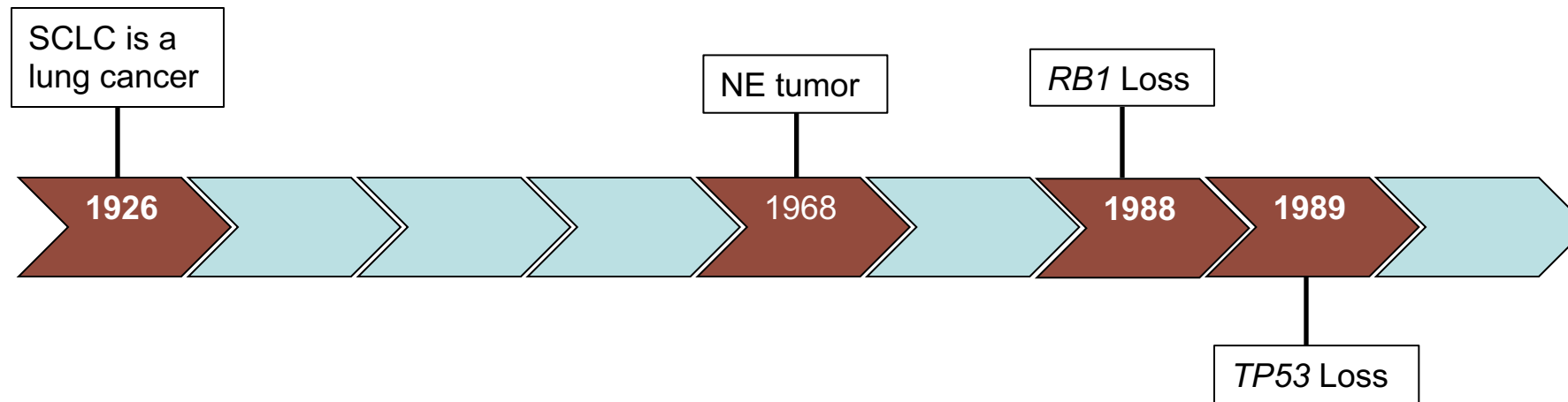


# Predictive Biomarkers in Small Cell Lung Carcinoma



Janakiraman Subramanian MD,  
MPH

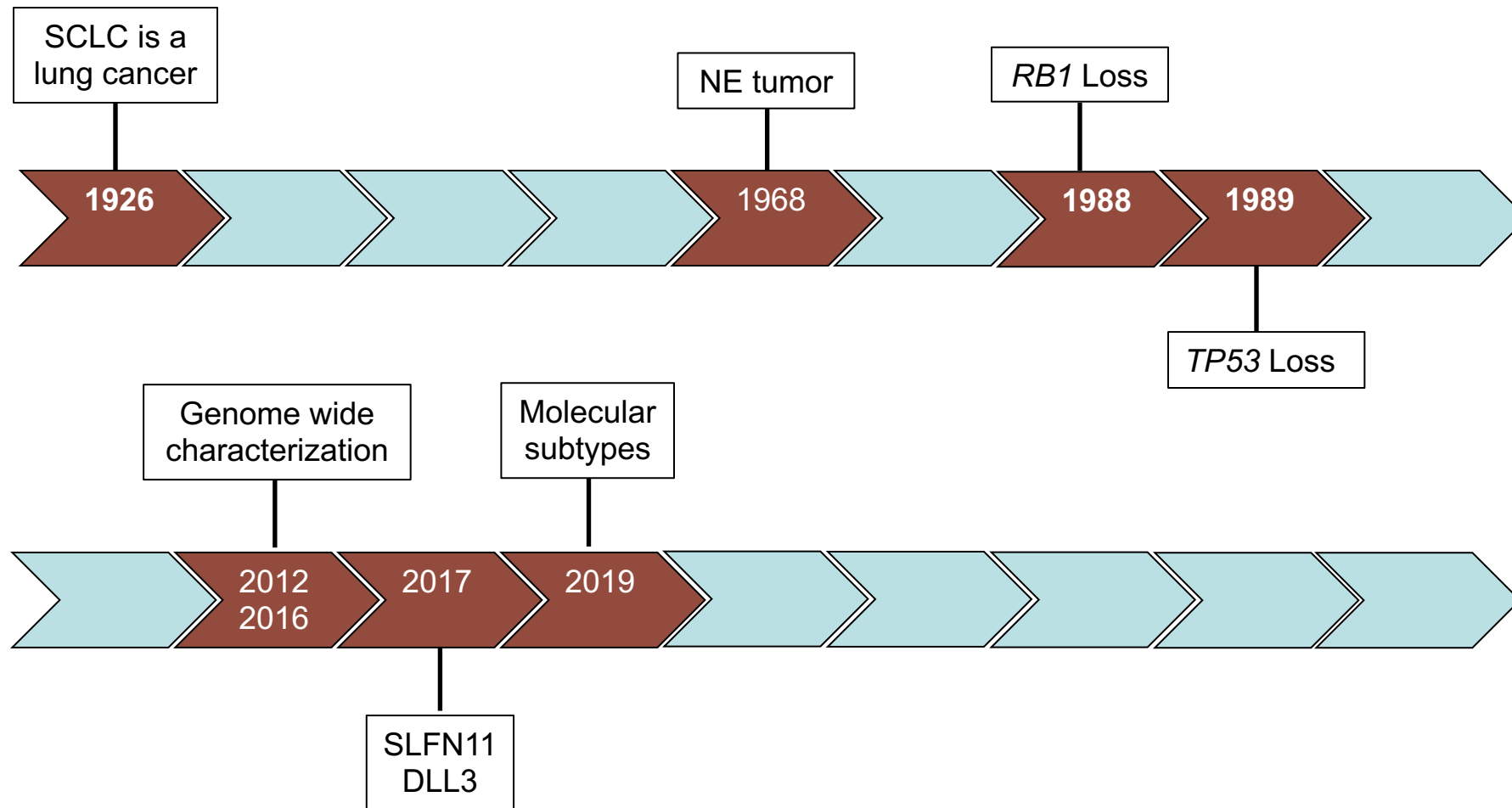
# Small Cell Lung Carcinoma



- Poorly differentiated neuroendocrine tumor characterized by lack of actionable driver mutations.
- Express at least 1 NE marker – Chromogranin A, synaptophysin, CD56 & INSM1 on IHC
- Near universal loss of *TP53* & *RB1*

Barnard. J Pathol Bacteriol 1926  
Bensch Cancer 1968  
Takahashi. Science 1989  
Harbour, Science 1988

# Small Cell Lung Carcinoma



Barnard. J Pathol Bacteriol 1926  
Bensch Cancer 1968  
Takahashi. Science 1989  
Harbour, Science 1988

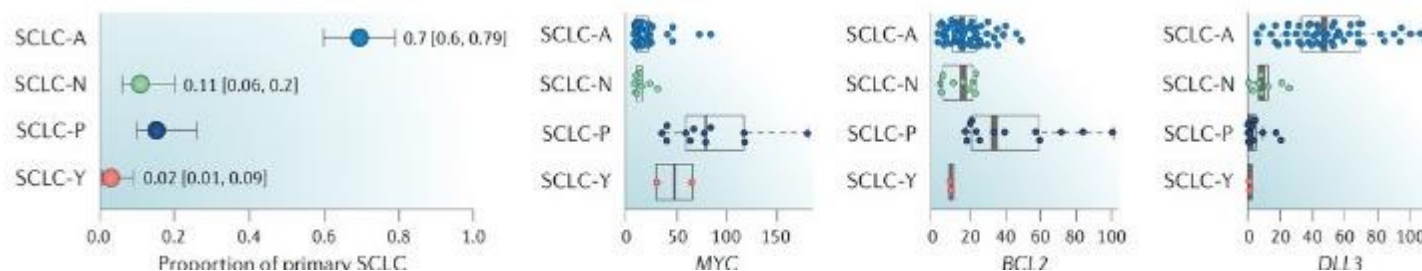
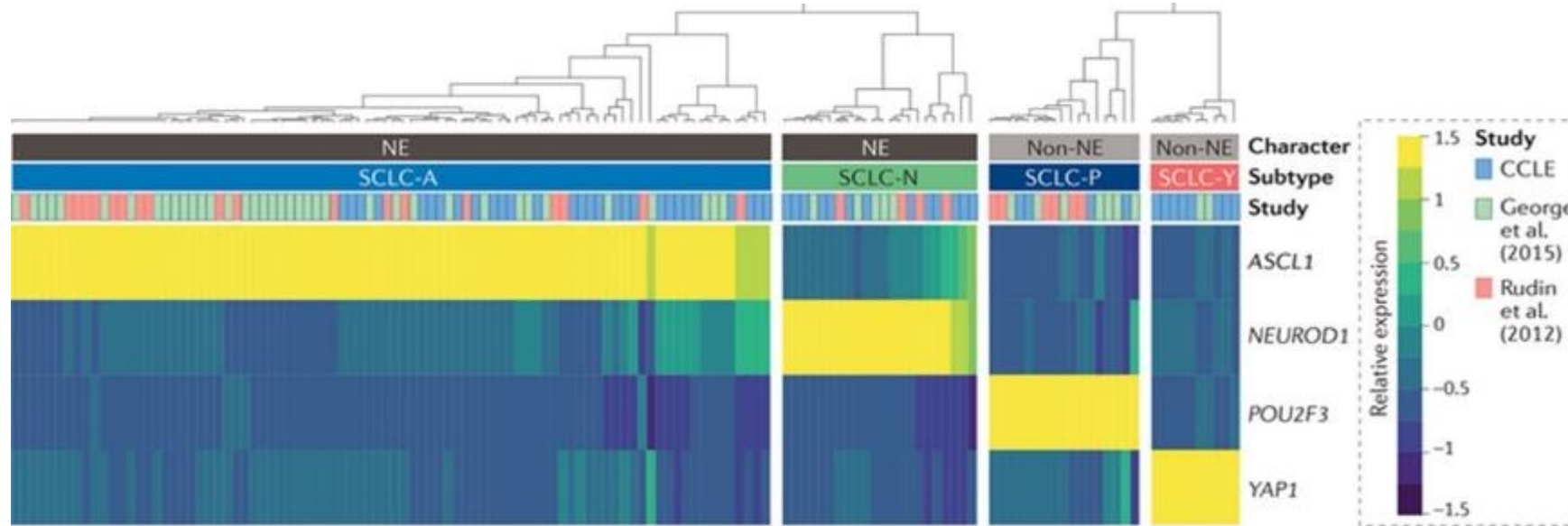
George. Nature 2014  
Rudin Nat Genet 2012  
Fernandez-Cuesta. Nat Genet 2012  
Gardner. Cancer Cell 2017

Stewart. Oncotarget  
Rudin. Lancet Oncol. 2017  
Rudin. Nat Rev Cancer 2019

# SCLC subtypes defined by dominant transcriptional regulator

## Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data

Charles M. Rudin<sup>1,\*</sup>, John T. Poirier<sup>1,\*</sup>, Lauren Averett Byers<sup>2</sup>, Caroline Dive<sup>3</sup>, Afshin Dowlati<sup>4</sup>, Julie George<sup>5</sup>, John V. Heymach<sup>2</sup>, Jane E. Johnson<sup>6</sup>, Jonathan M. Lehman<sup>7</sup>, David MacPherson<sup>8</sup>, Pierre P. Massion<sup>7</sup>, John D. Minna<sup>6</sup>, Trudy G. Oliver<sup>9</sup>, Vito Quaranta<sup>7</sup>, Julien Sage<sup>10</sup>, Roman K. Thomas<sup>5</sup>, Christopher R. Vakoc<sup>11</sup>, and Adi F. Gazdar<sup>6,12</sup>

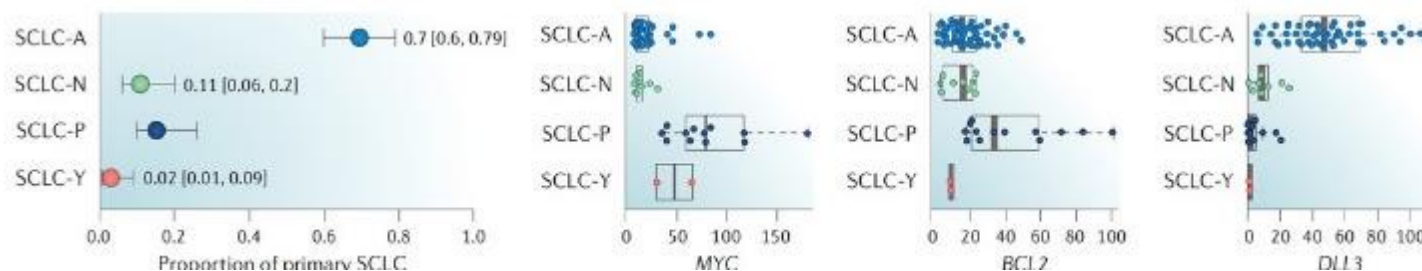
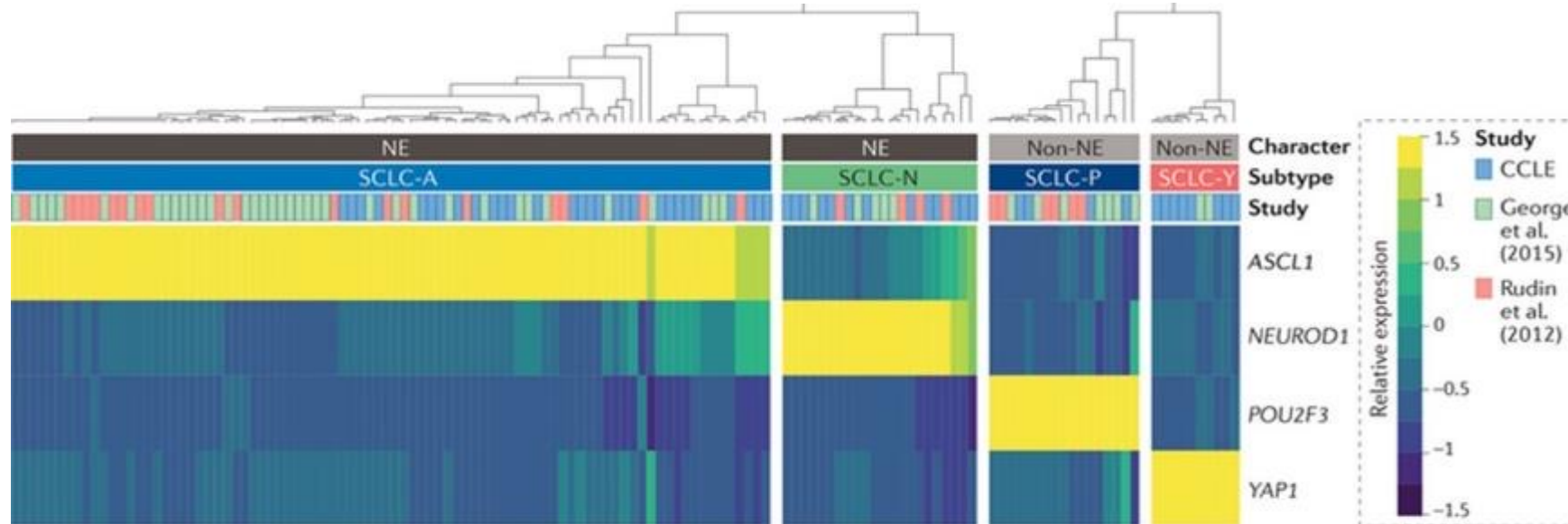


# SCLC subtypes defined by dominant transcriptional regulator

## Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data

Charles M. Rudin<sup>1,\*</sup>, John T. Poirier<sup>1,\*</sup>, Lauren Averett Byers<sup>2</sup>, Caroline Dive<sup>3</sup>, Afshin Dowlati<sup>4</sup>, Julie George<sup>5</sup>, John V. Heymach<sup>2</sup>, Jane E. Johnson<sup>6</sup>, Jonathan M. Lehman<sup>7</sup>, David MacPherson<sup>8</sup>, Pierre P. Massion<sup>7</sup>, John D. Minna<sup>6</sup>, Trudy G. Oliver<sup>9</sup>, Vito Quaranta<sup>7</sup>, Julien Sage<sup>10</sup>, Roman K. Thomas<sup>5</sup>, Christopher R. Vakoc<sup>11</sup>, and Adi F. Gazdar<sup>6,12</sup>

- 4 subtypes – SCLC-A, SCLC-P, SCLC-N & SCLC-Y!

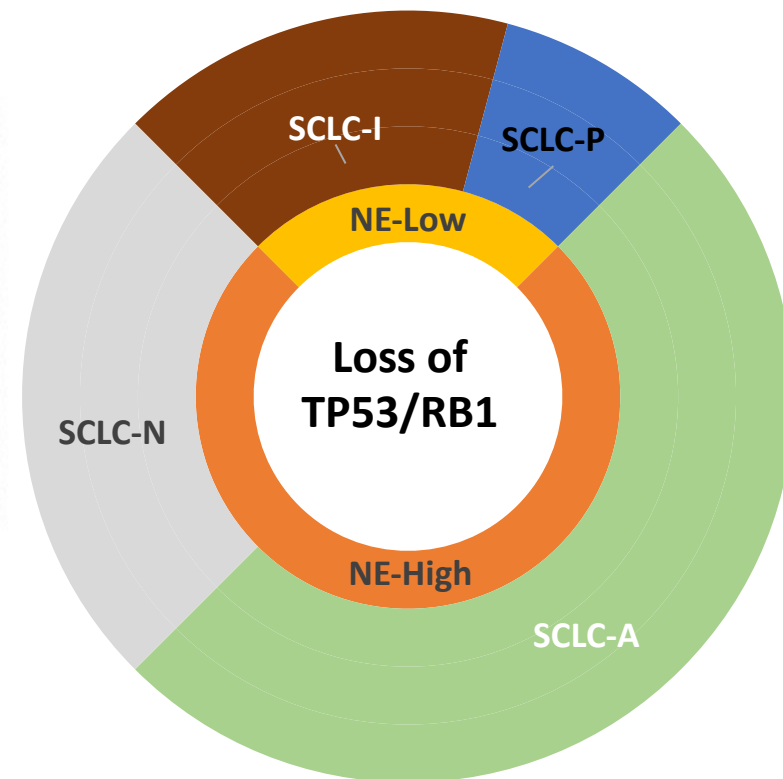
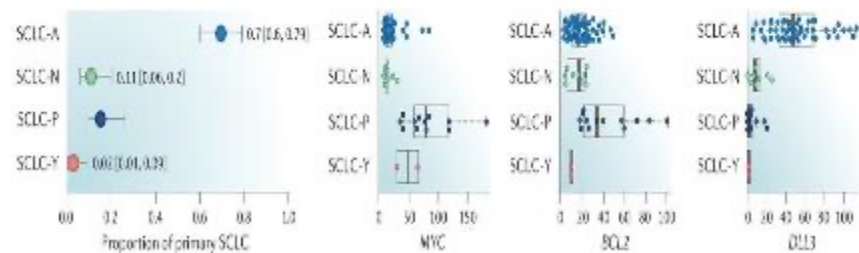
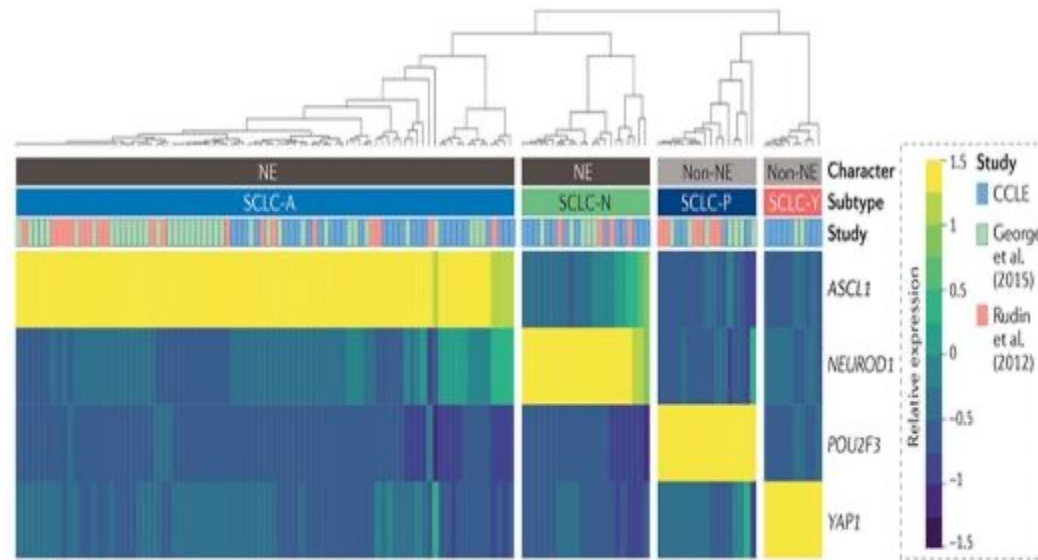


# SCLC subtypes defined by dominant transcriptional regulator

## Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data

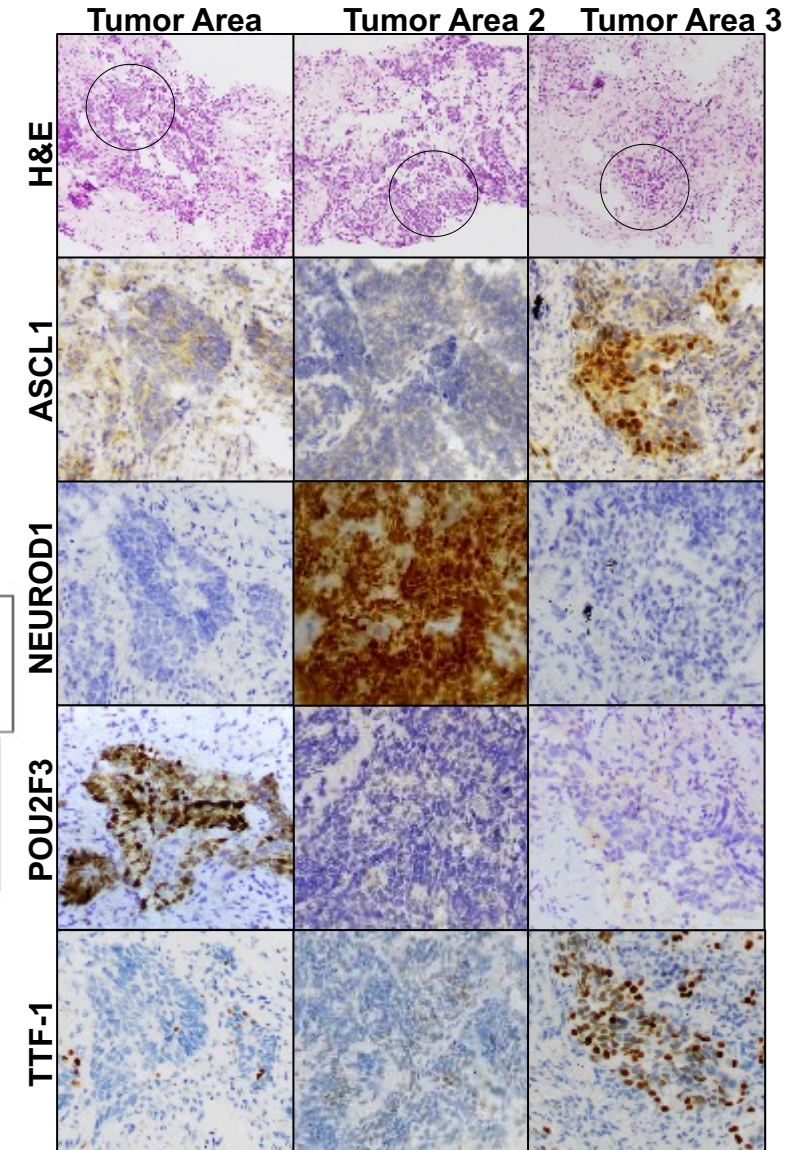
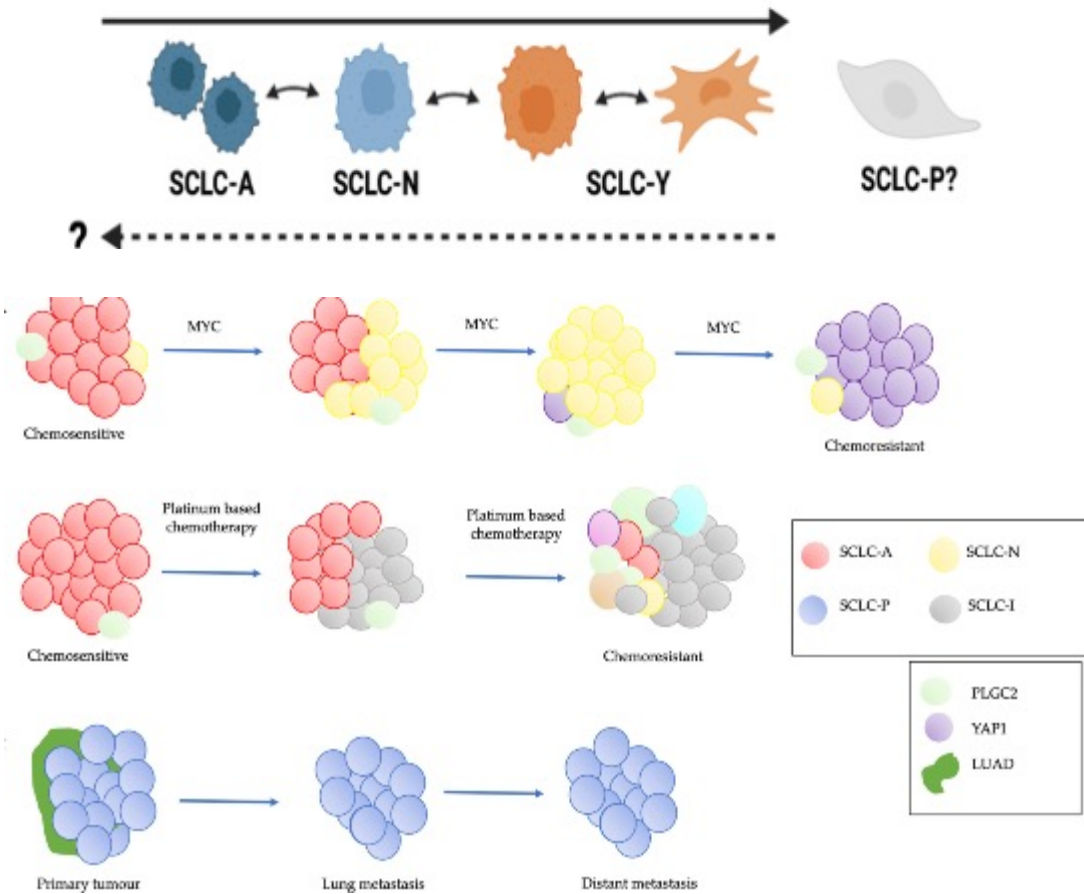
Charles M. Rudin<sup>1,\*</sup>, John T. Poirier<sup>1,\*</sup>, Lauren Averett Byers<sup>2</sup>, Caroline Dive<sup>3</sup>, Afshin Dowlati<sup>4</sup>, Julie George<sup>5</sup>, John V. Heymach<sup>2</sup>, Jane E. Johnson<sup>6</sup>, Jonathan M. Lehman<sup>7</sup>, David MacPherson<sup>8</sup>, Pierre P. Massion<sup>7</sup>, John D. Minna<sup>6</sup>, Trudy G. Oliver<sup>9</sup>, Vito Quaranta<sup>7</sup>, Julien Sage<sup>10</sup>, Roman K. Thomas<sup>5</sup>, Christopher R. Vakoc<sup>11</sup>, and Adi F. Gazdar<sup>6,12</sup>

- 4 subtypes – SCLC-A, SCLC-P, SCLC-N & SCLC-Y!
- SCLC-Y reclassified as SCLC-I – Inflamed phenotype

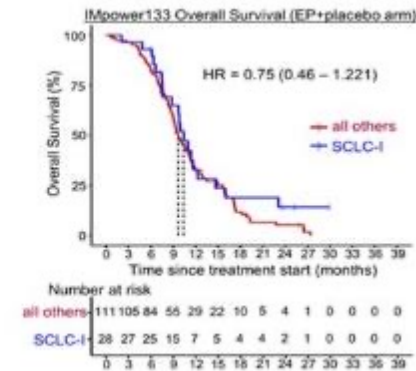
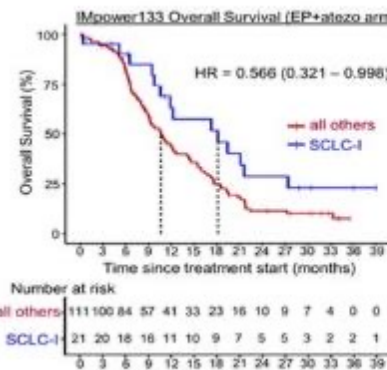
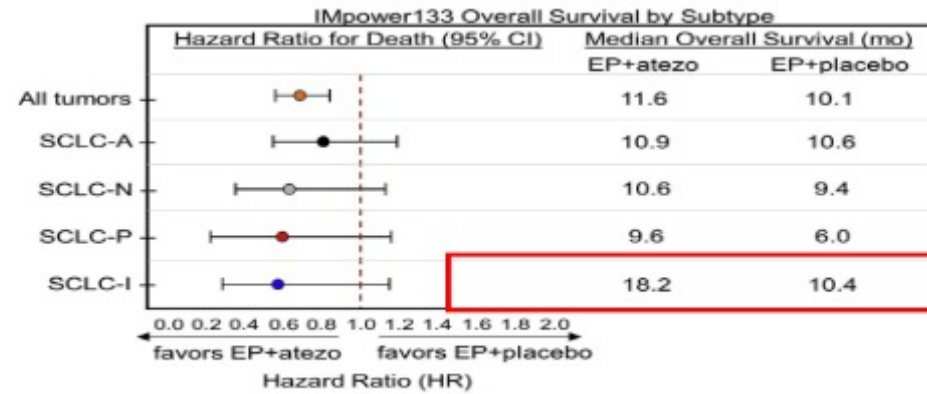
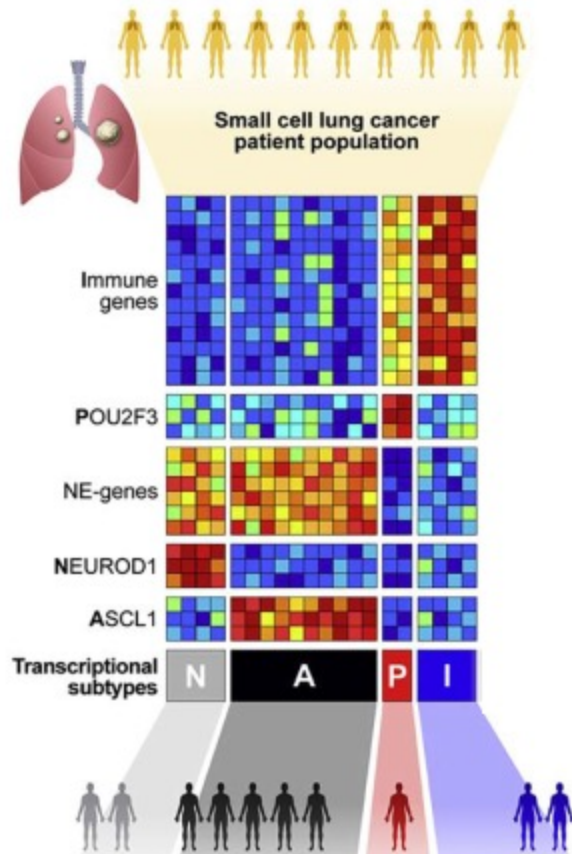


# There is more!... SCLC exhibits plasticity enhanced by treatment & tumor evolution

Subtype evolution during treatment with chemotherapy and/or disease progression



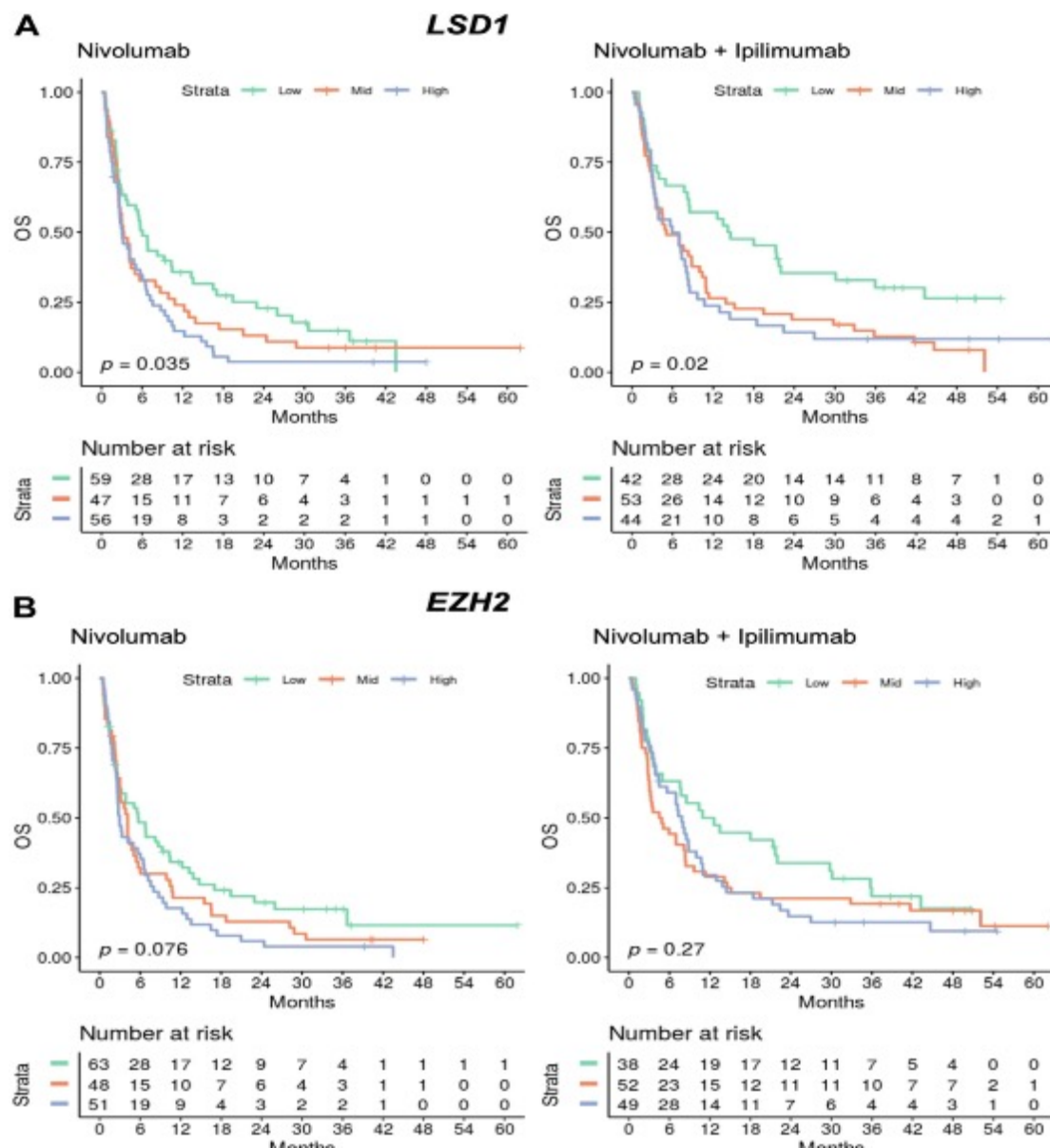
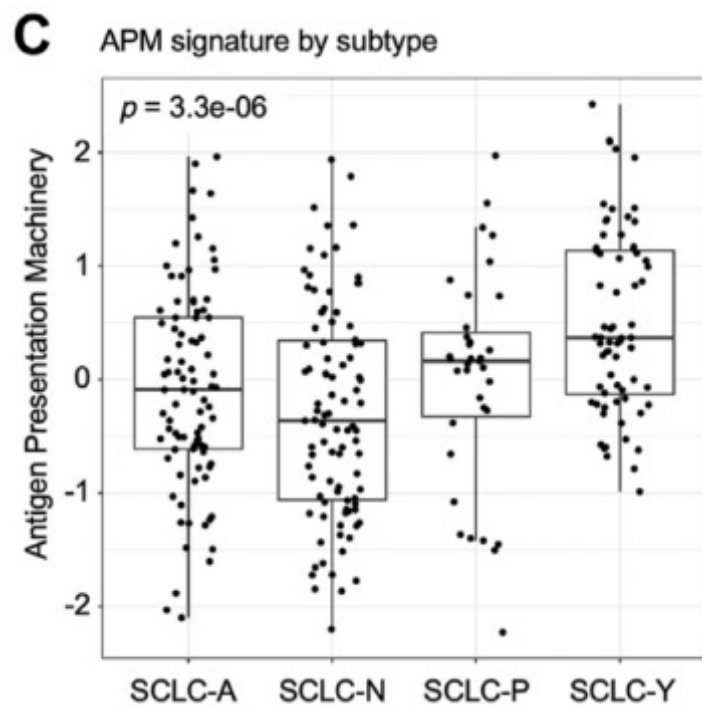
# Clinical Impact: SCLC-I subtype may predict response to immunotherapy



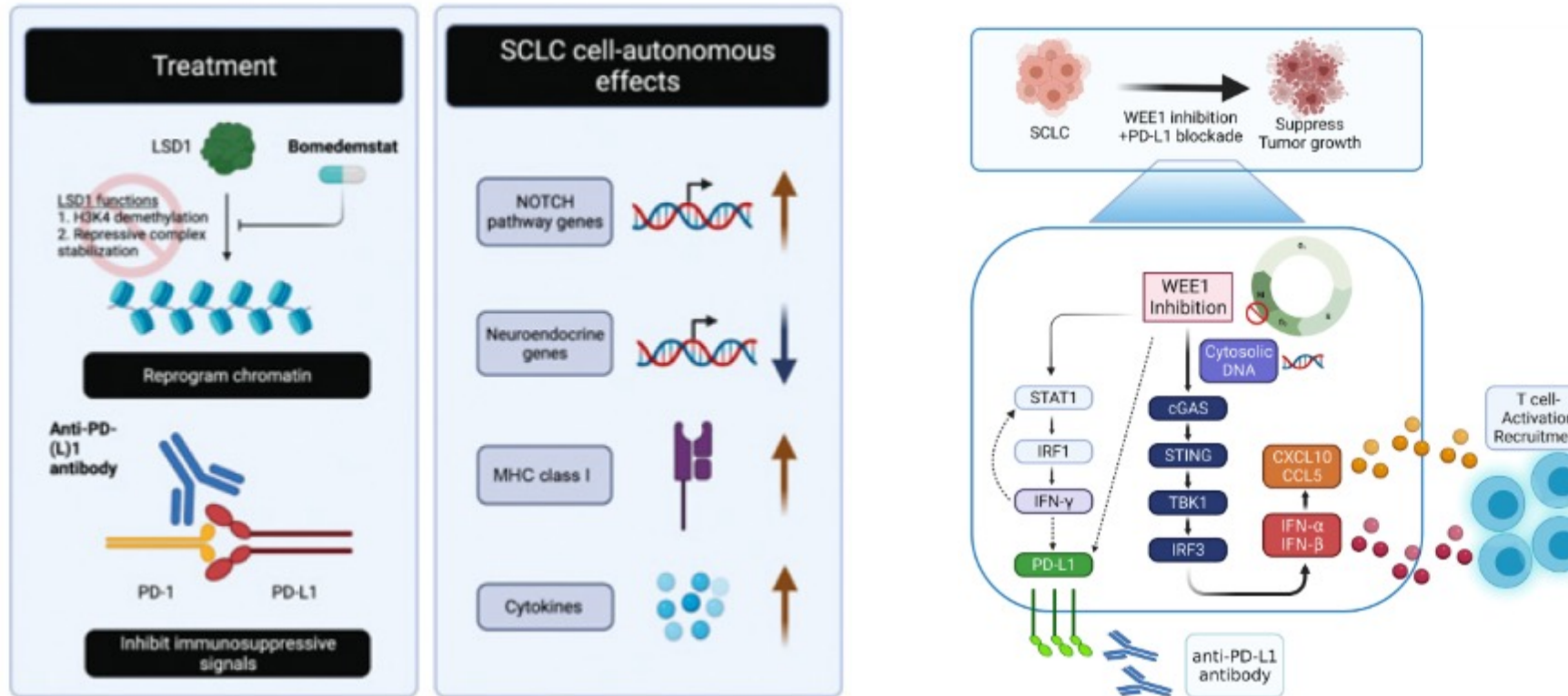
- SCLC-I subtype responsive to ICI
- But gene expression based signatures may not be viable in clinic



# ICI treatment – Role of Tumor antigen presentation and Epigenetic silencing



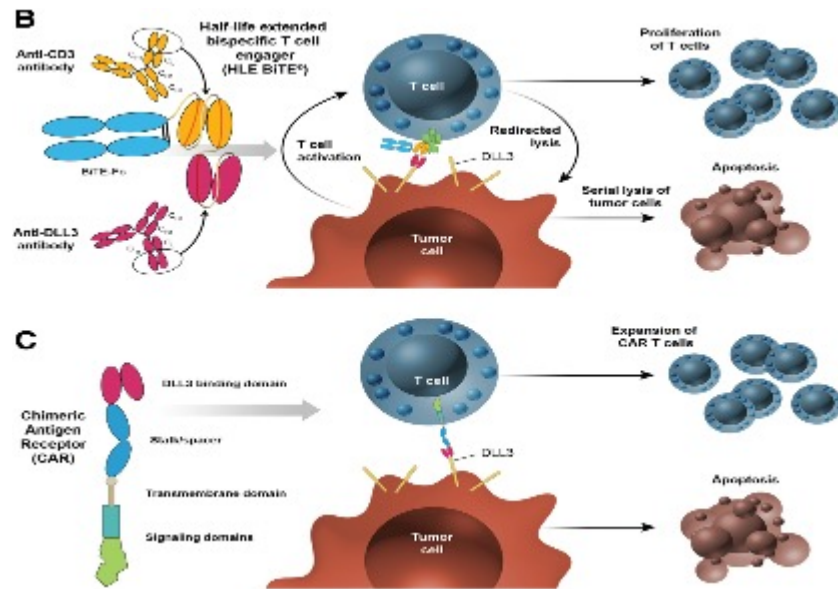
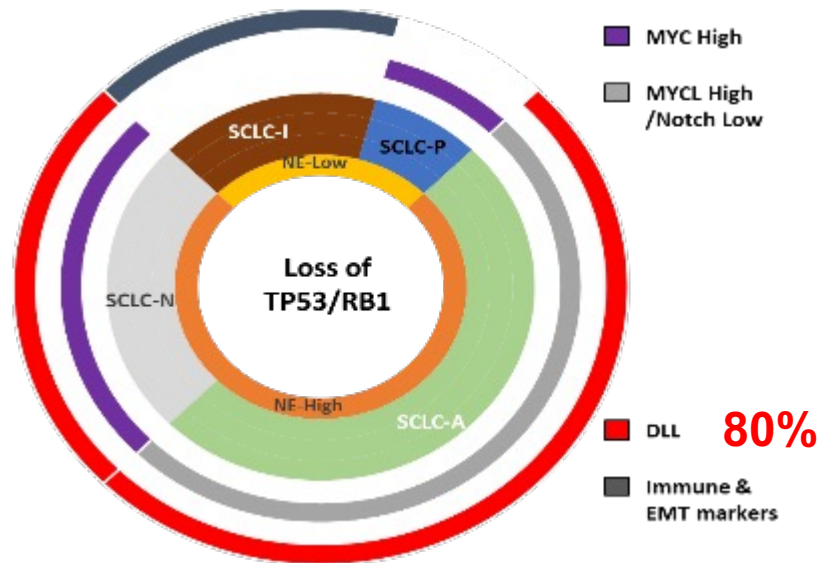
# Sensitizing SCLC to immune checkpoint inhibitors



Epigenetic reprogramming by EZH2 or LSD-1 inhibition

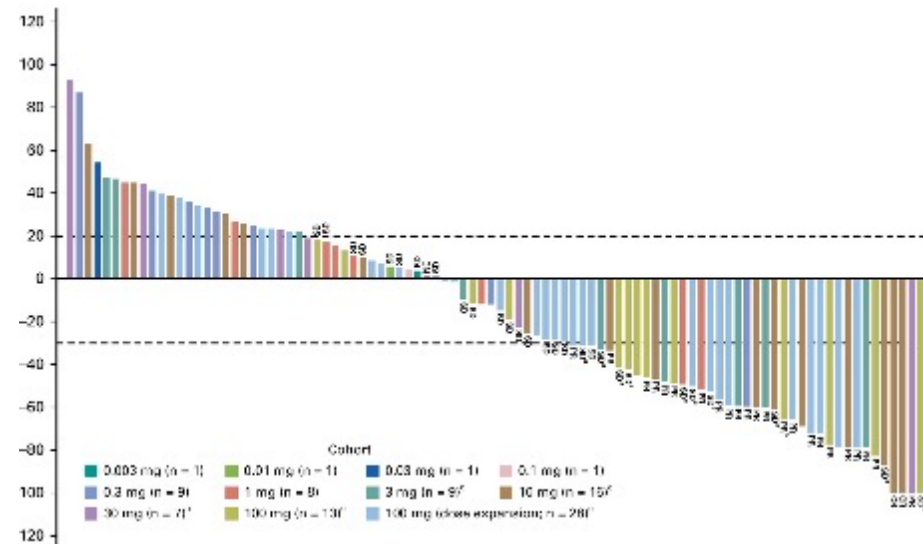
Targeting Cell Cycle or DNA damage repair

# Targeting DLL3 in SCLC



## Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study

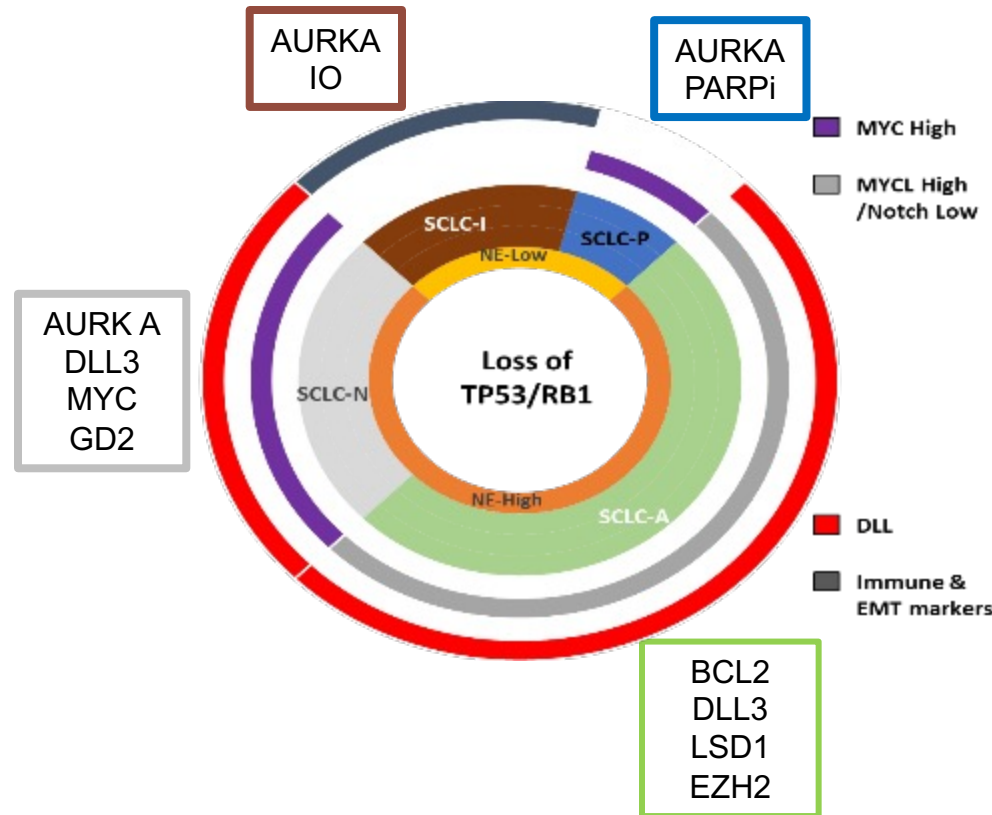
Luis Paz-Ares, MD, PhD<sup>1</sup>; Stephane Champiat, MD, PhD<sup>2</sup>; W. Victoria Lai, MD<sup>2</sup>; Hiroki Izumi, MD, PhD<sup>2</sup>; Ramaswamy Govindan, MD<sup>3</sup>; Michael Boyer, MB, BS, PhD<sup>4</sup>; Horst-Dieter Hummel, MD<sup>5</sup>; Hossein Borghaei, DO<sup>6</sup>; Melissa L. Johnson, MD<sup>7</sup>; Neeltje Steeghs, MD, PhD<sup>8</sup>; Fiona Blackhall, MD, PhD<sup>9</sup>; Afshin Dowlati, MD<sup>10</sup>; Noemi Reguart, MD, PhD<sup>11</sup>; Tatsuya Yoshida, MD, PhD<sup>12</sup>; Kai He, MD, PhD<sup>13</sup>; Shirish M. Gadgeel, MD<sup>14</sup>; Enriqueta Felip, MD, PhD<sup>15</sup>; Yiran Zhang, PhD<sup>16</sup>; Amrita Patil, PhD<sup>16</sup>; Mukul Minocha, PhD<sup>16</sup>; Sujay Mukherjee, MD<sup>10</sup>; Amanda Goldrick, MD<sup>16</sup>; Dirk Nagorsen, MD, PhD<sup>16</sup>; Nooshin Hashemi Sadraei, MD<sup>17</sup>; and Taofeek K. Owonikoko, MD, PhD<sup>18</sup>



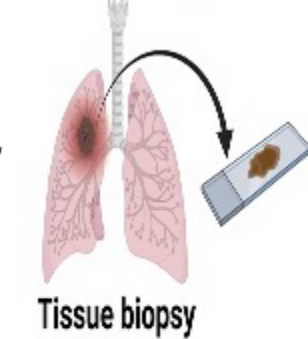
Owen. J Hematol Oncol 2019  
Paz-Ares. JCO 2023

# Clinical implications for SCLC subtypes

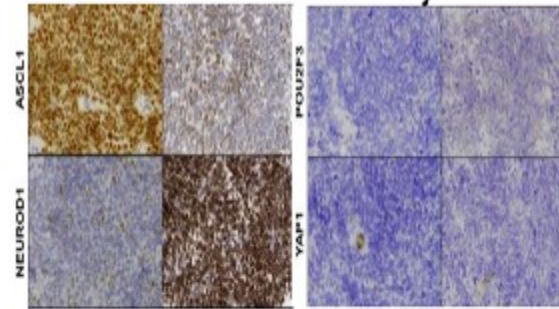
## SCLC subtype ID by tissue or blood



### Small cell lung cancer



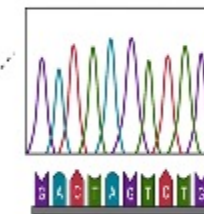
### Immunohistochemistry



Adapted from Baird et al. J Thorac Oncol 2003



### cfDNA



### NGS

- DNA-seq
- RNA-seq

### Fragmentomics

- DELFI

### Methylation profiling

- cfMeDIP-seq
- cfRRBS
- ChIP-seq (H3K4me3)
- EPICmethylation
- T7-MBD-seq



Lymphocyte subtraction

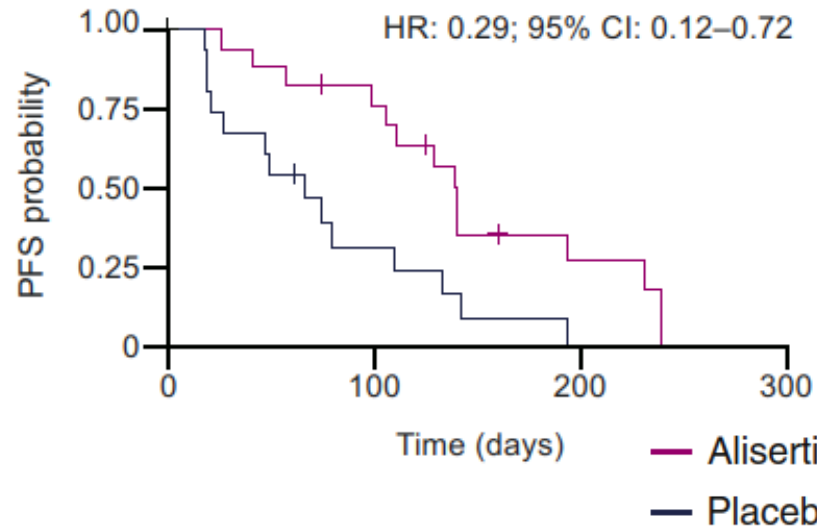
# Beyond the SCLC subtypes

## Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses

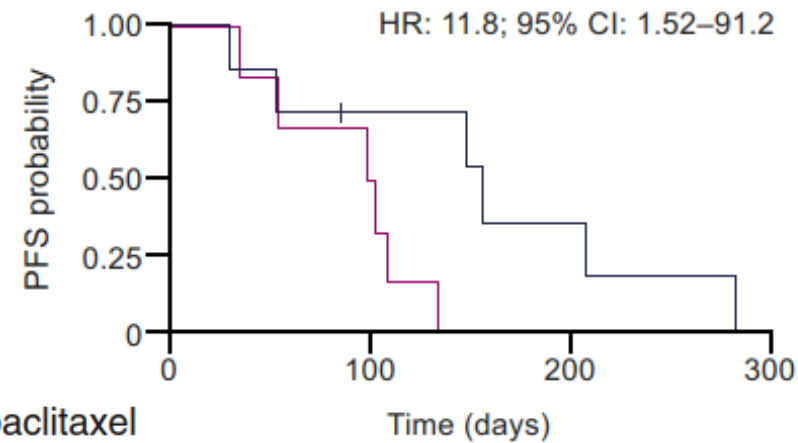
[Check for updates](#)

Taofeek K. Owonikoko, MD,<sup>a,\*</sup> Huifeng Niu, PhD,<sup>b</sup> Kristiaan Nackaerts, MD, PhD,<sup>c</sup> Tibor Csozsi, MD,<sup>d</sup> Gyula Ostoros, MD,<sup>c</sup> Zsuzsanna Mark, MD,<sup>f</sup> Christina Baik, MD, MPH,<sup>g</sup> Anil Abraham Joy, MD,<sup>h</sup> Christos Chouaid, MD,<sup>f</sup> Jesus Corral Jaime, MD,<sup>j</sup> Vitezslav Kolek, MD, PhD,<sup>k</sup> Margarita Majem, MD, PhD,<sup>l</sup>

c-Myc positive PFS

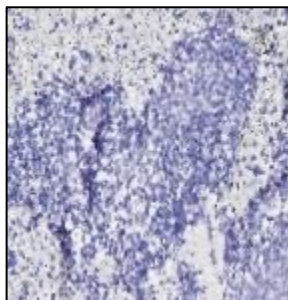


c-Myc negative PFS

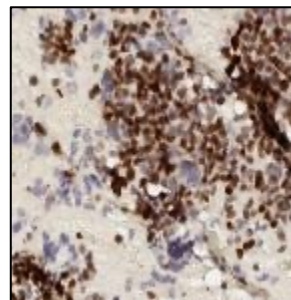


## SLFN11 predicted improved PFS and OS in Veliparib (PARPi) - Temozolomide (TMZ) combination cohort

SLFN11  
Negative

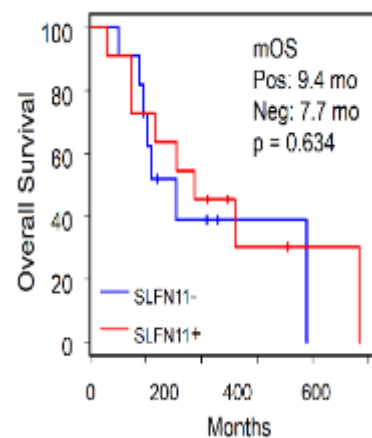


SLFN11  
Positive

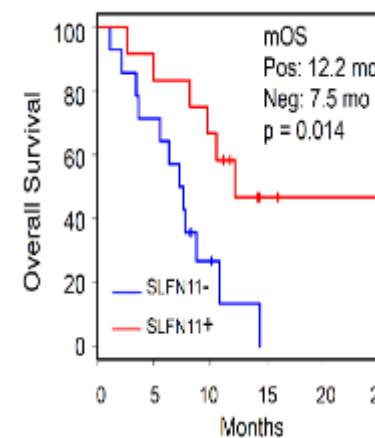


- FFPE sections from archival (diagnostic) tumors stained for SLFN11 (>1% = positive)
- **High SLFN11 (IHC) predicts improved outcome in Veliparib/TMZ arm (PFS, OS)**  
(Interaction *p*-value 0.009)

Placebo/TMZ

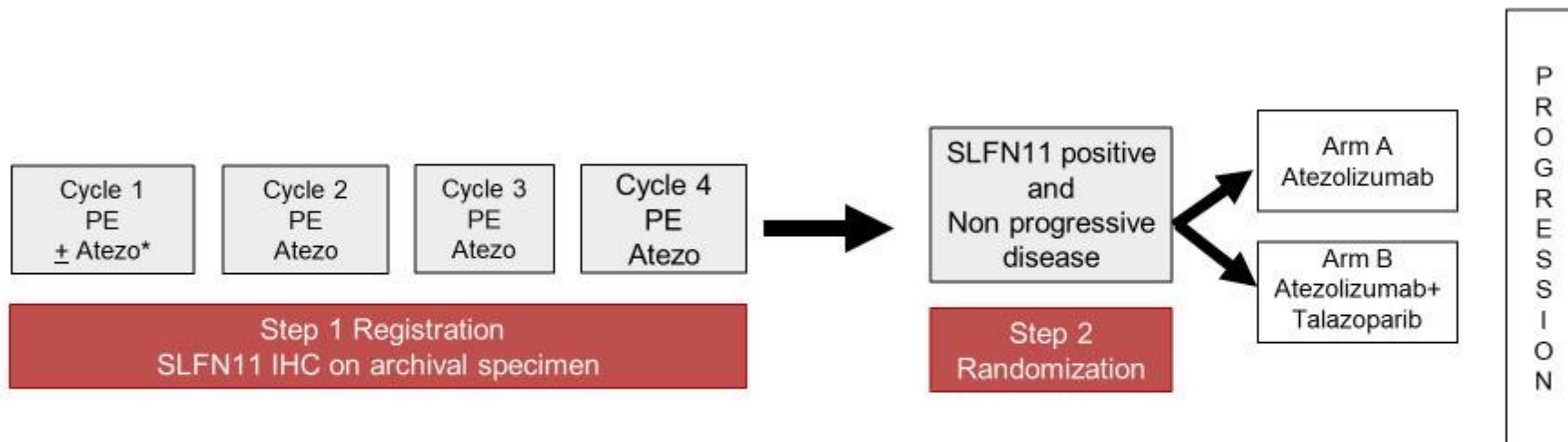


Veliparib/TMZ



OS 12.2 months in SLFN11+  
Patients vs SLFN11- (7.5mo)

# S1929: Phase II Study of Maintenance Atezolizumab Versus Atezolizumab in Combination with Talazoparib in Patients with SLFN11 Positive Extensive Stage Small Cell Lung Cancer (ES-SCLC) NCT04334941



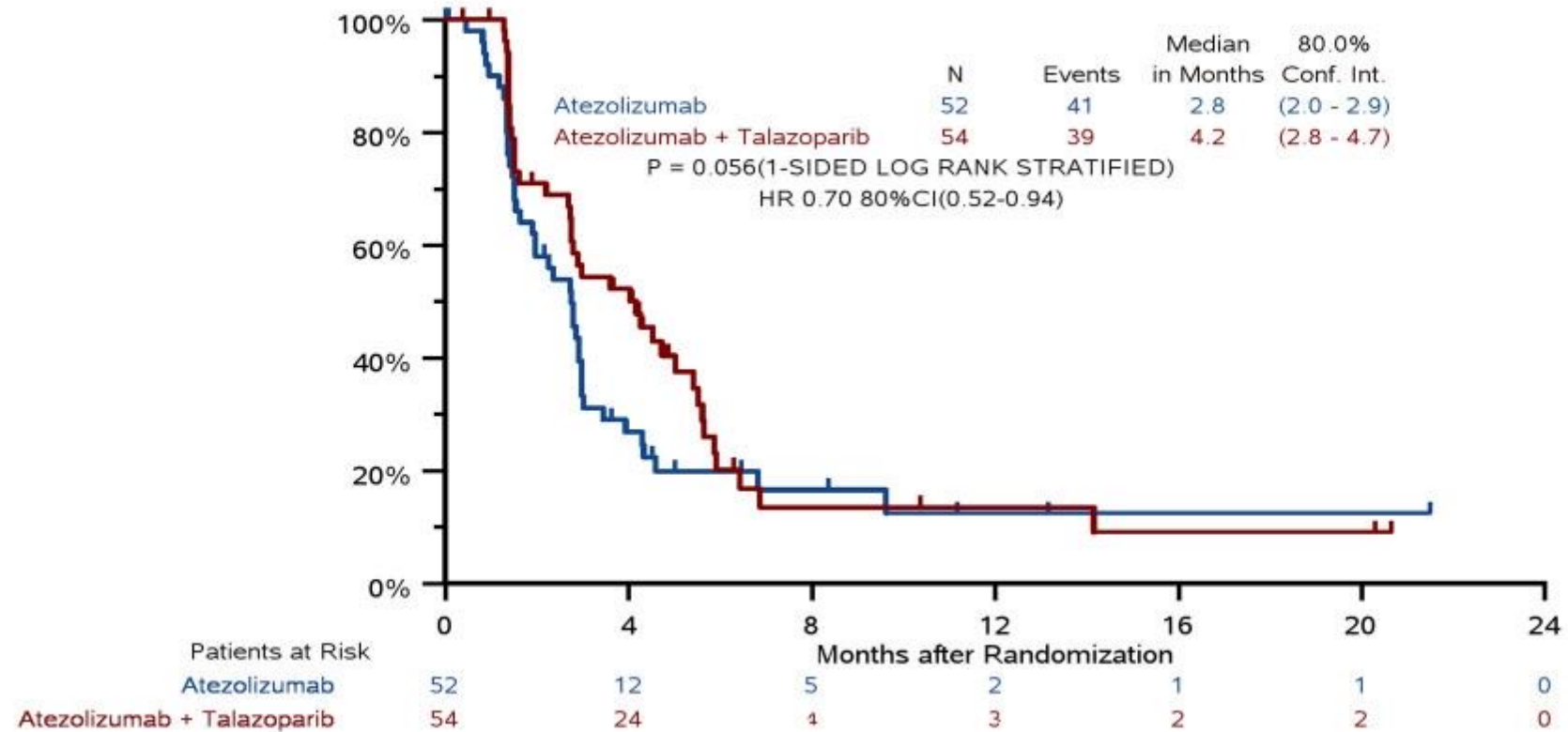
**Hypothesis: The addition of talazoparib to maintenance atezolizumab will improve PFS in SLFN11+ SCLC.**

**Primary Endpoint: PFS**  
 Secondary endpoints: OS, ORR, AE.  
 TM Objective: To bank specimens for future correlative studies.

*\*Atezolizumab was optional if the patient is hospitalized for cycle 1  
 A maximum of 9 weeks after the end of cycle 4 was allowed prior to randomization*

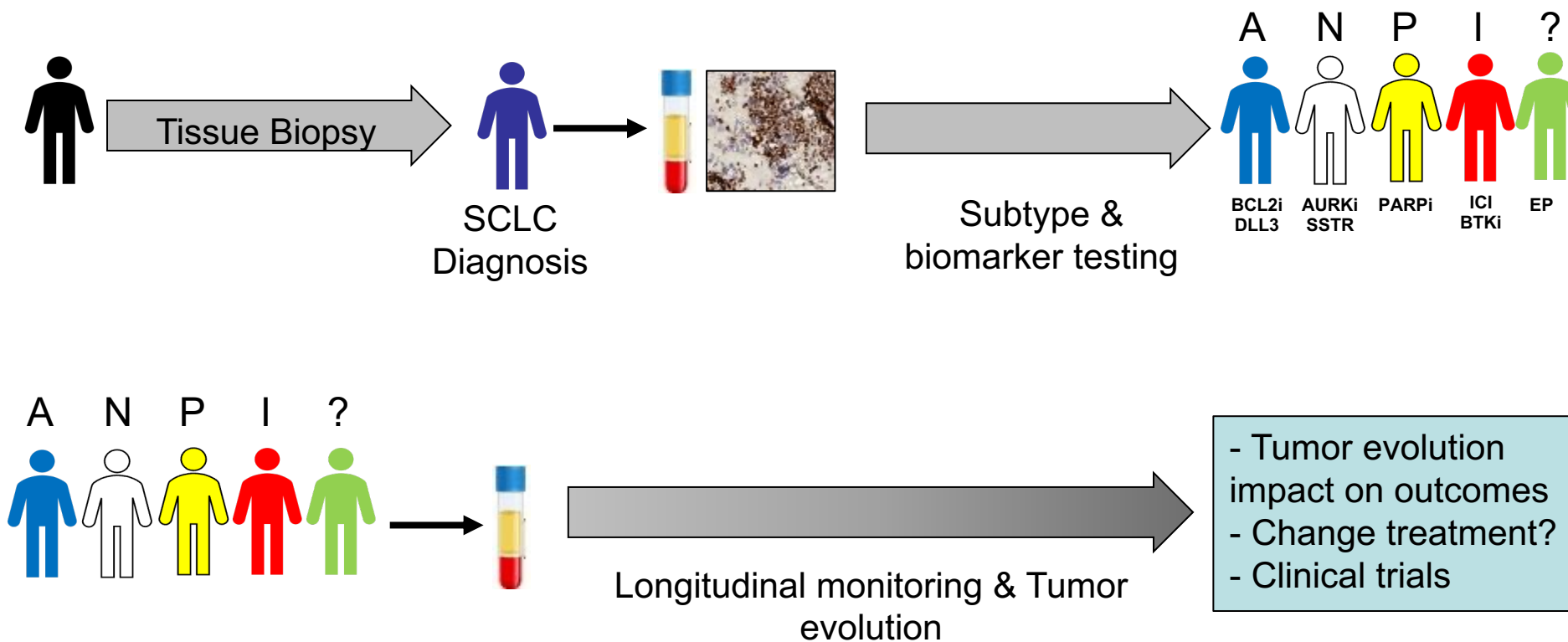










# Progression Free Survival



Median FU time among patients who are alive is 5 months with a range of (0, 21.5M)

# Personalizing SCLC Treatment



Biomarker	Status
PD-L1	
tTMB	
ecDNA	
CD8/MHC-I	
MYC	
SCLC subtypes	
SLFN11	
DLL3	

- At present biomarker testing in SCLC has minimal impact in clinic
- Transcriptional subtypes
  - Need simple & robust test platforms
    - IHC or blood-based testing
  - Guide selection of patients for clinical trials
- Continued surveillance during treatment
- BiTEs targeting DLL3 are promising
- Other targets – SLFN11, c-Myc and LSD1