Tumours with Squamous Differentiation: What are the Issues?

Ming S. Tsao, MD, FRCPC

M. Qasim Choksi Chair in Lung Cancer Translational Research

Princess Margaret Cancer Centre

University of Toronto

elcc

15-18 April 2015, Geneva, Switzerland

Organisers IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop Information | Research

Disclosure

- No conflict related to subject under discussion

Issues for Discussions

1. Major changes in 2015 classification
2. Definition and diagnostic markers
3. Basaloid carcinoma
4. Primary vs. metastasis
5. Molecular classification and insights

2004 (3rd Edition) of WHO Classification

Squamous cell carcinoma

- Papillary carcinoma
- Clear cell carcinoma
- Small cell carcinoma
- Basaloid carcinoma

Preinvasive lesions

- Squamous carcinoma in situ
- Atypical adenomatous hyperplasia
- DIPNECH

Large cell carcinoma

- Large cell neuroendocrine carcinoma
- Basaloid carcinoma
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- Large cell carcinoma with rhabdoid phenotype

2004 (3rd Edition) of WHO Classification

Squamous cell carcinoma

- Papillary carcinoma
- Clear cell carcinoma
- Small cell carcinoma
- **Basaloid carcinoma**

Preinvasive lesions

- Squamous carcinoma in situ
- Atypical adenomatous hyperplasia
- DIPNECH

Large cell carcinoma

- Large cell neuroendocrine carcinoma
- **Basaloid carcinoma**
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- Large cell carcinoma with rhabdoid phenotype

2004 (3rd Edition) of WHO Classification

Squamous cell carcinoma

- Papillary carcinoma
- Clear cell carcinoma
- Small cell carcinoma
- Basaloid carcinoma

Preinvasive lesions

- **Squamous carcinoma in situ**
- Atypical adenomatous hyperplasia
- DIPNECH

Large cell carcinoma

- Large cell neuroendocrine carcinoma
- Basaloid carcinoma
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- Large cell carcinoma with rhabdoid phenotype

2015 (4th Edition) of WHO Classification

- **Squamous cell carcinoma**
  - Keratinizing squamous cell carcinoma
  - Non-keratinizing squamous cell carcinoma
  - Basaloid squamous cell carcinoma
  - Preinvasive lesion:
    - Squamous cell carcinoma in situ

Definition of Squamous Cell Carcinoma

2004 (3rd Edition)

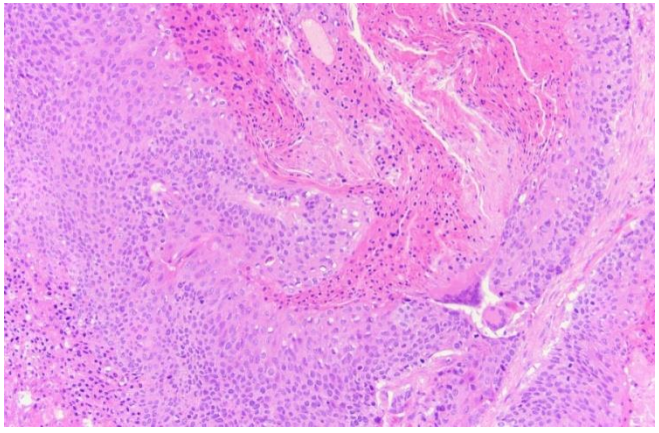
A malignant epithelial tumour showing keratinization and/or intercellular bridges that arises from bronchial epithelium

2015 (4th Edition)

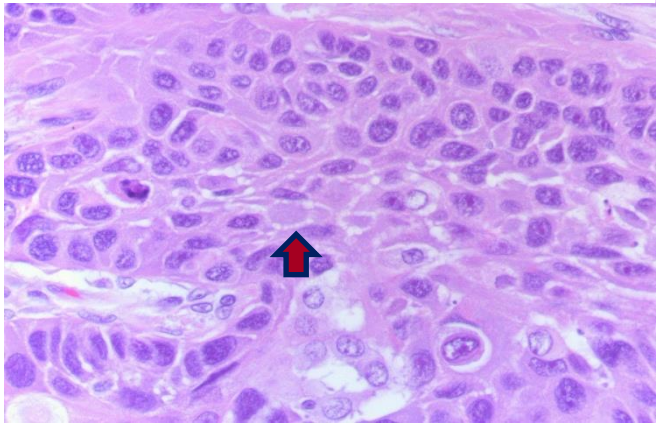
Malignant epithelial tumour that either shows keratinization and/or intercellular bridges, or is a morphologically undifferentiated non-smal l carcinoma that expresses immunohistochemical markers of squamous cell differentiation

Cytological and Morphological Features of Differentiated Squamous Cells

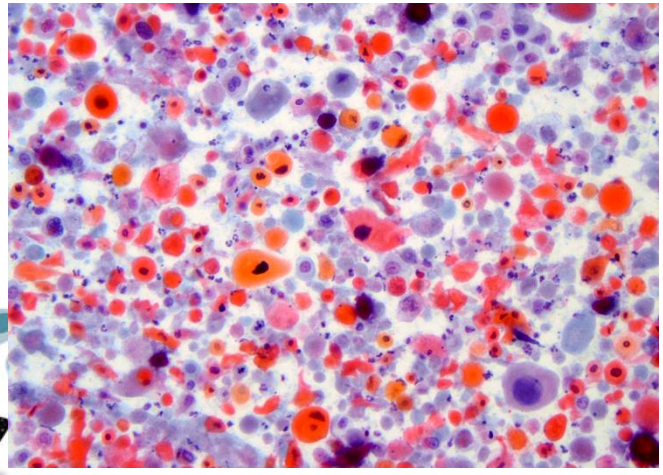
KERATIN



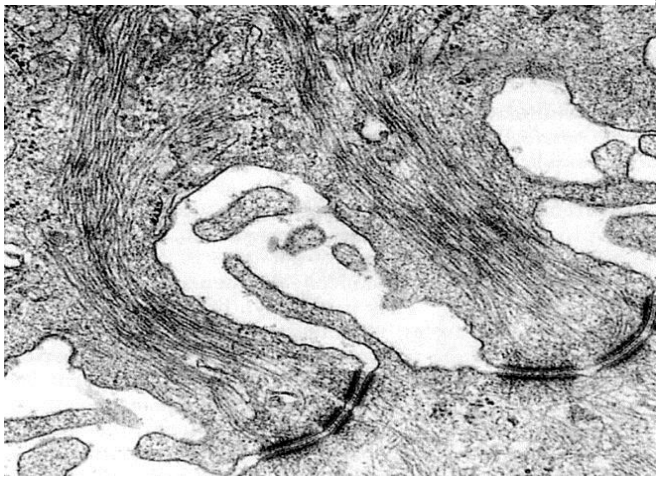
INTERCELLULAR BRIDGES



KERATINIZED CELLS

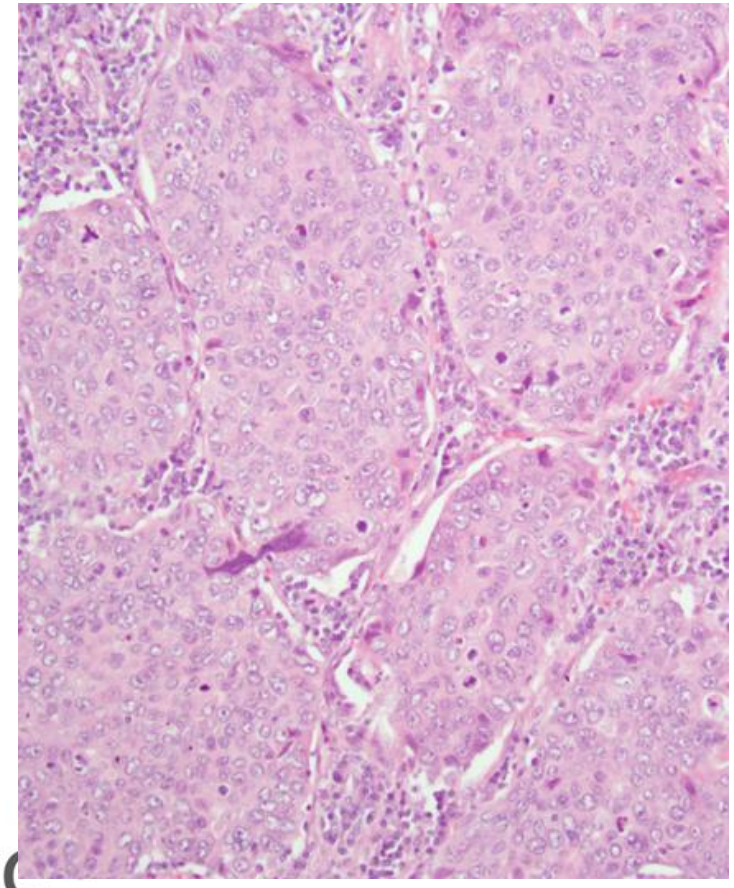


DESMOSOMES AND TONOFILAMENTS

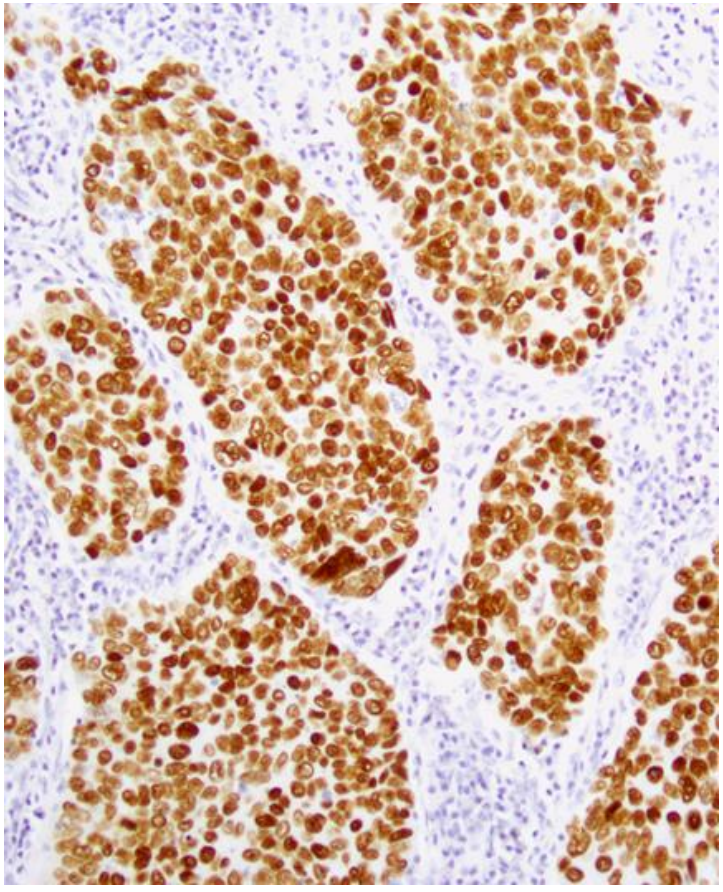


Non-Keratinizing Squamous Cells

LACK KERATINIZATION



IHC P40/P63 +



Sensitivity and Specificity of P63 and CK5/6 for Squamous Cell Carcinoma

Source	Marker (staining)	Sensitivity	Specificity	PPV	NPV	AUC
Loo	P63 (2+/>10%)	92%	74%	82%	88%	-
Terry	P63 (any)	84%	85%	86%	82%	0.84
Rekhtman	P63 (diffuse)	99%	96%	-	-	0.99
Pelosi	P63 (≥25%)	-	-	-	-	1.00
Bishop	P40 (≥ 5%)	100%	100%	100%	100%	-
Loo	CK5/6 (2+/>10%)	84%	79%	84%	79%	-
Terry	CK5/6 (any)	66%	95%	94%	72%	-
Rekhtman	CK5/6 (diffuse)	90%	97%	-	-	0.97
Pelosi	CK5/6 (≥25%)	-	-	-	-	1.00

Loo et al, JTO 2010; Terry et al, AJSP 2010; Rekhtman et al, JTO 2011; Pelosi et al, JTO 2011; Bishop JT et al, Mod Pathol 2012.

Table 1.20 Immunohistochemical typing of cytokeratin-positive, morphologically undifferentiated non-small cell lung carcinoma (NSCLC), with mucin stains already undertaken to exclude solid pattern adenocarcinoma[a]. Focal: 0–10% of cells positive; diffuse: > 10% of cells positive.

TTF1[b]	p63	p40	CK5/6	Diagnosis (resection)	Diagnosis (biopsy / cytology)
Positive (focal or diffuse)	Negative	Negative	Negative	Adenocarcinoma	NSCLC, favour adenocarcinoma
Positive (focal or diffuse)	Positive (focal or diffuse)	Negative	Negative	Adenocarcinoma	NSCLC, favour adenocarcinoma
Positive (focal or diffuse)	Positive (focal or diffuse)	Positive (focal)	Negative	Adenocarcinoma	NSCLC, favour adenocarcinoma
Positive (focal or diffuse)	Negative	Negative	Positive (focal)	Adenocarcinoma	NSCLC, favour adenocarcinoma
Negative	Any one of the above diffusely positive			Squamous cell carcinoma	NSCLC, favour squamous cell carcinoma
Negative	Any one of the above focally positive			Large cell carcinoma, unclear[c]	NSCLC, not otherwise specified
Negative	Negative	Negative	Negative	Large cell carcinoma-null[d]	NSCLC, not otherwise specified
No stains available	No stains available	No stains available	No stains available	Large cell carcinoma with no additional stains	NSCLC, not otherwise specified (no stains available)

2015 WHO Classification Book, Page 83

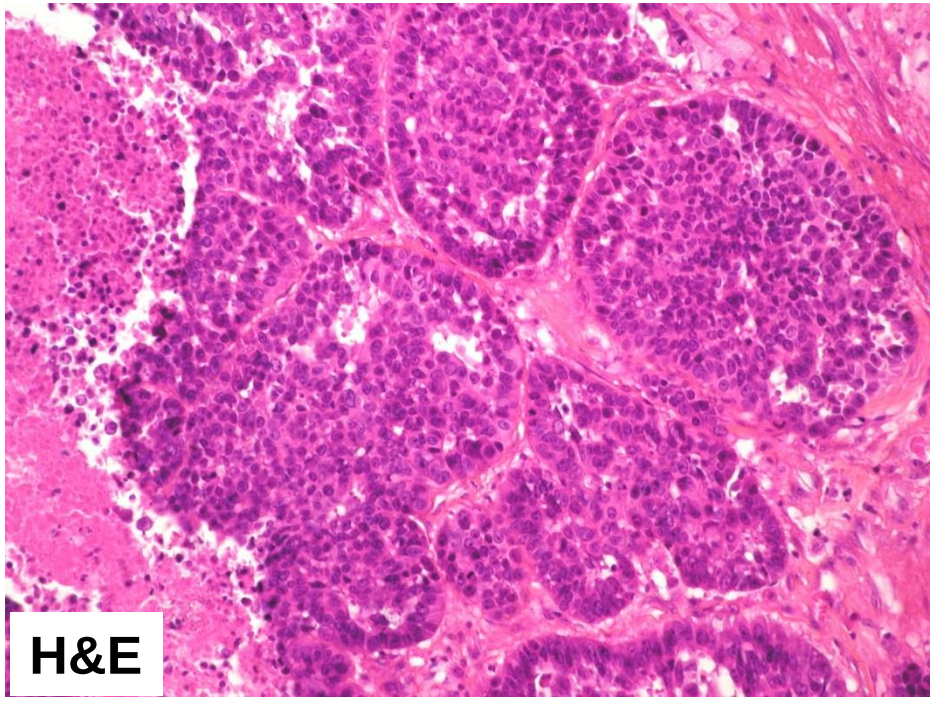
Basaloid Squamous Cell Carcinoma

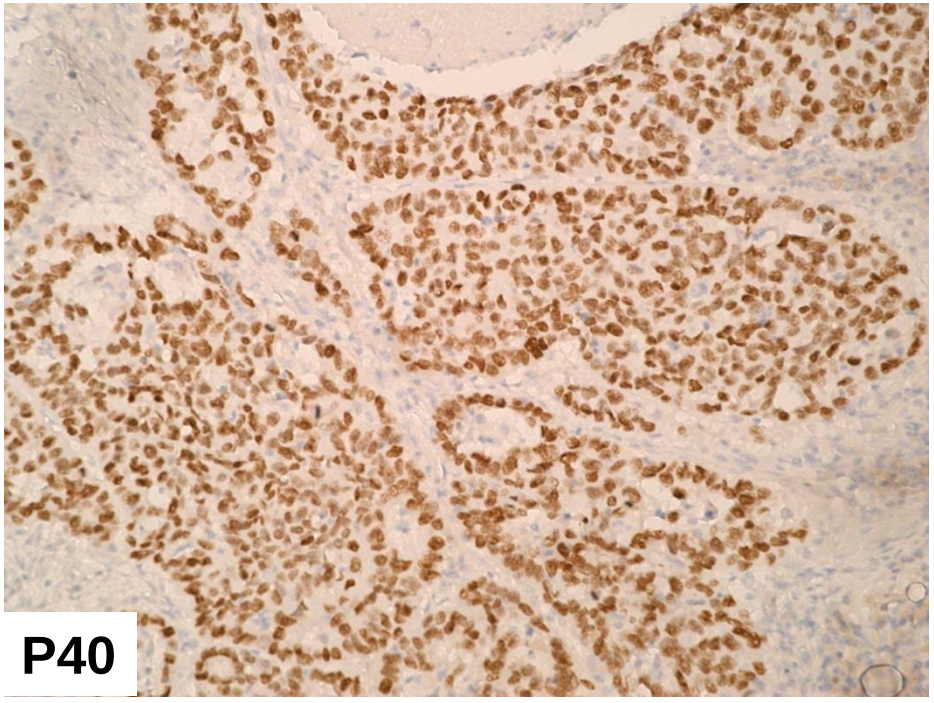
DEFINITION: A poorly differentiated malignant epithelial tumour that presents in its pure form as a *proliferation of small cells with lobular architecture and peripheral palisading*. These cells lack squamous morphology, but *show immunohistochemical expression of squamous markers*. Tumours with a keratinizing or non-keratinizing squamous cell component, but a basaloid component of >50%, are also classified as basaloid carcinoma. This tumour was previously considered a variant of large cell carcinoma, but was recognized as a distinct entity in the 1999 and 2004 WHO classifications.

- High mitotic rate (Ki-67 50-80%)
- Positive for p40/p63, CK5/10/14
- Negative for TTF1, CD56, chromogranin, synaptophysin

Brambilla E *et al*, *Hum Pathol. 1992;23:993-1003;*
Marci V *et al*, *Virchows Arch. 2007;451:729-36;*
Moro-Sibilot D *et al*. *Eur Respir J. 2008;31:854-9.*

Morphological Features of Basaloid Squamous Cell Carcinoma





elcc

15-18 April 2015, Geneva, Switzerland

Organisers IASLC International Association for the Study of Lung Cancer ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Eur Respir J 2008;31:854-59

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY · European Society of Thoracic Surgeons · 1993 · etop Information | Research

Lung carcinomas with a basaloid pattern: a study of 90 cases focusing on their poor prognosis

D. Moro-Sibilot*,#, S. Lantuejoul*,¶, S. Diab#, N. Moulai¶, A. Aubert*,+, J.F. Timsit*,#, C. Brambilla*,#, P.Y. Brichon*,+ and E. Brambilla*,¶

- **In third edition (2004) WHO Classification**
  - ***LCC variant:*** pure basaloid classified under large cell carcinoma
  - ***SCC variant:*** Presence of squamous differentiation in <50%

- **1979-2003: 90 of 1418 NSCLCs were classified as:**
  - Basaloid carcinoma (n=46)
  - Basaloid variant of squamous cell carcinoma (n=44)

Eur Respir J 2008;31:854-59

Basaloid Carcinoma: A distinct entity

	Stages	Survival	5-yr survival	P-value
Basaloid CA *vs* Non-basaloid (SCC/ADC/LC)	All	OS	26 vs. 38	0.05
	All	DFS	41 vs. 59	0.014
	I-II	OS	27 vs. 44	0.01
	I-II	DFS	45 vs. 65	0.008
	I	OS	33 vs. 51	0.01
Basaloid CA *vs* Squamous CA	All	OS	26 vs. 37	0.15
	All	DFS	41 vs. 61	0.005
	I	OS	33 vs. 51	0.02

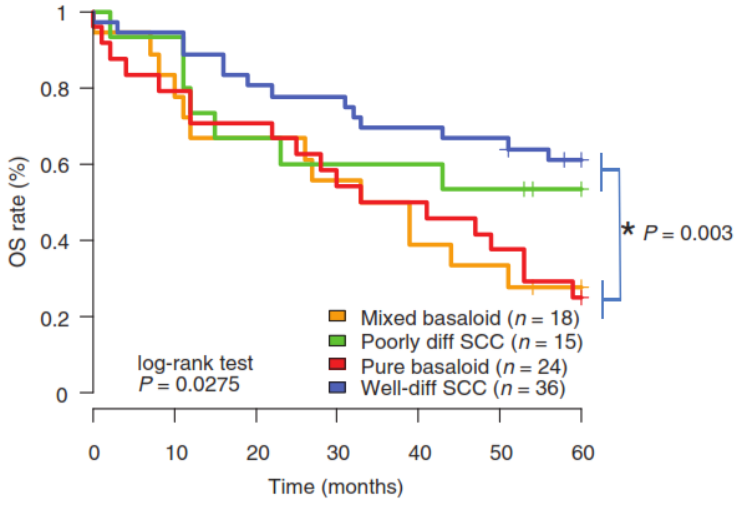
Moro-Sibilot D *et al*. *Eur Respir J. 2008;31:854-9.*

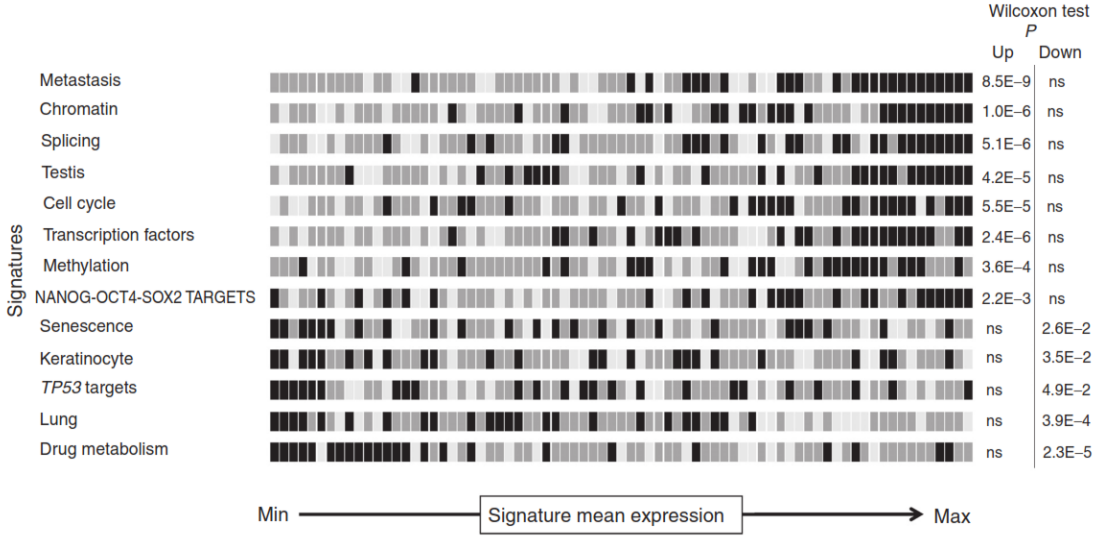
Clinical Cancer Research

Lung Squamous Cell Carcinomas with Basaloid Histology Represent a Specific Molecular Entity

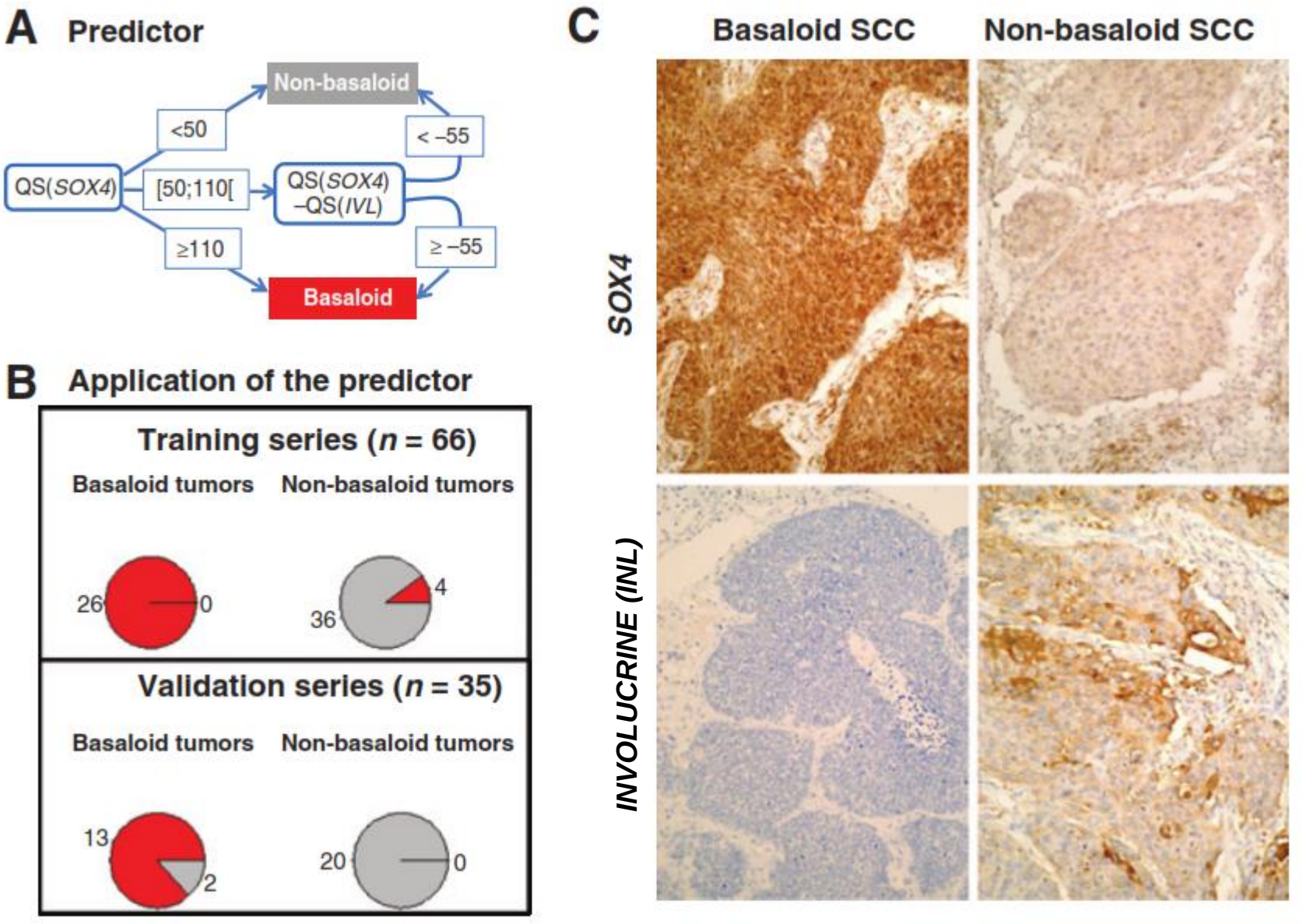
Christian Brambilla[1], Julien Laffaire[2], Sylvie Lantuejoul[3], Denis Moro-Sibilot[1], Hélène Mignotte[1], François Arbib[1], Anne-Claire Toffart[1], Fabien Petel[2], Pierre Hainaut[4], Sophie Rousseaux[5], Saadi Khochbin[5], Aurélien de Reyniès[2], and Elisabeth Brambilla[3]

93 SCC: 24 pure basaloid, 18 basaloid/SCC, 36 WD SCC, 15 PD SCC





Clin Cancer Res 2014;20:5777-86



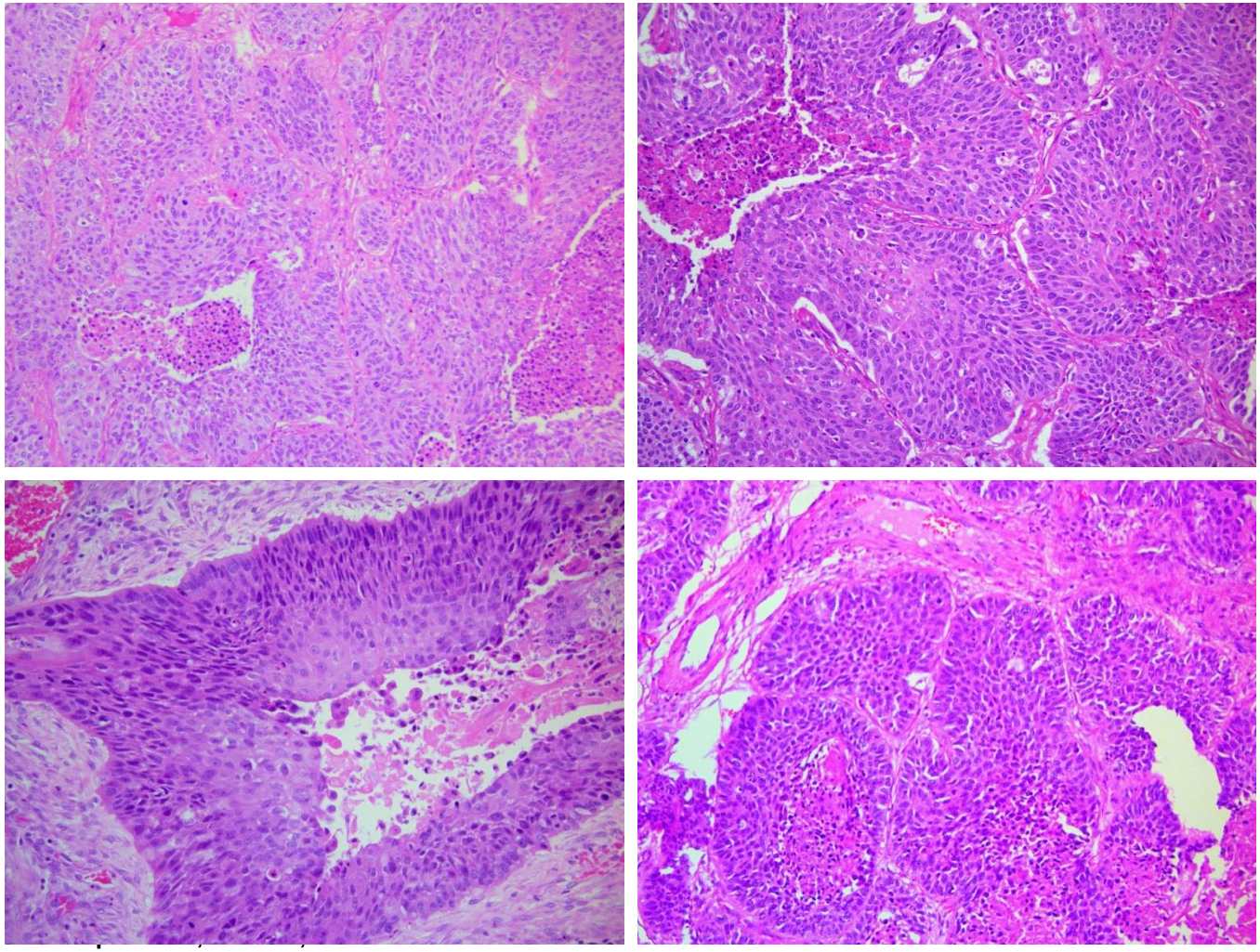
Brambilla C, et al. *Clin Cancer Res 2014;20:5777-86*

Primary vs. Metastasis

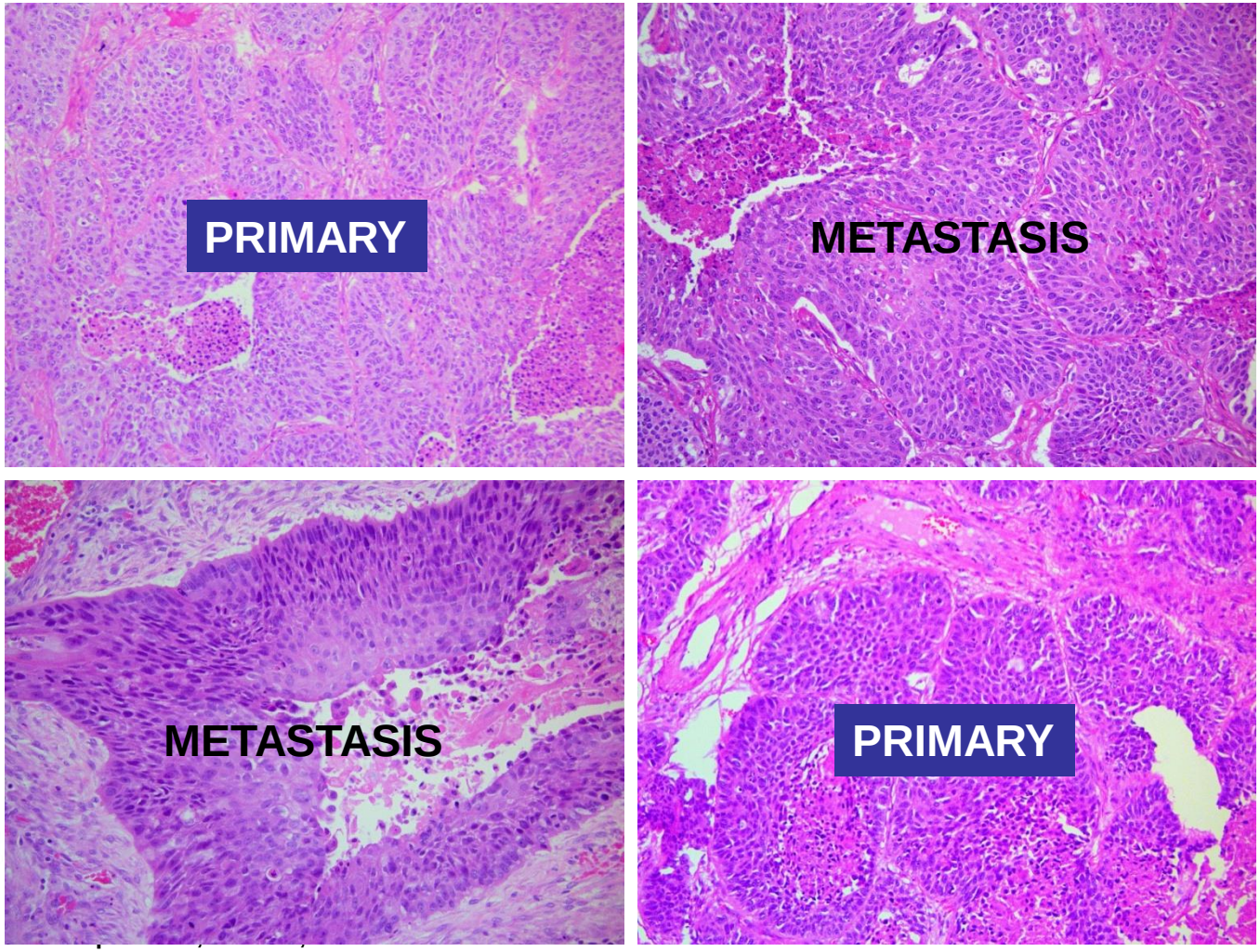
Potential primary origins of metastasis:

- Recurrence from previous lung SCC
- Metastases from other disease site:
  - Head & Neck
  - Esophagus
  - Cervix
  - Bladder (urothelial)

Primary *vs* Metastatic SCC on H&E Sections



Primary *vs* Metastatic SCC on H&E Sections



Selective Immunohistochemical Markers to Distinguish Between Metastatic High-Grade Urothelial Carcinoma and Primary Poorly Differentiated Invasive Squamous Cell Carcinoma of the Lung

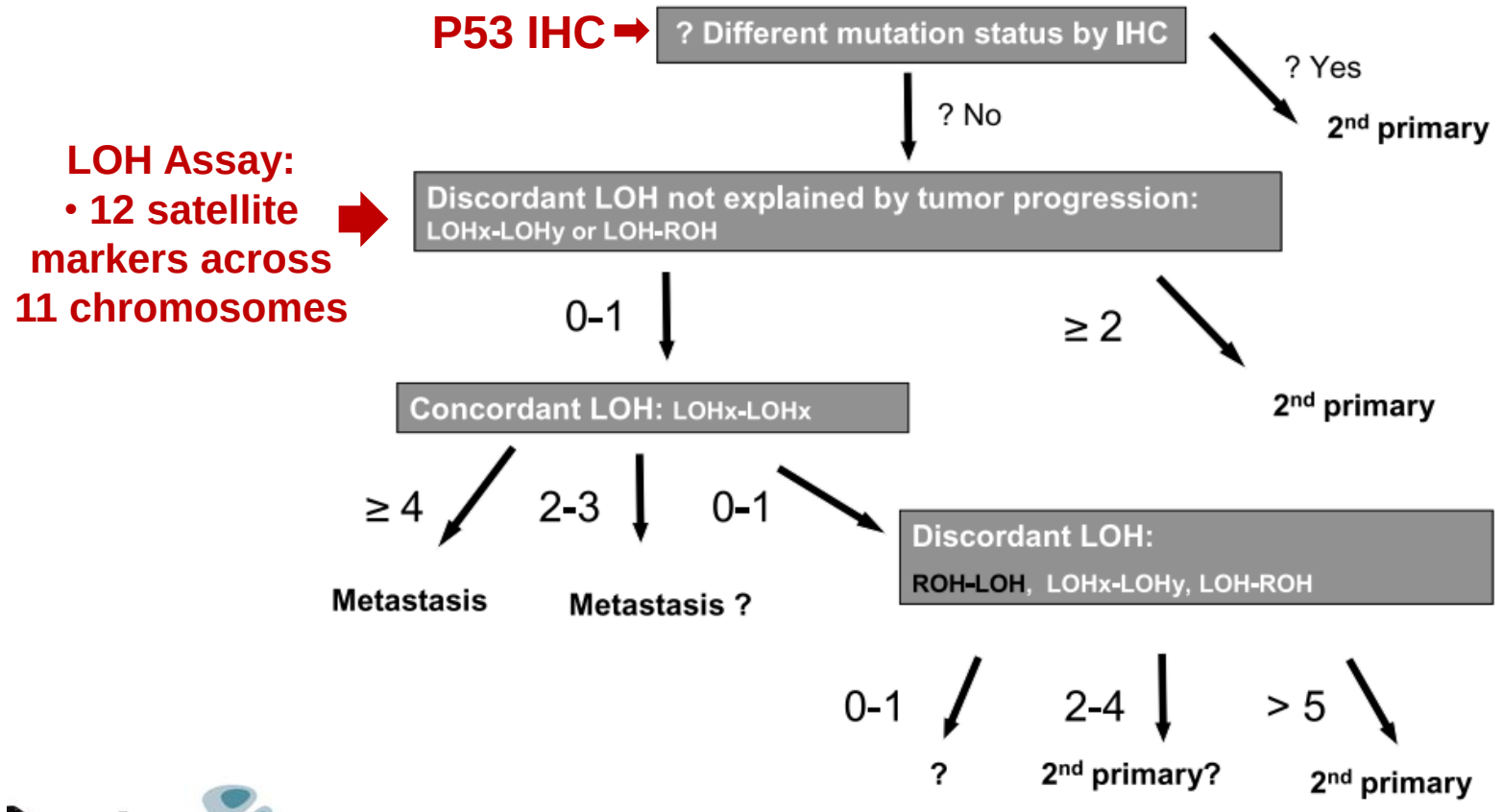
Aaron M. Gruver, MD, PhD; Mahul B. Amin, MD; Daniel J. Luthringer, MD; Danielle Westfall, MD; Komal Arora, MD; Carol F. Farver, MD; Adeboye O. Osunkoya, MD; Jesse K. McKenney, MD; Donna E. Hansel, MD, PhD

Immunostain	Primary Invasive Bladder UCa, % (n = 37)[a]	Primary Pulmonary SCC, % (n = 30)
CK7	100	33
CK20	54	7
HMCK	92	100
GATA-3	78	23
Napsin A	8	3
p63	78	93
S100A1	0	20
S100P	76	53
Surfactant protein A	0	0
Thrombomodulin	81	97
TTF-1	0	3
Uroplakin III	14	0
CK14	32	77
Desmoglein-3	11	87

Arch Pathol Lab Med 2012;136:1339-46

Differential Diagnosis of Pulmonary Carcinoma Following Head and Neck Cancer by Genetic Analysis

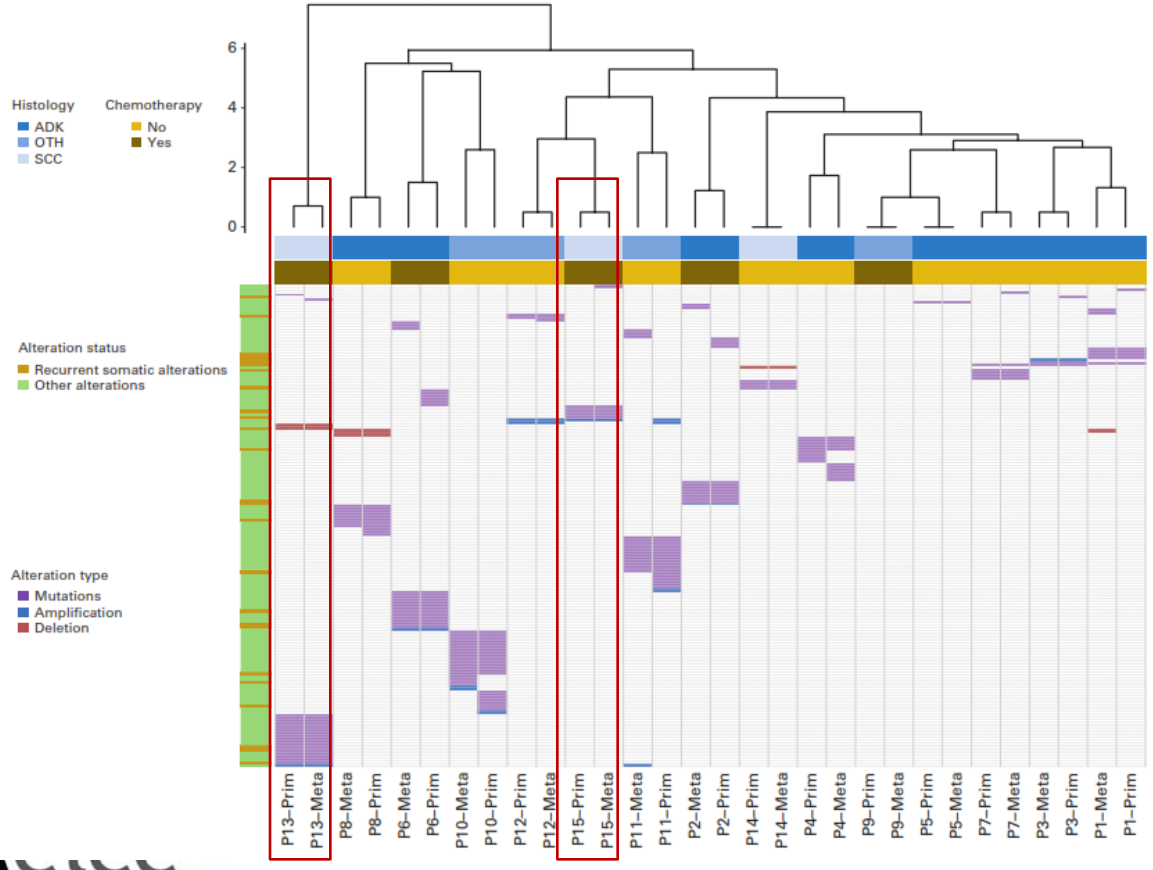
T.W. Geurts,[5] M.L.F van Velthuysen,[4] F. Broekman,[6] T. Hooft van Huysduynen,[6] M.W.M. van den Brekel,[1,5] N. van Zandwijk,[2] H. van Tinteren,[3] P. Nederlof,[4] A.J.M. Balm,[1,5] and R.H. Brakenhoff[6]



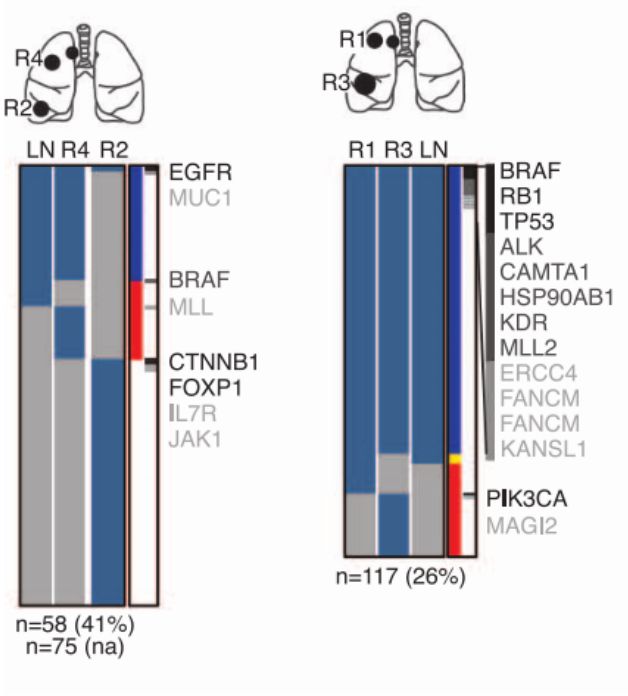
Clin Cancer Res 2005:6608-14
Clin Cancer Res 2009;15:980-85

Next-Generation Sequencing Reveals High Concordance of Recurrent Somatic Alterations Between Primary Tumor and Metastases From Patients With Non–Small-Cell Lung Cancer

Stéphane Vignot, Garrett M. Frampton, Jean-Charles Soria, Roman Yelensky, Frédéric Commo, Christian Brambilla, Gary Palmer, Denis Moro-Sibilot, Jeffrey S. Ross, Maureen T. Cronin, Fabrice André, Philip J. Stephens, Vladimir Lazar, Vincent A. Miller, and Elisabeth Brambilla



J Clin Oncol 31:2167-2172.



De Bruin EC, et al. *Science 2014:346:251-9*

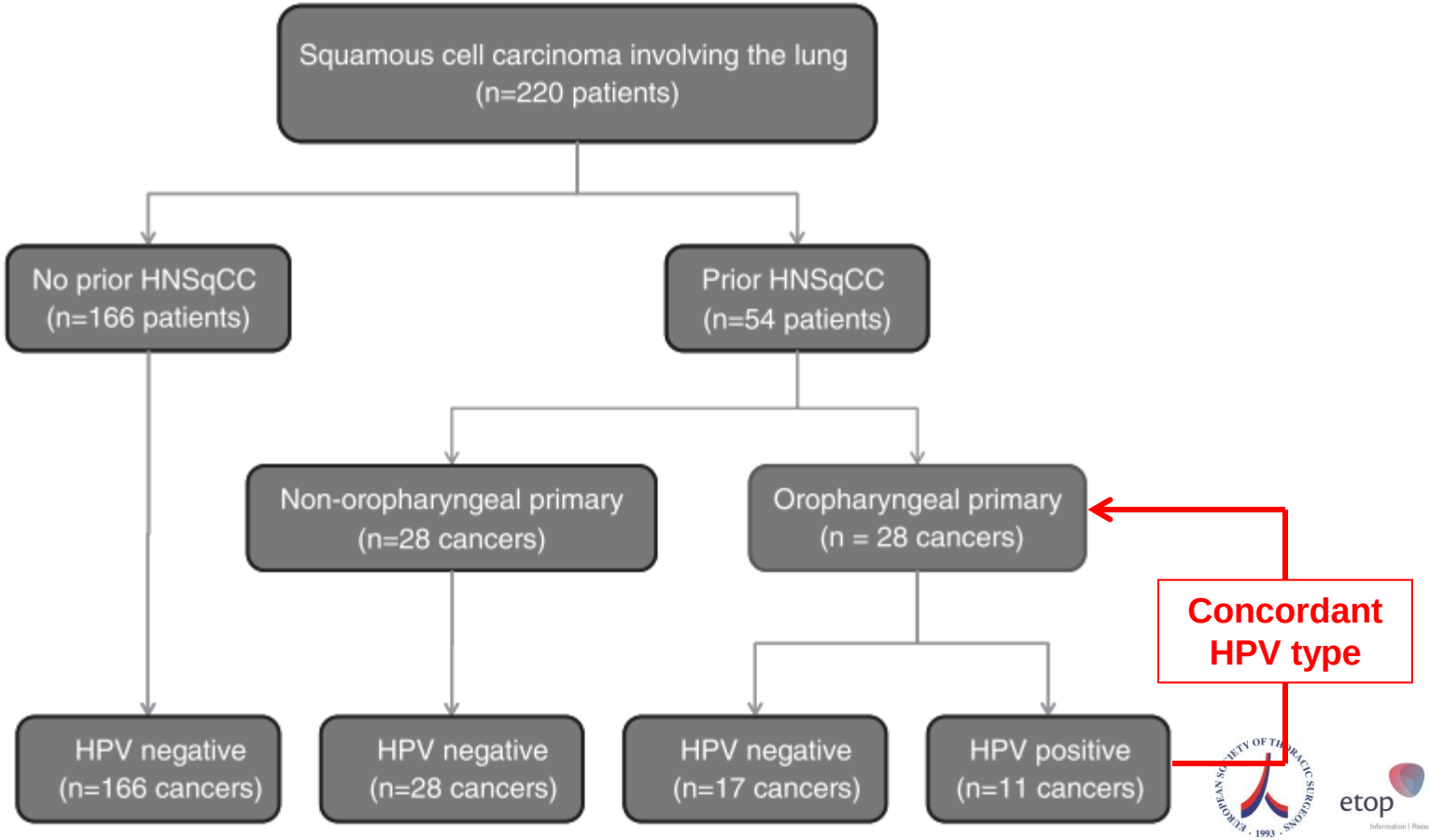
Organisers IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop Information | Research

HPV Analysis in Distinguishing Second Primary Tumors From Lung Metastases in Patients With Head and Neck Squamous Cell Carcinoma

Justin A. Bishop, MD, Takenori Ogawa, MD, PhD,† Xiaofei Chang, MD, PhD,† Peter B. Illei, MD,* Edward Gabrielson, MD,*‡ Sara I. Pai, MD, PhD,†‡ and William H. Westra, MD*†‡*

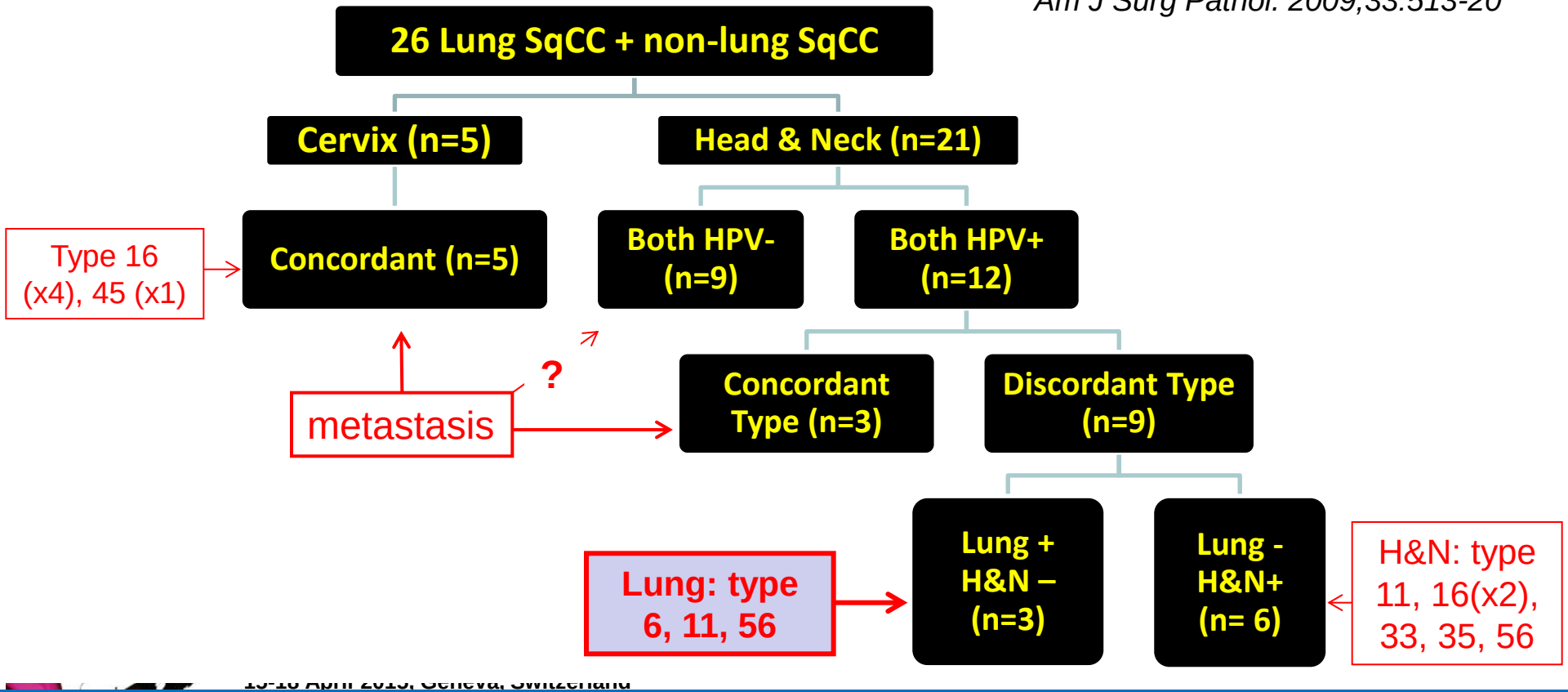
Am J Surg Pathol. 2012;36:142-8



Molecular HPV Typing as a Diagnostic Tool to Discriminate Primary From Metastatic Squamous Cell Carcinoma of the Lung

Wilko Weichert, MD, Christiane Schewe, PhD,* Carsten Denkert, MD,* Lars Morawietz, MD,* Manfred Dietel, MD,* and Iver Petersen, MD†*

Am J Surg Pathol. 2009;33:513-20



Conclusion: HPV typing is very useful diagnostic tool to discriminate primary from metastatic squamous cell carcinoma of the lung

Reported Detection of HPV DNA Sequences in NSCLC

	North America	Asia-Pacific	Europe	South America	Total
No. of reports	**4**	**25**	**16**	**2**	**46**
NSCLC	**265**	**2118**	**1416**	**105**	**3707**
HPV Positive	3.0%	33.9%	10.5%	28.6%	24.3%
Range	0-11%	0-78.3%	0-69.2%	27.8-29.0%	
Squamous cell carcinoma					
Number studied	96	1108	481	51	1674
HPV Positive	7.3%	36.2%	21.2%	41.2%	31.4%
Adenocarcinoma					
Number studied	102	453	188	45	686
HPV Positive	0	19.2%	14.9%	13.3%	17.6%
Large cell carcinoma					
Number studied	29	3	18	NA	21
HPV Positive	3.5%	33.3%	22.2%	NA	23.8%

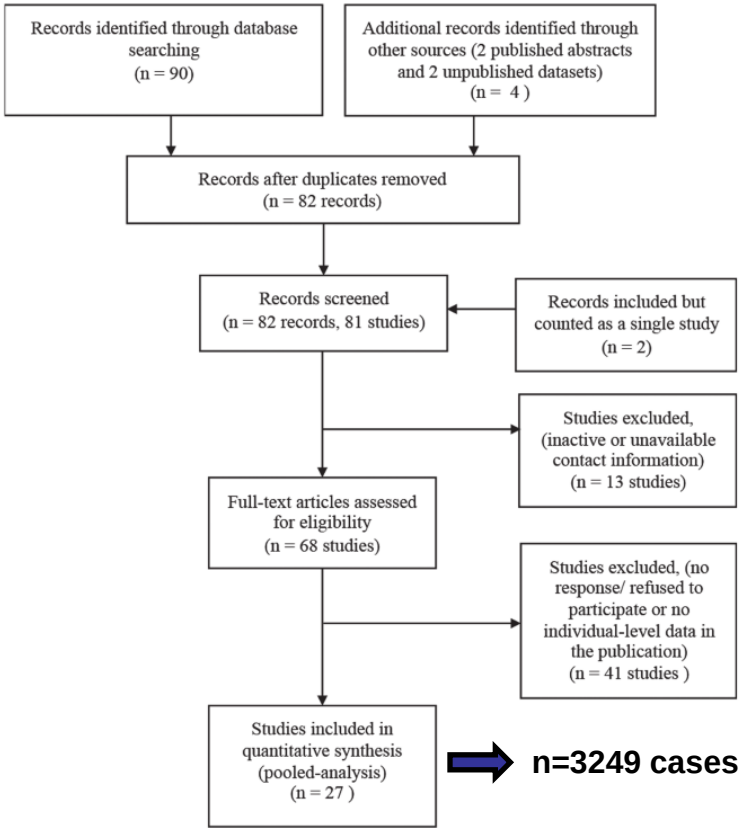
Yanagawa N, et al, Lung Cancer 2013; 79:215-220

Carcinogenesis vol.35 no.6 pp.1267–1275, 2014
doi:10.1093/carcin/bgu038
Advance Access publication February 12, 2014

HPV-associated lung cancers: an international pooled analysis

C Ragin, M Obikoya-Malomo, S Kim, Z Chen, *et al*.

	Adjusted Prevalence (95% CI)			
	Asia	**Europe**	**SA/CA**	**NA**
No. of cases	**1312 (40%)**	**1100 (34%)**	**105 (3%)**	**732 (23%)**
HPV 16/18	**4.6 (3.48-5.73)**	**3.03 (2.76-3.30)**	**21.90 (19.61-24.20)**	**3.78 (3.35-4.22)**
HPV 16	**1.49 (0.86-2.11)**	**2.94 (2.68-3.21)**	**19.18 (16.88-21.49)**	**2.03 (1.68-2.39)**
HPV 18	**1.09 (0.66-1.52)**	**0.82 (0.73-0.92)**	**7.78 (6.61-8.95)**	**2.49 (2.23-2.75)**



Landscape of DNA Virus Associations across Human Malignant Cancers: Analysis of 3,775 Cases Using RNA-Seq

Joseph D. Khoury,[a] Nizar M. Tannir,[b] Michelle D. Williams,[c] Yunxin Chen,[b] Hui Yao,[d] Jianping Zhang,[d] Erika J. Thompson,[e] the TCGA Network, Funda Meric-Bernstam,[f,g] L. Jeffrey Medeiros,[a] John N. Weinstein,[d] Xiaoping Su[d]

Departments of Hematopathology,[a] Genitourinary Medical Oncology,[b] Pathology,[c] Bioinformatics and Computational Biology,[d] Genetics,[e] Investigational Cancer Therapeutics,[f] and Surgical Oncology,[g] MD Anderson Cancer Center, Houston, Texas, USA

Elucidation of tumor-DNA virus associations in many cancer types has enhanced our knowledge of fundamental oncogenesis mechanisms and provided a basis for cancer prevention initiatives. RNA-Seq is a novel tool to comprehensively assess such associations. We interrogated RNA-Seq data from 3,775 malignant neoplasms in The Cancer Genome Atlas database for the presence of viral sequences. Viral integration sites were also detected in expressed transcripts using a novel approach. The detection capacity of RNA-Seq was compared to available clinical laboratory data. Human papillomavirus (HPV) transcripts were detected

Tumor type	No. of samples analyzed
Breast carcinoma	750
Clear cell renal cell carcinoma	460
Ovarian serous cystadenocarcinoma	419
Uterine corpus endometrioid carcinoma[a]	254
Head-and-neck squamous cell carcinoma	239
Lung adenocarcinoma	225
Lung squamous cell carcinoma	219
Cutaneous melanoma	214
Acute myeloid leukemia	179
Glioblastoma	168
Thyroid carcinoma	157
Colon adenocarcinoma[a]	138
Gastric adenocarcinoma	71
Rectal adenocarcinoma[a]	66
Prostate adenocarcinoma	53
Papillary renal cell carcinoma	47
Lower-grade glioma	47
Hepatocellular carcinoma	69

HPV viral transcript detected tumors

	No. tumors studied	HPV + cases (%)
Head and Neck SCC	**239**	**36 (15.06%)**
Lung SCC	**219**	**1 (0.5%)**
Endometrial carcinoma	**253**	**1 (0.4%)**

Patient had past hx of HPV + oropharyngeal SCC

J Virol 87(16):8916-26

Human papilloma virus genome is rare in North American non-small cell lung carcinoma patients

Lung Cancer 2013; 79:215-220

Naoki Yanagawa[a], Ami Wang[a], Derek Kohler[a], Gilda da Cunha Santos[a,c], Jenna Sykes[b], Jing Xu[a], Melania Pintilie[b], Ming-Sound Tsao[a,c,*]

P16 staining	HPV+ (%)	HPV – (%)	P value
High expression (++)	5 (100%)*	104 (30.9%)	
Normal-like (+)	0	28 (8.3%)	0.004
Negative (-)	0	199 (60.8%)	
Squamous Cell Carcinoma	**5**	**127**	
Adenocarcinoma	**0**	**204**	

* All type 16

Case	Lung Surgery	Sex	Smoking History	Stage	Size (cm)	Location	Other Prior Malignancy	Diagnosis	Tumor histology	Grade	Stage	HPV status	Treatment
1	Apr-03	M	Smoker	pT4N2	8	peripheral	Base of tongue	Oct-00	Sqcc	MD	pT2N3 (4B)	+	Hemimandibulectomy + radical neck dissection
2	Feb-06	F	Never	pT2bN2	5.5	peripheral	Cervix	Nov-01	Sqcc	NA	c2B	+	Chemoradiation
3	Feb-07	F	Never	pT1aN0	2	peripheral	Endocervix	Aug-05	Sqcc	PD	c-2B	NA	Chemoradiation
4	Mar-08	M	Never	pT2aN0	3.5	central	Oropharynx	May-07	Sqcc	MD	pT4aN2b (4B)	NA	Chemoradiation + Neck dissection
5	Mar-08	F	Smoker	pT2bN1	6	peripheral	Cervix	Sep-03	Sqcc	MD	pT1bN0 (1B)	NA	LEEP + chemoradiation

Importance of Determining Role of HPV in Lung Carcinoma

1. In oropharynx, HPV+ cancer represents a different disease with much better prognosis (Fakhry C, et al. J Natl Cancer Inst 2008;100: 261–69; Rischin D, et al. J Clin Oncol 2010;28:4142-8.)
2. Distinguishing primary vs metastatic nature of HPV+ lung carcinoma

Other key references:

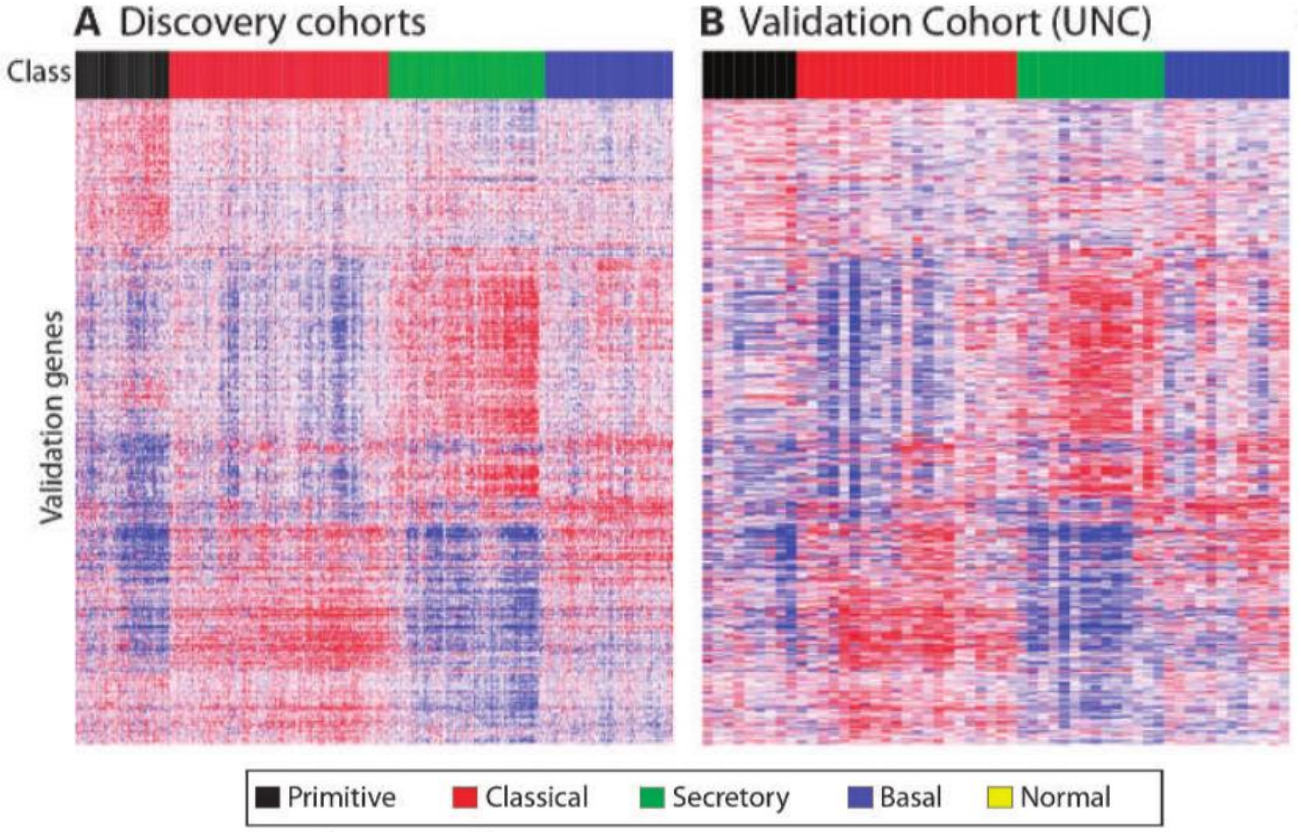
- Klein F, et al. Incidence of human papilloma virus in lung cancer. Lung Cancer 2009;65:13-18.
- Koshiol J, et al. Assessment of human papillomavirus in lung tumor tissue. J Natl Cancer Inst 2011;103:501-507.

HPV and Lung Cancer (Summary)

1. HPV determination and typing is useful to distinguish primary from metastasis in lung cancer patients with past history of H&N or Cervical cancer
2. In this situation, P16 IHC cannot be used as a surrogate marker for HPV assay
3. There is an urgent need to conduct an international molecular epidemiological study to re-evaluate the role of HPV in lung cancer, using stringently controlled and robust assays

Lung Squamous Cell Carcinoma mRNA Expression Subtypes Are Reproducible, Clinically Important, and Correspond to Normal Cell Types

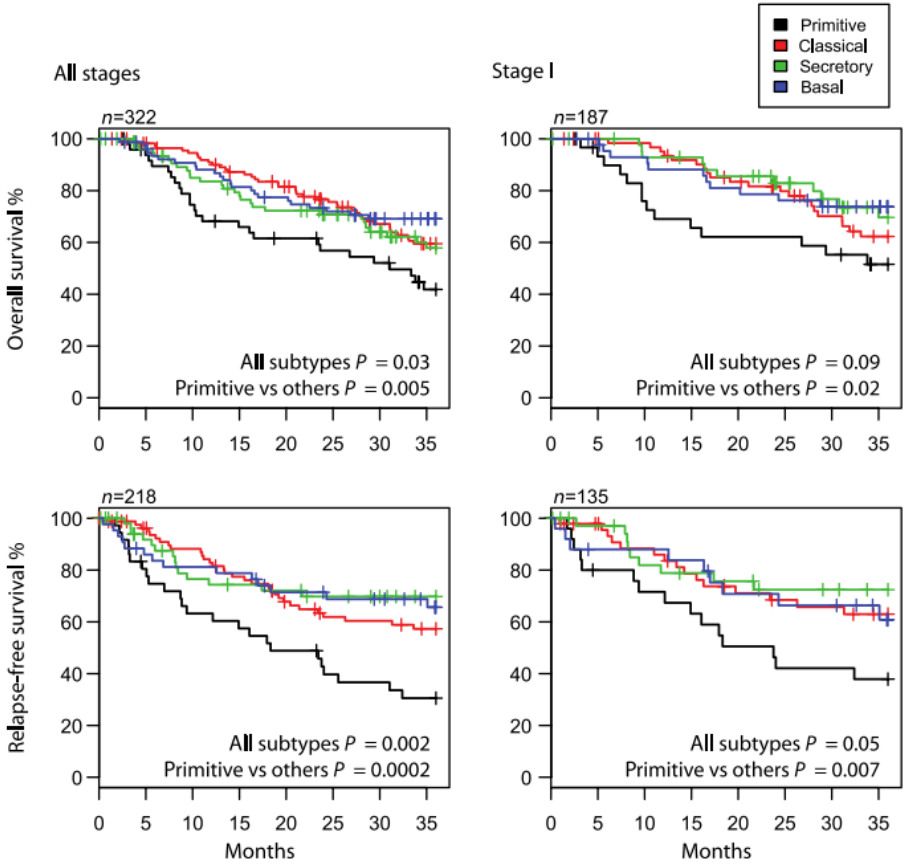
Matthew D. Wilkerson[1], Xiaoying Yin[1], Katherine A. Hoadley[1,2], Yufeng Liu[3,4], Michele C. Hayward[1], Christopher R. Cabanski[3], Kenneth Muldrew[5], C. Ryan Miller[1,5], Scott H. Randell[1,6], Mark A. Socinski[1,7], Alden M. Parsons[7], William K. Funkhouser[1,5], Carrie B. Lee[1,7], Patrick J. Roberts[1], Leigh Thorne[1,5], Philip S. Bernard[8], Charles M. Perou[1,2], and D. Neil Hayes[1,7]



Clin Cancer Res; 16(19); 4864–75

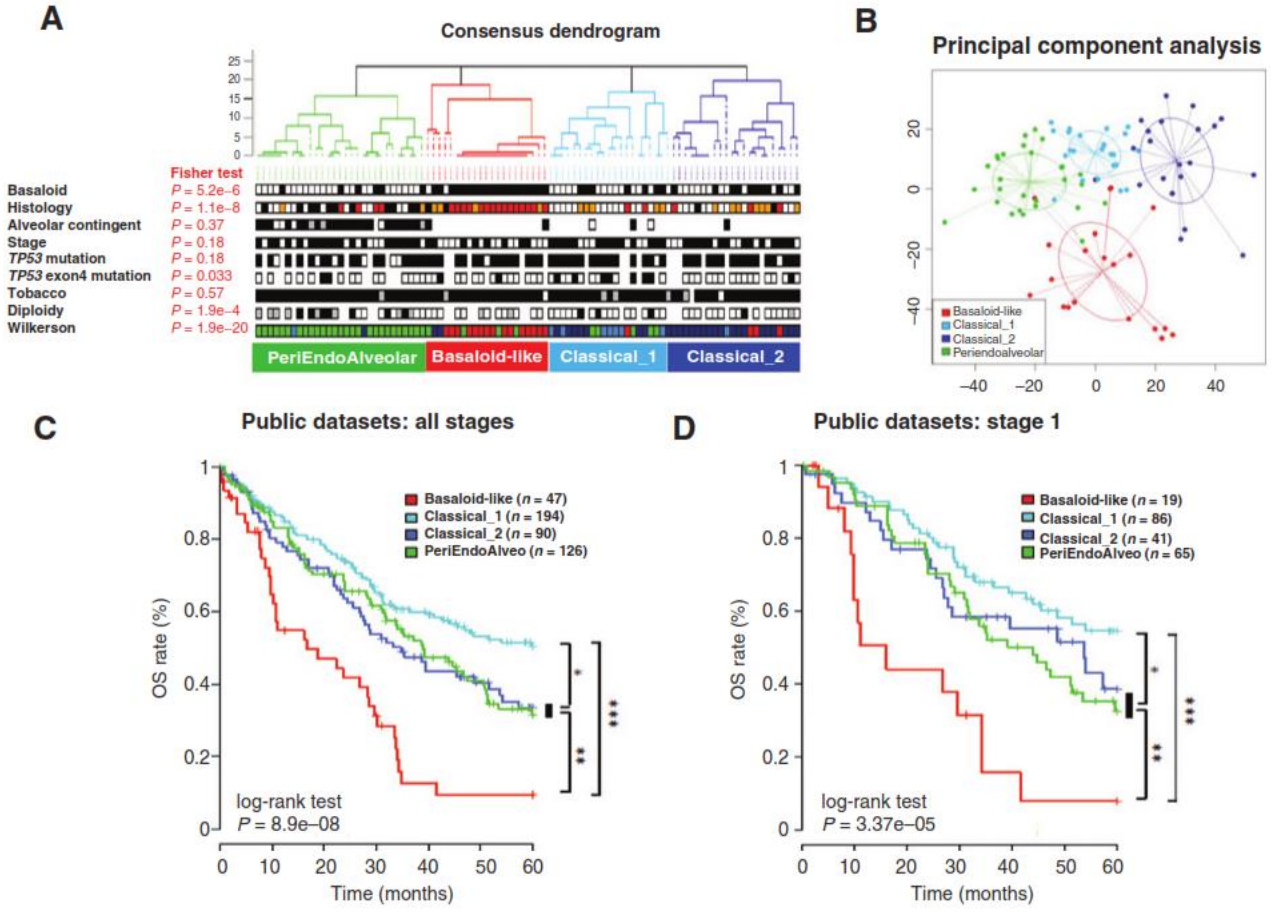
Lung Squamous Cell Carcinoma mRNA Expression Subtypes Are Reproducible, Clinically Important, and Correspond to Normal Cell Types

Expression subtype	Enriched Pathway	Model system
Primitive	Proliferation, RNA processing, DNA repair	Mouse early lung development
Classical	Energy and xenobiotics metabolism	No specific model
Secretory	Immune response	Normal lung: LCM submucosal glands
Basal	Cell adhesion, epidermal development	Basal cell phase of HBEC-air surface interface culture



Lung Squamous Cell Carcinomas with Basaloid Histology Represent a Specific Molecular Entity

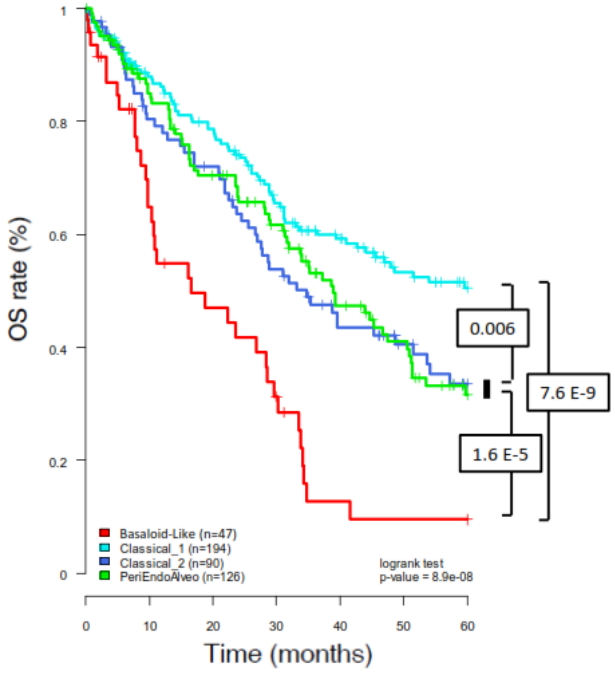
Christian Brambilla[1], Julien Laffaire[2], Sylvie Lantuejoul[3], Denis Moro-Sibilot[1], Hélène Mignotte[1], François Arbib[1], Anne-Claire Toffart[1], Fabien Petel[2], Pierre Hainaut[4], Sophie Rousseaux[5], Saadi Khochbin[5], Aurélien de Reyniès[2], and Elisabeth Brambilla[3]



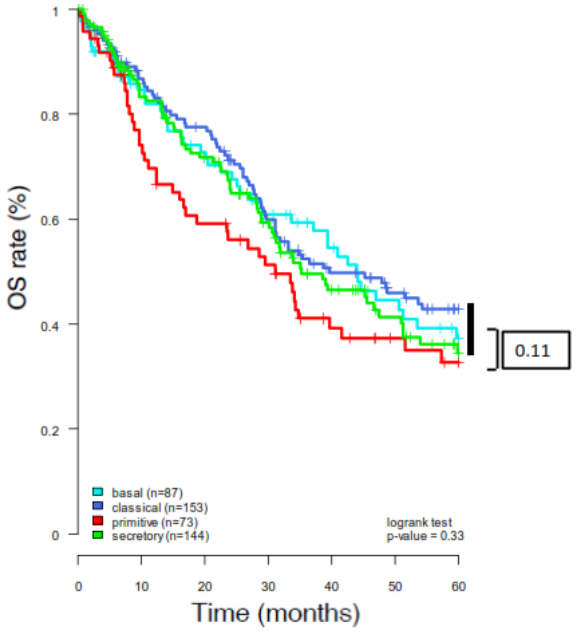
Brambilla C, et al. *Clin Cancer Res 2014;20:5777-86*

		Wilkerson molecular subtypes (prediction)			
		basal	classical	primitive	secretory
CIT molecular subtypes (prediction)	Basaloid-Like	6	3	**57**	12
	Classical_1	**73**	**111**	18	37
	Classical_2	8	**94**	27	0
	PeriEndoAlveo	19	4	2	**155**

CIT subtypes in public datasets



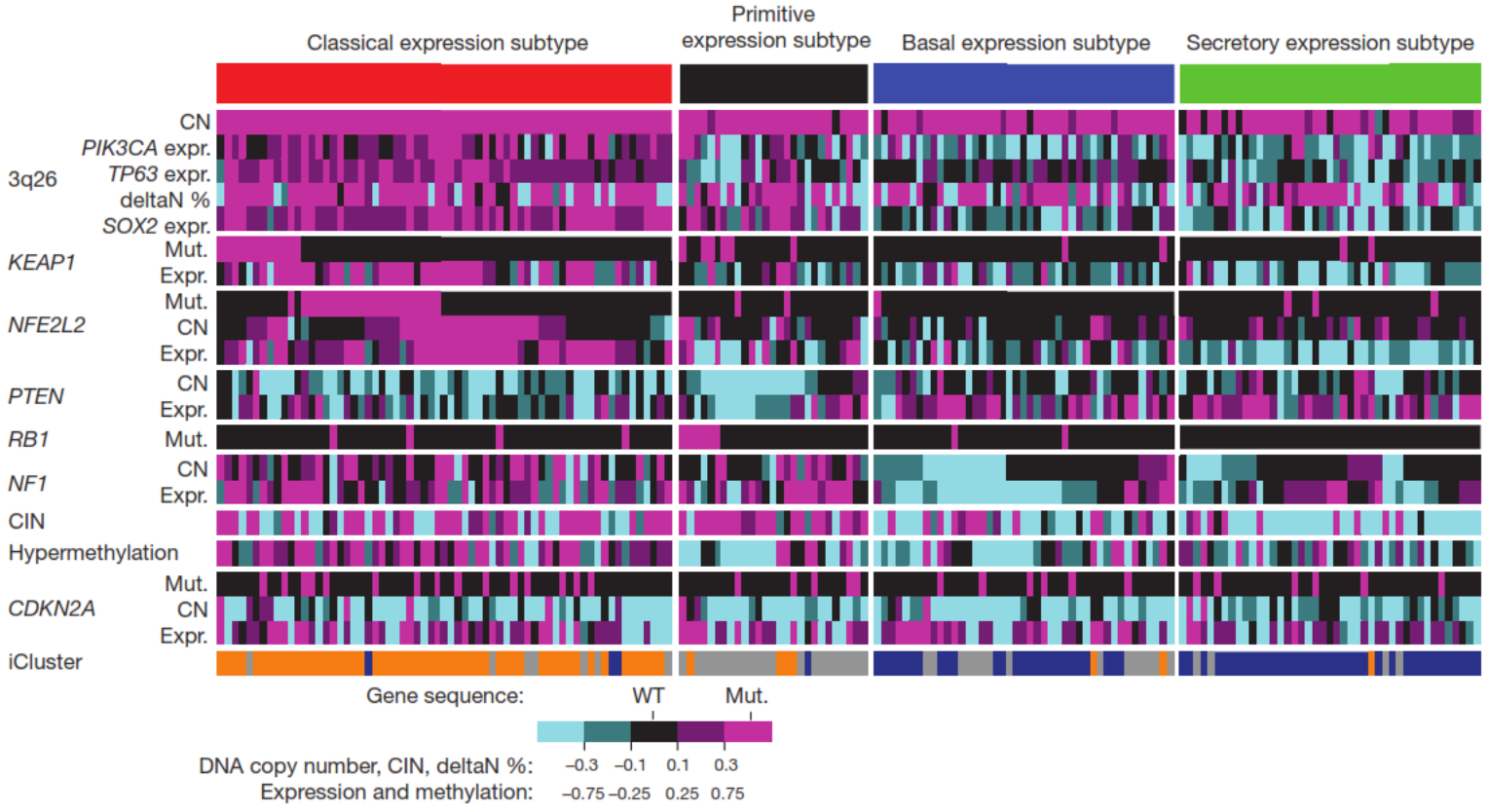
Wilkerson subtypes in public datasets



Brambilla C, et al. *Clin Cancer Res 2014;20:5777-86*

Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network*



15-18 April 2015, Geneva, Switzerland

Organisers

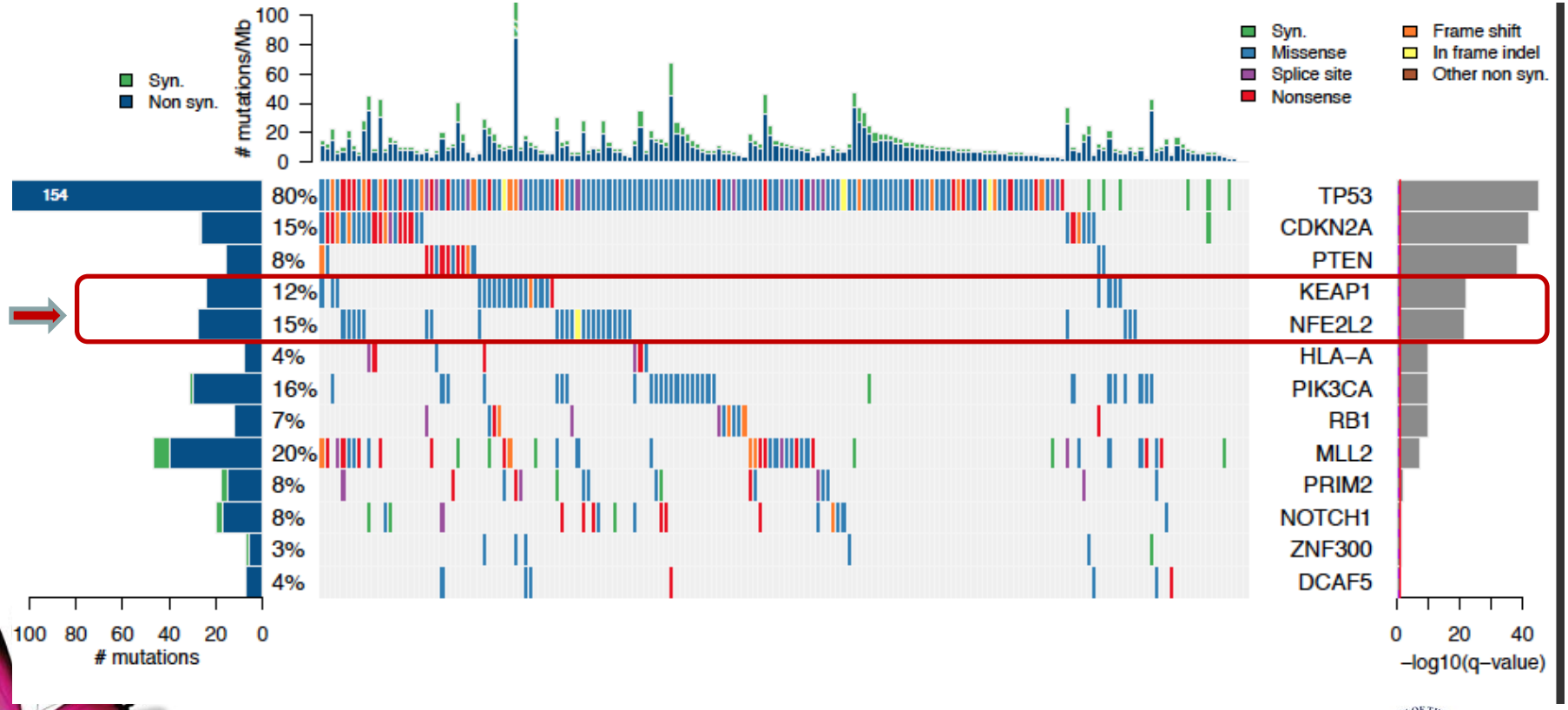
Partners

Comprehensive genomic characterization of squamous cell lung cancers

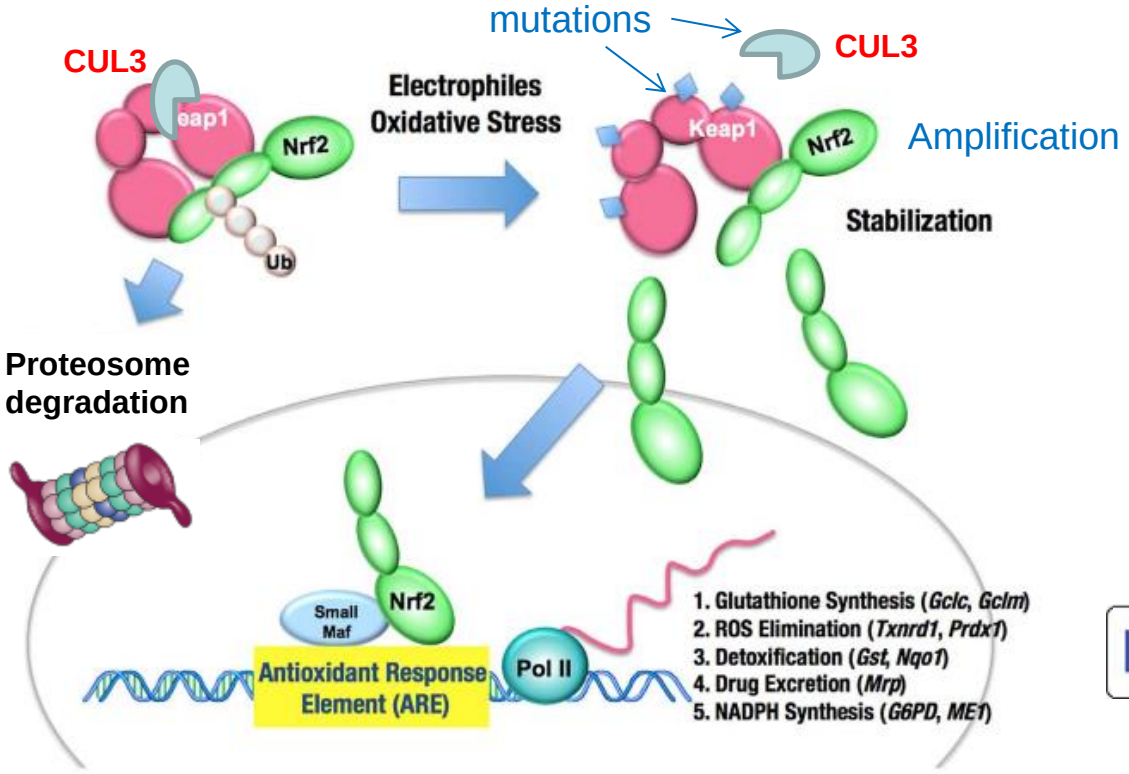
The Cancer Genome Atlas Research Network*

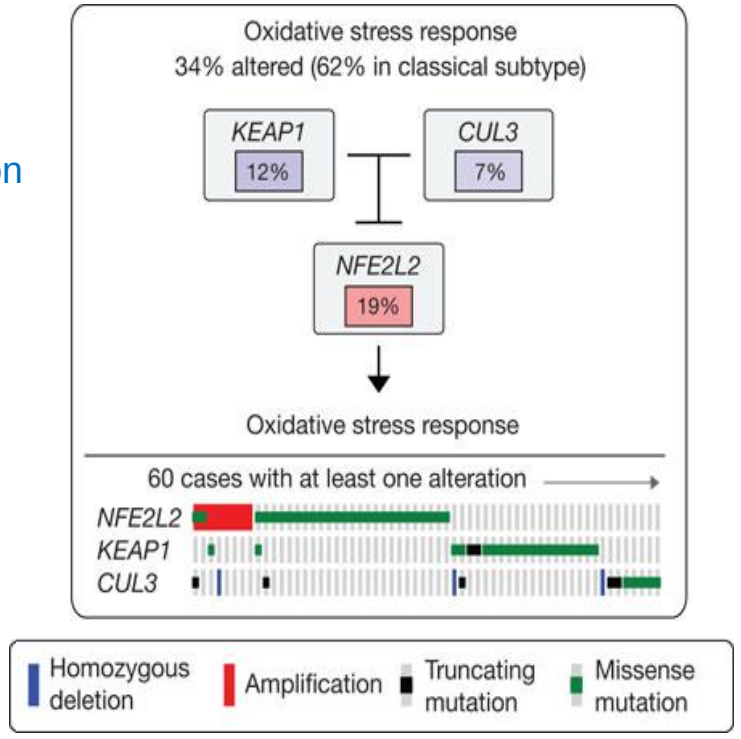
Potentially Targetable Mutated/Amplified Genes

PI3KCA	PTEN	AKT 1-3	FGFR 1-3	EGFR	ERBB2	BRAF	NOTCH	RAS
16%	8%	20%	12%	9%	4%	4%	13%	6%



NRF2 Pathway Alterations in Lung SqCC





Mitsuishi Y, et al. Frontiers in Oncol 2012;2:1
Sporn MB, Libby T, Nat Rev Cancer 2012;12:564
Hammerman P, et al., Nature September 9, 2012

Personalized Medicine and Imaging

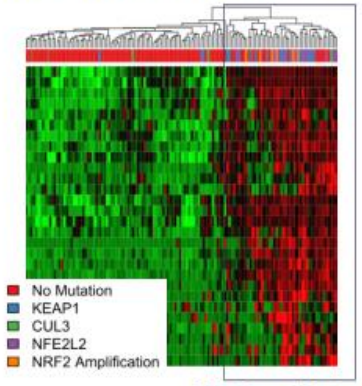
Clinical Cancer Research

In press

NRF2 Pathway Activation and Adjuvant Chemotherapy Benefit in Lung Squamous Cell Carcinoma

David W. Cescon[1,2], Desmond She[3], Shingo Sakashita[3,4], Chang-Qi Zhu[3], Melania Pintilie[5], Frances A. Shepherd[1,2], and Ming-Sound Tsao[3,4]

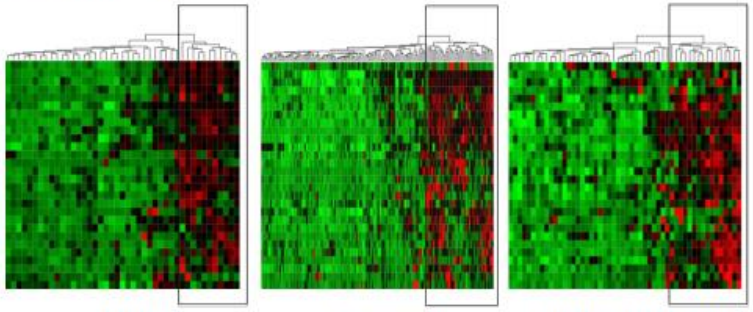
28-gene list separates NRF2-pathway altered and NRF2-normal cases in SqCC TCGA



NRF2-activated

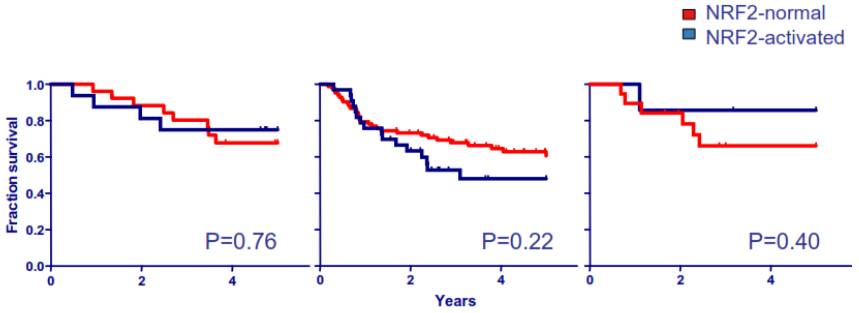
Figure 2. Re-clustering of SqCC TCGA cases using 28-genes. The NRF2-activated subgroup is highly enriched for cases with somatic alterations of NRF2 pathway genes (P<0.0001)

NRF2 signature identifies subgroups in other SqCC datasets



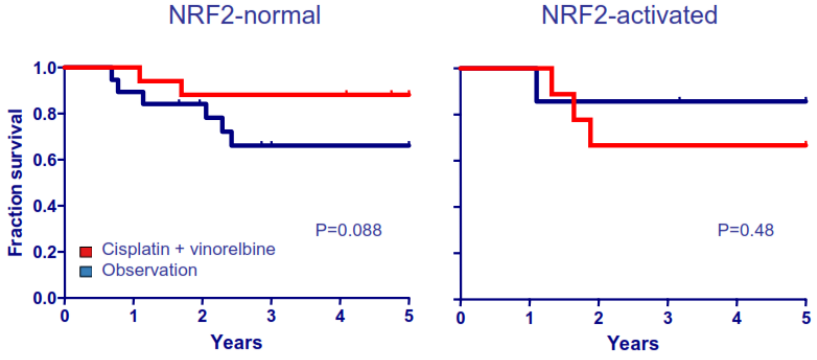
UHN[3] Raponi[4] NCIC JBR.10[5,6]

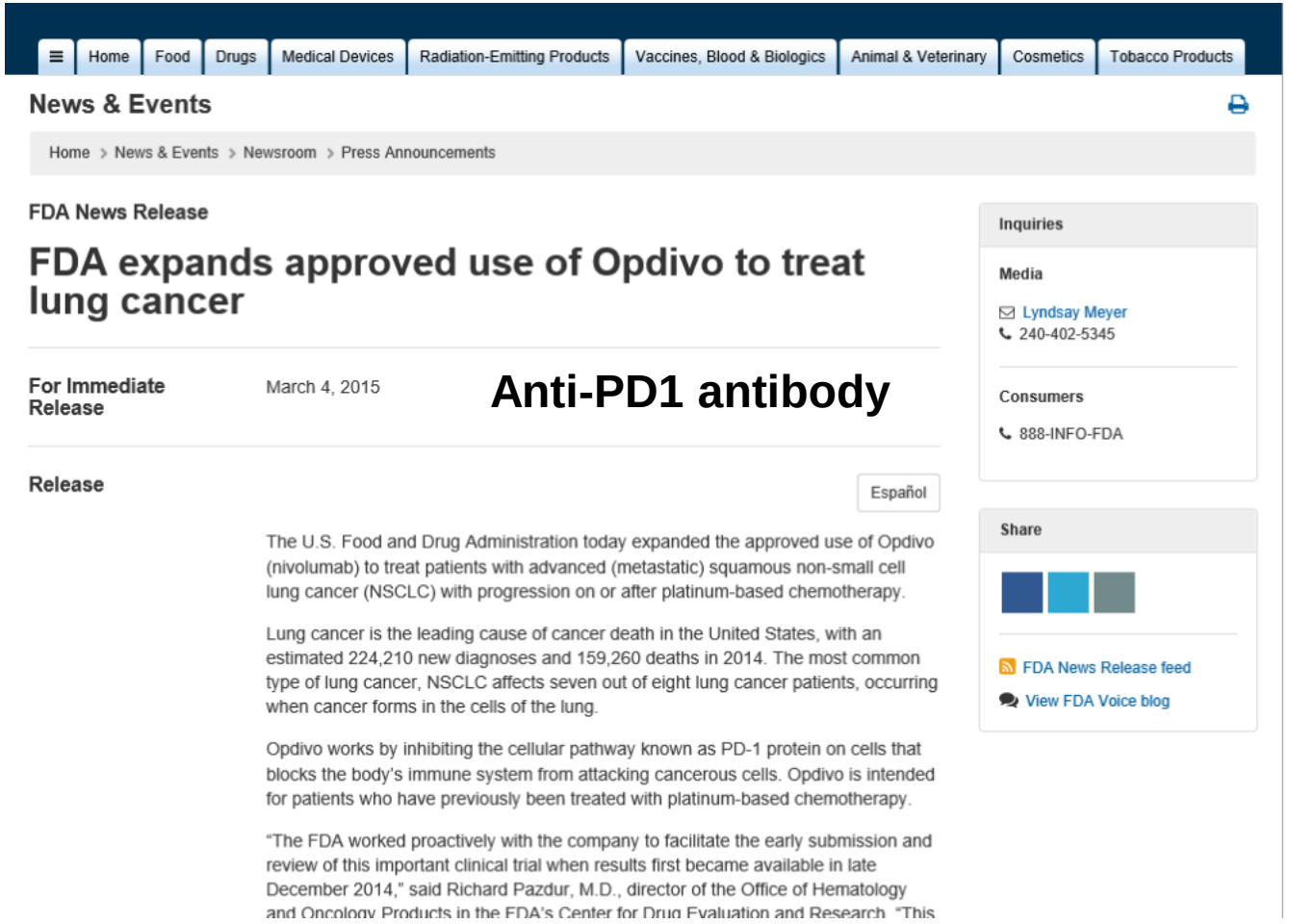
The NRF2 gene signature is not prognostic in SqCC patients treated with surgery alone



UHN[1] Raponi[2] NCIC JBR.10[3]

NRF2-activated SqCC subgroup appears not to benefit from adjuvant chemotherapy in NCIC JBR.10[1,2]





Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA expands approved use of Opdivo to treat lung cancer

For Immediate Release

March 4, 2015

Anti-PD1 antibody

Release

Español

The U.S. Food and Drug Administration today expanded the approved use of Opdivo (nivolumab) to treat patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

Lung cancer is the leading cause of cancer death in the United States, with an estimated 224,210 new diagnoses and 159,260 deaths in 2014. The most common type of lung cancer, NSCLC affects seven out of eight lung cancer patients, occurring when cancer forms in the cells of the lung.

Opdivo works by inhibiting the cellular pathway known as PD-1 protein on cells that blocks the body's immune system from attacking cancerous cells. Opdivo is intended for patients who have previously been treated with platinum-based chemotherapy.

"The FDA worked proactively with the company to facilitate the early submission and review of this important clinical trial when results first became available in late December 2014," said Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "This

Inquiries

Media

Lyndsay Meyer
240-402-5345

Consumers

888-INFO-FDA

Share

FDA News Release feed

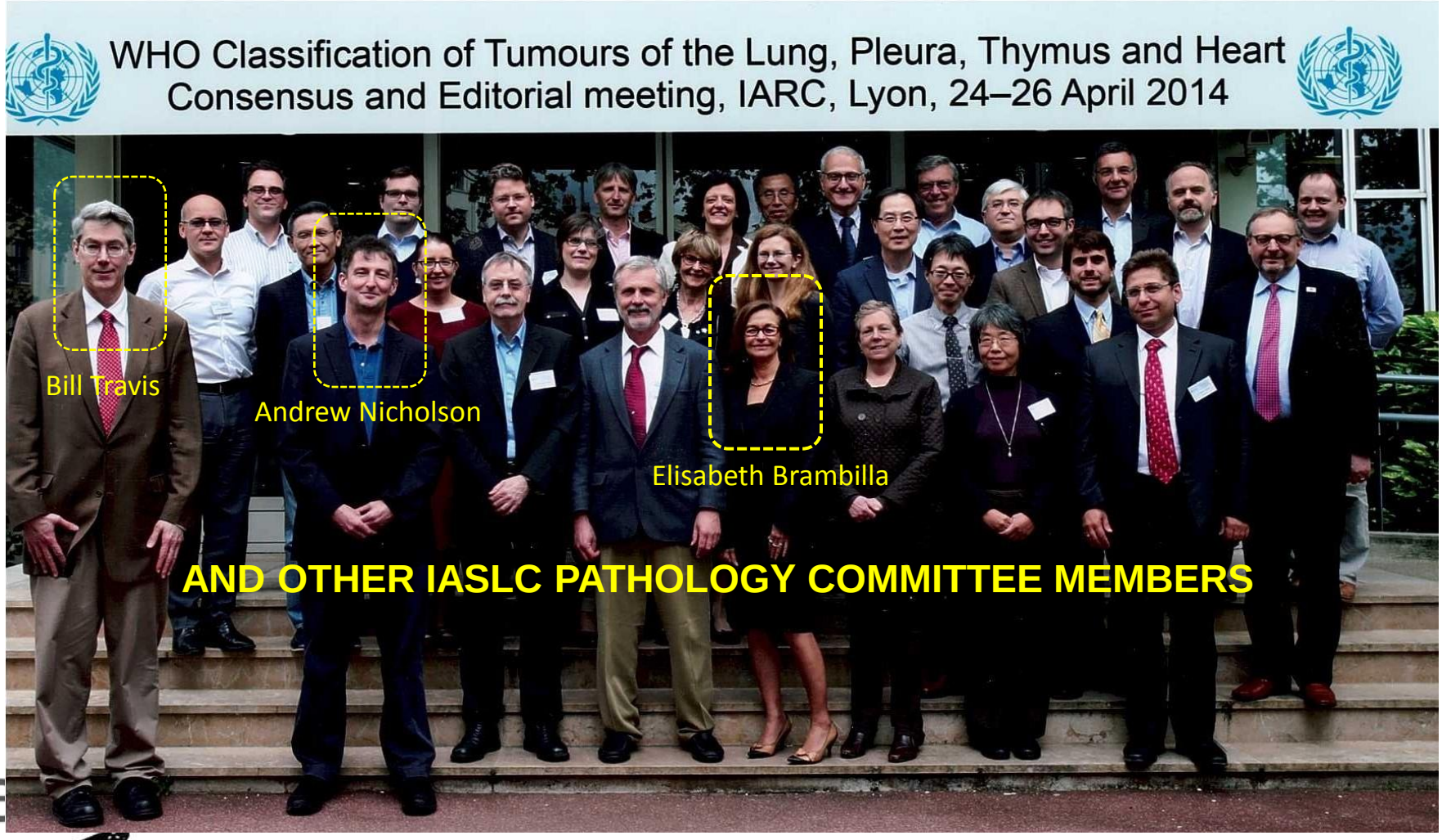
View FDA Voice blog

Opdivo's efficacy to treat squamous NSCLC was established in a randomized trial of 272 participants, of whom 135 received Opdivo and 137 received docetaxel. The trial was designed to measure the amount of time participants lived after starting treatment (overall survival). On average, participants who received Opdivo lived 3.2 months longer than those participants who received docetaxel.

Conclusions

1. **Immunohistochemical profiling using p40/p63/CK5 is integral to the diagnosis of non-keratinizing squamous cell carcinoma**
2. **Basaloid carcinoma is a squamous cell carcinoma with distinct histological and genomic profile and poor prognosis**
3. **In the setting of a past history of HPV-related cancers, HPV genotyping can help to differentiate between metastatic recurrence of independent lung primary**
4. **Additional genomic sequencing and profiling studies on squamous cell carcinoma may provide additional insights into personalized treatment of this disease**

Acknowledgements



15-18 April 2015, Geneva, Switzerland

Organisers IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop Information | Research