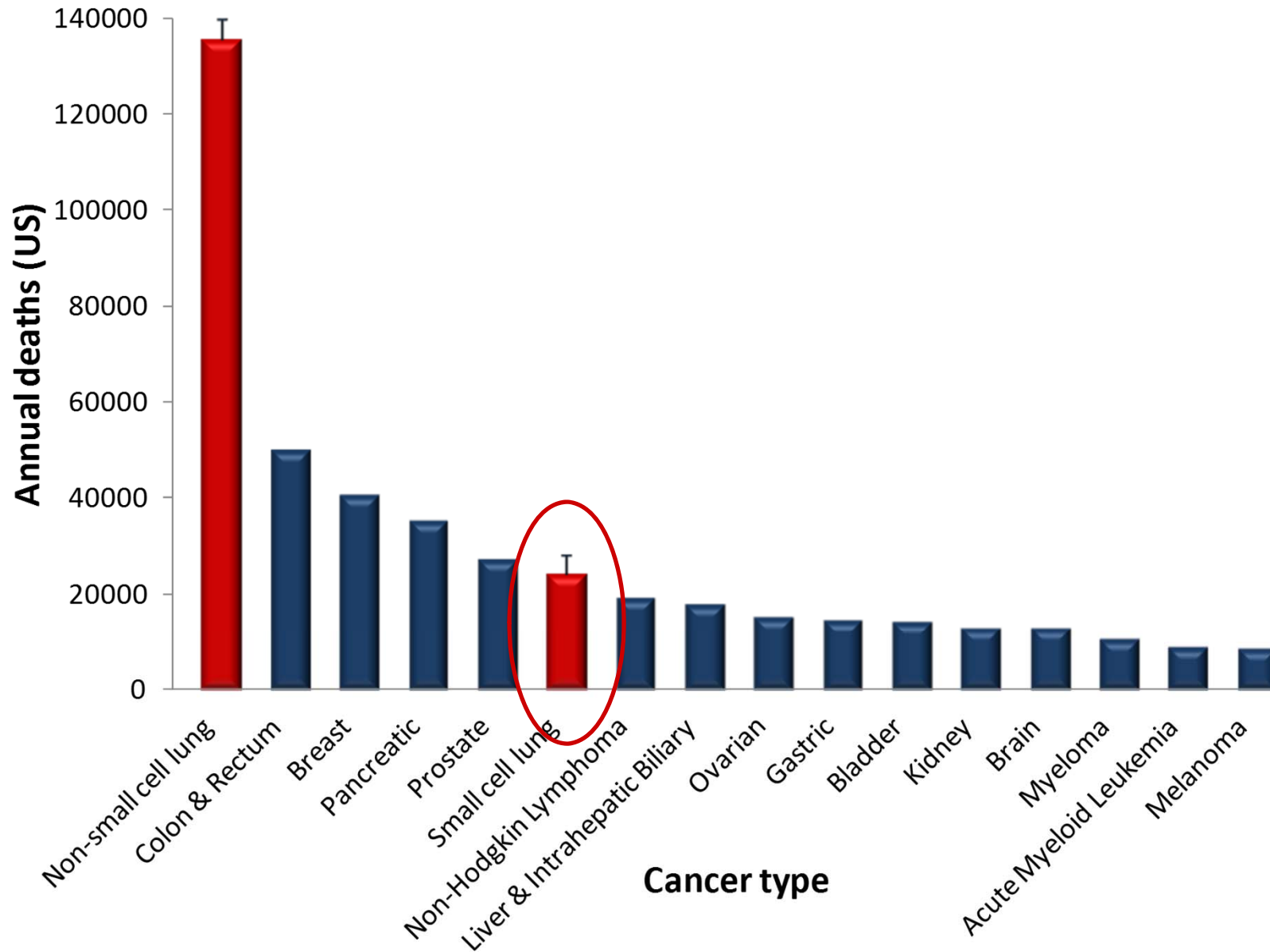


**Clinical Trials and Translational Research  
Advisory Committee (CTAC)  
SCLC Progress Working Group**

*Charles Rudin MD PhD*

*July 13, 2016*

# 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

# Recalcitrant Cancer Research Act (RCRA)

- Enacted by Congress in September 2012 as an amendment to the Public Health Service Act
- Requires the NCI to develop scientific frameworks for two or more cancers with a 5-year relative survival rate of  $< 20\%$  and that cause  $\geq 30,000$  deaths in the U.S. per year
- *Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)*
  - submitted to Congress in February 2014
- *Scientific Framework for Small Cell Lung Cancer (SCLC)*
  - submitted to Congress in June 2014

# Oversight of NCI's Implementation and Progress Related to the RCRA

## ➤ NCI Action Planning Groups (APG)

- Internally track progress by a small APG for each disease site
- Provide data on grants and other projects relevant to NCI leadership and extramural working groups

## ➤ Extramural Working Groups

- Convene an **external group of stakeholders** for each disease (CTAC Working Groups) approximately one year after the submission of the relevant framework to discuss progress and identify new scientific opportunities
- The Working Groups assess the research progress and identify new scientific opportunities related to the initiatives of the relevant framework in response to the Recalcitrant Cancer Research Act of 2012.
- Members will include scientific experts, clinicians, and patient advocates

## ➤ CTAC

- Working Groups report research progress to CTAC approximately annually beginning in 2016

# Deliverables

The primary purpose of the SCLC Progress WG is to monitor NCI's progress related to the initiatives set of the scientific framework.

## ➤ Short and intermediate term

- Assess NCI progress to date
- Assess whether there have been any important new advances or opportunities since the development of the scientific framework that should be considered
- Provide recommendations for process and frequency of future assessment reports to CTAC and update of scientific framework

## ➤ Long term

- Review and update the scientific framework no later than 5 years after initial development (2019)
- Submit a report to Congress on the effectiveness of the scientific framework no later than 6 years after the initial development (2020)

# Assessment Process

- Provided SCLC Progress WG members with data
  - FY14 extramural grants, cooperative agreements, and intramural programs with links to abstracts
  - Current and recent clinical trials
  - Program Announcements for the “SCLC Consortium”
  - Summary of progress for each recommendation/initiative
- WG members completed form to assess progress, identify gaps and new opportunities, and propose recommendations
- SCLC Progress WG webinar to review findings prior to drafting written report



# Initiatives to Expand Research in SCLC



# Initiatives to Expand Research in SCLC

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

# SCLC Framework Initiative 1

## Better Research Tools for the Study of SCLC

Build better research tools for the study of SCLC by (a) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC (from initial diagnosis to disease recurrence following radio-chemotherapy) and (b) developing new tumor models (conditionally-reprogrammed cell lines, PDX, and GEMMs) that reflect the phases of SCLC found in the clinic.

### Implementation Plan

- Support infrastructure for SCLC specimen collection
  - 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.

# SCLC Consortium (U01 and U24 FOAs)

release 12/2015; receipt 3/2016; review 7/2016

## ➤ Central U24 Coordinating Center

- Support of better research tools: central –omics databases; centralized tissue banking for human specimens and virtual biospecimen database; SCLC model repository; Consortium website; administration; meetings
- U24 mechanism has flexibility to include limited projects to support the Consortium

## ➤ Series of U01s

- Prevention and Early Detection
- Therapeutic Development Efforts
- Mechanisms Underlying Treatment Response and Emergence of Drug and Radiation Resistance
- Because of the need for clinically-relevant SCLC models, U01 projects may include model development to underpin the therapeutic development studies

# Initiative 1: Summary of Implementation Progress

- The U24 Coordinating Center will:
  - Secure centralized tissue banking for specimens submitted by the members of the SCLC Consortium and a virtual biospecimen database that would include all tissue resources of the SCLC Consortium
  - Establish SCLC in vivo and in vitro model repositories and distribution units

## Initiative 1: Summary of Progress (2)

- NCI Patient-Derived Models (PDM) Repository will establish and provide PDX models, frozen tumor fragments, and cultured cells from SCLC patient tumors and CTCs; DNA and RNA pellets from PDX, CDX, and primary cell lines; 70 human SCLC cell lines and associated array and screening data
- Supplemental funding has been provided to NCORP sites for collection of blood specimens for the PDM Repository, with an emphasis on recalcitrant cancer samples (including SCLC).

## Initiative 1: Summary of Progress (3)

- NCI participated in the [2015 International Association for the Study of Lung Cancer \(IASLC\) SCLC Workshop](#) conducted at MSKCC, including an assessment of SCLC research resources
  - Summarized in Bunn et al., J Thorac Oncol, 2016
- Many groups are now making PDX routinely
- CTC-derived PDX (CDX) has emerged as an important model (e.g., Hodgkinson et al., Nat Med, 2014) and CTC-derived cell lines are being generated as well
- New GEMMs are also emerging that are providing important insights, including the role of ASCL1 and other key determinants
  - McFadden et al., Cell, 2014; others

# Initiative 1: Conclusions and Recommendations

## Conclusions

- Implementation is on target
- SCLC model development has advanced considerably since the drafting of the scientific framework
- Too early to assess scientific progress

## Recommendations

- Remain committed to the SCLC Consortium over multiple funding cycles
- Consider maintenance of clinically-annotated TMAs at NCI for use by the research community
- Work with the NCTN Groups and with community and academic centers to enhance and coordinate biospecimen collection
- Facilitate sharing of SCLC samples, genomics data, and other research resources

## SCLC Framework Initiative 2

### Comprehensive Genomic Profiling of SCLC

Expand comprehensive genomic profiling studies of clinically-annotated SCLC specimens to improve the basic understanding of the frequency, distribution, and range of molecular abnormalities that exist both at diagnosis and following therapeutic relapse.

#### Implementation Plan

- 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.



## Initiative 2: Summary of Progress

- In addition to the objectives defined under Recommendation 1, the SCLC Consortium Coordinating Center will:
  - Create and support database(s) for -omics or other data pertinent to the SCLC Consortium
  - Provide centralized biostatistics, bioinformatics and data analysis support

## Initiative 2: Recent Scientific Advances

- Recent important manuscripts on SCLC genomic profiling have identified potentially targetable pathways in SCLC such as Notch, the AKT/mTOR pathway, and epigenetic regulatory mechanisms
  - Ross et al., J Clin Pathol 2014; Umemura et al., J Thorac Oncol 2014; George et al., Nature 2015
- A recent investigation of the SCLC methylome has revealed a potential role for EZH2 in tumor growth
  - Poirier et al., Oncogene 2015

# Initiative 2: Conclusions and Recommendations

## Conclusions

- Implementation mostly on target
- Too early to assess scientific progress

## Recommendations

- Consider mechanisms for centralized NGS at the NCI
- Support collection of clinically-annotated specimens for genomic studies from both primary and metastatic sites, including post-mortem collection
- Prioritize characterization of “typical” SCLC genomes (i.e., not early-stage disease)
- Encourage studies of clinically-defined subsets from clinical trials such as responders vs. non-responders and exceptional responders

# SCLC Framework Initiative 3

## New Diagnostic Approaches for SCLC

Investigate new diagnostic approaches for populations at high risk of developing SCLC

### Implementation Plan

- 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

## Initiative 3: Summary of Progress

- In December 2015 NCI released a funding announcement for “Innovative Approaches to the Prevention and Early Detection of SCLC”, funding individual U01 sites that will be part of the SCLC Consortium to conduct studies:
  - to expand the understanding of the critical molecular changes in the lung that precede the development of frank SCLC; and/or,
  - to identify populations at particularly high risk for SCLC
- The U01 sites will share data, materials, models, and results with the Coordinating Center, which will support the administrative coordination of the SCLC Consortium.

# Initiative 3: Conclusions and Recommendations

## Conclusions

- Implementation on target, too early to assess scientific progress

## Recommendations

- Support additional focused projects for early detection

# SCLC Framework Initiatives 4 & 5

## Therapeutic Development Efforts

### Mechanisms of Initial Response and Emergence of Resistance

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

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.

#### Implementation Plan

- 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.

## Initiatives 4 & 5: Summary of Progress

- In December 2015 NCI released a funding announcement for “Therapeutic Development and Mechanisms of Resistance”, funding individual U01 sites that will be part of the SCLC Consortium to conduct preclinical studies:
  - to improve SCLC therapeutics, focusing on understanding how the molecular vulnerabilities of this cancer could be used to develop targeted agent combinations; and/or,
  - to gain a better understanding of the rapid development of clinical resistance to drug and radiation therapy.
- The U01 sites will share data, materials, models, and results with the Coordinating Center, which will support the administrative coordination of the SCLC Consortium.



## Initiatives 4 & 5: Summary of Progress (2)

- The Frederick National Laboratory for Cancer Research executed high-throughput screening of approved and investigational drugs against a panel of small cell lung cancer cell lines
  - Polley, et al., JNCI 2016
- CTEP meeting on opportunities for biomarker-driven trials in SCLC
  - May 8, 2015 in Shady Grove
  - Participants included representatives from all NCTN Groups
- The NCI Thoracic Malignancy Steering Committee has made “rapid testing of new agents and strategies for the treatment of small cell lung cancer” one of its strategic priorities for 2015

## Initiatives 4 & 5: Recent Scientific Advances

- There have been new insights into mechanisms of PARP inhibitor sensitivity
  - Owonikoko et al., Cancer Med 2014, Cardnell et al., PLoS One 2016
- Notable clinical advances include substantial responses to immunotherapy and a DLL3-directed antibody-drug conjugate
  - Reck et al., Future Oncol 2016 (review)
  - Saunders et al., Sci Transl Med 2015
- New therapeutic approaches which target “transcriptional addictions” in SCLC are being discovered
  - Augert et al., Cancer Cell 2014; Christensen et al., Cancer Cell 2014; others

# Initiatives 4 & 5: Conclusions and Recommendations

## Conclusions

- Implementation on target, too early to assess scientific progress

## Recommendations

- Continue to engage with the NCTN and ETCTN to develop biomarker-driven trials for SCLC
- Work with the NCTN Groups and with community and academic centers to accelerate accrual to trials
- Consider the inclusion of non-pulmonary small cell histologies on SCLC trials
- Emphasize inclusion of less common subsets such as non-smokers

## Additional Recommendations

- Organize additional meetings like the April 2015 IASLC SCLC workshop, possibly in conjunction with SCLC Consortium meetings
- Organize/promote SCLC-focused sessions at major meetings
  - AACR, ASCO, EORTC-NCI-AACR Molecular Targets, etc.
- Partner with lung cancer advocacy groups to publicize SCLC research and promote clinical trial accrual
- Partner with lung cancer foundations to share a consensus on high priority research areas in SCLC
- Consider career development awards for SCLC investigators

## Future Plans

- The WG will meet next in early 2018 to assess progress again and report to CTAC
  - ~1 year after the U24 and the first round of U01 sites are funded
- Revision of the scientific framework (June 2019).
- Evaluation of effectiveness of the scientific framework (June 2020).

# SCLC Progress Working Group

**Chair:** Charles Rudin, M.D., Ph.D.

**Exec. Secretary:** Wolf Lindwasser, Ph.D.

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Peter Ujhazy, M.D., Ph.D.

# Questions

*Motion to accept the report?*





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