

# Small cell lung cancer

Haobin Chen, M.D., Ph.D.  
Assistant Clinical Investigator  
TGIB, NCI

# Small cell lung cancer (SCLC)

## Small cell lung cancer (SCLC)

- SCLC accounts for 10% to 15% of all lung cancer cases, and it is closely linked to the intensity and duration of tobacco smoking.

### Major histological types:

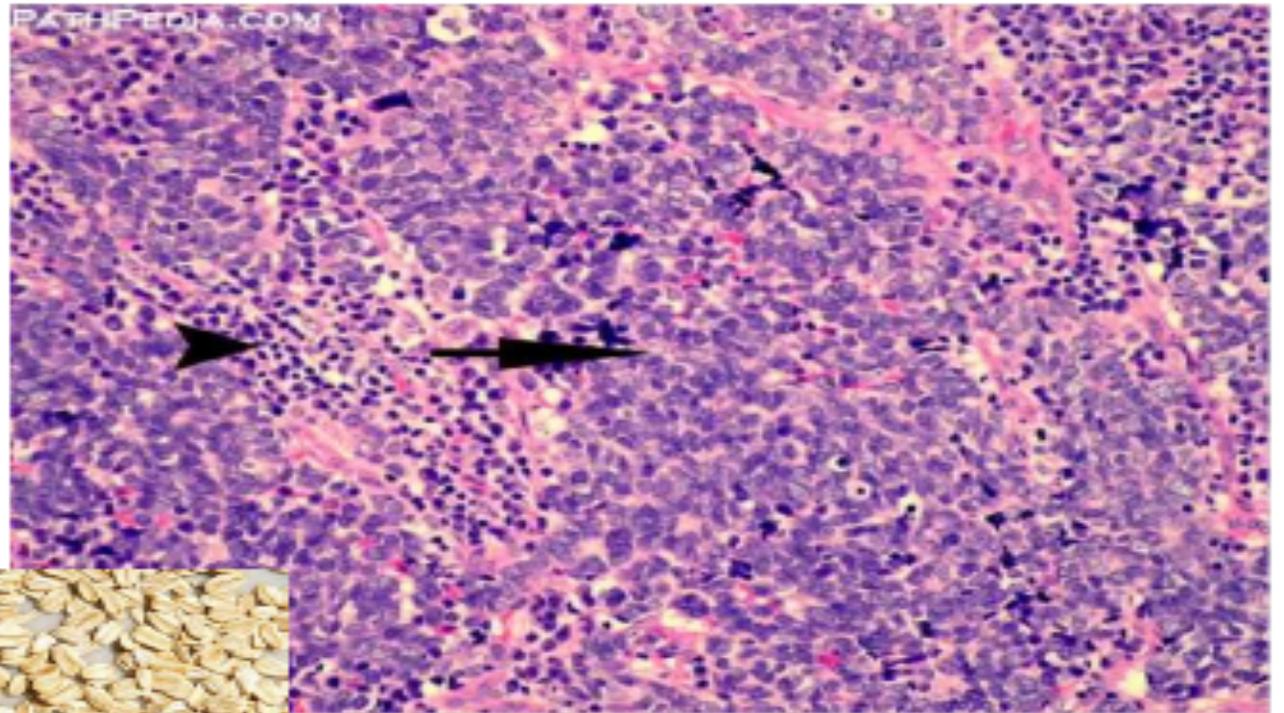
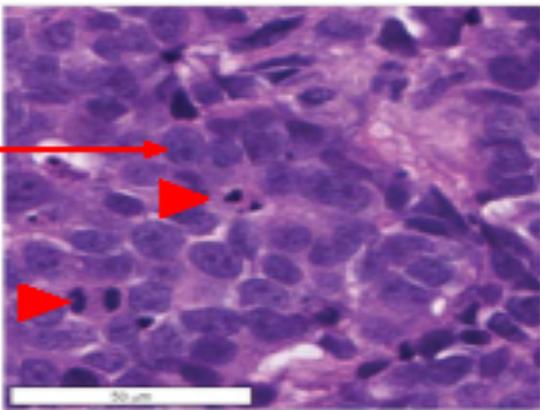
- Small cell lung cancer
- Squamous cell lung cancer
- Lung adenocarcinoma
- Large cell lung cancer

} Non-small cell lung cancer

# SCLC morphology

## Morphology of SCLC

SCLC is also known as oat cell carcinoma. Its morphology resembles oat grains and appears as small oval cells with scanty cytoplasm.



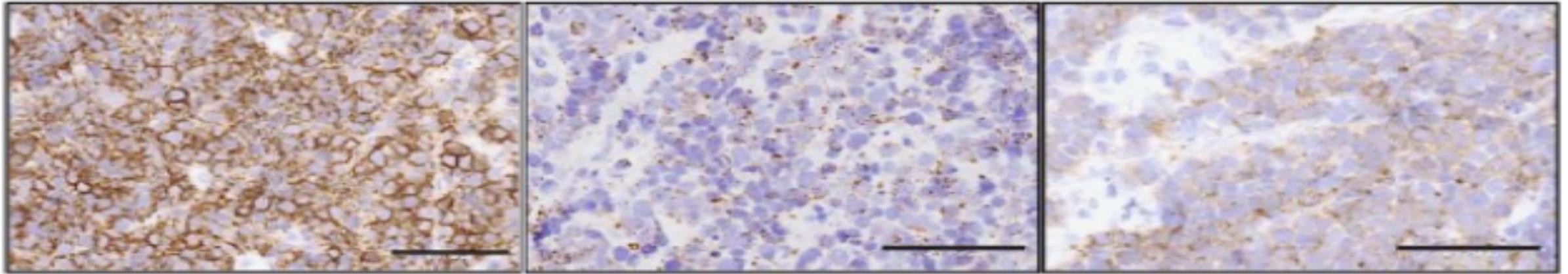
# IHC staining

## IHC staining to diagnose SCLC

CD56

Chromogranin

Synaptophysin



# Extrapulmonary SCLC

## Extrapulmonary small cell carcinoma (EPSCC)

**Table 1**  
Frequency of EPSCC per site of origin.

	Percentage of SCC/total per site of origin	Estimated number of patients in US per year*
Pulmonary	15–20%	32,250–43,000
Oesophagus	0.8–2.4%	130–395
Larynx	0.5–1%	60–120
Bladder	0.3–1.0%	200–680
Cervix	±1%	±110
Prostate	±2%	±250
Unknown primary	7–30% of all EPSCC	70–300

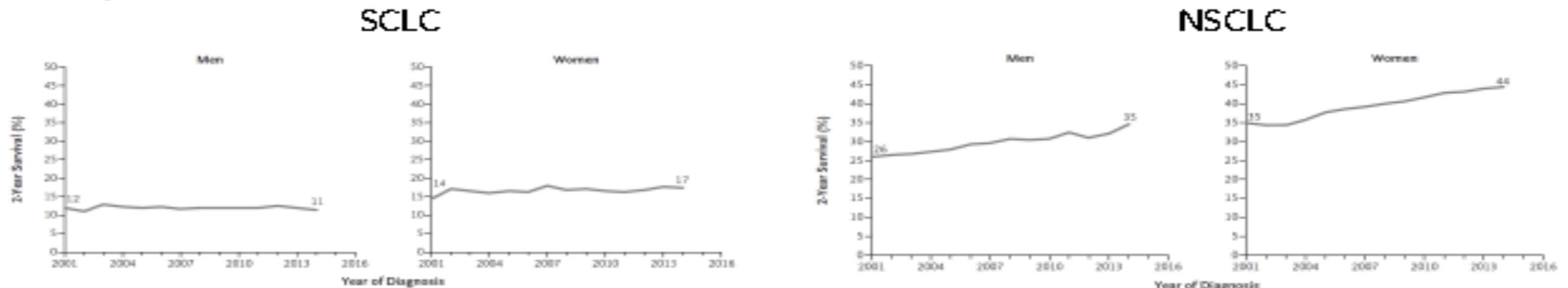
SCC denotes small cell carcinoma; EPSCC denotes extrapulmonary small cell carcinoma.

\* <http://www.cancer.gov/cancertopics/pdq>.

# SCLC treatment

## SCLC is a difficult cancer to treat

- Compared to NSCLC, SCLC tends to disseminate earlier in the course of its natural history and displays a more aggressive clinical behavior.
- SCLC is notorious for rapid development of drug resistance.
- From 2000-2014, 2-year survival rates in patients with SCLC had not improved.



# SCLC is considered as a recalcitrant cancer

- Recalcitrant Cancer Research Act of 2012.
- Recalcitrant cancer:
  - Have a 5-year relative survival rate of less than 20%
  - Estimated to cause the death of at least 30,000 individuals in the United States per year.
- NCI identified four major obstacles to progress in 2014:
  - Continuing risk of developing the disease that remains for decades after smoking cessation.
  - Most patients have widely metastatic tumors at the time of diagnosis.
  - Rapid development of resistance to chemotherapy in more than 95% of SCLC patients.
  - Lack of tumor tissue for clinical, molecular , and cell biological studies.

# SCLC systemic therapy

## Systemic therapy of SCLC

Standard of Care	Before Dec 2017	After Dec 2017
1 <sup>st</sup> Line	Platinum + Etoposide	Carboplatin + Etoposide + immune checkpoint inhibitors
2 <sup>nd</sup> Line	Topotecan (Irinotecan)	Topotecan (Irinotecan)/Lurbinectedin
3 <sup>rd</sup> Line		Nivolumab or Pembrolizumab

- It was learned quite early in the 1970s that combinatory therapy produces superior survival compared with single-agent treatment based on several randomized trials.

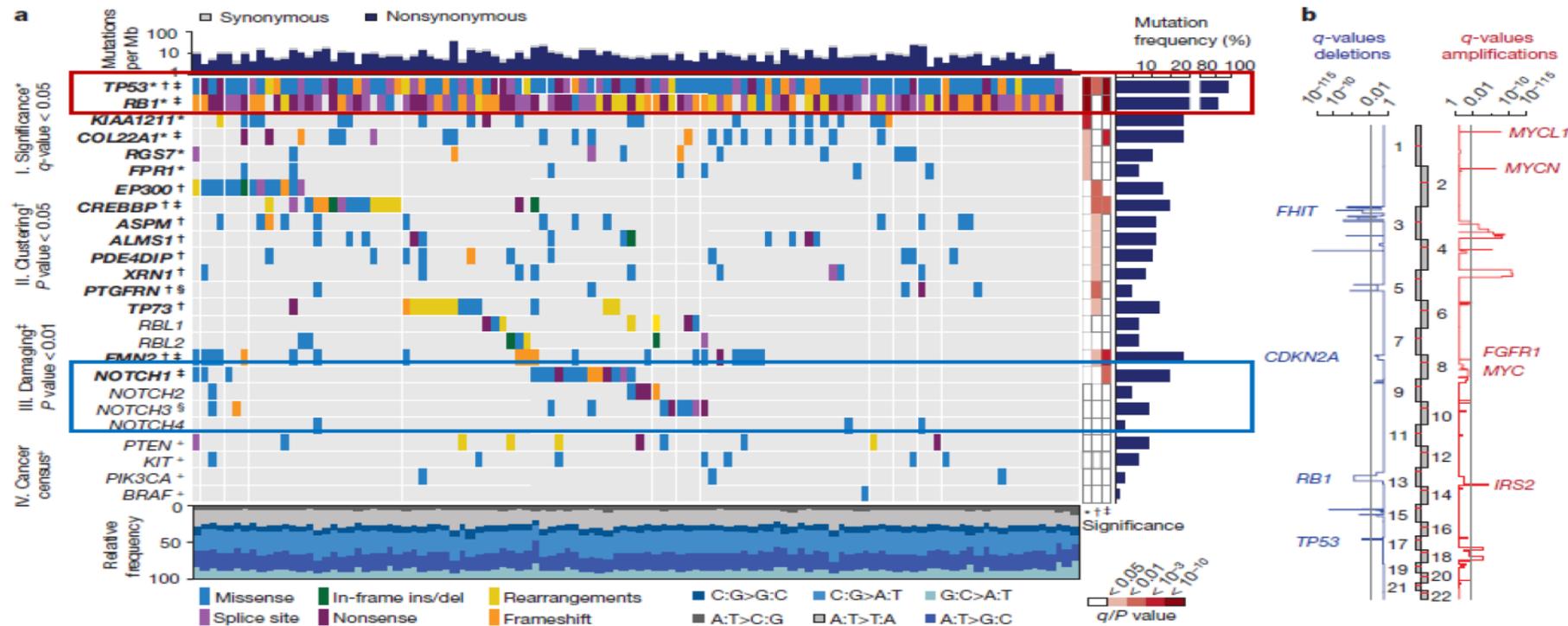
# Genomic abnormalities

## Genomic abnormalities of SCLC

1. Inactivation of Rb and TP53
2. Inactivation of Epigenetic genes EP300 and CREBBP
3. Inactivation of Notch signaling

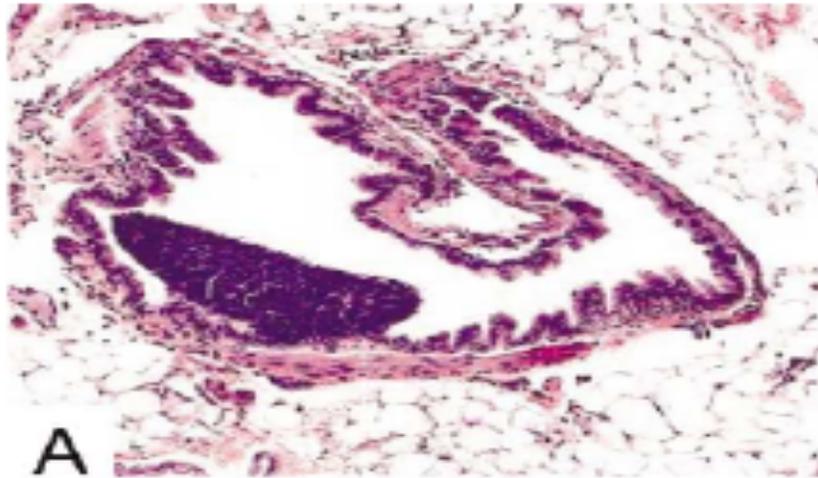
# Genetic abnormalities

## Genetic abnormalities of SCLC: WES Analysis

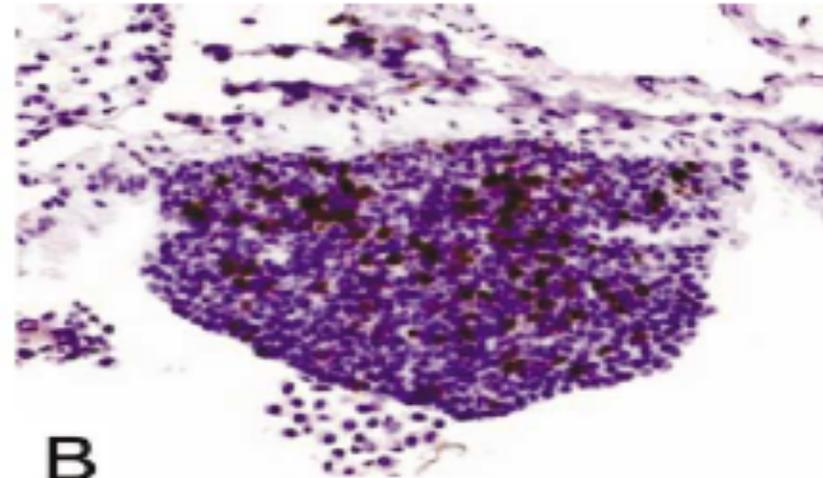


# Trp53 and Rb1

Causal relationship between SCLC and inactivation of Trp53 and Rb1



A  
Pre-malignant lesion in large airway  
(H&E staining)

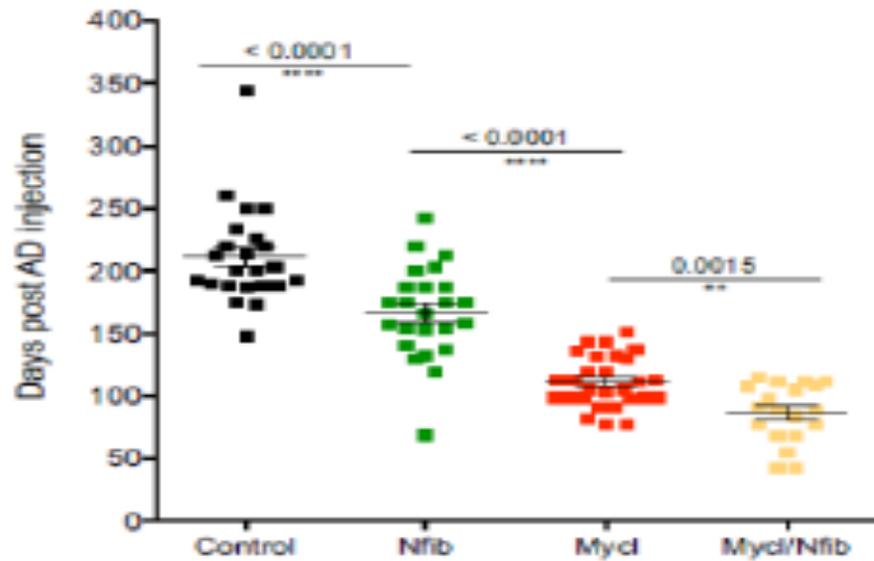


B  
Anti-BrdU staining

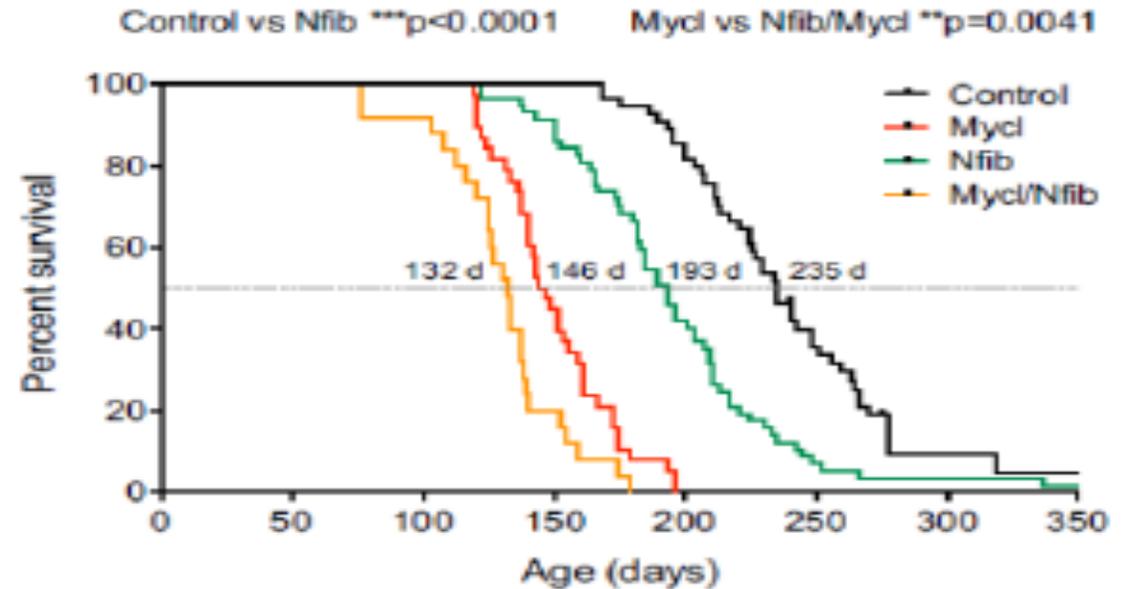
SCLC became detectable within 196-350 days in the mouse model with tissue-specific inactivation of TP53 and Rb1.

# Gene mutations

Acceleration of SCLC tumor formation by introducing additional gene mutations

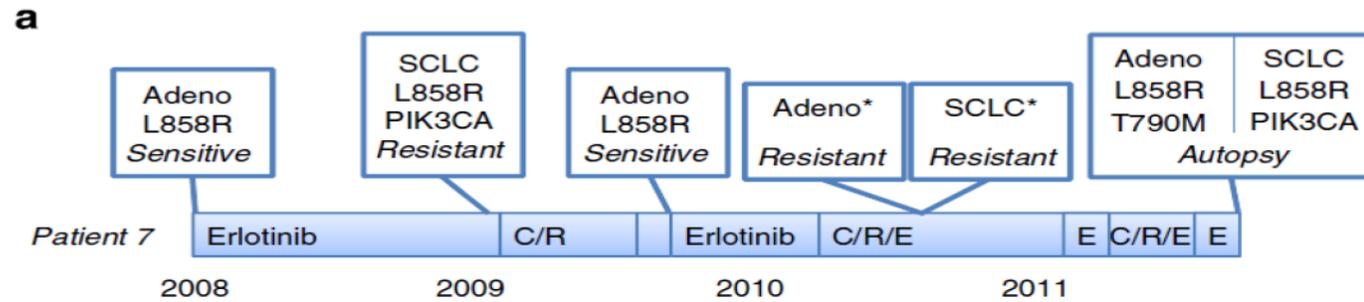


C



# SCLC conversion

SCLC conversion as a resistance mechanism to EGFR TKI in lung adenocarcinoma: Loss of TP53 and Rb genes



**b**

Sample	Normal liver	Diaphragm tumour	Lung tumour	Liver tumour
Histological features	Normal tissue	Adenocarcinoma	SCLC	SCLC
Number of reads	179,298,190	350,864,233	388,189,232	318,482,313
Average coverage	146	287	319	253
Primary EGFR mutation	WT	L858R	L858R	L858R
Secondary EGFR mutation	WT	T790M	WT	WT
PIK3CA status	WT	WT	E545K	E545K
TP53 status	WT	WT/ $\Delta$ 154-163	-/ $\Delta$ 154-163	-/ $\Delta$ 154-163

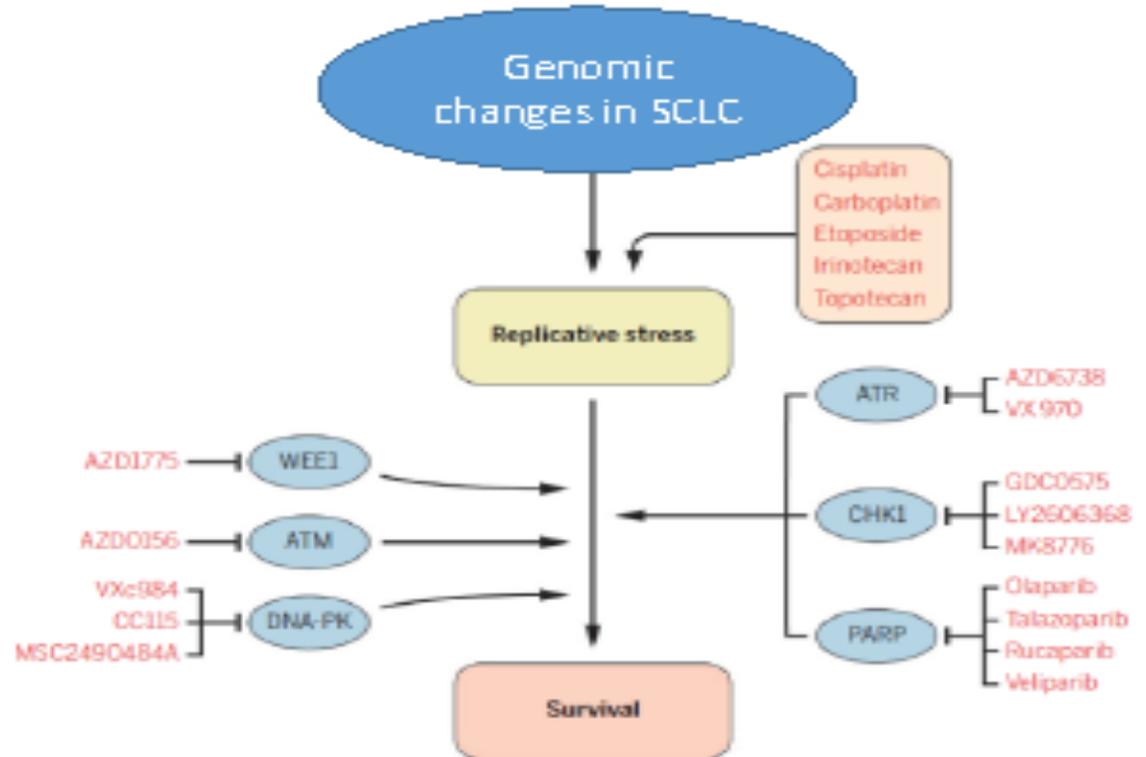
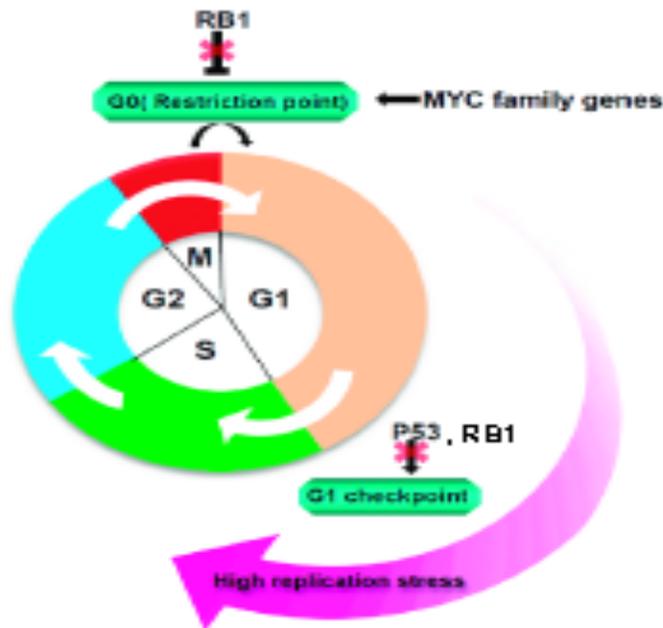
Table 1 | RB status of TKI-resistant patients.

Patient	Cancer type	Resistance	Histology	RB status	Detection method
1	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	NE	Neg	IHC/genetic
2	Lung	Pre	Adeno	Pos	IHC
	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC
	Lung	Post	NE	Neg	IHC
3	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
4	Lung	Post	NE	Neg	IHC
	Lung	Post	NE	Neg	IHC
5	Lung	Post	NE	Neg	IHC
	Lung	Post	NE	Neg	IHC
6	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC/genetic*
7	Lung	Post	Adeno	Pos	IHC/genetic
	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	NE	Neg	Genetic
8	Lung	Post	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
9	Lung	Post	NE	Neg	IHC
	Lung	Post	Adeno	Neg	IHC
10	Lung	Post	Adeno	Neg	IHC
	Lung	Pre	Adeno	Pos	IHC
11	Lung	Post	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
12	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
13	Lung	Post	Adeno	Pos	IHC
	Lung	Pre	Adeno	Pos	IHC
14	Lung	Post	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
15	Lung	Post	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
16	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
17	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
18	Lung	Post	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
19 <sup>†</sup>	Lung	Intrinsic	NE	Neg	IHC

# Translational implications

# Targeting replication stress

## Targeting replication stress in SCLC - Synthetic lethality



# ATR inhibitor plus topotecan

## Example 1: ATR inhibitor Plus Topotecan

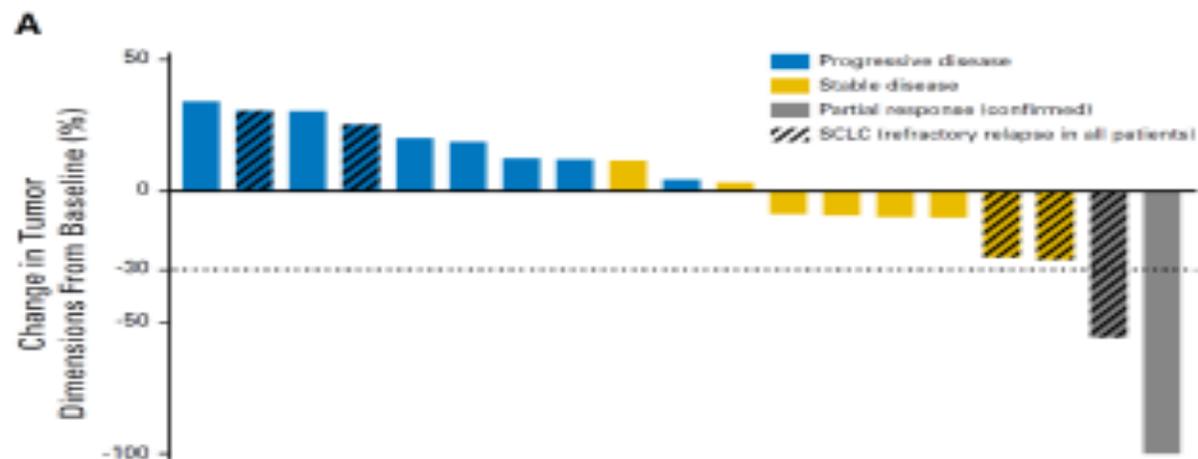
VOLUME 35 • NUMBER 12 • JUNE 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

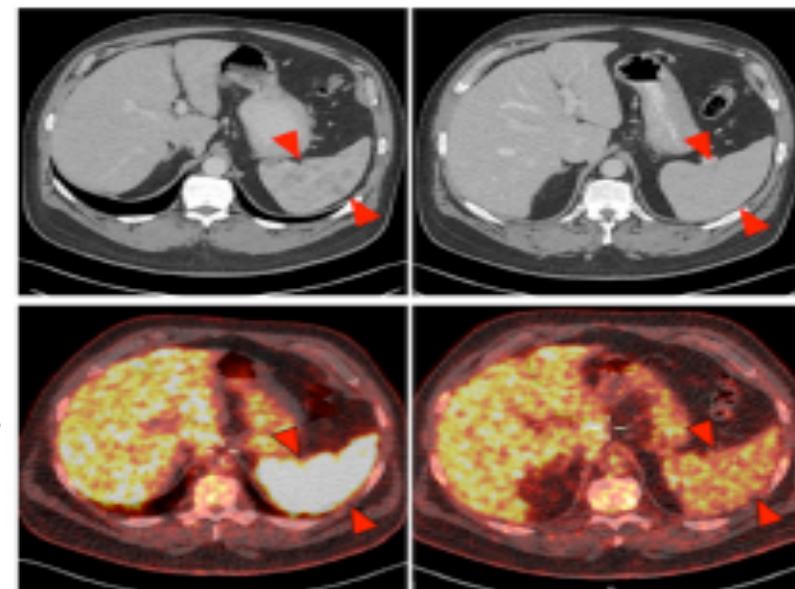
### Phase I Study of ATR Inhibitor M6620 in Combination With Topotecan in Patients With Advanced Solid Tumors

Anish Thomas, Christophe E. Rekol, Linda Scivta, Emerson Paderniss, Jinying Ji, Min-Jung Lee, Akira Yusa, Sammie Lee, Yiping Zhang, Lue Tian, William Yutzy, Arun Rajan, Utkarsh Gada, Haobin Chen, Raffi Hassan, Christine C. Alewine, Eric Szabo, Susan E. Bates, Robert J. Kissler, Seth M. Steinberg, James H. Doroshow, Mirit L. Adajewa, Jose B. Topol, and Yves Fouquier



Before treatment

After treatment

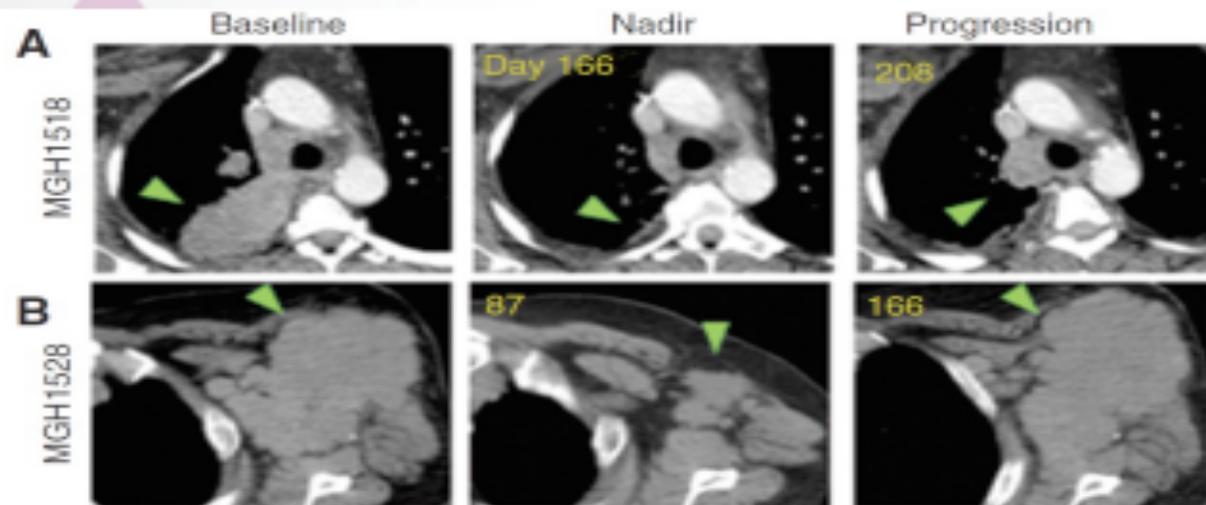
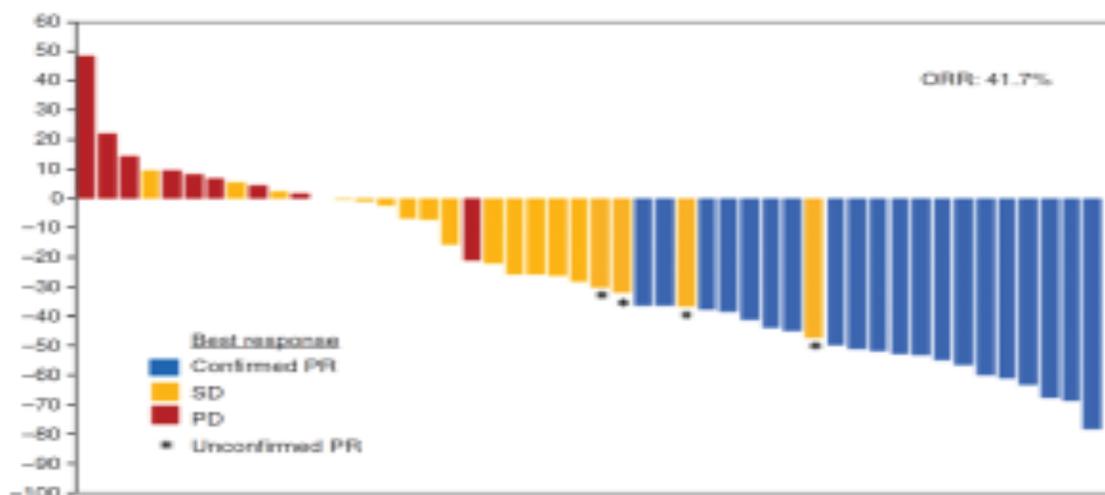


# Olaparib plus temozolomide

## Example 2: Olaparib Plus Temozolomide

### Combination Olaparib and Temozolomide in Relapsed Small-Cell Lung Cancer

Anna F. Farago<sup>1,2</sup>, Beow Y. Yeap<sup>1,2</sup>, Marcello Stanzione<sup>1</sup>, Yin P. Hung<sup>1,2</sup>, Rebecca S. Heist<sup>1,2</sup>, J. Paul Marcoux<sup>2,3</sup>, Jun Zhong<sup>1</sup>, Deepa Rangachari<sup>2,4</sup>, David A. Barbie<sup>2,3</sup>, Sarah Phat<sup>1</sup>, David T. Myers<sup>1</sup>, Robert Morris<sup>1</sup>, Marina Kem<sup>1</sup>, Taronish D. Dubash<sup>1</sup>, Elizabeth A. Kennedy<sup>1</sup>, Subba R. Digumarthy<sup>2,5</sup>, Lecia V. Sequist<sup>1,2</sup>, Aaron N. Hata<sup>1,2</sup>, Shyamala Maheswaran<sup>1,2</sup>, Daniel A. Haber<sup>1,2,6</sup>, Michael S. Lawrence<sup>1,2</sup>, Alice T. Shaw<sup>1,2</sup>, Mari Mino-Kenudson<sup>1,2</sup>, Nicholas J. Dyson<sup>1,2</sup>, and Benjamin J. Drapkin<sup>1,2</sup>



# Clinical questions

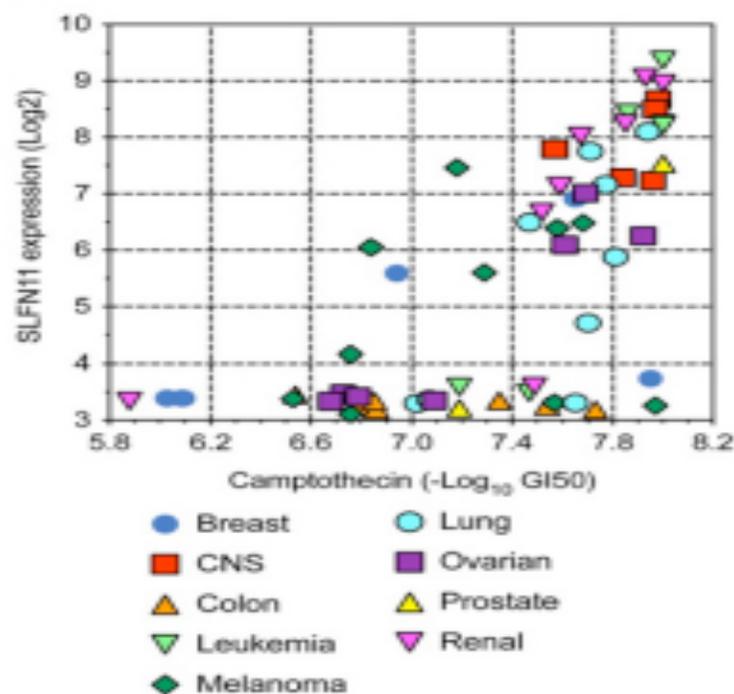
## Clinical questions

1. Differential responses - Biomarker discovery
2. Short duration of response - Drug resistance mechanism

# Predictive biomarker

## SLFN11 (Schlafen Family Member 11) as a predictive biomarker

Correlation between camptothecin sensitivity and SLFN11 expression in NCI60 cell lines

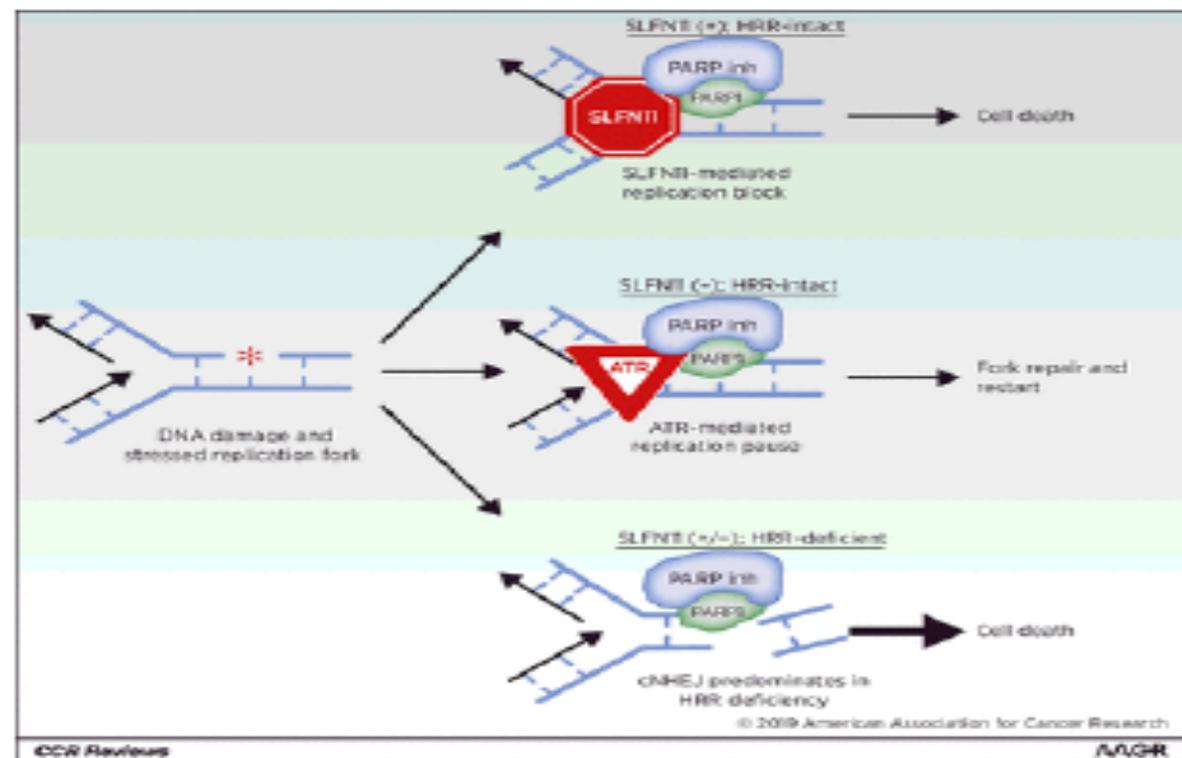
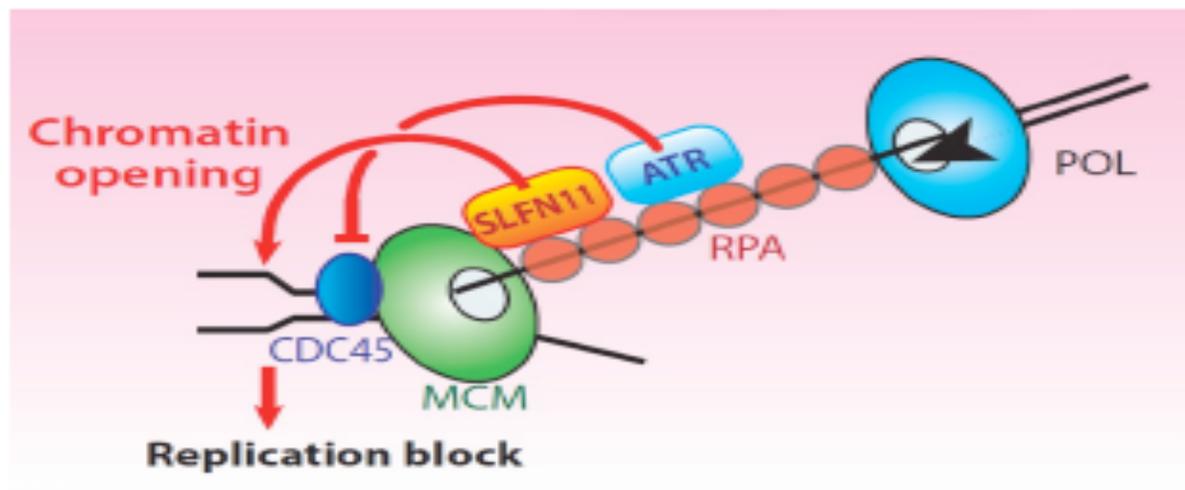


Correlation between olaparib sensitivity and SLFN11 expression in SCLC cell lines



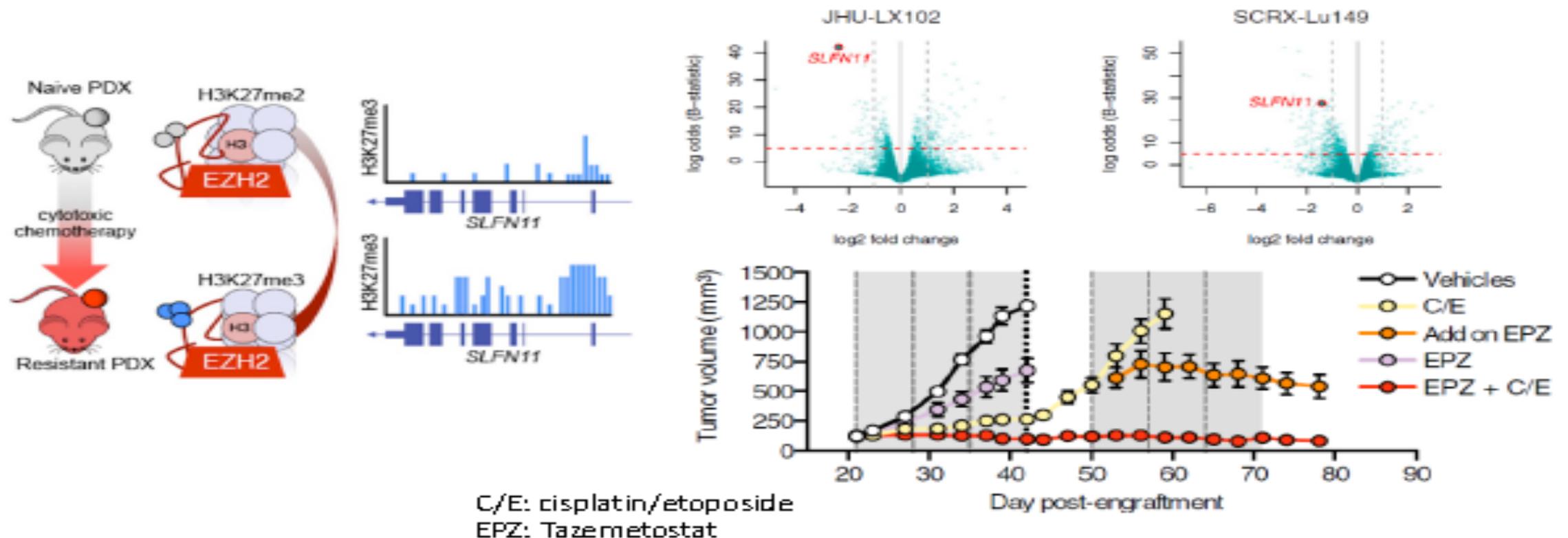
# SNFN11 mechanism

**SLFN11 blocks stressed replication forks and triggers cell death**



# SLFN11 silencing

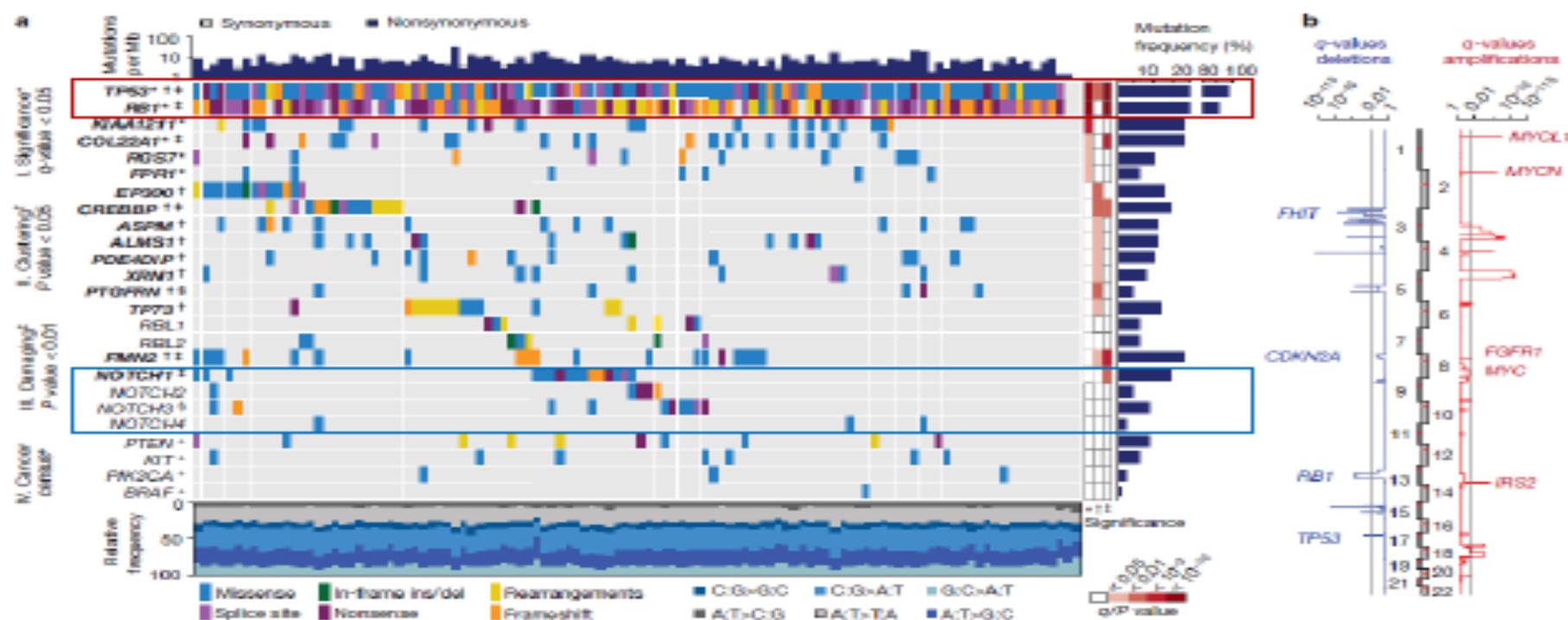
SLFN11 is silenced when drug resistance develops



# Other genomic changes of SCLC

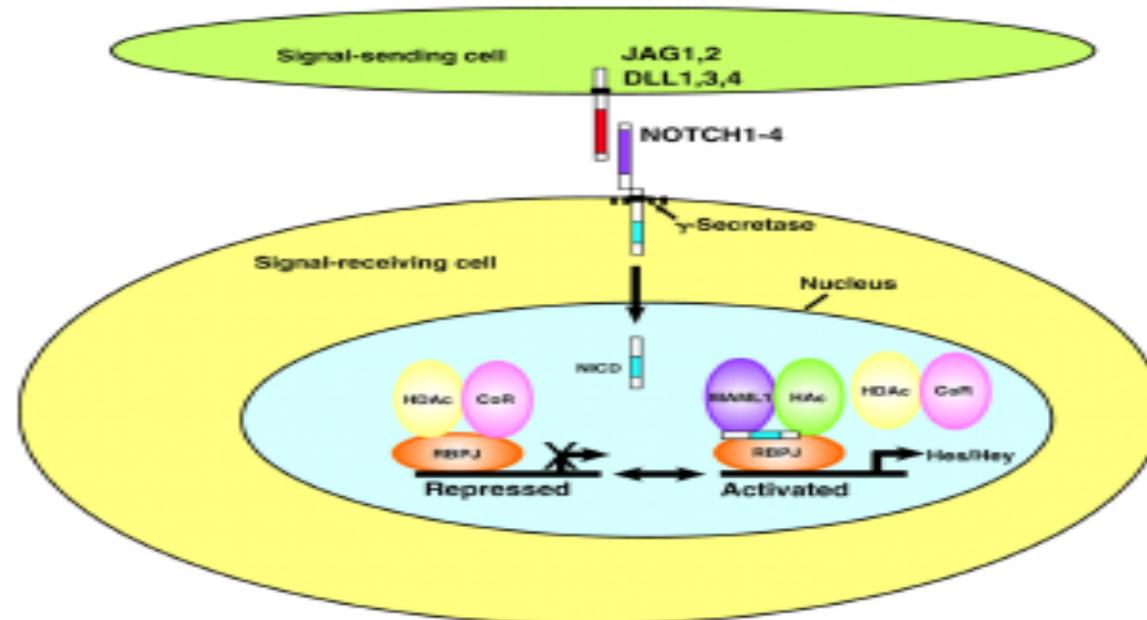
# Genetic abnormalities

## Genomic abnormalities of SCLC: WES Analysis



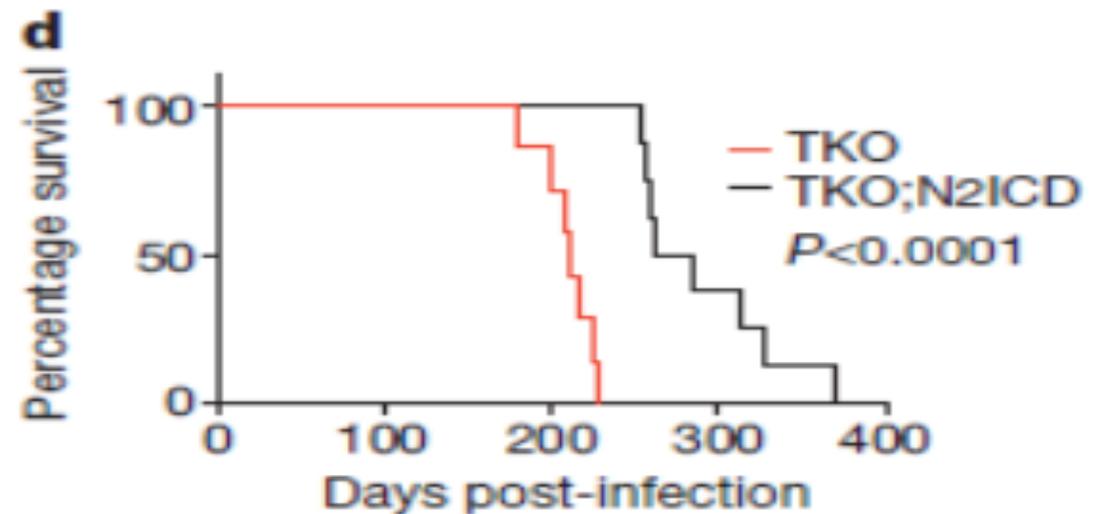
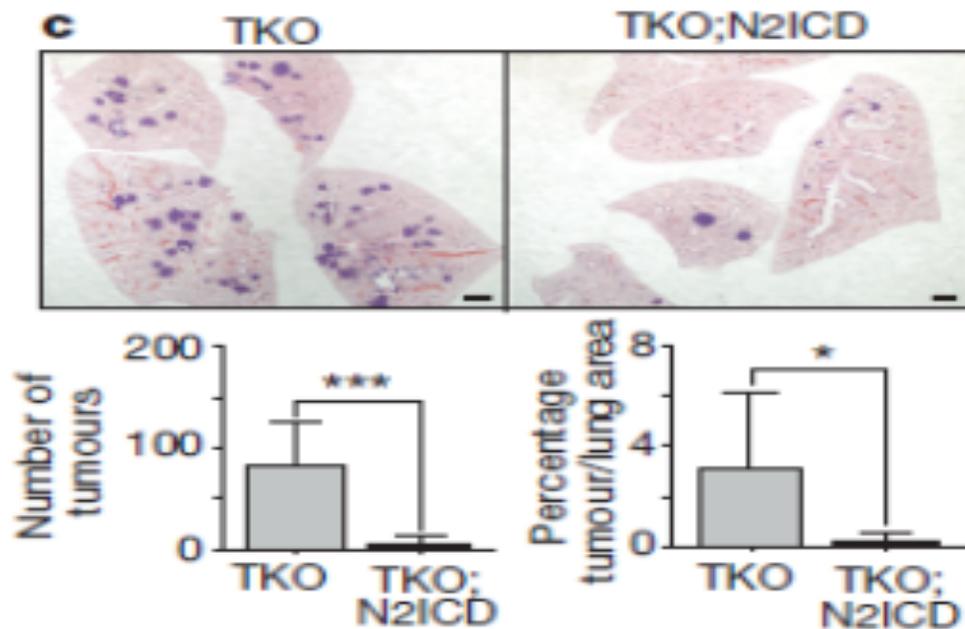
# Notch signaling pathway

## Notch Signaling Pathway



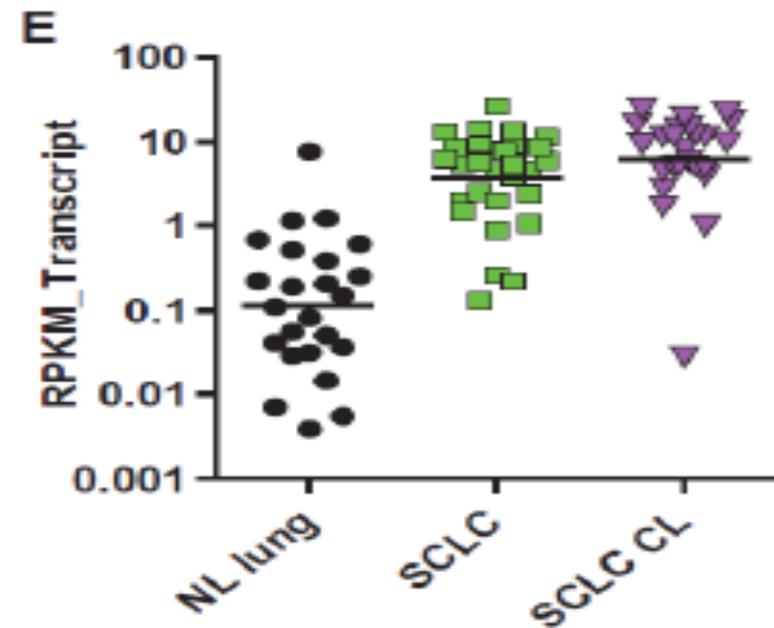
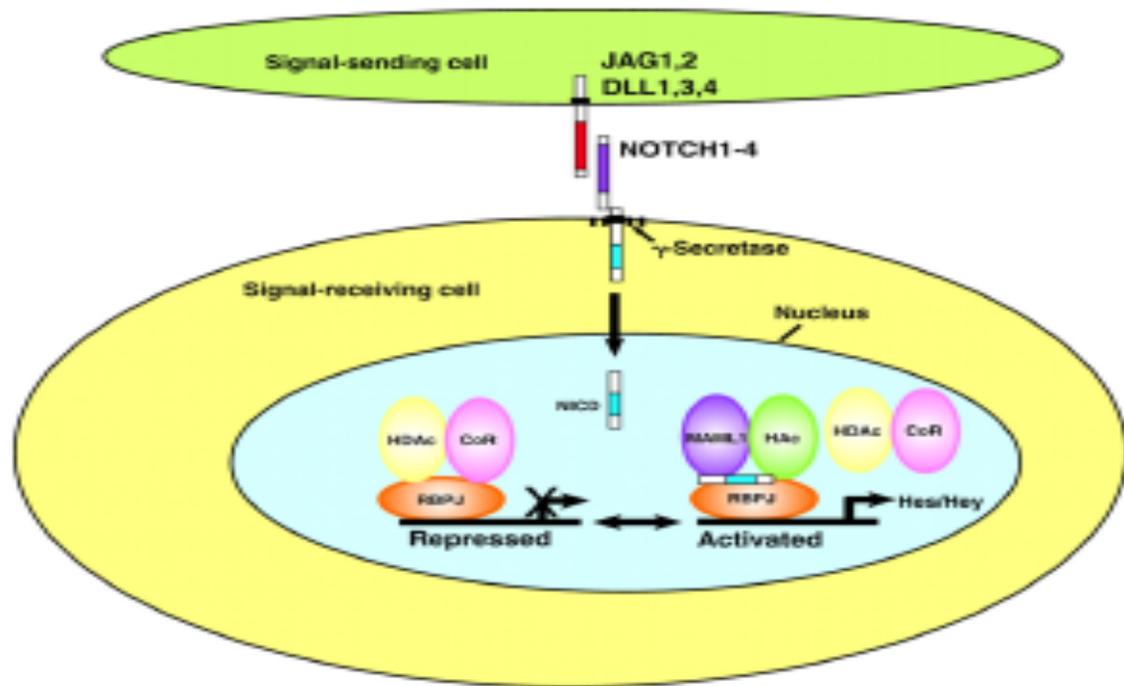
# Notch signaling

Forced activation of Notch signaling decreased SCLC growth in a transgenic mouse model



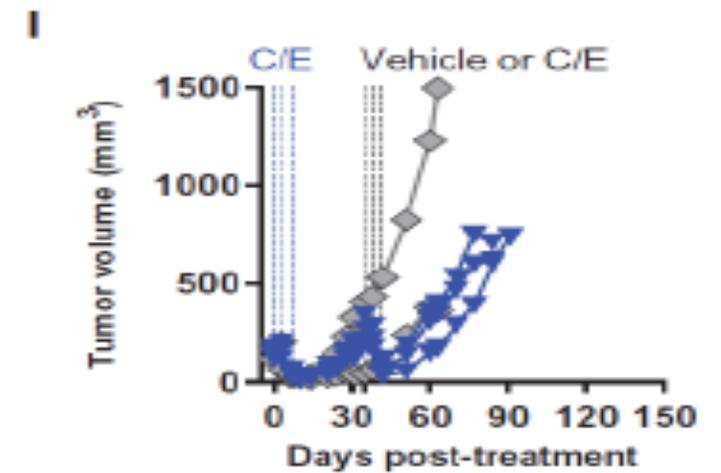
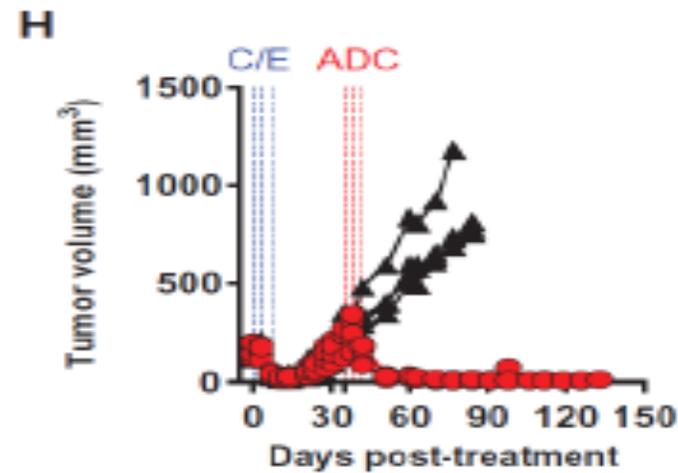
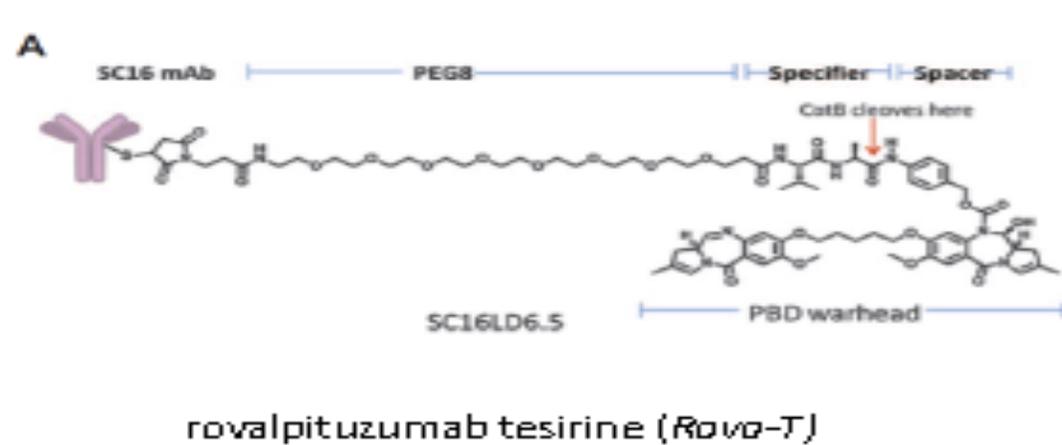
# DLL3 overexpression

## Overexpression of DLL3 in SCLC



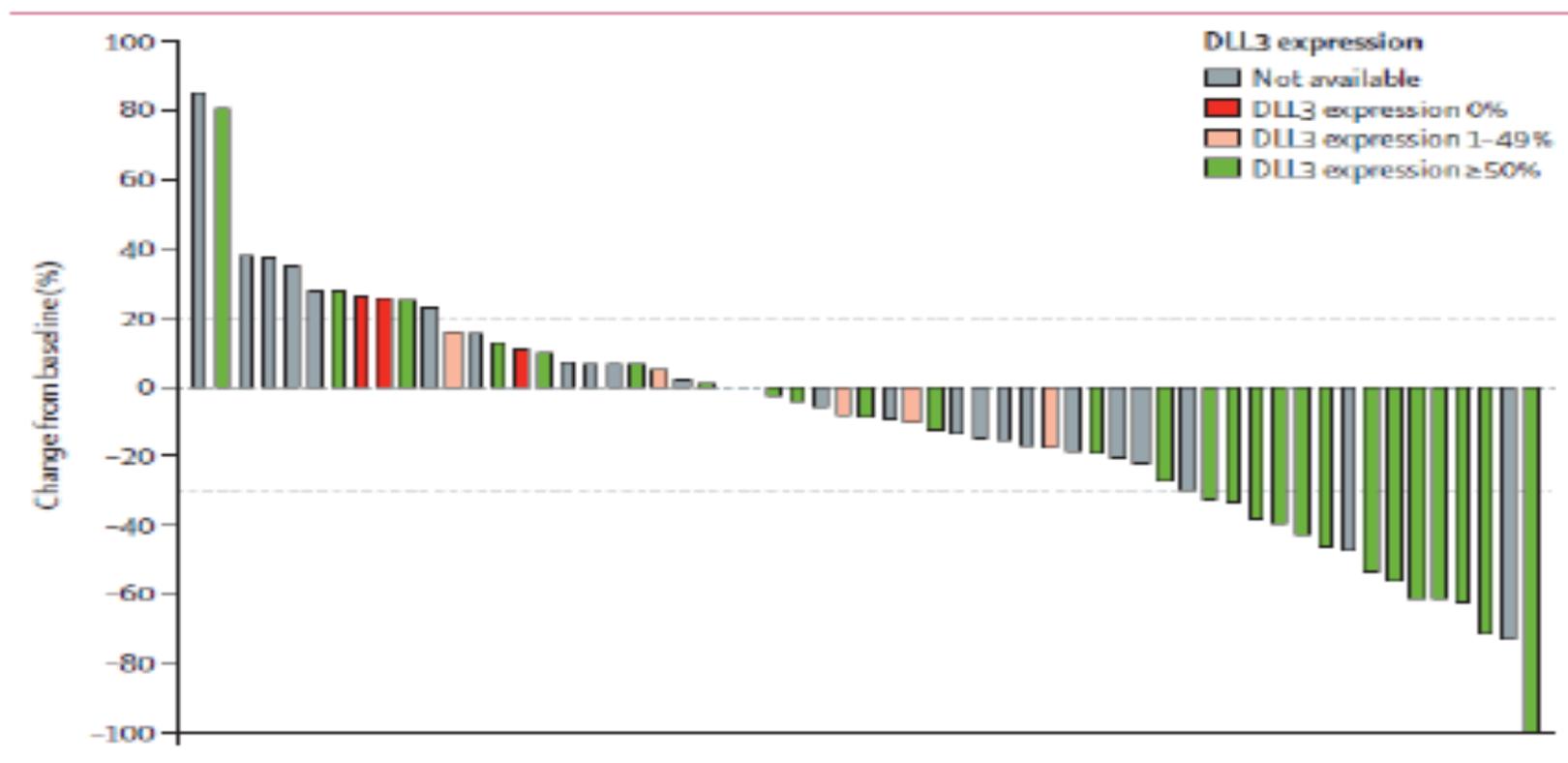
# Rova-T

Rova-T: a DLL3 targeting antibody-drug conjugate



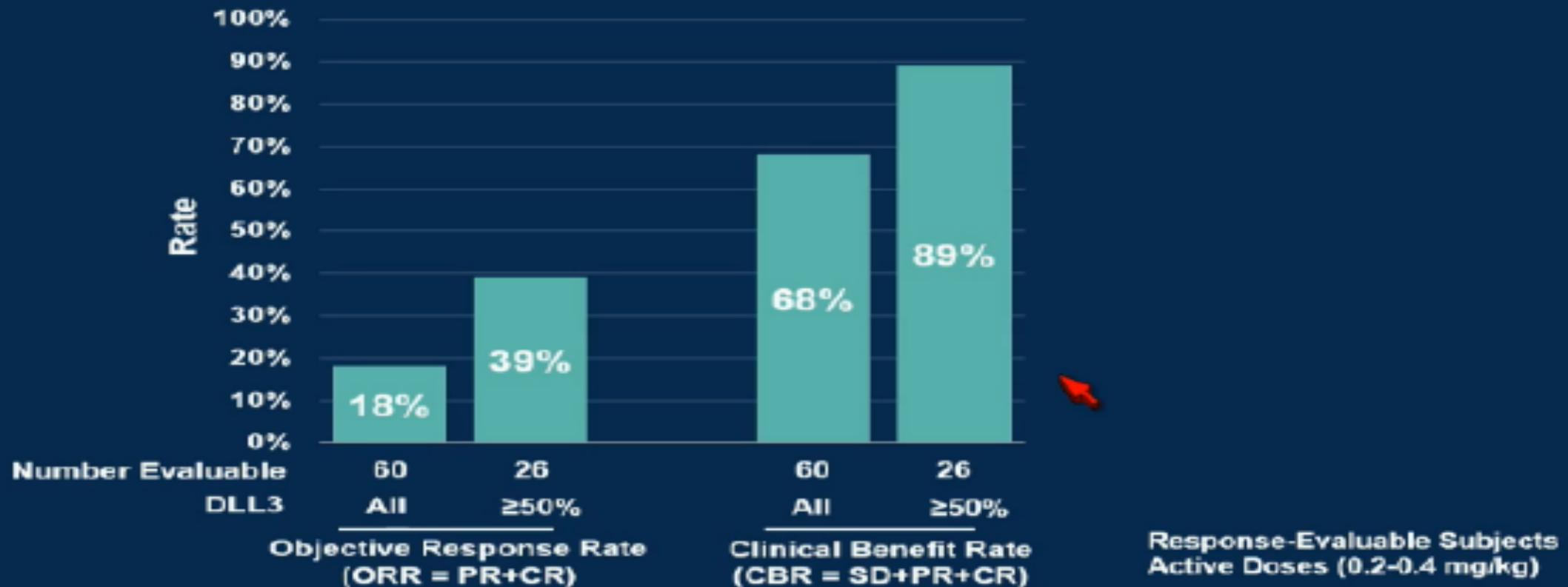
# Waterfall plot

Waterfall plot showing best change in tumor burden from baseline at active treatment doses (N=60)



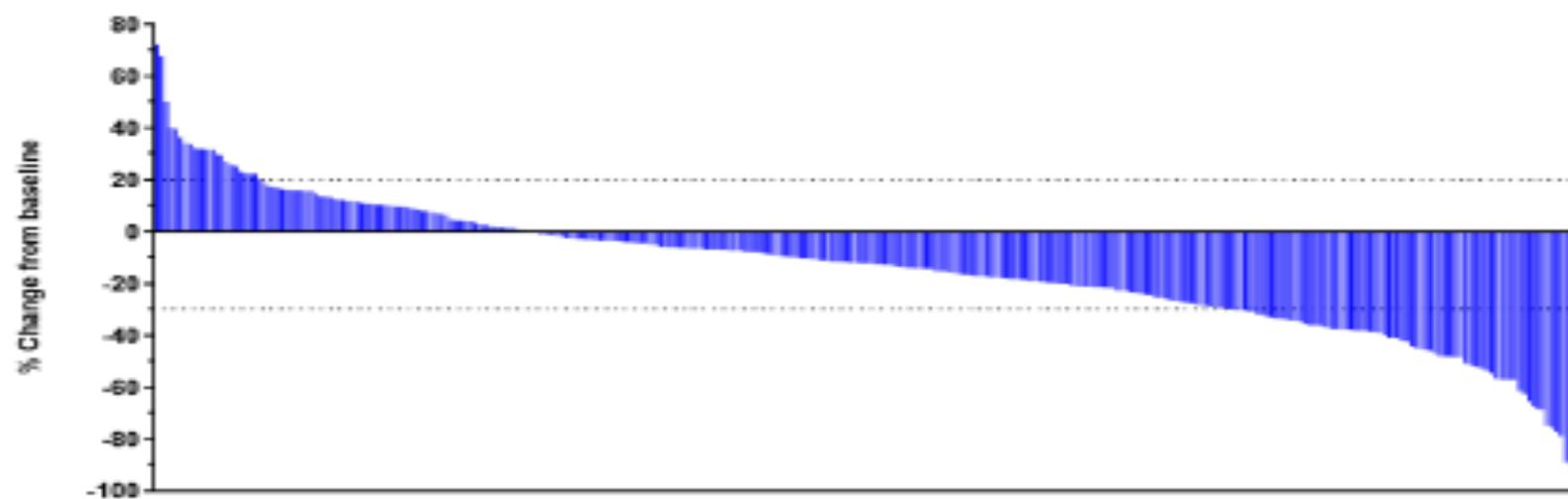
# RECIST responses

## RECIST Confirmed Responses per Investigator



# Rova-T trial

## Disappointing Phase II result of Rova-T (TRINITY Trial)



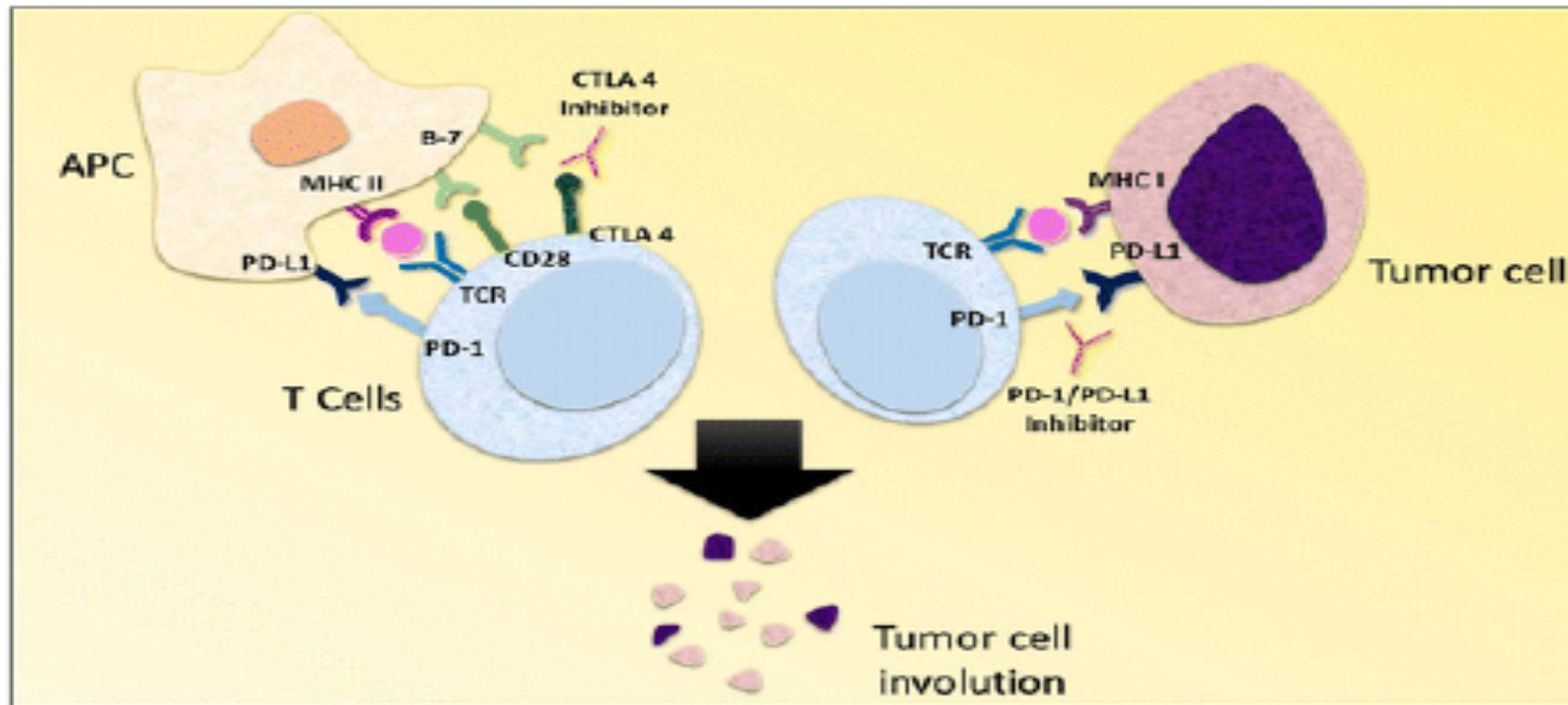
ORRs were 12.4%, 14.3% and 13.2% in all, DLL3<sup>high</sup>, and DLL3<sup>+</sup> patients, respectively.  
Median OS was 5.6 months in all patients.

**Due to the disappointing results, clinical development of Rova-T was terminated.**

# Immunotherapy in SCLC

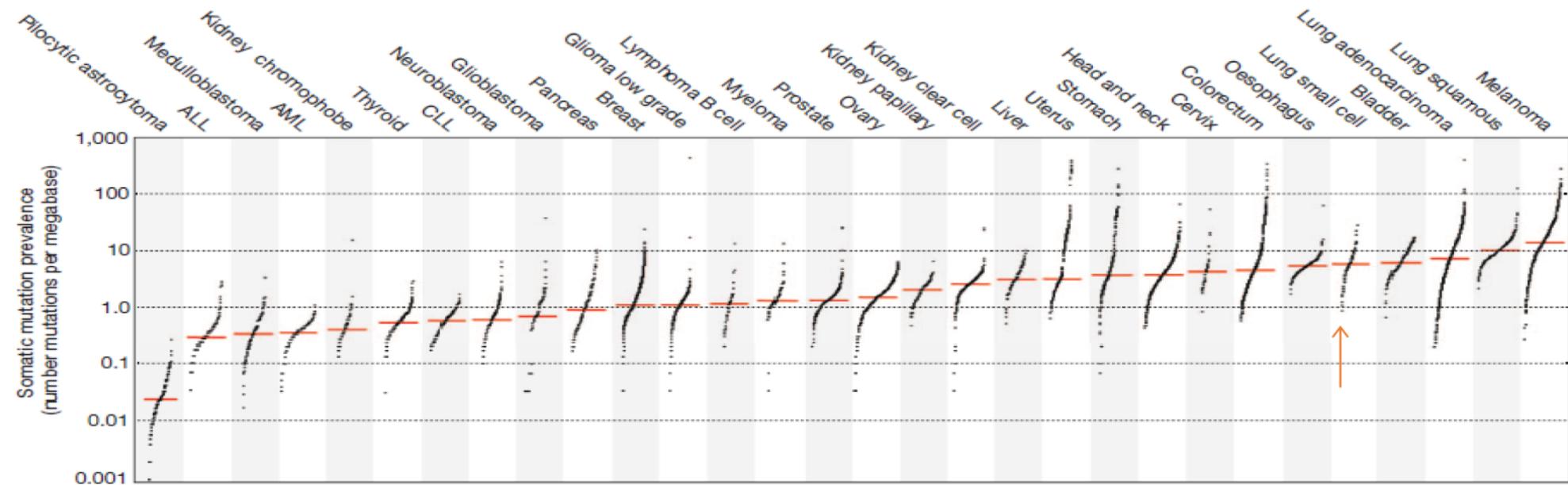
# Immune checkpoints

## Immune checkpoints



# Mutation loads

## Mutation loads in different cancer types

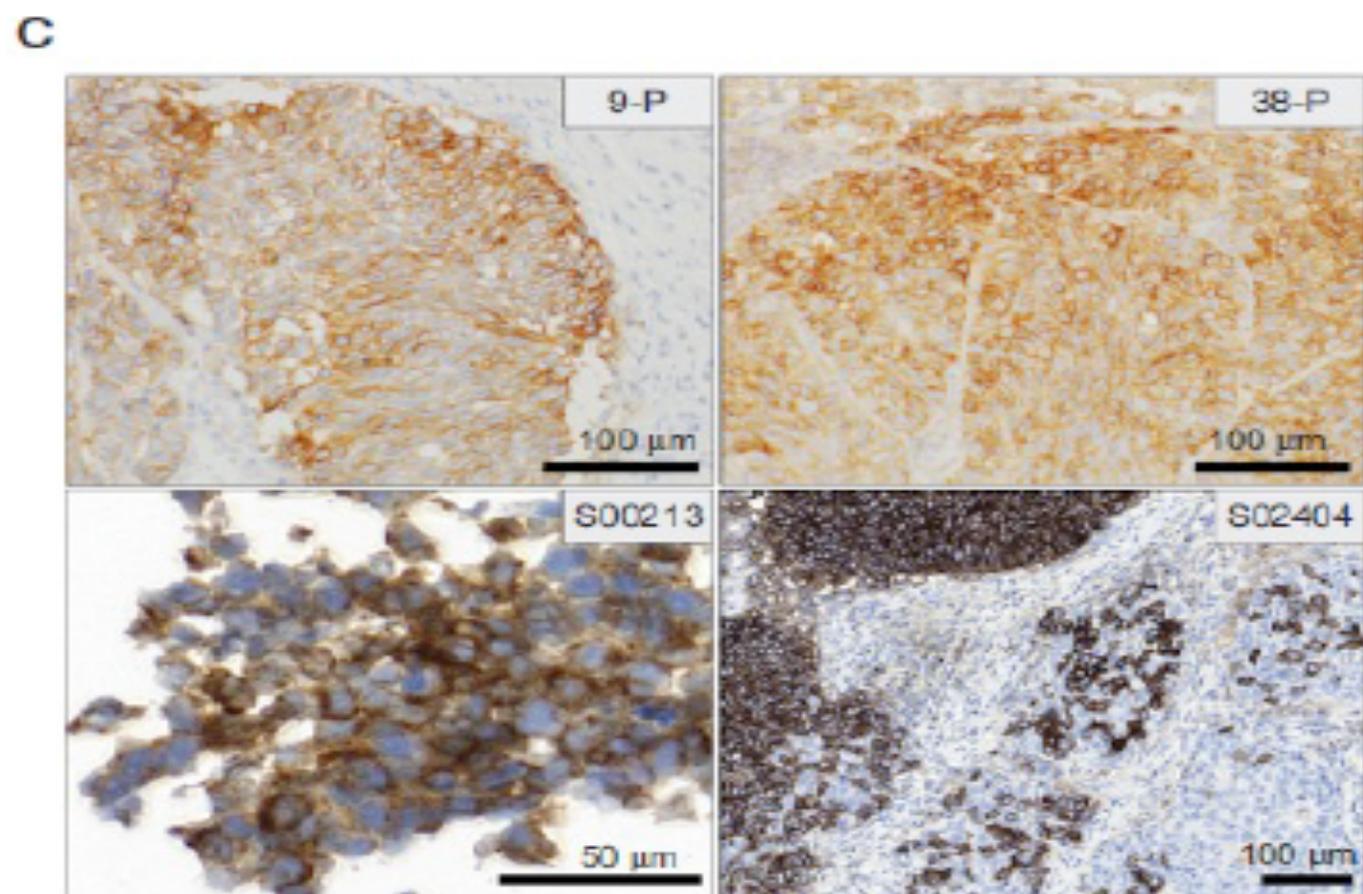
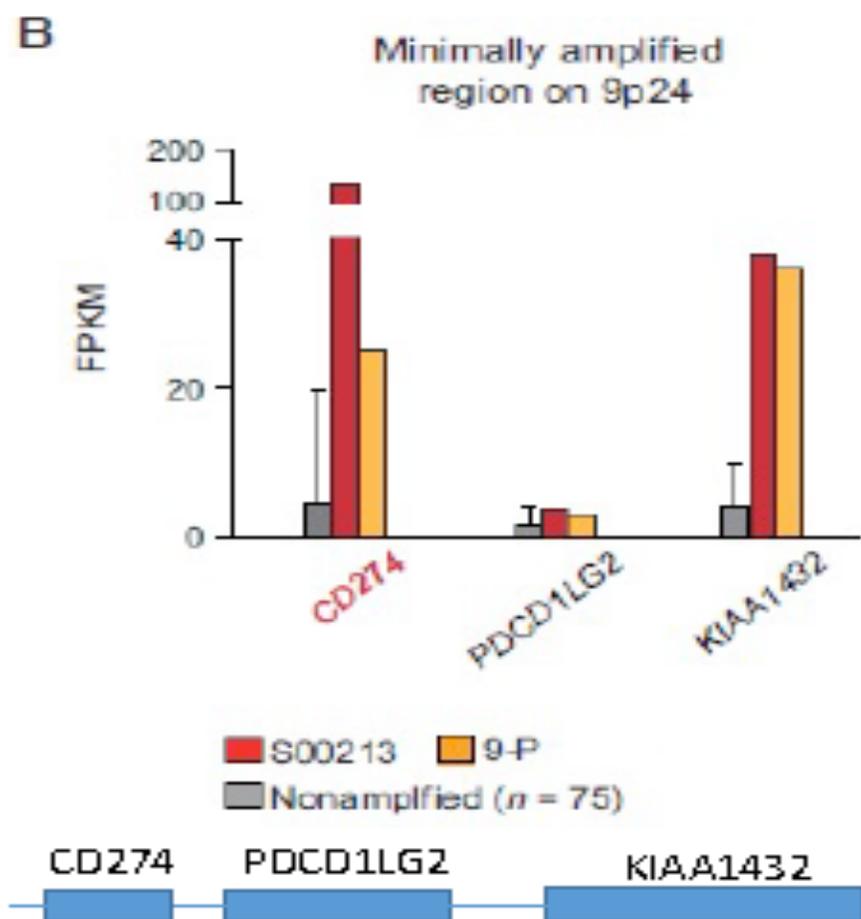


**Figure 1 | The prevalence of somatic mutations across human cancer types.** Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different

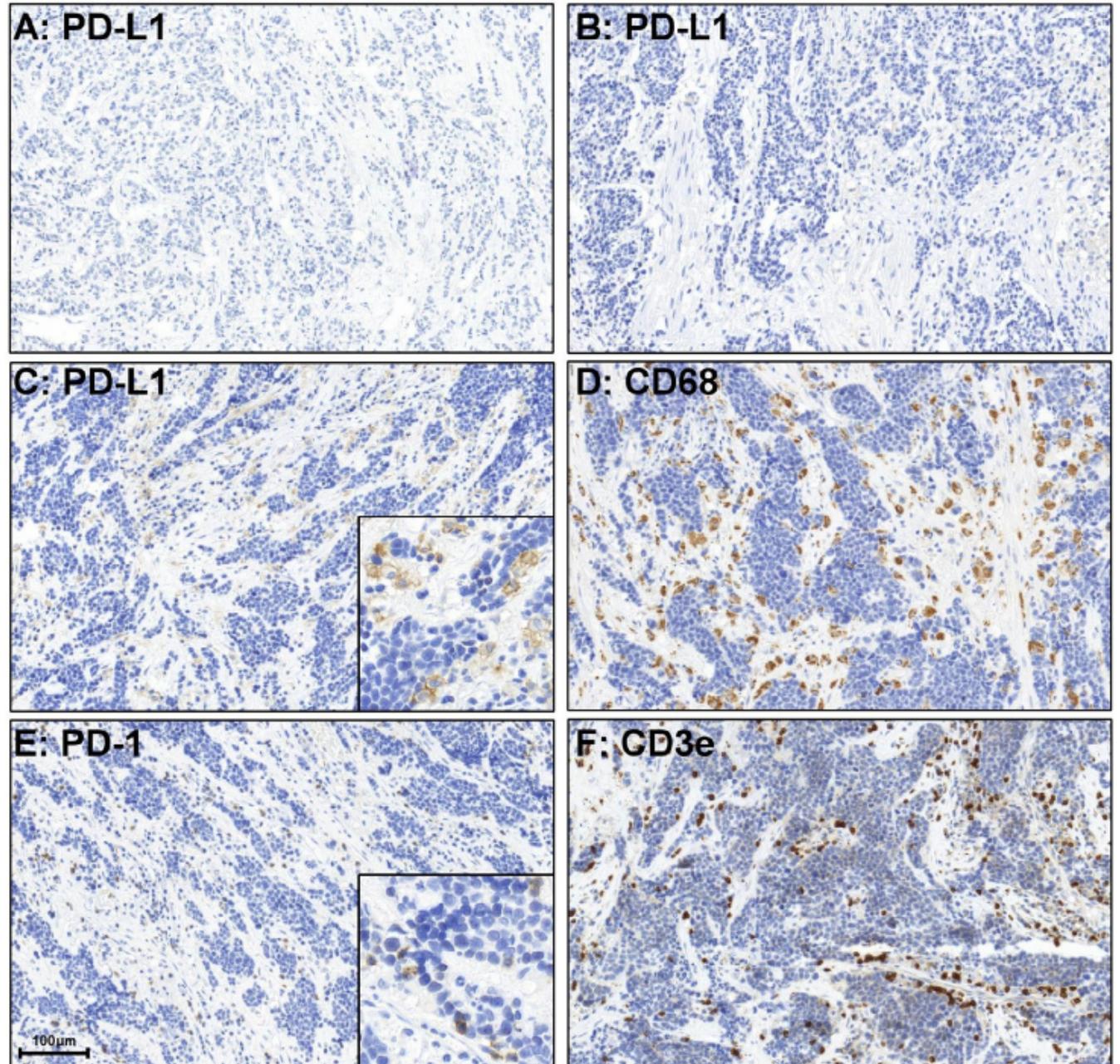
cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure<sup>26</sup>. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

# PD-L1

CD274 (PD-L1) gene is amplified in 1.9% of SCLC



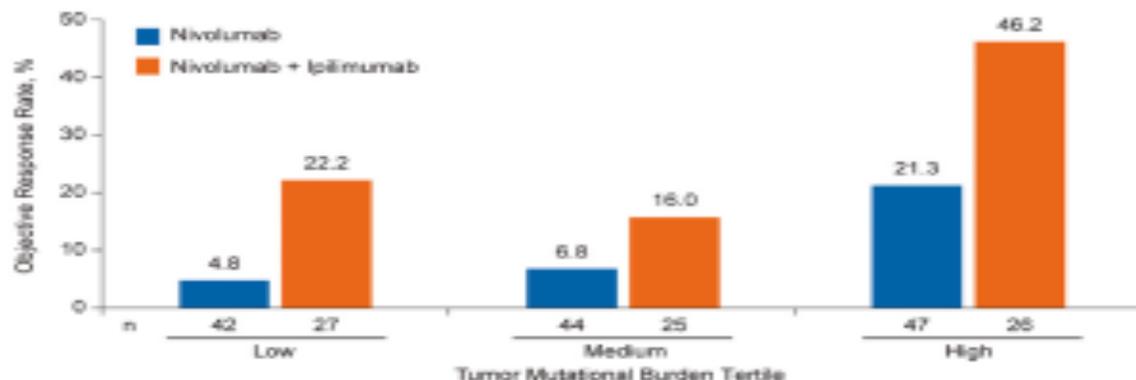
PD-1 and PD-L1 are expressed in the tumor stroma of small cell carcinoma.



# Tumor burden and PD-L1

Tumor mutation burden and PD-L1 expression are potential biomarkers to predict response to anti-PD1 therapy

CheckMate 032 Nivolumab w/ or w/o ipilimumab



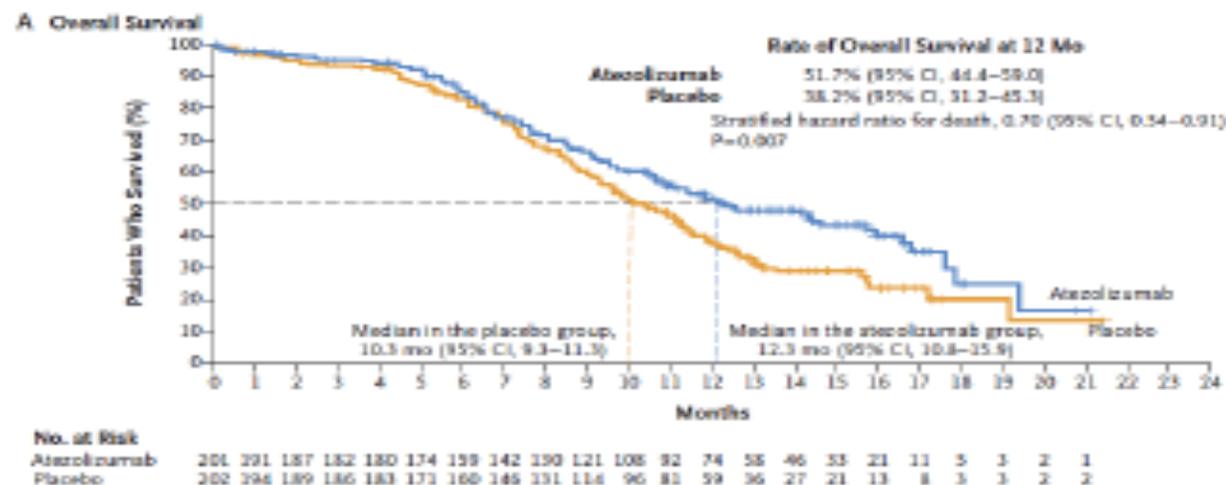
KEYNOTE-028 Pembrolizumab

Table 3. Confirmed Efficacy Results (investigator-assessed) in the Total Population

Efficacy	Value of Patient Population (n = 24)
ORR*, No. (%) [95% CI]	8 (33.3 [15.6-55.3])
CR, No. (%)	1 (4.2)
PR, No. (%)	7 (29.2)
SD, No. (%)	1 (4.2)
Median DOR, months† (range)	19.4 (≥ 3.6 to ≥ 20.0)
Median TTR, months (95% CI)	2.0 (1.7-3.7)
DCR‡, No. (%) [95% CI]	8 (33.3 [15.6-55.3])
Progressive disease, No. (%)	13 (54.2)
Not evaluable, No. (%)	2 (8.3)
PFS	
Events, No. (%)	20 (83.3)
Median, months (95% CI)	1.9 (1.7-5.9)
Six-month rate, % (95% CI)	28.6 (12.4-47.2)
Twelve-month rate, % (95% CI)	23.8 (9.1-42.3)
OS	
Events, No. (%)	15 (62.5)
Median, months (95% CI)	9.7 (4.1-NR)
Six-month rate, % (95% CI)	66.0 (43.3-81.3)
Twelve-month rate, % (95% CI)	37.7 (18.4-57.0)

# Add ICI to front-line chemotherapy

Addition of ICI to front-line chemotherapy improved survival of SCLC patients (Impower 133 trial)



**Table 2. Response Rate, Duration of Response, and Disease Progression.\***

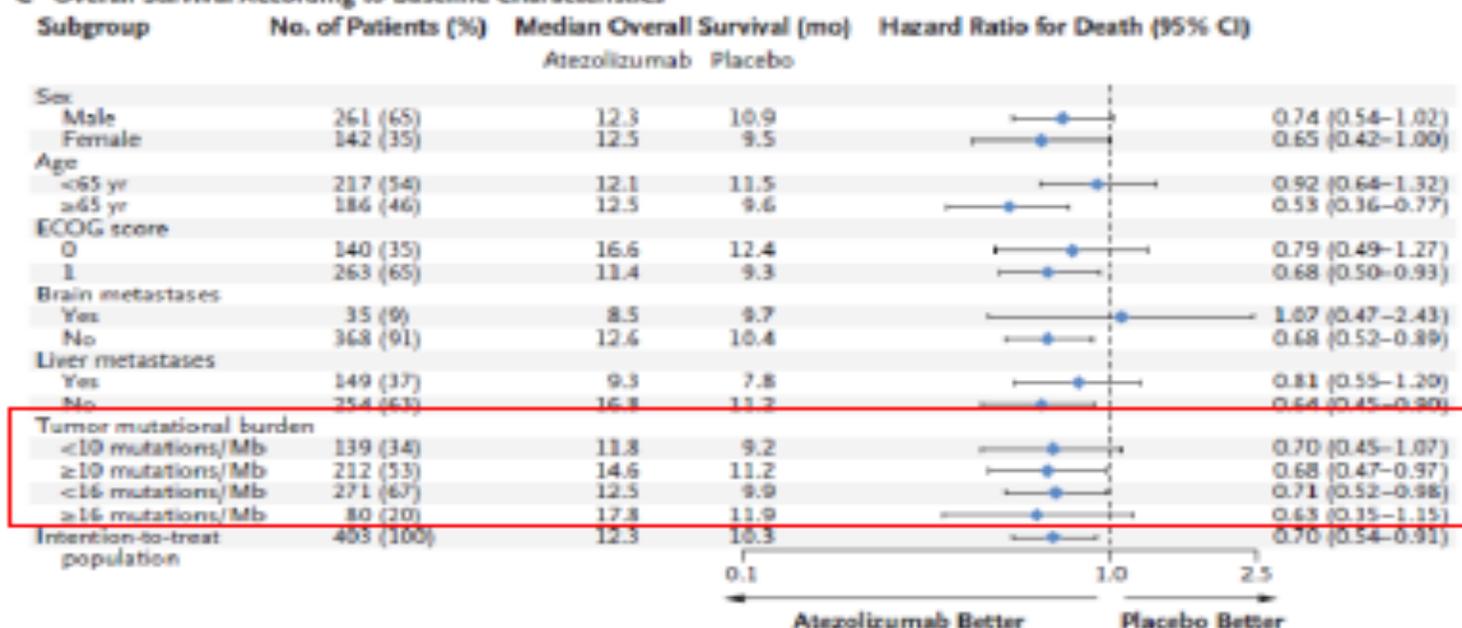
Variable	Atezolizumab Group (N=201)	Placebo Group (N=202)
Objective confirmed response†	121 (60.2 [52.3–67.0])	130 (64.4 [57.3–71.6])
Complete response — no. (%) [95% CI]	3 (2.5 [0.8–5.7])	2 (1.0 [0.3–3.5])
Partial response — no. (%) [95% CI]	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.6])
Median duration of response (range) — mo‡	4.2 (1.4–19.5)	3.9 (2.0–16.1)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (%) [95% CI]	43 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.4])
Progressive disease — no. (%) [95% CI]	22 (10.9 [7.0–16.1])	14 (8.9 [5.8–12.4])

# Biomarkers

## Lack of good predictive biomarker for combinatorial chemoimmunotherapy

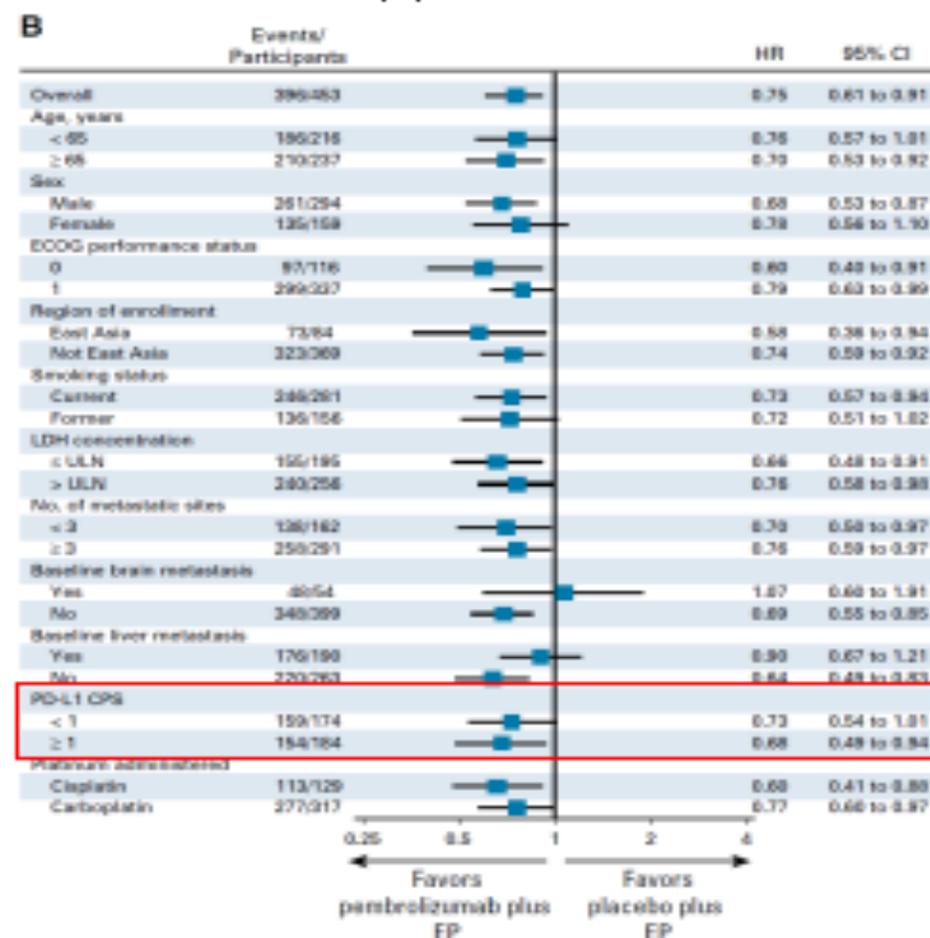
### Chemotherapy + Atezolizumab

C Overall Survival According to Baseline Characteristics



Horn et al. NEJM 379, 23:2220-2229

### Chemotherapy + Pembrolizumab

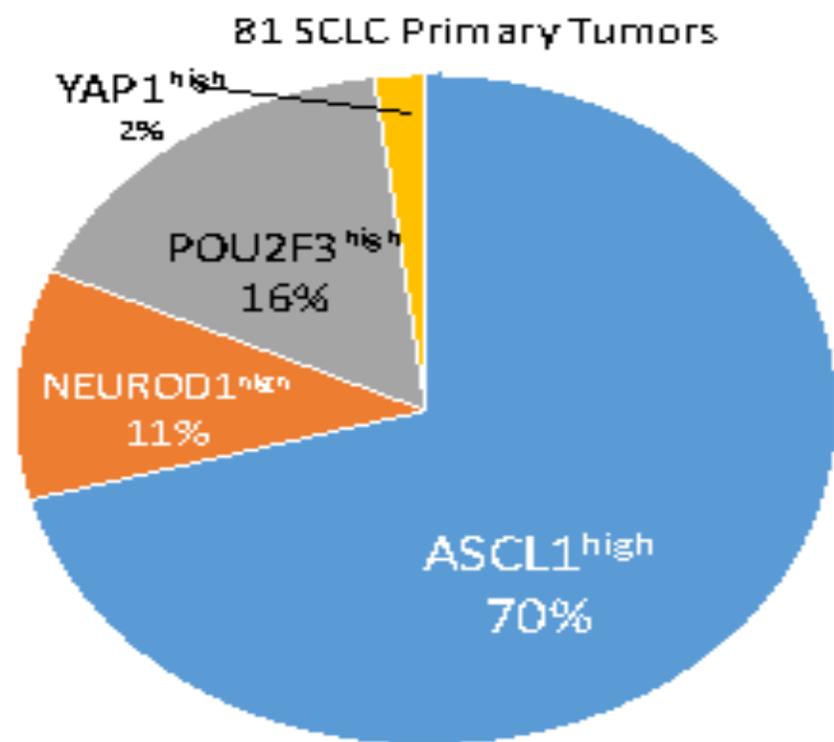
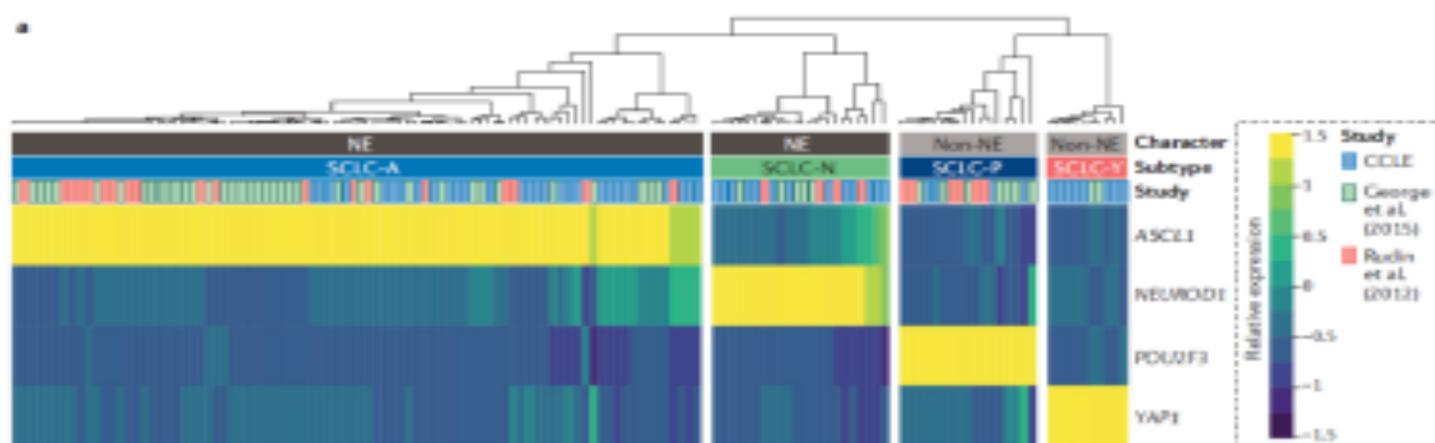


Rudin et al. JCO, 38:2369-2379

# Tumor heterogeneity in SCLC

# SCLC subtypes

## Four Molecular Subtypes of SCLC

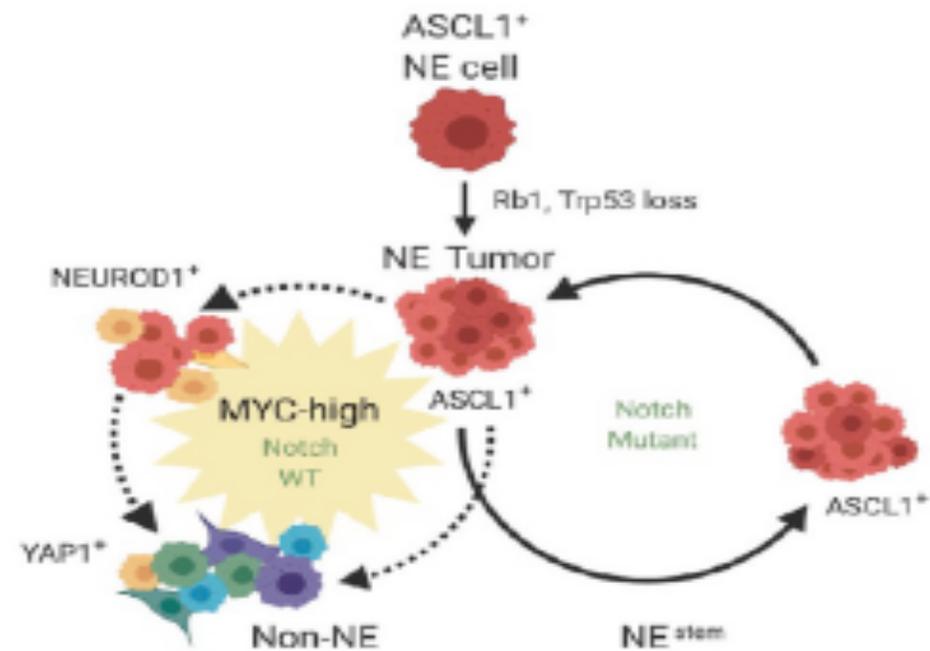
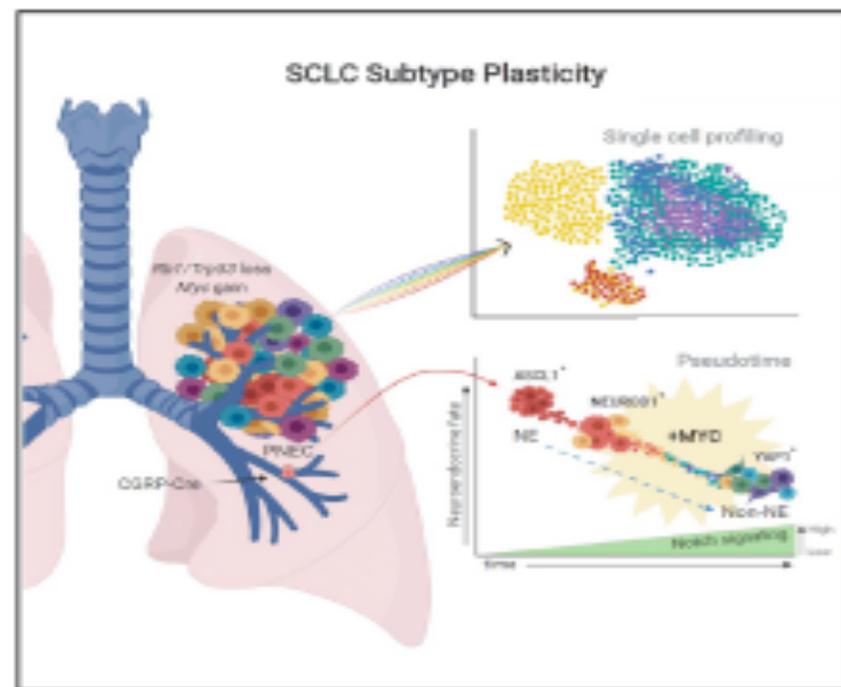


# Myc

Article

## Cancer Cell

### MYC Drives Temporal Evolution of Small Cell Lung Cancer Subtypes by Reprogramming Neuroendocrine Fate



# Summary

## Summary

- SCLC is a recalcitrant cancer and new therapy is urgently needed.
- Inactivation of TP53 and RB1 is almost universal in SCLC. Other gene mutations may facilitate development and/or growth of SCLC.
- Excessive replication stress forms the basis of synthetic lethality therapies in SCLC.
- Immune checkpoint inhibitor has changed treatment paradigm of small cell lung cancer.
- Tumor heterogeneity remains a big challenge in SCLC.