Best of WCLC 2020:

Tumor Biology, Pathology, Novel Diagnostics

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United States

DISCLOSURES

Commercial Interest	Relationship(s)
Pfizer, Merck, Hengrui, LabyRx, OncoImmune (Oncoc4), Tempus	Research Grant
Eisai	Consultant/Honorarium

OUTLINE

1. Insights from TRACERx: immune evasion; trunk vs subclonal neoantigens
2. The New WHO Classification of Lung Tumors
3. Genetic risk of lung cancer
4. Vertical transmission of lung cancer

PL03.03

Lung Cancer Immune Evasion: insights from TRACERx

IASLC January 2021

Charles Swanton

THE FRANCIS CRICK INSTITUTE

CANCER RESEARCH UK | TRACERx

CANCER RESEARCH UK | LUNG CANCER CENTRE OF EXCELLENCE

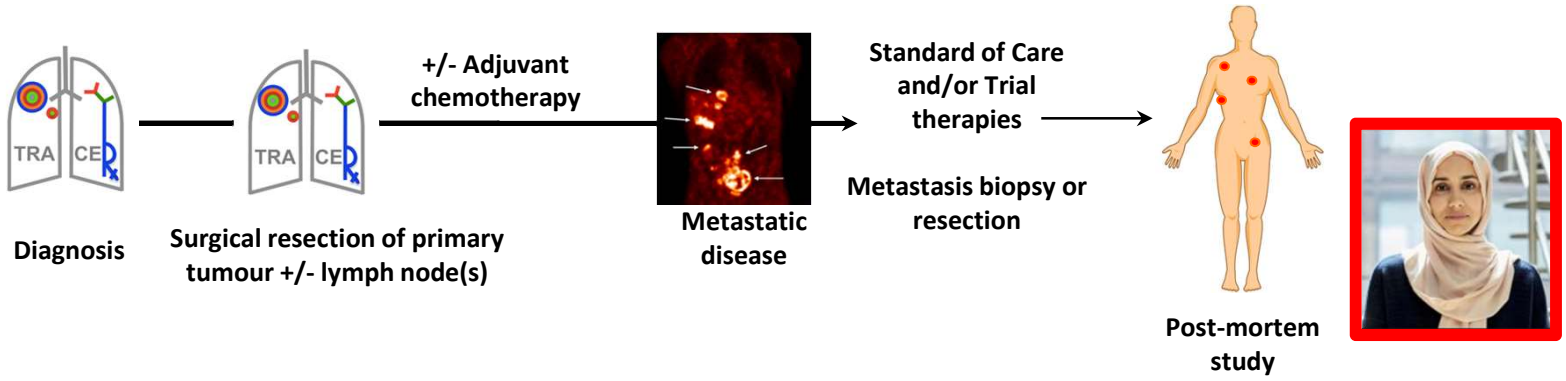
UCL Cancer Institute

UCL

TRACERx : TRAcking Cancer Evolution through Therapy (Rx)

PEACE Study

13 Hospital Sites

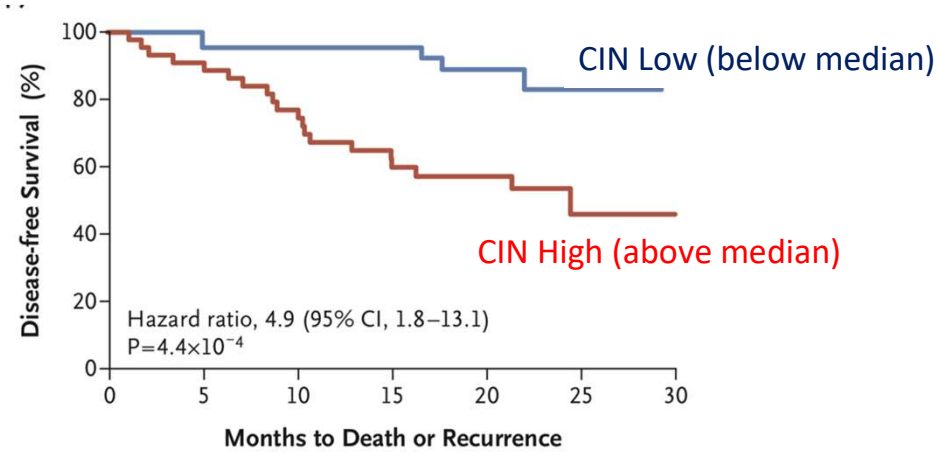


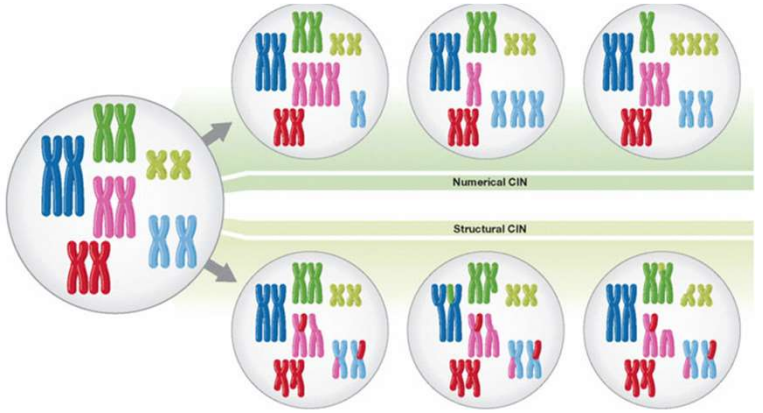
- TRACERx : 842 Lung and 350 renal cancer patients – primary surgical resection through to cure or recurrence
  - Serial blood sampling CTCs and cfDNA, metastatic biopsies, **Spatial and temporal multi-region sequencing to resolve evolution**
- TRACERx patient who develops metastatic disease may consent for PEACE
- Tumour progression, drug resistance & metastasis from diagnosis to death

Extensive tumor sampling will help distinguish metastatic competent from incompetent subclones in the same patient

Chromosomal Instability, Hopeful Monsters and Cancer Outcome

TRACERx 100 Patients: CIN and Outcome





"Hopeful monsters"

Richard Goldschmidt
Macroevolution

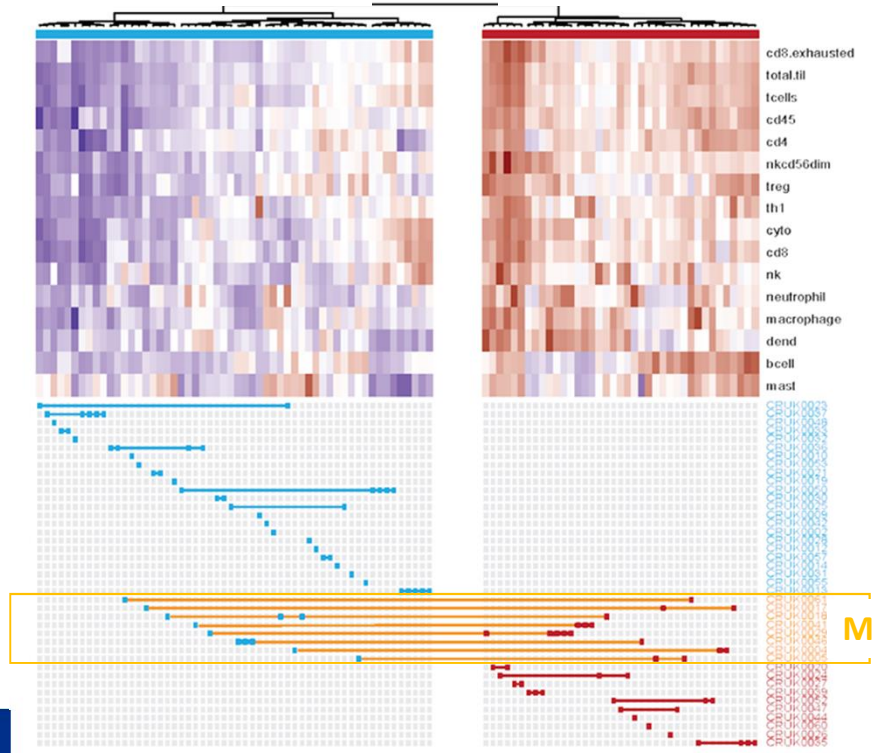
Rare karyotypic rearrangements result in profound change and phenotypic advantage:

How and Why?

TRACERx immune landscape

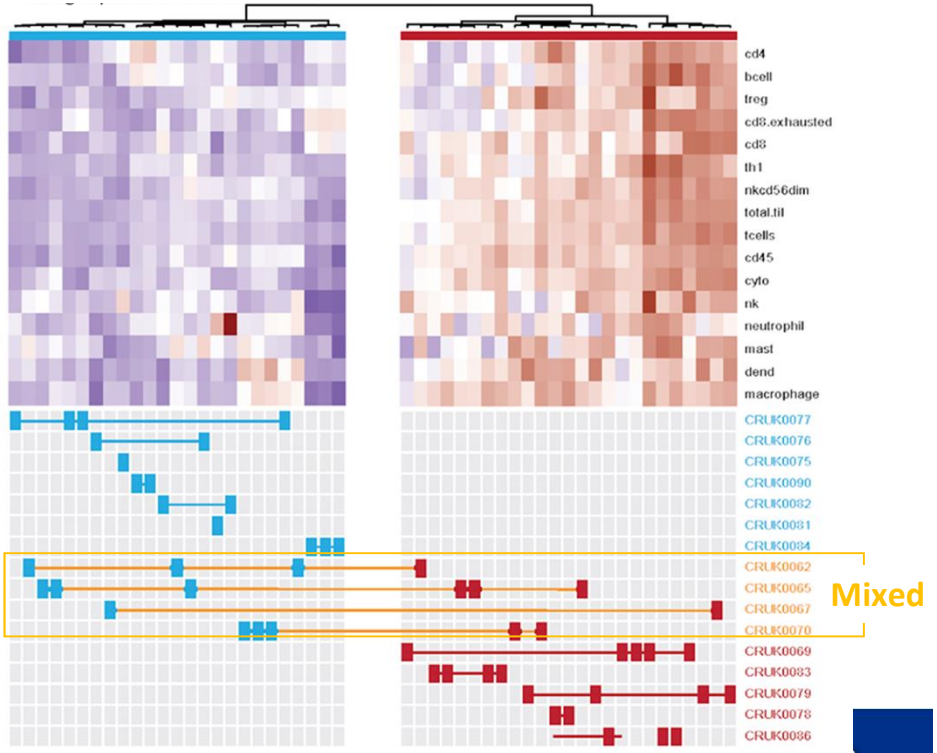
Lung Adenocarcinoma

Low Infiltrate. High Infiltrate



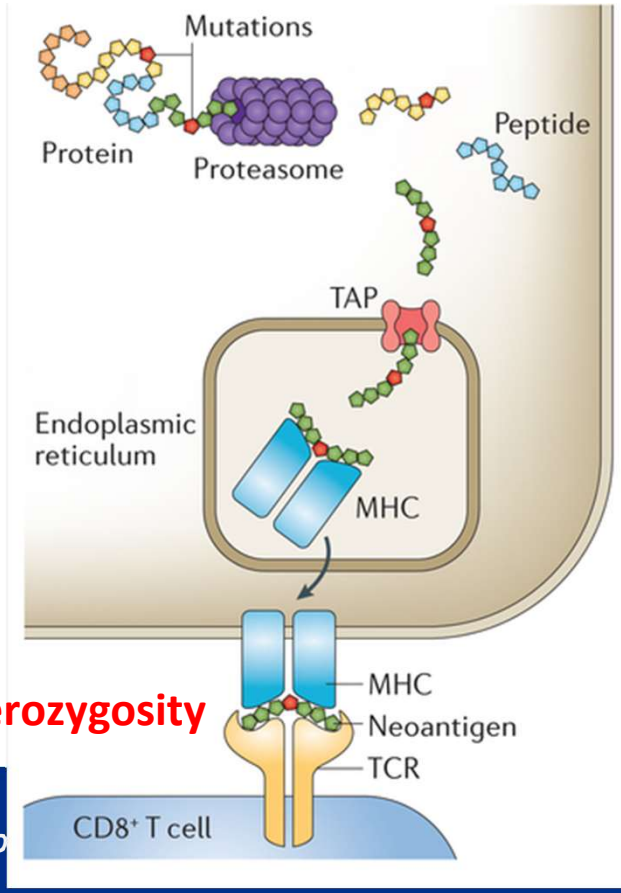
Lung Squamous Carcinoma

Low Infiltrate. High Infiltrate



Diverse Cell Intrinsic Mechanisms of Immune Evasion

56-78% of early stage NSCLC have HLA LOH or antigen presentation disruption



1. HLA Loss of Heterozygosity

2. Neoantigen evolution

Neo-antigen DNA Copy Number Loss

Neo-antigen Transcript repression

Selection against clones harbouring neoantigens

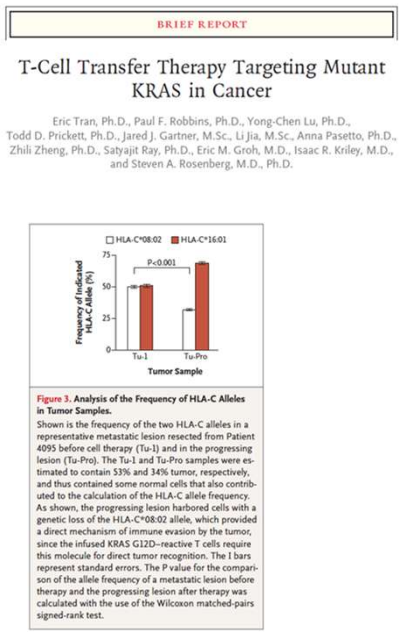
Enriched in Immune Hot Tumours
Mutually Exclusive

3. Antigen Presentation Disruption

HLA enhanceosome
Peptide generation
Chaperones
MHC complex

CIITA, IRF1, PSME1, PSME2, PSME3, ERAP1, ERAP2, HSPA, HSPC, TAP1, TAP2, TAPBP, CALR, CNX, PDIA3, B2M.

Checkpoint Inhibitor Acquired Resistance


BRIEF REPORT

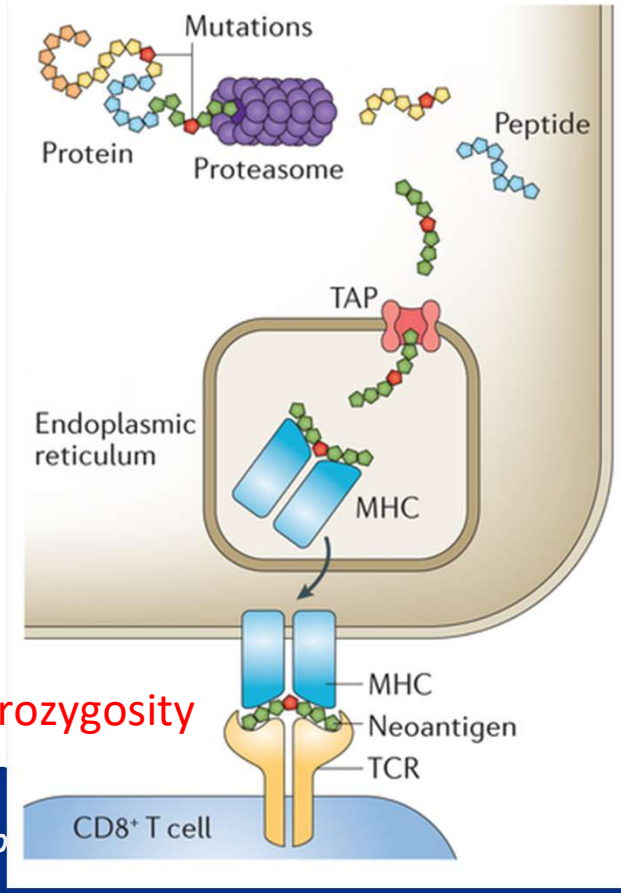
T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

Figure 3. Analysis of the Frequency of HLA-C Alleles in Tumor Samples.

Shown is the frequency of the two HLA-C alleles in a representative metastatic lesion resected from Patient 4095 before cell therapy (Tu-1) and in the progressing lesion (Tu-Pro). The Tu-1 and Tu-Pro samples were estimated to contain 53% and 34% tumor, respectively, and thus contained some normal cells that also contributed to the calculation of the HLA-C allele frequency. As shown, the progressing lesion harbored cells with a genetic loss of the HLA-C*08:02 allele, which provided a direct mechanism of immune evasion by the tumor, since the infused KRAS G12D–reactive T cells require this molecule for direct tumor recognition. The I bars represent standard errors. The P value for the comparison of the allele frequency of a metastatic lesion before therapy and the progressing lesion after therapy was calculated with the use of the Wilcoxon matched-pairs signed-rank test.

1. HLA Loss of Heterozygosity



2. Neoantigen Copy Number Loss


RESEARCH BRIEF

Evolution of Neoantigen Landscape during Immune Checkpoint Blockade in Non-Small Cell Lung Cancer

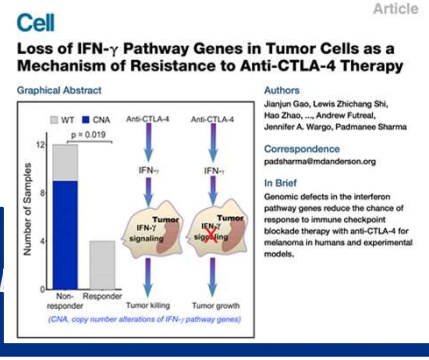

ABSTRACT

Immune checkpoint inhibitors have shown significant therapeutic responses against tumors containing increased mutation-associated neoantigen load. We have examined the evolving landscape of tumor neoantigens during the emergence of acquired resistance in patients with non-small cell lung cancer after initial response to immune checkpoint blockade with anti-PD-1 or anti-PD-1/anti-CTLA-4 antibodies. Analyses of matched pretreatment and resistant tumors identified genomic changes resulting in loss of 7 to 18 putative mutation-associated neoantigens in resistant clones. Peptides generated from the eliminated neoantigens elicited clonal T-cell expansion in autologous T-cell cultures, suggesting that they generated functional immune responses. Neoantigen loss occurred through elimination of tumor subclones or through deletion of chromosomal regions containing truncal alterations, and was associated with changes in T-cell receptor clonality. These analyses provide insight into the dynamics of mutational landscapes during immune checkpoint blockade and have implications for the development of immune therapies that target tumor neoantigens.

SIGNIFICANCE: Acquired resistance to immune checkpoint therapy is being recognized more commonly. This work demonstrates for the first time that acquired resistance to immune checkpoint blockade can arise in association with the evolving landscape of mutations, some of which encode tumor neoantigens recognizable by T cells. These observations imply that widening the breadth of neoantigen reactivity may mitigate the development of acquired resistance. *Cancer Discov; 7(3); 264–76. ©2017 AACR.*

See related commentary by Yong, p. 250.

3. Antigen Presentation Disruption


Article

Cell

Loss of IFN-γ Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy

Graphical Abstract

Authors
Jianjun Gao, Lewis Zhichang Shi, Hao Zhao, ..., Andrew Futreal, Jennifer A. Wargo, Padmanee Sharma

Correspondence
padsharma@mdanderson.org

In Brief

Genomic defects in the interferon pathway genes reduce the chance of response to immune checkpoint blockade therapy with anti-CTLA-4 for melanoma in humans and experimental models.

Managing Heterogeneity

Target multiple trunk/clonal events in every cell

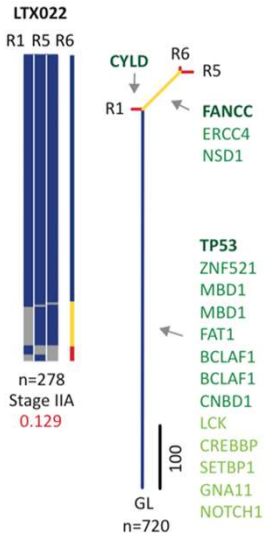
How?

Each patient needs a unique therapy

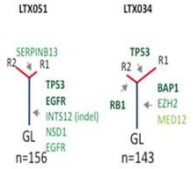
Nicky Mcgranahan, Andrew Furness, Rachel Rosenthal, Sine Hadrup, Sergio Quezada

High Burden of Trunk Mutations in Tobacco associated NSCLC

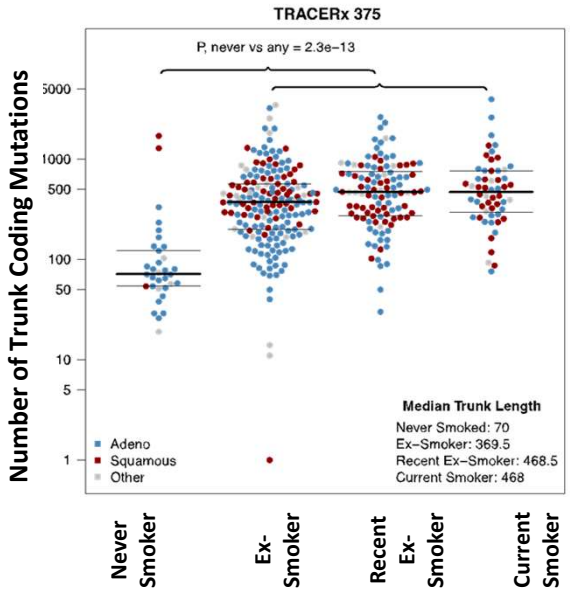
NSCLC: Smoker



NSCLC: Non-Smoker

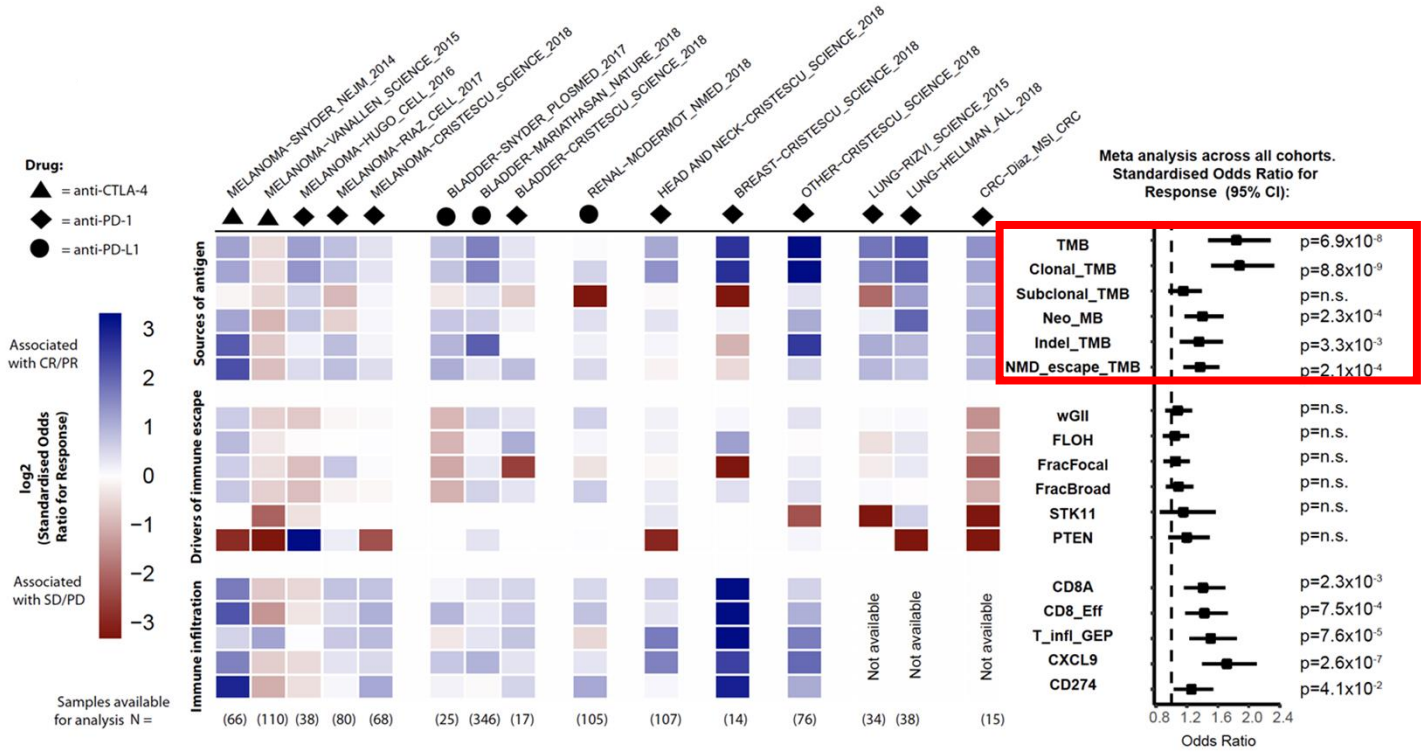


Number of Trunk Coding Mutations in TRACERx Cohort

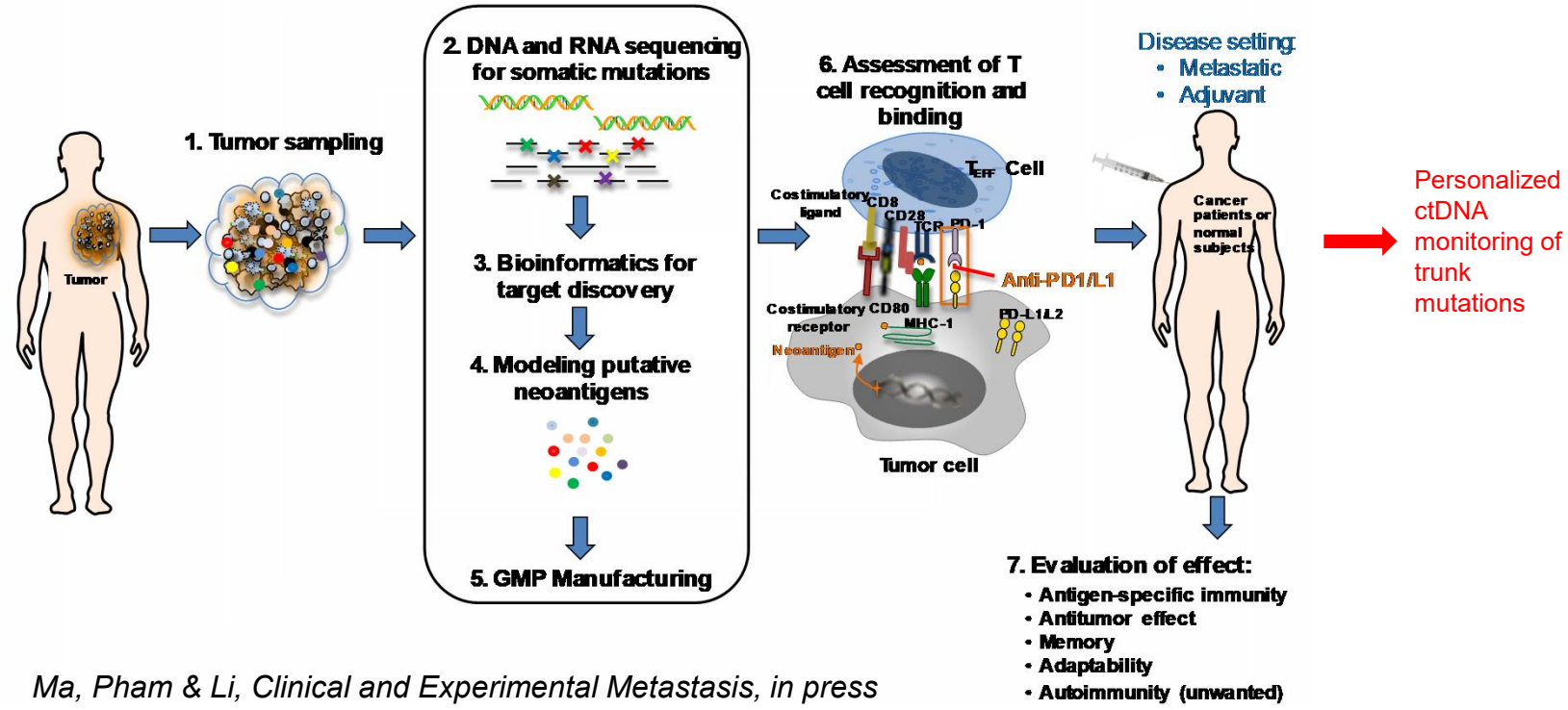


Nicky Mcgranahan, Nicolai Birkbak, Gareth Wilson, Tom Watkins, Crispin Hiley

Meta-analysis of ICI Response >1000 Patients
Clonal but not Subclonal TMB predicts ICI Response



Schema for Personalized Neoagntigen Vaccines and ctDNA Monitoring

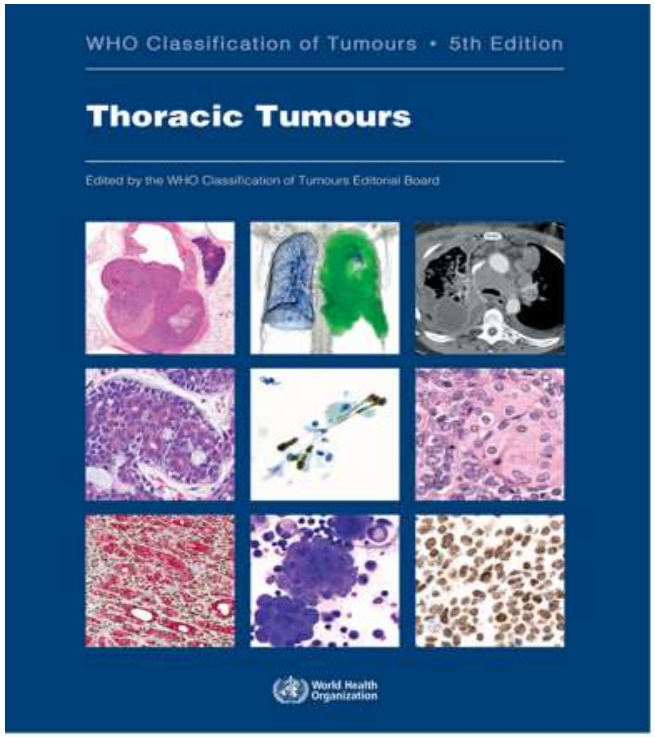


Ma, Pham & Li, Clinical and Experimental Metastasis, in press

Presented by Tianhong "Tina" Li; UCDCCC; thli@ucdavis.edu

New features in 5th Edition

- ICD-11 coding (in addition to ICD-O)
- Related terminology (replace synonym):
  - "Acceptable" or "Not recommended"
- New sections:
  - Diagnostic molecular pathology
  - Essential and desirable diagnostic criteria



- On-line subscription: includes access to scanned slide images

Summary of Key Points

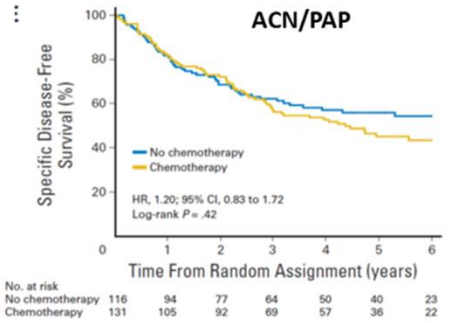
- There are few new tumour types since the 2015 Edition
- New tumour grading systems for:
  - non-mucinous lung adenocarcinoma
  - diffuse malignant mesothelioma
- Emerging data for molecular subtypes of lung neuroendocrine neoplasms
- The 5th Edition of WHO thoracic tumor classification book includes new features that harmonize and improve its use in clinical practice

Non-mucinous adenocarcinoma subtypes are prognostic

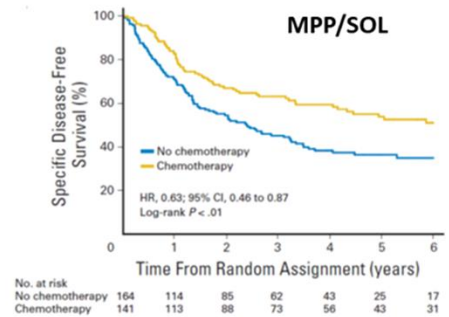
			LEP	ACN/PAP		MPP/SOL		
Study	Stage	Total number	Lepidic	Acinar	Papillary	Micro Papillary	Solid	others
Yoshizawa (2011)	I	514	5.6%	45.1%	27.8%	2.3%	13%	6.2%
Russell (2011)	I-III	210	5%	40%	12%	7%	23%	13%
Warth (2012)	I-IV	487	8.4%	42.5%	4.7%	6.8%	37.6%	0%
Woo (2012)	I	179	24.0%	33.0%	8.9%	0.6%	6.7%	26.9%
Gu (2012)	I-III	292	10.6%	38.4%	12.3%	10.3%	17.8%	10.6%
Westaway (2013)	I-III	152	9.9%	46.7%	3.9%	4.6%	30.3%	4.6%
Zhang (2013)	IA	176	8.0%	22.7%	40.9%	5.7%	6.8%	15.9%
Yanagawa (2013)	I	191	26.7%	20.9%	27.2%	0%	10.5%	14.7%
Nitadori (2013)	I	734	17.0%	42.0%	18.4%	5.9%	12.8%	4.0%
Tsuta (2013)	I-IV	904	15.1%	10.8%	37.4%	6.7%	13.7%	16.3%
Song (2013)	I	261	7.3%	29.1%	30.7%	16.1%	13.0%	3.8%
Hung (2013)	I	283	11.0%	31.1%	34.6%	15.2%	8.1%	0%
Yoshizawa (2013)	I-IIIA	440	8.1%	13.8%	40.7%	4.3%	17.7%	15.1%
Relative survival outcome:			Good	Intermediate		Poor		

Tsao MS et al. (25918286)

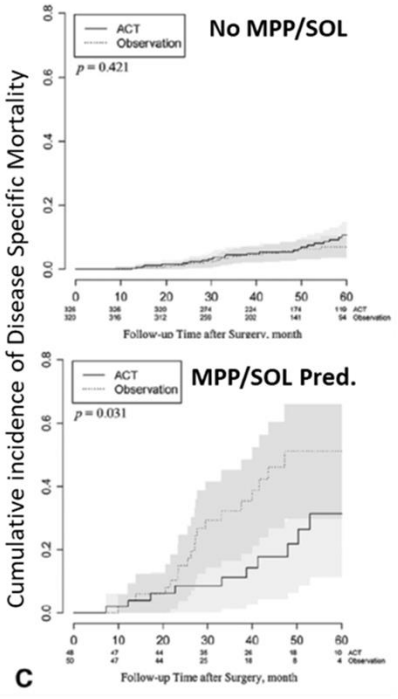
Micropapillary/Solid predominant patterns might be predictive of benefit from adjuvant chemotherapy



LACE-Bio

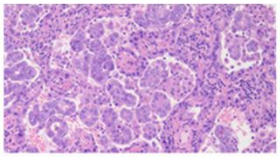


Tsao MS et al. (25918286)

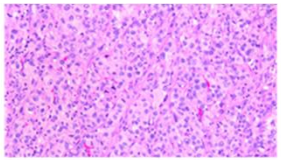


Qian F, et al. (29223834)

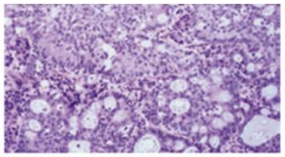
A Grading System for Invasive Pulmonary Adenocarcinoma: A Proposal From the International Association for the Study of Lung Cancer Pathology Committee



micropapillary



solid



Complex glands

	Training (n=284)	Validation (n=212)	Testing (n=300)
Stage I+II	100%	100%	87%
III	0	0	13%
Lepidic	7%	32%	10%
Acinar/Pap	64%	47%	58%
MPP/Solid/ Complex gland	28%	21%	32%

Factors included in Model construction:

- Histologic patterns
- Mitotic grade
- STAS
- Nuclear grade
- Cytologic grade
- Necrosis

Reproducibility also assessed

	Recurrence		Death	
Variables in the Model	C-Index	AUC	C-Index	AUC
Baseline + predominant + high-grade patterns (20% cutoff)	0.739	0.749	0.732	0.787
Mitotic grade + nuclear grade + cytologic grade + STAS[a]	0.741	0.746	0.775	0.761
Mitotic grade + cytologic grade + STAS[a]	0.743	0.748	0.787	0.769
Cytologic grade + STAS[a]	0.741	0.752	0.785	0.768
STAS[a]	0.740	0.752	0.785	0.765

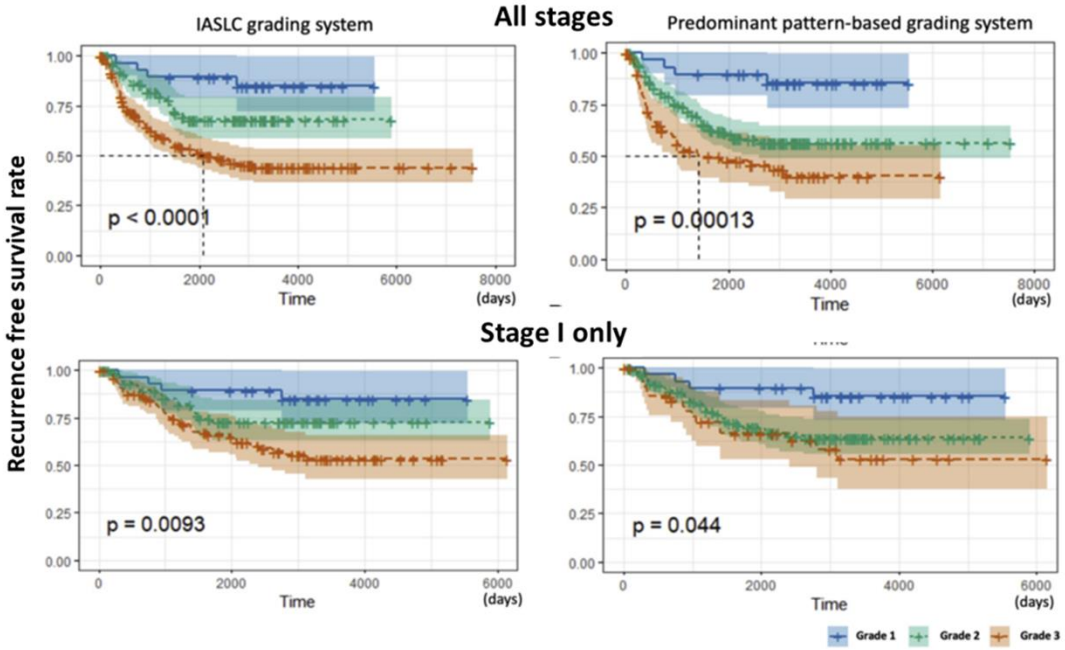
[a]Training set: adding the histologic features to baseline + predominant plus high-grade patterns (backward selection, remove the least significant variable each time). Addition of other histologic features (nuclear grade, mitotic grade, STAS, etc.) did not improve the model.
AUC, area under the ROC curve; C-index, concordance index; ROC, receiver operating characteristic; STAS, spread through airspace.

IASLC PULMONARY ADENOCARCINOMA GRADING SYSTEM

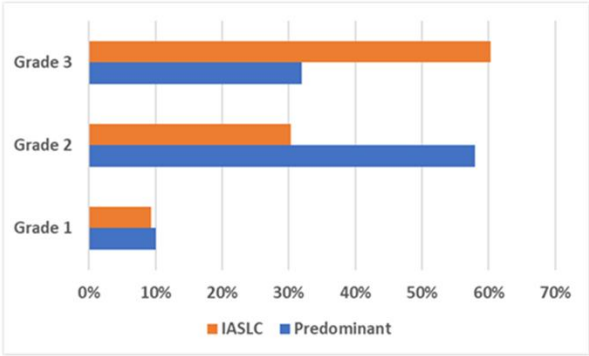
Grade	Differentiation	Pred. Pattern	High grade patterns
1	Well	Lepidic	<20%
2	Moderately	Acinar/Papillary	<20%
3	Poor	Any pattern	≥ 20%

Moreira AL, et al. J Thorac Oncol. 2020 Oct;15(10):1599-1610

New proposed IASLC grading improves RFS grouping vs. predominant pattern-based grading system (test set: n=300)



IASLC system would classify more patients in grade 3 group



Dr. Andre Moreira, personal communication

Moreira AL, et al. J Thorac Oncol. 2020 Oct;15(10):1599-1610

Thoracic SMARCA4-deficient undifferentiated tumour

SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas *Nat Gen 2015*

Francois Le Loarer[1–3], Sarah Watson[4,5], Gaelle Pierron[6], Vincent Thomas de Montpreville[7], Stelly Ballet[6],

SMARCA4-deficient Thoracic Sarcomas

Clinicopathologic Study of 30 Cases With an Emphasis on Their Nosology and Differential Diagnoses *AJSP 2019*

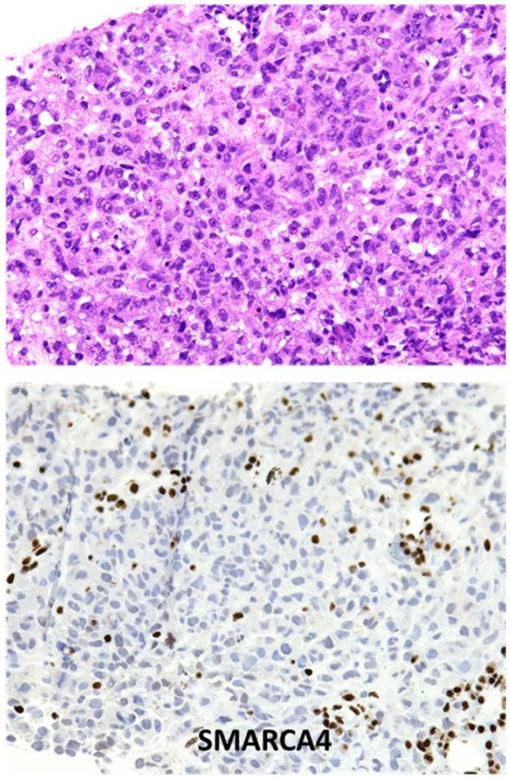
Raul Perret, MSc, MD, Lara Chalabreysse, MD,† Sarah Watson, MD, PhD,‡*

Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities *JTO 2017*

Akihiko Yoshida[1,2], Eisuke Kobayashi[2,3], Takashi Kubo[4], Makoto Kodaira[2,5,12], Toru Motoi[6], Noriko Motoi[1], Kan Yonemori[2,5], Yuichiro Ohe[7], Shun-ichi Watanabe[8], Akira Kawai[2,3], Takashi Kohno[9], Hiroshi Kishimoto[10], Hitoshi Ichikawa[4,11] and Nobuyoshi Hiraoka[1]

***SMARCA4*-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior** *JTO 2017*

Jennifer L Sauter[1,4], Rondell P Graham[1], Brandon T Larsen[2], Sarah M Jenkins[3], Anja C Roden[1] and Jennifer M Boland[1]



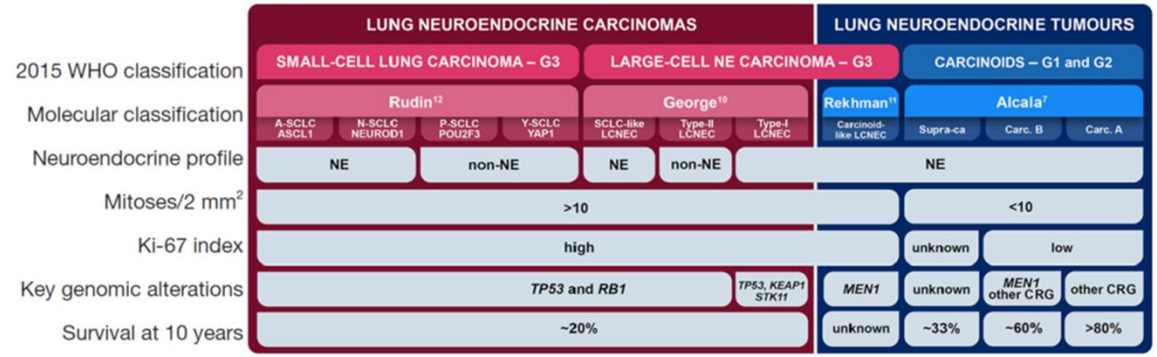
Distinct clinicopathological features

- Highly malignant undifferentiated tumour
- **Related terminology**:
  - Not recommended: SMARCA4-deficient thoracic sarcoma; SMARCA4-deficient thoracic sarcomatoid tumour
- Typically involve mediastinum, lung and hilum, ± pleura or chest wall invasion. Rare cases may seem to lack lung involvement, being overshadowed by the mediastinal lesion.
- Bulky tumour manifests the presenting symptoms, common widespread metastases
- Most patients: heavy smokers, younger age (median 48, range 27-90), M>F
- **Driver mutations**: *SMARCA4* (mostly nonsense/frameshift), *TP53,KRAS,STK11,KEAP1,NF1*
- **DDx:** Lymphoma, NUT ca, germ cell, NE ca, Large cell ca, melanoma, other sarcomas
  - To be distinguished from 5% of typical NSCLC with *SMARCA4* mutations.
- **Diagnostic criteria**:
  - Essential criteria: appropriate histopathology, SMARCA4 loss by IHC
  - Desirable criteria: SMARCA2 loss by IHC, other IHC markers: CD34, SOX2, SALL4
- **Median survival**: 4-7 months

Neuroendocrine Neoplasms

- **DIPNECH** (diffuse idiopathic pulmonary neuroendocrine cell hyperplasia)
- **Carcinoids**: typical, atypical (neuroendocrine tumors)
- **Small cell carcinoma** (small cell carcinoma, combined small cell carcinoma)
- **Large cell neuroendocrine carcinoma** (LCNEC)

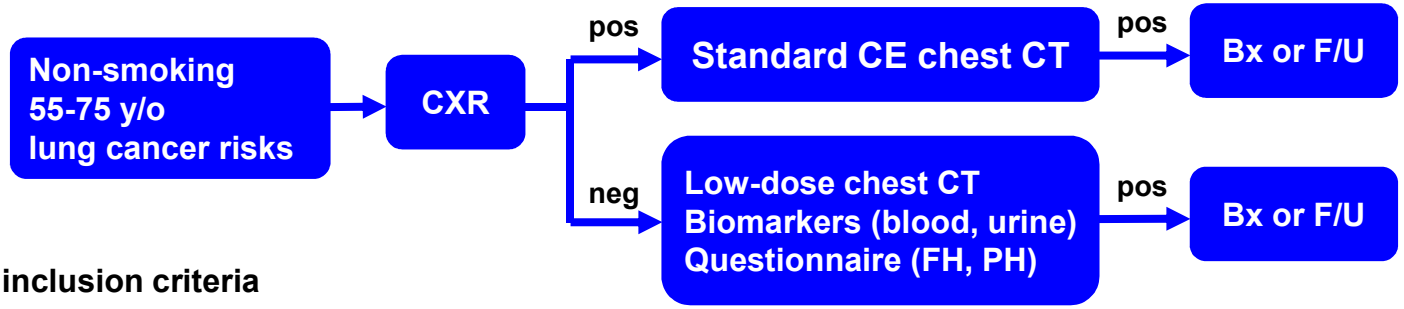
Emerging evidence for molecular subtypes in lung NENs



Fernandez-Cuesta L and Foll M. Trans Lung Cancer Res 2019;8 (Suppl 4): S430-434.
Rudin et al (30926931); Rekhtman et al (26960398, 30923345); George et al (29535388), Lantuejoul et al (33209646); Alcala (31431620)

Taiwan Lung Cancer Screening in Never Smoker Trial (TALENT)

From Feb 2015 to July 2019, 17 medical centres participated



- **Key inclusion criteria**
  - **55-75 y/o[a]**
  - **Never smoking or SI < 10 PY and had quit > 15 yrs**
  - **Having one of the following risks**
    - **family history of lung cancer (≤ 3-degree)**
    - **environmental tobacco smoking history**
    - **chronic lung disease (TB, COPD)**
    - **cooking index[b] ≥ 110**
    - **cooking without using ventilation**
  - **Negative CXR**

- **Data cutoff: September 30, 2020**
- **13,207 subjects screened, 12,011 enrolled**
- **6009 (50%) with family history**

[a] Subjects with lung cancer FH: >50 yrs or > the age at diagnosis of the youngest lung cancer case in the family
[b] 2/7 x days with cooking by pan-frying, stir-frying, or deep-frying in 1 week (maximum=21) x Yrs with cooking

TALENT vs Other LDCT Lung Cancer Screening Studies

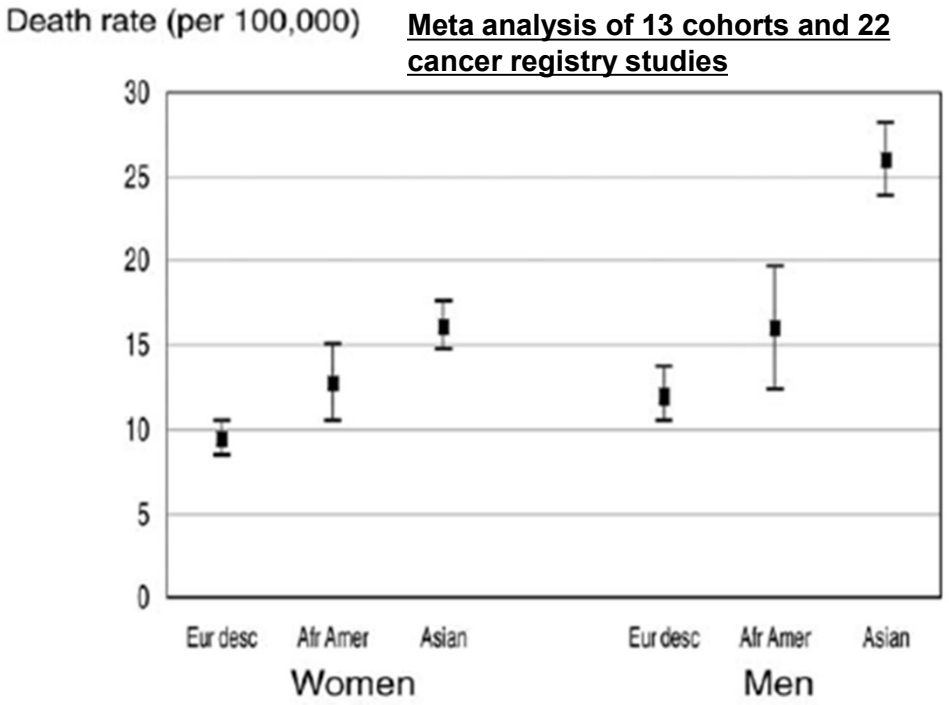
	TALENT			NLST[1]	NELSON[2]	UKLS-pilot[3]	I-ELCAP[4]
	w/ FH	w/o FH	ALL	LDCT arm	LDCT arm	LDCT arm	ALL
Population	Never or light ex- smoker[5]			Smoker	Smoker	Smoker[6]	Mixed[7]
Patient number	6009	6002	12011	26309	7557	1994	31567
LDCT positive rate	17.7%	17.1%	17.4%	27.3%	20.8%[8]	13.3%	26.9%
T0 LC detection rate	**3.2%**	**2.0%**	**2.6%**	**1.1%**	**0.9%**	**1.7%**	**1.1%**
Sensitivity	91.7%	92.5%	92.0%	93.8%	94.6%	97.6%	98.8%
Specificity	84.7%	84.4%	84.6%	73.4%	98.3%	74.6%	87.9%
PPV	**16.6%**	**10.8%**	**13.8%**	3.8%	35.7%	7.6%	9.7%
NPV	99.7%	99.8%	99.7%	99.9%	99.9%	99.9%	100.0%
Stage 0-I (%)	**96.4%**	**96.7%**	**96.5%**	**54.8%**	**63.9%**	**66.7%**	**85%[9]**

[1] NEJM 2013, [2] NEJM 2020, [3] Thorax 2016, [4] NEJM 2006,
[5] 6.7% are light ex-smokers, [6] 99.9% are smokers, [7] 82.8% are smokers,
[8] by the first scans, [9] including baseline and annual scans
Taiwan LDCT Lung Cancer TALENT Study Group, 2020

Prevalence of Lung Cancer in Different Subpopulations

	Absence		Presence		R.R. (95% CI)		p
	n	%	n	%			
Lung cancer family history	**120/6002**	**2.0**	**193/6009**	**3.2**	**1.61**	**(1.28—2.01)**	**< 0.001**
First-degree family	**127/6432**	**2.0**	**186/5579**	**3.3**	**1.69**	**(1.35—2.11)**	**< 0.001**
Father	281/10377	2.7	32/1634	2.0	0.72	(0.50—1.04)	0.077
Mother	**251/10241**	**2.5**	**62/1770**	**3.5**	**1.43**	**(1.09—1.88)**	**0.010**
Brother	**260/10901**	**2.4**	**53/1110**	**4.8**	**2.00**	**(1.50—2.67)**	**< 0.001**
Sister	**244/10367**	**2.4**	**69/1644**	**4.2**	**1.78**	**(1.37—2.32)**	**< 0.001**
Second degree family	307/11645	2.6	6/366	1.6	0.62	(0.28—1.39)	0.238
Third degree family	312/11947	2.6	1/64	1.6	0.60	(0.09—4.20)	1.000
Environmental tobacco exposure	53/1999	2.7	254/9923	2.6	0.97	(0.72—1.29)	0.813
Chronic lung disease history	284/10568	2.7	19/1142	1.7	0.62	(0.39—0.98)	0.038
Cooking index ≥110	209/7591	2.8	104/4395	2.4	0.86	(0.68—1.08)	0.201
Cooking without ventilation	306/11800	2.6	7/211	3.3	1.28	(0.61—2.67)	0.513

Lung Cancer in *Never-smoking* Asians



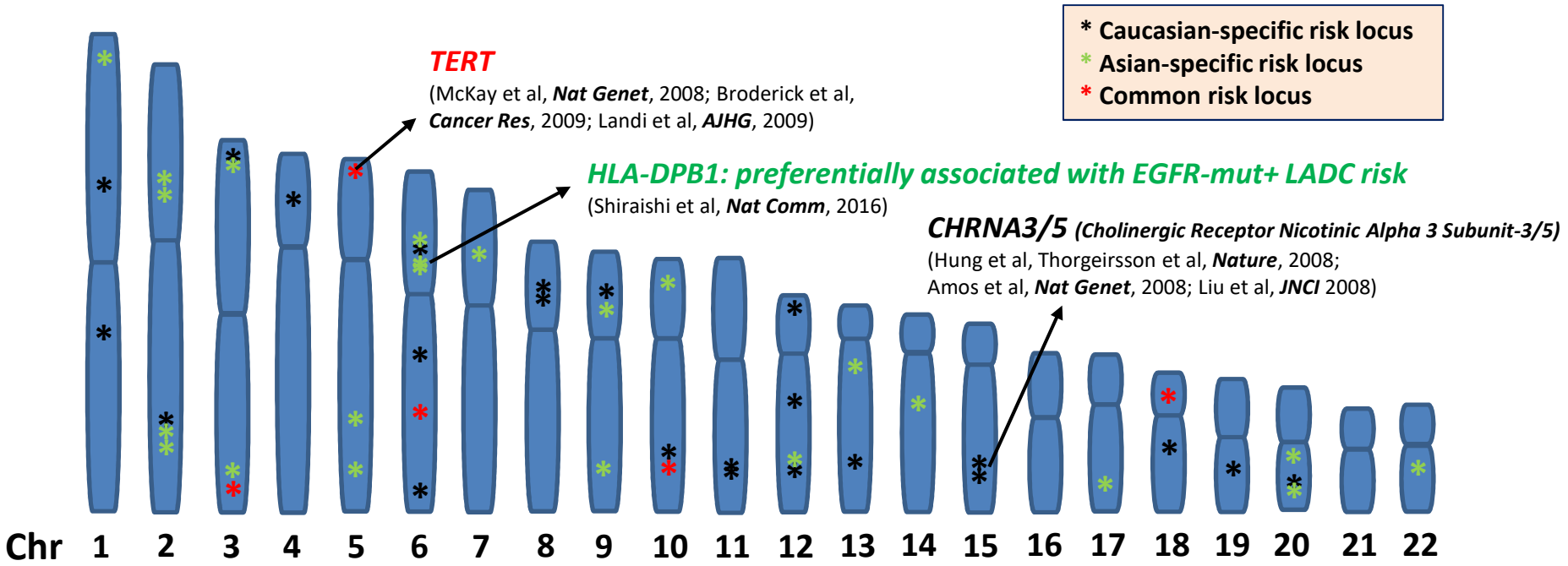
(Thun et al, ***PLoS Med***, 2008)

Environmental factors?

Passive smoking
Cooking oil vapors

Genetic factors?

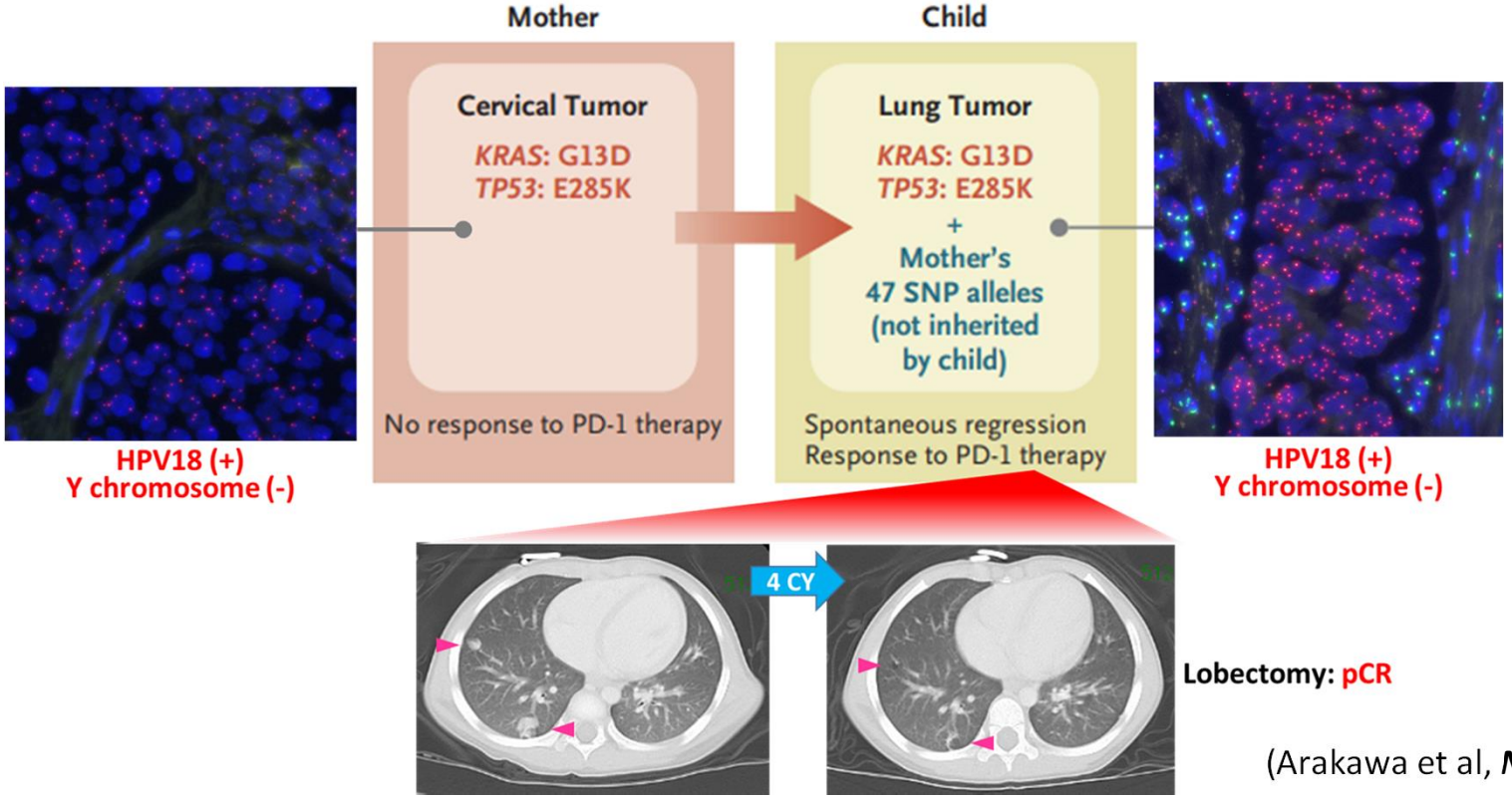
Common Variants Affect Lung Cancer Risk in an Ethnicity-dependent Manner



(Adapted from Bossé et al, *CEBP*, 2018)

Vaginal Transmission of Cancer from Mothers with Cervical Cancer to Infants: A New Cause of Lung Cancer

Aspiration of mother's cervical cancer cells in amniotic fluids into the lungs at birth



(Arakawa et al, ***NEJM***, 2021)

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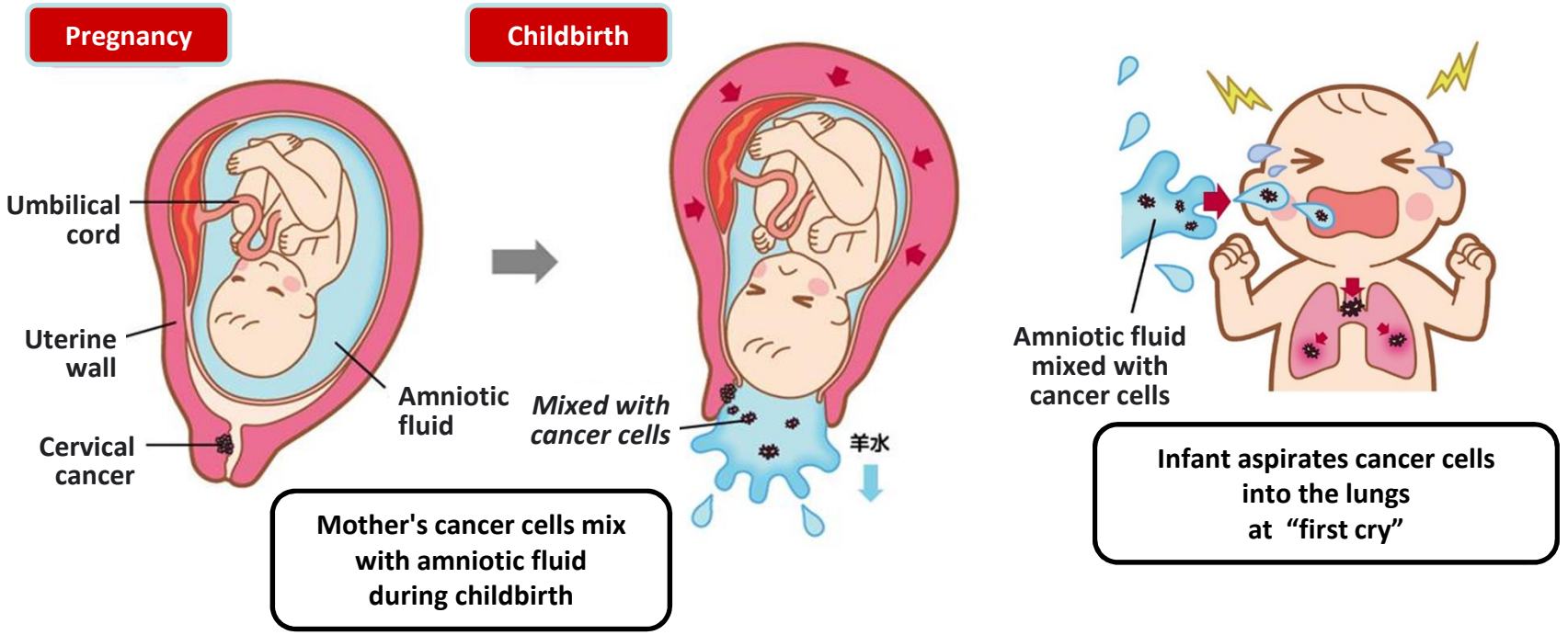

(Arakawa et al, ***NEJM***, 2021)

TAKE HOME MESSAGES

1. Advances in NGS technology and computational bioinformatics have greatly enhanced our understanding of tumor heterogeneity and progression in individual tumors.
2. Clinical use of these tools will continue to transform the diagnosis and treatment of lung cancer towards the goal of precision oncology.
3. There are a growing number to new molecular subtypes of lung cancer.
4. Unmet needs to understand the impact of familiar lung cancer risk and to develop the strategy for lung caner screening in never smokers.
5. New route of lung cancer transmission through body fluid?