New horizons for small cell lung cancers

Charles Rudin MD PhD
US cancer deaths

Annual deaths (US) vs Cancer type

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

- 2/3 patients present with extensive stage at diagnosis
  - Median survival less than 1 year from diagnosis
  - Standard combination chemotherapy
    - 1980: Cisplatin + etoposide
    - 2011: Cisplatin + etoposide

- There is a *critical need* for more effective therapy for this disease
Global mutational spectrum of SCLC

Non-synonymous mutation rate
5.5/Mb

175 mutations per tumor

G → T transversions predominate (consistent with tobacco carcinogenesis)

Rudin et al., Nat Genet 2012
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
- ...

Filters for functional significance of mutations

Rudin et al., Nat Genet 2012
SOX family dysregulation in SCLC

SOX family mutations

SOX2 expression

Focal amplification in 27%

Rudin et al., Nat Genet 2012
Targeted SOX2 inhibition blocks SCLC proliferation

H69

scramble shRNA control

SOX2 shRNA

H720
SCLC – chemosensitivity but poor outcome

- **Response rate**: 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
Hedgehog signaling in lung development

Mouse embryonic lung, dpc 11.5

*Shh* (ligand)  
*Ptc1* (receptor)

SP-C *Shh* transgenic mouse

Belluscì et al., *Devel*, 1997
Lung development \textit{requires} Sonic Hedgehog

\textit{Shh} knock-out mouse

\textbf{dpc 12.5}

\textbf{dpc 18.5}

Hh inhibition delays recurrence in primary SCLC models

Park et al., *Nat Med* 2011
E1508: a randomized phase II study of chemotherapy +/- inhibitors of hedgehog or IGF-1R

Chemotherapy
Cycles 1-4

Arm A
Cisplatin 75 mg/m², day 1
Etoposide 100 mg/m², days 1-3
Every cycle for a maximum of 4 cycles

Arm B
Cisplatin 75 mg/m², day 1
Etoposide 100 mg/m², days 1-3
GDC-0449 150 mg, daily
Every cycle for a maximum of 4 cycles

Arm C
Cisplatin 75 mg/m², day 1
Etoposide 100 mg/m², days 1-3
IMC-A12 6 mg/kg, days 1, 8, 15
Every cycle for a maximum of 4 cycles

Hedgehog inhib

Maintenance
Cycles 5 and beyond
(Observation/Maintenance)

Observation only - until disease progression or non-protocol treatment regimen is initiated

GDC-0449 150 mg, daily - until disease progression or unacceptable toxicity

IGF-1R moAb

Belani & Rudin
Neither targeted inhibitor improved outcome in patients with SCLC

Belani & Rudin
Bromodomain and extraterminal (BET) family proteins

- **BET family**
  - BRD2, BRD3, BRD4, BRDT
  - Each has 2 highly conserved bromodomains
  - Regulate histone acetylation

Filippakopoulos et al, *Nature* 2010
Genes downregulated by BET inhibitor JQ1

Delmore et al, *Cell* 2011
Mertz et al, *PNAS* 2011
• I-BET762 (GSK525762)
  – orally bioavailable; structurally related to JQ1
  – High affinity for BRD2, 3, and 4
  – Phase I/II study in targeted tumor types including SCLC
    • Hopkins, Penn, DFCC, MDACC

Mirguet et al, J Med Chem 2013
Temozolomide in recurrent SCLC

• Rationale
  – Alkylating agents have single agent activity in SCLC
  – Temozolomide crosses BBB; CNS mets are common
  – SCLC has aberrantly methylated MGMT

Pietanza et al., Clin Cancer Res, 2012
Temozolomide in recurrent SCLC

- Overall RR 20% (95% CI 11 – 32%)
  - 13% in refractory cohort
- Of 13 patients with brain metastases
  - 4/13 with CR in brain; 1/13 with PR
  - ORR 38% in the CNS
Temozolomide in recurrent SCLC

Pietanza et al., Clin Cancer Res, 2012

Chemosensitive

Chemoresistant
Proteomic analysis of SCLC

- Reverse-phase protein array (RPPA) approach
  - 34 SCLC and 74 NSCLC
  - 193 total and phosphoproteins

Byers et al., *Cancer Discovery*, 2012
A few interesting targets in SCLC

- Novel and not-so-novel…

Byers et al., *Cancer Discovery*, 2012
PARP1 expression and sensitivity to PARP inhibitor therapy

Byers et al., *Cancer Discovery*, 2012
Randomized phase II study of temozolomide with or without veliparib

**Eligibility:****
- Recurrent SCLC after 1 or 2 prior regimens
- No chemotherapy or radiotherapy in prior 3 weeks
- ECOG PS ≤1

**Treatment:****
- **Veliparib**
  - 40mg PO BID × 7 days
  - Temozolomide 200mg/m²/d × 5 days
  - 28 day cycle

- **Placebo**
  - 40mg PO BID × 7 days
  - Temozolomide 200mg/m²/d × 5 days
  - 28 day cycle

**Study Chair:** Cathy Pietanza MD

**Participating Sites:**
- MSKCC
- SKCCC at JHU
- MDACC
- Seidman CC
Summary:
new horizons in targeting SCLC

• Recent genomic, transcriptomic, and proteomic analyses providing new possible targets in SCLC

• Embryonic/stem cell targeting
  – Hedgehog pathway and others now emerging (SOX2?)

• Apoptotic pathway targeting
  – Bcl-2 family and recent synergy data

• Oncolytic viral therapy
  – Activity may be focused in a subset of SCLC

• Epigenetic regulatory pathways
  – EZH2, BRD4, and others

• DNA damage and defects in DNA repair
  – PARP1 and others