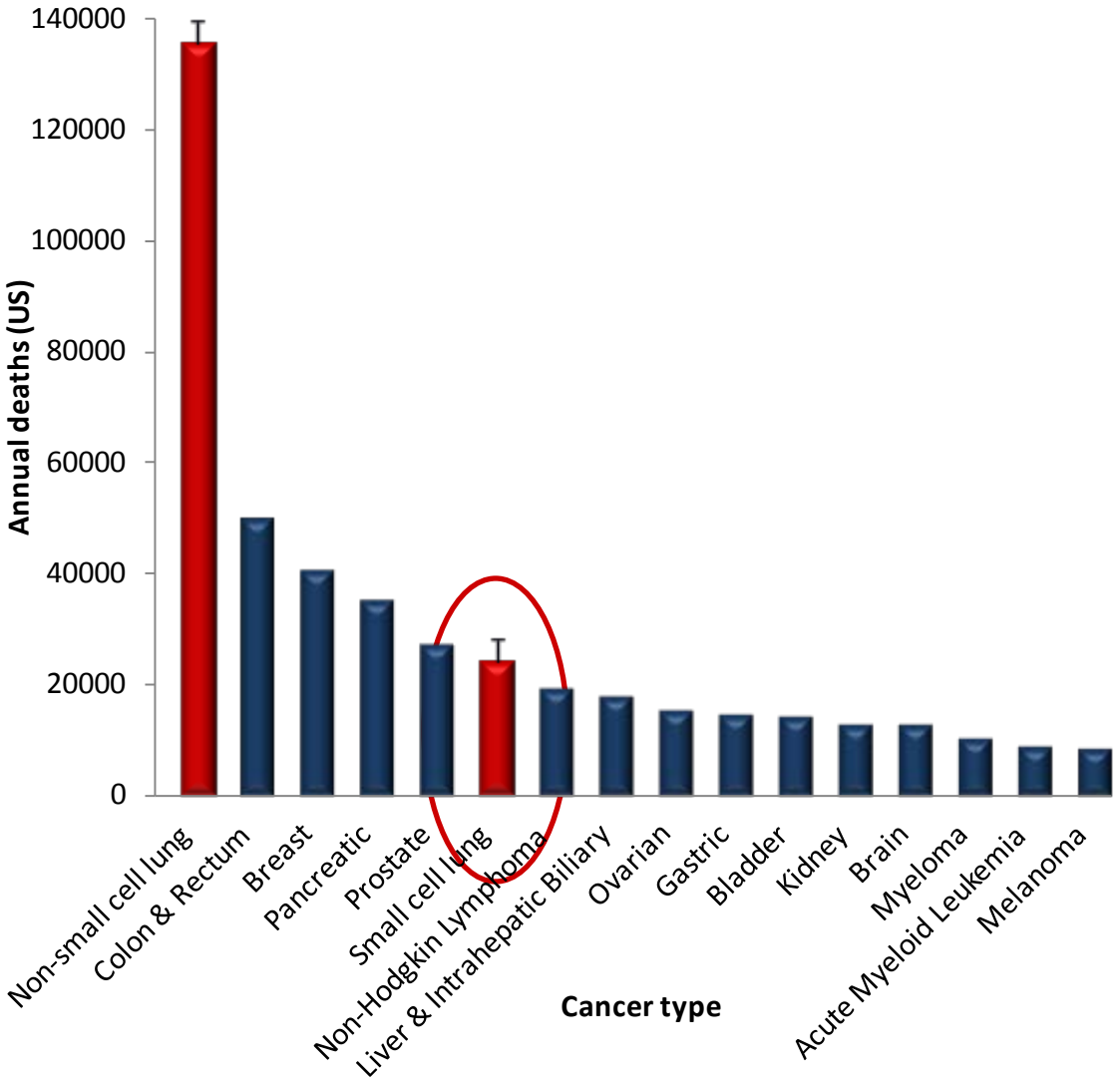
Interim Report to NCI CTAC: Small Cell Lung Cancer Working Group

Charles Rudin MD PhD

Memorial Sloan-Kettering Cancer Center

US cancer deaths



Small cell lung cancer: a recalcitrant cancer in need of novel approaches

- 2/3 patients present with extensive stage at diagnosis
  - Median survival approximately 9 months from diagnosis
  - Standard combination chemotherapy
    - 1980: Cisplatin + etoposide
    - 2011: Cisplatin + etoposide
- 1/3 present with limited stage disease
  - Median survival approximately 18 months from diagnosis
  - Same standard chemotherapy, plus concomitant radiation
- There is a *critical need* for more effective therapy for this disease

NCI Workshop on Small Cell Lung Cancer

July 8 – 9, 2013; Bethesda

Chairs: Rudin and Minna

- 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

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

Recent progress in defining drivers and targets in SCLC

Comprehensive genomic analysis identifies *SOX2* as a frequently amplified gene in small-cell lung cancer

Charles M Rudin[1,8], Steffen Durinck[2,3,8], Eric W Stawiski[2,3,8], John T Poirier[1,8], Zora Modrusan[2,8],

NATURE GENETICS VOLUME 44 | NUMBER 10 | OCTOBER 2012

Recurrent mutations in *PTEN*, *PIK3CA, EP300, MLL2*; amplification of *SOX2*, recurrent fusion of *RLF-MYCL1*

Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer

Martin Peifer[1,2,57], Lynnette Fernández-Cuesta[1,2,57], Martin L Sos[1–4], Julie George[1,2], Danila Seidel[1,2,5],

VOLUME 44 | NUMBER 10 | OCTOBER 2012 NATURE GENETICS

Recurrent mutations in *CREBBP*, *EP300*, *MLL*; mutations in *PTEN*, *SLIT2*, *EPHA7*; amplification of *FGFR1*

A framework for identification of actionable cancer genome dependencies in small cell lung cancer

Martin L. Sos[a,b,c,d,1,2], Felix Dietlein[a,b,1], Martin Peifer[a,b], Jakob Schöttle[a,b], Hyatt Balke-Want[a,b], Christian Müller[a,b],

17034–17039 | PNAS | October 16, 2012 | vol. 109 | no. 42

Cell line sensitivity screening suggests aurora kinase inhibitors active in *MYC*-amplified SCLC

Proteomic Profiling Identifies Dysregulated Pathways in Small Cell Lung Cancer and Novel Therapeutic Targets Including PARP1

Lauren Averett Byers, Jing Wang, Monique B. Nilsson, et al.

SEPTEMBER 2012 CANCER DISCOVERY | 799

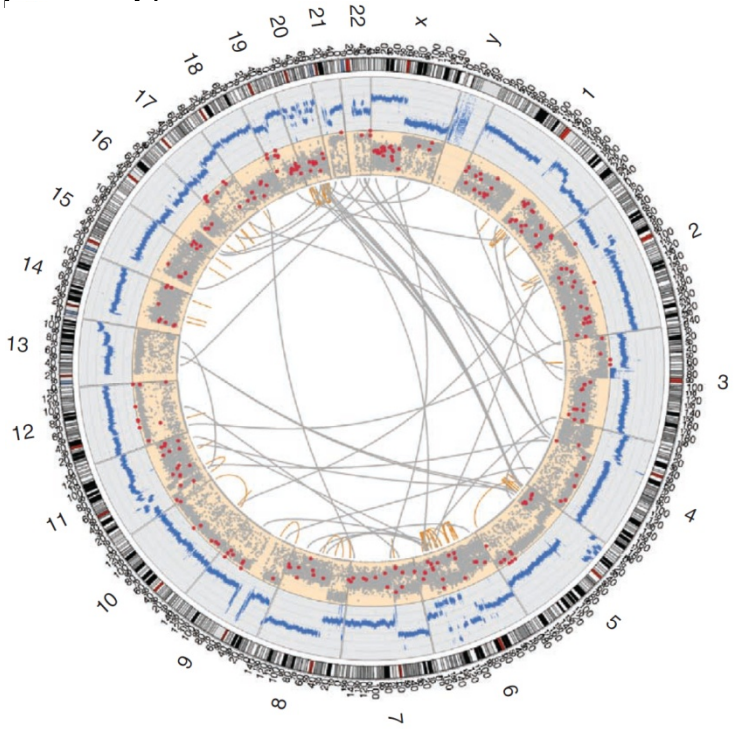
Proteomic profiling suggests EZH2 and PARP1 as therapeutic targets in SCLC

Characterization of the SCLC genome

- 2 comprehensive genomics papers last year defined important 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
  - However, for tumors of this complexity, this N is not sufficient

Non-synonymous mutation rate
5.5/Mb

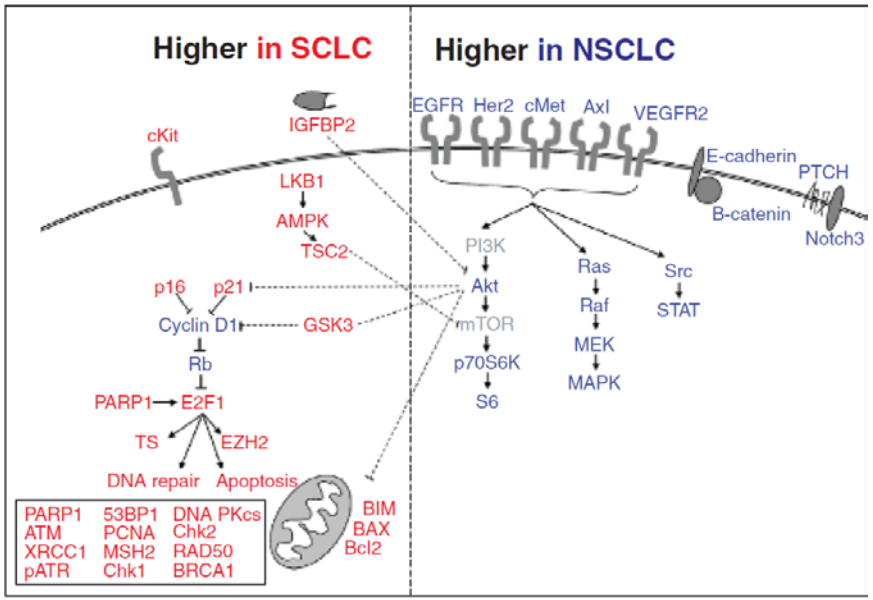
175
mutations per tumor

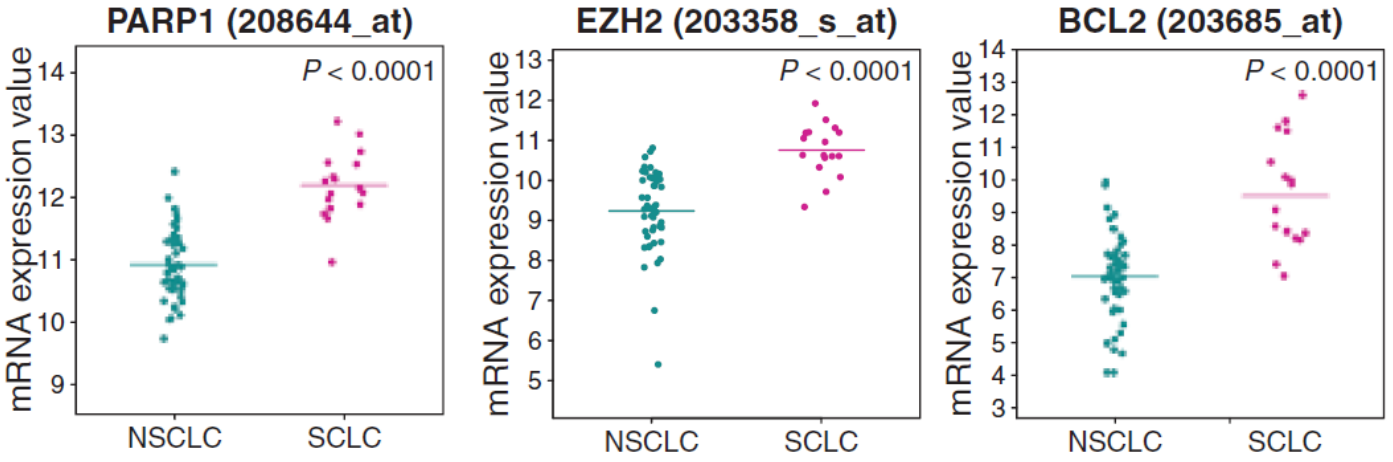


Approaches to identifying relevance

- Hot spot mutations
  - *TP53, RB1, PIK3CA, CDKN2A, PTEN*
  - RAS family regulators (*RAB37, RASGRF1, RASGRF2*)
  - Chromatin modifiers (*EP300, DMBX1, MLL2, MED12*, etc.)
- Hot spot mutations *PLUS* q-score
  - *RUNX1T1, CDYL, RIMS2*
- Gene families and pathways
  - PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family
- Focal amplifications
  - *MYC, SOX2, SOX4, KIT*
- Recurrent translocations and fusion genes
  - Recurrent: *RLF–MYCL1*
  - Kinase fusions
- ...

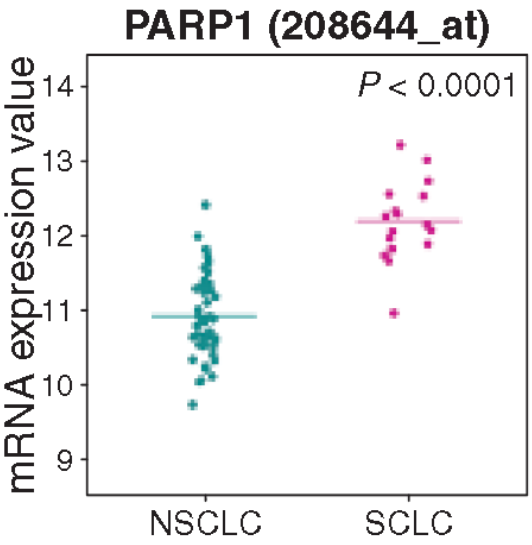
Proteomic profiling in SCLC using RPPA

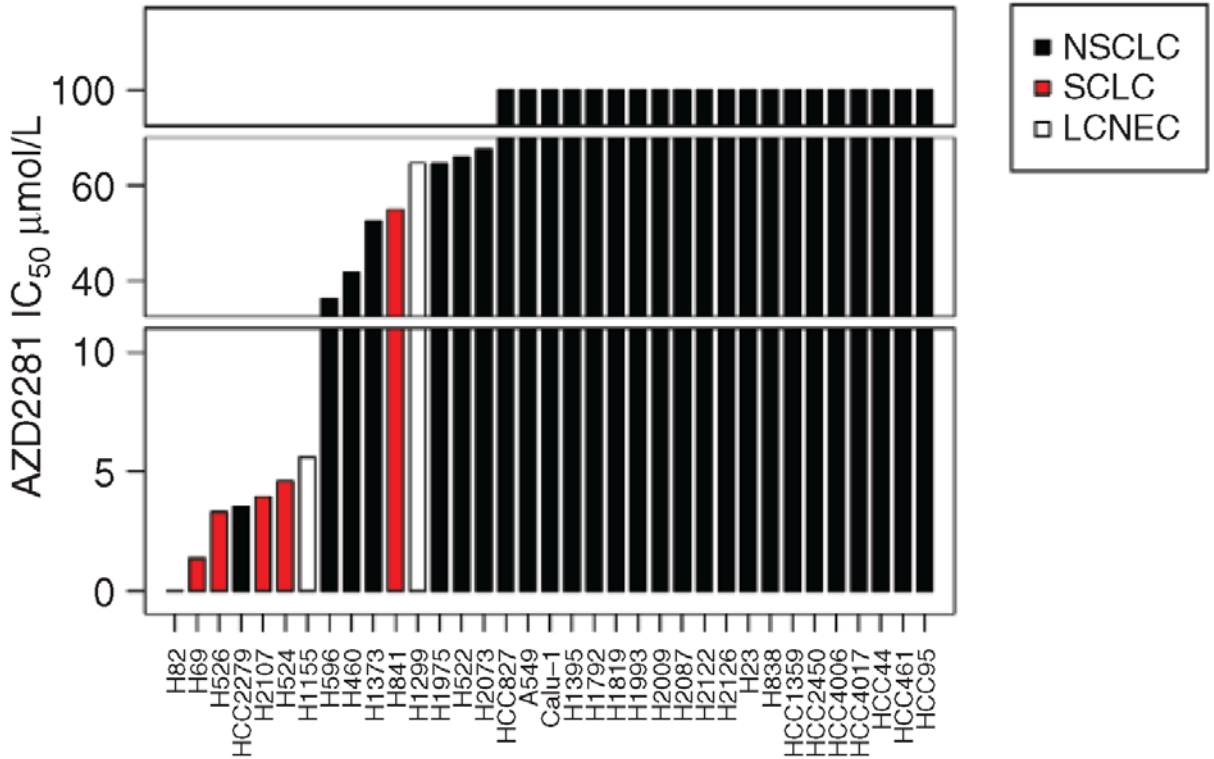




Byers et al., *Cancer Discovery* 2012

PARP1 expression and sensitivity to PARP inhibitor therapy

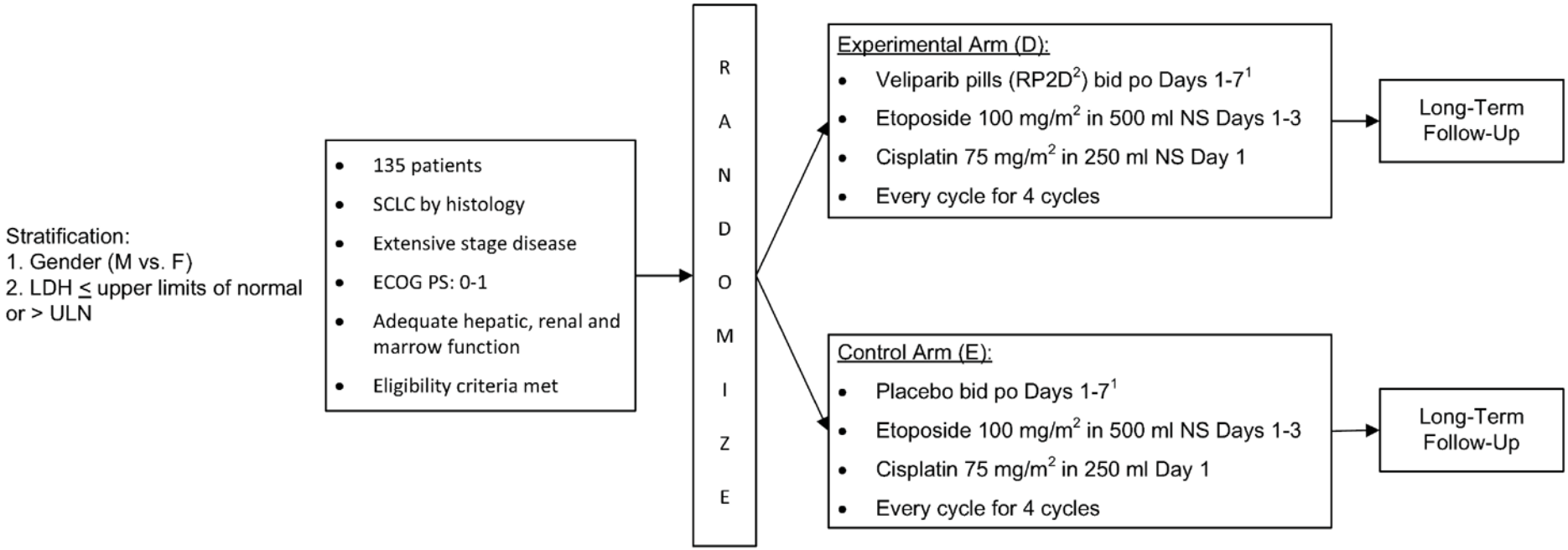




Byers et al., *Cancer Discovery,* 2012

ECOG 2511
Phase I/II cisplatin/etoposide +/- veliparib (ABT-888)

- Placebo-controlled first line randomized phase II study



Phase II Accrual Goal = 150
Cycle = 3 weeks (21 days)
IV doses are based on actual weight

Study Chair: Taofeek Owonikoko MD PhD

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 XRT)
- These responses are remarkably short-lived, with acquired resistance rapidly developing, resulting in chemorefractory recurrence and median survival of 9 mo (extensive stage) or 18 mo (limited stage) from diagnosis

- The basis for this shift from *de novo* chemosensitivity to subsequent chemoresistance is almost entirely unstudied.
  - Lack of repeat biopsies

TP53 and *RB* as gatekeeper mutations in SCLC

- Almost all SCLC are characterized by concomitant loss of these two key tumor suppressor genes
- A mouse model in which these 2 genes are deleted in lung epithelial cells results in a cancer closely resembling SCLC
  - Anton Berns
  - Further analyzed by Tyler Jacks and Julien Sage

- The biology of the interaction between these 2 signature events has not been extensively studied
  - Does this create unique tumor cell vulnerabilities?

MYC family members in SCLC

- *c-MYC* is amplified and/or overexpressed in many SCLC
- A recurrent fusion transcript *RFL-MYCL1* was found in genomic profiling of SCLC
  - In a primary SCLC and 2 cell lines
  - *MYCL1* siRNA suppresses proliferation

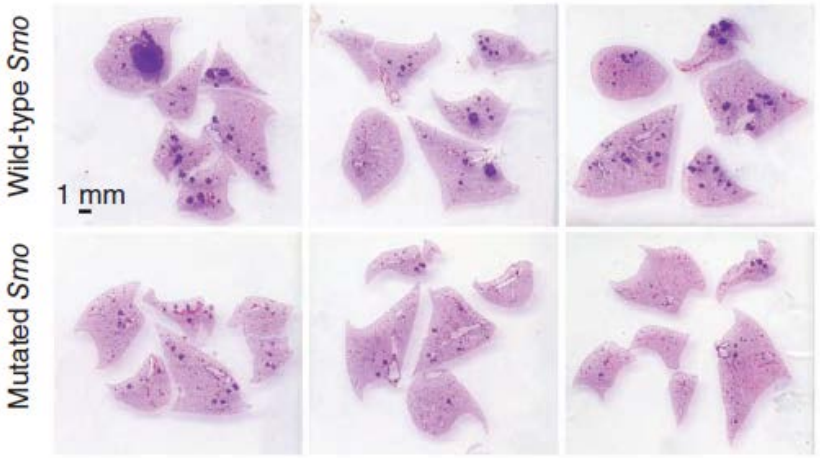
- Could a focused program to look at anti-MYC strategies yield progress in SCLC
  - Direct and indirect inhibitors (e.g. BRD4 inhibitors)

Developmental and stem cell signaling pathways in SCLC

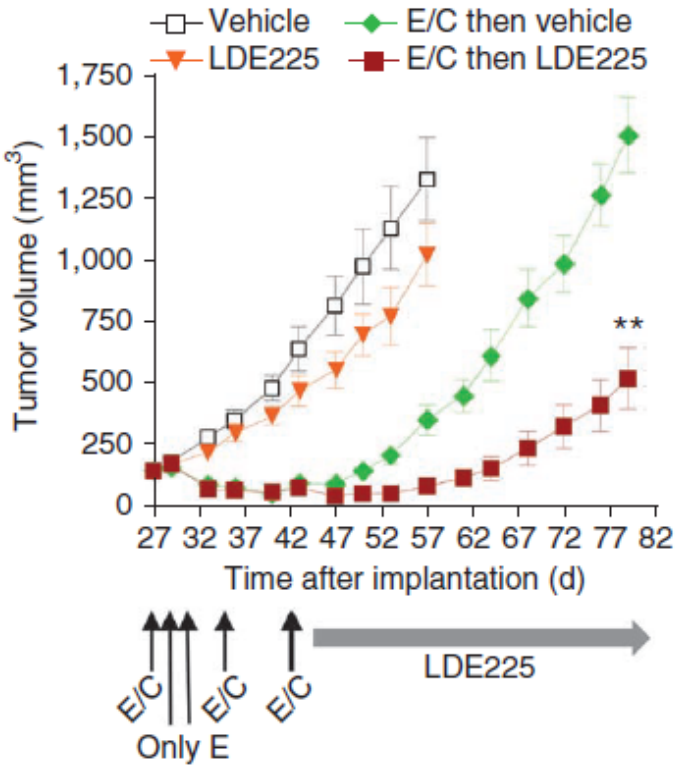
- SCLC is a highly clonogenic tumor characterized by early and widespread metastasis
- Multiple developmental regulatory pathways that may influence clonogenic capacity have been implicated in SCLC biology
  - ASCL1/Notch
  - Hedgehog
    - The first clinical trial of a HH inhibitor in extensive stage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

An apparent requirement for Hedgehog signaling

Oncogenesis in p53$^{-/-}$ RB$^{-/-}$ conditional mutant mouse

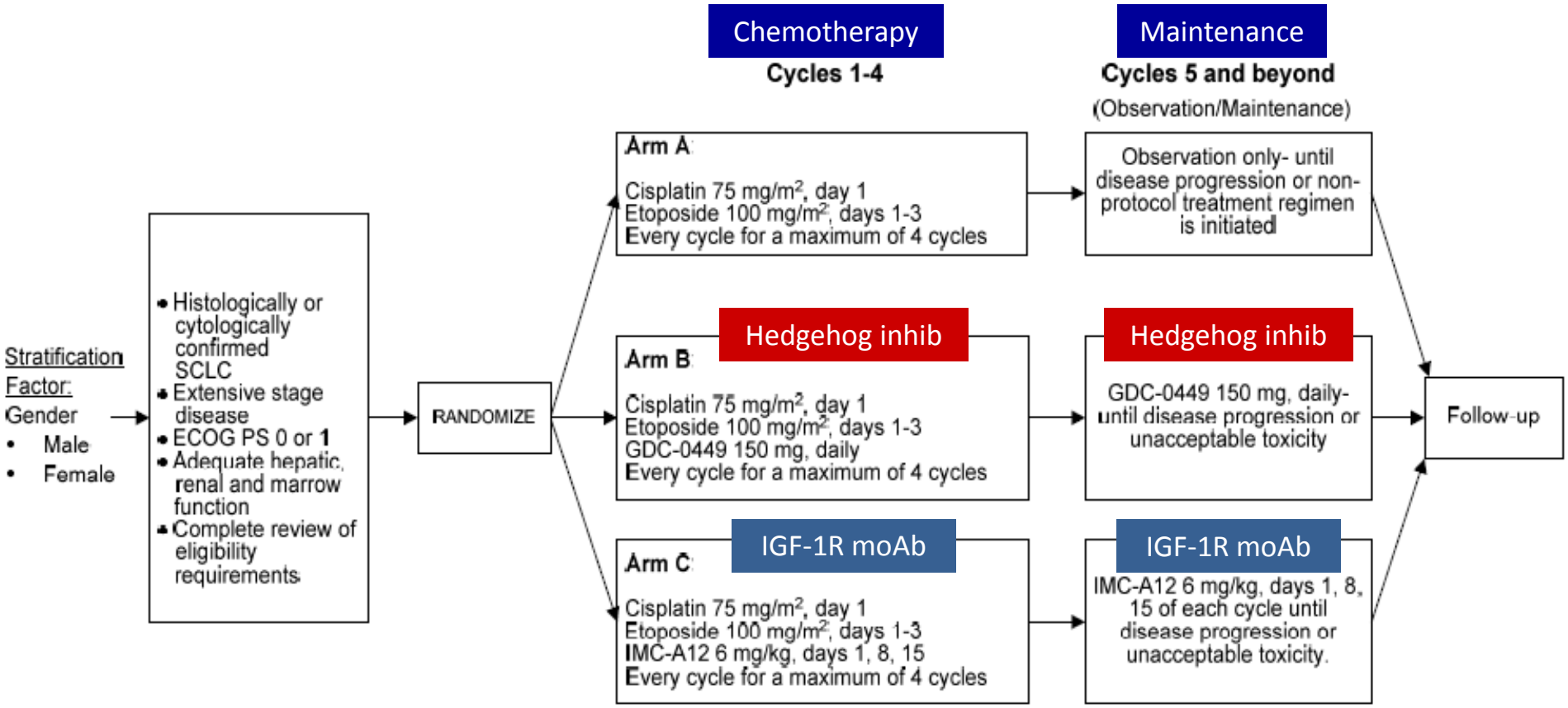


Inhibition of growth in a human PDX model



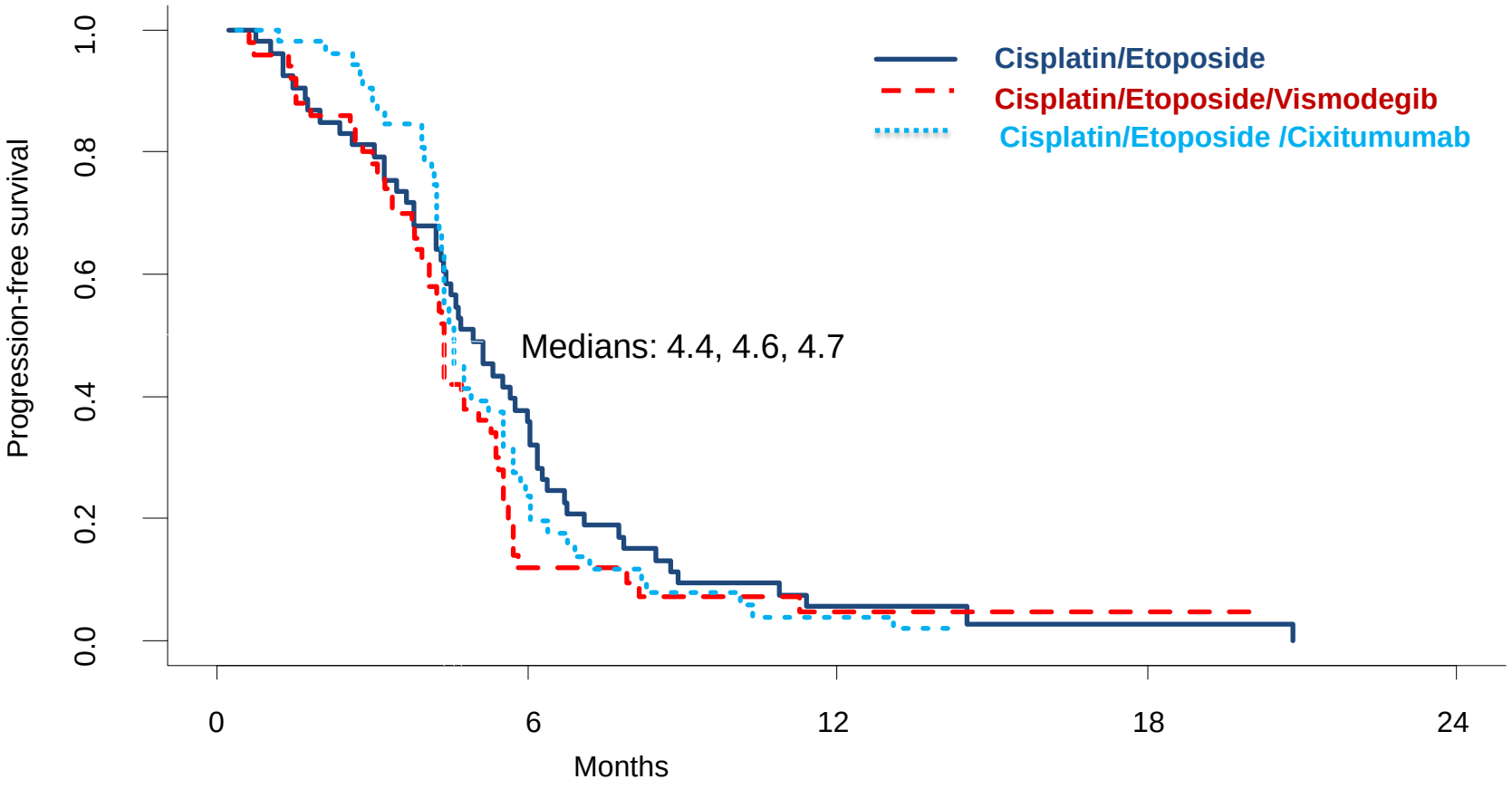
Park et al., *Nature Med* 2011

E1508: a randomized phase II study of chemotherapy +/- inhibitors of Hedgehog signaling or IGF-1R



Belani & Rudin

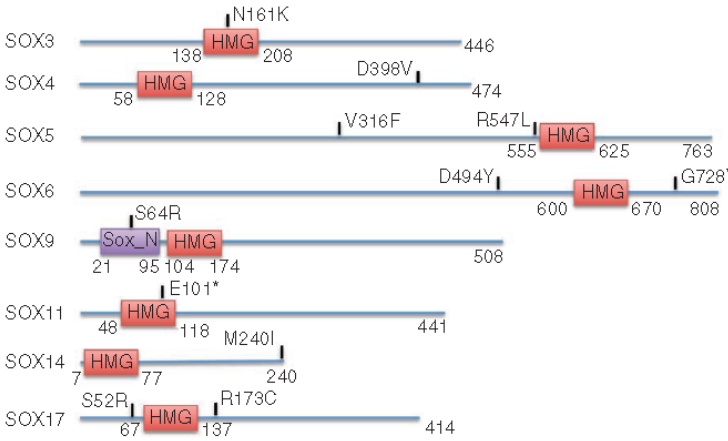
Neither targeted inhibitor improved outcome in patients with SCLC

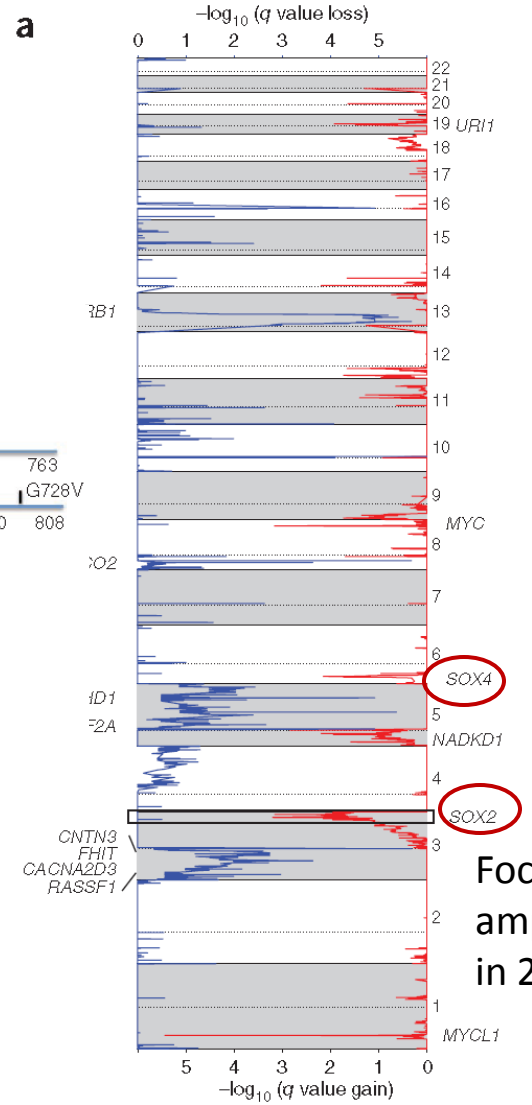


Belani & Rudin

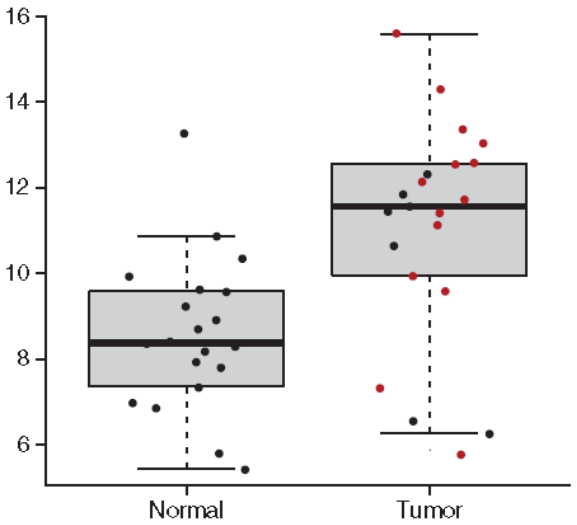
SOX family dysregulation in SCLC

SOX family mutations



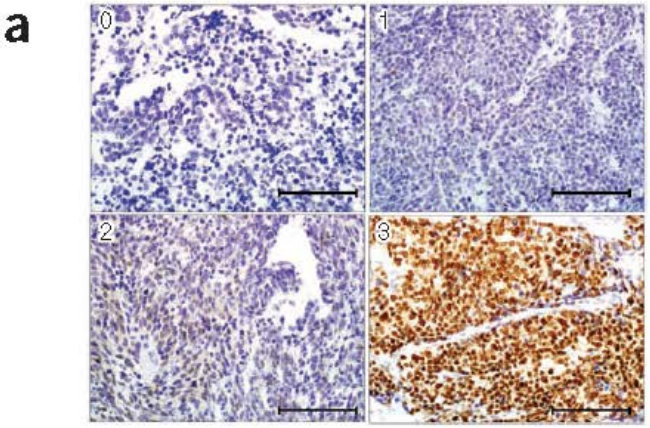


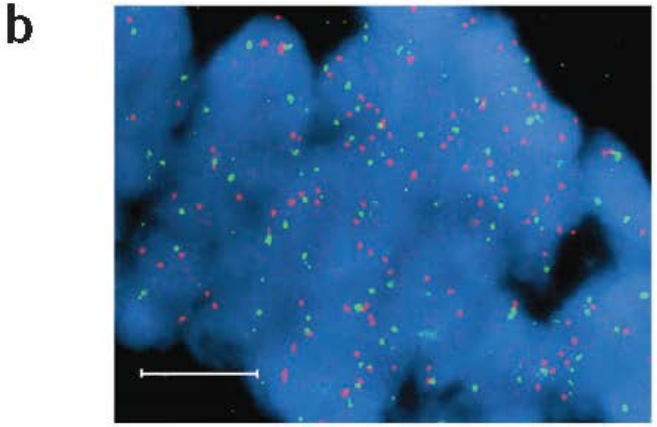
SOX2 expression

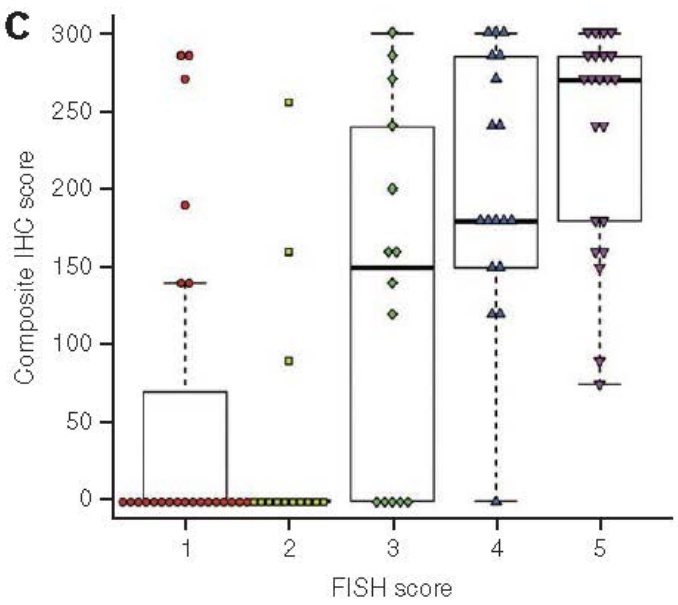


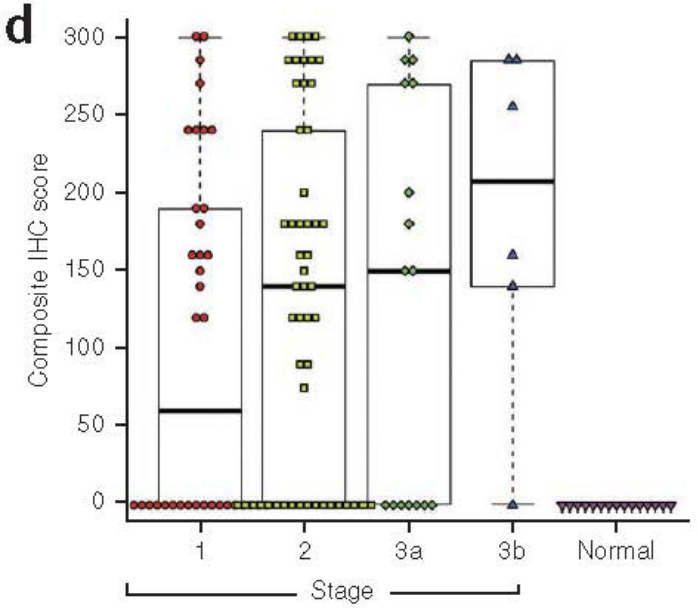
Focal amplification in 27%

SOX2 copy number correlates with expression and stage

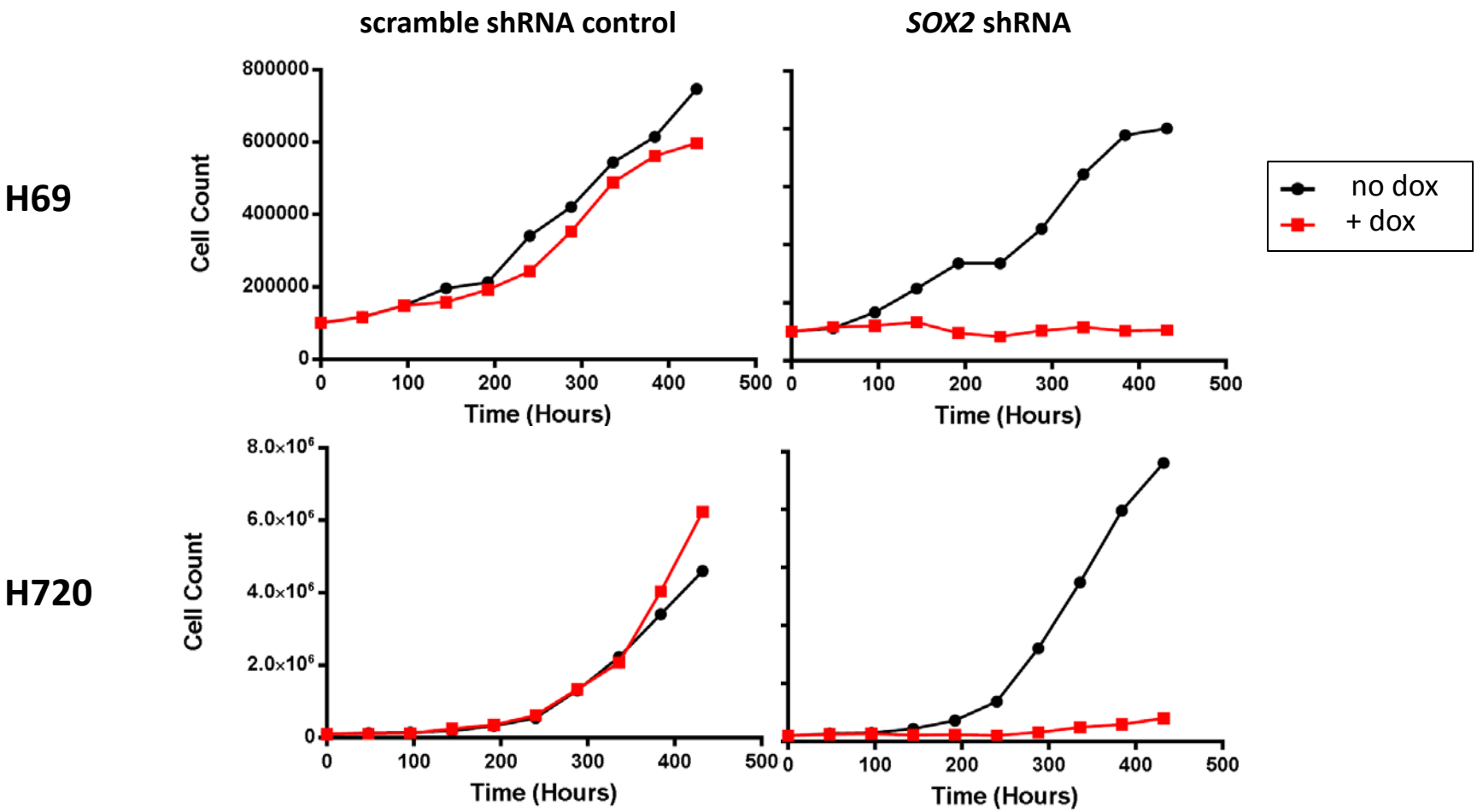








Targeted *SOX2* inhibition blocks SCLC proliferation



Recommended initiatives

- Optimizing collection of SCLC representing distinct phases of the disease
  - Need for additional biopsy material was a consistent theme
  - Notable lack of paired samples of newly diagnosed and recurrent dx

- Focused mutational profiling
  - Need for much more extensive genomic and proteomic analysis to define targets and their frequencies (e.g. *FGFR1* amplification; PARP1 overexpression)

- Targeting driver oncogenes and tumor suppressors in SCLC
  - *TP53/RB*
  - *MYC* family members
  - Developmental regulatory pathways