DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
23rd CLINICAL TRIALS AND TRANSLATIONAL RESEARCH
ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
June 18, 2014

WEBINAR
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
WEBINAR

Summary of Meeting
June 18, 2014

The 23rd meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held by webinar on Wednesday, June 18, 2014, at 4:00 p.m. The CTAC Chair, Dr. James L. Abbruzzese, Chief, Division of Medical Oncology; Associate Director, Clinical Research, Department of Medicine, Duke Cancer Institute, Duke University Medical Center, presided. The meeting adjourned at 5:07 p.m.

Chair
James L. Abbruzzese, Chair

CTAC Members
Susan G. Arbuck
Monica M. Bertagnolli
Curt I. Civin (absent)
Kevin J. Cullen
Nancy E. Davidson (absent)
J. Phillip Kuebler
Michael LeBlanc (ad hoc)
Scott M. Lippman (absent)
Mary S. McCabe
Edith P. Mitchell
Nikhil C. Munshi
Lisa A. Newman (absent)
Nancy Roach
Peter G. Shields
George W. Sledge, Jr.
Chris H. Takimoto
Gillian M. Thomas (absent)
Frank M. Torti (absent)
Miguel A. Villalona-Calero
George J. Weiner (absent)

Ex Officio Members
James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, CMS
Lee J. Helman, NCI (absent)
Michael J. Kelley, VA
Richard Pazdur, FDA (absent)
Alan S. Rabson, NCI (absent)

Executive Secretary
Sheila A. Prindiville, NCI
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I. WELCOME AND OPENING REMARKS—DR. JAMES L. ABBRUZZESE

Dr. Sheila A. Frindiville, Director, Coordinating Center for Clinical Trials, NCI and Executive Secretary of the CTAC, called roll and confirmed that a quorum of CTAC members was present.

Dr. Abbruzzese called the 23rd meeting of the CTAC to order and welcomed participants to the meeting. He also welcomed the co-chairs of the CTAC Small Cell Lung Cancer (SCLC) Working Group, Dr. Charles M. Rudin, Chief, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center (MSKCC) and Professor, Weill Cornell Medical Center as well as Dr. John D. Minna, Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research, Hamon Center for Therapeutic Oncology, University of Texas Southwestern Medical Center. Dr. Abbruzzese noted that the purpose of the meeting was to review and accept the report from the CTAC SCLC Working Group and that the webinar was open to the public and was being recorded.

Dr. Abbruzzese reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Frindiville within 10 days of the meeting.

II. REPORT OF THE SMALL CELL LUNG CANCER (SCLC) WORKING GROUP—DR. CHARLES M. RUDIN

Dr. Rudin presented the CTAC SCLC Working Group Report, which is available at http://ideainfo.nci.nih.gov/advisory/ctac/0614/SCLCworkshopReport.pdf. NCI formed this Working Group in response to the Recalcitrant Cancer Research Act of 2012 (H.R. 733). The Working Group’s mission was to identify key scientific areas in order to identify where focused research could have the greatest impact. Dr. Rudin commented that SCLC is a recalcitrant cancer in critical need of more effective therapies. He noted that he had previously reported on the scientific deliberations of the Working Group at the November 6, 2013, CTAC meeting, which are available at http://ideainfo.nci.nih.gov/advisory/ctac/1113/index.htm. In addition to the five research recommendations outlined below, Dr. Rudin noted the importance of attracting new investigators to the study of SCLC through the use of targeted funding opportunities as well as through interactions and collaborations with scientific associations, such as the International Association for the Study of Lung Cancer (IASLC).

Dr. Rudin’s presentation focused on the following five recommendations made by the Working Group:

1. 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 (conditionally reprogrammed cell lines, patient-derived xenografts [PDXs], and genetically-engineered mouse models) that reflect the phases of SCLC found in the clinic;
(2) 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) Investigate new diagnostic approaches for populations at high risk of developing SCLC;

(4) Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC (tumor suppressor genes, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy);

(5) 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 completion of treatment.

Dr. Minna commented on the fact that the recommendations for SCLC will likely be applicable to the biology of other cancers.

III. NCI's Implementation Plan for the SCLC Working Group Report—Dr. James Doroshow

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, NCI, explained that NCI will use the CTAC SCLC Working Group Report to develop a scientific framework for research on SCLC. A report to Congress, due in July 2014, will incorporate the Working Group’s report as well as NCI’s plans to implement the following initiatives in response to the Working Group’s report:

To build better research tools to study SCLC (which addresses Recommendation 1), NCI will support infrastructure for SCLC specimen collection over the next 3 years. Specifically, NCI will

- fund collaborative projects across NCI’s research networks to expand the generation of PDXs and conditionally-reprogrammed cell lines and

- obtain specimens from biopsies of SCLC patients enrolled in clinical trials or for whom detailed clinical information is available.

Over the next 3 to 5 years, NCI’s Center for Cancer Genomics will characterize the genetic and molecular features of the SCLC specimens that have been collected in The Cancer Genome Atlas (TCGA) project at diagnosis and relapse in order to comprise a comprehensive genomic profiling of SCLC, which addresses Recommendation 2.

In an effort to address Recommendation 3, NCI will issue a Program Announcement to support studies focused on discovering early molecular changes in histologically normal lung, blood (including circulating DNA) as well as other relevant tissues that could be applied to subsequent screening studies in high risk populations.

In terms of therapeutic efforts, specifically related to initial response and eventual resistance, NCI will issue a Program Announcement to support studies focused on the following areas of research that could be developed to identify molecular vulnerabilities of SCLC that could be used to develop target
agent combinations as well as the high rate of initial response and rapid development of clinical resistance to drug and radiation therapy.

NCI will establish the SCLC Action Planning Group (comprised of extramural experts and NCI staff), support a scientific workshop in 2015 in conjunction with the IASLC, and report implementation progress publicly to the CTAC at least annually beginning in 2015.

IV. Discussion—Dr. James Abbruzzese

[A note relates to a public comment is included on page 6.]

Following Drs. Doroshow’s and Rudin’s presentations, Dr. Abbruzzese asked about practical considerations for tissue acquisition given that surgery isn’t a large part of treatment for SCLC and that patients are often treated, at least initially, at community sites. Dr. Rudin responded that because molecular profiling has become standard of care for many types of lung cancer, obtaining a sufficient amount of biopsy tissue will become easier, including samples from repeat biopsies at disease progression. Nevertheless, a dedicated, focused effort will be needed. It may also be possible to use samples from blood or serum such as circulating tumor cells (CTCs) and cell free DNA.

Dr. Edith P. Mitchell, Clinical Professor of Medicine and Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University noted that community physicians take care of most SCLC patients. They should be engaged in the effort to collect clinical samples. Dr. Rudin added that centralized tissue management would facilitate access to samples by investigators. Dr. Minna commented on the fact that this could be an opportunity for academic sites and Cancer Centers to partner with community oncologists and that access to these samples is critical to the work on the mechanism of resistance.

Dr. J. Phillip Kuebler, Principal Investigator, Columbus Community Clinical Oncology Program (CCOP), Columbus Oncology Associates, Inc. related his site’s experience. The Columbus CCOP has partnered with an academic site by sending patients there for a second opinion, which includes providing clinical samples to the academic site. Because patients return to the CCOP for treatment following their evaluation, it was noted that this approach is beneficial for both sites.

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, applauded NCI’s use of initiatives like this one and the RAS initiative. She encouraged targeting other diseases as a way to move them forward cohesively. Dr. Doroshow responded that each disease has its own scientific opportunities and barriers, which must be addressed by a different mix of expert-recommended preclinical and clinical activities. For example in SCLC, new models are needed, as noted in the Working Group’s report.

Dr. Miguel A. Villalona-Calero, Division Director, Medical Oncology, The Ohio State University suggested that NCI investigate a rapid autopsy Initiative. Similar to organ donation, cancer patients or their relatives could be approached, at an appropriate time, regarding an autopsy for research use. Increasing the supply of tissue from patients with multi-site metastatic disease would allow insight into the diversity of disease. This could be applied across many kinds of cancer.

Dr. Minna justified the use of repeat biopsies in the context of a research protocol. A mutation might be found that could affect a patient’s subsequent treatment. Given the expected results from novel studies such as breaking immune tolerance, mouse models, and new genomics, there likely will be a host of mutations discovered. As is being seen in non-small cell lung cancer, targeted treatment trials with
enrollment biomarkers provide ethical justification for obtaining tissue. Needle and core biopsies, CTCs and cell free DNA produce sufficient material for study.

A motion to accept the CTAC SCLC Working Group’s report was made, seconded and passed unanimously.

V. Wrap Up—Dr. James Abbruzzese

Dr. Abbruzzese asked that participants send comments on their webinar experience to Dr. Prindiville.

Dr. Abbruzzese reminded everyone that the next CTAC meeting is scheduled for July 16 from 11 a.m. to 1 p.m. and will be held via webinar. The main agenda item is a presentation of the CTAC NCI National Clinical Trials Network (NCTN) Working Group’s final report, which will be presented by Dr. George Sledge.

VI. ADJOURNMENT—DR. JAMES L. ABBRUZZESE

There being no further business, the 23rd meeting of the CTAC was adjourned at 5:07 p.m. on Wednesday, June 16, 2014.

\[7/16/14\]  
James L. Abbruzzese, M.D., Chair

\[7/16/14\]  
Sheila A. Prindiville, M.D., M.P.H., Executive Secretary
Addendum - Public comment

Dr. David Shames, a Senior Scientist at Genentech Inc., noted that biopsies are justified in non-small cell lung cancer. Now that there are active agents for this disease, and a clear cost-benefit ratio, there is less concern about biopsies. In contrast, in SCLC, there are no active treatments with which to justify biopsies. He also mentioned the fact that he didn’t see any plans for a treatment study to justify tissue collection.
Report to NCI CTAC:
Small Cell Lung Cancer Working Group

Charles Rudin MD PhD
John Minna MD
Annual US cancer deaths

Annual deaths (US)

Cancer type

- Non-small cell lung
- Colon & Rectum
- Breast
- Pancreatic
- Prostate
- Small cell lung
- Non-Hodgkin Lymphoma
- Liver & Intrahepatic Biliary
- Ovarian
- Gastric
- Bladder
- Kidney
- Brain
- Myeloma
- Acute Myeloid Leukemia
- Melanoma
Small cell lung cancer: a recalcitrant cancer in need of novel approaches

• Affects ~30,000 Americans each year
• Exceptionally high case fatality rate
  – Overall 5 year survival under 7%
  – Median survivals
    • Extensive stage: ~ 9-11 months from diagnosis
    • Limited stage: ~ 18 months from diagnosis
• Essential initial treatment paradigms unchanged over the past 30 years
  – Cisplatin + etoposide, with radiation for limited stage
  – No defined approach to early detection/prevention
• There is a critical need for more effective therapy for this disease
• Recalcitrant Cancer Research Act of 2012 (HR 733)
  – Charges NCI to develop scientific frameworks that will assist in making progress against recalcitrant or deadly cancers

• Goals of the workshop
  – Identify key scientific opportunities and critical areas where focused research could have greatest impact on SCLC:
    • Prevention
    • Detection
    • Disease outcome
  – Report to CTAC on findings and recommendations
    • to inform NCI in development of a scientific framework for SCLC
NCI SCLC Workshop – sessions

• Emerging opportunities in omics, molecular pathology, and early detection
  – Chairs: Steve Baylin and Eric Haura
  – Speakers: Linnoila, Wistuba, Thomas, Byers, Poirier

• Emerging opportunities in preclinical models and targeting cancer stem cells
  – Chairs: Anton Berns and Tyler Jacks
  – Speakers: Peacock, McFadden, Jahchan, Berns, Ball, White

• Emerging opportunities in therapeutics and new drug targets
  – Chairs: Bruce Johnson and Joan Schiller
  – Speakers: Teicher, Krug, Pietanza, Hann, Dylla

• Attracting investigators to the field of small cell lung cancer
  – Chair: Paul Bunn

• Summary and recommendations
  – Chairs: John Minna and Charles Rudin
Current approaches – risk assessment and screening

• *Strongly* associated with tobacco use
  – Other predisposing factors (genetic/environmental) not determined

• No defined screening approach
  – No validated blood or tissue biomarkers
  – CT screening by the NCI-sponsored National Lung Cancer Screening Trial (NLST)
    • 125 SCLC detected (out of ~54,000 screened over 3 years)
    • No apparent impact on SCLC stage distribution or clinical outcome
      – 86% extensive stage at diagnosis

Metastatic dissemination and/or therapeutic resistance develop early in SCLC
Current approaches – diagnosis, staging, monitoring

• Diagnosis most often by fine needle aspirate
  – Histologic confirmation, with IHC for neuroendocrine markers

• Staging and monitoring
  – Hx, physical, labs (LDH)
  – Imaging
    • Body CT with infusion, brain MRI
    • FDG-PET has high sensitivity and specificity in SCLC
  – Functional staging still predominantly used for clinical research
    • Limited v. Extensive stage: “limited” confined to one hemithorax; encompassed within a radiation port
Current approaches – therapy and resistance

• Limited stage
  – Platinum/etoposide with concomitant radiation
  – BID radiation preferred; PCI for patients with good response

• Extensive stage
  – Platinum/etoposide (alternative: platinum/irinotecan)
  – PCI considered for patients with good response

• Recurrent disease
  – Topotecan is the only FDA-approved therapy for recurrent disease
    • Only effective in chemosensitive relapse (progression > 60-90 days after completion of first line therapy)
  – Several other regimens have efficacy
    • Temozolomide, CAV, and others

• Clinical research
  – ~ 100 interventional studies in ClinicalTrials.gov since 12/2007
  – ~ 1/3 with NCI support
Recent scientific advances and emerging research questions

- Characterization of the SCLC genome, transcriptome, and epigenome
- Analysis of acquired chemotherapy resistance in SCLC
- \textit{TP53} and \textit{RB} as gatekeeper mutations in SCLC
- \textit{MYC} family members in SCLC
- Developmental and stem cell signaling pathways in SCLC
#1. Characterization of the SCLC genome / transcriptome

- 2 comprehensive genomics papers in 2012 defined aspects of the genomic landscape of SCLC
  - *Rudin et al.* 35 primary tumors and 28 cell lines
  - *Peifer et al.* 29 primary tumors
  - These provide needed insight into the genomic landscape of SCLC
  - For tumors of this complexity, this N is not sufficient

Non-synonymous mutation rate 5.5/Mb

175 mutations per tumor
Commonly mutated genes in SCLC – predominance of tumor suppressors

Peifer et al., Nat Genet 2012
Emerging research questions

• What are critical drivers beyond \(TP_{53}\) and \(RB\) loss?

• Are there relevant molecularly defined subsets?
  – Distinct clinical outcomes
  – Distinct therapeutic vulnerabilities

• Are there molecular differences between primary and metastatic disease?

• Can drivers of metastasis be specifically targeted?
One of the exceptional features of SCLC is its initial responsiveness to therapy

- 70% RR for extensive stage disease
- Higher for limited with radiation

These responses are remarkably short-lived, with rapid development of acquired resistance.

The basis for this shift from *de novo* chemosensitivity to subsequent chemoresistance is almost entirely unstudied.

- Lack of repeat biopsies
SCLC – chemosensitivity but poor outcome

- **Response**: May be largely determined by behavior of the (large) *chemosensitive* cell population
- **Survival**: May be determined primarily by behavior of the (small) *chemoresistant* cell population

**Implications:**
- New anticancer agents that kill more of the same chemosensitive population may not lead to further improvement in survival
- Analysis of the properties of the small chemoresistant population may be informative

Rudin et al., *JNCCN*, 2008
Emerging research questions

• What are molecular differences between *de novo* and recurrent SCLC?
  – Are the changes in recurrent SCLC distinct from those in primary refractory SCLC?

• Are mechanisms of acquired resistance targetable with existing drugs?

• To what extent can the mechanisms of acquired resistance be phenocopied in animal models of SCLC?
#3. **TP53** and **RB** as gatekeeper mutations in SCLC

- Essentially all SCLC are characterized by concomitant loss of these two key tumor suppressor genes.
- Mouse models in which these 2 genes are deleted in lung epithelial cells results in a cancer closely resembling SCLC.
- The biology of the interaction between these 2 signature events has not been extensively studied.
  - Does this create unique tumor cell vulnerabilities?

Emerging research questions

• What effects do joint loss of $TP_53$ and $RB$ have on signaling circuitry of the cell?
  – Distinct from loss of either single gene

• Does concurrent loss of these 2 genes result in unique vulnerabilities in SCLC?
  – Can these vulnerabilities be targeted by existing or novel drugs?
#4. MYC family members in SCLC

- **MYC, MYCL1, and MYCN** are amplified and/or overexpressed in SCLC
- A recurrent fusion transcript **RFL-MYCL1** was found in genomic profiling of SCLC
  - In a primary SCLC and cell lines
  - **MYCL1** siRNA suppresses proliferation

Romero et al., *Cancer Discov* 2014
Emerging research questions

• Could a reinvigorated effort focused on inhibition of MYC family members create novel therapeutics?

• Are there common dependencies among MYC-driven tumors?

• Could MYC targeting lead to durable responses in SCLC?
• SCLC is a highly clonogenic tumor characterized by early and widespread metastasis

• Multiple developmental regulatory pathways that may influence clonogenic capacity have been implicated in SCLC biology
  – ASCL1/Notch
  – Hedgehog
    • The first clinical trial of a HH inhibitor in SCLC was negative
  – SOX2

• Might these represent unique targets of vulnerability in SCLC?
Emerging research questions

• In which clinical context(s) would targeting embryonic signaling pathways have the most impact?

• How should such strategies be integrated with standard approaches?
  – Cytotoxic chemotherapy
  – Radiation
  – Surgery
Recommended initiative #1. Develop better research tools for the study of SCLC

- Optimize tumor tissue collection of SCLC
  - Research protocols
    - Controlled standardized biopsy approaches
    - Distinct phases of the disease progression
    - Standardized banking, molecular profiling, xenografting

- Develop new SCLC models
  - Novel approaches to cell line generation
  - PDX and blood-based xenografting (CDX)
  - Novel approaches in genetically engineered mouse models
    - Greater genetic heterogeneity
    - Chemosensitive and chemoresistant pairs
    - Effects of tobacco smoke extract
    - Models of metastasis
Recommended initiative #2. Focused and comprehensive genomic profiling

- Larger and homogeneously defined collections of tumors
  - Patients on clinical trials
  - Genomic, epigenetic, transcriptomic and proteomic analyses
- Comparative analyses within individuals and unique populations
  - Paired \textit{de novo} chemosensitive and recurrent chemoresistant disease
  - Paired primary and metastatic sites
  - Focused analysis of “outliers” with long-term survival
  - Familial studies
Recommended initiative #3. Develop new diagnostic approaches

• Analysis of molecular steps in SCLC oncogenesis
  – Molecular analyses of histologically normal peritumoral epithelium

• Development of non-invasive biomarker approaches
  – CTC
  – cfDNA
  – Breath condensate
  – Quantitative and functional imaging approaches

• Support for clinical trials of these approaches in patients and in populations at risk
  – Primary and secondary detection
Recommended initiative #4. Facilitate novel therapeutic development efforts

• Targeting $TP_{53}/RB$ loss
  – Synthetic lethality studies, functional restoration approaches

• Targeting $MYC$, $ASCL{1}$, and other developmental regulators
  – Support renewed efforts to target these critical dependencies

• Assessment of novel immunotherapy strategies
  – Checkpoint inhibitors
  – Therapeutic vaccines
  – Defining biomarkers of immunotherapy response
  – Defining mechanisms of escape from immune surveillance
Recommended initiative #5. Define mechanisms of rapid response and acquired resistance in SCLC

• Analysis of the exceptional initial sensitivity of SCLC to platinum-based therapy
• Focused studies to elucidate molecular mechanisms of resistance
  – Genetic and epigenetic evolution of drug resistance in patients, and in relevant preclinical models
• Studies are predicated on enhanced, targeted sample collection
And finally... Attracting investigators to the field

• Barriers include:
  – lack of historical progress
  – relative paucity of available tumor tissue

• Strategies for NCI to consider:
  – Dedicated funding opportunities for SCLC
  – Organize cross-institutional tissue acquisition and utilization
  – Collaboration with IASLC and others to support dedicated SCLC research conferences
Dr. Minna and I wish to thank

The NCI leadership for the opportunity to coordinate this initiative

The workshop participants for their dedicated time and effort

Colleagues and friends who have made key contributions

Patients and advocates for active engagement in promoting research
Small Cell Lung Cancer

Seizing on Opportunities to Translate Recent Research into the Clinic for New Diagnostics and Interventions

The Small Cell Lung Cancer Working Group

Clinical Trials and Translational Research Advisory Committee

June 2014
Organization of the Report

A. The Workshop

(1) Origin of the Workshop

(2) Overview of the Workshop Program

B. Current Approaches to SCLC

(1) Risk Assessment and Screening

(2) Diagnosis, Staging and Monitoring

(3) Therapy and Resistance

C. Recent Scientific Advances and Emerging Research Questions

(1) Characterization of the SCLC Genome, Transcriptome, and Epigenome

(2) Analysis of Acquired Chemotherapy Resistance in SCLC

(3) TP53 and RB as Gatekeeper Mutations in SCLC

(4) MYC Family Members in SCLC

(5) Developmental and Stem Cell Signaling Pathways in SCLC

D. Attracting Investigators to the Field of SCLC

E. Recommended Initiatives

(1) Develop Better Research Tools for the Study of SCLC
(A) Optimize Collections of Tumor Tissues

(B) Develop New SCLC Models.

(2) Assemble Comprehensive Genomic Profiling for SCLC

(3) Develop New Diagnostic Approaches

(4) Facilitate Therapeutic Development Efforts

(5) Understand Mechanisms Underlying Both the High Initial Rate of Response and the Rapid Emergence of Drug and Radiation Resistance

F. Summary

G. References

H. List of Abbreviations
A. The Workshop

(1) Origin of the Workshop

The Recalcitrant Cancer Research Act of 2012 (H.R. 733) requires the National Cancer Institute (NCI) to “develop scientific frameworks” that will assist in making “progress against recalcitrant or deadly cancers.” Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than 7 percent and the loss of approximately 30,000 lives per year. The NCI convened a group of experts in the field of SCLC for a workshop held in Bethesda, Maryland on July 8-9, 2013 to evaluate research opportunities that could improve the scientific understanding and medical control of SCLC. The group, chaired by Drs. John Minna and Charles Rudin, included laboratory scientists, medical oncologists, surgeons, radiation oncologists, pathologists, biostatisticians, patient advocates, and NCI staff (see Addendum 1 – SCLC Working Group Roster).

The goals of the workshop were to identify key scientific opportunities and critical areas where focused research efforts could have the greatest impact on prevention, detection, or disease outcome for patients with SCLC. Workshop participants were asked to discuss recent advances in "omics", molecular pathology, and the prospects for early detection of SCLC; key developments in animal models for SCLC; and putative new drug targets and other areas of vulnerability of SCLC that may lead to new therapeutic approaches.

The findings and recommendations arising from the workshop are to be discussed with the NCI’s Clinical Trials and Translational Research Advisory Committee (CTAC) and to
inform the NCI in the development of a scientific framework for SCLC in accordance with the Recalcitrant Cancer Research Act of 2012.

(2) Overview of the Workshop Program

The workshop agenda topics included three thematic scientific sessions, a special session focused on attracting investigators to SCLC research, and a series of smaller breakout sessions designed to identify top research priorities and opportunities related to each of the three scientific sessions. A final session summarized the outcomes of the breakout sessions and prioritized recommendations. (See Addendum 2 – SCLC Workshop Agenda)

The first session focused on emerging opportunities in “omics”, molecular pathology, and early detection for SCLC. In a series of presentations and discussions, workshop participants reviewed the classification of neuroendocrine lung cancer molecular pathology and epidemiology, focusing on approaches to molecular characterization and early pathogenesis of putative precursor lesions of SCLC; current data and gaps in knowledge about the SCLC genome and transcriptome, with emphasis on known and suspected driver oncogenes and tumor suppressors\(^1\)\(^2\); recent and ongoing studies of the SCLC proteome, including potential therapeutic targets identified through this approach\(^3\); and new data on the SCLC epigenome, defining additional putative targets for intervention\(^4\).

The second session addressed emerging opportunities in preclinical models and on targeting cancer stem cells in SCLC. Workshop participants reviewed and discussed patient-derived xenograft (PDX) models as a platform for enhancing the biological
understanding of SCLC and for therapeutic testing⁵; recent and ongoing genomic studies of genetically engineered mouse models (GEMMs) of SCLC⁶-⁸; recent and ongoing studies using SCLC GEMMs as a platform for defining putative cells of origin for SCLC; developmental signaling pathways in SCLC; and a relatively unbiased approach to identifying critical oncogenic drivers in lung cancer through the use of synthetic lethal siRNA/shRNA screens.

The third session focused on emerging therapeutic opportunities, and new drug targets. Workshop participants discussed an ongoing study at the NCI Frederick National Laboratory assessing the relative activity of 103 oncology drugs and 420 investigational compounds of interest against a panel of approximately 60 SCLC cell lines characterized by genomic and gene expression profiles; recent studies and novel opportunities for immunotherapy in SCLC, including vaccine approaches as well as agents targeting immune checkpoints⁹; and recent clinical data using temozolomide both as a single agent¹⁰ and with a poly-(ADP-ribose)-polymerase (PARP) inhibitor¹¹. Finally, promising opportunities for targeting Bcl-2 in SCLC¹² were discussed.

In addition to the three scientific sessions, a fourth session focused on the scientific workforce in the field of SCLC. The group discussed barriers to entry to the field, noting that despite the relatively high incidence of SCLC, a relatively small number of scientists and clinicians are attracted to the study of this disease. A number of ideas were proposed to attract both new and established investigators to the study of SCLC.

This was followed by individual breakout sessions during which workshop participants proposed specific recommendations to address scientific opportunities that had been
identified during the aforementioned discussions. On the second day of the workshop, the entire group was reconvened to summarize the outcomes of the breakout sessions and prioritize a final set of recommendations.

B. Current Approaches to SCLC

Clinical approaches to SCLC have not advanced significantly in three decades. Although the focus of the workshop was on the identification of critical scientific advances and the prioritization of research opportunities, the current standard of care provides a necessary backdrop to the group's findings and is described in brief in this section.

(1) Risk Assessment and Screening

Although SCLC is, in most cases, a disease associated with tobacco use, little is known about predisposing genetic or non-genetic factors that lead to the development of the disease in certain current or former smokers but not in others. Somatic mutations accumulate during the lifetime of an individual exposed to the carcinogens in tobacco smoke. There is a need for further study of the germline (i.e., heritable) traits that contribute to the development of SCLC as well as the interactions between environmental exposures and individual inherited predispositions to SCLC.

Screening for SCLC is also a challenge. There are currently no validated biomarkers that can be measured in blood or other tissues to detect SCLC at an early stage. Furthermore, the recent NCI-sponsored National Lung Screening Trial\cite{13-15} that proved
the value of screening individuals at high risk of developing lung cancer with low-dose helical computed tomography (CT) also demonstrated that screening did not improve survival for the subset of SCLC patients detected by CT screening, unlike those with adenocarcinoma or squamous cell cancer of the lung. The majority of patients with SCLC detected by CT screening (86% of the 125 patients) were diagnosed with advanced stage disease, similar to the percent seen in the absence of dedicated screening. Consistent with this distribution of stages, subsequent therapy did not evidently prolong the survival of screened patients. These results suggest that metastatic dissemination and/or resistance to systemic therapy may develop early in the natural history of SCLC.

(2) Diagnosis, Staging, and Monitoring

The diagnosis of SCLC, whether the patient is symptomatic or not, usually begins with histologic confirmation of an abnormality detected on imaging studies, typically by fine needle aspirate biopsy. Immunohistochemical evaluation employing a variety of neuroendocrine or other markers confirms the diagnosis of SCLC. Medical history, physical examination, routine laboratory tests, and computed tomographic scans of the chest and abdomen with infusion of contrast material, and magnetic resonance imaging of the brain complete the initial evaluation. For patients without evidence of disease outside one hemithorax on these studies, $^{18}$Fluoro-deoxyglucose positron emission tomography (PET) is useful for optimal staging, and can detect bone metastases. Staging for patients with SCLC is most commonly categorized using the Veterans Administration Lung Study Group system; limited-stage disease (LD), which occurs in approximately one third of patients, is defined as SCLC confined to the hemithorax of
origin, the mediastinum, or the supraclavicular nodes, which can be encompassed within a tolerable radiation therapy port. Extensive-stage disease (ED) SCLC has spread beyond the supraclavicular areas and is too widespread to be included within the definition of LD. Patients with distant metastases by definition have ED\textsuperscript{16}.

Monitoring of response to therapy is usually performed by imaging techniques capable of providing accurate measurements of tumor size; these size measurements are interpreted by Response Evaluation Criteria In Solid Tumors (RECIST) criteria that define categories of response to treatment\textsuperscript{16}. PET staging now approaches a 100% level of sensitivity and greater than 90% specificity\textsuperscript{17-20}. The use of PET scanning to both stage and follow the effect of treatment for patients with SCLC has enhanced the accuracy by which the effectiveness of new treatment modalities can be examined.

(3) Therapy and Resistance

Current therapeutic approaches for SCLC are of modest long-term benefit despite the exceptionally good response to first-line therapy. Treatment for LD includes a standard first line chemotherapy regimen\textsuperscript{21,22} with concomitant radiation that can be encompassed in a single radiation port\textsuperscript{23,24}. Treatment for ED includes the same chemotherapy options, without concomitant radiation\textsuperscript{22}. In some instances, particularly for small peripheral lung nodules, surgery can also be considered\textsuperscript{25}.

Treatment programs for SCLC have changed little over the past three decades; the most important advances have improved the precision of radiation therapy and have introduced better supportive care measures, such as more effective antiemetic regimens. The generally accepted standard for first-line systemic therapy, etoposide
combined with either cisplatin or carboplatin, has been in use since the early 1980s\textsuperscript{23,26-28}. An alternative first-line chemotherapy regimen, cisplatin and irinotecan, appeared to be superior in a Phase III study conducted in Japan\textsuperscript{29}, but these results could not be confirmed in subsequent US comparative trials\textsuperscript{22}. SCLC is an unusually chemosensitive and radiosensitive disease, at least initially, resulting in objective response rates of 60 to 80\% in patients without substantive co-morbid conditions. However, essentially all patients with ED, and most patients with LD, experience disease progression within months of completing first-line therapy. A recent genome-wide association study suggested that germline genetic variations may affect resistance to irinotecan, and thus may be associated with decreased overall survival of SCLC patients treated with chemotherapy\textsuperscript{30}. Certain single nucleotide polymorphisms (SNPs) that were associated with shorter overall survival may affect the expression of transcription factors involved in the epithelial-to-mesenchymal transition, a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties that may be involved in the development of metastases.

There is only one FDA-approved therapy for recurrent SCLC: topotecan, a topoisomerase 1 inhibitor\textsuperscript{31-33}. Recurrent SCLC is substantially less responsive to therapy than primary disease. Response rates for topotecan are approximately 25\% for relapses occurring at least 3 months after completion of first-line therapy, and as low as 3 – 6\% for progressive disease occurring at the time of or shortly after completion of first-line therapy. Objective responses to a third line of chemotherapy are uncommon\textsuperscript{34}. Hence, no consensus has been reached on treatment regimens for patients whose disease has progressed after first- and second-line therapy.
Prophylactic whole brain irradiation, in the absence of detectable brain metastases, is an important component of therapy for most limited stage, and some extensive stage, patients with SCLC. It is typically administered to those individuals who respond well to initial treatment shortly after completion of first-line combined modality therapy, Prophylactic cranial radiation therapy decreases the risk of subsequent, clinically significant brain metastases and improves survival in patients with LD and ED. Approximately 100 SCLC interventional clinical trials have been registered in the ClinicalTrials.gov database since December 2007; about one-third of which are supported by the NCI. These studies include efforts to target the neuroendocrine character of SCLC, its dependence on the (PARP) pathway, and the use of immunological interventions including therapeutic vaccines, antibody radio-immunoconjugates, or checkpoint inhibitors intended to stimulate anti-cancer immune responses.

C. Recent Scientific Advances and Emerging Research Questions

The workshop participants discussed recent advances in SCLC research across many areas including genomics and proteomics, molecular pathology, animal models, cancer stem cells, and new drug targets. A number of critical scientific advances and emerging research questions were defined in the discussion.
(1) Characterization of the SCLC Genome, Transcriptome, and Epigenome

Two recent studies have assessed the genomic landscape of SCLC using next generation sequencing approaches, including full exome sequencing, transcriptome profiling by RNASeq, copy number analyses, and limited whole genome sequencing to identify translocations\(^1,2\). In large part because of its association with smoking, SCLC has one of the highest densities of mutation per tumor\(^1\). Most of the mutations are of the \textit{passenger} type, which means that they do not necessarily contribute to the initiation or progression of the disease. More important are \textit{driver} mutations that directly contribute to carcinogenesis. These two reports confirmed what had been previously proposed in smaller studies, namely that the most prevalent inactivated tumor suppressor genes in SCLC are \textit{TP53} and \textit{RB}\(^{40-42}\). Concomitant inactivation of these tumor suppressors is nearly universal in SCLC. Novel mutations were also found, such as those in genes controlling epigenetic regulators, stem cell genes, as well as other driver mutations within established proto-oncogene and tumor suppressor gene families (including \textit{MYC} family genes, \textit{Bcl-2}, \textit{PTEN}, \textit{CREBBP}, \textit{FGFR1}, \textit{SLIT2}, and \textit{EPHA7}, among others).

The number of primary SCLCs for which data have been reported at the level of full exome sequencing comprises only 82 samples (compared with the baseline number of 500 specimens per disease used in The Cancer Genome Atlas [TCGA] initiative) and is inadequate to characterize the spectrum of potential oncogenic driver mutations in SCLC to include those alterations with a frequency of occurrence below 10\% with statistical significance. To highlight this, \textit{FGFR1} amplification was detected at a rate of 6\% in one study\(^1\), while such alterations were not observed at all in the other\(^2\). Another
limitation of these investigations is that many of the samples analyzed were from surgically resected early stage and chemo-naïve patients, and do not represent the full natural history of the disease with regard to development of metastases and changes induced by therapeutic intervention.

Critical research questions that emerged from these discussions included: What are the critical driver mutations present in SCLC beyond TP53 and RB inactivation? Are there molecularly defined subsets of SCLC with distinct clinical outcomes and distinct therapeutic vulnerabilities? Are there important molecular differences between primary SCLC and metastatic disease? Can drivers of metastasis, the dominant cause of death in SCLC patients, be specifically targeted?

(2) Analysis of Acquired Chemotherapy Resistance in SCLC

SCLCs possess a set of specific biological characteristics. They are often fast growing and rapidly metastatic, initially highly responsive to both chemotherapy and radiation, but often rapidly recurrent, with recurrent disease that is markedly more resistant to therapy\textsuperscript{22}. Recurrent SCLCs are rarely biopsied. Recurrence is expected in SCLC, and repeat biopsy is not known to be useful in guiding decisions regarding second-line therapy. Hence, remarkably little is known, at the molecular level, about the evolution of disease with treatment.

Questions that emerged during discussions of acquired resistance to SCLC therapy included: What are the molecular differences between \textit{de novo} chemosensitive and subsequent chemo-resistant disease? Are these differences distinct from those in patients whose SCLCs are resistant to initial therapy? Are the mechanisms of acquired
resistance targetable using existing drugs? To what extent can the mechanisms of acquired resistance in patients with SCLC be phenocopied in animal models?

(3) **TP53 and RB as Gatekeeper Mutations in SCLC**

One of the major advances in the preclinical modeling of SCLC was the demonstration that targeted disruption of both TP53 and RB led to the development of lung cancer closely resembling human SCLC in a GEMM\(^6\). This model has been subsequently refined and revalidated, and used by a number of groups to investigate critical questions including the molecular heterogeneity of metastases\(^6,43,44\). These models have also been used to explore the biology of SCLC, including cell of origin studies and examinations of the development of metastases in SCLC\(^8\). As described above, recent genomic sequencing studies of SCLC have identified a number of genes of interest that may be important in subsets of SCLC but also reconfirmed that these two critical tumor suppressors, TP53 and RB, were jointly disrupted in the large majority of SCLC.

**Important questions that arose in discussions concerning gatekeeper mutations in SCLC**: What effects do joint loss of TP53 and RB have on the signaling circuitry of the cell, distinct from loss of either single gene? Does concurrent loss of these two genes result in unique vulnerabilities in SCLC (i.e. are there synthetic lethalities associated with their joint disruption)? Can these vulnerabilities be targeted by existing or novel drugs?

(4) **MYC Family Members in SCLC**

Altered MYC signaling in SCLC (like that of TP53 and RB) was originally described many years ago\(^45\). It was confirmed and further refined in recent genomic sequencing
studies of SCLC\(^1\,^2\). New observations included identification of a recurrent in-frame fusion involving \textit{RLF} and \textit{MYCL1} in a primary SCLC tumor and four SCLC cell lines, and that siRNA targeting \textit{MYCL1} in such lines inhibited proliferation\(^2\). In contrast to the tumor suppressors \textit{TP53} and \textit{RB}, \textit{MYC} family members are activated oncogenes in SCLC and other cancers\(^4\). Previous efforts to design specific inhibitors of MYC signaling have been, broadly speaking, disappointing, but many new research tools and approaches are emerging\(^4\).

Questions regarding the role of MYC signaling in SCLC: Could a reinvigorated effort focused on inhibition of MYC family members create novel MYC-directed therapeutics? Are there common dependencies among MYC-driven tumors? Could MYC-targeting lead to durable responses in SCLC?

(5) Developmental and Stem Cell Signaling Pathways in SCLC

SCLC is unusual in that it seems to appear fully formed in the lung epithelium: no defined histologic precursor of SCLC has been described. \textit{ASCL1}-dependent embryonic developmental signaling and Hedgehog stem cell signaling pathways in particular have been implicated in SCLC clonogenic potential\(^4\). Despite disappointing results of a randomized clinical trial of a Hedgehog pathway inhibitor in extensive stage SCLC\(^5\), these pathways continue to be attractive potential targets as are other agents that target SCLC progenitor cells.

Questions regarding developmental signaling in SCLC: In which clinical context would targeting embryonic signaling pathways have the most impact? How should such strategies be optimally integrated with cytotoxic chemotherapy, radiation, and surgery?
D. Attracting Investigators to the Field of SCLC

Despite the frequency of SCLC, few scientists and clinicians are attracted to the study of this disease. Lack of improvement in the clinical course of SCLC over several decades may be a major barrier to attracting and retaining clinical investigators. The difficulties in obtaining sufficient quantities of human tissue for in-depth studies may also have reduced enthusiasm for further investigative efforts in the field.

To attract both new and established investigators to the study of SCLC, the NCI is encouraged to consider: 1) establishing dedicated funding opportunities for SCLC; 2) modifying the grant criteria for the Specialized Programs of Research Excellence (SPOREs) to promote the study of SCLC; 3) forming a Task Force on cross-institutional standardized tissue acquisition, utilization, and sharing; and 4) collaborating with scientific associations such as the International Association to Study Lung Cancer (IASLC) to co-sponsor a meeting dedicated to SCLC in which critical collaborative projects could be proposed and planned. Moreover, making SCLC a higher priority at national lung cancer meetings and workshops could enhance the interest of new investigators to the disease.

E. Recommended Initiatives

In the final session the workshop participants recommended five initiatives for the NCI to consider incorporating within its scientific framework for SCLC:
(1) Develop Better Research Tools for the Study of SCLC

There is a critical need to acquire better biospecimens to enhance the biological understanding of SCLC, as well as mechanisms of drug and radiation sensitivity and resistance. Moreover, the complex biology of SCLC could be understood at greater depth by developing new tumor models that better mirror the human disease.

(A) Optimize Collections of Tumor Tissues

The diagnosis of SCLC is frequently made by cytological examination of biopsy material obtained by fine needle aspiration; repeat biopsies, performed during distinct stages of disease progression, are rarely attempted. The paucity of available biospecimens for this disease is striking, and is a primary barrier to progress in SCLC research. Newer image-guided diagnostic approaches, such as endoscopic bronchial ultrasound-guided core biopsies, can be safely performed and yield substantially more tumor for molecular characterization. The use of these newer biopsy approaches underscores the importance of incorporating specialists in pulmonary medicine, cardiothoracic surgeons, and interventional radiologists (who perform the diagnostic procedures) as active members of the multidisciplinary team of health care professionals who care for patients with SCLC.

Beyond changing standard of care approaches to diagnostics, investigators in the field should be encouraged to implement biopsy protocols to ensure that good quality biospecimens are obtained under optimized conditions for banking, molecular profiling, creating xenografts, and/or cell line derivation. Research protocols to permit well-controlled and standardized repeat biopsies over time (and during the multiple phases
of SCLC disease progression) should also be strongly encouraged. These will provide the tumor tissues with which to answer critical questions about SCLC regarding the range of driver mutations involved, mechanisms of progression, acquired resistance to therapeutics, and factors promoting metastasis.

(B) Develop New SCLC Models

The complex biology of SCLC could be understood at greater depth by developing new tumor models that better mirror the human disease. SCLC cell lines currently used for tissue culture studies have a number of potential deficiencies, including low growth fractions and a tendency to proliferate as multi-cell tumor aggregates, making their use for drug screening difficult. Furthermore, many SCLC lines do not have germline DNA available to permit certain identification somatic mutations, and most SCLC lines have been continuously propagated for years using standard methods that may drastically alter their molecular composition compared with the primary tumors from which they were derived. New techniques, including the development of conditionally reprogrammed tumor cell lines (developed with Rho kinase inhibitors), initiated from small tumor biopsies, offer the possibility of rapid establishment of SCLC cell lines with both germline DNA available and molecular pedigrees much closer to primary tumors51. These models, especially if well-annotated clinically and developed using sequential tumor biopsies from individual patients, could be used to study mechanisms underlying the early evolution of drug resistance, a phenomenon that occurs regularly following initial therapy in patients with SCLC.
In addition to new, clinically-annotated cell lines from patients with SCLC, the need also exists for development of a larger collection of PDX models that have been derived from paired biopsies obtained before combined modality therapy is initiated, and then at the time of disease progression in the same patients. Such models would be of value for understanding mechanisms of both primary and acquired drug resistance.

Current GEMMs have elucidated the cell of origin for SCLC and essential driver mutations for this disease; however, the long latency period required for the development of SCLCs in GEMMs has limited the broad applicability of these models, in particular for drug screening. There is a need to improve such models by: 1) incorporating a greater degree of genetic heterogeneity during their elaboration; 2) producing GEMMs that integrate acquisition of drug resistance into the model development process (which would be useful for screening second line therapies) and, 3) evaluating the effects of tobacco smoke on the carcinogenic process in GEMMs. Recently, other models have been developed that may be suitable to study SCLC metastases. In these systems, newly-developed mouse strains that lack functional B-, T-, and NK cells (Pfp/Rag2 double-knockout) have been used to facilitate the production of mice carrying SCLC xenografts that undergo spontaneous metastases; this model more clearly mirrors the clinical course of SCLC.

(2) Assemble Comprehensive Genomic Profiling

The small number of SCLCs that have been analyzed by exome or whole genome sequencing is inadequate to define the full spectrum and distribution of driver mutations in this disease. Efforts to characterize a much larger set of tumors from patients with
SCLC, particularly from patients entered on clinical trials, for genomic, epigenetic, and transcriptome alterations, should be strongly encouraged. Furthermore, comparative analyses of paired biospecimens from single individuals, obtained from chemo-sensitive and chemo-resistant disease, or from primary and metastatic sites, should permit a more focused description of the driver alterations associated with changes in disease state. A comprehensive molecular analysis of specimens from the small subset of patients with long-term survival from SCLC would also be of substantial interest. Studies of the SCLC genomics should be accompanied by an evaluation of genetic changes in the germline of SCLC patients as well as individuals at high risk of developing SCLC to identify possible heritable predispositions to this disease. Finally, coordination of these complementary efforts with a comprehensive proteomic characterization of SCLC is necessary for the validation of novel diagnostic and therapeutic targets appropriate for intervention.

(3) Develop New Diagnostic Approaches

In view of the need for new approaches to the diagnosis and prevention of SCLC, the unique genetic dependencies that underlie the pathogenesis of SCLC, and the multiple genetic alterations found in the histologically “normal” lung epithelia of patients with SCLC, there is an opportunity to expand understanding of the critical molecular changes in the lung that precede the development of frank SCLC. Assessment of field cancerization in the normal epithelium surrounding tumors is already ongoing in patients with adenocarcinomas of the lung; preliminary data indicate a distinction between a noncancerous smoker’s transcriptome signature and that from a smoker with cancer\(^ {53}\). Further, the failure of spiral CT screening to detect SCLC early enough for successful
intervention has focused attention on the potential to develop early tissue- or blood-based molecular predictors of SCLC; hence, molecular profiling efforts as described above should also include studies of tobacco-exposed but non-malignant lung tissues, including tissues adjacent to SCLCs.

Recent improvements in non-invasive diagnostic techniques that can use circulating tumor cells (CTCs) or DNA from blood to characterize genetic alterations specific for an individual patient’s tumor\textsuperscript{54, 55} suggest that more sensitive screening tests for SCLC, perhaps incorporating assessments of mutant \textit{RB} and \textit{TP53} in CTCs or circulating DNA, are possible. Validation of non-invasive methods to detect early stage SCLC or to more clearly identify molecular risk factors in individuals with a long history of smoking could provide critical insights into the natural history of SCLC. Using another non-invasive technique, preliminary studies indicate that measurement of volatile compounds and DNA abnormalities in the breath of patients with lung cancer may enable early diagnosis\textsuperscript{56}. Establishing the relevance of these tests for the early detection and/or monitoring of SCLC will require validation in prospective clinical studies.

Another opportunity to improve the early detection of SCLC lies in the use of improved quantitative and functional imaging with multi–detector CT, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), and combined PET and CT imaging\textsuperscript{19}. These techniques allow more reliable detection and staging of SCLCs; for example, PET-based staging appears to be superior to conventional staging, and can significantly alter patient management, particularly with regard to the design of radiotherapy fields\textsuperscript{20}. Major advances in the early diagnosis of SCLC may result from complementary
combinations of molecular and imaging tests designed for use in high-risk populations. New studies are needed for individuals at high risk of developing SCLC to ascertain, for example, whether molecular profiling of bronchial epithelial cells or sequencing circulating DNA from blood for the hallmarks of SCLC (such as mutations in \( RB \) or \( TP53 \)) might permit early diagnosis of a pre-invasive stage of small cell neoplasia of the lung.

**(4) Facilitate Therapeutic Development Efforts**

The nearly universal loss of functional \( TP53 \) and \( RB \) tumor suppressor genes is a hallmark of SCLC. GEMMs developed by combined knockout of these tumor suppressor genes effectively mimic the pathologic features of this disease. Research to examine targetable vulnerabilities associated with loss of these two genes could lead to new therapeutic approaches focused on molecular pathways that are altered by the loss of RB and TP53 function. While it is currently not possible to restore the activity of malfunctioning tumor suppressor genes, synthetic lethality approaches could target multiple proteins that these suppressor genes regulate\(^{57,58}\), potentially restoring control of cancer cell growth. An additional experimental approach involves local delivery of tumor suppressor genes via gene therapy\(^{59}\). MYC, ASCL1, and Hedgehog signaling pathways represent other important therapeutic targets in SCLC; preclinical models suggest that SCLCs demonstrate dramatic “addiction” to the function of these pathways. Despite prior difficulties in developing therapies directed against transcription factors such as MYC and ASCL1, renewed efforts to target these critical dependencies in SCLC may be appropriate because of recent advances in chemical biology and drug screening\(^{47}\).
In addition to small molecule therapeutics, new immunotherapy strategies, such as the use of checkpoint inhibitors targeting immune suppressor mechanisms in the tumor microenvironment, as well as therapeutic vaccine approaches, have recently been applied to the treatment of lung cancer\textsuperscript{60, 61}. Recent results from Phase II studies suggest that the human anti-CTLA-4 monoclonal antibody ipilimumab adds to the therapeutic benefit of chemotherapy in SCLC\textsuperscript{62}. An ongoing Phase III clinical trial that compares the etoposide/platinum combination plus or minus ipilimumab will help to define the role of immune suppressors in SCLC patients with extensive disease\textsuperscript{63}; results from this and other studies should be used to broaden the range of therapeutic approaches applicable to patients with SCLC. As part of this it will be important to define the targets of cytotoxic immune responses after breaking tolerance including whether the immune targets include oncopeptide mutations, and also defining mechanisms of escape from such immune surveillance.

(5) Understand Mechanisms Underlying Both High Initial Rate of Relapse and the Rapid Emergence of Drug and Radiation Resistance

Patients with SCLC often respond very well to first-line chemo-radiotherapy; however, disease progression almost invariably occurs within months of achieving an initial remission\textsuperscript{22}. Recurrence is usually characterized by rapidly progressive, treatment-resistant disease. Understanding the mechanisms underlying early therapeutic sensitivity for most SCLC patients and the rapid molecular changes involved in the acquisition of resistance to drug and radiation treatment are critical to improving long-term outcomes. Recent studies suggest that the mechanisms of therapeutic response and resistance to chemo-radiotherapy for SCLCs are pleiotropic, and include: 1) altered
mRNA expression levels of several genes (ERCCI, BRCA1, ATP7B, PKM2, TOPOI, TOPOIIA, TOPOIIB, and C-MYC)\textsuperscript{64}; 2) the expression of certain cancer stem cell markers (CD133) that are associated with the overexpression of mitogenic neuropeptide receptors\textsuperscript{65,66}; 3) elevated levels of DNA repair proteins and/or activation of the PI3K/mTOR pathway\textsuperscript{67}; and 4) overexpression of ATP-binding cassette transporters\textsuperscript{68}, among many. However, definitive studies to elucidate molecular mechanisms of resistance, including the genetic evolution of drug resistance patterns, await the ready availability of clinical SCLC tumor samples obtained before and after treatment, and the development of model systems more reflective of acquired drug and radiation resistance in patients. Until such tumor tissues and models are available, definitive interventions to overcome SCLC resistance, and predictive biomarkers to guide those interventions, will remain difficult to develop. Thus, the development of new approaches to understanding the rapid emergence of drug and radiation resistance in SCLC using new, clinically-annotated SCLC models is of central importance if the outcome for patients with this disease is to be improved.

F. Summary

A workshop of SCLC experts examined the recent advances in risk assessment, screening, diagnosis, staging, monitoring, therapy and resistance of SCLC and identified new scientific opportunities for investigation that have the potential to improve outcome for patients with this disease. Based on an appreciation of the current state of knowledge and standard of clinical care used in SCLC, workshop participants
recommended five research opportunities for expanding NCI’s research programs for SCLC:

(1) Building 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 (conditionally reprogrammed cell lines, patient-derived xenografts, and genetically-engineered mouse models) that reflect the phases of SCLC found in the clinic;

(2) Expanding 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) Investigating new diagnostic approaches for populations at high risk of developing SCLC;

(4) Focusing therapeutic development efforts on specific molecular vulnerabilities of SCLC (tumor suppressor genes, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy);

(5) Examining the mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of treatment.
G. References


H. List of Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
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<td>genetically engineered mouse model</td>
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<td>Response Evaluation Criteria In Solid Tumors</td>
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<td>SNP</td>
<td>single nucleotide polymorphism</td>
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<td>Specialized Programs of Research Excellence</td>
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<td>TCGA</td>
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NCI Workshop on Small Cell Lung Cancer: Seizing on Opportunities to Translate Recent Research into the Clinic for New Diagnostics and Interventions

Dates: Monday, July 8 – Tuesday, July 9, 2013
Place: Natcher Conference Center, NIH Main Campus, Bethesda, MD
General Session Room: E1/E2

Day 1: Monday, July 8, 2013

8:00 – 8:15 AM  Welcome and Charge
Harold Varmus, M.D. and James Doroshow, M.D.
John Minna, M.D. and Charles Rudin, M.D., Ph.D. (Co-Chairs)

8:15-10:15 AM  Session 1: Emerging Opportunities in Omics, Molecular Pathology, and Early Detection

Session Co-Chairs: Stephen Baylin, M.D. and Eric Haura, M.D.

Speakers: Ilona Linnoila, M.D. – Neuroendocrine Lung Cancer Molecular Pathology and Epidemiology
Ignacio Wistuba, M.D. – Molecular Characterization and Early Pathogenesis of SCLC
Roman Thomas, M.D. – SCLC Genome Studies in US and Europe
Lauren Byers, M.D. – Proteomic Analysis of SCLC
John Poirier, Ph.D. – SCLC Epigenome

Roundtable: Denise Aberle, M.D., Ramaswamy Govindan, M.D., David Harpole, M.D, John Heymach, M.D., Ph.D., Paul Hwang, M.D., Ph.D., Matthew Meyerson, M.D., Ph.D., Deborah Morosini, M.D, Rich Simon, D.Sc., Ming Tsao, M.D.

10:15-10:30 AM  Morning Break (on your own)

10:30 AM-12:30 PM  Session 2: Emerging Opportunities in Preclinical Models and Targeting Cancer Stem Cells

Session Co-Chairs: Anton Berns, Ph.D. and Tyler Jacks, Ph.D.

Speakers: Craig Peacock, Ph.D. – Patient Derived Xenograft Models
David McFadden, M.D. – Genome Sequencing of Murine SCLC
Nadine Jahchan, Ph.D. – Study of Murine Models of SCLC
Anton Berns, Ph.D. – Defining Cell of Origin/Cancer Stem Cells for SCLC
Douglas Ball, M.D. – Developmental Signaling Pathways in SCLC
Michael White, Ph.D. – Synthetic Lethal siRNA, shRNA Screens
**Roundtable:** Paul Bunn, M.D., David Carbone, M.D., Ph.D., Jeffrey Engelman, M.D., Andrea Ferris, M.B.A., Adi Gazdar, M.D., William Pao, M.D., Ph.D., David Shames, Ph.D.

12:30-1:30 PM  **Lunch Break (on your own)**

1:30-3:30 PM  **Session 3: Emerging Opportunities in Therapeutics and New Drug Targets**

**Session Co-Chairs:** Bruce Johnson, M.D. and Joan Schiller, M.D.

**Speakers:**
- Beverly Teicher, Ph.D. – *Drug Library Screening*
- Lee Krug, M.D. – *Immunotherapy Strategies in SCLC – Vaccines and Immune Checkpoint Blockade*
- Catherine Pietanza, M.D. – *DNA Damage Repair, PARP, and Temozolomide*
- Christine Hann, M.D. – *Targeting Bcl-2 and mTOR in SCLC*
- Scott Dylla, Ph.D. – *Anti-Stem Cell Targeted Monoclonal Therapy*

**Roundtable:** Eli Glatstein, M.D., Glenwood Goss, M.D., Roy Herbst, M.D., Ph.D., Mark Kris, M.D., Taofeek Owonikoko, M.D., Ph.D., Suresh Ramalingam, M.D., Regina Vidaver, Ph.D., Everett Vokes, M.D.

3:30-3:45 PM  **Afternoon Break (on your own)**

3:45 -4:15 PM  **Special Session: Attracting Investigators to the Field of Small Cell Lung Cancer**

**Session Chair:** Paul Bunn, M.D.

**Roundtable:** Dara Aisner, M.D., Ph.D., Christine Hann, M.D., Roy Herbst, M.D., Ph.D., Nadine Jahchan, Ph.D., Lee Krug, M.D., David McFadden, M.D., William Pao, M.D., Ph.D., David Shames, Ph.D.

4:15-5:30 PM  **Breakout sessions on each of the 3 topics above**
Participants summarizing key opportunities and needs
- **Session 1 Breakout Room:** Room C1/C2
- **Session 2 Breakout Room:** Room D
- **Session 3 Breakout Room:** Room A

5:30-6:30 PM  **Session chairs (only) confer to develop session summaries, slides, outline of report**

6:30 PM  **Adjourn (End of Day One)**
Day 2: Tuesday, July 9, 2013

8:00-8:15 AM  **Review Charge**  
John Minna, M.D. and Charles Rudin, M.D., Ph.D.

8:15 AM-12:00 PM  **Summary and Recommendations**  

**Session Co-Chairs:** John Minna, M.D. and Charles Rudin, M.D., Ph.D.

8:15-9:15 AM  **Emerging Opportunities in Omics, Molecular Pathology, and Early Detection: Recommendations**  
Stephen Baylin, M.D. and Eric Haura, M.D.

9:15-10:15 AM  **Emerging Opportunities in Preclinical Models and Targeting Tumor Stem Cells: Recommendations**  
Anton Berns, Ph.D. and William Pao, M.D., Ph.D.

10:15-11:15 AM  **Emerging Opportunities in Therapeutics and New Drug Targets: Recommendations**  
Bruce Johnson, M.D. and Joan Schiller, M.D.

11:15-12:00 PM  **Summary of Recommendations and Next Steps**  
John Minna, M.D. and Charles Rudin, M.D., Ph.D.

12:00 PM  **Adjourn**
Small Cell Lung Cancer (SCLC) Working Group Report: Next Steps

Presented to CTAC

James H. Doroshow
June 18, 2014
• Working Group report will be included in the SCLC Scientific Framework report submitted to Congress in July

• Congressional report will include:
  – Summary of the literature and recent advances
  – SCLC research supported by NCI
  – Scientific opportunities for SCLC research & plans for implementation of the recommend initiatives (as identified by the SCLC Working Group/Workshop)
Recommendation 1: Better Research Tools for Study of SCLC

- Support infrastructure for SCLC specimen collection over the next 3 years
  - Fund collaborative projects across NCI’s research networks to expand the generation of PDX and conditionally-reprogrammed cell lines
  - Specimens to be obtained from biopsies of SCLC patients enrolled in clinical trials or for whom detailed clinical information is available
Recommendation 2: Comprehensive Genomic Profiling of SCLC

- Characterize the genetic and molecular features of the SCLC specimens that have been collected at diagnosis and relapse over the next 3 to 5 years
Recommendation 3: New Diagnostic Approaches for SCLC

• Issue a Program Announcement in the second half of 2015
• Support studies focused on discovering early molecular changes in histologically normal lung, blood (including circulating DNA), and other relevant tissues that could be applied to subsequent screening studies in high risk populations
Recommendations 4 & 5: Therapeutic Development Efforts

• Issue a Program Announcement in the second half of 2015
• Support studies focused on understanding the unique features of SCLC that could be used to develop new therapeutics
  1) Molecular vulnerabilities that could be used to develop target agent combinations
  2) High rate of initial response and rapid development of clinical resistance to drug and radiation therapy
• **SCLC Action Planning Group**
  – Establish in 2014 to oversee implementation of recommendations
  – Extramural experts and NCI staff

• **Scientific Workshop**
  – International Association of the Study of Lung Cancer (IASLC) workshop in 2015

• **CTAC**
  – Report implementation progress publically to CTAC at least annually beginning in 2015