Small cell lung cancer

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10/17/2022

TRACO Lecture

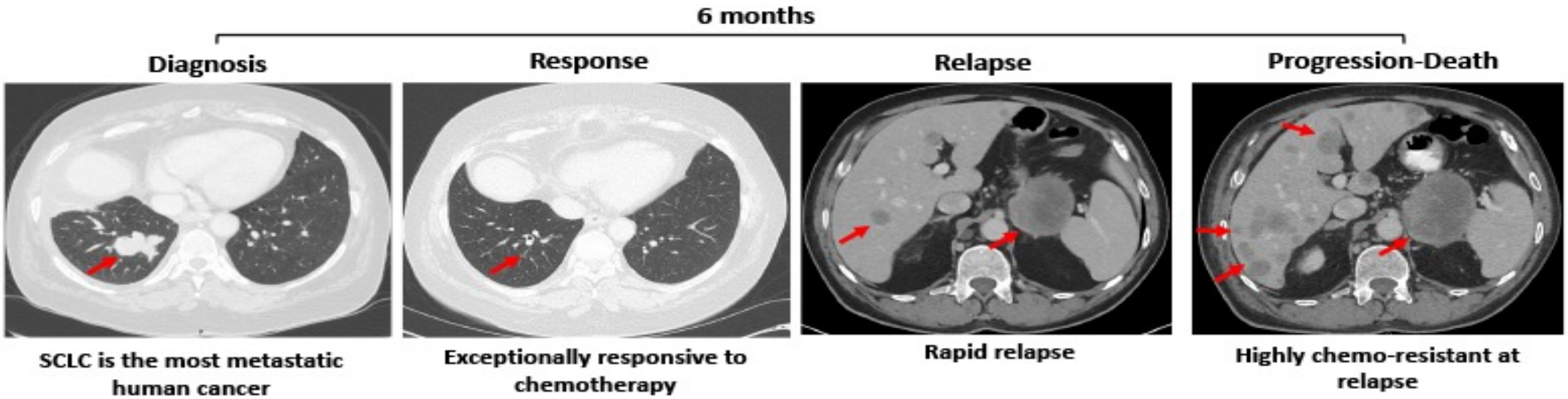
Anish Thomas, MD

Investigator

Developmental Therapeutics Branch

SCLC metastasis

SCLC is exceptionally metastatic and highly chemo-resistant



SCLC affects 250,000 individuals and kills at least 200,000 globally each year
Median SCLC survival is 7 months

SCLC and smoking

SCLC is a smoking related cancer

Lung cancer develops in only 15% of smokers

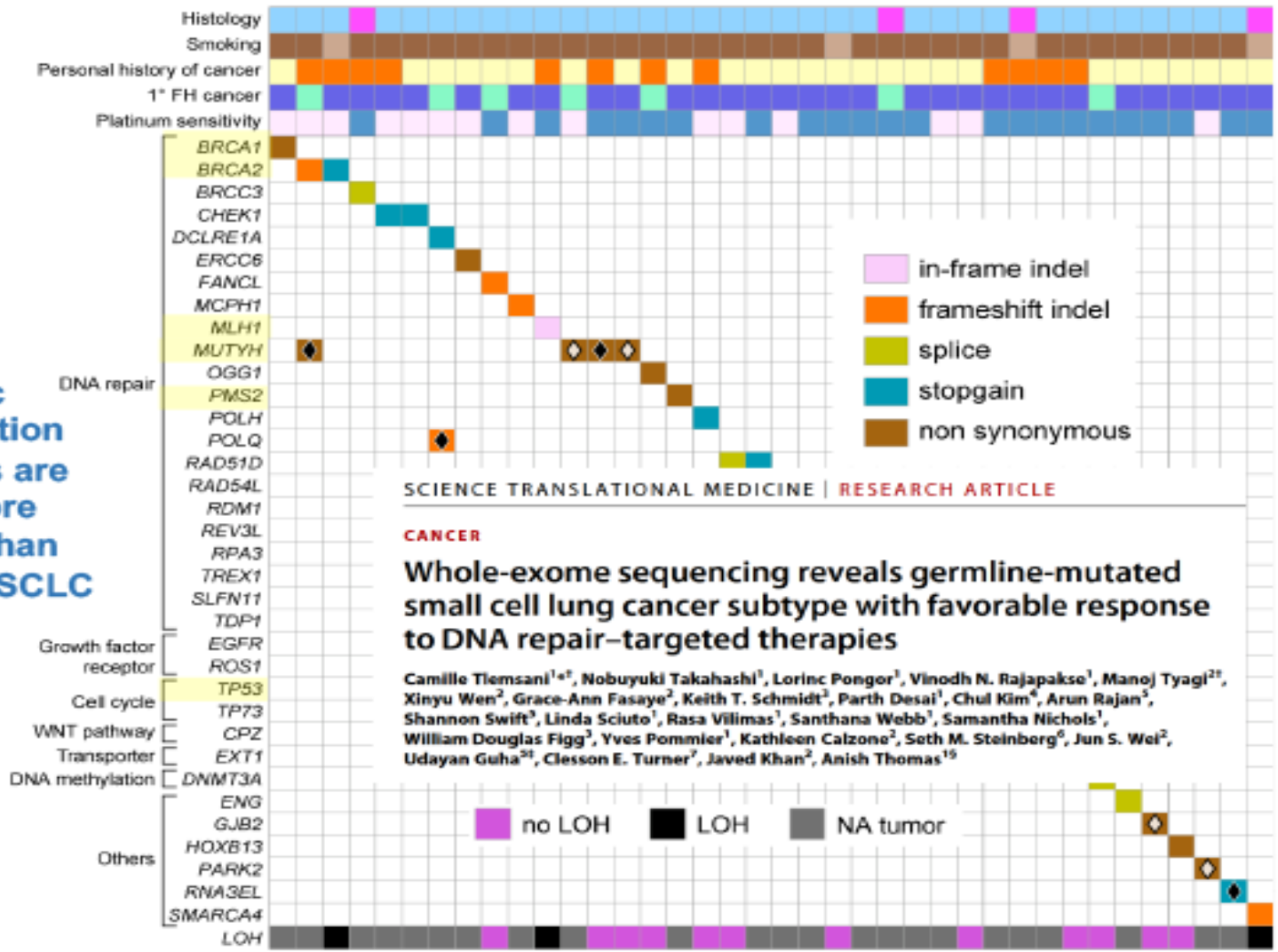
~2-3% of patients with SCLC are never-smokers

Thomas, Takahashi, et al. Chest 2020

Variations in genetic profiles → differential susceptibility to tobacco carcinogens ?

SCLC syndromes

Genetic predisposition syndromes are much more common than expected in SCLC



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Whole-exome sequencing reveals germline-mutated small cell lung cancer subtype with favorable response to DNA repair–targeted therapies

Camille Tlemsani[1*†], Nobuyuki Takahashi[1], Lorinc Pongor[1], Vinodh N. Rajapakse[1], Manoj Tyagi[2†], Xinyu Wen[2], Grace-Ann Fasaye[2], Keith T. Schmidt[3], Parth Desai[1], Chul Kim[4], Arun Rajan[5], Shannon Swift[3], Linda Sciuto[1], Rasa Vilimas[1], Santhana Webb[1], Samantha Nichols[1], William Douglas Figg[3], Yves Pommier[1], Kathleen Calzone[2], Seth M. Steinberg[6], Jun S. Wei[2], Udayan Guha[2†], Clesson E. Turner[7], Javed Khan[2], Anish Thomas[1§]

38 patients (43.7%) with pathogenic variants

10.3% patients ACMG cancer genes (24 high-penetrance actionable genes)

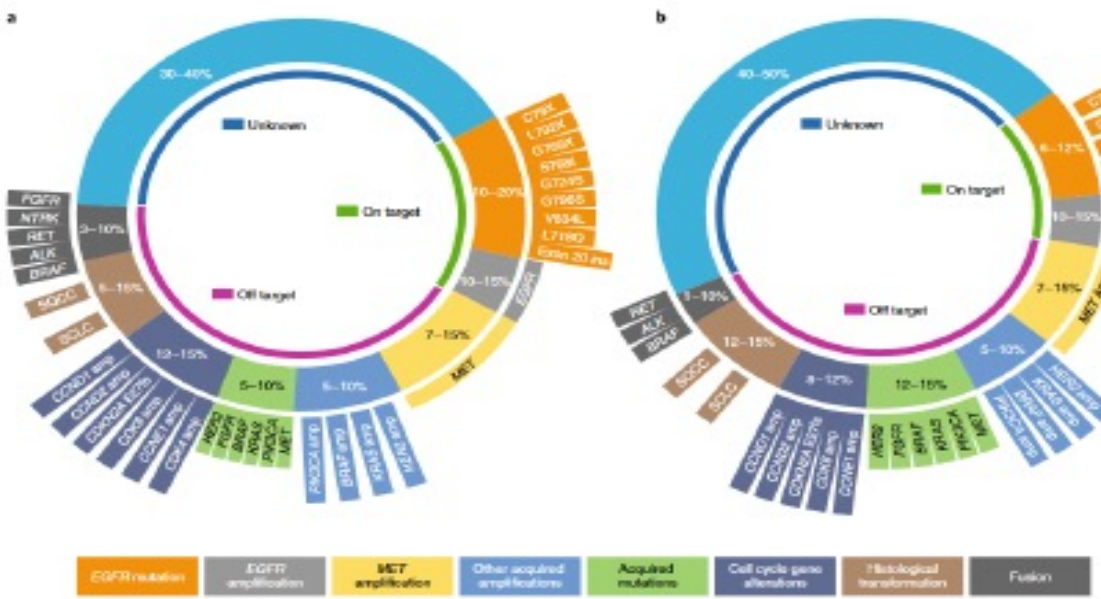
Kalia et al. Genet. Med. 2017

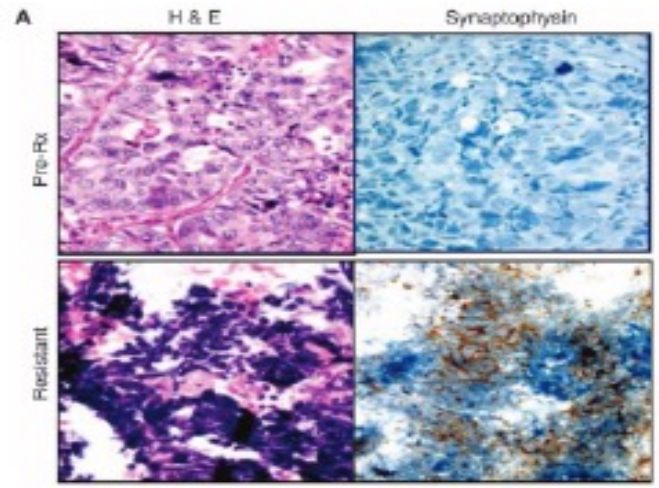
19.5% patients BROCA panel (77 hereditary cancer predisposition genes)

Shirts et al. Genet. Med. 2016

Lineage plasticity

SCLC also occurs due to lineage plasticity: transformed small cell





Lineage plasticity in cancer: a shared pathway of therapeutic resistance

Álvaro Quintanal-Villalonga[1], Joseph M. Chan[1,2,3], Helena A. Yu[1], Dana Pe'er[2,3], Charles L. Sawyers[4,5], Triparna Sen[1] and Charles M. Rudin[1]

Sequist Sci Trans Med 2011
Pasaro Nat Cancer 2021
Quintanal-Villalonga. Nat Reviews 2020

Perspectives

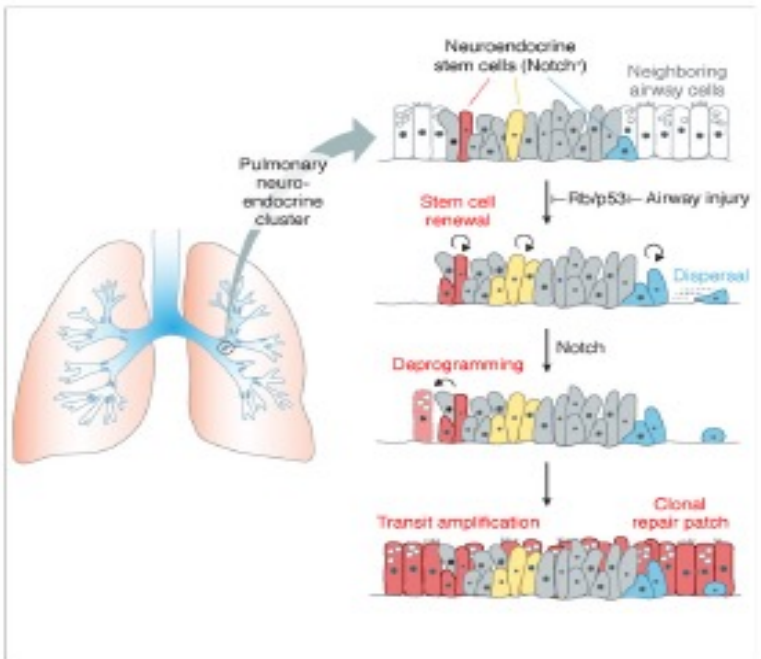
Clinical Cancer Research

The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance

Himisha Beltran[1], Andrew Hruszkewycz[2], Howard I. Scher[3], Jeffrey Hildesheim[2], Jennifer Isaacs[2], Evan Y. Yu[4], Kathleen Kelly[2], Daniel Lin[4], Adam Dicker[5], Julia Arnold[2], Toby Hecht[2], Max Wicha[6], Rosalie Sears[7], David Rowley[8], Richard White[3], James L. Gulley[2], John Lee[4], Maria Diaz Meco[9], Eric J. Small[10], Michael Shen[11], Karen Knudsen[5], David W. Goodrich[12], Tamara Lotan[13], Amina Zoubeidi[14], Charles L. Sawyers[3], Charles M. Rudin[3], Massimo Loda[15], Timothy Thompson[16], Mark A. Rubin[17], Abdul Tawab-Amiri[2], William Dahut[2], and Peter S. Nelson[4]

SCLC origin

SCLC origin is thought to originate from neuroendocrine cells activated by injury



- Injury induces stem cell renewal, dispersal, transit amplification, and reprogramming
- Tumor suppressors Rb, p53, and Notch control specific steps in stem cell program
- Small-cell lung cancer arises by genetic activation of stem cell renewal and dispersal

Ouadah Y. Cell 2019

SCLC carcinogenesis

SCLC carcinogenesis

Mouse model for NE lung tumors can be established by conditional inactivation of Rb1 and Trp53 in mouse lung epithelial cells (*Meuwissen R. Cancer Cell 2003*)

NE cells (centrally located) serve as the most efficient cell-of-origin of SCLC (*Sutherland. Cancer Cell 2011*)

SPC+ cells (peripherally located) can also give rise to SCLC at lower frequency and after a longer latency

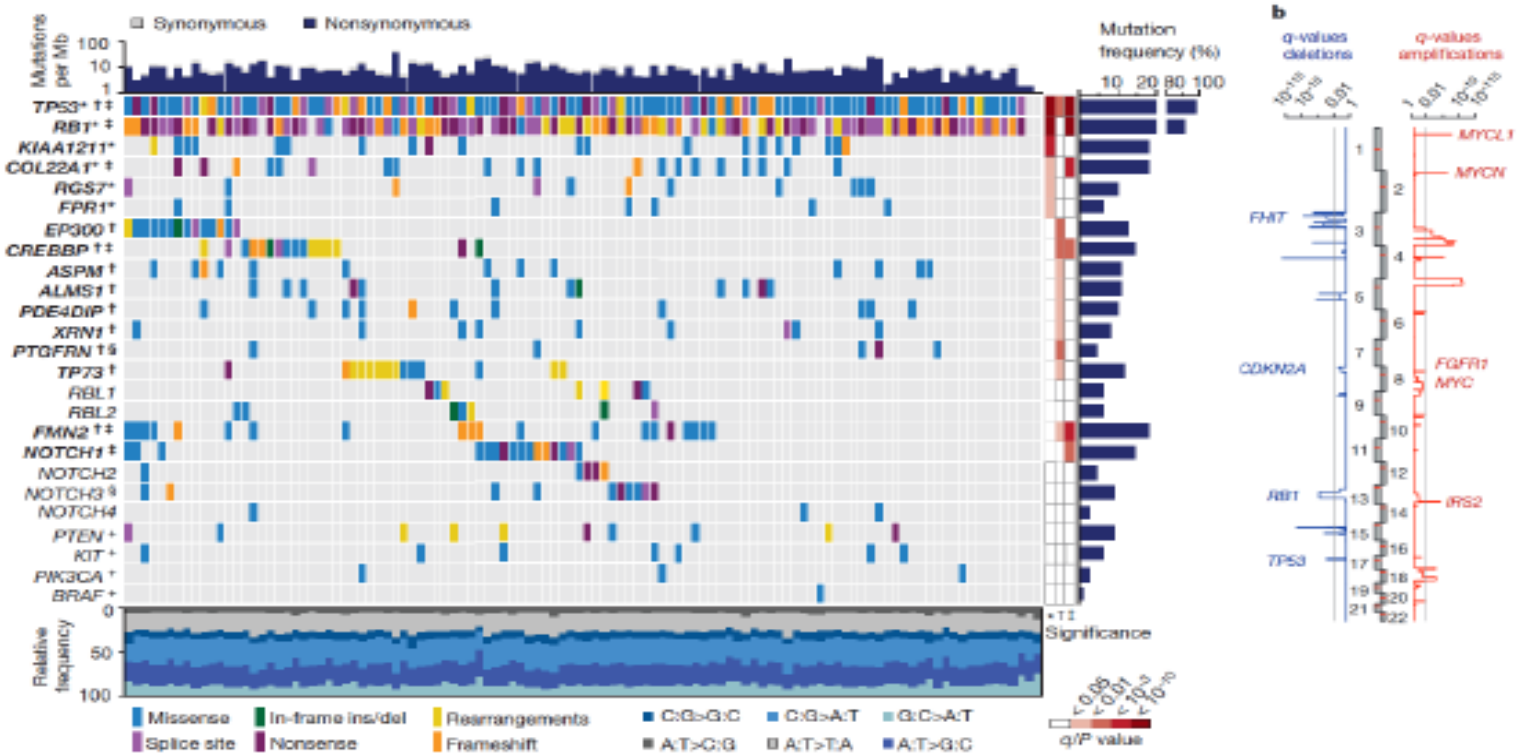
Clara cells are resistant to transformation

Does the cell of origin influence tumor characteristics??

SCLC genomics

SCLC genomics

P53 inactivation (90%)
Rb inactivation (90%)
MYC amplification (30%)

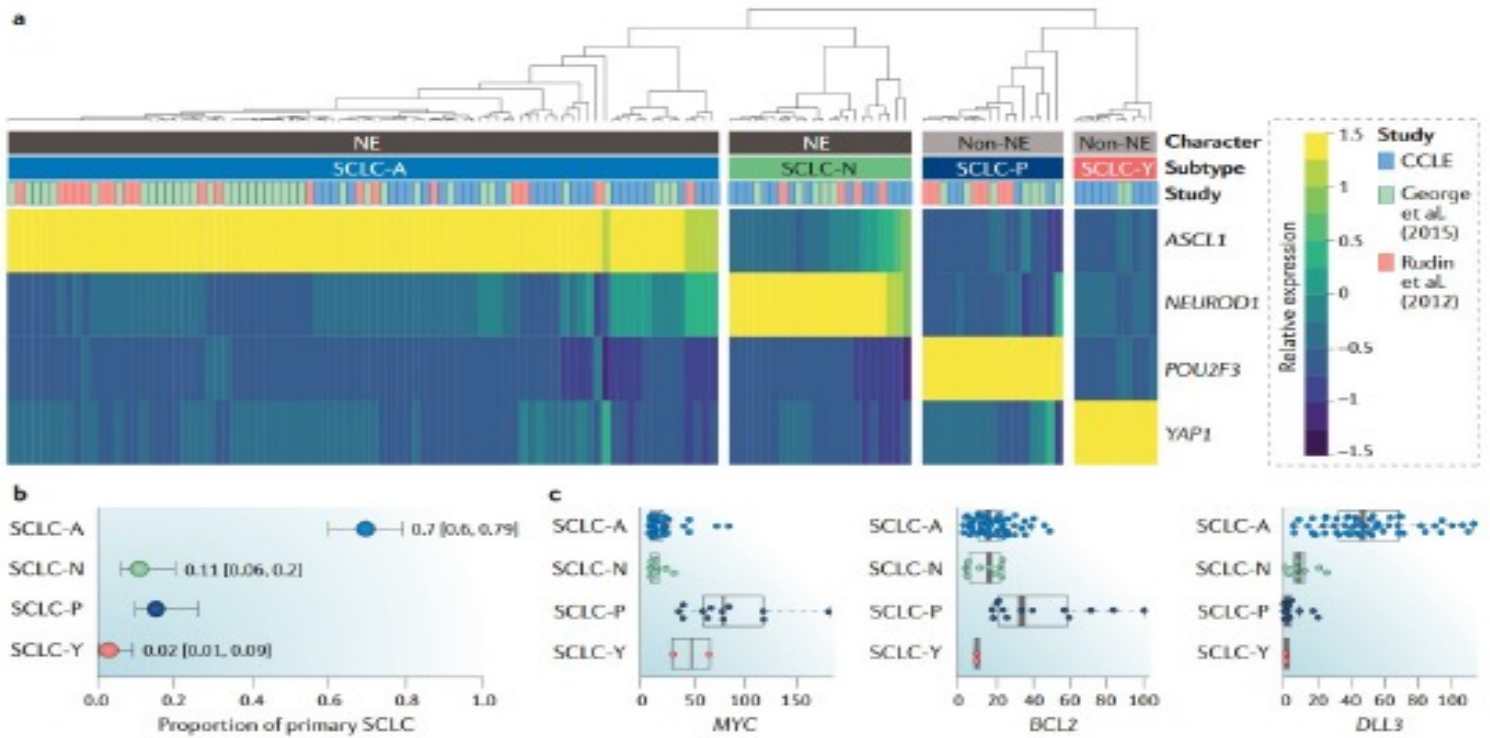


No "targetable driver" genes
Limited genetic heterogeneity

George J. Nature 2015

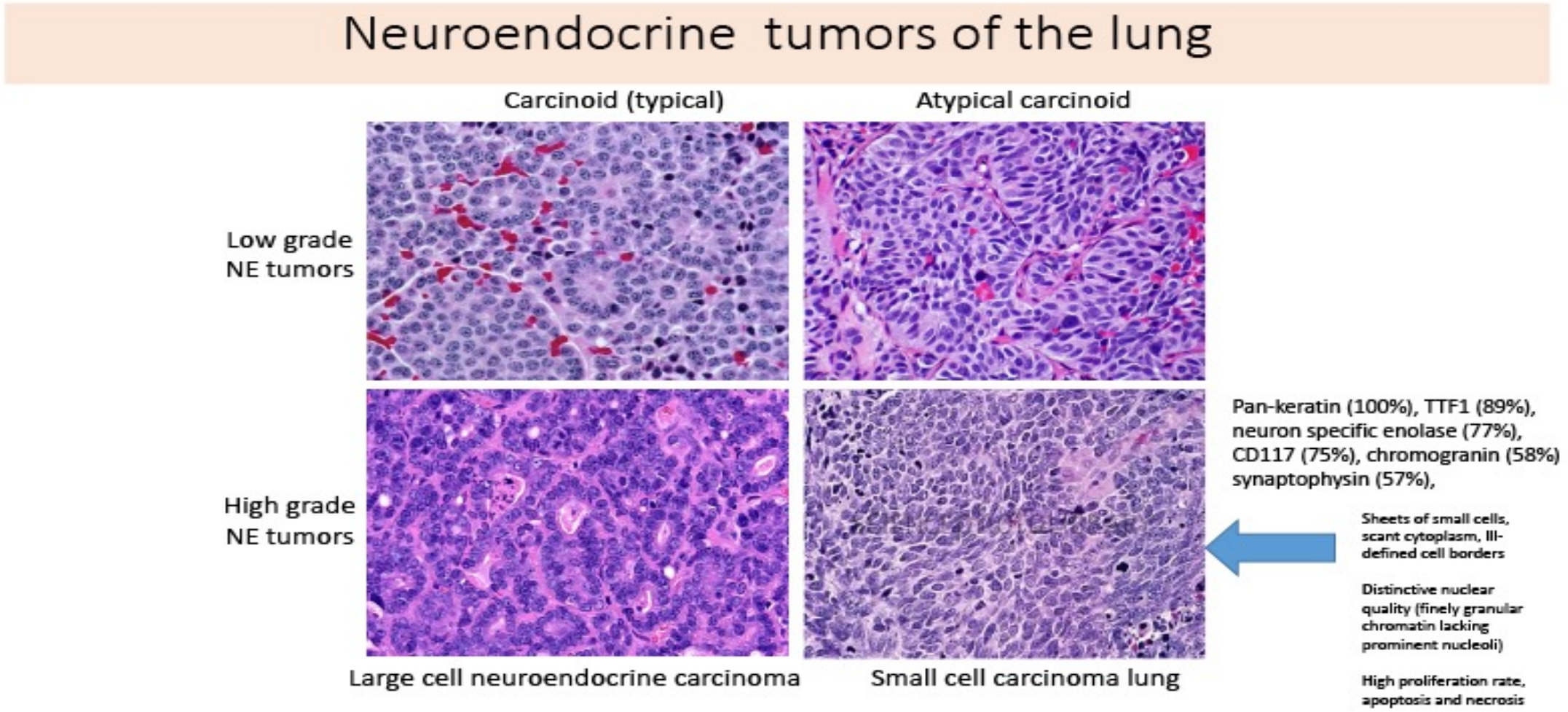
Heterogeneity

Marked transcriptional heterogeneity



Rudin, Nat reviews 2019

Neuroendocrine tumors



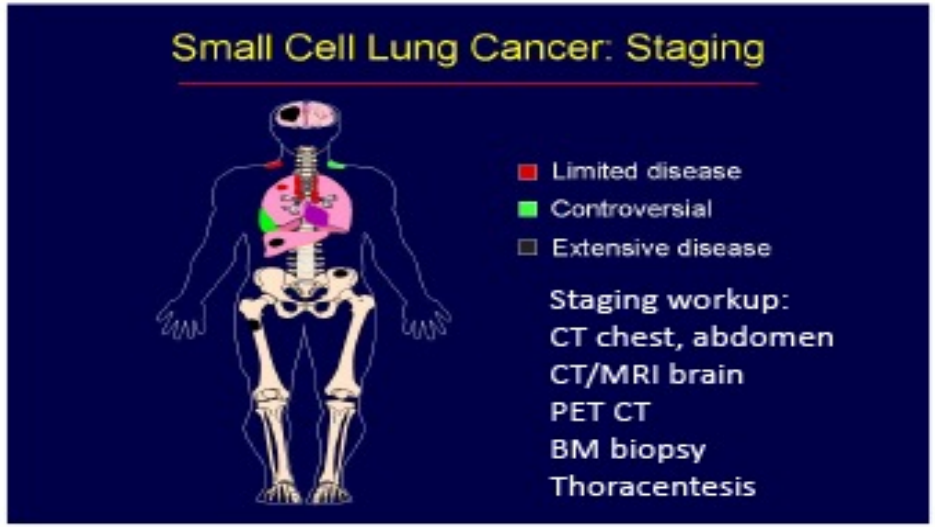
Chemo-resistance

SCLC is exceptionally metastatic and highly chemo-resistant

- ✓ **Origins/molecular characteristics**
  - Aggressive, smoking-related cancer; germline impact likely
  - On the high end of the spectrum of NE cancers
  - Loss of TP53/RB1 important
  - Heterogeneity driven by gene expression patterns
- ? Cells of origin other than NE cells/ ? Impact on clinical course

Cancer staging

Staging and initial work up



Modification of the VALG staging 1957
Brain is a frequent site of metastasis

Systemic disease

SCLC is a systemic disease at diagnosis

Autopsy study of patients (N=19) who underwent surgical resection with a curative intent within 30 days prior to their death ----------Distant metastatic disease in 60% cases

Metastasize most frequently to the liver, bone, adrenals, brain and abdominal lymph nodes.

Matthews MJ, et al,
Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer.
Cancer chemotherapy reports, 1973

Mary J Matthews, d. 1987
Pathologist NCI MOB

MEDICAL RESEARCH COUNCIL COMPARATIVE TRIAL OF SURGERY AND RADIOTHERAPY FOR PRIMARY TREATMENT OF SMALL-CELLED OR OAT-CELLED CARCINOMA OF BRONCHUS

Ten-year Follow-up

WALLACE FOX J. G. SCADDING
Medical Research Council Tuberculosis and Chest Diseases Unit and Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP

Summary This report gives the 10-year results of a controlled trial of a policy of surgery and a policy of radical radiotherapy in the treatment of patients with small-celled or oat-celled carcinoma of the bronchus diagnosed preoperatively on bronchial biopsy and thought likely to be operable. The analysis included 144 patients, 71 allocated at random to the surgery series and 73 to the radical-radiotherapy series. There were no 10-year survivors in the surgery series, but in the radiotherapy series 3 remained alive and well. The mean survival for the surgery series was 199 days and for the radical-radiotherapy series 300 days—a statistically significant difference ($P=0.04$). This reinforces the conclusion of the 5-year report that in this trial radical radiotherapy has given, in terms of survival, a somewhat better result than surgery in the treatment of patients with small-celled or oat-celled carcinoma of the bronchus diagnosed preoperatively on bronchial biopsy and judged to be operable.

Fox. Lancet 1973

Screening

SCLC systemic disease - even when diagnosed by screening

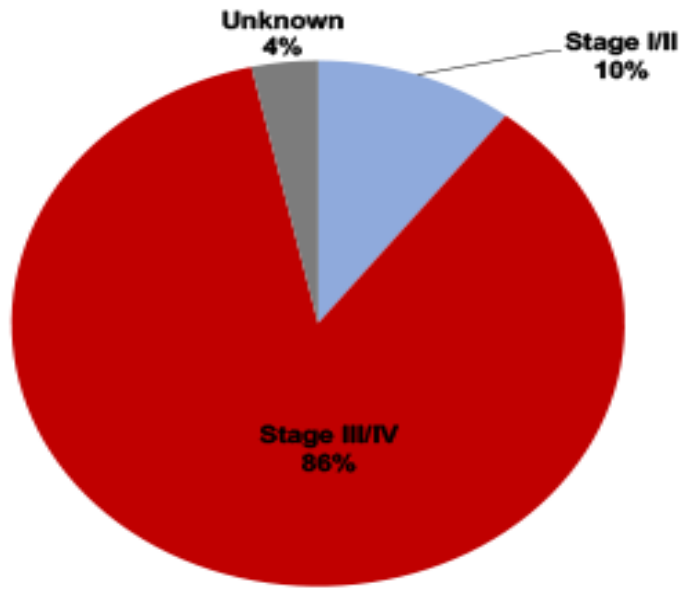
NLST trial
High-Risk Subjects
N=53,464

55-74 years
Current/ former smokers ≥30 pack-years
Former smokers must have quit ≤ 15 years
Asymptomatic and no prior Hx lung cancer
No chest CT in prior 18 months

Low dose CT arm

Chest X-ray arm

3 annual screens: T0, T1, T2; Followed annually
for incident cancers/survival



Thomas, Szabo, Pinsky. Chest 2018

SCLC treatment

Treatment outline

	Extensive Stage, 1L	Limited Stage, 1L	2L
FDA Approved	• Platinum + etoposide + atezolizumab • Platinum + etoposide + durvalumab		• **Lurbinectedin** • Topotecan
NCCN Guidelines[1] ***Preferred regimens***	• Platinum + etoposide + atezolizumab • Platinum + etoposide + durvalumab	• Cisplatin + etoposide +/- RT	• Relapse ≤ 6 months: topotecan or clinical trial

Additional chemotherapy

MORE chemotherapy IS NOT BETTER

- Unusually intensive induction regimens
  - High dose vs. std. dose chemotherapy (CAV/ EP)
    - Johnson DH. JCO 1987
    - Ihde SC. JCO 1994
  - Increasing dose density
    - Klasa RJ JCO 1991
  - Chemo with auto-BMT
    - Humblet Y JCO 1987
  - Sequential non-cross-resistant regimens (CAV vs. EP-CAV)
    - Roth BJ. JCO 1992

Daniel C. Ihde, d. 2005
Deputy Chief, NCI-Navy MOB

Cranial irradiation

Prophylactic Cranial Irradiation

- Approximately two thirds of patients with SCLC develop brain metastases after 2 yr[1]
- PCI a mainstay in treatment of LS SCLC following curative chemoradiation
  - 5.4% absolute survival benefit at 3 yr[2]
- PCI now used less often in ES SCLC given conflicting data from EORTC trial (OS benefit) and Japanese trial data (no OS benefit)[3-5]
- Ongoing research and debate on role of PCI for ES SCLC
- MRI brain surveillance Q3M is reasonable in lieu of PCI for patients with ES SCLC responding to treatment

1. Arriagada. J Natl Cancer Inst. 1995;87:183. 2. Aupérin. NEJM. 1999;34:476. 3. Slotman. NEJM. 2007;357:664.
4. Takahashi. Lancet Oncol. 2017;18:663. 5. Gjyshi. JAMA Netw Open. 2019;2:e199135.

Chemo + IO

ES-SCLC: good response to chemo+IO→ PCI ± → What's next?

Table S4. Subsequent Cancer Therapies.

	Atezolizumab Group (N=201)	Placebo Group (N=202)
Line of therapy		
Second	101 (50.2)	116 (57.4)
Third	29 (14.4)	38 (18.8)
Fourth	3 (1.5)	15 (7.4)
Therapy type		
Total number of patients with at least one treatment	104 (51.7)	116 (57.4)
Total number of treatments — no.	138	176
Chemotherapy/non-anthracycline	81 (40.3)	88 (43.6)
Chemotherapy/anthracycline	31 (15.4)	46 (22.8)
Immunotherapy	6 (3.0)	15 (7.4)
Other	2 (1.0)	2 (1.0)
Targeted therapy	2 (1.0)	1 (0.5)

Aggressive clinical course
Steep decline in patients getting subsequent therapies

Maintenance therapies shown no benefit

Options:

- Clinical trials
- Topotecan
- Lurbinectidin
- Taxol/CAV etc.

No targeted therapies

Horn L et al. N Eng J Med 2018; 379(23): 2220-2229.

SCLC metatasis

SCLC is exceptionally metastatic and highly chemo-resistant

- ✓ Aggressive, smoking-related cancer; germline impact likely
- ✓ Cell of origin, genetics determine disease phenotypes
- ✓ SCLC is a systemic disease = all patients need systemic treatment
- ✓ Aggressive clinical course
- ✓ Limited treatment options

Transcriptomic heterogeneity

SCLCs exhibit remarkable transcriptomic heterogeneity

SCLC now: Same treatment for all patients, most patients die within a year

Rudin et al. *Nat Rev Cancer 2019*

Molecular basis

The challenge: very little is known of the molecular basis of human SCLC

- Metastases
- Chemoresistance
- Heterogeneity

A major barrier : Limited availability of clinical samples for research

TCGA The Cancer Genome Atlas
33 cancers
11,000 tumors

PCAWG PanCancer Analysis of WHOLE GENOMES
38 cancers
2600 whole genomes

SCLC is not included in large-scale sequencing studies

Most of our knowledge about the biology and molecular pathogenesis of SCLC has evolved from continuous cell cultures and mouse models

Translational research

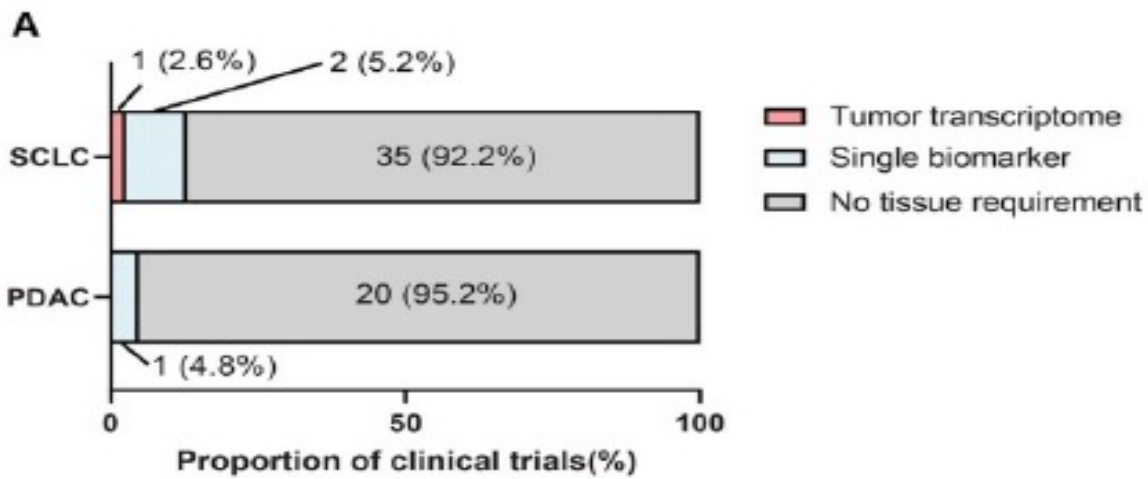
Cancer Cell

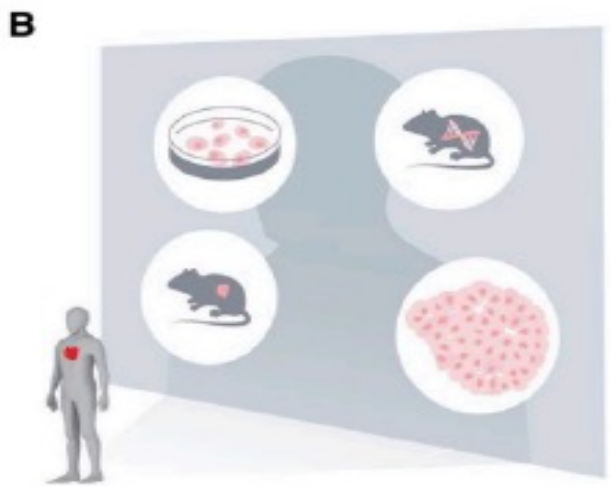
CellPress

Commentary

Translational research: A patient-centered approach to bridge the valley of death

Anish Thomas,[1,*] Parth Desai,[1] and Nobuyuki Takahashi[1,2,3]

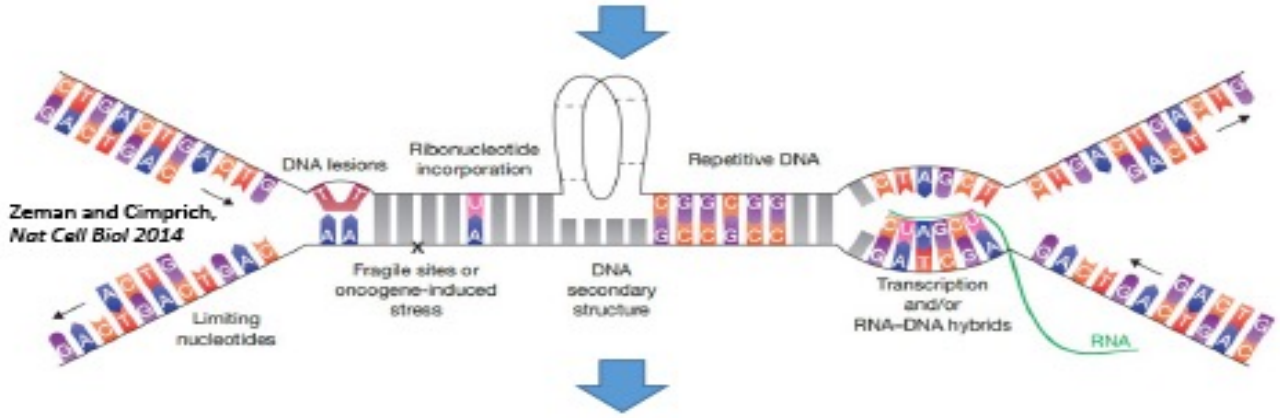




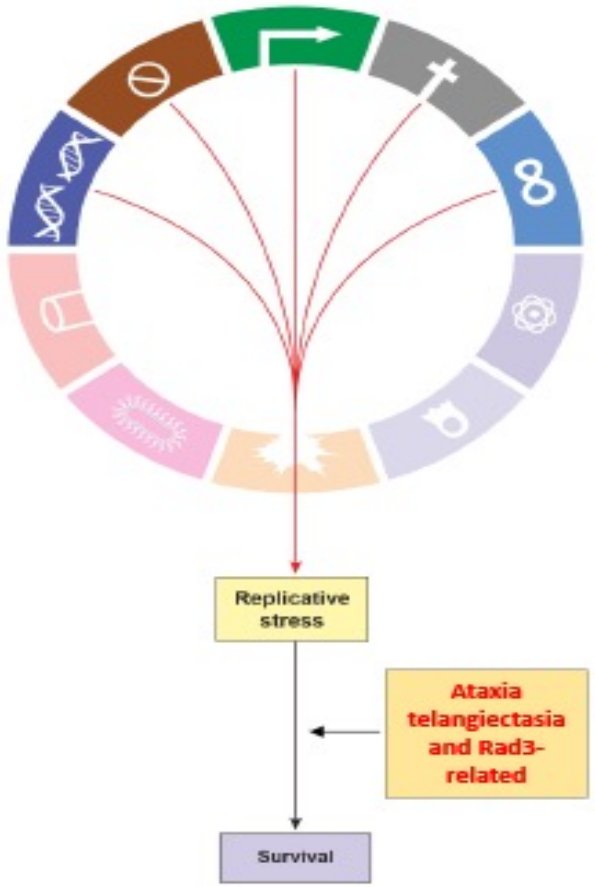
Replication stress

Replication stress is a SCLC hallmark

Frequent RB1 and TP53 loss; MYC amplification
Sustained high expression of lineage transcription factors



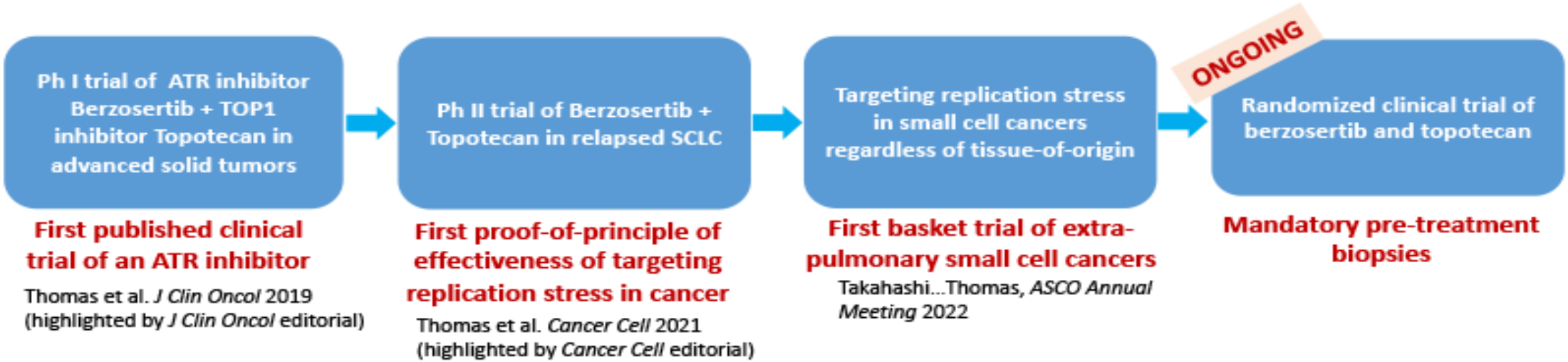
High degree of genomic instability, mutation load, aneuploidy
Striking responses to DNA damaging chemotherapy



Thomas and Pommier. *Sci Transl Med 2016*

SCLC vulnerability

Discovery of replication stress as a transformative vulnerability of SCLC; paving the way for rational patient selection (2015-2022)

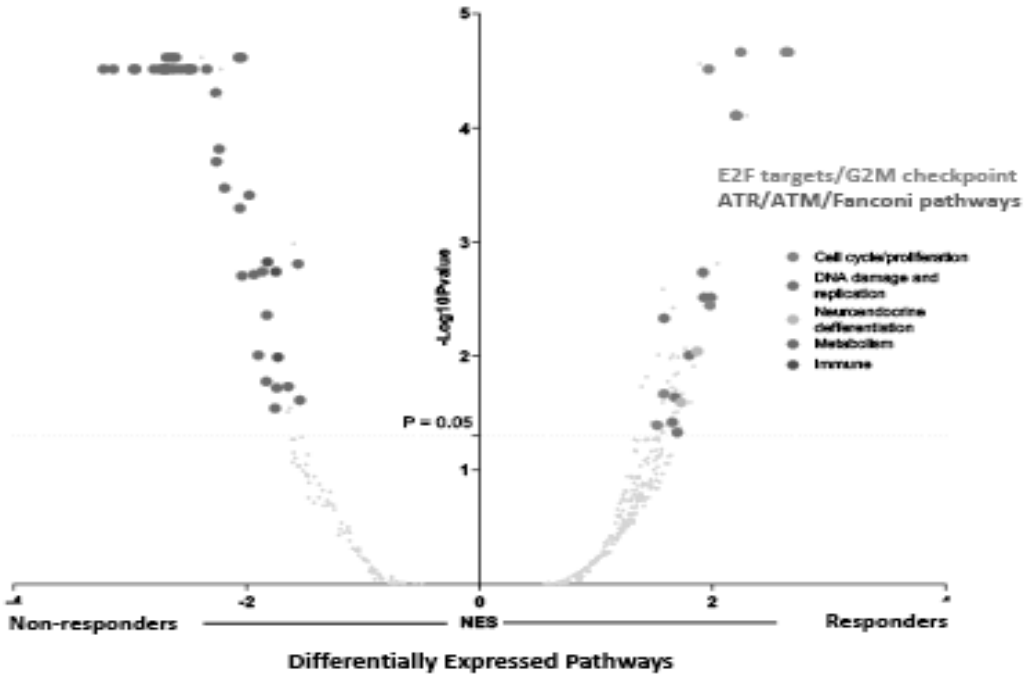


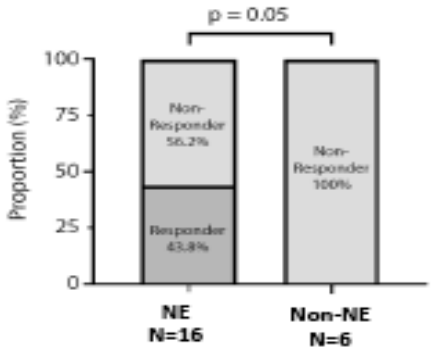
ONGOING

- Determinants of response in SCLC
- Molecular basis of SCLC replication stress
- Signatures of replication stress
- Improving the therapeutic index of replication stress-targeted therapies

ATR/TOP1 inhibitors

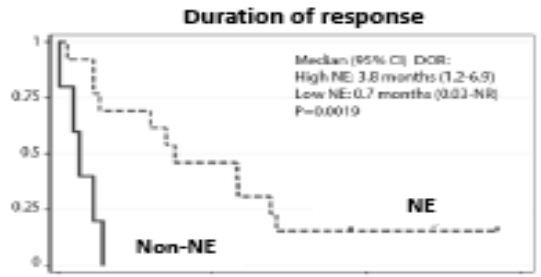
Tumors responding to ATR/TOP1 inhibition are under replication stress

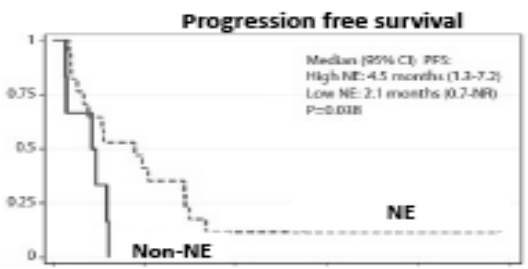




We are examining the pre-treatment tumors from the randomized study to better understand the predictive role of NE differentiation in responses to ATR inhibition

- Mandatory pre-treatment biopsies
- Tumor gene expression



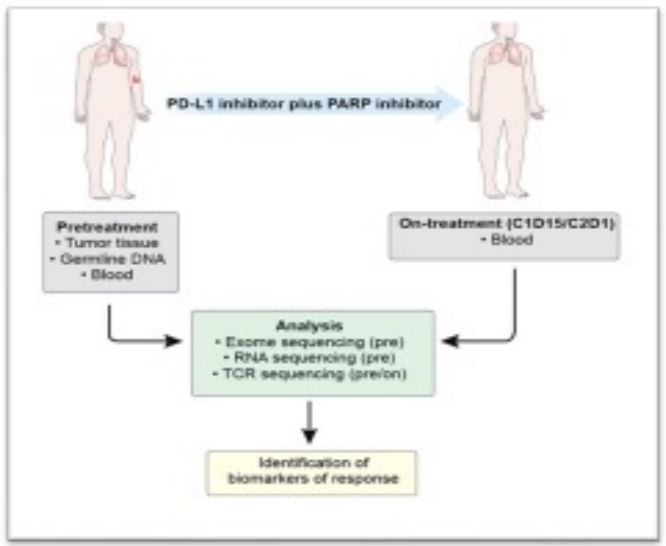


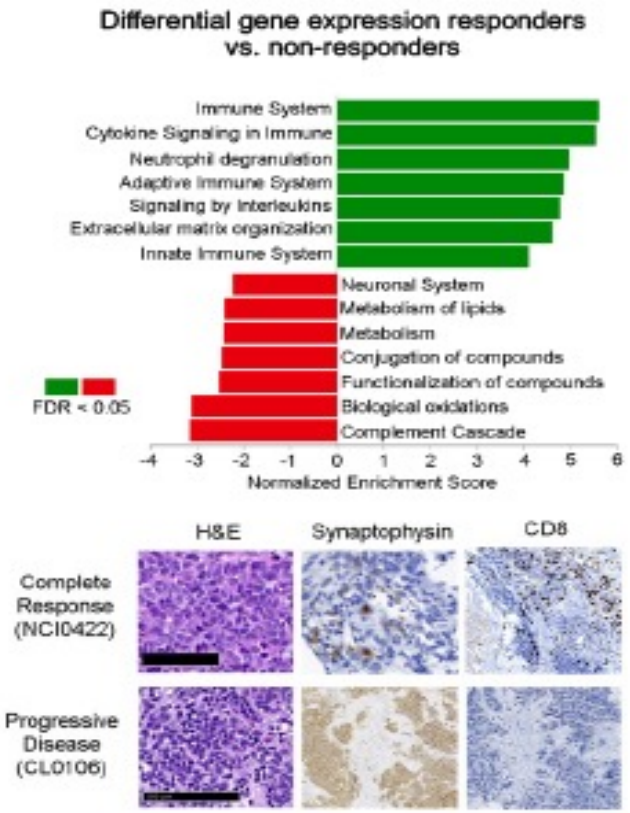
NE gene expression defines a subset of SCLC under high replication stress

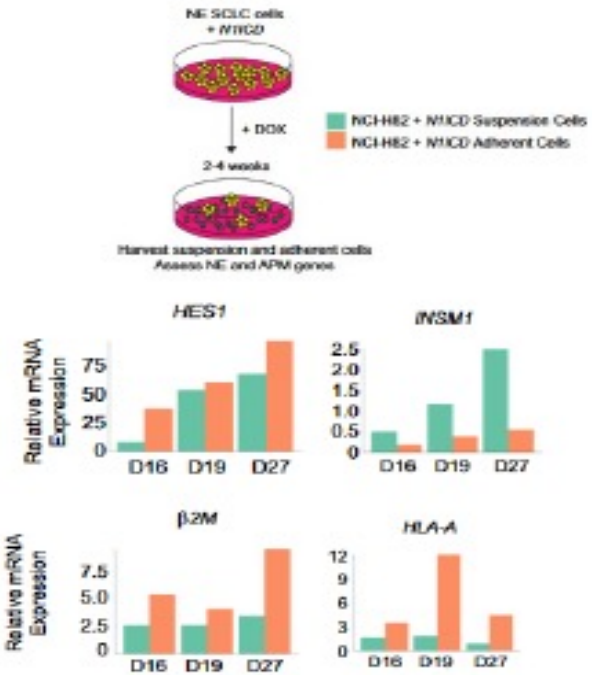
Thomas et al. *Cancer Cell 2021*

Immunotherapy

Low NE tumors are more likely to respond to immunotherapy





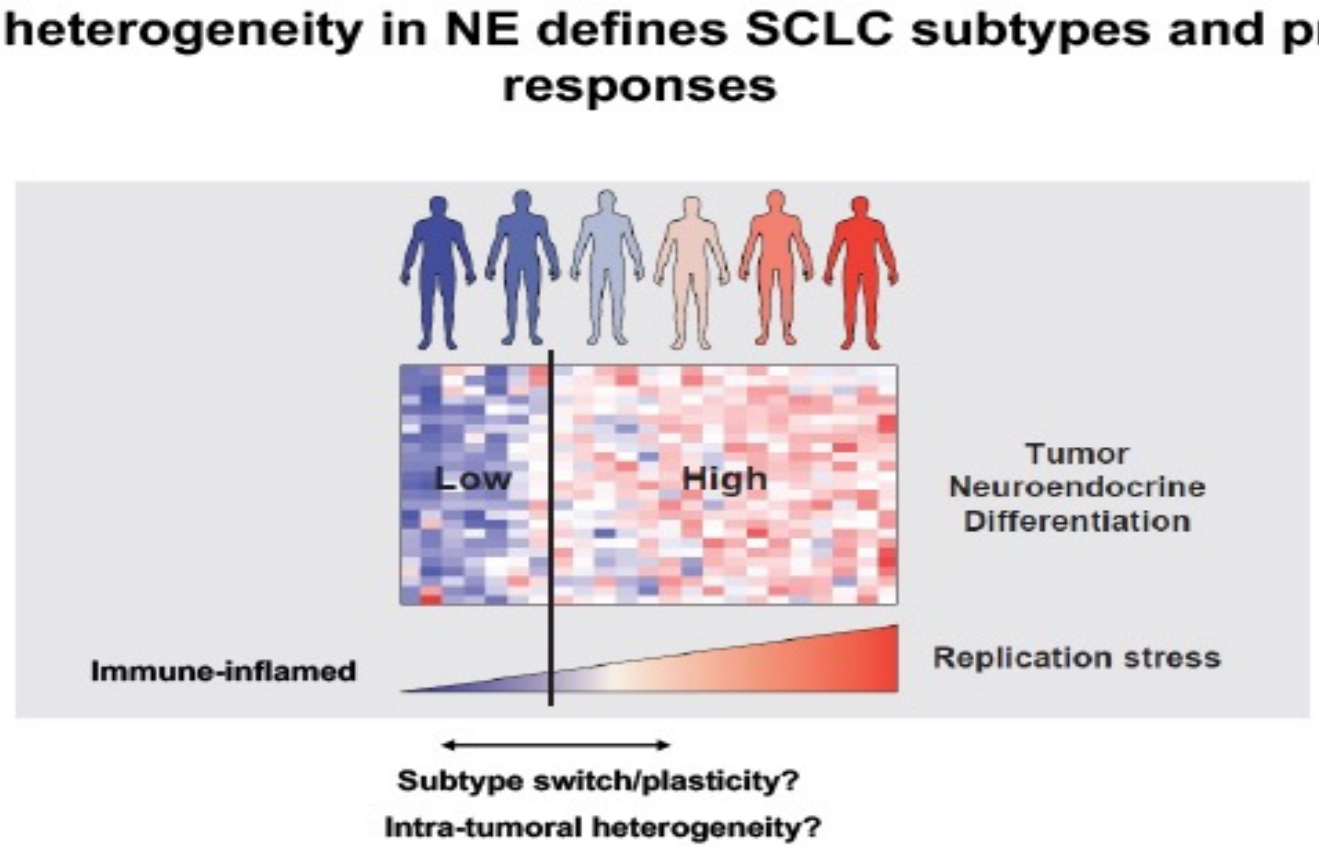


Thomas et al. J Thoracic Oncology 2019
Roper et al. Nat Comm 2021

Activation of Notch upregulates intrinsic tumor immunity through decreased NE differentiation

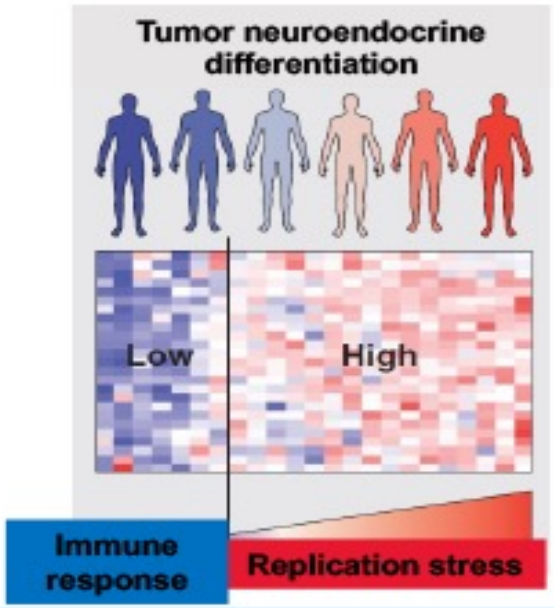
Similar results:
Gay et al. Cancer Cell 2021
Owonikoko et al. JTO 2021
Chen et al. JTO CRR 2021
Mahadevan et al. Can Discov 2021….

Inter-tumoral heterogeneity



SCLC subgroups

Our goal: 1) Identify SCLC subgroups; 2) Define subgroup-specific vulnerabilities



Article

Cancer Cell

Therapeutic targeting of ATR yields durable regressions in small cell lung cancers with h replication stress

April 12, 2021

Anish Thomas,[1,11,*] Nobuyuki Takahashi,[1] Vinodh N. Rajapakse,[1] Xiaohu Zhang,[2] Yilun Sun,[1] Michele Ceribelli,[2] Kelli M. Wilson,[2] Yang Zhang,[1] Erin Beck,[2] Linda Sciuto,[1] Samantha Nichols,[1] Brian Elenbaas,[3,10] Janusz Puc,[3,10] Heike Dahmen,[4] Astrid Zimmermann,[4] Jillian Varonin,[5] Christopher W. Schultz,[1] Sehyun Kim,[1] Hirity Shimellis,[1] Parth Desai,[1] Carleen Klumpp-Thomas,[2] Lu Chen,[2] Jameson Travers,[2] Crystal McKnight,[2] Sam Michael,[2] Zina Itkin,[2] Sunmin Lee,[1] Akira Yuno,[1] Min-Jung Lee,[1] Christophe E. Redon,[1] Jessica D. Kindrick,[6] Cody J. Peer,[6] Jun S. Wei,[7] Mirit I. Aladjem,[1] William Douglas Figg,[6] Seth M. Steinberg,[8] Jane B. Trepel,[1] Frank T. Zenke,[4] Yves Pommier,[1] Javed Khan,[7] and Craig J. Thomas[2,9]

nature COMMUNICATIONS

Heterogeneity of neuroendocrine transcriptional states in metastatic small cell lung cancers and patient-derived models

Delphine Lissa[1,10], Nobuyuki Takahashi[2,3,10], Parth Desai[2], Irena Manukyan[4], Christopher W. Schultz[2], Vinodh Rajapakse[2], Moises J. Velez[5], Deborah Mulford[6], Nitin Roper[2], Samantha Nichols[2], Rasa Vilimas[2], Linda Sciuto[2], Yuanbin Chen[7], Udayan Guha[8], Arun Rajan[8], Devon Atkinson[9], Rajaa El Meskini[9], Zoe Weaver Ohler[9] & Anish Thomas[2]

April 19, 2022

nature communications

Notch Signaling and Efficacy of PD-1/PD-L1 Blockade in Relapsed Small Cell Lung Cancer

Nitin Roper[1], Moises Velez[2], Alberto Chiappori[3], Yoo Sun Kim[1], Jun S. Wei[4], Sivasish Sindiri[4], Nobuyuki Takahashi[1], Deborah Mulford[2], Suresh Kumar[1], Kris Ylaya[5], Christopher Trindade[3], Irena Manukyan[5], Anna-Leigh Brown[6], Jane B. Trepel[1], Jung-Min Lee[7], Stephen Hewitt[5], Javed Khan[4], Anish Thomas[1*]

June 23, 2021