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
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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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WEDNESDAY, JUNE 18, 2014

I. WELCOME AND OPENING REMARKS—DR. JAMES L. ABBRUZZESE

Dr. Sheila A. Prindiville, 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 23nd 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. Prindiville 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://deainfo.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://deainfo.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 hat 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 publically to the CTAC at least annually beginning in 2015.

IV. Discussion— Dr. James Abbruzzese

[A note related 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.

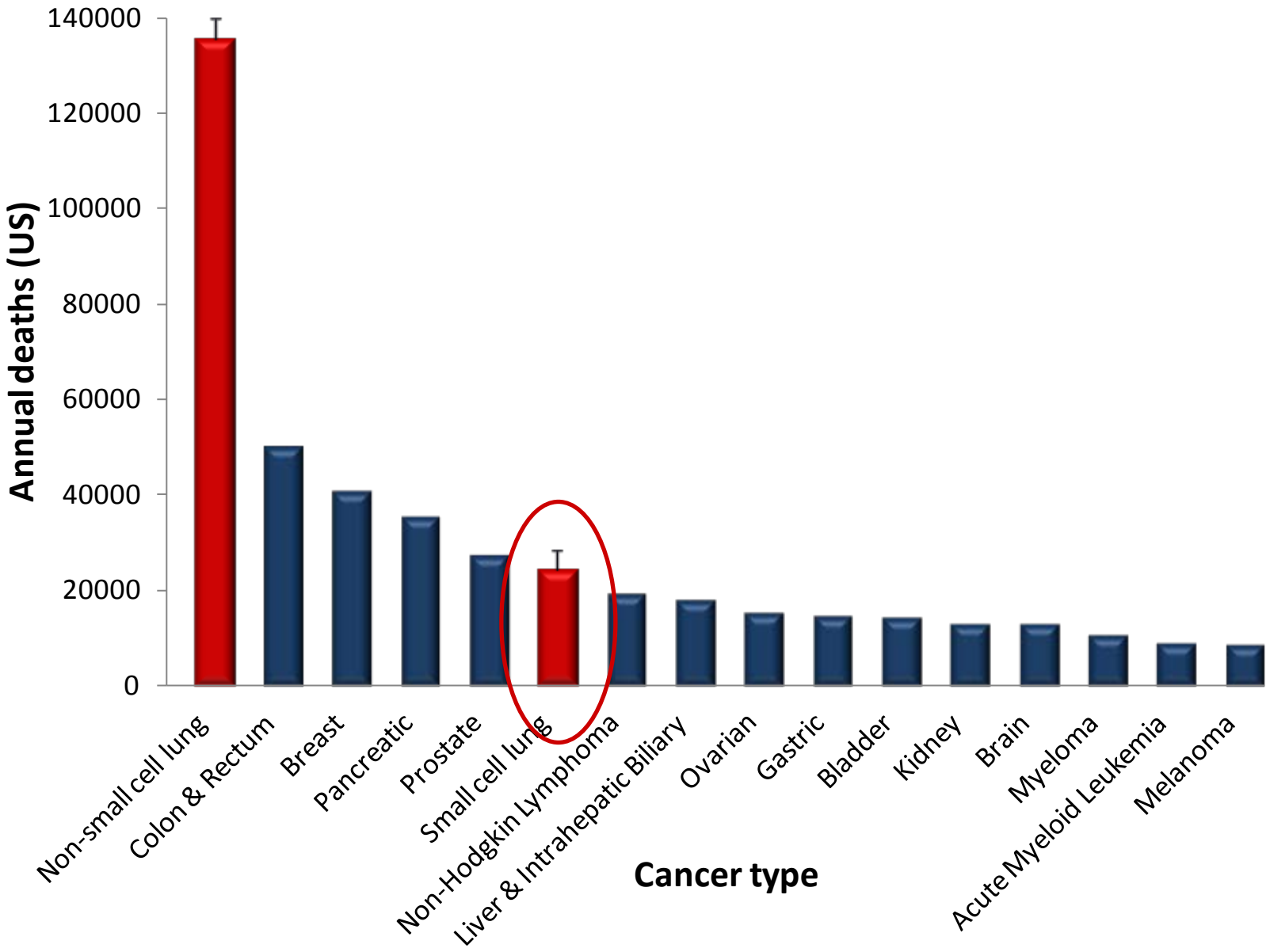
Addendum - Public comment

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



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

NCI Workshop on Small Cell Lung Cancer

July 8 – 9, 2013; Bethesda MD

- 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

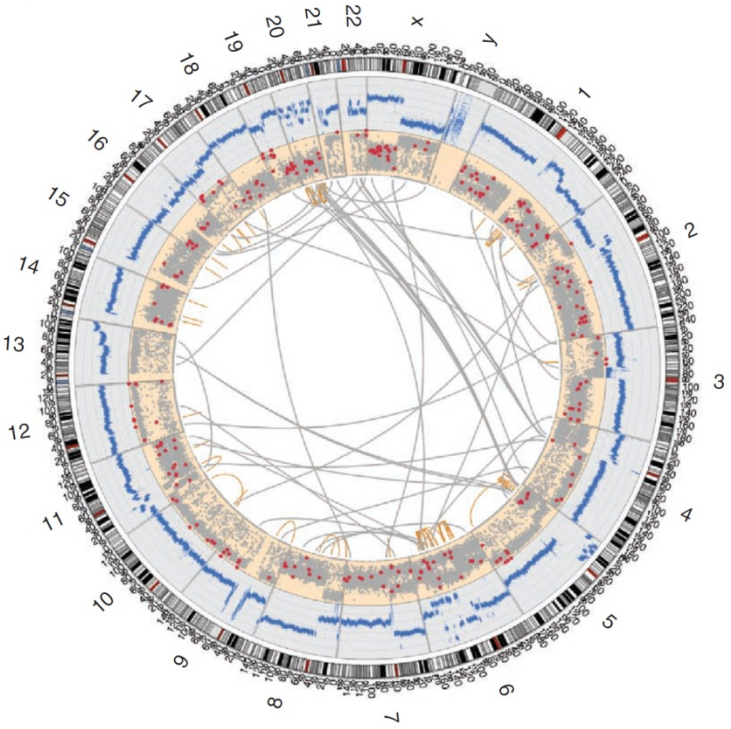
- Characterization of the SCLC genome, transcriptome, and epigenome
- Analysis of acquired chemotherapy resistance in SCLC
- *TP53* and *RB* as gatekeeper mutations in SCLC
- *MYC* family members in SCLC
- Developmental and stem cell signaling pathways in SCLC

#1. Characterization of the SCLC genome / transcriptome

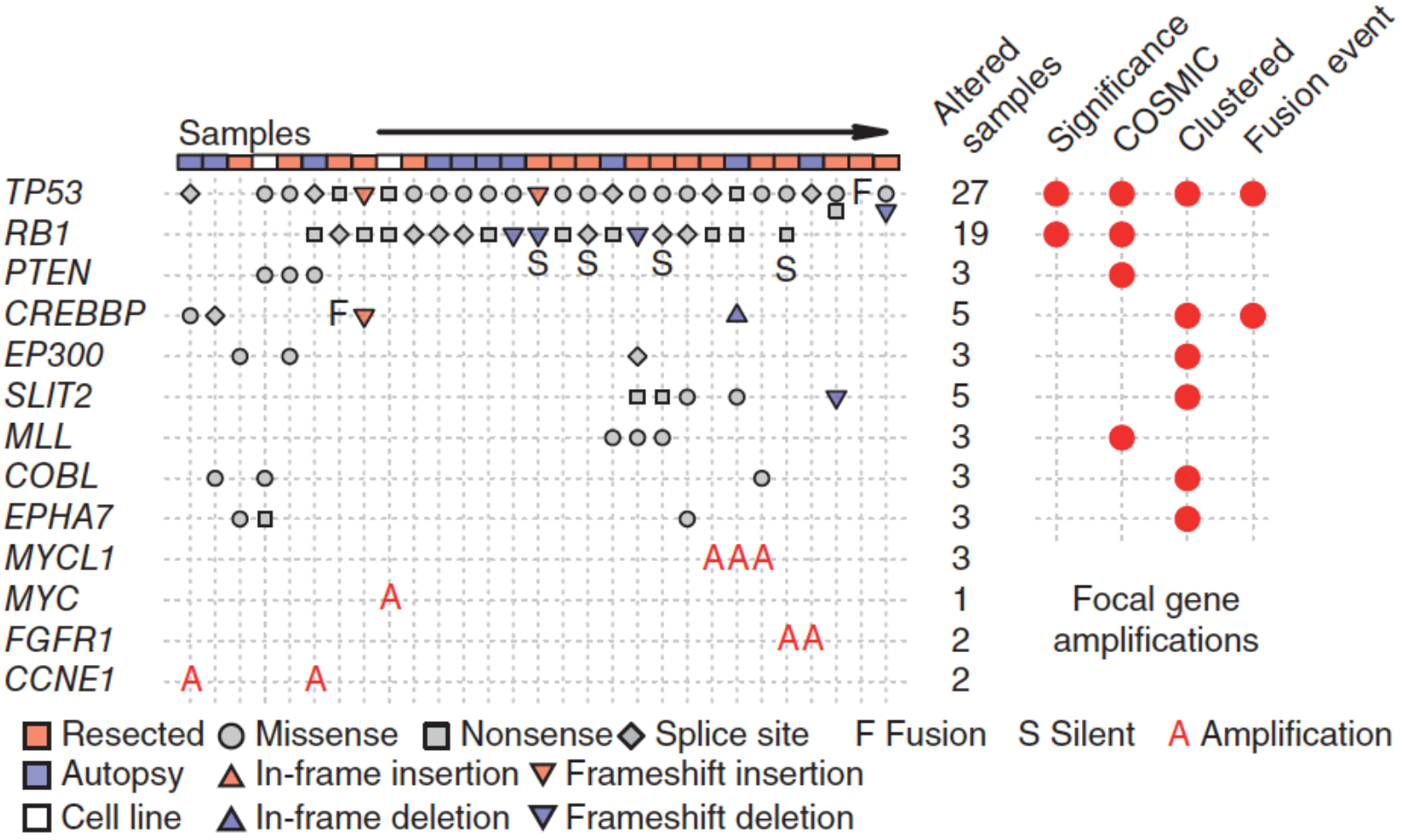
- 2 comprehensive genomics papers in 2012 defined aspects of the genomic landscape of SCLC
  - *Rudin et al.* 35 primary tumors and 28 cell lines
  - *Peifer et al.* 29 primary tumors
  - These provide needed insight into the genomic landscape of SCLC
  - For tumors of this complexity, this N is not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

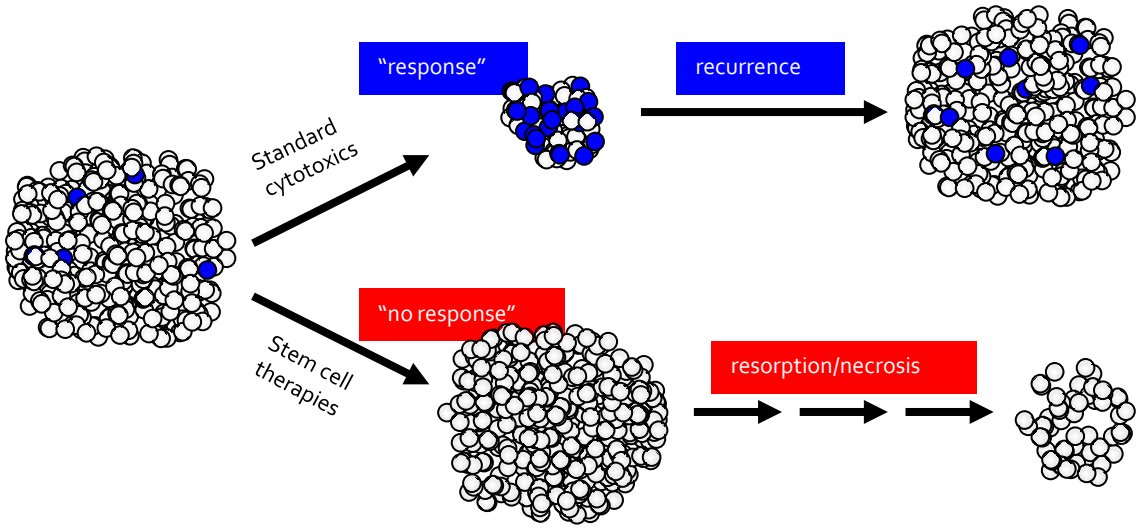
- What are critical drivers beyond *TP53* and *RB* loss?
- Are there relevant molecularly defined subsets?
  - Distinct clinical outcomes
  - Distinct therapeutic vulnerabilities
- Are there molecular differences between primary and metastatic disease?
- Can drivers of metastasis be specifically targeted?

#2. Analysis of acquired chemotherapy resistance in SCLC

- 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

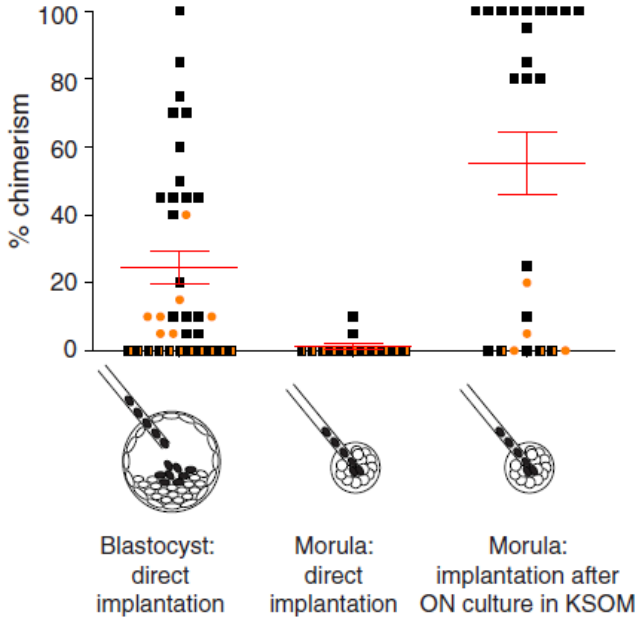
Emerging research questions

- 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?

A newer approach



Huijbers et al., *EMBO Mol Med*, 2014

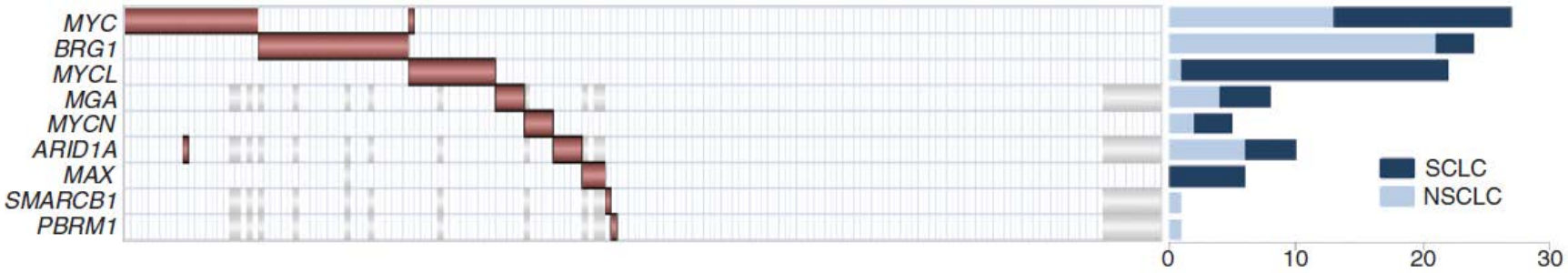
Emerging research questions

- What effects do joint loss of *TP53* 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?

#5. Developmental and stem cell signaling 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 embryronic 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 *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 *TP53/RB* loss
  - Synthetic lethality studies, functional restoration approaches
- Targeting *MYC*, *ASCL1*, 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

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(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 testing[5]; recent and ongoing genomic studies of genetically engineered mouse models (GEMMs) of SCLC[6-8]; 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 checkpoints[9]; and recent clinical data using temozolomide both as a single agent[10] and with a poly-(ADP-ribose)-polymerase (PARP) inhibitor[11]. Finally, promising opportunities for targeting Bcl-2 in SCLC[12] 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[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[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[16]. PET staging now approaches a 100% level of sensitivity and greater than 90% specificity[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[21, 22] with concomitant radiation that can be encompassed in a single radiation port[23, 24]. Treatment for ED includes the same chemotherapy options, without concomitant radiation[22]. In some instances, particularly for small peripheral lung nodules, surgery can also be considered[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[23, 26-28]. An alternative first-line chemotherapy regimen, cisplatin and irinotecan, appeared to be superior in a Phase III study conducted in Japan[29], but these results could not be confirmed in subsequent US comparative trials[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[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[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[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[35, 36]. Prophylactic cranial radiation therapy decreases the risk of subsequent, clinically significant brain metastases and improves survival in patients with LD and ED[24, 37].

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[38]. These studies include efforts to target the neuroendocrine character of SCLC, its dependence on the (PARP) pathway[11], and the use of immunological interventions including therapeutic vaccines[39], antibody radio-immunoconjugates[40], or checkpoint inhibitors intended to stimulate anti-cancer immune responses[28].

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 *passenger* type, which means that they do not necessarily contribute to the initiation or progression of the disease. More important are *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 *TP53* and *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 *MYC* family genes, *Bcl-2, PTEN, CREBBP*, *FGFR1, SLIT2,* and *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, *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[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 *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 *RLF* and *MYCL1* in a primary SCLC tumor and four SCLC cell lines, and that siRNA targeting *MYCL1* in such lines inhibited proliferation[2]. In contrast to the tumor suppressors *TP53* and *RB*, *MYC* family members are activated oncogenes in SCLC and other cancers[46]. Previous efforts to design specific inhibitors of MYC signaling have been, broadly speaking, disappointing, but many new research tools and approaches are emerging[47].

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. ASCL1-dependent embryonic developmental signaling and Hedgehog stem cell signaling pathways in particular have been implicated in SCLC clonogenic potential[48, 49]. Despite disappointing results of a randomized clinical trial of a Hedgehog pathway inhibitor in extensive stage SCLC[50], 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 tumors[51]. 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[52]. 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[54, 55] suggest that more sensitive screening tests for SCLC, perhaps incorporating assessments of mutant *RB* and *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[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[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[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[60, 61]. Recent results from Phase II studies suggest that the human anti-CTLA-4 monoclonal antibody ipilumumab adds to the therapeutic benefit of chemotherapy in SCLC[62]. An ongoing Phase III clinical trial that compares the etoposide/platinum combination plus or minus ipilumumab will help to define the role of immune suppressors in SCLC patients with extensive disease[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[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*)[64]; 2) the expression of certain cancer stem cell markers (CD133) that are associated with the overexpression of mitogenic neuropeptide receptors[65, 66]; 3) elevated levels of DNA repair proteins and/or activation of the PI3K/mTOR pathway[67]; and 4) overexpression of ATP-binding cassette transporters[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

1. Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012;44:1104-10.
2. Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet. 2012;44:1111-6.
3. Byers LA, Wang J, Nilsson MB, Fujimoto J, Saintigny P, Yordy J, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov. 2012;2:798-811.
4. Kalari S, Jung M, Kernstine KH, Takahashi T, Pfeifer GP. The DNA methylation landscape of small cell lung cancer suggests a differentiation defect of neuroendocrine cells. Oncogene. 2013;32:3559-68.
5. Daniel VC, Marchionni L, Hierman JS, Rhodes JT, Devereux WL, Rudin CM, et al. A primary xenograft model of small-cell lung cancer reveals irreversible changes in gene expression imposed by culture in vitro. Cancer Res. 2009;69:3364-73.
6. Meuwissen R, Linn SC, Linnoila RI, Zevenhoven J, Mooi WJ, Berns A. Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. Cancer Cell. 2003;4:181-9.
7. Schaffer BE, Park KS, Yiu G, Conklin JF, Lin C, Burkhart DL, et al. Loss of p130 accelerates tumor development in a mouse model for human small-cell lung carcinoma. Cancer Res. 2010;70:3877-83.
8. Park KS, Liang MC, Raiser DM, Zamponi R, Roach RR, Curtis SJ, et al. Characterization of the cell of origin for small cell lung cancer. Cell Cycle. 2011;10:2806-15.
9. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol. 2013;24:75-83.
10. Pietanza MC, Kadota K, Huberman K, Sima CS, Fiore JJ, Sumner DK, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. Clin Cancer Res. 2012;18:1138-45.
11. National Cancer Institute. Temozolomide With or Without Veliparib in Treating Patients With Relapsed or Refractory Small Cell Lung Cancer In: ClinicalTrialsgov [Internet]. 2000 - [cited 2014 May 15]. ed. Bethesda (MD): National Library of Medicine (US); Available from http://clinicaltrials.gov/show/NCT01638546 NLM Identifier: NCT01638546.
12. Juin P, Geneste O, Gautier F, Depil S, Campone M. Decoding and unlocking the BCL-2 dependency of cancer cells. Nat Rev Cancer. 2013;13:455-65.
13. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med. 2013;369:920-31.
14. The National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409.
15. The National Lung Screening Trial Research Team, Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368:1980-91.
16. Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging. 2011;11:253-8.
17. Oh JR, Seo JH, Hong CM, Jeong SY, Lee SW, Lee J, et al. Extra-thoracic tumor burden but not thoracic tumor burden on (18)F-FDG PET/CT is an independent prognostic biomarker for extensive-disease small cell lung cancer. Lung Cancer. 2013;81:218-25.

18. Faivre-Finn C, Lorigan P. Efficacy of positron emission tomography staging for small-cell lung cancer: a systematic review and cost analysis in the Australian setting. J Thorac Oncol. 2012;7:e25; author reply e6.
19. Nishino M, Jackman DM, Hatabu H, Janne PA, Johnson BE, Van den Abbeele AD. Imaging of lung cancer in the era of molecular medicine. Acad Radiol. 2011;18:424-36.
20. Ruben JD, Ball DL. The efficacy of PET staging for small-cell lung cancer: a systematic review and cost analysis in the Australian setting. J Thorac Oncol. 2012;7:1015-20.
21. Jiang L, Yang KH, Guan QL, Mi DH, Wang J. Cisplatin plus etoposide versus other platin-based regimens for patients with extensive small-cell lung cancer: a systematic review and meta-analysis of randomised, controlled trials. Intern Med J. 2012;42:1297-309.
22. Levy B, Saxena A, Schneider BJ. Systemic therapy for small cell lung cancer. J Natl Compr Canc Netw. 2013;11:780-7.
23. Amini A, Byers LA, Welsh JW, Komaki RU. Progress in the management of limited-stage small cell lung cancer. Cancer. 2014;120:790-8.
24. Videtic GM. The role of radiation therapy in small cell lung cancer. Curr Oncol Rep. 2013;15:405-10.
25. Anraku M, Waddell TK. Surgery for small-cell lung cancer. Semin Thorac Cardiovasc Surg. 2006;18:211-6.
26. Aisner J, Whitacre M, Abrams J, Propert K. Doxorubicin, cyclophosphamide, etoposide and platinum, doxorubicin, cyclophosphamide and etoposide for small-cell carcinoma of the lung. Semin Oncol. 1986;13:54-62.
27. Turrisi AT, 3rd, Glover DJ, Mason BA. A preliminary report: concurrent twice-daily radiotherapy plus platinum-etoposide chemotherapy for limited small cell lung cancer. Int J Radiat Oncol Biol Phys. 1988;15:183-7.
28. William WN, Jr., Glisson BS. Novel strategies for the treatment of small-cell lung carcinoma. Nat Rev Clin Oncol. 2011;8:611-9.
29. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med. 2002;346:85-91.
30. Han JY, Lee YS, Shin ES, Hwang JA, Nam S, Hong SH, et al. A genome-wide association study of survival in small-cell lung cancer patients treated with irinotecan plus cisplatin chemotherapy. Pharmacogenomics J. 2014;14:20-7.
31. O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cucevia B, Juhasz G, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006;24:5441-7.
32. Perez-Soler R, Glisson BS, Lee JS, Fossella FV, Murphy WK, Shin DM, et al. Treatment of patients with small-cell lung cancer refractory to etoposide and cisplatin with the topoisomerase I poison topotecan. J Clin Oncol. 1996;14:2785-90.
33. GlaxoSmithKline. GSK receives approval for Hycamtin® (topotecan) capsules for the treatment of relapsed small cell lung cancer [Press Release]. 2007 ed. Retreived from http://www.gsk.com/media/press-releases/2007/gsk-receives-approval-for-hycamtin-topotecan-capsules-for-the-treatment-of-relapsed-small-cell-lung-cancer.html.
34. Simos D, Sajjady G, Sergi M, Liew MS, Califano R, Ho C, et al. Third-line chemotherapy in small-cell lung cancer: an international analysis. Clin Lung Cancer. 2014;15:110-8.
35. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007;357:664-72.
36. Slotman BJ, Mauer ME, Bottomley A, Faivre-Finn C, Kramer GW, Rankin EM, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life

and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol. 2009;27:78-84.
37. Sas-Korczynska B, Sokolowski A, Korzeniowski S. The influence of time of radio-chemotherapy and other therapeutic factors on treatment results in patients with limited disease small cell lung cancer. Lung Cancer. 2013;79:14-9.
38. U.S. National Library of Medicine (NLM). In: ClinicalTrialsgov [Internet]. [accessed June 3, 2014] ed.
39. Antonia SJ, Mirza N, Fricke I, Chiappori A, Thompson P, Williams N, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res. 2006;12:878-87.
40. D'Amico D, Carbone D, Mitsudomi T, Nau M, Fedorko J, Russell E, et al. High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumors. Oncogene. 1992;7:339-46.
41. Yuan J, Knorr J, Altmannsberger M, Goeckenjan G, Ahr A, Scharl A, et al. Expression of p16 and lack of pRB in primary small cell lung cancer. J Pathol. 1999;189:358-62.
42. Heighway J, Betticher DC. Lung: small cell cancer. Atlas of Genetics and Cytogenetics in Oncology and Haematology. June 2004 edURL : http://atlasgeneticsoncology.org/Tumors/LungSmallCellID5142.html.
43. Sutherland KD, Proost N, Brouns I, Adriaensen D, Song JY, Berns A. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. Cancer Cell. 2011;19:754-64.
44. Dooley AL, Winslow MM, Chiang DY, Banerji S, Stransky N, Dayton TL, et al. Nuclear factor I/B is an oncogene in small cell lung cancer. Genes Dev. 2011;25:1470-5.
45. Little CD, Nau MM, Carney DN, Gazdar AF, Minna JD. Amplification and expression of the c-myc oncogene in human lung cancer cell lines. Nature. 1983;306:194-6.
46. Dang CV. MYC on the path to cancer. Cell. 2012;149:22-35.
47. Fletcher S, Prochownik EV. Small-molecule inhibitors of the Myc oncoprotein. Biochim Biophys Acta. 2014.
48. Jiang T, Collins BJ, Jin N, Watkins DN, Brock MV, Matsui W, et al. Achaete-scute complex homologue 1 regulates tumor-initiating capacity in human small cell lung cancer. Cancer Res. 2009;69:845-54.
49. Park KS, Martelotto LG, Peifer M, Sos ML, Karnezis AN, Mahjoub MR, et al. A crucial requirement for Hedgehog signaling in small cell lung cancer. Nat Med. 2011;17:1504-8.
50. Belani CP, Dahlberg SE, Rudin CM, Fleisher M, Chen HX, Takebe N, et al. Three-arm randomized phase II study of cisplatin and etoposide (CE) versus CE with either vismodegib (V) or cixutumumab (Cx) for patients with extensive stage-small cell lung cancer (ES-SCLC) (ECOG 1508). J Clin Oncol. 2013;31.
51. Liu X, Ory V, Chapman S, Yuan H, Albanese C, Kallakury B, et al. ROCK inhibitor and feeder cells induce the conditional reprogramming of epithelial cells. Am J Pathol. 2012;180:599-607.
52. Muller I, Ullrich S. The PFP/RAG2 double-knockout mouse in metastasis research: small-cell lung cancer and prostate cancer. Methods Mol Biol. 2014;1070:191-201.
53. Kadara H, Fujimoto J, Yoo SY, Maki Y, Gower AC, Kabbout M, et al. Transcriptomic architecture of the adjacent airway field cancerization in non-small cell lung cancer. J Natl Cancer Inst. 2014;106:dju004.
54. Newman AM, Bratman SV, To J, Wynne JF, Eclov NC, Modlin LA, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nat Med. 2014;20:548-54.
55. Igawa S, Gohda K, Fukui T, Ryuge S, Otani S, Masago A, et al. Circulating tumor cells as a prognostic factor in patients with small cell lung cancer. Oncol Lett. 2014;7:1469-73.

56. Dent AG, Sutedja TG, Zimmerman PV. Exhaled breath analysis for lung cancer. J Thorac Dis. 2013;5:S540-S50.
57. Sos ML, Dietlein F, Peifer M, Schottle J, Balke-Want H, Muller C, et al. A framework for identification of actionable cancer genome dependencies in small cell lung cancer. Proc Natl Acad Sci U S A. 2012;109:17034-9.
58. Weidle UH, Maisel D, Eick D. Synthetic lethality-based targets for discovery of new cancer therapeutics. Cancer Genomics Proteomics. 2011;8:159-71.
59. Kamat CD, Shmueli RB, Connis N, Rudin CM, Green JJ, Hann CL. Poly(beta-amino ester) nanoparticle delivery of TP53 has activity against small cell lung cancer in vitro and in vivo. Mol Cancer Ther. 2013;12:405-15.
60. Brahmer JR. Harnessing the immune system for the treatment of non-small-cell lung cancer. J Clin Oncol. 2013;31:1021-8.
61. Forde PM, Kelly RJ, Brahmer JR. New strategies in lung cancer: translating immunotherapy into clinical practice. Clin Cancer Res. 2014;20:1067-73.
62. Spigel DR, Socinski MA. Rationale for chemotherapy, immunotherapy, and checkpoint blockade in SCLC: beyond traditional treatment approaches. J Thorac Oncol. 2013;8:587-98.
63. Bristol-Myers Squibb. Trial in Extensive-Disease Small Cell Lung Cancer (ED-SCLC) Subjects Comparing Ipilimumab Plus Etoposide and Platinum Therapy to Etoposide and Platinum Therapy Alone. In: ClinicalTrialsgov [Internet]. 2000 - [cited 2014 May 15]. ed. Bethesda (MD: National Library of Medicine (US); Available from http://clinicaltrials.gov/show/NCT01450761 NLM Identifier: NCT01450761.
64. Karachaliou N, Papadaki C, Lagoudaki E, Trypaki M, Sfakianaki M, Koutsopoulos A, et al. Predictive value of BRCA1, ERCC1, ATP7B, PKM2, TOPOI, TOPOmicron-IIA, TOPOIIB and C-MYC genes in patients with small cell lung cancer (SCLC) who received first line therapy with cisplatin and etoposide. PLoS One. 2013;8:e74611.
65. Kubo T, Takigawa N, Osawa M, Harada D, Ninomiya T, Ochi N, et al. Subpopulation of small-cell lung cancer cells expressing CD133 and CD87 show resistance to chemotherapy. Cancer Sci. 2013;104:78-84.
66. Sarvi S, Mackinnon AC, Avlonitis N, Bradley M, Rintoul RC, Rassl DM, et al. CD133+ cancer stem-like cells in small cell lung cancer are highly tumorigenic and chemoresistant but sensitive to a novel neuropeptide antagonist. Cancer Res. 2014;74:1554-65.
67. Cardnell RJ, Feng Y, Diao L, Fan YH, Masrorpour F, Wang J, et al. Proteomic markers of DNA repair and PI3K pathway activation predict response to the PARP inhibitor BMN 673 in small cell lung cancer. Clin Cancer Res. 2013;19:6322-8.
68. Minami T, Kijima T, Otani Y, Kohmo S, Takahashi R, Nagatomo I, et al. HER2 as therapeutic target for overcoming ATP-binding cassette transporter-mediated chemoresistance in small cell lung cancer. Mol Cancer Ther. 2012;11:830-41.

H. List of Abbreviations

ADP	adenosine diphosphate
ATP	adenosine triphosphate
CT	computed tomography
CTAC	Clinical Trials and Translational Research Advisory Committee
CTC	circulating tumor cell
DCE	dynamic contrast-enhanced
DNA	deoxyribonucleic acid
ED	extensive-stage disease
FDA	Food and Drug Administration
GEMM	genetically engineered mouse model
IASLC	International Association to Study Lung Cancer
LD	limited-stage disease
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NK cells	natural killer cells
PDX	patient-derived xenograft
PET	positron emission tomography
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RNASeq	RNA sequencing
SCLC	small cell lung cancer
shRNA	short hairpin RNA
siRNA	small interfering RNA
SNP	single nucleotide polymorphism
SPORE	Specialized Programs of Research Excellence
TCGA	The Cancer Genome Atlas

National Institutes of Health
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Clinical Trials and Translational Research Advisory Committee (CTAC)
Small Cell Lung Cancer Working Group

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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**

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Small Cell Lung Cancer (SCLC) Working Group Report: Next Steps

Presented to CTAC

James H. Doroshow

June 18, 2014

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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SCLC Working Group Report

- 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)

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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

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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

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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

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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

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Oversight

- 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

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