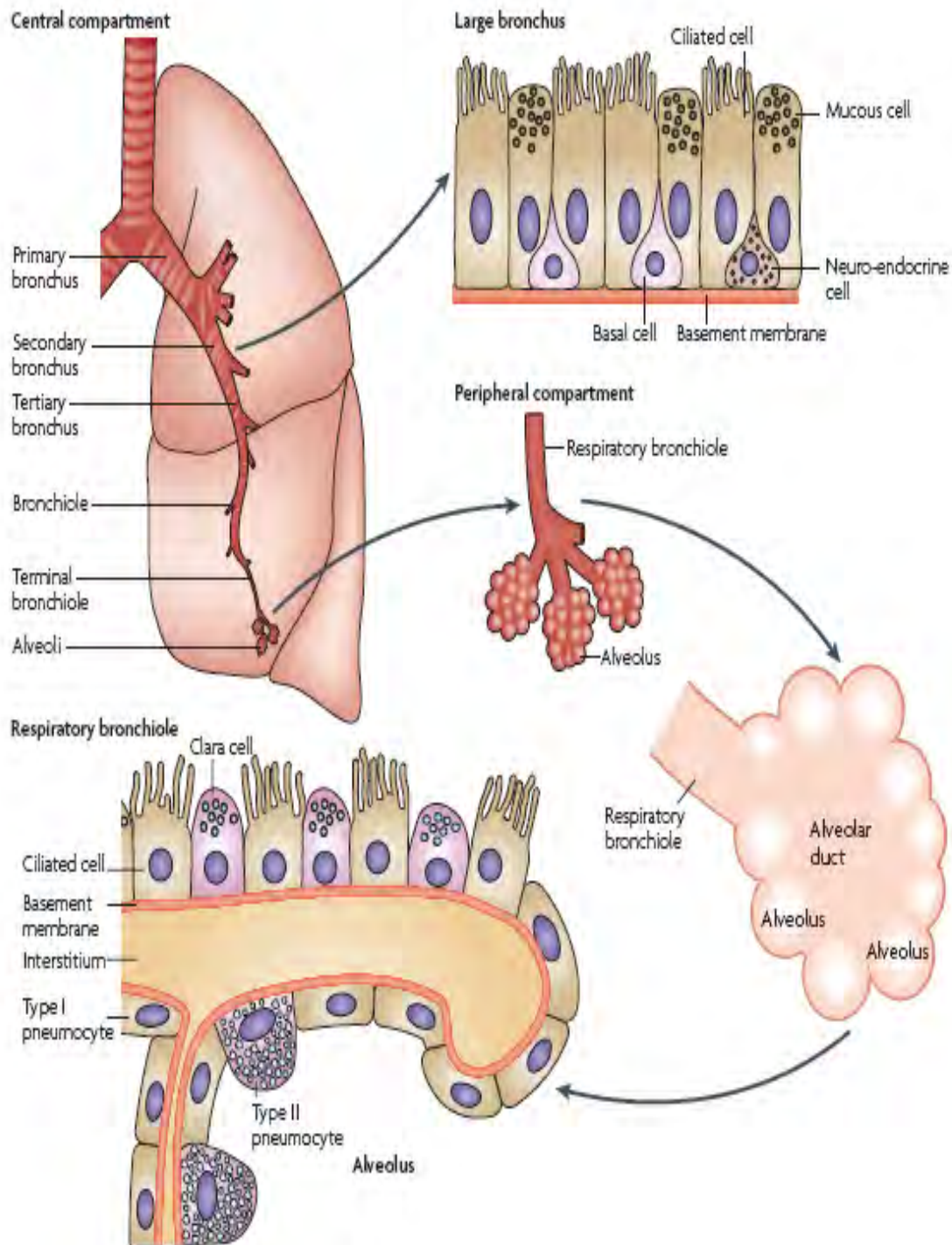


Classification histomoléculaire du cancer pulmonaire

Martine ANTOINE
Hôpital Tenon
GOLF
8 octobre 2018 Paris



AUTOPSIE D'UN MEURTRIER

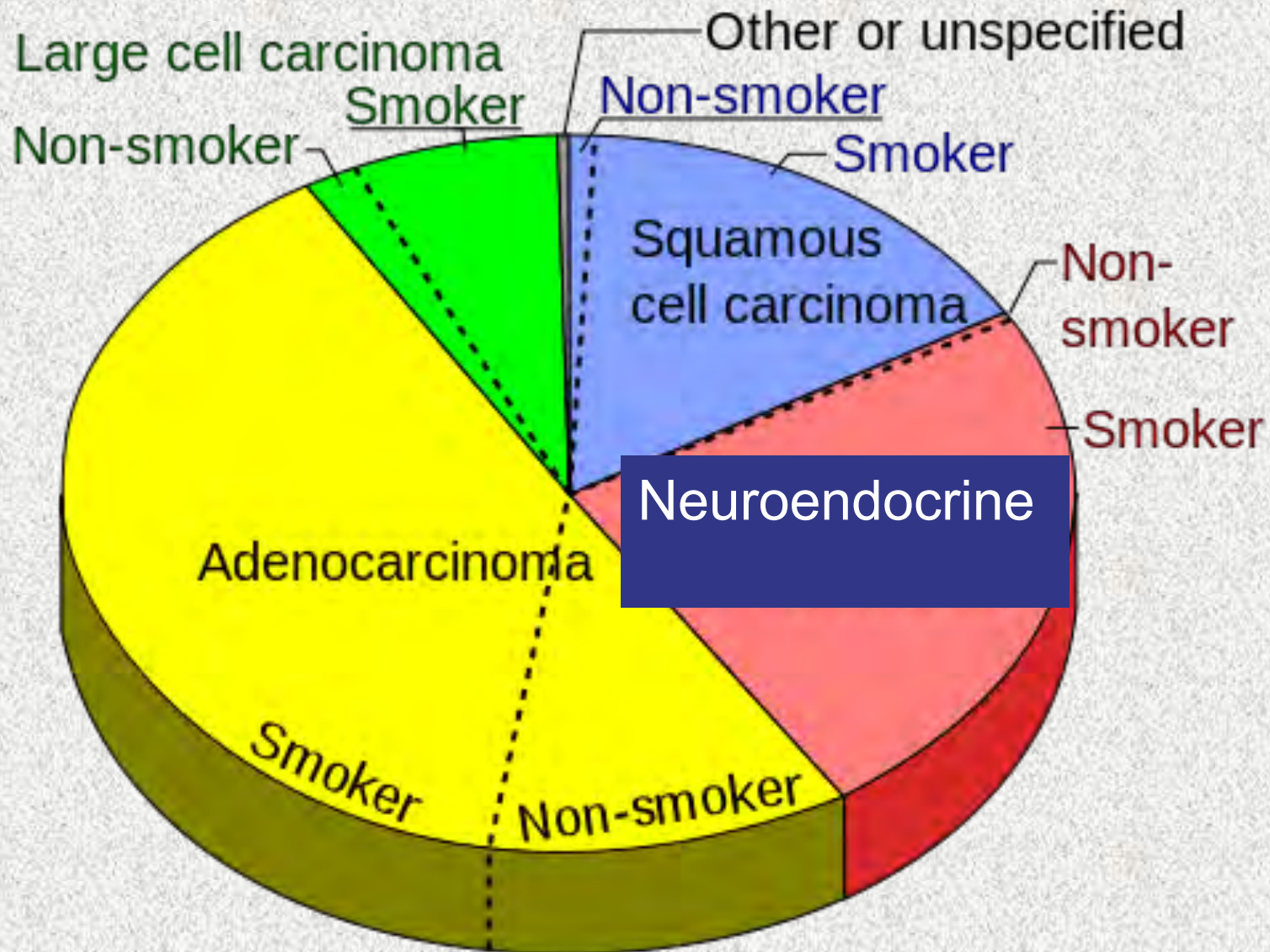


Lors de sa combustion, la cigarette produit une fumée qui contient environ 4000 substances toxiques (dont au moins 50 cancérigènes). Certains composés proviennent de l'environnement (pesticides, produits radioactifs), d'autres composés sont ajoutés, comme l'ammoniac qui favorise la fixation de la nicotine et la dépendance.



* SUBSTANCES CANCÉRIGÈNES CONNUES 0810 111 101

Carcinomes: types histologiques



•Préinvasif

- Hyperplasie adénomateuse atypique

non mucineux < 0.5 cm

- Adénocarcinome in situ (BAC)

- non mucineux
- Mucineux

< 3 cm
lepidique sans stroma réaction
ni invasion vasculaire ou pleurale

•« Adénocarcinome avec invasion minime »

- non mucineux
- Mucineux

invasion < 0.5 cm, sans nécrose ni invasion
vasculaire ou pleurale

• Invasif

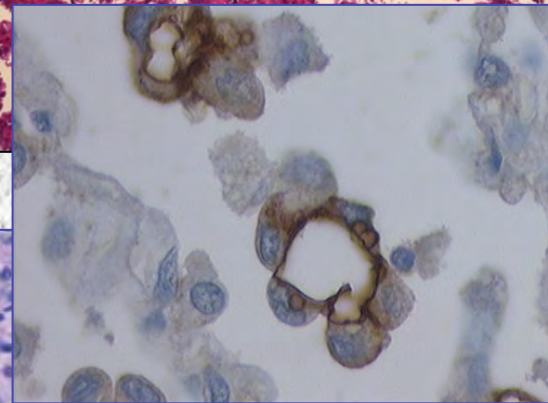
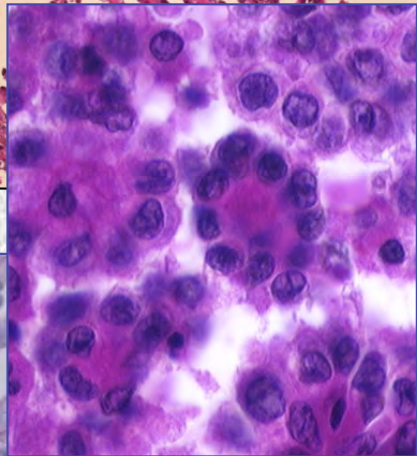
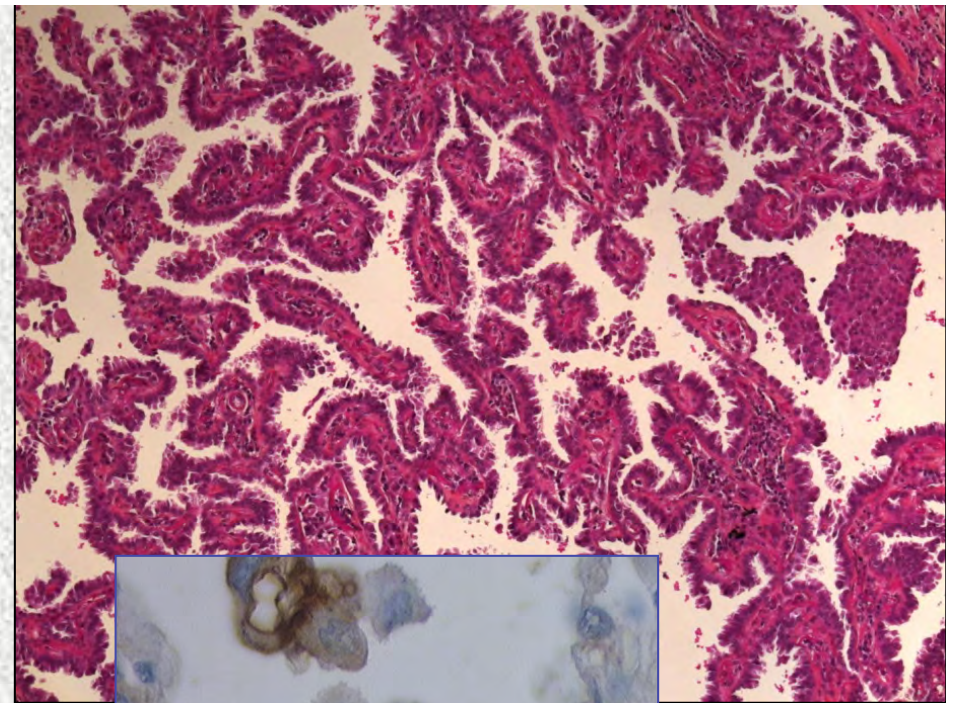
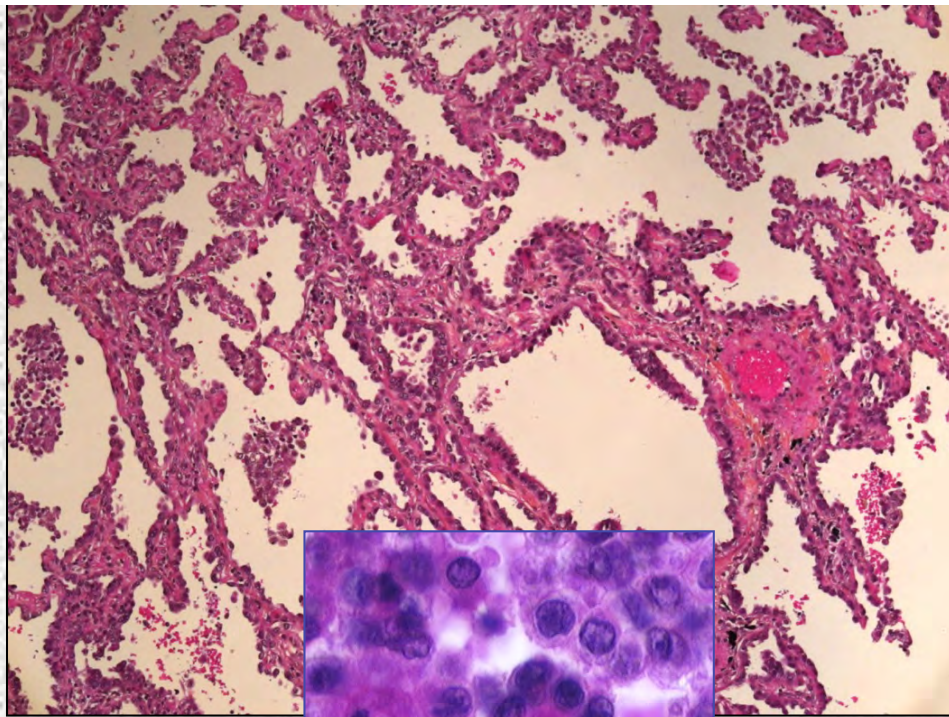
- À prédominance lepidique (non mucineux)
- À prédominance acineuse
- À prédominance papillaire
- À prédominance micropapillaire
- À prédominance solide

invasion > 0.5 cm
sous type architectural

•Invasifs Mucineux (ou mixte)

- Colloïde
- Foetal (bas et haut grade)
- Entérique

mixte BAC mucineux

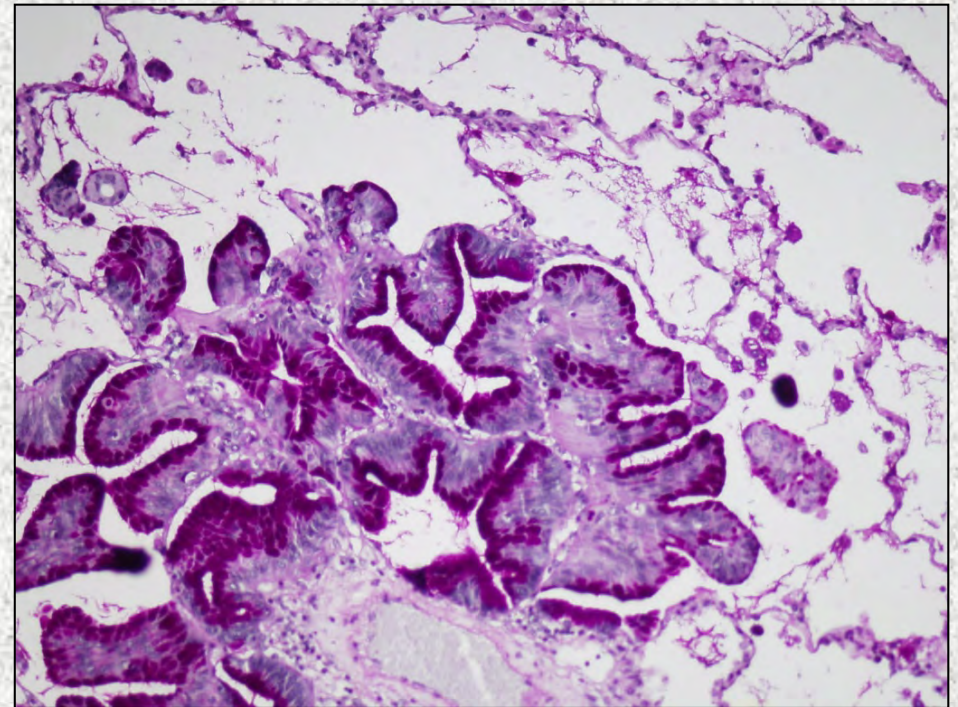
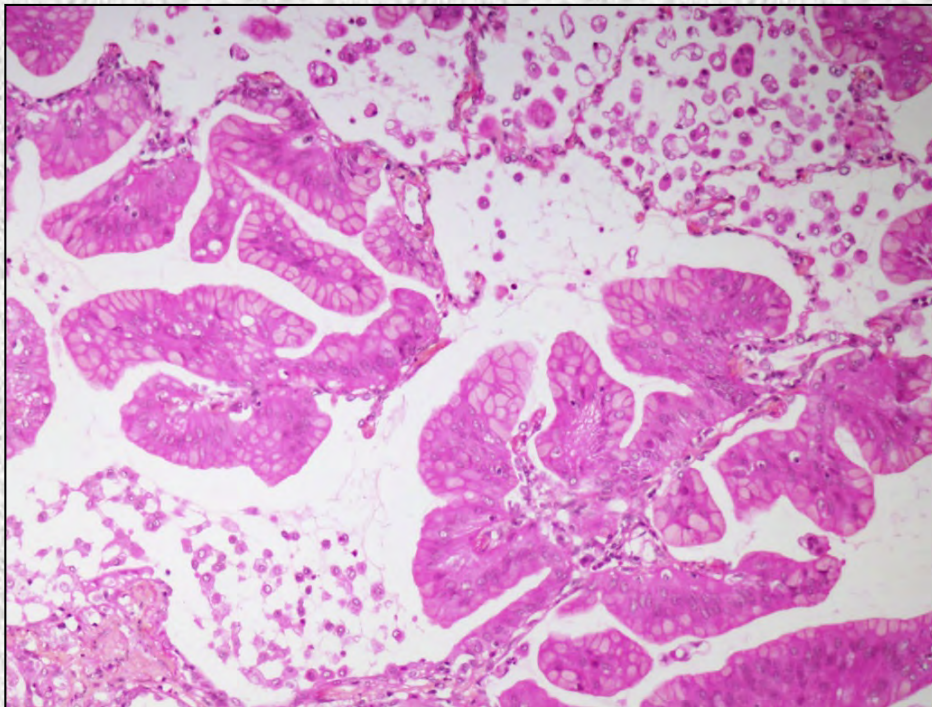


**Solide et micropapillaire
de mauvais pronostic**

Mucineux



Diffusion aérologène
STAS



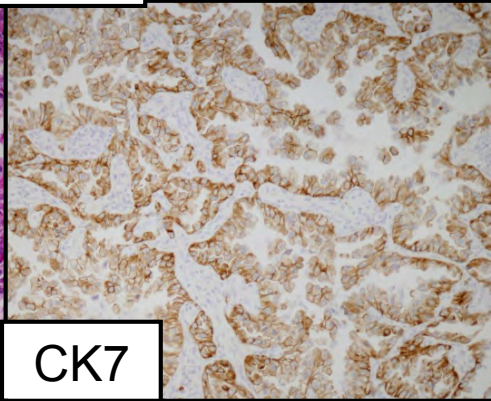
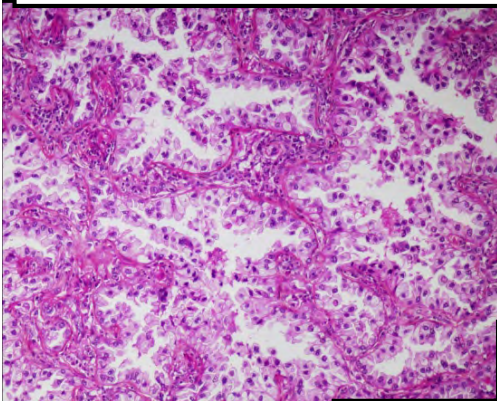
TTF1-,
WT EGFR
RAS mut
Muc2-5-6, CDX2

lepidique

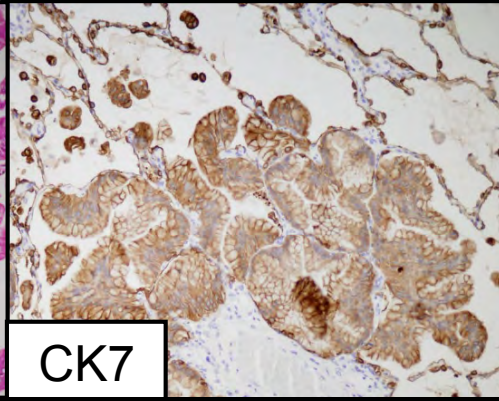
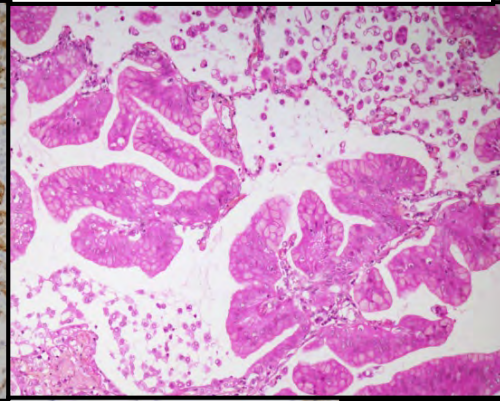
mucineux

BAC Non-mucineux

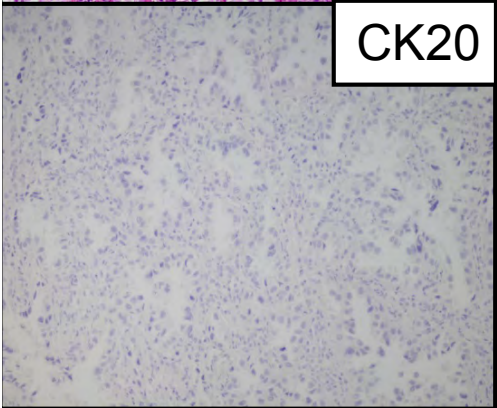
BAC Mucineux



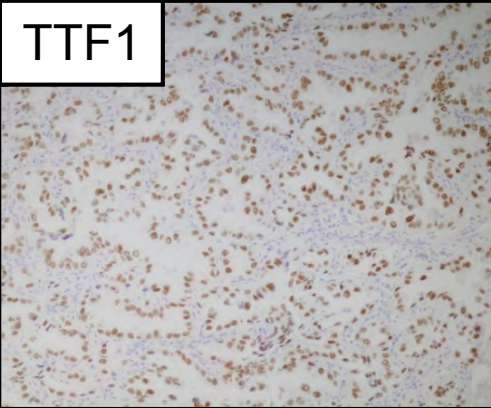
CK7



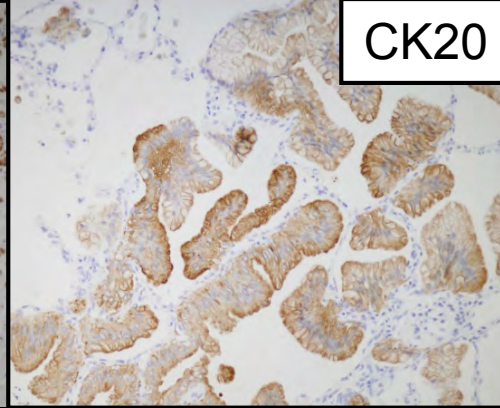
CK7



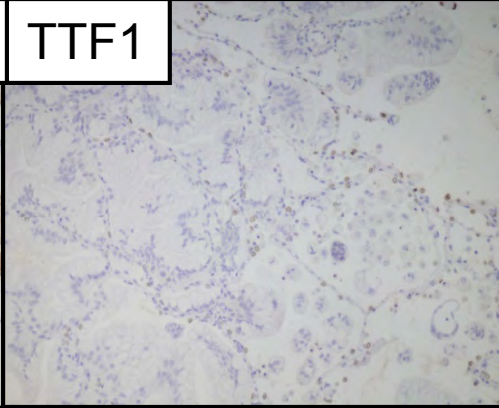
CK20



TTF1



CK20



TTF1

8

EGFR

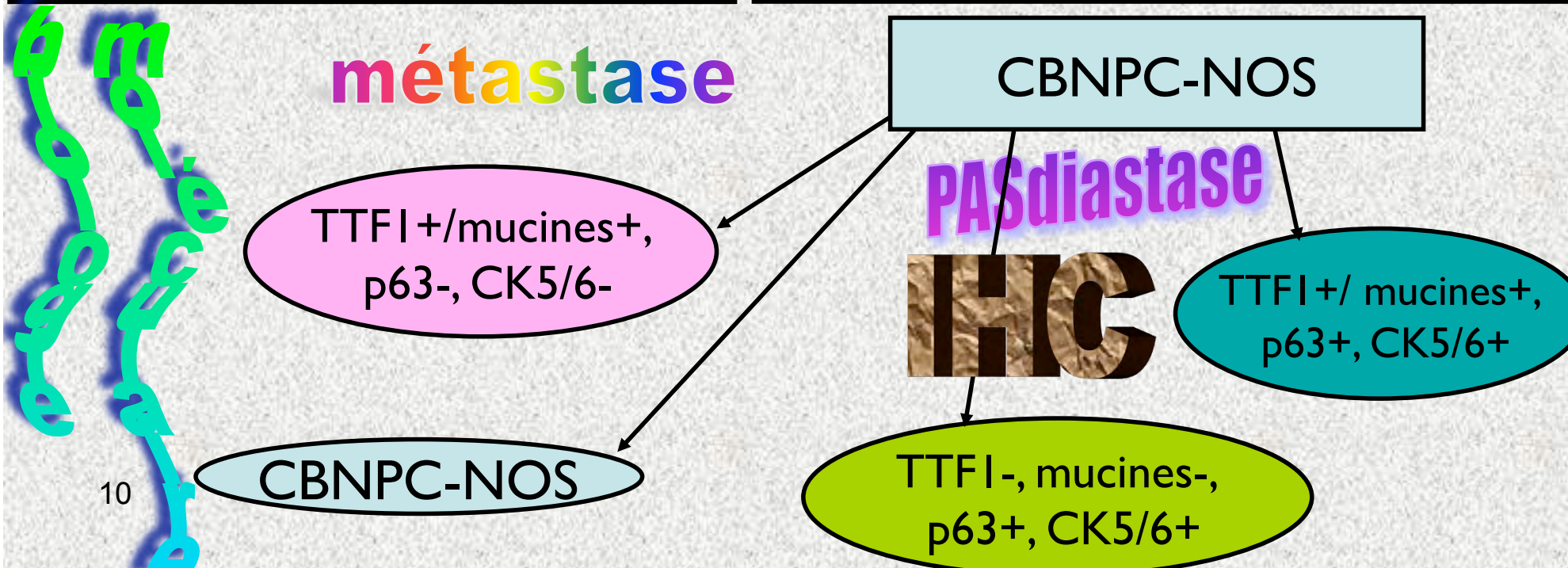
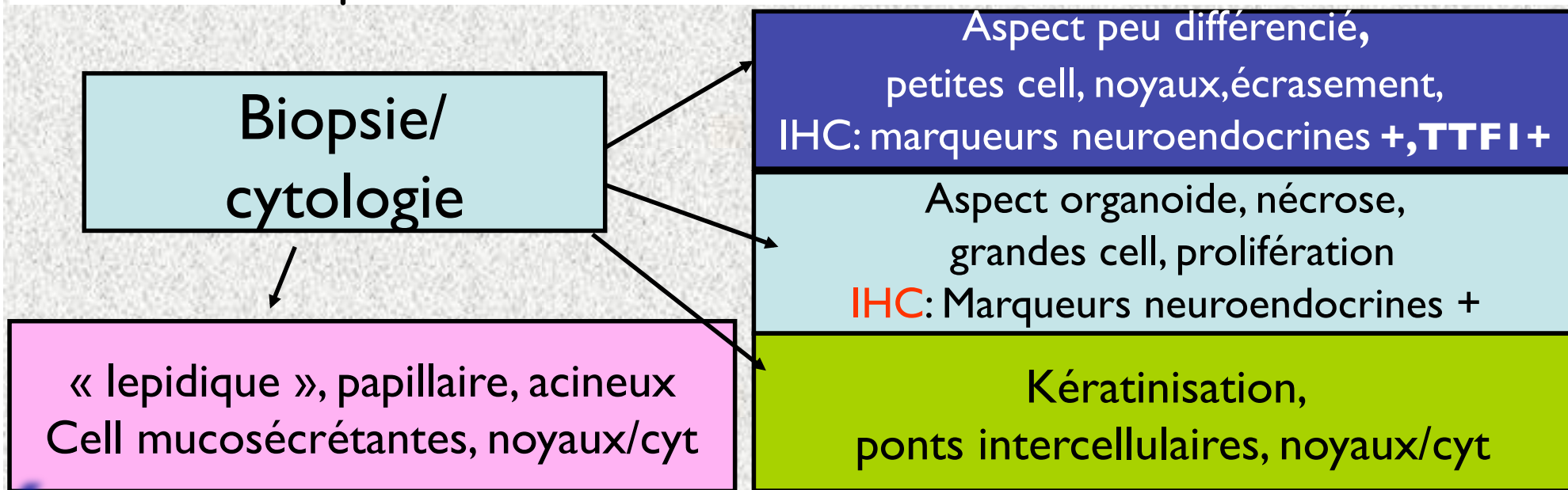
K RAS

Corrélations morphologie et moléculaire

904 Adénocarcinomes
IASLC/ATS/ERS
classification
2011

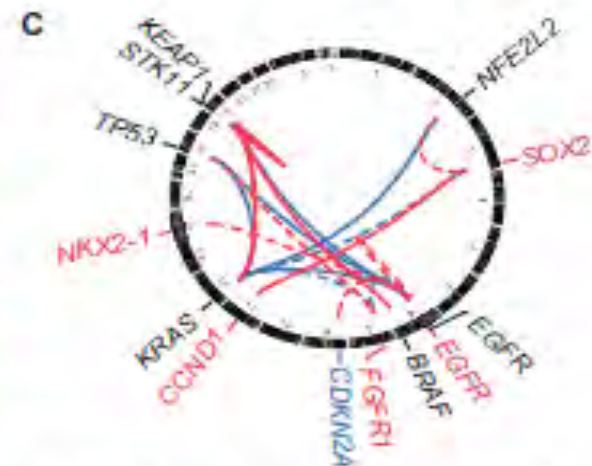
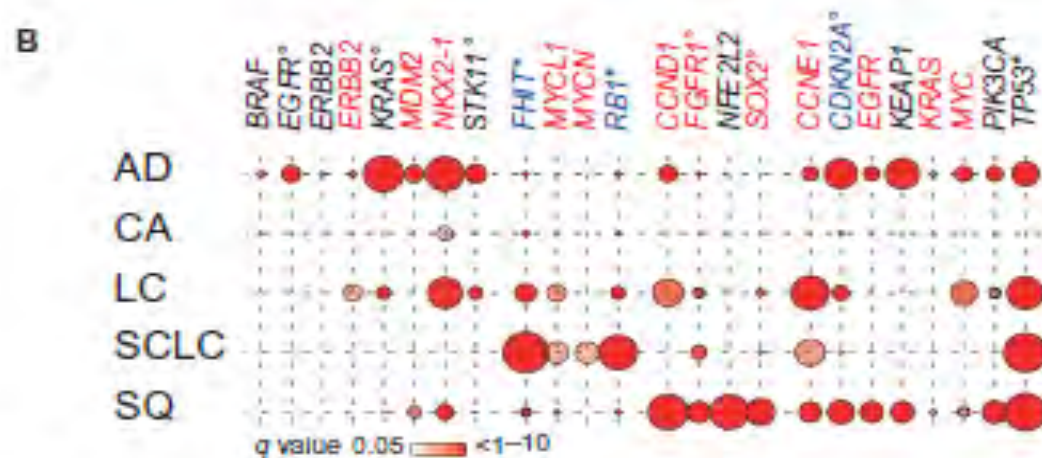
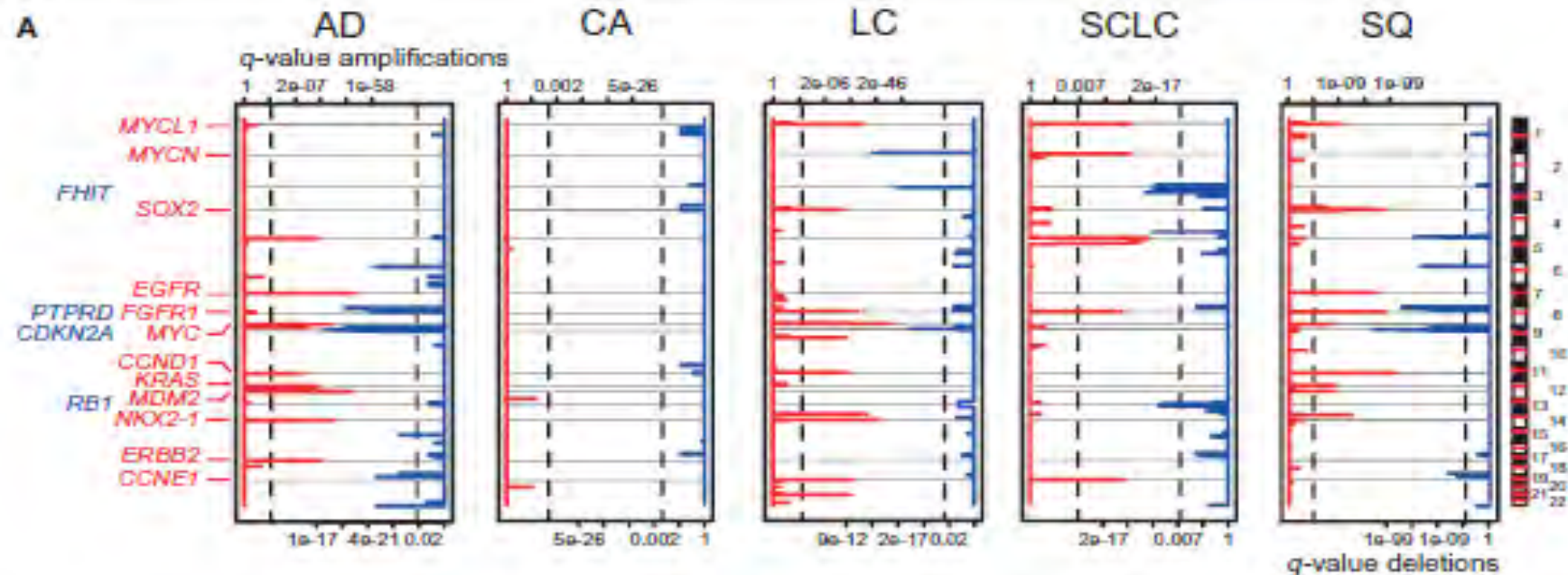


Architecture, noyaux (taille, nucléole), cytoplasme, prolifération, nécrose, mucosécrétion

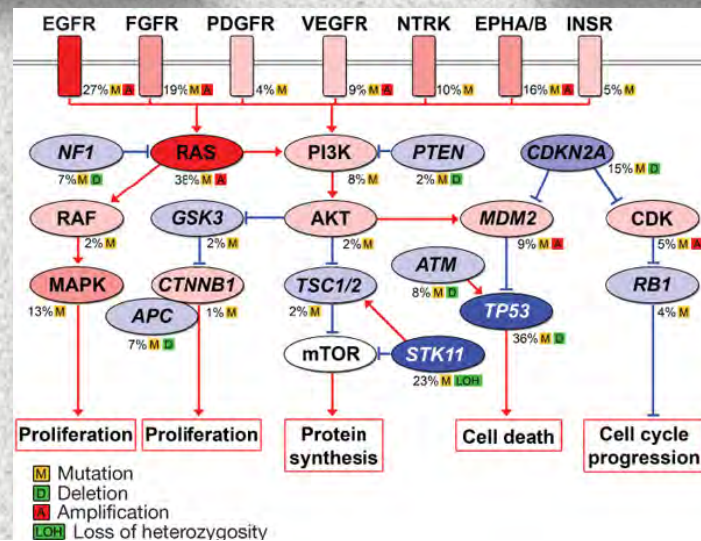
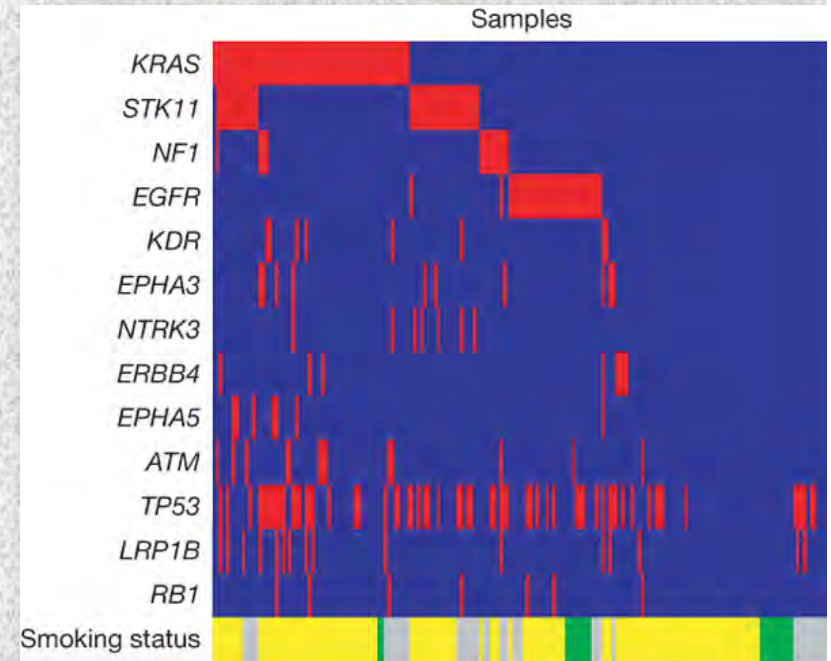
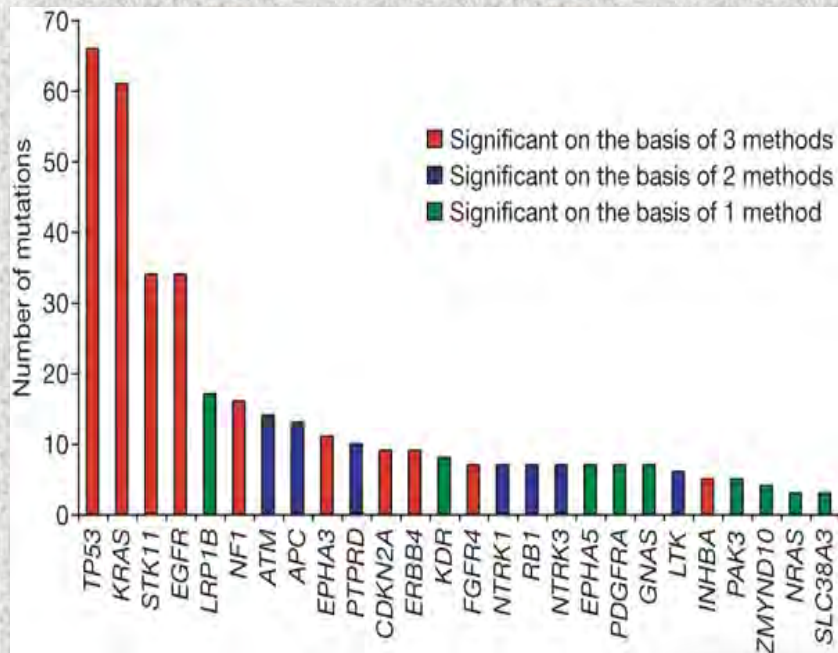


Altérations génomiques dans les différents types de cancer du poumon

Seidel Sc Translat Med 2013



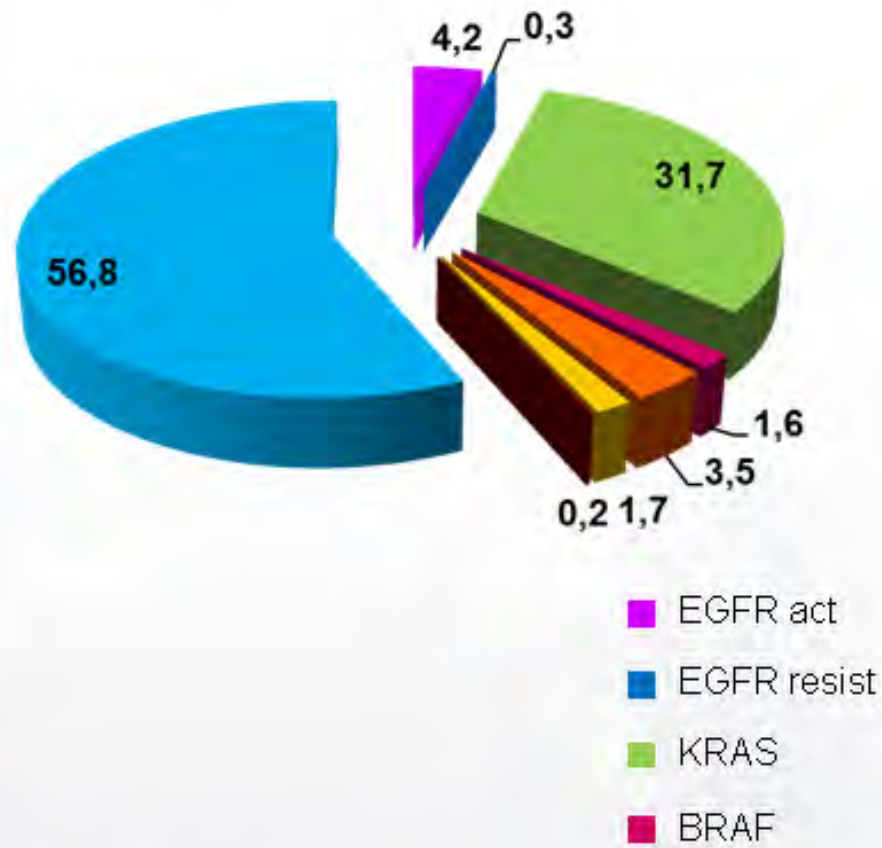
- Genes mutés dans l'adénocarcinome pulmonaire
- Exclusion mutuelle des différentes mutations géniques
- Mutations sur des voies de transcription spécifique



Ding Nature 2008

Fréquence des altérations génétiques

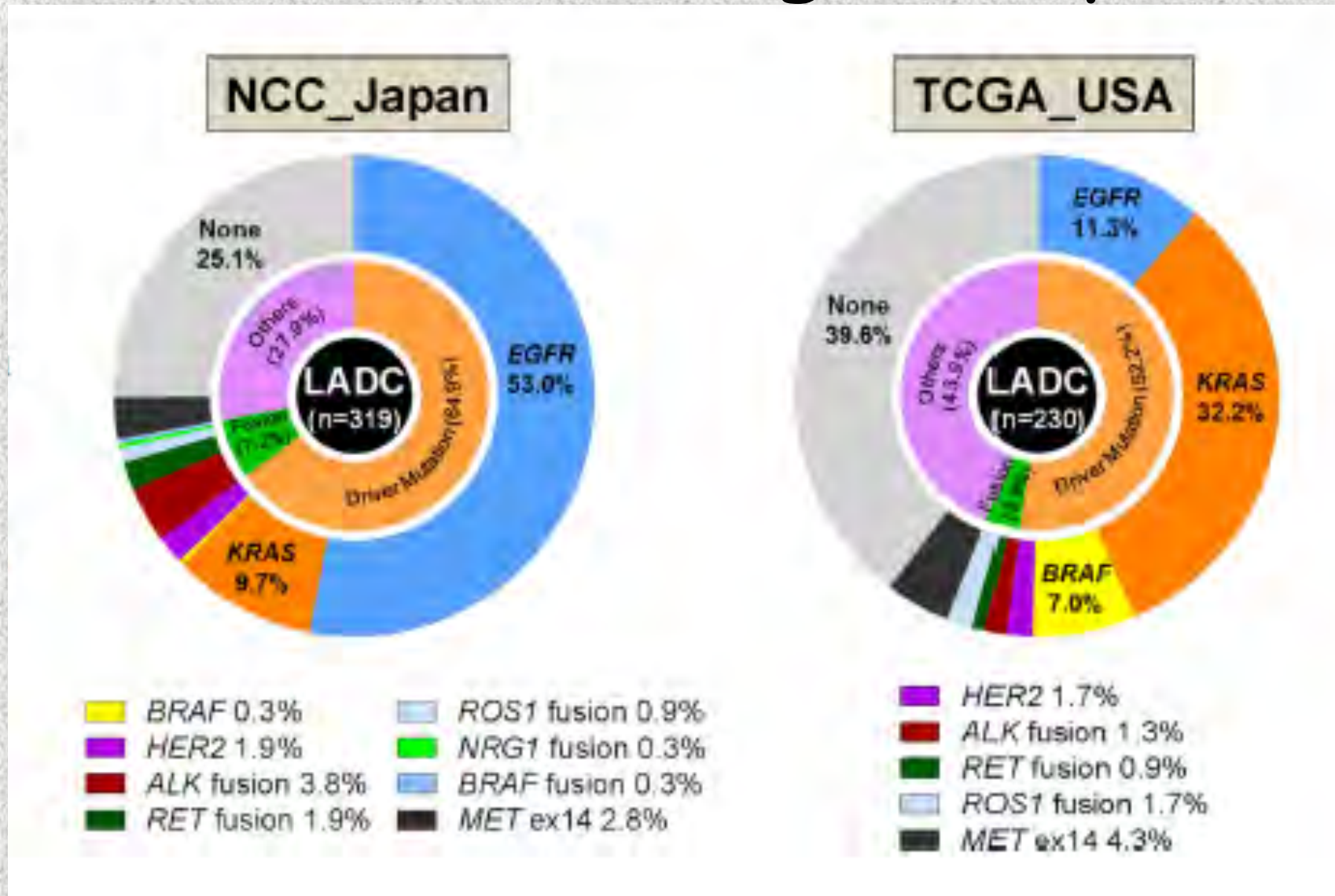
Smoking



Non smoking



Fréquence des altérations génétiques





résistantes



T790M (50%)*
 D770_N771 (ins NPG)
 D770_N771 (ins SVQ)
 D770_N771 (ins G), N771T
 V769L
 S768I

D761Y
 (<1%)

(5%)

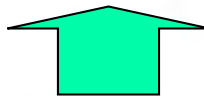


G719C
G719S
G719A
 V689M
 N700D
 E709K/Q
 S720P
 (5%)

ΔE746-A750
 ΔE746-T751
 ΔE746-A750 (ins RP)
 ΔE746-T751 (ins A/I)
 ΔE746-T751 (ins VA)
 ΔE746-S752 (ins A/V)
 ΔL747-E749 (A750P)
 ΔL747-A750 (ins P)
 ΔL747-T751
 ΔL747-T751 (ins P/S)
 ΔL747-S752
 ΔL747-752 (E746V)
 ΔL747-752 (P753S)
 ΔL747-S752 (ins Q)
 ΔL747-P753
 ΔL747-P753 (ins S)
 ΔS752-I759
 (45%)

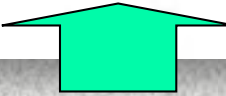
V765A
T783A
 (<1%)

L858R (40-45%)
 N826S
 A839T
 K846R
 L861Q
 G863D
 (40-45%)



activatrices

Mutations EGFR



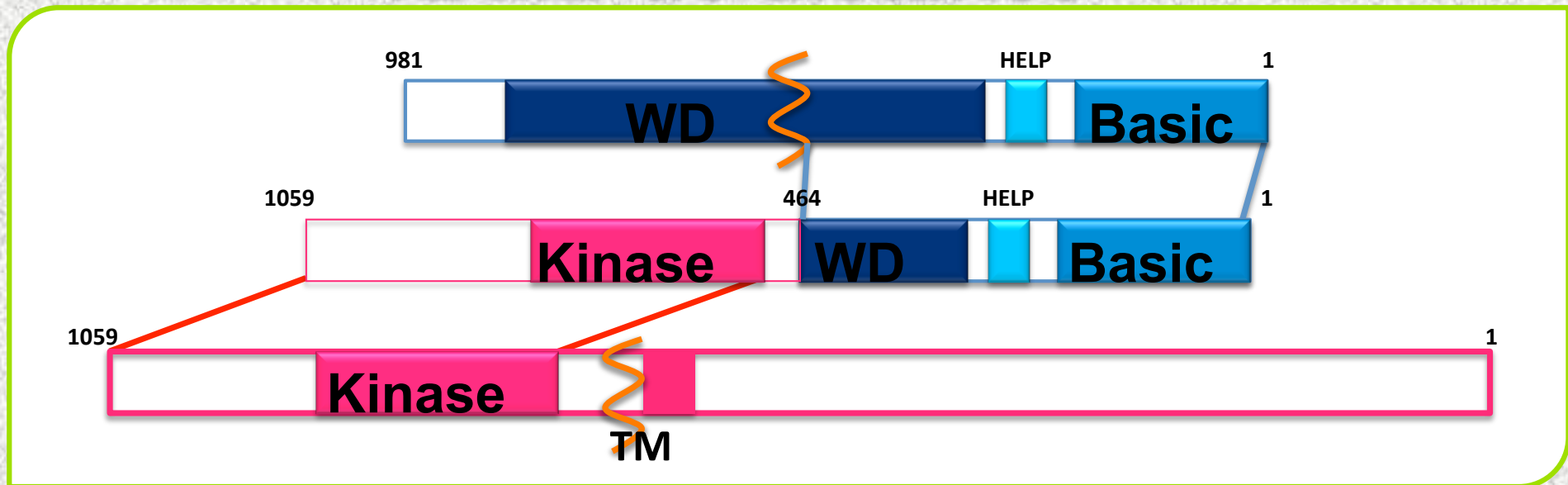
ALK-EML4 5 %

inv (2) (p21;p23)

- Diversité des points de cassure EML4
EML4 variant **ALK constant**
- Autres partenaires TFG, KIF5B, PTPN3
- Patients jeunes
- Non fumeurs
- Femmes
- Mutuellement exclusif
- **Taux de réponse objective crizotinib 74 %**

Translocation EML4-ALK dans CBNPC inv (2) (p21;p23)

12 MB de distance



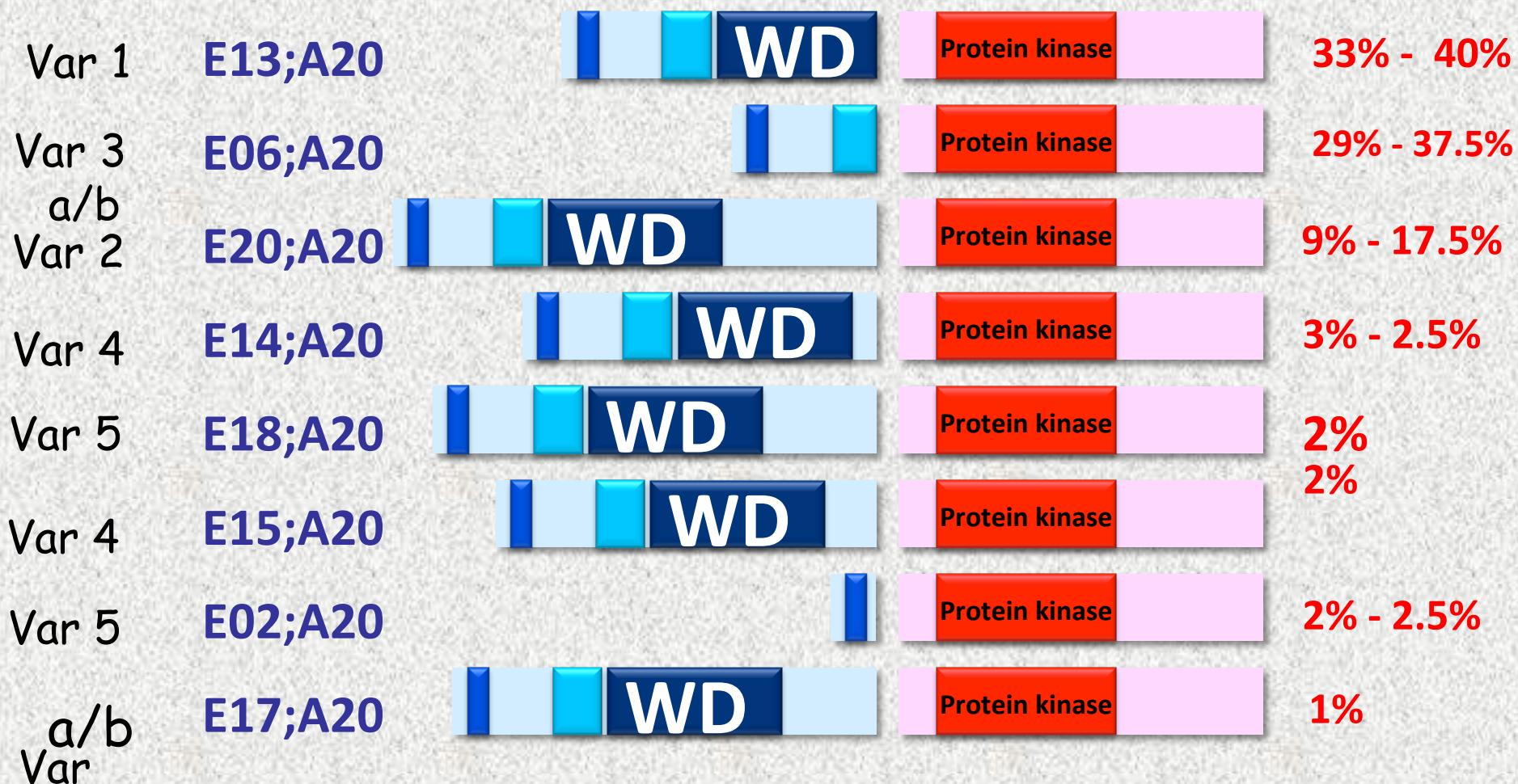
- EML4 ; echinoderm-microtubule-associated protein-like 4 : domaine basique N-terminal, domaine hydrophobe d'association avec les microtubules (HELP) ; domaine de répétition WD nécessaire aux interactions protéiques
 - **ALK : Anaplastic Lymphoma Kinase**
- Fusion EML4-**ALK**: le domaine basique de EML4 essentiel à la dimérisation de la protéine de fusion et à son activation

Les différentes translocations dans CBNPC inv (2) (p21;p23)

diversité de la région de cassure EML4

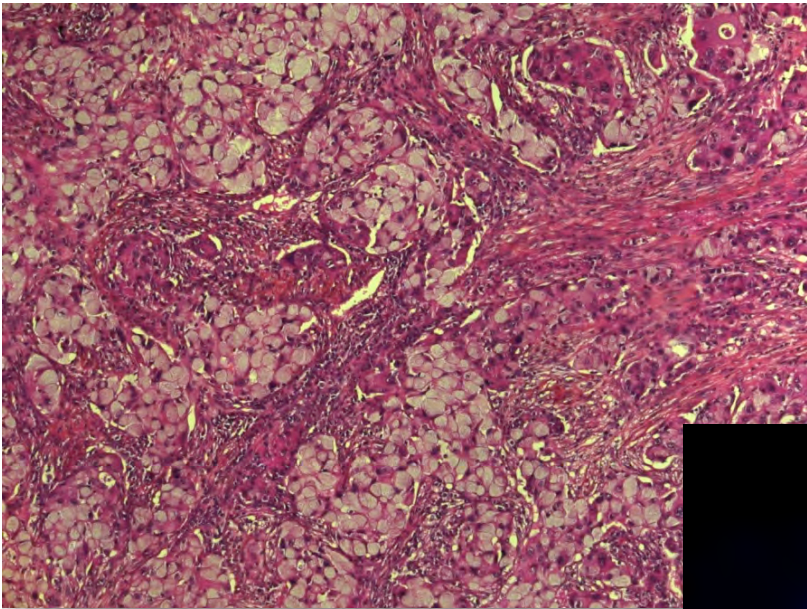
EML4 variant

ALK constant

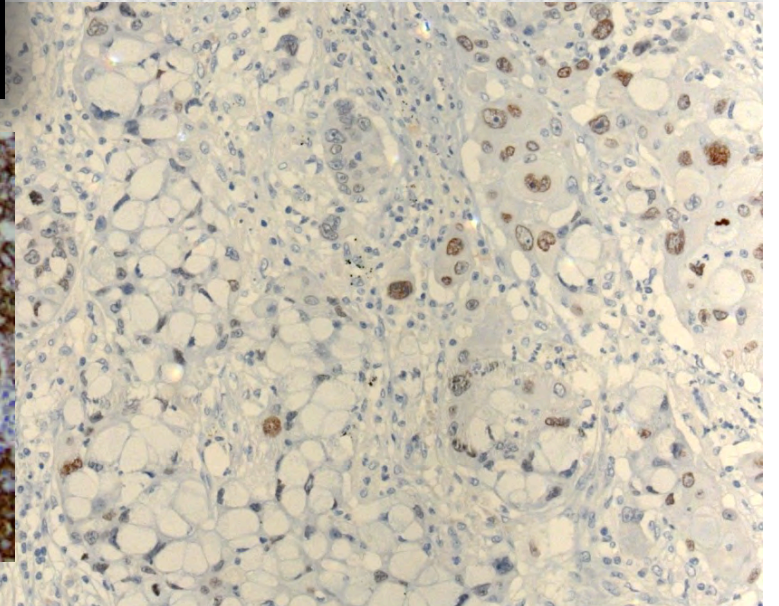
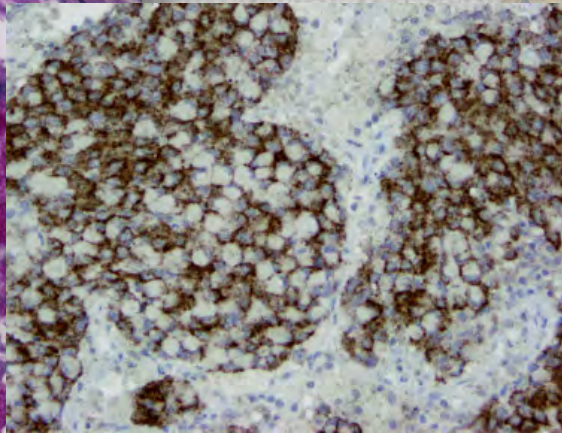
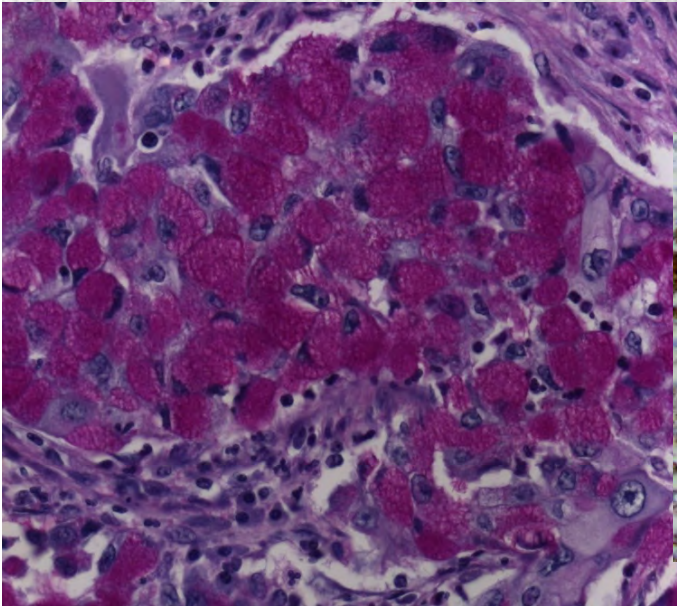
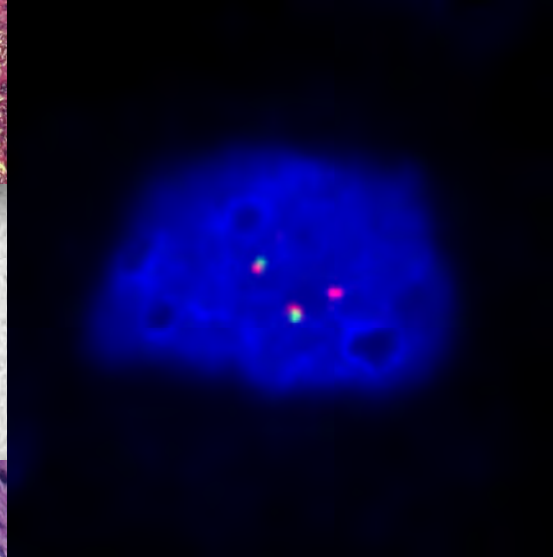
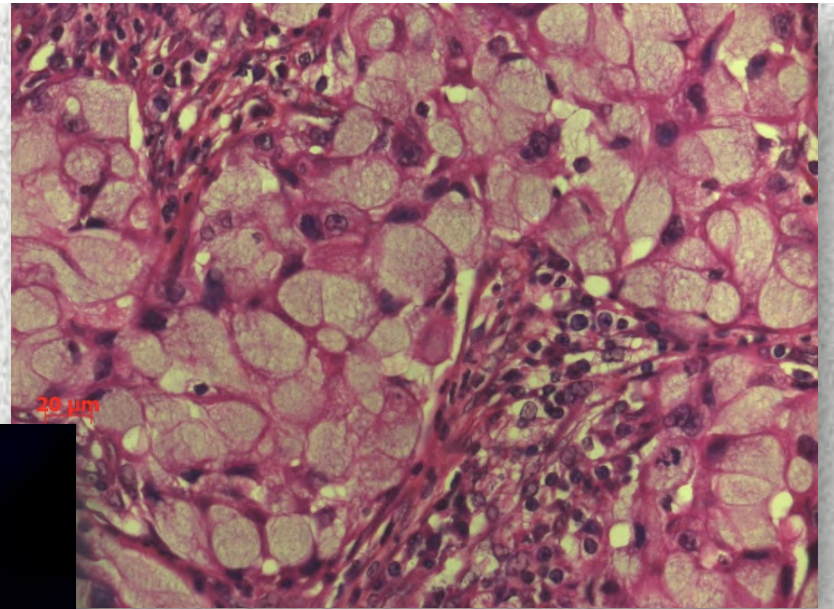


 Super hélice  Help domain

Takeuchi K *et al.* Nature Medicine 2012;18:378-81
Sasaki T *et al.* Eur J cancer 2010;46:1773-80

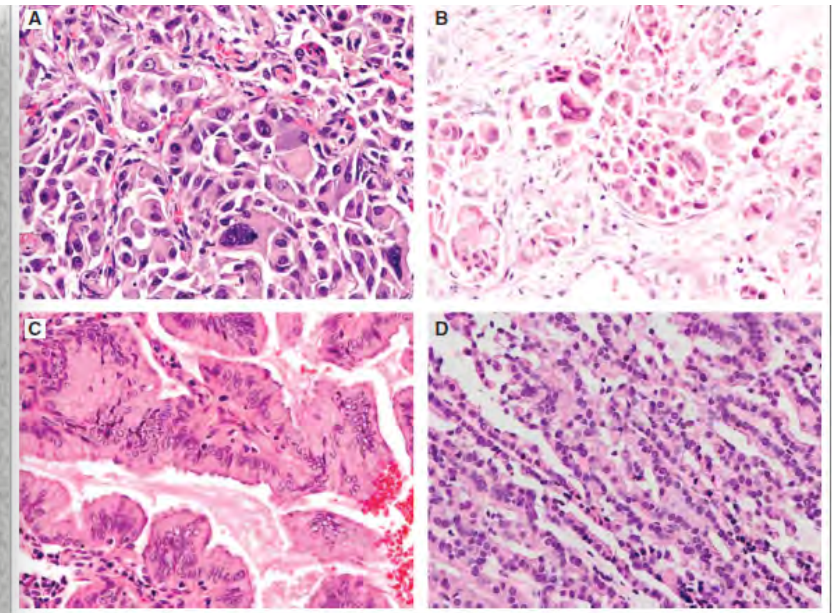
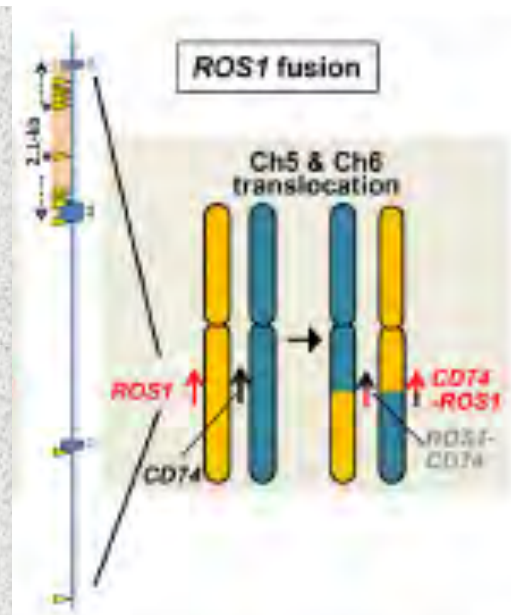


WT EGFR
WT KRAS

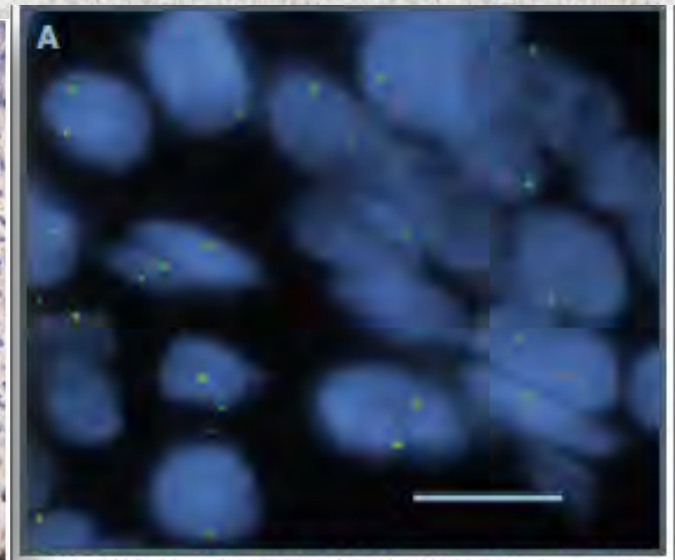
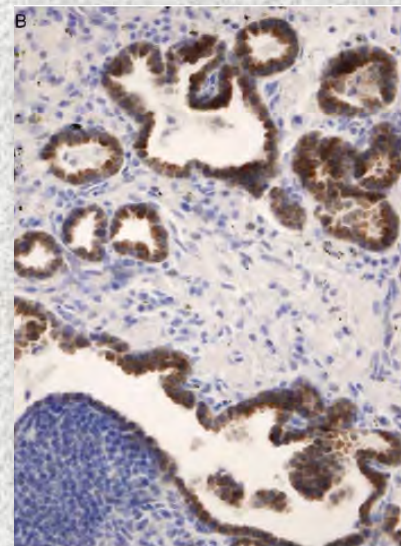


ROS1

1-2 %



Réarrangement ch5 ch6
Différents partenaires
Patients jeunes
Non fumeurs
Mutuellement exclusif
Taux de réponse objective
Crizotinib 80%



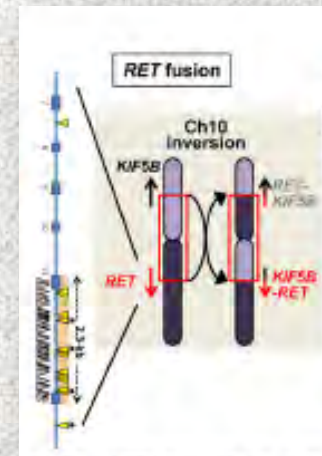
Immunohistochomie **Mab D4D6**
FISH

Bergethon et al JCO 2012

Autres réarrangements actionnables

- RET

- différents partenaires
- 1-2 % (2,52% *Degay Oncotarget 2017 in WT*)
- Fumeur/non fumeur
- ADC, femme, # âge
- Vandetanib

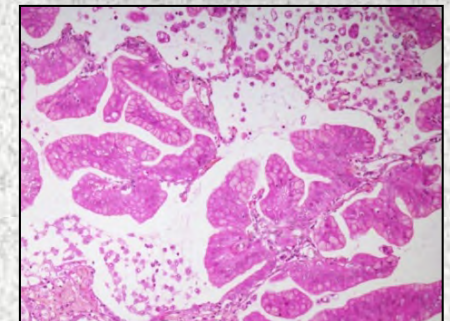
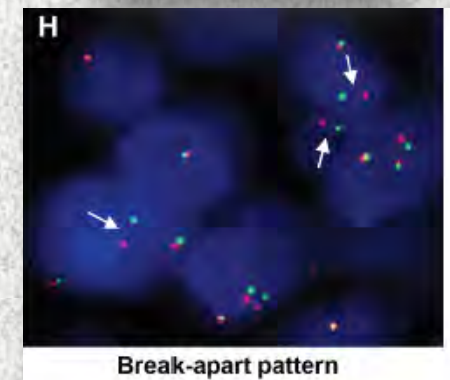


- NTRK1

- 1-3 %, ADC, fumeurs
- famille de gènes, autres organes
- TT? LOXO101

- NRG1

- femme, non fumeuse, mucineux 8-27 %,
 - Plusieurs partenaires
- voie HER2-HER3 pan TKI



BRAF 3%

- Braf V600 E 50 %
 - Non fumeur
- Braf non V600E 50%
 - fumeur
- Mutuellement exclusif
- **Dabrafenib+Trametinib**
(antiMEK) V600 E
Vemurafenib

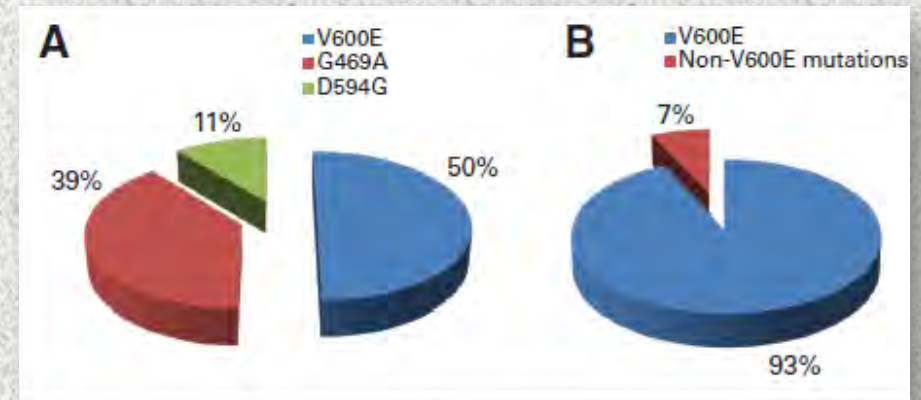
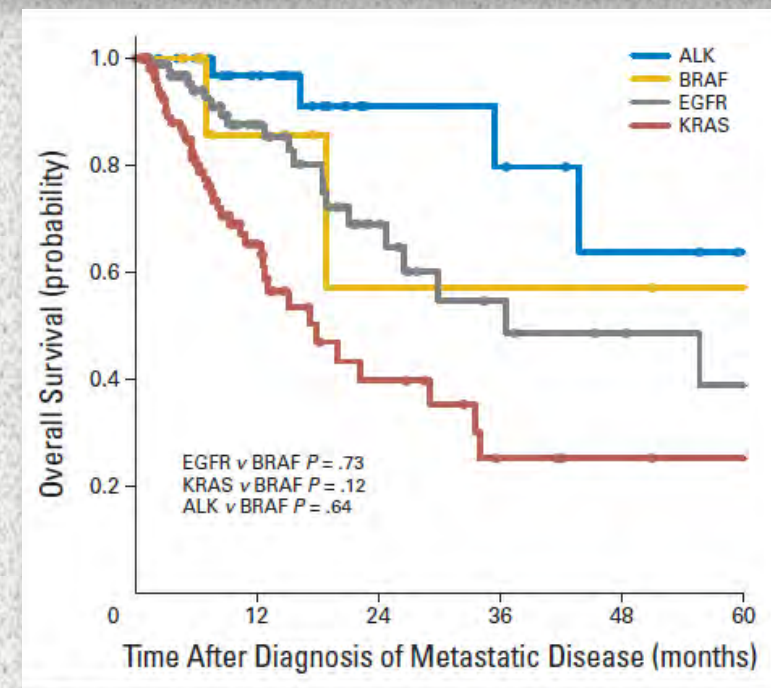
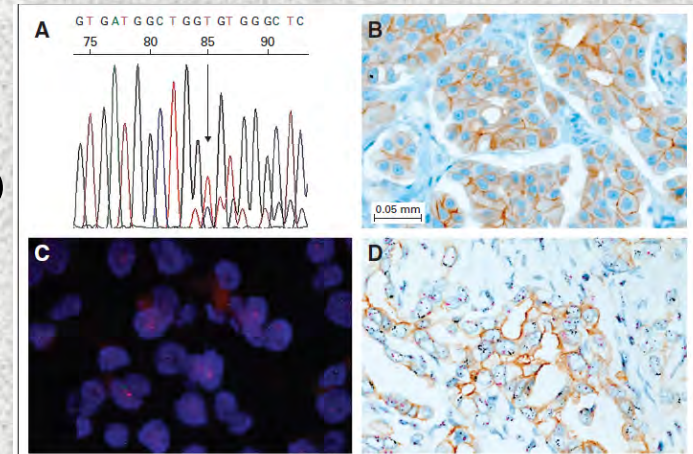


Fig 1. Relative frequency of *BRAF* mutations in (A) lung adenocarcinoma versus (B) melanoma.



Mutations HER2 3 %

- Insertions of exon 20: 3 a 12 pdb
 - 775 to 881: 83
 - Insertion of 3 pdb 8
- Mutations L755S et L776C 8
- femme, non fumeuse, 60 ans, adénocarcinome, multimétastatique, nodules avec excavation, pronostic péjoratif
- Trastuzumab, TDM1
- Lapatinib, Neratinib,



KRAS

25%



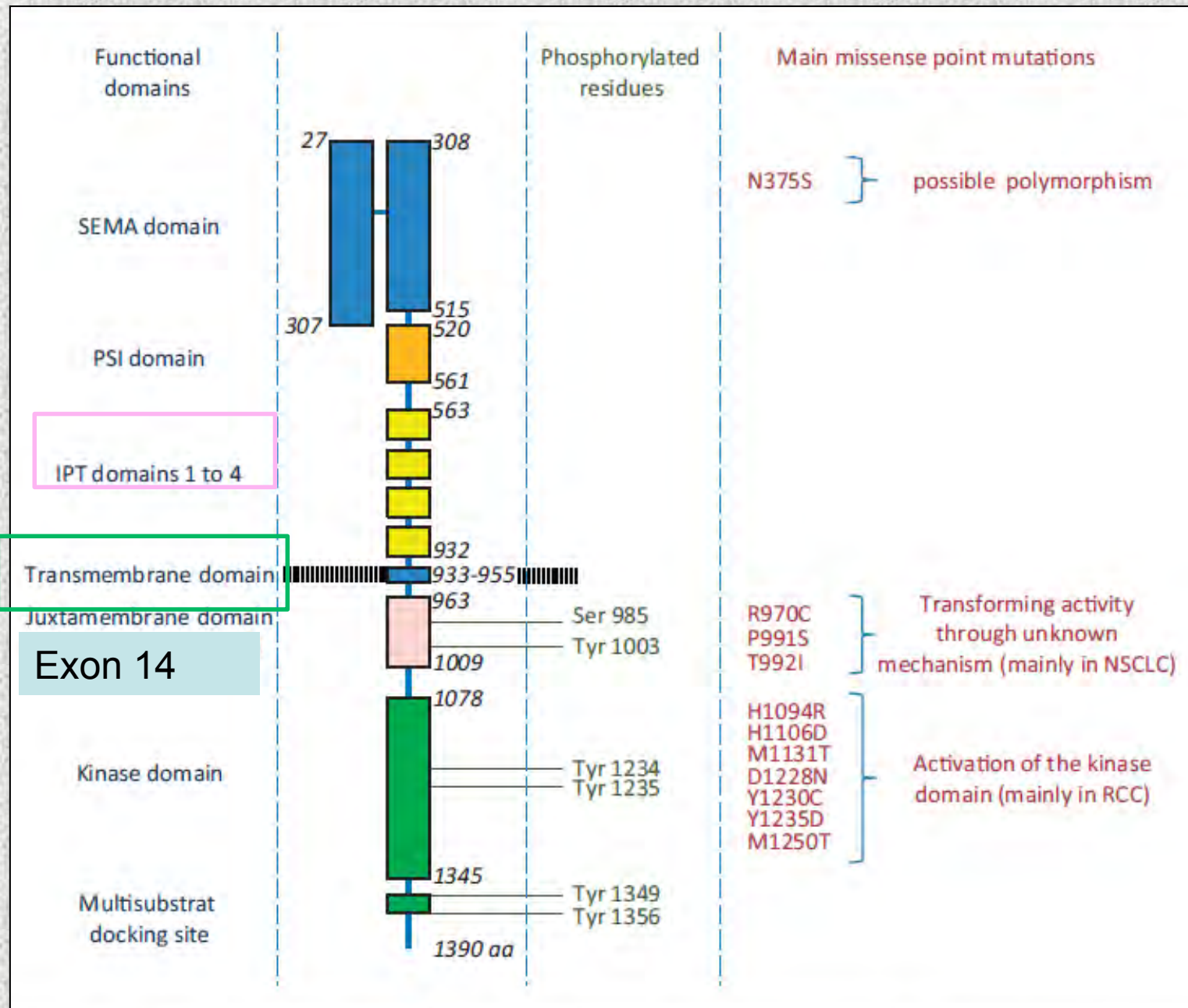
- situé ch 12 et codant GTPase voie MAPKinase
- Mutations codon 12, rares codons 13, 10, 61
- Transversions (pyrimidine<--->purine)
 - G vers T: G12C fumeurs
- Transitions (pyrimidine/pyrimidine et purine/purine) non fumeurs et CE
- Type Mucineux G12D G12V
- Mauvais pronostic
- Chimiorésistance?
 - AntiMEK selumetinib
 - Immunothérapie?

KRAS hétérogénéité moléculaire

- Comutations TP 53 42 %
 - Augmentant la prolifération cellulaire, réponse immune, taux de mutations +++, réponse ICI
- Comutations STK11/LKB1 29%
 - Suppression de la réponse immune, résistance ICI, KEAP1, inhibiteur HSP90
- Comutations CDKN2A/B
 - Mucineux, TTF1 faible (NKX2-1), HNF4A, voie mTORC1 <

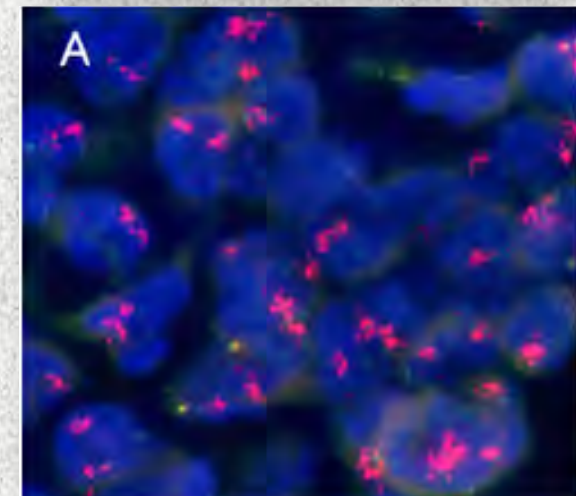
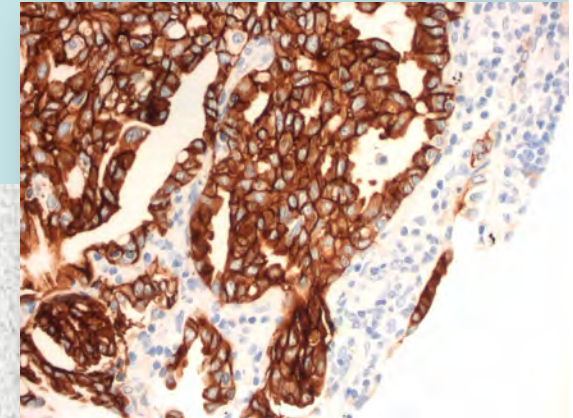
Skoulidis Cancer Discovery 2016

Structure Gène MET Ch 7

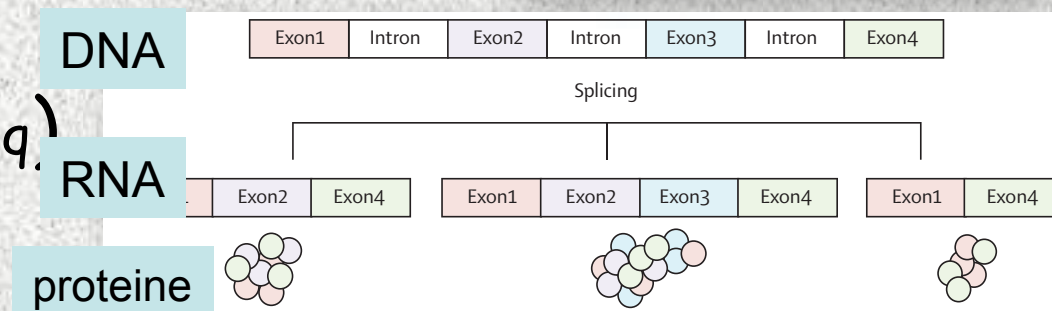


Ligand
HGF

MET



- Surexpression 17 - 70 %
 - Phase III negative onartuzumab
- Amplification
 - 4 %, polysomy#amplification
 - Crizotinib
 - Resistance to TKI EGFR
- Mutations exon 14
 - 4% NSCLC (Adc and ADSq)
 - Sarcomatoid 5-22%
 - Crizotinib, Cabozantinib, Capmatinib



PIK3CA 1%

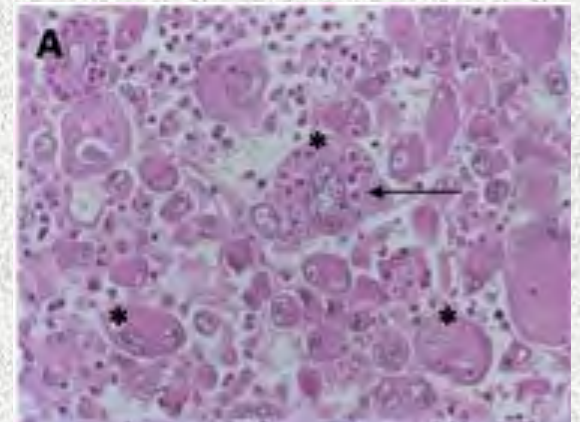
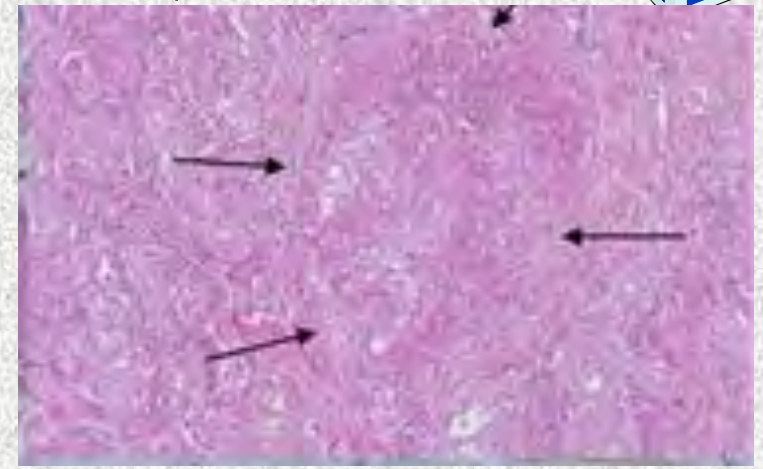
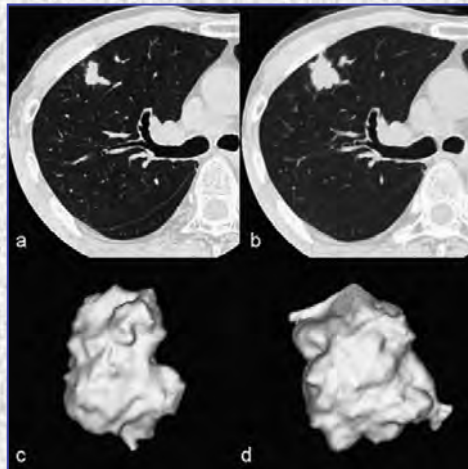
- Kinase intracytoplasmique
- Pas de phénotype clinique particulier
- Squameux et ADC
- Résistance mutation EGFR
- TT?

Carcinome sarcomatoïde sarcoma-like à cellules fusiformes ou géantes



- 1 %

4♂/1♀



Carcinome pléomorphe

Carcinome à cellules fusiformes

Carcinome à cellules géantes

Carcinosarcome Blastome pulmonaire

Inflammation, PDL1

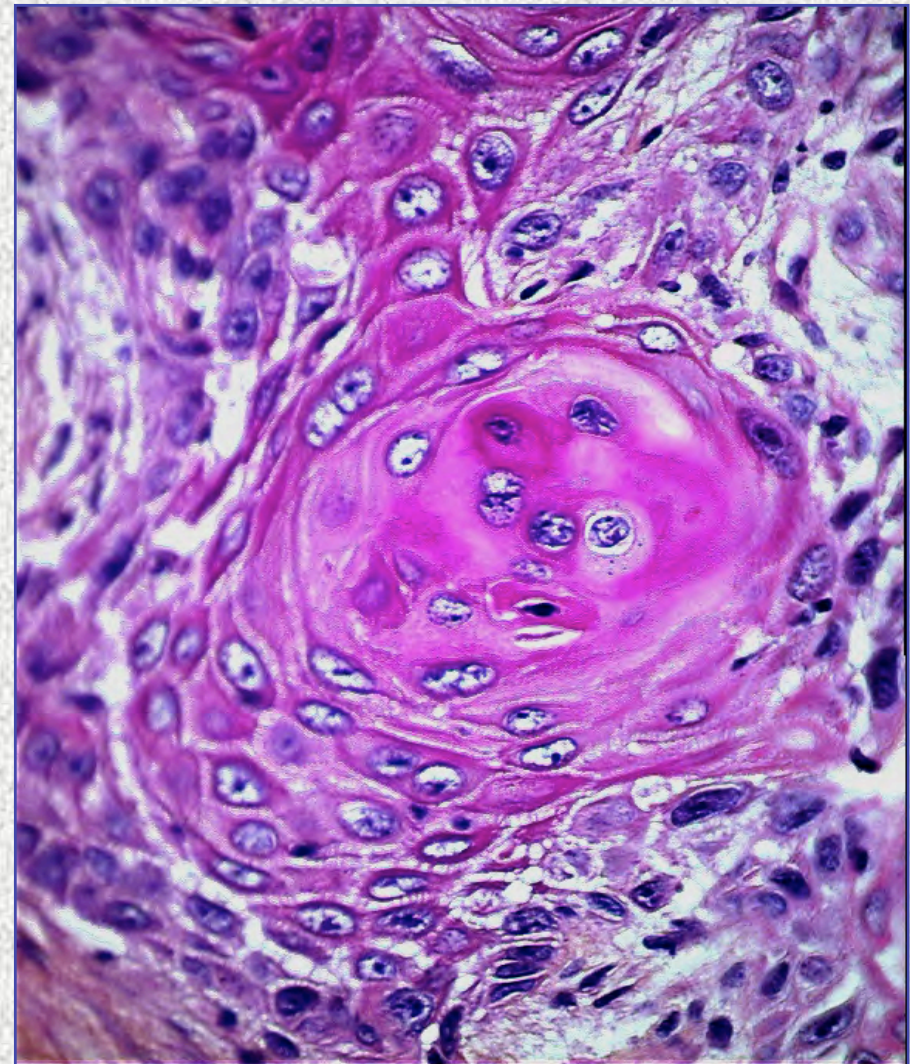
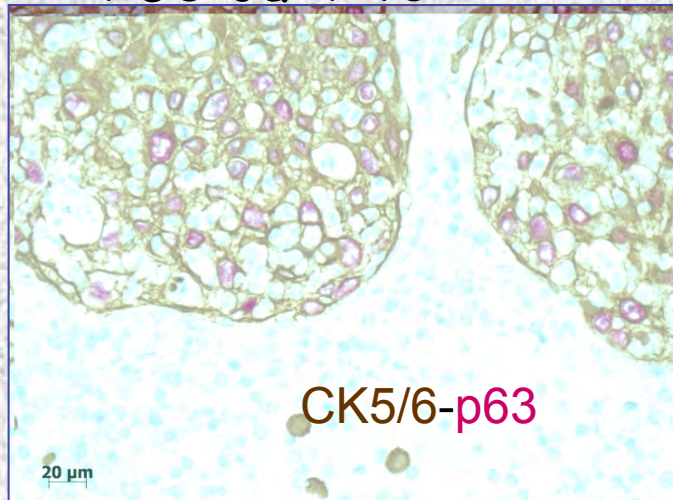
Mutations RAS, rares EGFR, TP53, STK11 et exon 14 MET

Carcinome épidermoïde

carcinome basaloïde



- Central ou périphérique
- Kératinisation
- Ponts d'union
- IHC
 - CK basales: CK5/6
 - P63 ou P40



Hétérogénéité moléculaire

fréquence des mutations somatiques/type tumoral

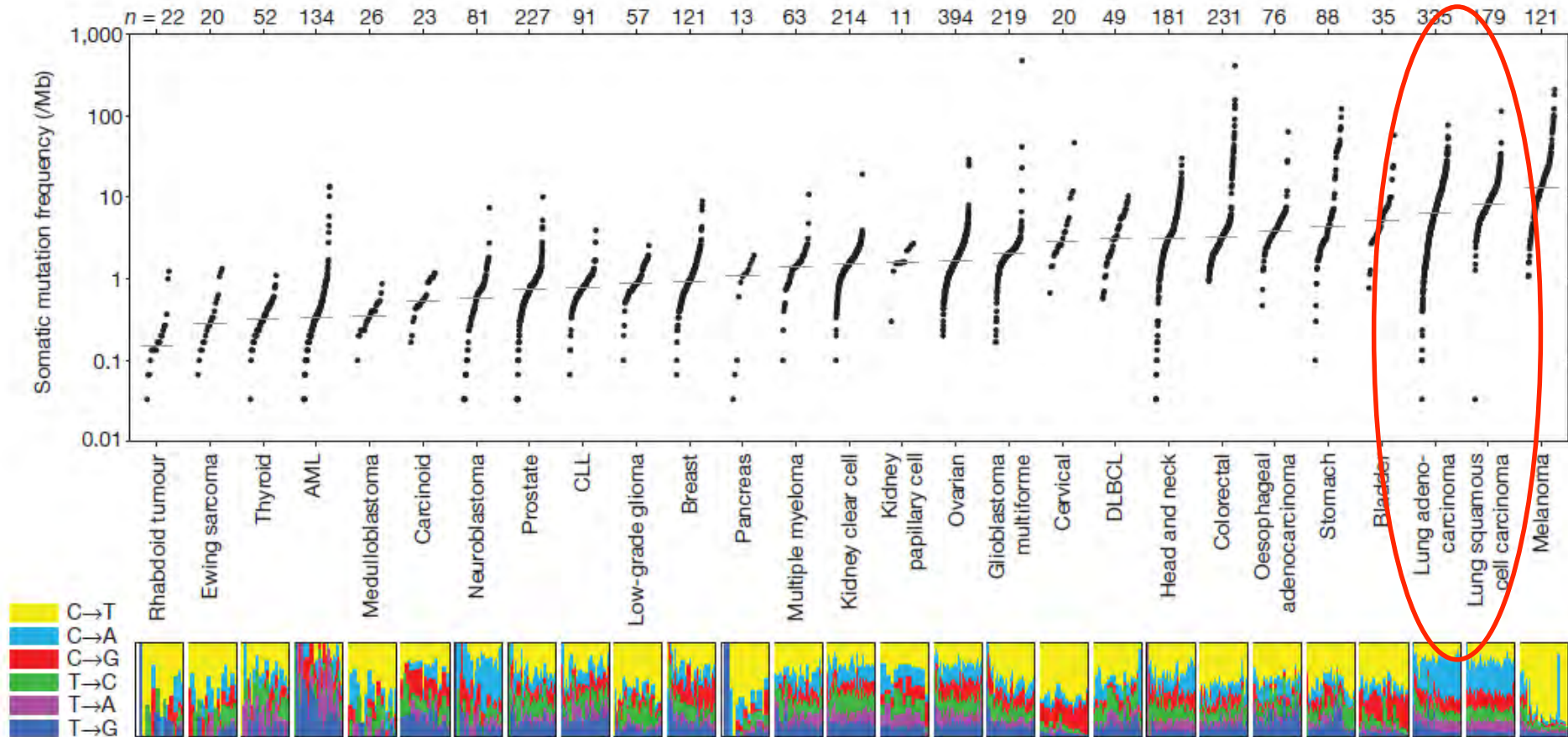
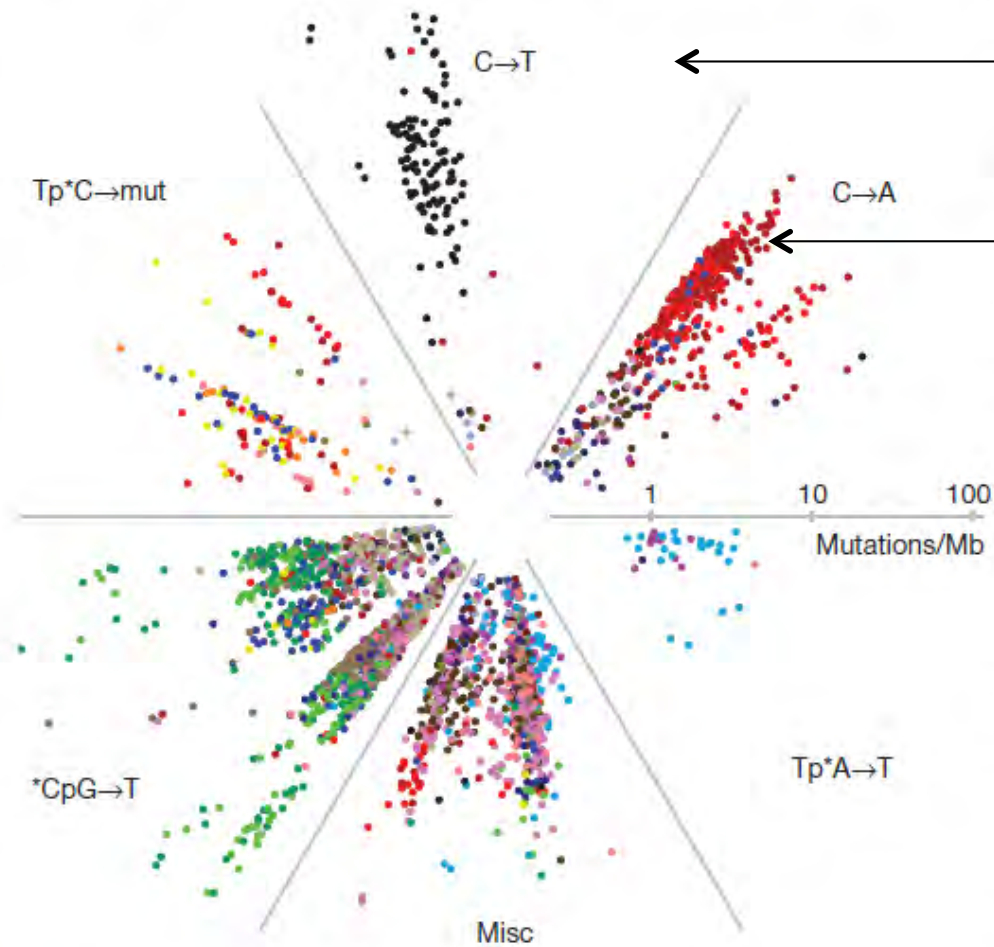


Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour-normal pairs. Each dot corresponds to a tumour-normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens

such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.



Melanome

Cancer pulmonaire

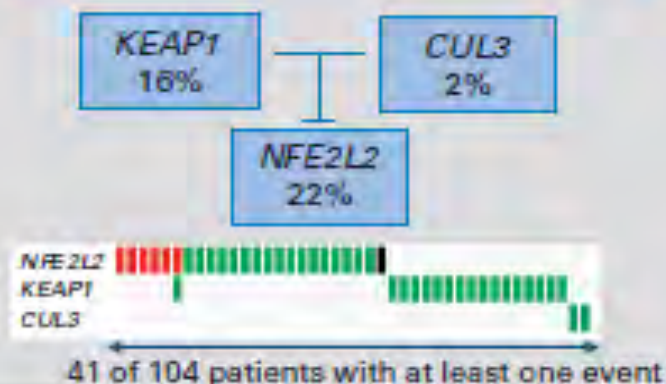
Mutations type/cancer

Mécanisme Biologique

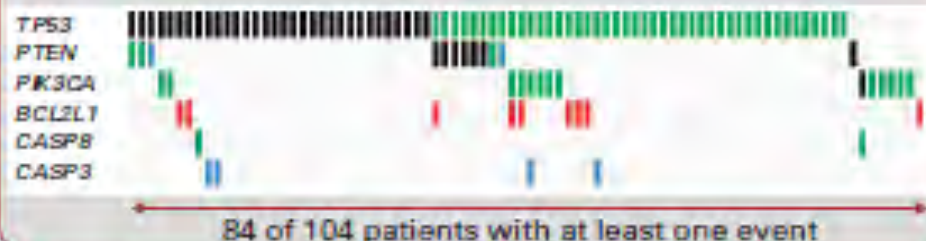
Carcinogénèse

- | | |
|------------------------------|--------------------------------|
| ● AML | ● Low-grade glioma |
| ● Bladder | ● Lung adenocarcinoma |
| ● Breast | ● Lung squamous cell carcinoma |
| ● CLL | ● Multiple myeloma |
| ● Colorectal | ● Medulloblastoma |
| ● Carcinoid | ● Melanoma |
| ● Cervical | ● Neuroblastoma |
| ● DLBCL | ● Ovarian |
| ● Oesophageal adenocarcinoma | ● Pancreas |
| ● Ewing sarcoma | ● Prostate |
| ● Glioblastoma multiforme | ● Rhabdoid tumor |
| ● Head and neck | ● Stomach |
| ● Kidney clear cell | ● Thyroid |
| ● Kidney papillary cell | |

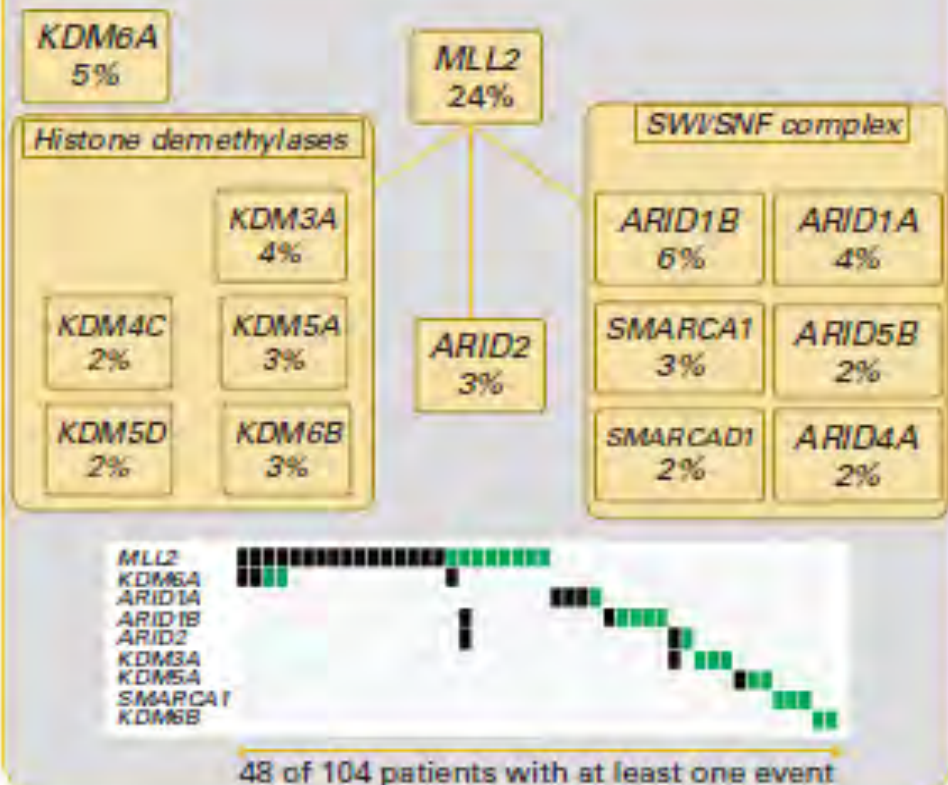
Redox stress



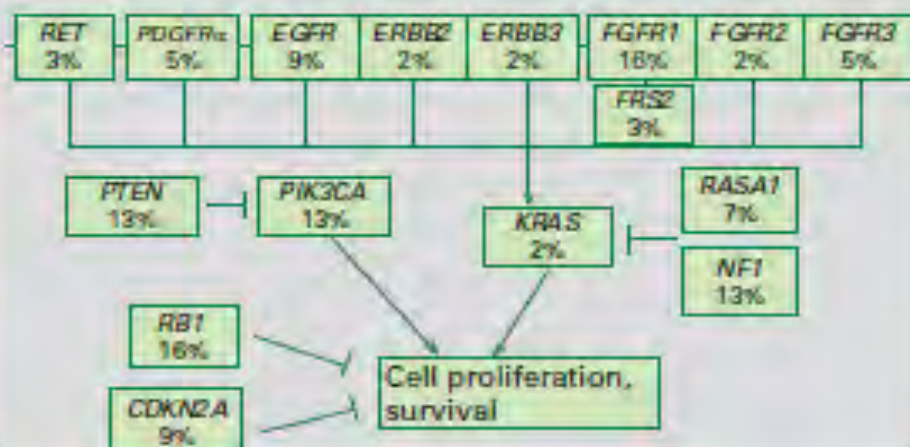
Apoptosis



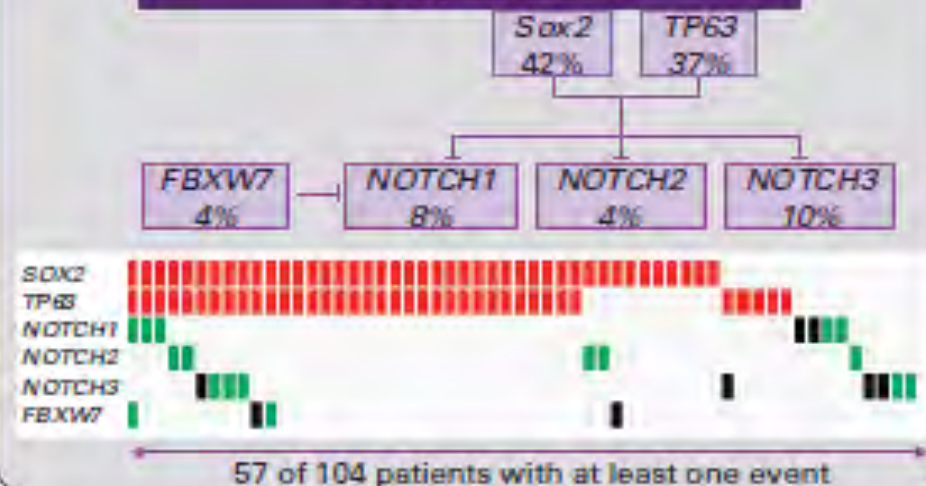
Chromatin remodelers



Cell proliferation, survival

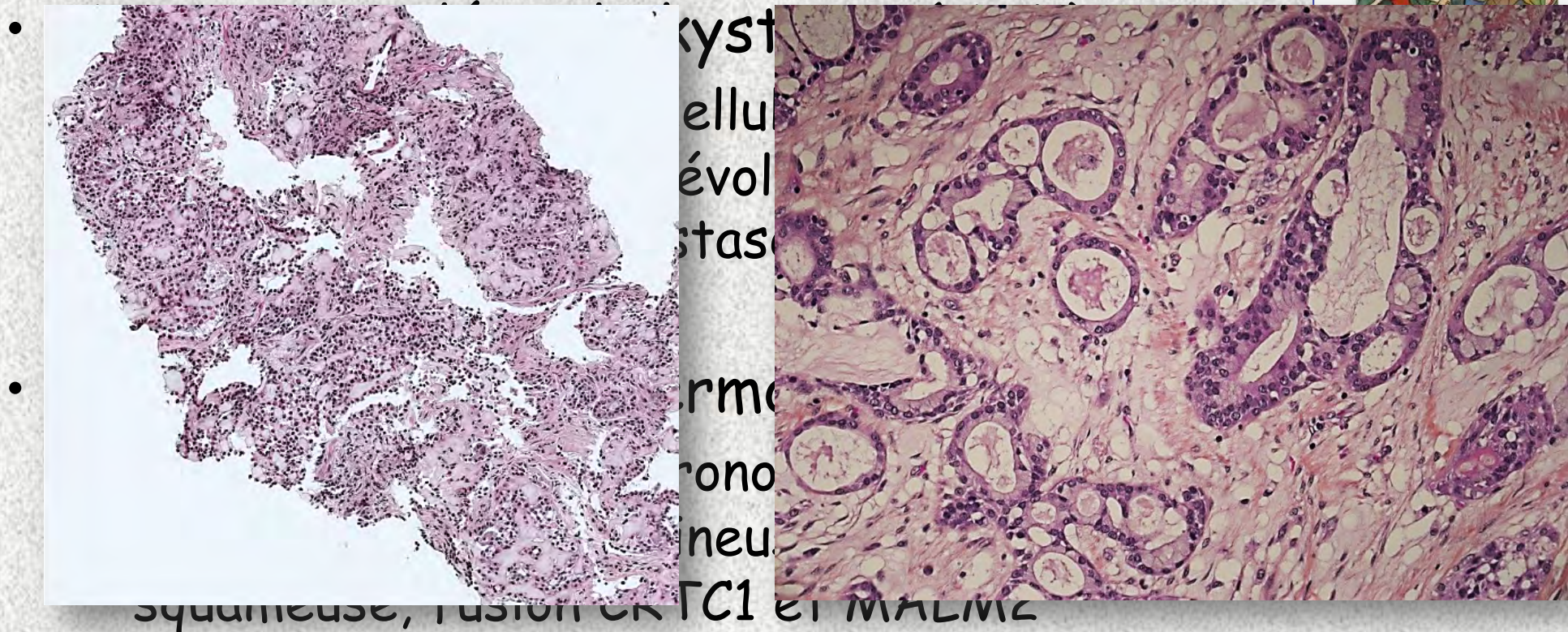


Differentiation



Tumeurs des glandes bronchiques

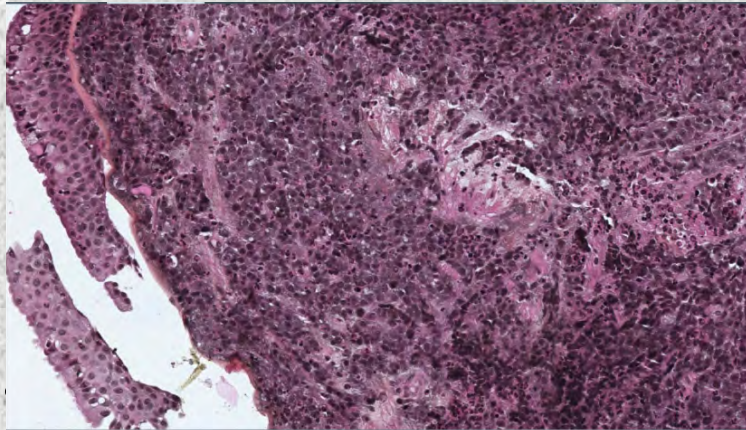
Communauté histologique et moléculaire avec les tumeurs des glandes salivaires



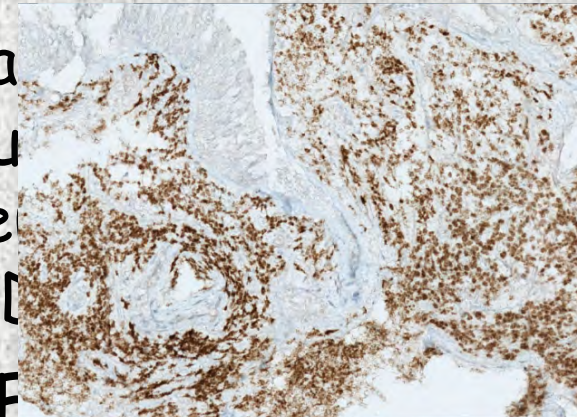
- Carcinome épithélial-myoépithélial , adénome plémomorphe

Tumeurs rares

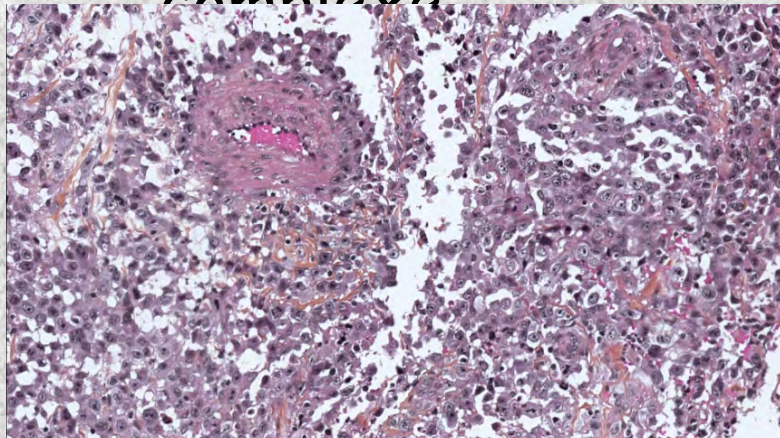
- Carcinomes NUT 1



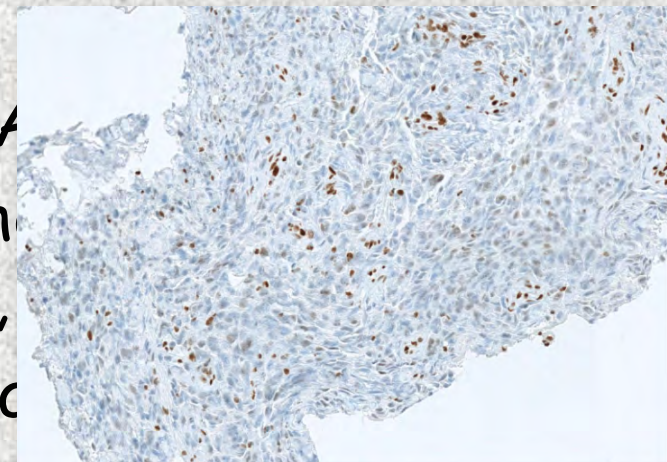
autres organes
agressif et peu
+, non fumeur
NUT et BRCA
SWI/SNF



- Mutation d'une des différentes sous unités du complexe



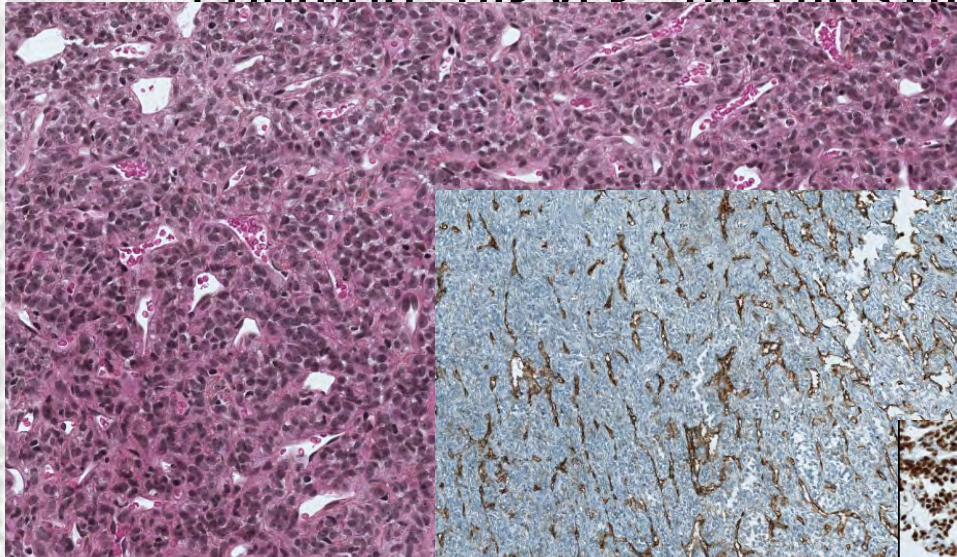
es SMARCA
r, paroi th
luminuese,
iforme, rho



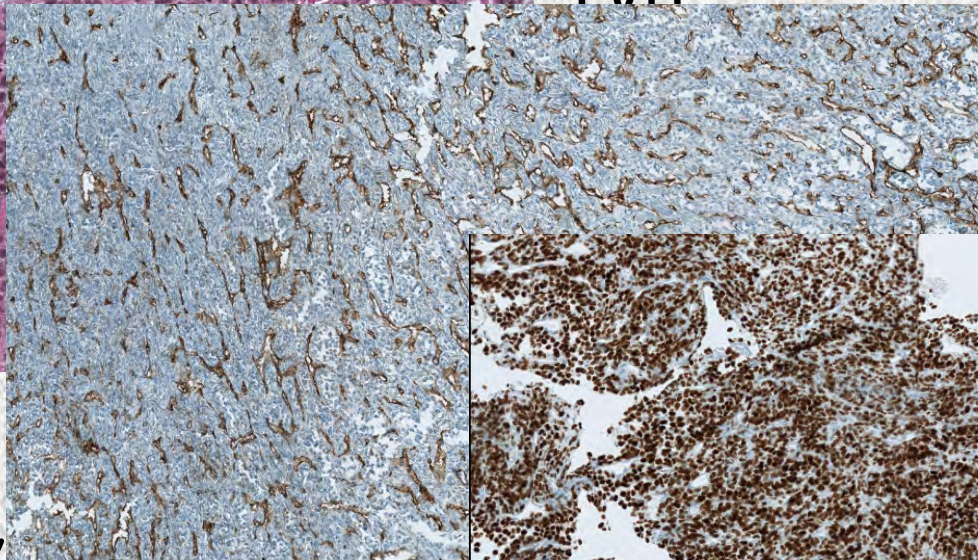
- Faible CK, CD34, SAL4, SOX2, perte SMARCA4

Tumeurs mésoenchymateuses

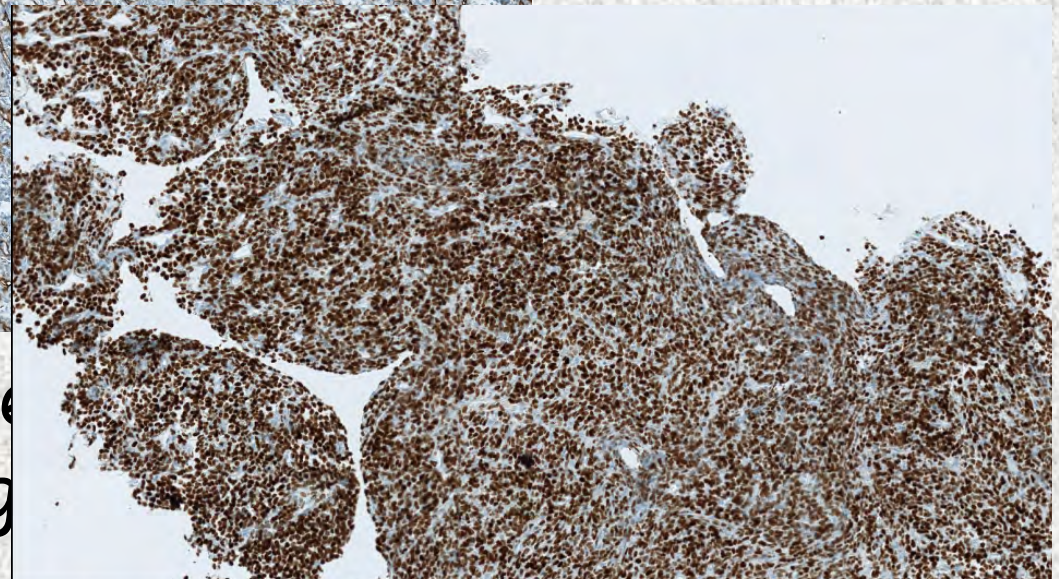
- Tumeur myofibroblastique inflammatoire
 - Poumon plèvre médiastin



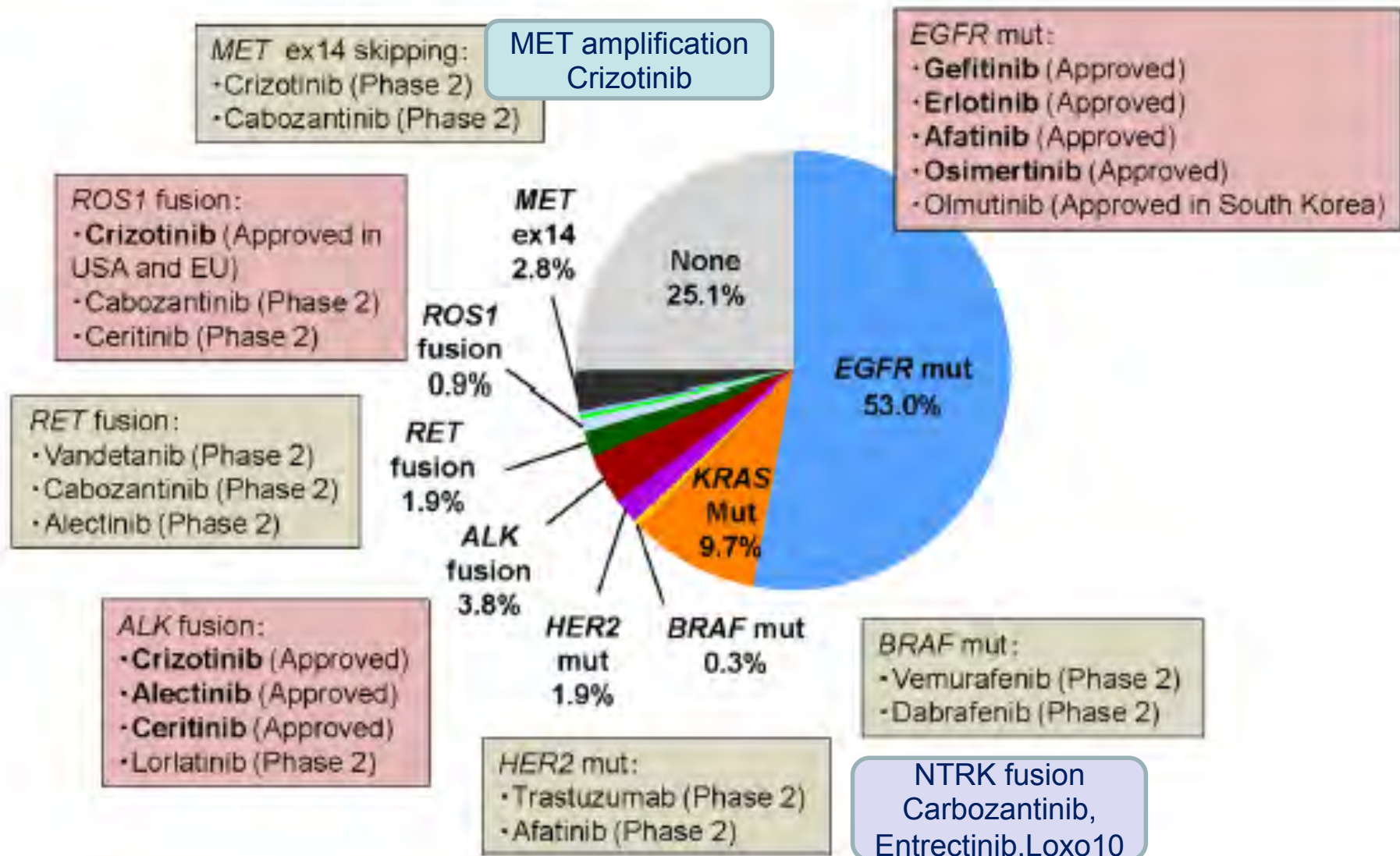
ETV6



- Sarcome
 - poumon,
- Hémangioendothéliome fibromyxoïde de bas grade
 - l'artère pulmonaire



Traitement selon les altérations moléculaires



Histologie	Altération Molaire	PDL1 status	Traitement L1	Traitement Maintenance	Traitement L2
Sq CBNPC	Na	<50%	Doublet Platine Gemcitabine/ Cisplatine Necitumumab	Necitumumab	Immunothérapie Chemothérapie Docetaxel+ Ramucirumab Afatinib
	Na	>50%	Pembrolizumab	Pembrolizumab	Doublet Platine
Non Sq CBNPC	EGFR	Na	Erlotinib+Beva Erlotinib Afatinib Gefitinib	Erlotinib+Beva Erlotinib Afatinib Gefitinib	Osimertinib Doublet Platine
	ALK	Na	Crizotinib(ROS1) Ceritinib	Crizotinib(ROS1) Ceritinib	Ceritinib Alectinib Doublet Platine
	Wildtype	<50%	Doublet Platine Pemetrexed Beva (optionnel)	Pemetrexed Beva (optionnel)	Chemothérapie Immunothérapie Docetaxel+ Ramucirumab Docetaxel+ Nindetanib Erlotinib
	Wildtype	>50%	Pembrolizumab	Pembrolizumab	Doublet Platine

Prise en charge des « biopsies »

Qualité du traitement

