

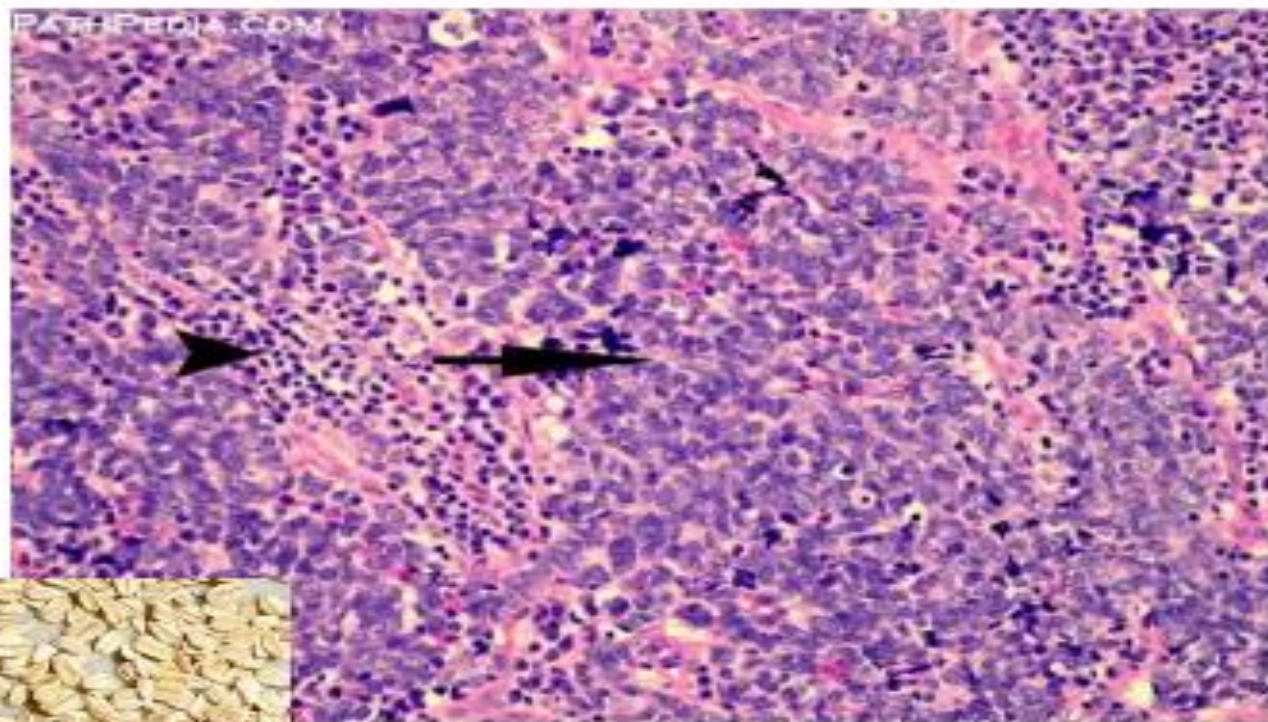
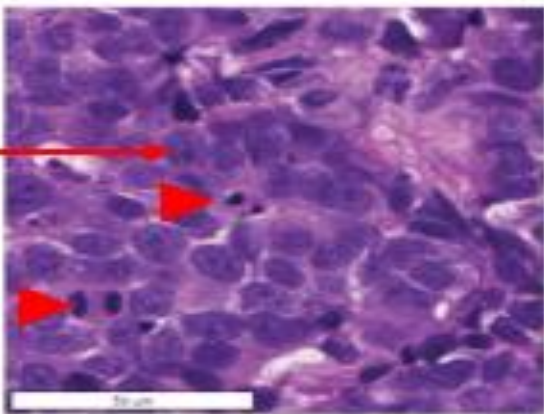
# Small cell lung cancer

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TGIB, NCI

# 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.



# 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

# Difference between SCLC and NSCLC

## Difference between SCLC and NSCLC

- SCLC:
  - Disseminates earlier and is more aggressive.
  - Has neuroendocrine features.
  - Is generally not a cancer for surgery.
  - Is notorious for rapid development of drug resistance.

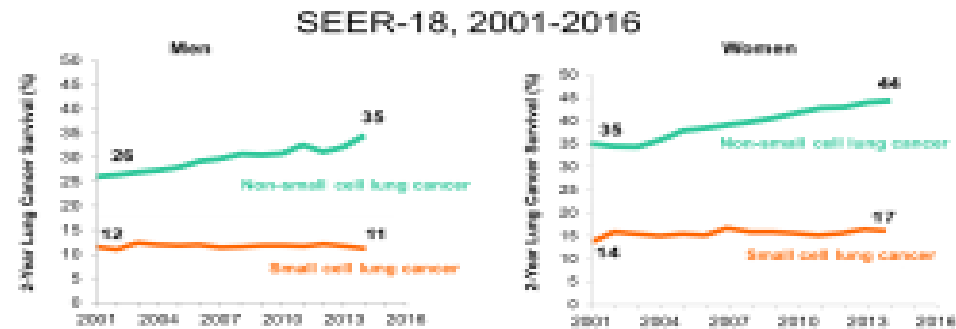
# SCLC is considered as a recalcitrant cancer

- 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 is difficult to treat

## SCLC Remains a Difficult Cancer

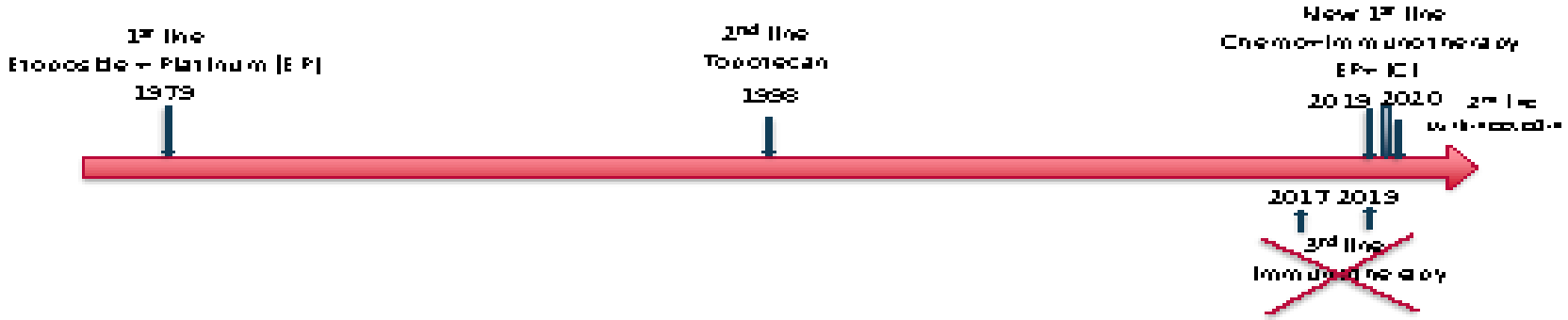
- From 2000-2014, 2-year survival rates in patients with SCLC had not improved.



Howlader et al. *NEJM* 2020

# SCLC therapies

## Standard SCLC Therapies



# How is SCLC formed?



How is SCLC formed?



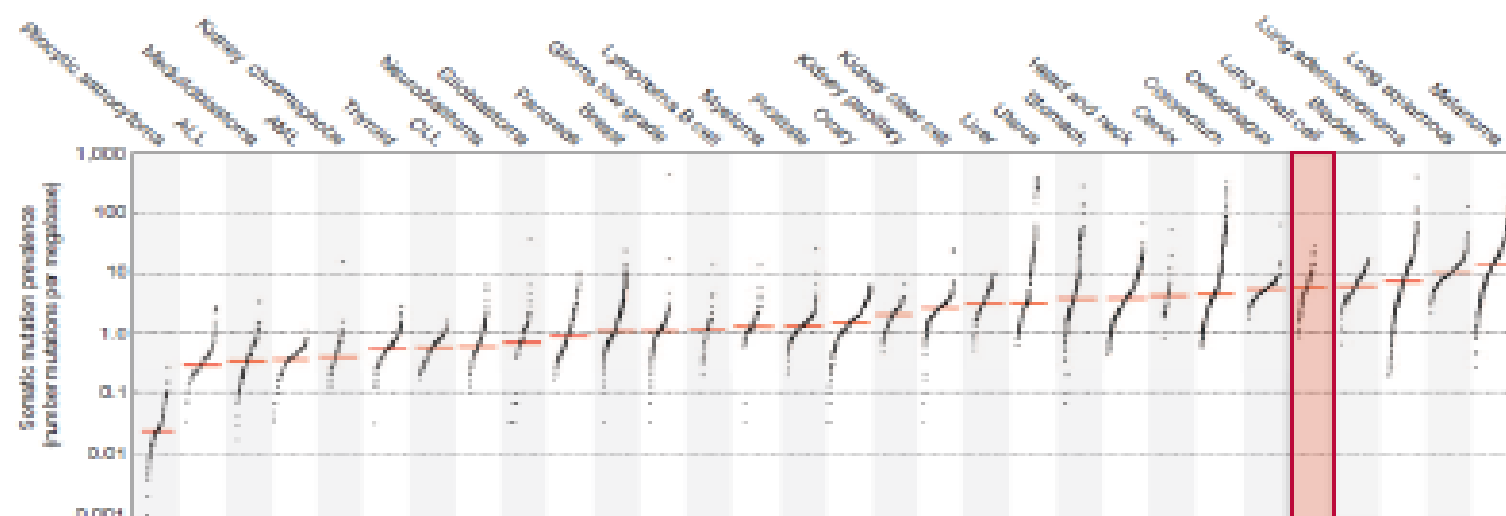
# What causes SCLC?

## What Causes SCLC?

- A smoker's disease
- Never-smokers (~1.8%)<sup>1,2</sup>
  - are more likely to be female
  - have no significant overall survival advantage compared to smokers.
- Conversion from NSCLC (up to 14% of TKI-resistant tumors<sup>3,4</sup>)

# Mutational burden

SCLC Generally Has a High Mutation Burden



Alexandrov LB, Nature 2013

# Genomic abnormalities

## Genomic Abnormalities Identified in SCLC (Before the Genome Sequencing Era)

- 1980s Deletion of chr. 3p21<sup>1</sup>
  - FHIT, BAP1, and RASSF1 are positioned in this region
- 1983 MYC amplification<sup>2</sup>
- 1988 Deletion of chr. 13q.
  - Loss of Rb<sup>3</sup>
- 1989 Deletion of chr. 17p.
  - Loss of TP53<sup>4</sup>

<sup>1</sup>Cot et al. *Nature* 1987

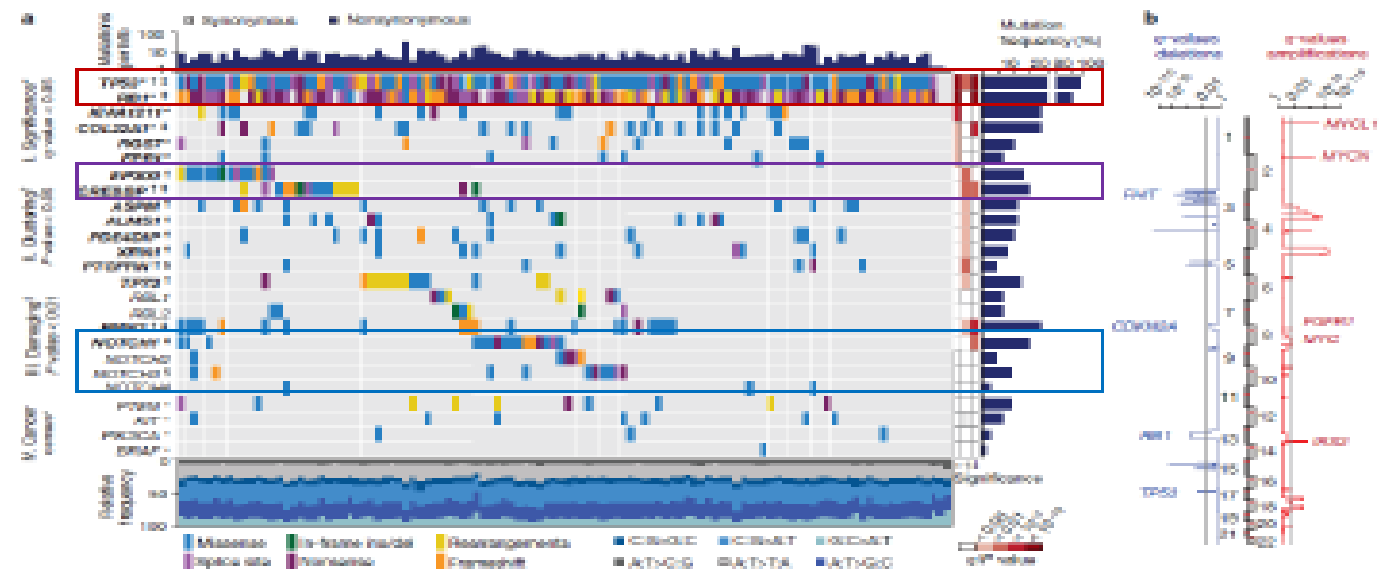
<sup>2</sup>Little et al. *Nature* 1983

<sup>3</sup>Harbour et al. *Science* 1988

<sup>4</sup>Takahashi et al. *Science* 1989  @NCIResearchCtr 12

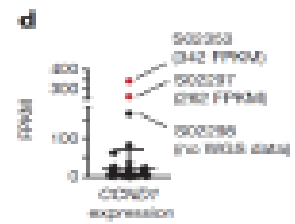
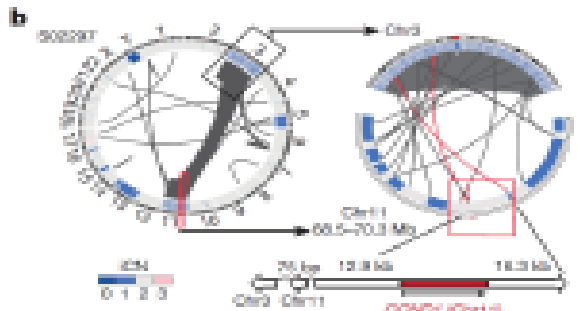
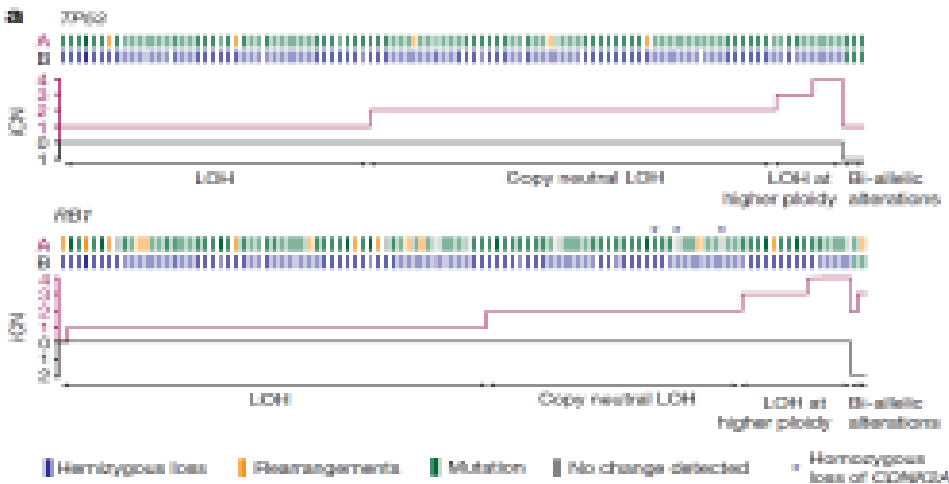
# Genomic changes

## Genomic Changes Identified in SCLC (Genome Sequencing Era)



# TP53 and RB1

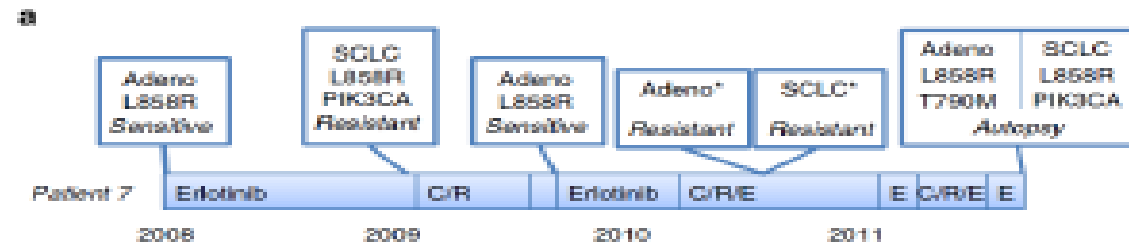
## Universal Bi-allelic Inactivation of TP53 and RB1





# Loss of TP53 and RB1 genes

Transformed SCLC: Loss of TP53 and RB1 genes



**b**

Sample	Normal liver	Diaphragm tumour	Lung tumour	Liver tumour
Histological features	Normal tissue	Adeno carcinoma	SCLC	SCLC
Number of reads	178,288,190	390,864,233	388,188,232	318,482,313
Average coverage	145	287	319	252
Primary EGFR mutation	WT	L858R	L858R	L858R
Secondary EGFR mutation	WT	T790M	WT	WT
PIK3CA status	WT	WT	E545K	E545K
TP53 status	WT	WT(Δ194-193)	Δ194-193	Δ194-193

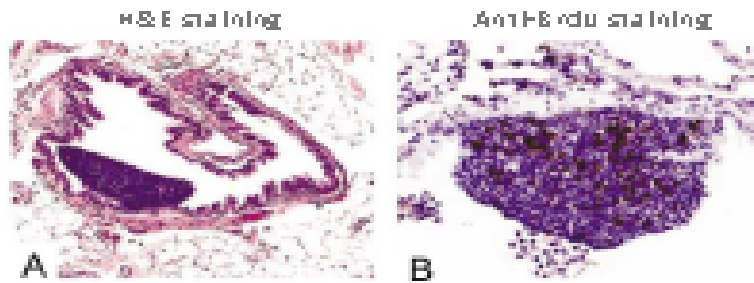
Niederst MJ et al. Nat Commun. 2015

**Table 1 | RB status of TKI-resistant patients.**

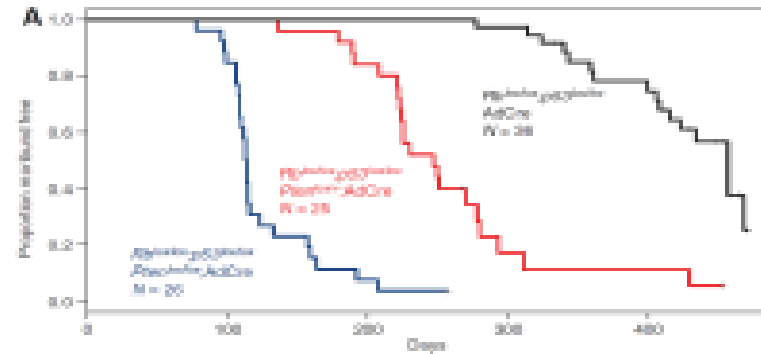
Patient	Cancer type	Resistance	Histology	RB status	Detection method
1	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC/genetic
2	Lung	Post	NE	Neg	IHC/genetic
	Lung	Pre	Adeno	Pos	IHC
3	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC
4	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
5	Lung	Post	NE	Neg	IHC
	Lung	Pre	Adeno	Neg	IHC
6	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	Adeno	Pos	IHC/genetic
7	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	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
11	Lung	Pre	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	Pre	NE	Neg	IHC

# SCLC mouse models

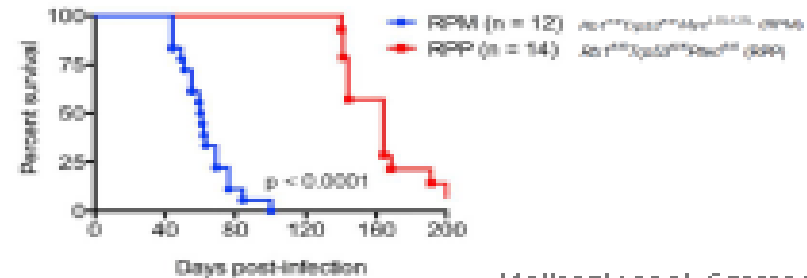
## Conditional Inactivation of Trp53 and Rb1 Led to SCLC in Mouse Models



Meuwissen et al. *Cancer Cell*. 2003



Cui et al. *Mol Cancer Res*. 2014



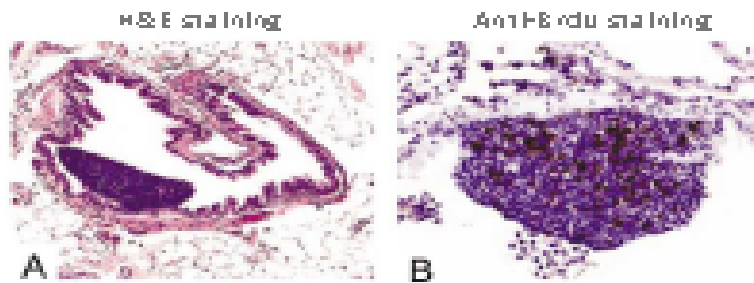
Mollaoglu et al. *Cancer Cell* 2017

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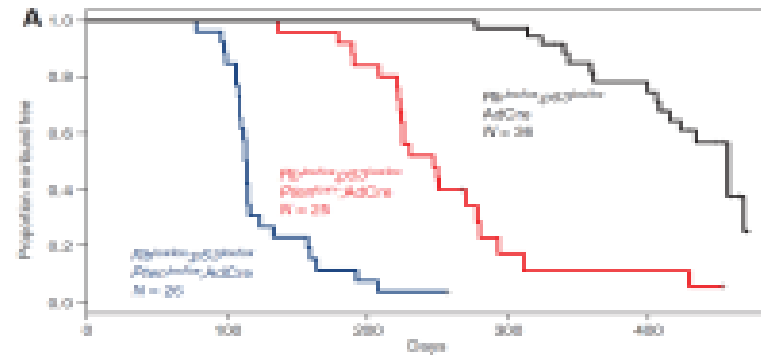


# Mouse models

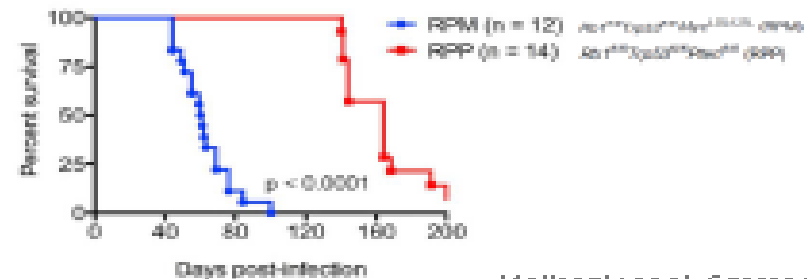
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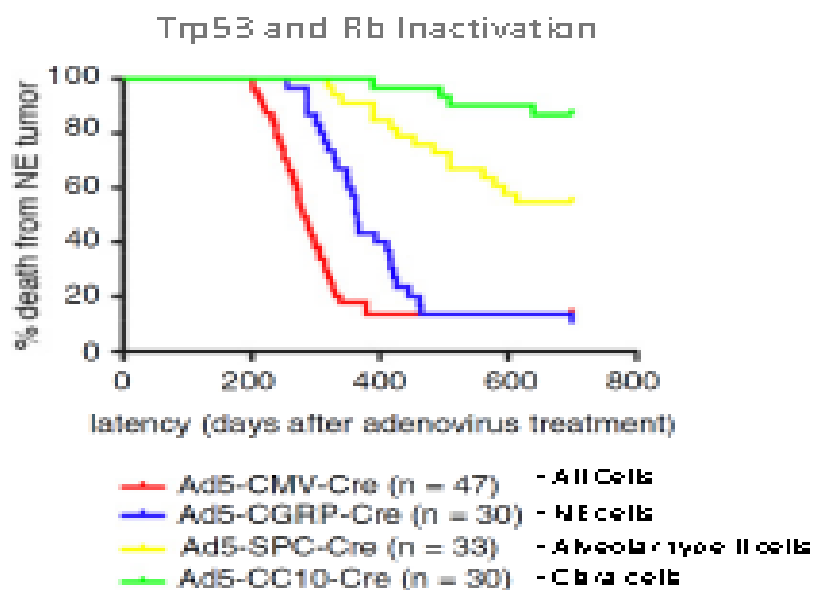


Mollaoglu et al. *Cancer Cell* 2017

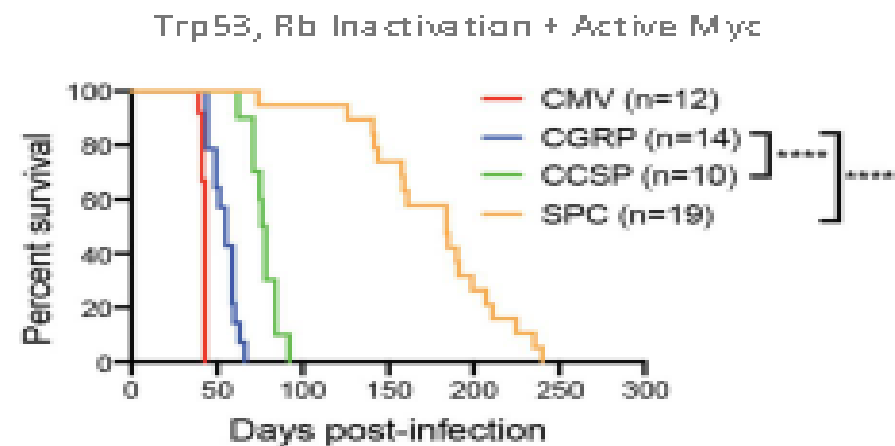
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# Cell origin

## Cell Origin of SCLC



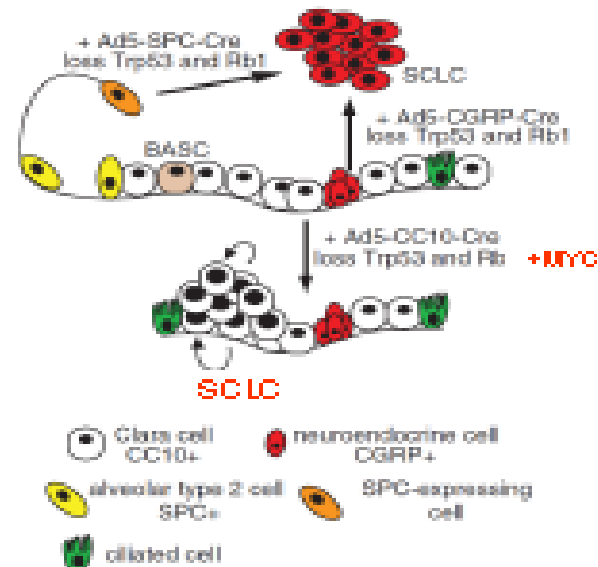
Sutherland et al., *Cancer Cell*, 2011



Olsen et al., *Genes Dev.*, 2011

# SCLC origin

## Cell Origin of SCLC (Summary)

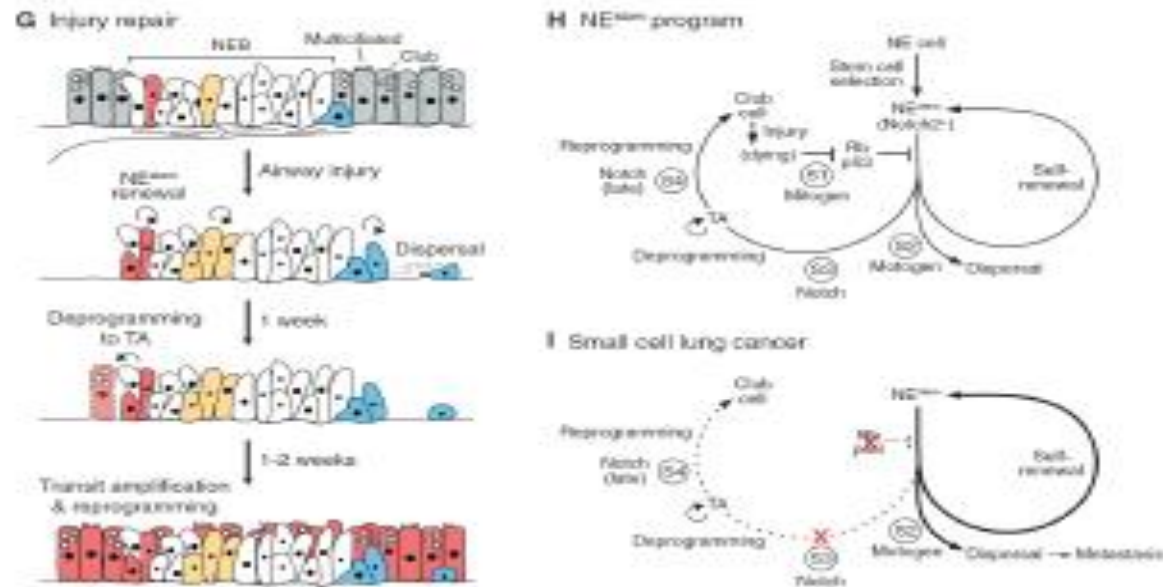


Adapted from Sutherland et al., *Cancer Cell* 2011

Cell of origin and genetic alterations all play a role in formation of SCLC.

# SCLC tumorigenesis

## A Model of SCLC Tumorigenesis by TP53 and RB1 Inactivation



# SCLC heterogeneity



Heterogeneity of SCLC

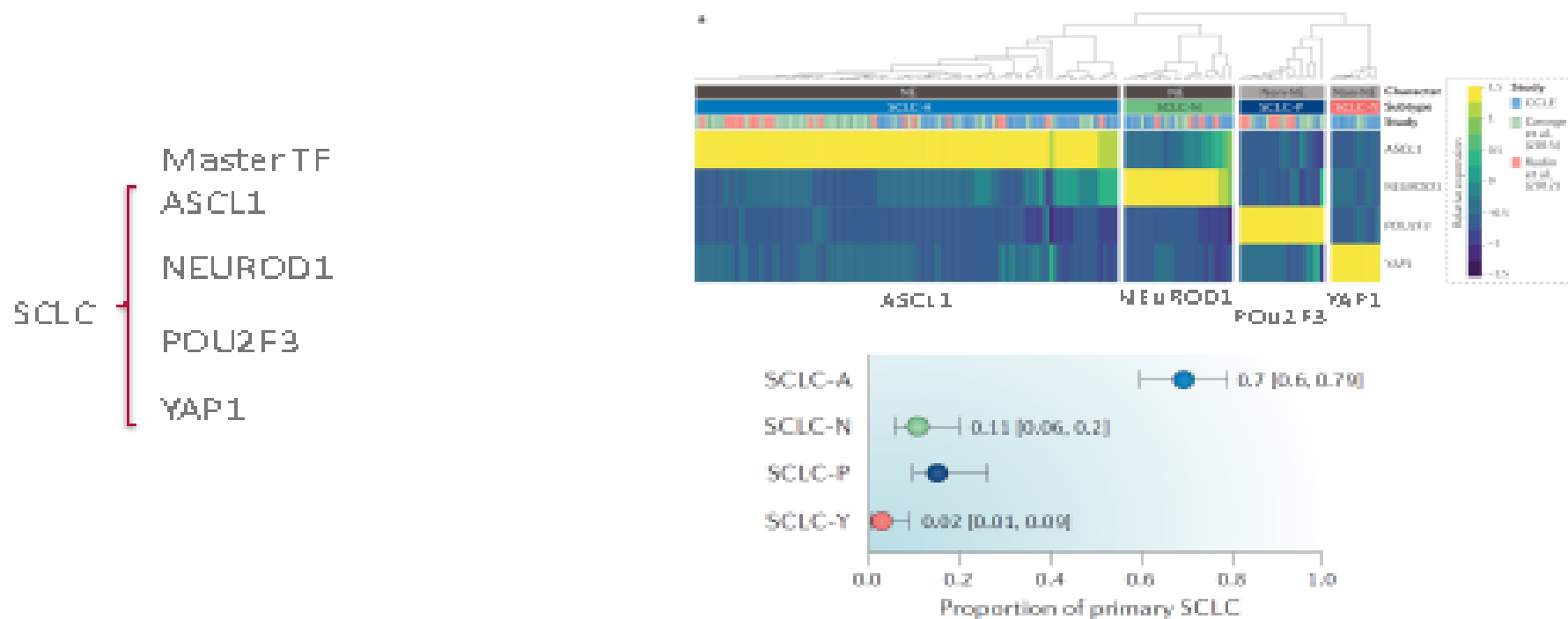
# Classic and variant SCLC

## Classic vs. Variant Subtypes of SCLC



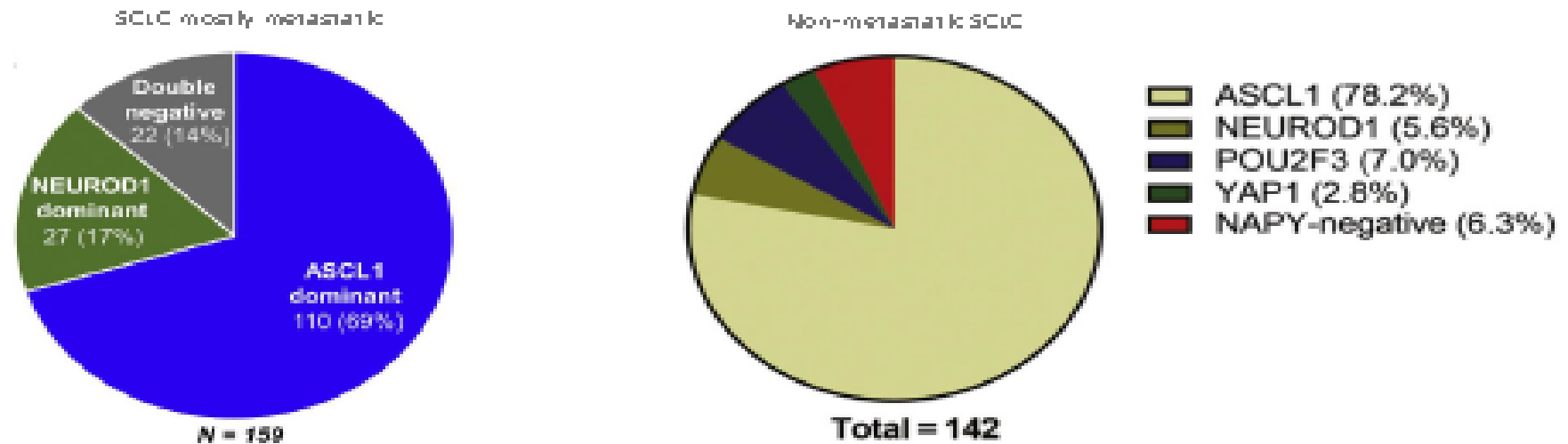
# SCLC molecular subtypes

## 2019 Molecular Subtype Classification of SCLC



# Subtype classification

## Verification of Molecular Subtype Classification Using IHC



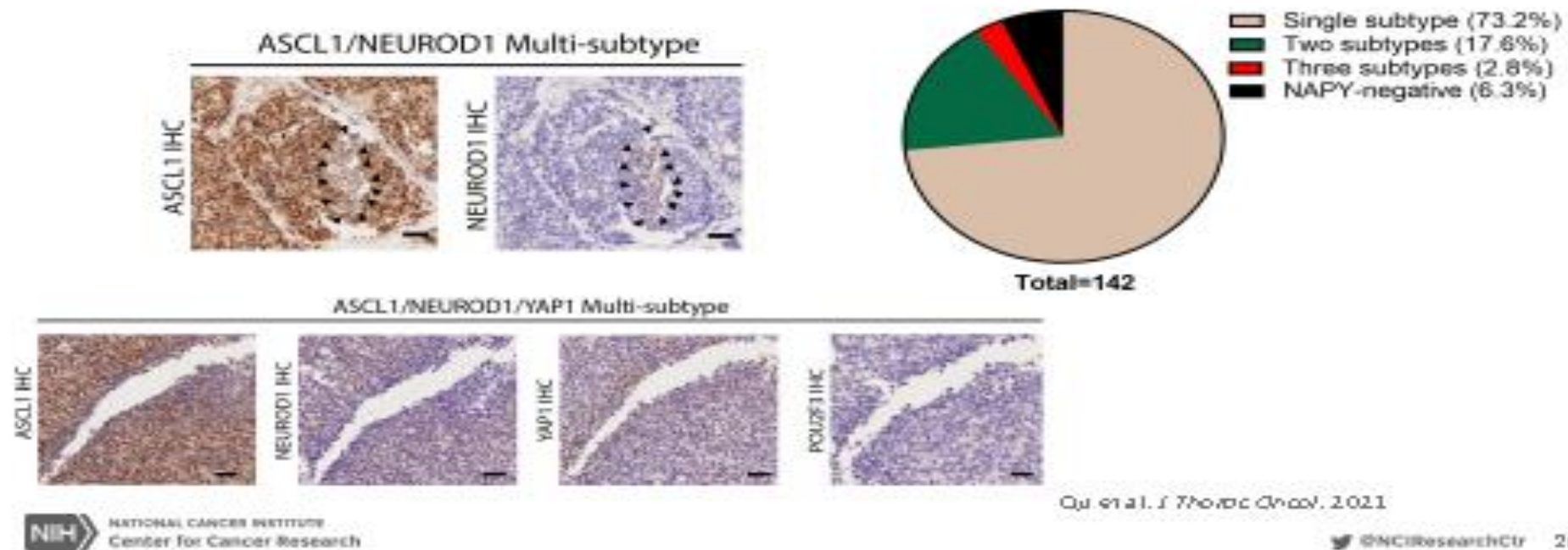
Balvin et al. *J Thorac Oncol*. 2020

Qu et al. *J Thorac Oncol*. 2021



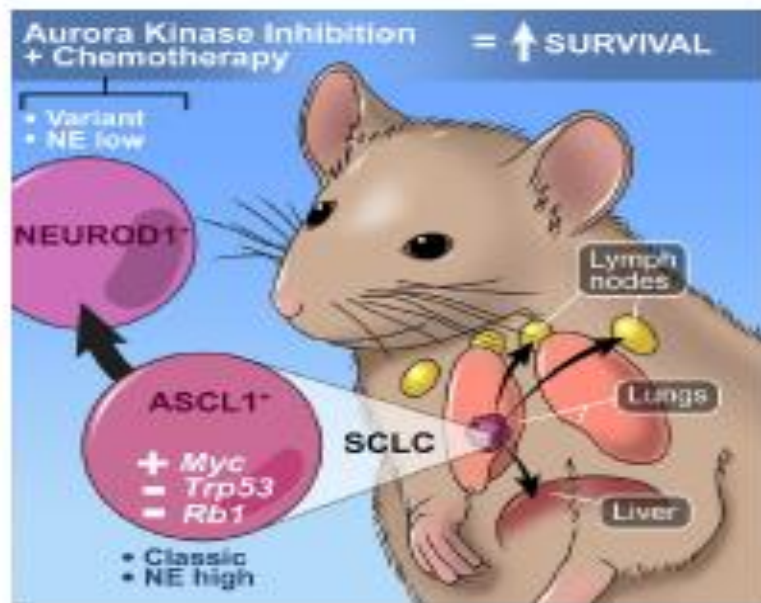
# Intratumoral heterogeneity

## Intratumoral Heterogeneity of SCLC

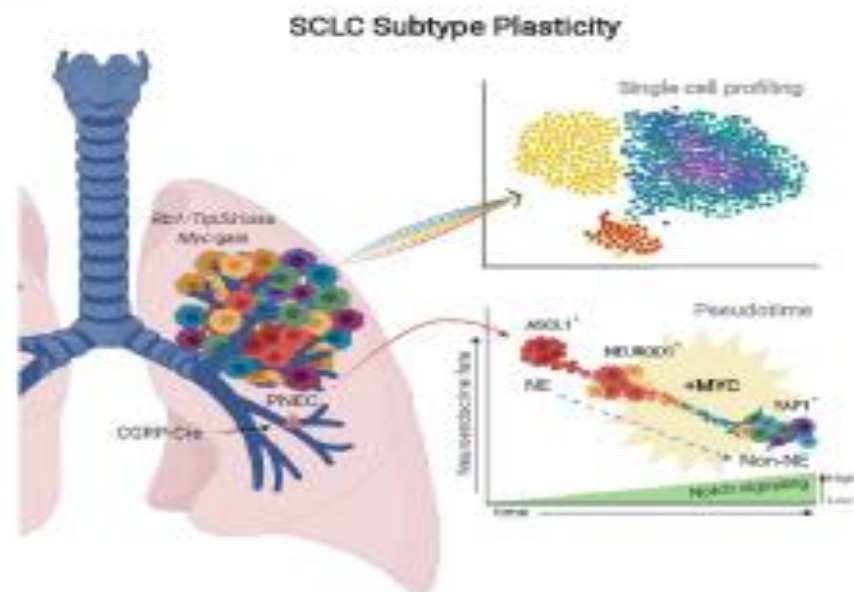


# SCLC plasticity

## SCLC Has High Plasticity



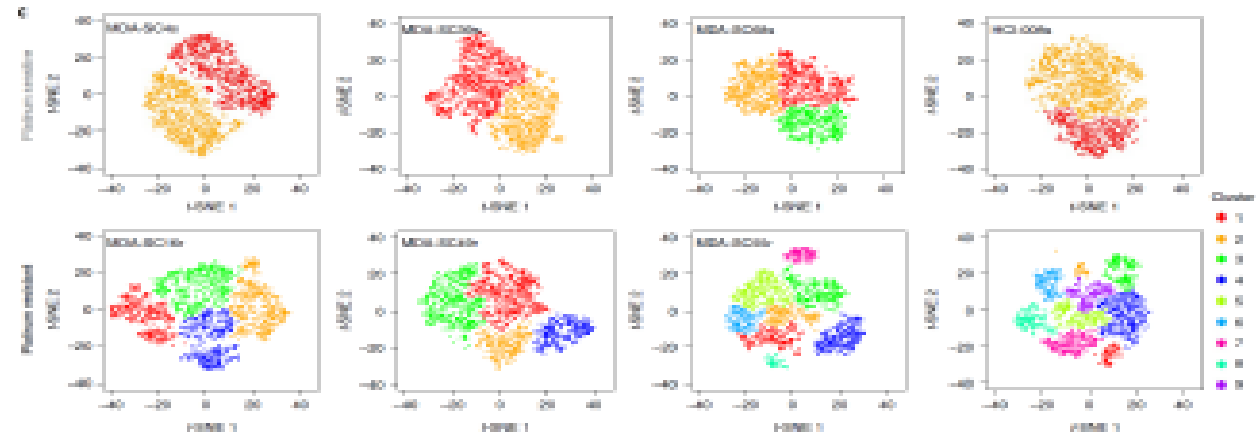
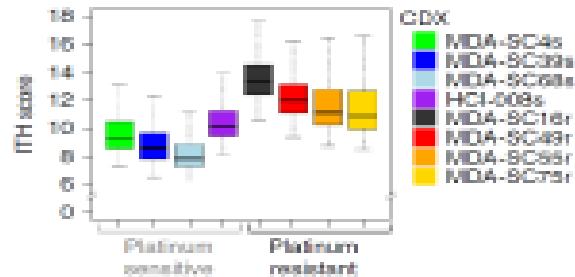
Mollaoglu et al. *Cancer Cell*. 2019



Ireland et al. *Cancer Cell*. 2021

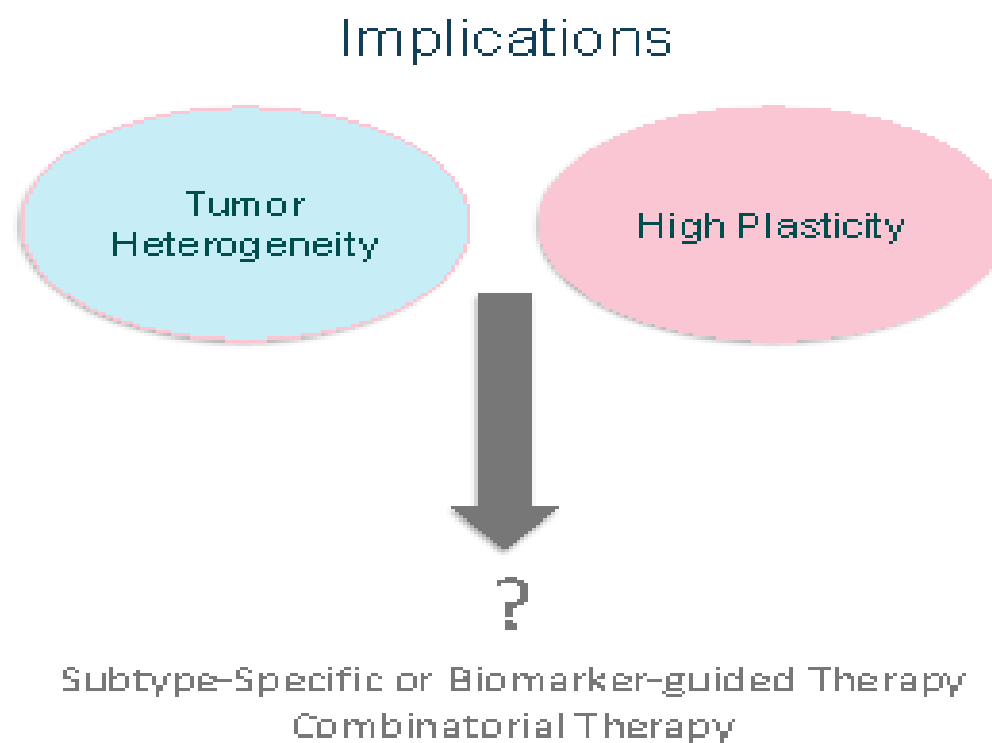
# Platinum-resistance

Heterogeneity is Increased in Platinum-resistant SCLC



Allison Stewart et al. Nature Cancer, 2020

# Implications



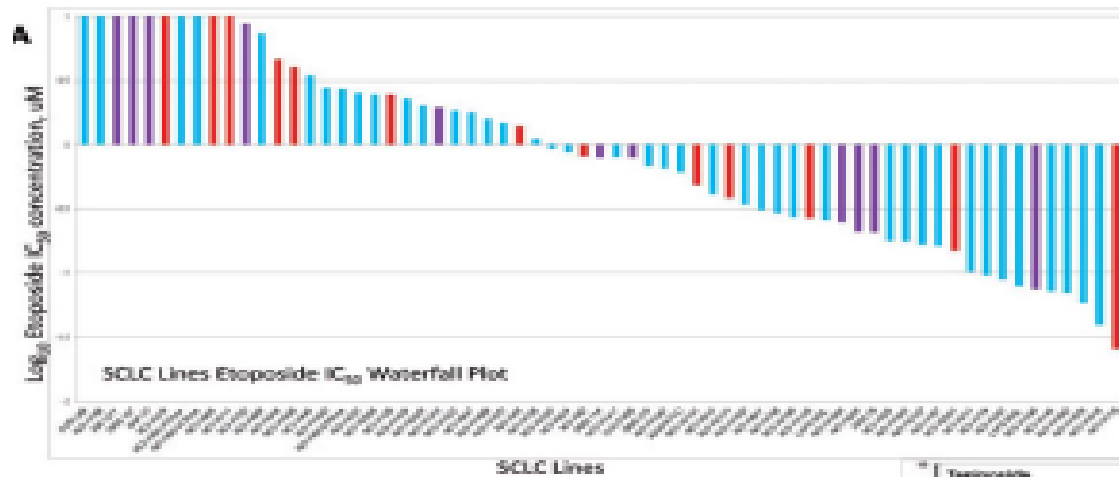
# New therapies



Development of  
New Therapy

# Drug screens

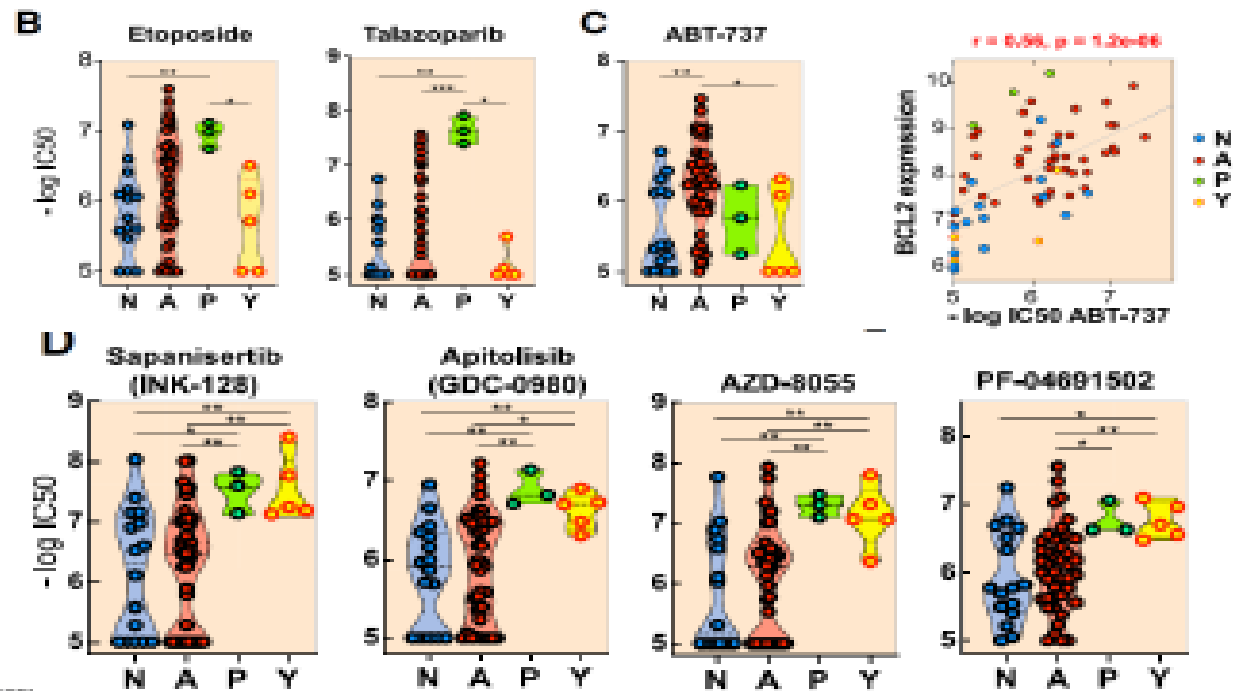
The Peril of 'One-size fits all'



Two large drug screens have failed to identify a drug that is effective in most of SCLC cell lines.

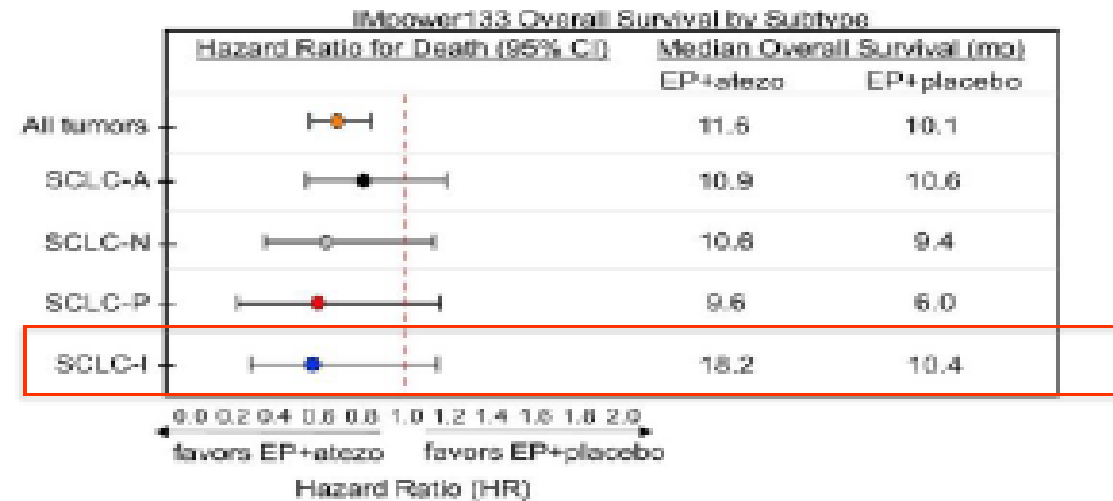
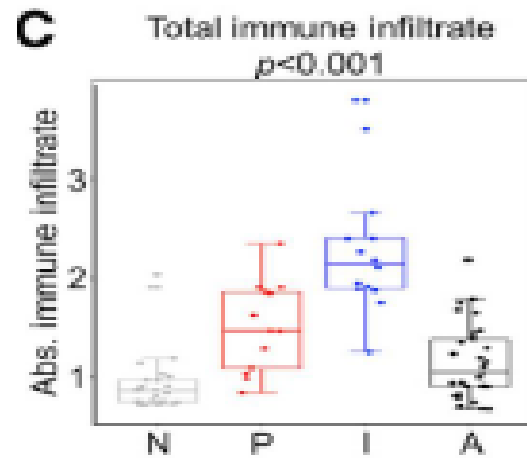
# SCLC susceptibility

## Distinct Susceptibility of Each Subtype of SCLC



# Subtype therapy

## Subtype-stratified Therapy Is Promising



■ NEUROG1-driven (N)

■ Inflamed (I)

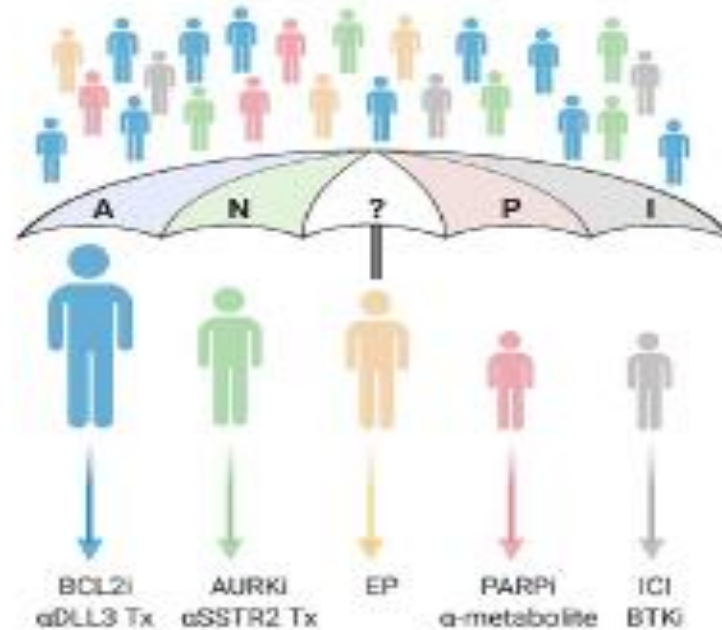
■ POU2F3-driven (P)

■ ASCL1-driven (A)



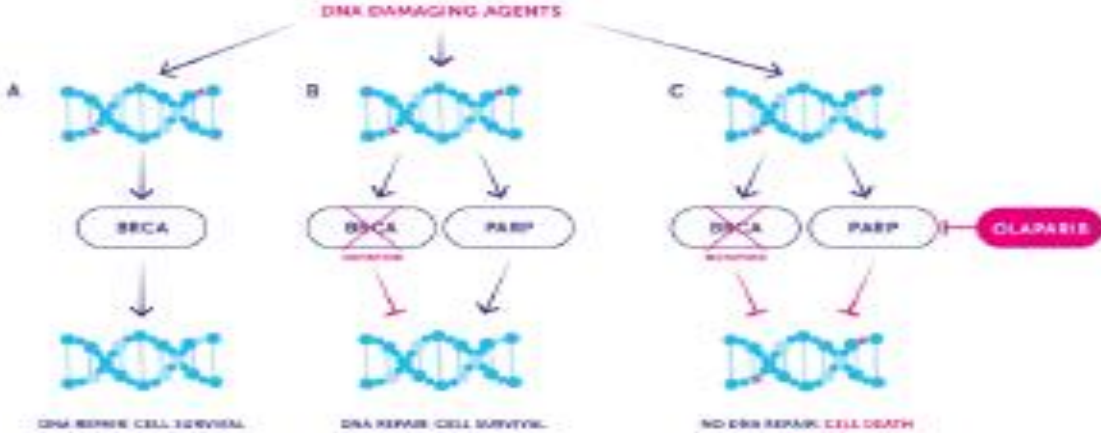
# SCLC subtype treatment

Single Umbrella Trial to Select Treatments Based on Molecular Subtypes of SCLC



# Synthetic lethality

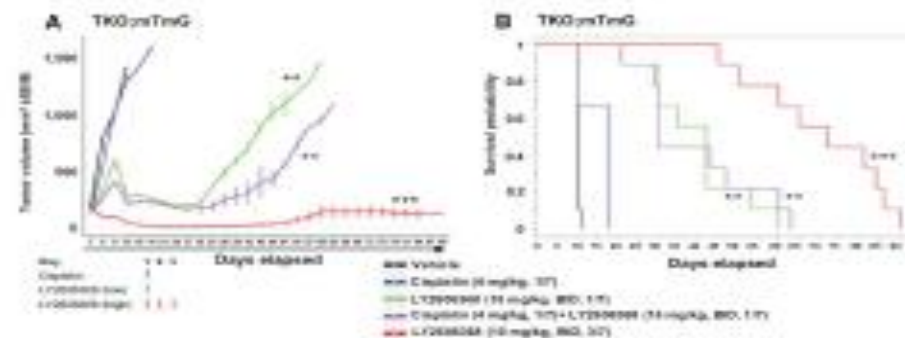
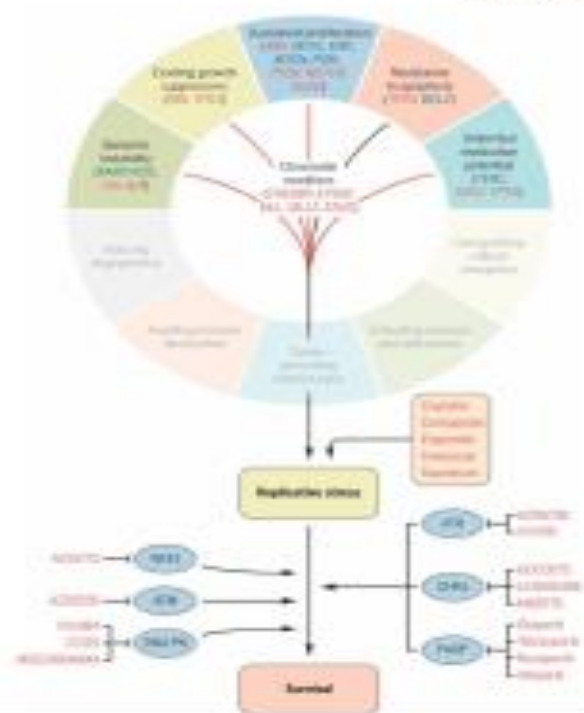
## Synthetic Lethality



<https://med.unc.edu/mf@CRU/Research/olaparib-repairing-the-promises-of-genetic-testing-for-cancer-prevention>

# Replication stress

## Replication Stress in SCLC



LY2606368, CHK1 Inhibitor

Seh et al. Cancer Research, 2017







