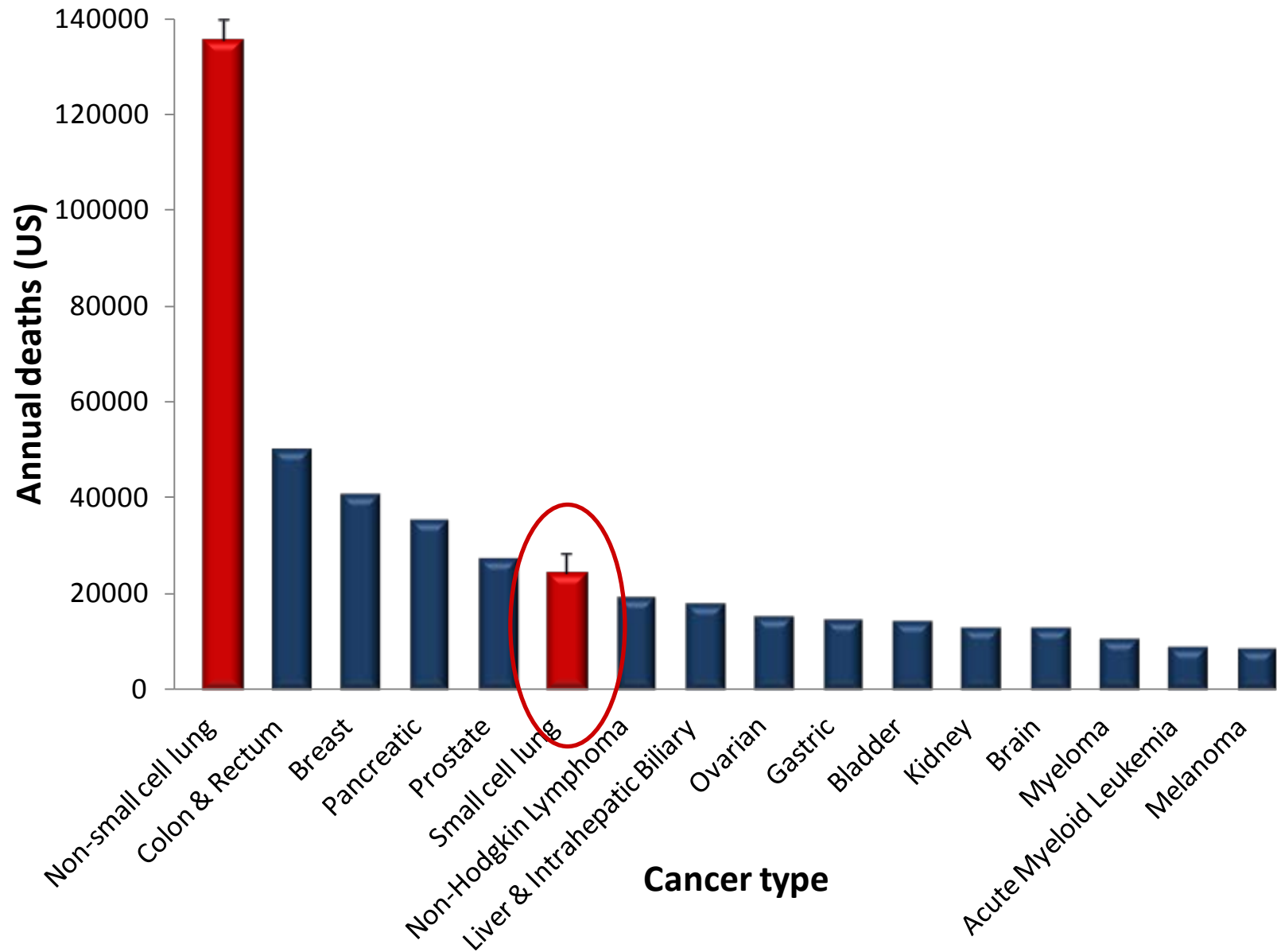# Report to NCI CTAC:
Small Cell Lung Cancer Working Group

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

- 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

- 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

- 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
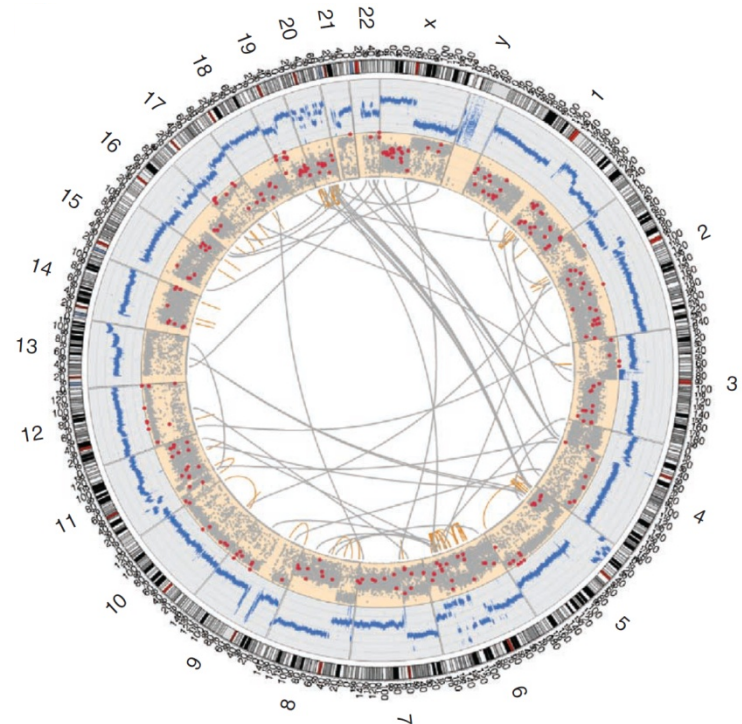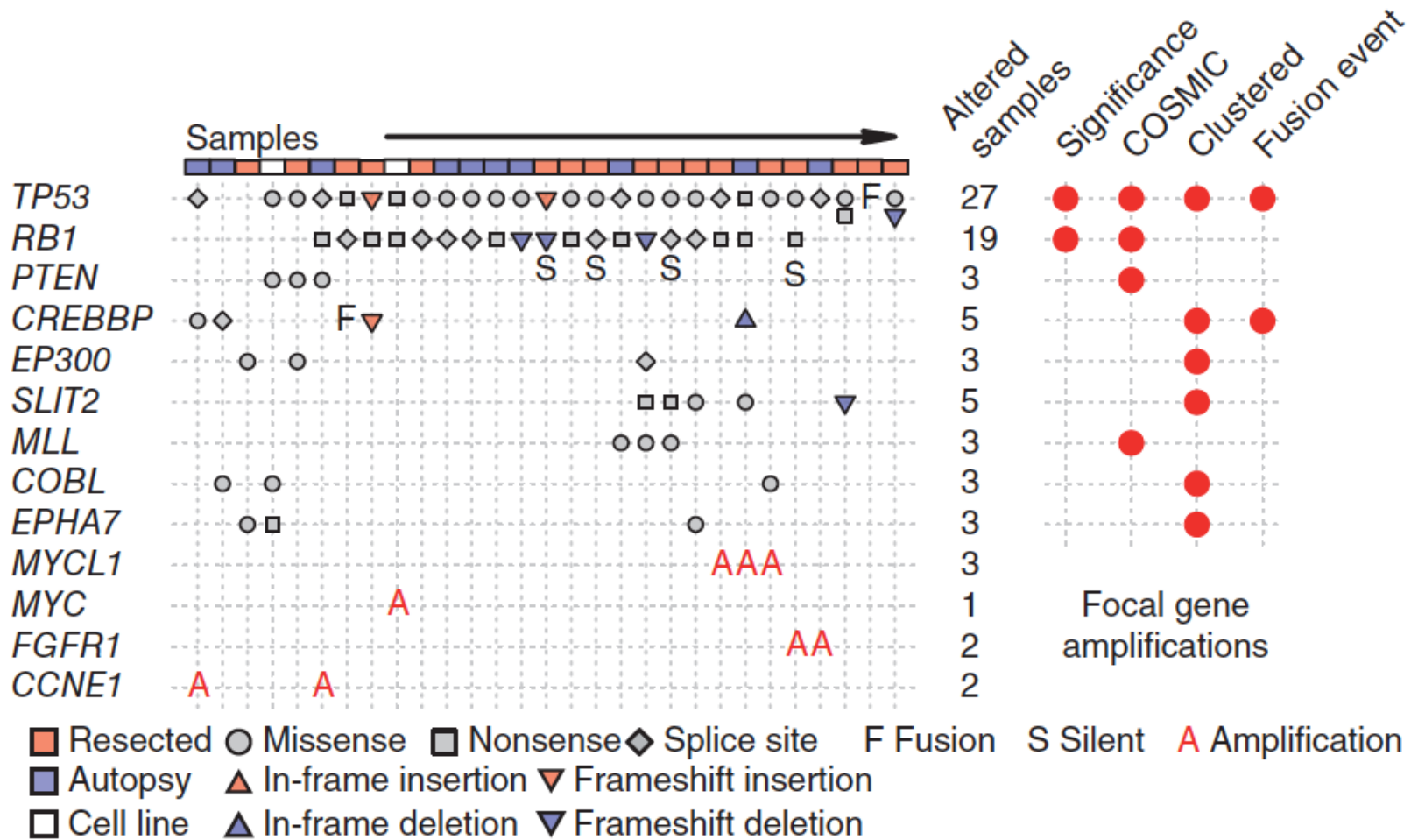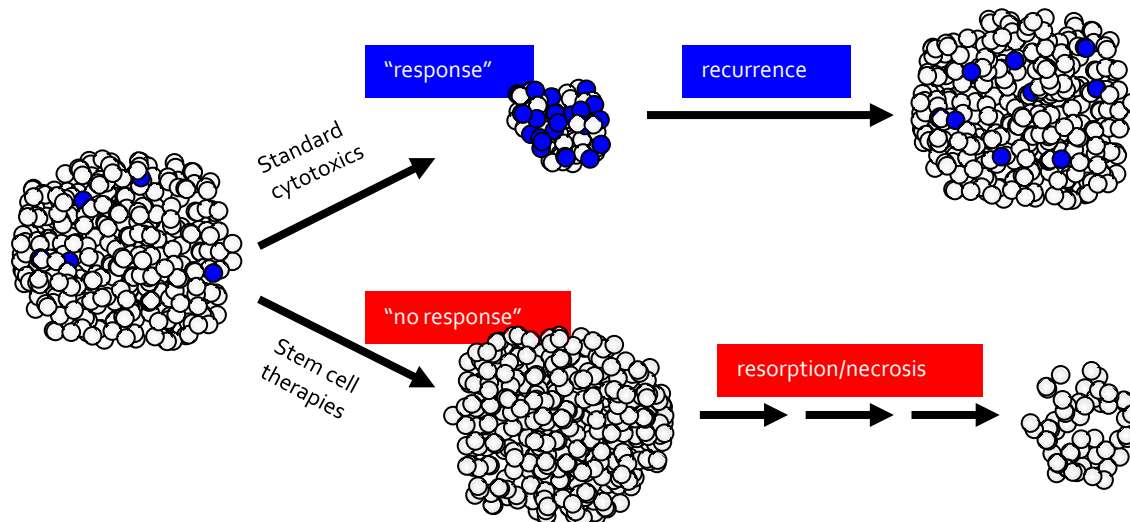
Emerging research questions

- 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?

- 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

- <u>Response</u>: May be largely determined by behavior of the (large) *chemosensitive* cell population

- <u>Survival</u>: 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

"response" recurrence

Standard cytotoxics

Stem cell therapies

"no response"

resorption/necrosis

Rudin et al., *JNCCN*, 2008

- 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
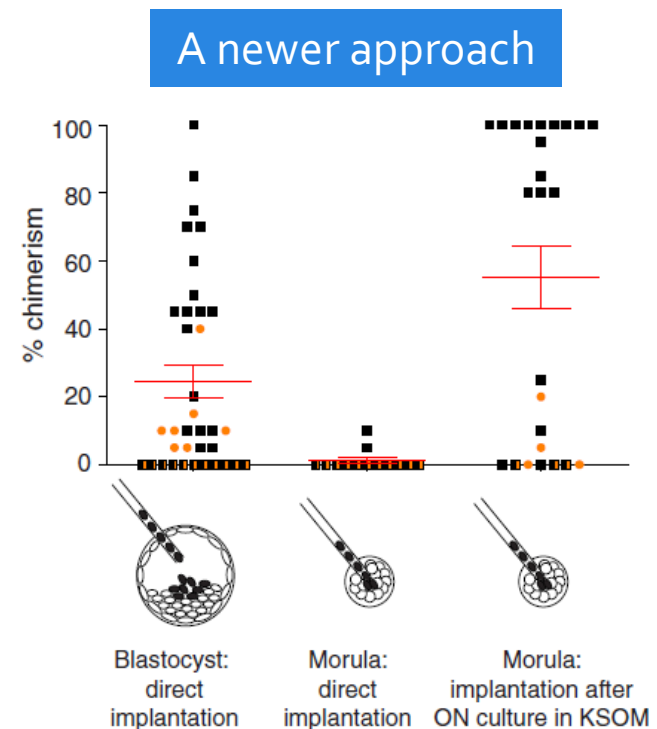
- What effects do joint loss of *TP53* and *RB* have on signaling circuitry of the cell?
  - Distinct from loss of either single gene

- Does concurrent loss of these 2 genes result in unique vulnerabilities in SCLC?
  - Can these vulnerabilities be targeted by existing or novel drugs?

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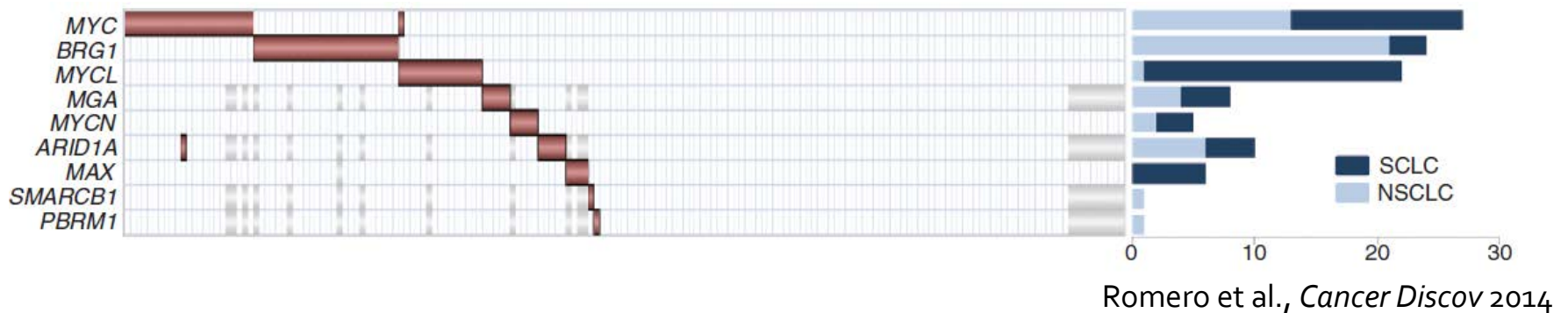
- Could a reinvigorated effort focused on inhibition of MYC family members create novel therapeutics?

- Are there common dependencies among MYC-driven tumors?

- Could MYC targeting lead to durable responses in SCLC?

- SCLC is a highly clonogenic tumor characterized by early and widespread metastasis
- Multiple developmental regulatory pathways that may influence clonogenic capacity have been implicated in SCLC biology
  - ASCL1/Notch
  - Hedgehog
    - The first clinical trial of a HH inhibitor in SCLC was negative
  - SOX2
- Might these represent unique targets of vulnerability in SCLC?

- 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

- 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