic Lethal with pRB Loss	DANA-FARBER CANCER INST
5K08HL129081-03	KUO, CHRISTIN SUCHENG	Genetic and Molecular Dissection of Pulmonary Neuroendocrine (NE) Cell Development	STANFORD UNIVERSITY
2P30CA043703-28 (8085)	LETTERIO, JOHN JAMES	Developmental Therapeutics Research Program	CASE WESTERN RESERVE UNIVERSITY
5R01CA181449-04	MACPHERSON, DAVID	Interrogation of MLL2 as a tumor suppressor gene in lung cancer	FRED HUTCHINSON CANCER RESEARCH CENTER

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Project Number	Principal Investigators	Title	Institution
5R01CA194461-04	PARK, KWON-SIK	(PQ4A) Metabolic Plasticity of Pre-Malignant Cells During Tumor Progression	UNIVERSITY OF VIRGINIA
5R01CA194470-04	JANES, KEVIN A	(PQB4) Stochastic Profiling of Functional Single-Cell States Within Solid Tumors	UNIVERSITY OF VIRGINIA
5R01CA197936-03	RUDIN, CHARLES M	Determinants of acquired resistance in small cell lung cancer	SLOAN-KETTERING INST CAN RESEARCH
5R01CA200547-02	MACPHERSON, DAVID	Investigating CREBBP as a tumor suppressor in small cell lung cancer	FRED HUTCHINSON CANCER RESEARCH CENTER
5R01CA200905-02	DENG, XINGMING	Modulation of BAK in Lung Cancer Therapeutics	EMORY UNIVERSITY
5R01CA201513-03	SAGE, JULIEN	Notch signaling in small cell lung carcinoma	STANFORD UNIVERSITY
5R01CA202956-03	WISNIVESKY, JUAN P (contact); KONG, CHUNG	Optimizing Treatment of Lung Cancer Patients with Comorbidities	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
5R01CA206540-03	SAGE, JULIEN	Molecular and cellular mechanisms of SCLC metastasis	STANFORD UNIVERSITY
5R01CA207295-03	BYERS, LAUREN AVERETT	Therapeutic strategies for targeting PARP1 in small cell lung cancer	UNIVERSITY OF TX MD ANDERSON CAN CTR
5R01CA211095-02	BENEVOLENSKAYA, ELIZAVETA V	Role of KDM5A in pRB-mediated differentiation	UNIVERSITY OF ILLINOIS AT CHICAGO
5R01CA213448-02	POIRIER, JOHN THOMAS (contact); LEWIS, JASON S; RUDIN, CHARLES M	Immuno-PET imaging of high-grade neuroendocrine lung tumors using 89Zr-rovalpituzumab, a DLL3-targeting monoclonal antibody	SLOAN-KETTERING INST CAN RESEARCH

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Project Number	Principal Investigators	Title	Institution
1R01CA218545-01A1	NASSER, MOHD WASIM	Novel approach to attenuate small cell lung cancer growth and metastasis	UNIVERSITY OF NEBRASKA MEDICAL CENTER
5R03CA215777-02	PARK, KWON-SIK	Engineered precancerous cells and tissues for discovery of lung cancer drivers	UNIVERSITY OF VIRGINIA
1R21CA216504-01A1	OLIVER, TRUDY GALE	Identifying Therapeutic Vulnerabilities of c-MYC-driven Small Cell Lung Cancer	UNIVERSITY OF UTAH
5R21CA218778-02	SINHA, SUBARNA (contact); SAMBUCETTI, LIDIA C	Discovery of Predictive Biomarkers for Cancer Therapies using Synthetic Lethality	SRI INTERNATIONAL
5R21CA218787-02	HAURA, ERIC B	Applying Chemical Biology to Target Deubiquitinating Enzymes in Lung Cancer	H. LEE MOFFITT CANCER CTR & RES INST
1R21CA226322-01	DOWLATI, AFSHIN	Identification and Targeting of Chemotherapy Refractory Small Cell Lung Cancer	CASE WESTERN RESERVE UNIVERSITY
5R35CA210068-03	KAELIN, WILLIAM G	New Paradigms for Targeting Truncal Driver Mutations	DANA-FARBER CANCER INST
5U01CA209414-02	CHRISTIANI, DAVID C	The Boston Lung Cancer Survival Cohort	HARVARD SCHOOL OF PUBLIC HEALTH
5U01CA213273-02	HEYMACH, JOHN V (contact); BYERS, LAUREN AVERETT; SAGE, JULIEN	Novel therapeutic approaches for enhancing anti-tumor immunity in SCLC	UNIVERSITY OF TX MD ANDERSON CAN CTR
5U01CA213285-02	HANASH, SAMIR M	Development of Risk and Early Detection Biomarker for Small Cell Lung Cancer	UNIVERSITY OF TX MD ANDERSON CAN CTR
5U01CA213330-02	NANA-SINKAM, SERGE P (contact); LEE, LY JAMES	Extracellular Vesicles in Small Cell Lung Cancer Early Detection	VIRGINIA COMMONWEALTH UNIVERSITY

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Project Number	Principal Investigators	Title	Institution
5U01CA213333-02	WONG, KWOK KIN (contact); GRAY, NATHANAEL SCHIANDER	Targeting the transcriptional and epigenetic landscape in chemo-refractory Small-Cell Lung Cancer	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
5U01CA213338-02	MINNA, JOHN D	Developing ASCL1 and NeuroD1 lineage oncogene targeted therapy for small cell lung cancer	UT SOUTHWESTERN MEDICAL CENTER
5U01CA213359-02	POIRIER, JOHN THOMAS	Preclinical development of a DLL3-targeted theranostic for small cell lung cancer	SLOAN-KETTERING INST CAN RESEARCH
5U01CA215845-02	QUARANTA, VITO (contact); LOPEZ, CARLOS FEDERICO	Phenotype Transitions in Small Cell Lung Cancer	VANDERBILT UNIVERSITY
1U01CA220323-01A1	DYSON, NICHOLAS J (contact); FARAGO, ANNA FLORA	Using patient-derived models to understand drug responses in SCLC	MASSACHUSETTS GENERAL HOSPITAL
1U01CA224276-01A1	WEAVER, ALISSA M (contact); LOVLY, CHRISTINE M; SAGE, JULIEN	Phenotype Interactions in SCLC Development and Detection	VANDERBILT UNIVERSITY
1U01CA224293-01A1	PARK, KWON-SIK	Targeting BCAT1 and branched-chain amino acid metabolism for the detection and prevention of SCLC	UNIVERSITY OF VIRGINIA
1U01CA224326-01	VARMUS, HAROLD E	Studies of the initiation and progression of small cell lung cancer using cells derived by differentiation from human pluripotent stem cells	WEILL MEDICAL COLL OF CORNELL UNIV
1U01CA231776-01	MARCHIONNI, LUIGI (contact); HANN, CHRISTINE L; TRAN, PHUOC T	Bioinformatic-Chemical Approach to Credential Molecular Targets to Combat Rapid Chemo-Radiation Resistance in SCLC	JOHNS HOPKINS UNIVERSITY

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Project Number	Principal Investigators	Title	Institution
1U01CA231844-01	GOVINDAN, RAMASWAMY (contact); GRIFFITH, OBI L; OLIVER, TRUDY GALE	Genomic and Functional Identification of Chemotherapy Resistance Mechanisms in Small Cell Lung Cancer	WASHINGTON UNIVERSITY
1U01CA231851-01	KRASNOW, MARK A	Molecular mechanisms of SCLC initiation and detection in mice and humans	STANFORD UNIVERSITY
1U01CA233074-01	WITTE, OWEN N (contact); CROOKS, GAY M; XING, YI	Targeting alternative splicing for TCR discovery in small cell carcinomas	UNIVERSITY OF CALIFORNIA LOS ANGELES
5U24CA213274-02	RUDIN, CHARLES M	Coordinating center for the NCI small cell lung cancer research consortium	SLOAN-KETTERING INST CAN RESEARCH
1U2CCA233284-01 (8209)	IACOBUZIO-DONAHUE, CHRISTINE A	Biospecimen Acquisition, Processing and Classification Unit	SLOAN-KETTERING INST CAN RESEARCH
1U54CA217450-01A1	QUARANTA, VITO	Phenotype Heterogeneity and Dynamics in SCLC	VANDERBILT UNIVERSITY

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Intramural Projects

Project Number	Principal Investigators	Title
1ZIABC011787-02	CHEN, HAOBIN	Predictive biomarker of BET bromodomain inhibitor in Small cell lung cancer
1ZICBC011820-01	REINHOLD, WILLIAM	DNA methylation data development and for small cell lung cancer
1ZIABC011793-01	THOMAS, ANISH	Exploiting DNA Replicative Stress for Novel Small Cell Lung Cancer Therapies
1ZIABC011839-01	CHEN, HAOBIN	Developing an Effective BET bromodomain inhibitor Drug Combo to Target SCLC
1ZIABC011672-03	GUHA, UDAYAN	Clinical Protocols in the Cancer Signaling Networks Section
1ZIDBC011540-05	HASSAN, RAFFIT	Thoracic and Gastrointestinal Malignancies Branch Clinical Core

Appendix 5
Summary of Research Gaps and Opportunities

RESEARCH GAPS

- Role of transcription, epigenetics, and metabolomics in SCLC
- Cells of origin and relevant cell lineages involved in SCLC initiation and progression
- Microenvironment factors, including immune cells and inflammatory processes
- Tumor heterogeneity
- Mechanisms of metastasis
- Molecular drivers of resistance

RESEARCH OPPORTUNITIES

BIOLOGY AND GENETICS/GENOMICS

- Cell-of-origin studies
- Molecular characterization of late stage disease, metastases, pre- and post-therapy, and exceptional responders
- Investigations of the SCLC transcriptome, epigenome, and metabolome

MODELS

- Models for newly identified subsets of SCLC and of conversion from adenocarcinoma to SCLC
- Preclinical models specific to therapeutic targets and development of resistance, including models for testing of immunotherapy approaches
- Models for smoking-related damage to tissues and DNA

PREVENTION/SCREENING/DIAGNOSIS

- Improvements in imaging modalities to detect early SCLC
- ctDNA to detect or monitor development of SCLC
- Molecularly-targeted imaging agents for detection and/or response assessment

THERAPY AND RESISTANCE

- New approaches to clinical trials for SCLC
- A clearer understanding of both the potential and limitations of immunotherapy in SCLC
- Studies focused on understanding the unique features of SCLC that could be used to develop new therapeutics
- Identification of new molecular vulnerabilities that could be used to develop targeted agents
- Investigations into potential mechanisms of response and resistance
- Longitudinal studies that track and study the evolution of ctDNAs in patients
- A standard set of PROs for SCLC trials
- Address the deleterious effects of PCI
- Methods to improve palliative and supportive care including optimization of pain management and end-of-life care