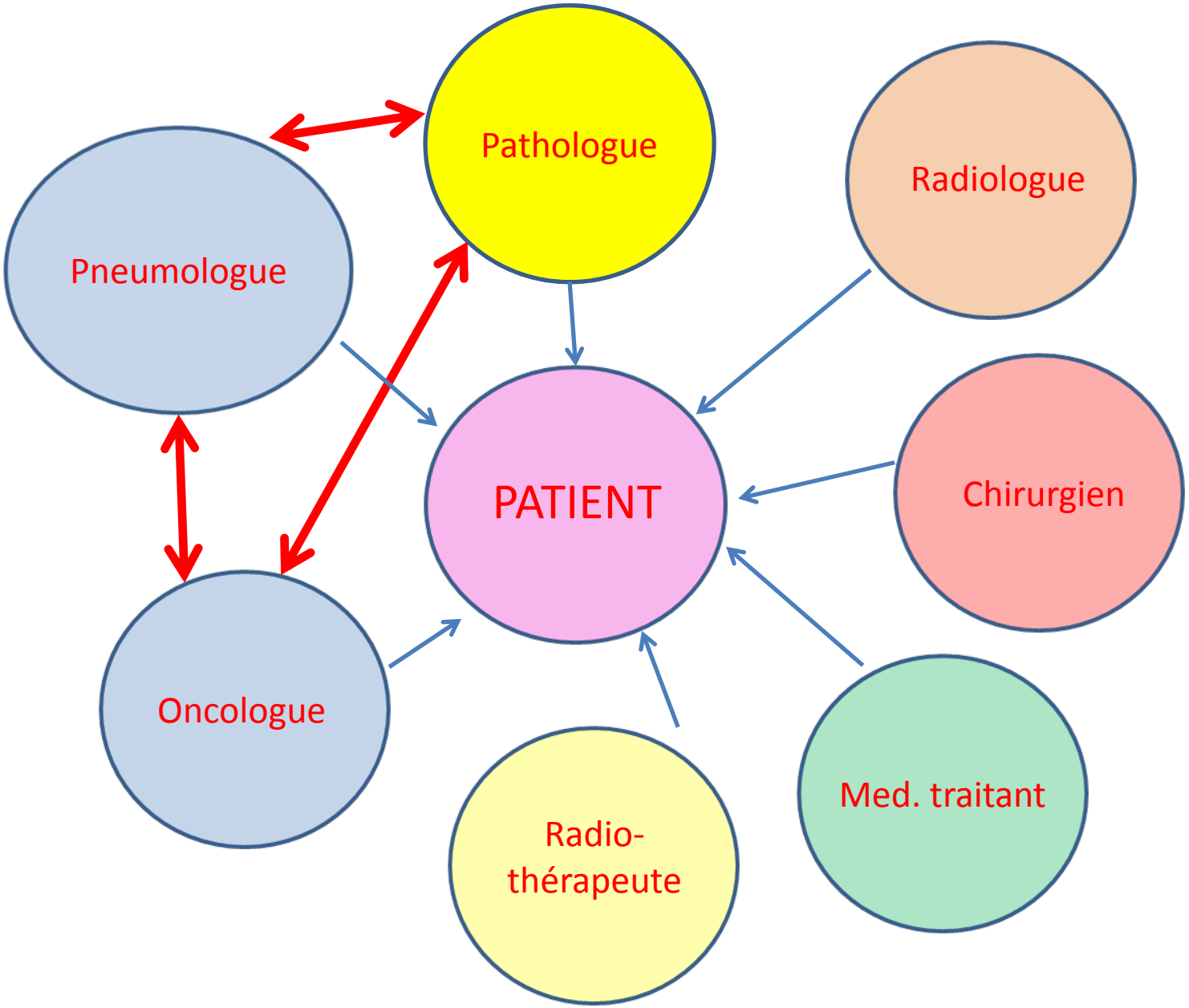
Poumon,
Alerte aux envahisseurs

Techniques moléculaires et prise en charge
~~du cancer~~ des cancers du poumon

Nicolas Mach, Service d'Oncologie, HUG


Pathologue
Radiologue
Pneumologue
PATIENT
Chirurgien
Oncologue
Radio-
thérapeute
Med. traitant

Cancer du poumon ≠envahisseur mais =Ennemi N°1

Estimated Deaths

Males			Females		
Lung & bronchus	86,220	29%	Lung & bronchus	71,080	26%
Prostate	32,050	11%	Breast	39,840	15%
Colon & rectum	26,580	9%	Colon & rectum	24,790	9%
Pancreas	18,770	6%	Pancreas	18,030	7%

Décès par cancer en 2010 aux USA:

N°2	Colon	51’370
N°3	Sein	39’840
N°4	Pancréas	36’800
N°5	Prostate	32’050
N°2-5		**128’335**
N°1	**Poumon**	**157’300**

Cancer du poumon baisse de la mortalité depuis 15 ans

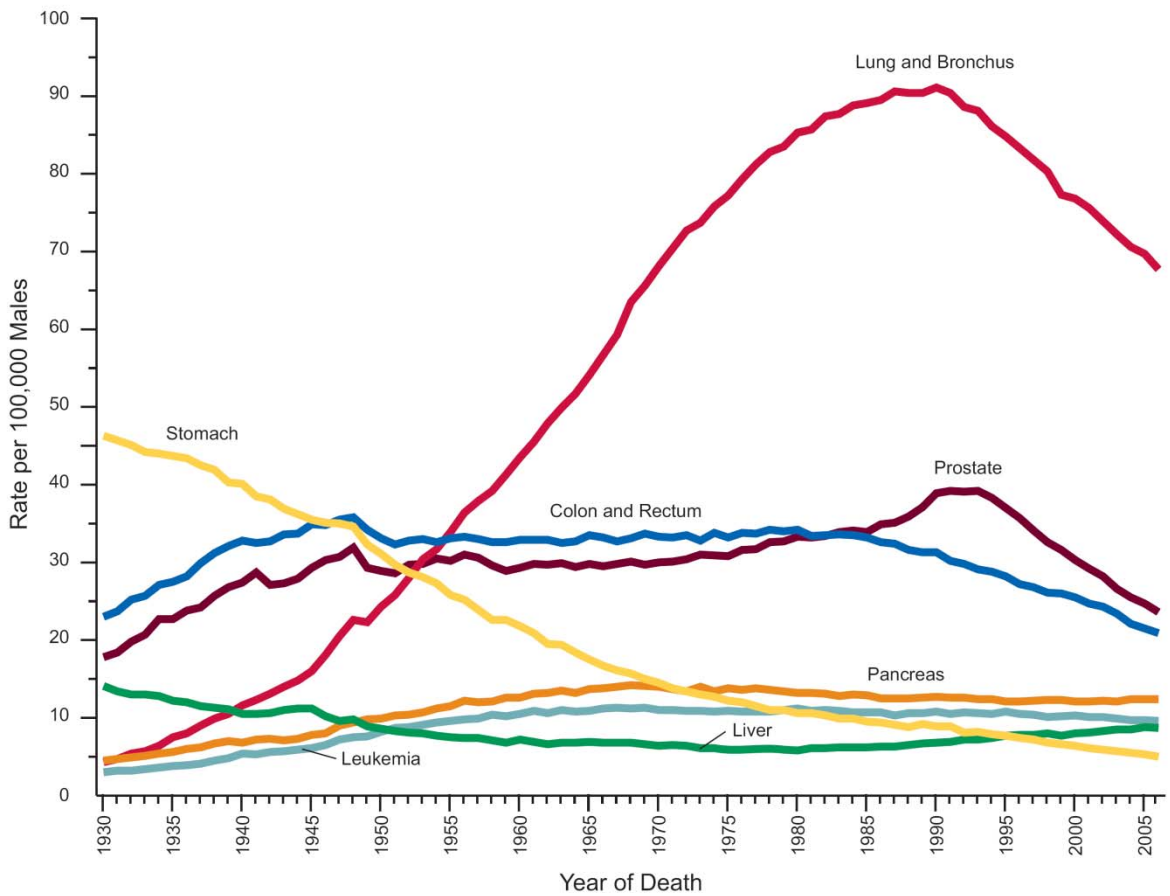
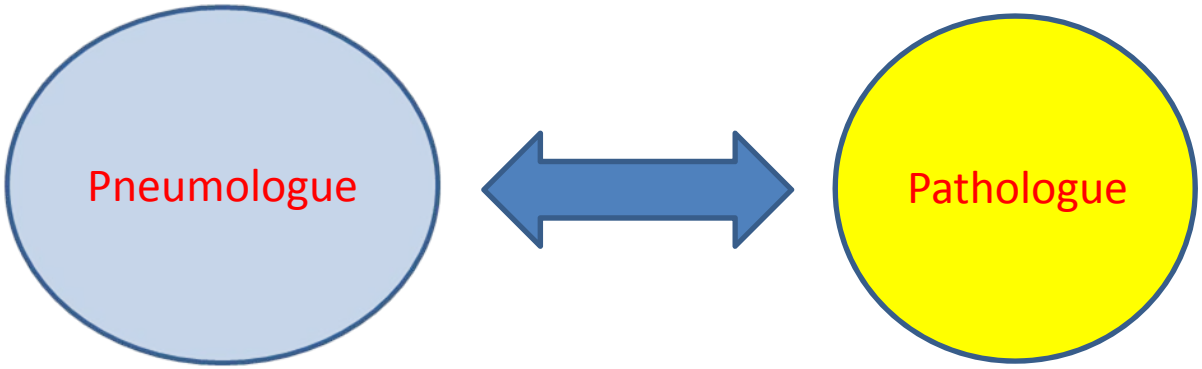


FIGURE 4. Annual Age-Adjusted Cancer Death Rates* Among Males for Selected Cancers, United States, 1930 to 2006.

Cancer du poumon Survie à 5 ans misérable

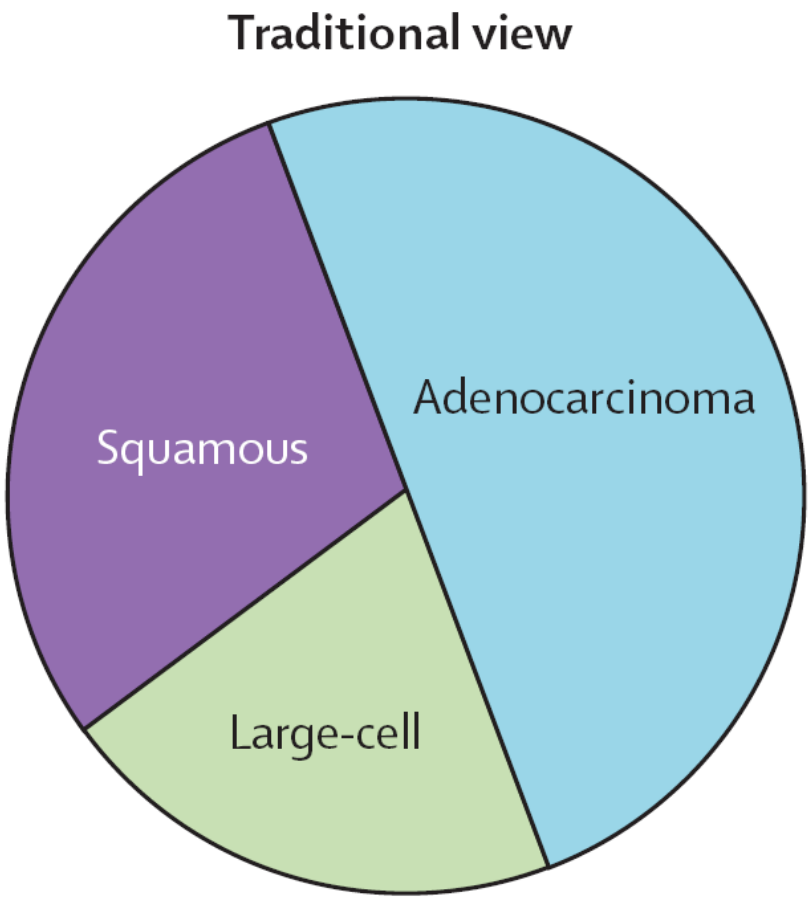
	ALL RACES		
	1975 TO 1977	1984 TO 1986	1999 TO 2005
All sites	50	54	68†
Brain	24	29	36†
Breast (female)	75	79	90†
Colon	52	59	66†
Esophagus	5	10	19†
Hodgkin lymphoma	74	79	86†
Kidney	51	56	69†
Larynx	67	66	63†
Leukemia	35	42	54†
Liver & bile duct	4	6	14†
Lung & bronchus	13	13	16†
Melanoma of the skin	82	87	93†
Myeloma	26	29	37†
Non-Hodgkin lymphoma	48	53	69†
Oral cavity	53	55	63†
Ovary	37	40	46†
Pancreas	3	3	6†
Prostate	69	76	100†
Rectum	49	57	69†
Stomach	16	18	27†
Testis	83	93	96†

Techniques moléculaires et prise en charge des cancers du poumon



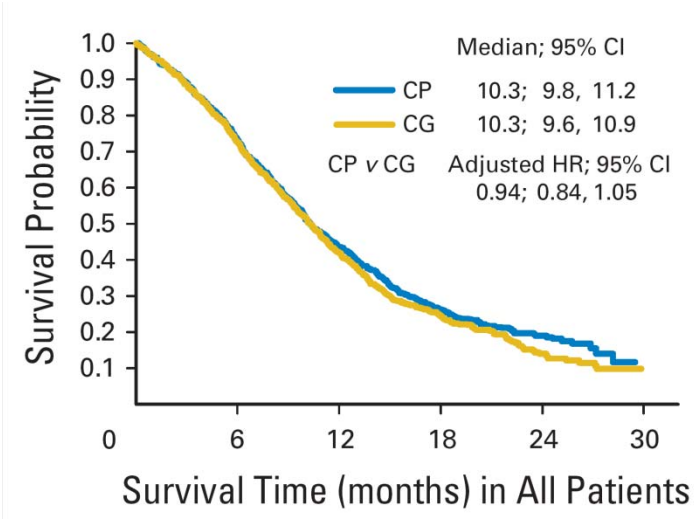
?? Que demander au pathologue ??

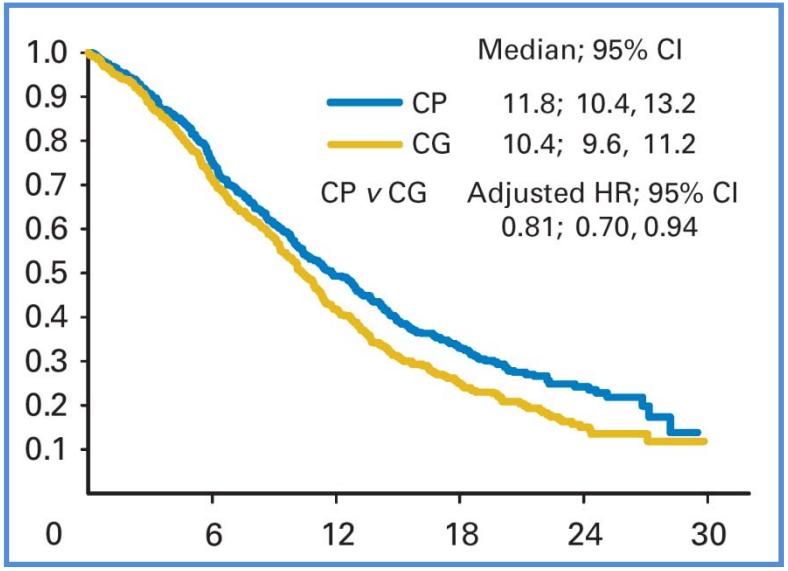
Cancer du poumon Les connaissances évoluent



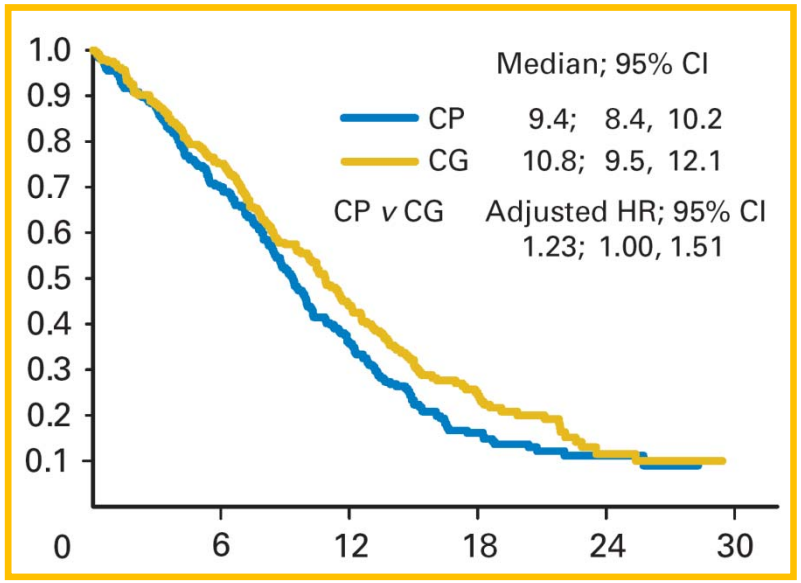
?? Que demander au pathologue ?? Un diagnostic

Le type histologique est important





Non-Epi

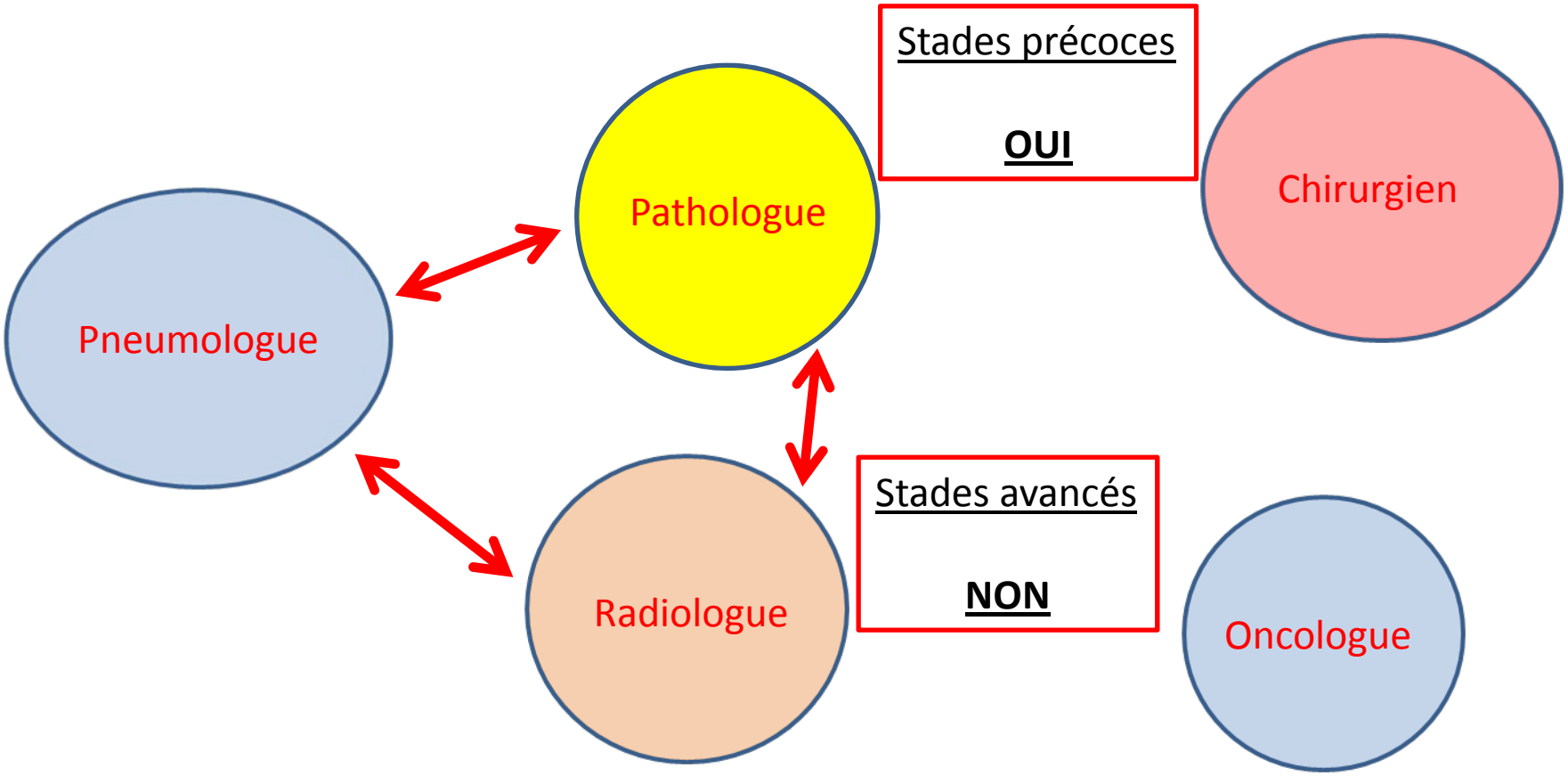


Epi

Cancer du poumon avancé

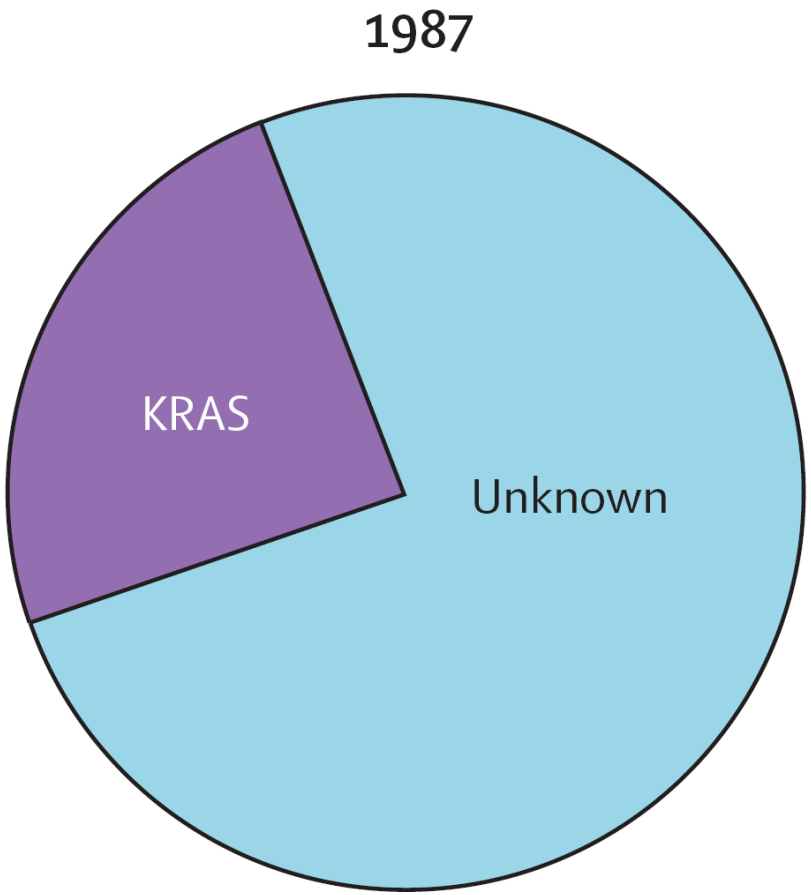
?? Que demander au pathologue ??

Un diagnostic pathologique simple est-il suffisant ?



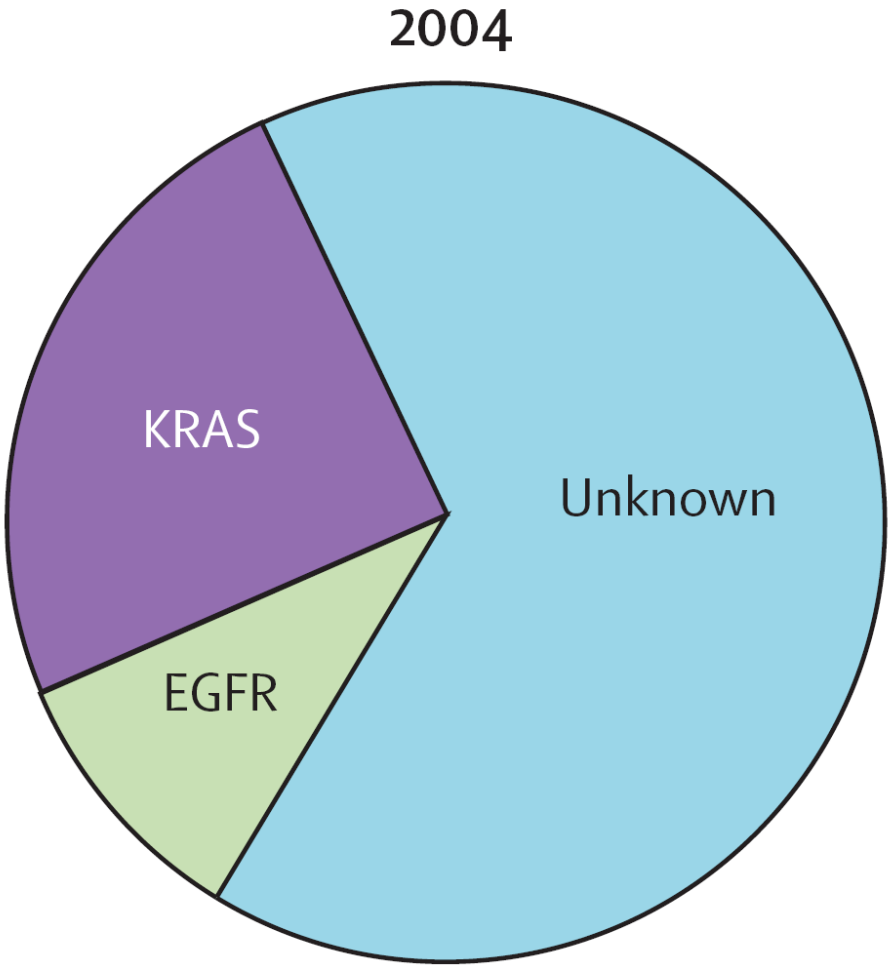
Cancer du poumon Les connaissances évoluent

Un diagnostic moléculaire était-il utile en 1987 ?



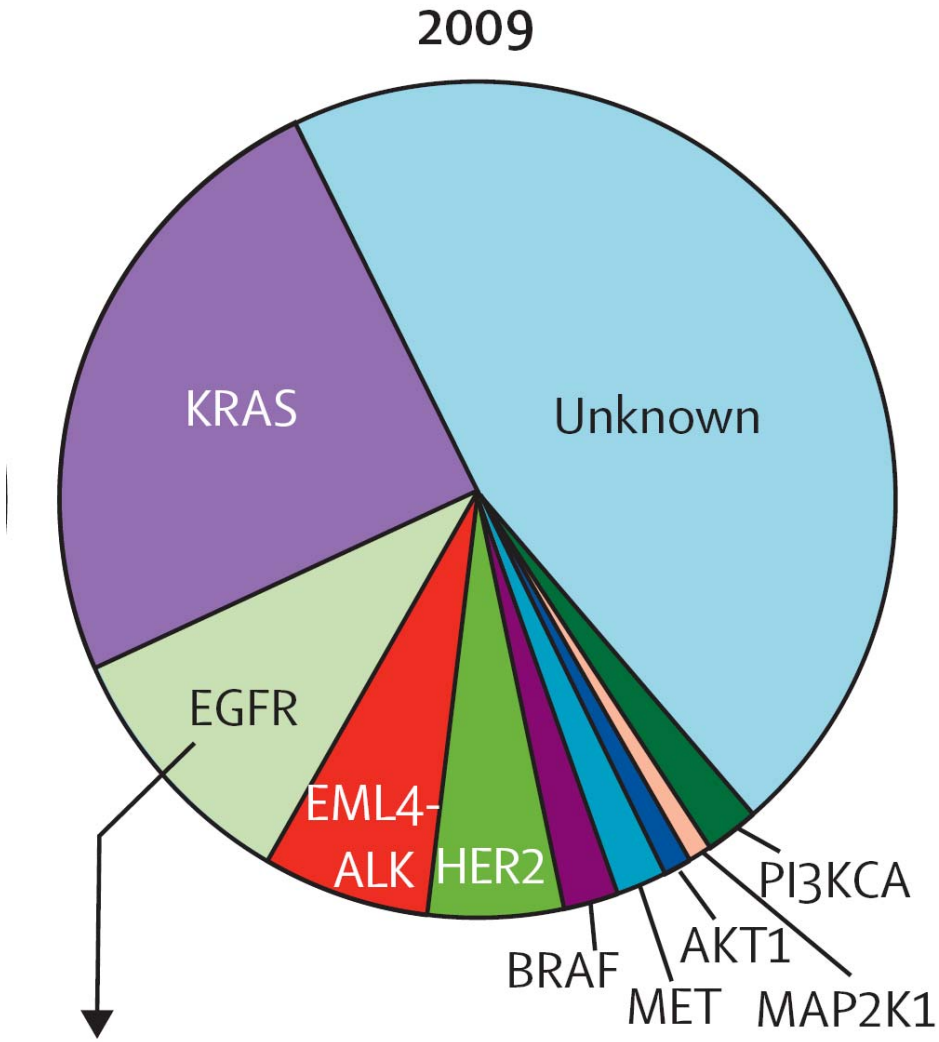
Cancer du poumon Les connaissances évoluent

Un diagnostic moléculaire était-il utile en 2004 ?

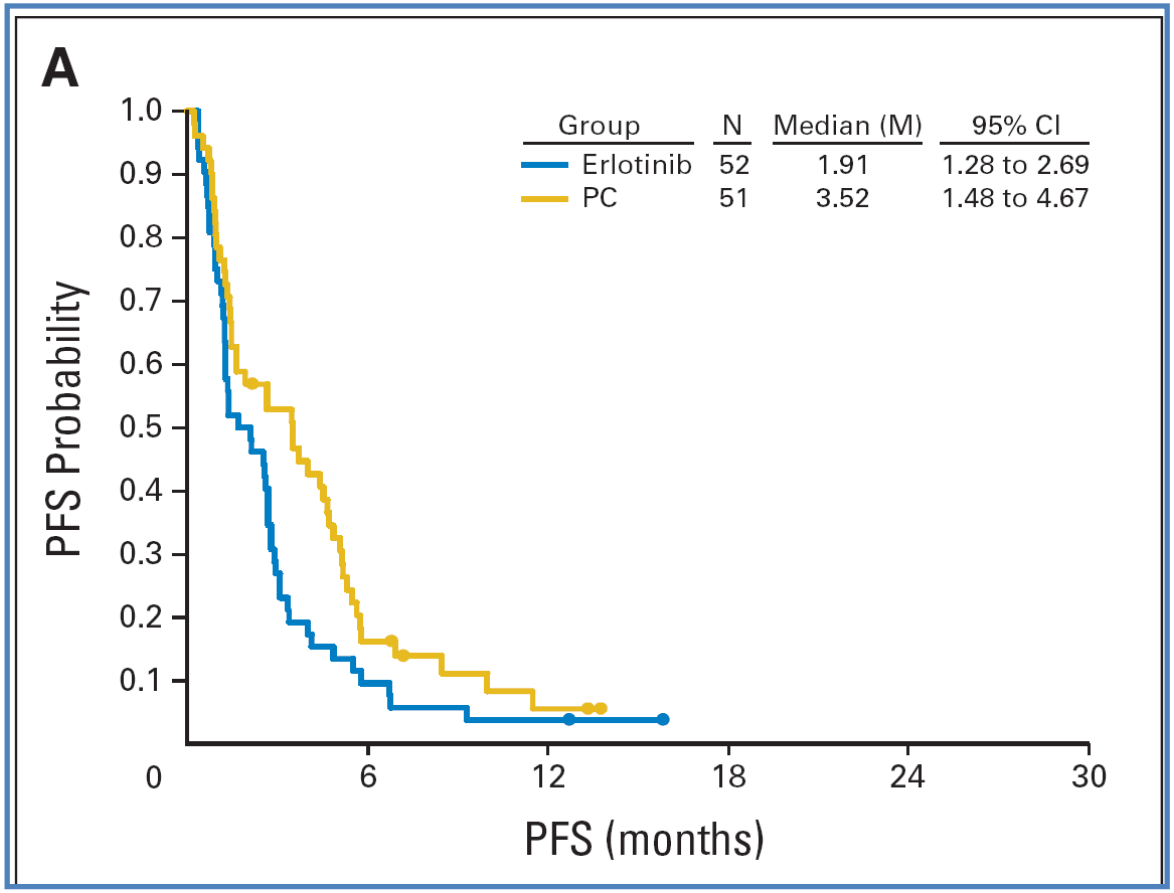


Cancer du poumon Les connaissances évoluent

Un diagnostic moléculaire était-il utile en 2009 ?

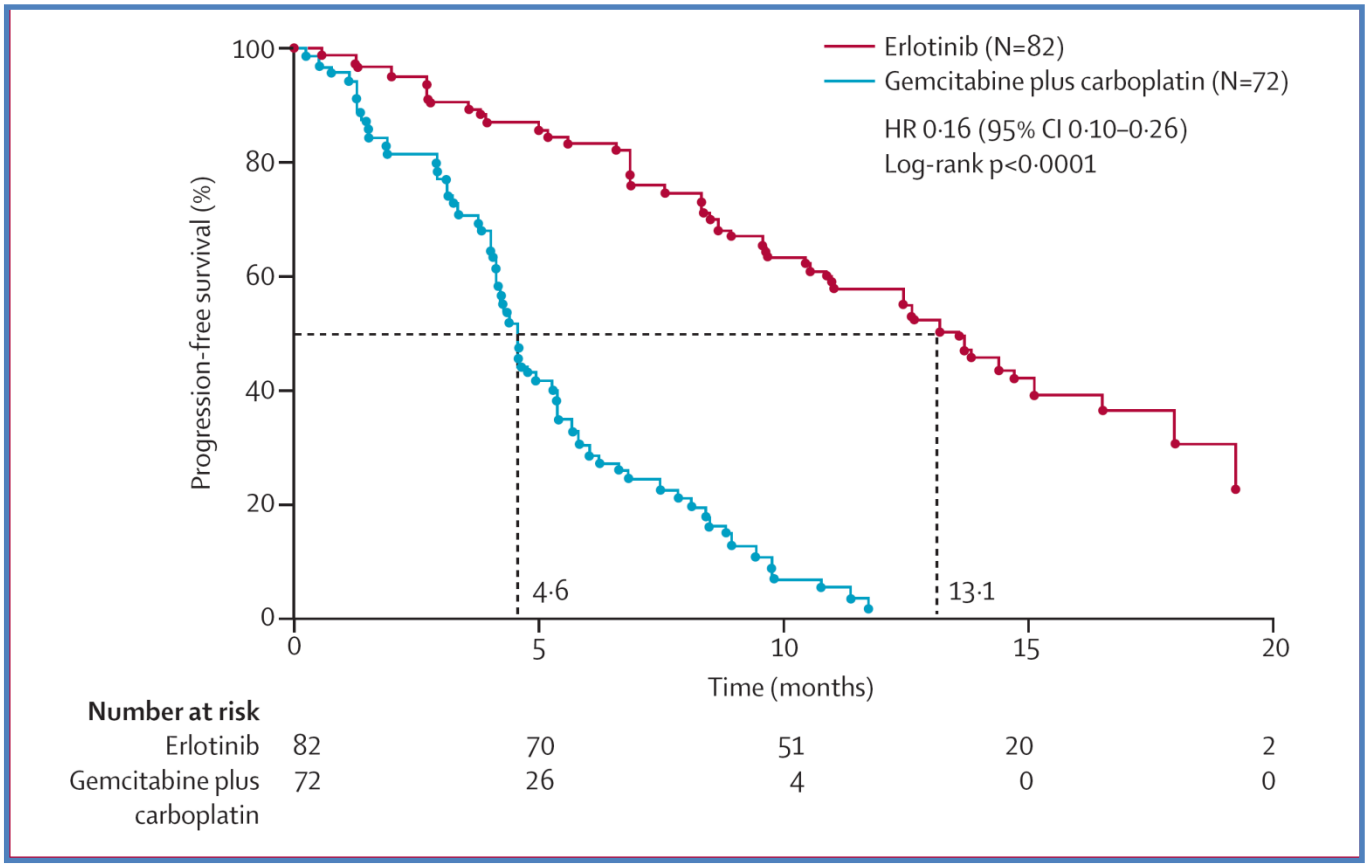


Cancer du Poumon NSCLC avancé tout venant
traitement de première intention



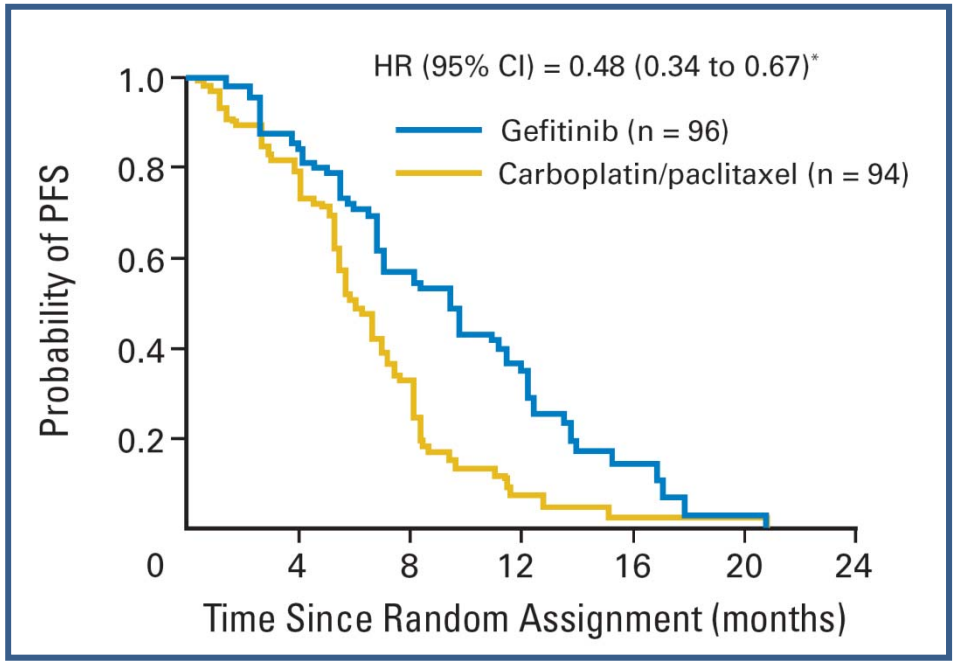
JCO 2008

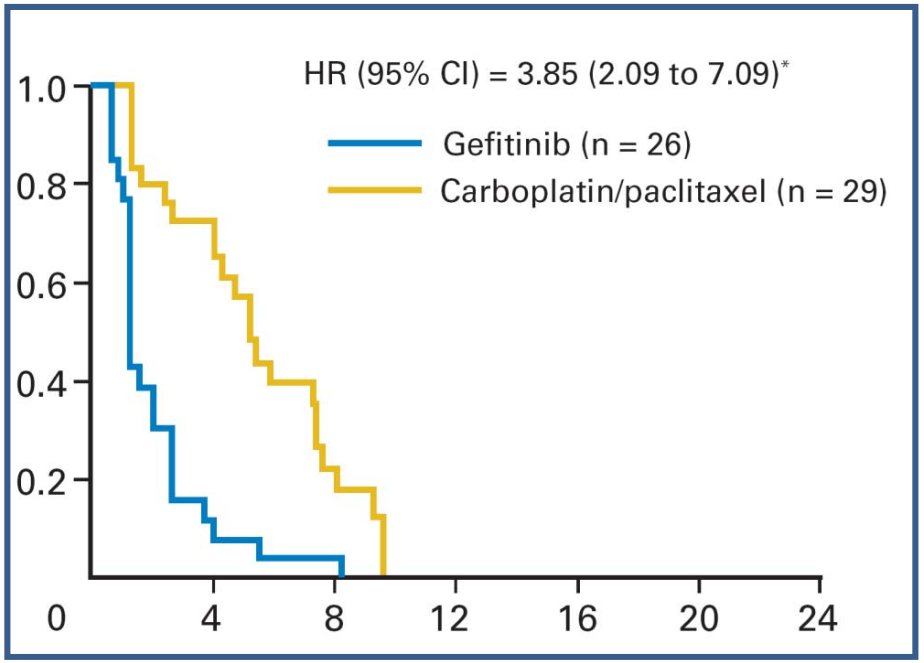
Cancer du Poumon NSCLC avancé sous-groupe avec mutation EGFR
traitement de première intention



Lancet oncology 2011

Cancer du poumon avancé non petites cellules, non épidermoide





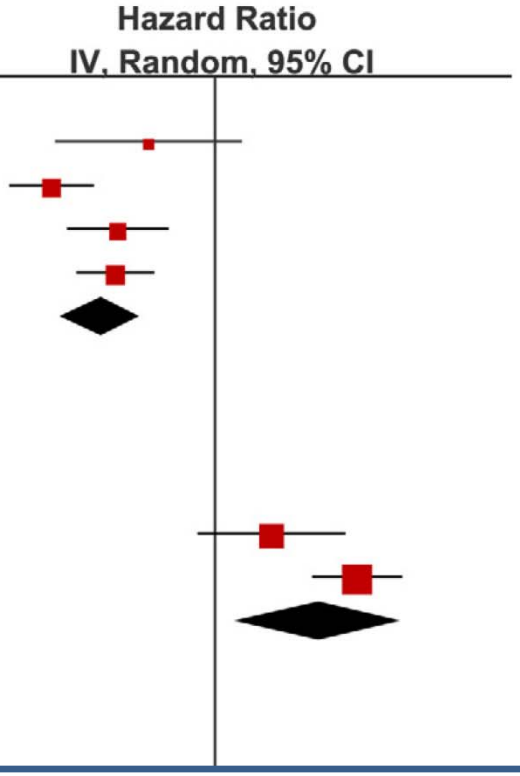
EGFR muté

EGFR non muté

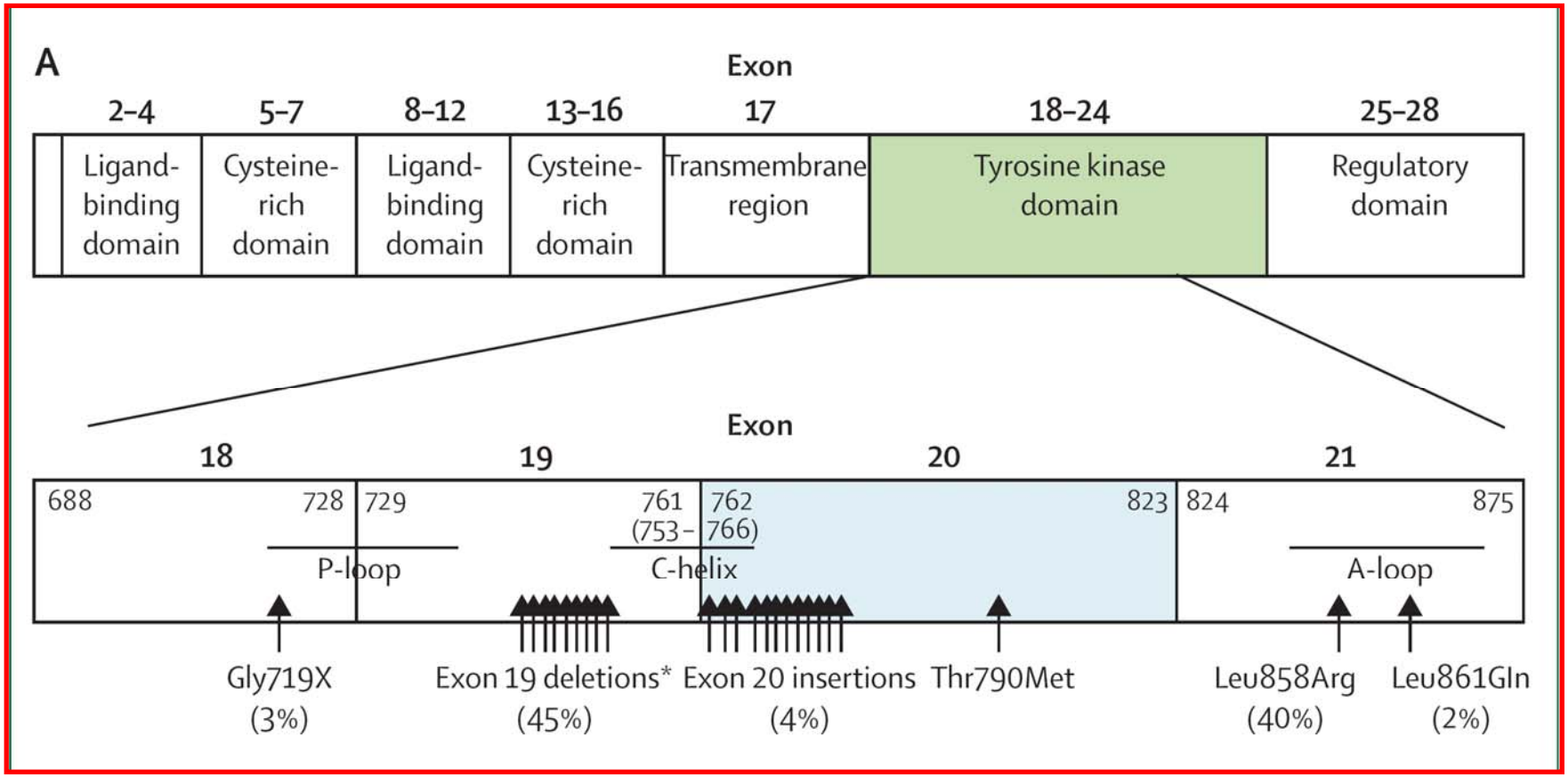
Un diagnostic moléculaire est indispensable en 2011

Meta-analyse des essais cliniques avec thérapie ciblée chez EGFR mutés

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Random, 95% CI
1.1.1 Patients with EGFR mutation treated with gefitinb monotherapy.			
Lee 2009	-0.4894	0.3514	0.61 [0.31, 1.22]
Maemondo 2010	-1.204	0.1588	0.30 [0.22, 0.41]
Mitsudomi 2010	-0.7154	0.1909	0.49 [0.34, 0.71]
Tony S. 2009	-0.734	0.1468	0.48 [0.36, 0.64]
Subtotal (95% CI)			**0.43 [0.32, 0.58]**
Heterogeneity: Tau² = 0.05; Chi² = 7.11, df = 3 (P = 0.07); I² = 58%			
Test for overall effect: Z = 5.64 (P < 0.00001)			
1.1.2 Patients without EGFR mutation treated with gefitinb monotherapy.			
Lee 2009	0.4167	0.2778	1.52 [0.88, 2.61]
Tony S. 2009	1.0473	0.1692	2.85 [2.05, 3.97]
Subtotal (95% CI)			**2.16 [1.17, 3.99]**
Heterogeneity: Tau² = 0.15; Chi² = 3.76, df = 1 (P = 0.05); I² = 73%			
Test for overall effect: Z = 2.46 (P = 0.01)			



Nécessaire de connaître la mutation du gène de l'EGFR



- **Mutations associated with drug sensitivity**
  EGFR Gly719X, exon 19 deletion, Leu858Arg, Leu861Gln
- **Mutations associated with primary drug resistance**
  EGFR exon 20 insertions
- **Mutations associated with acquired drug resistance**
  EGFR Thr790Met, Asp761Tyr, Leu747Ser, Thr854Ala

	Adenocarcinoma	Squamous-cell carcinoma
EGFR	5–15%*	<5%†
ALK	5–15%	<5%
HER2	<5%	0
BRAF	<5%	0
KRAS	>15%	<5%
PIK3CA	<5%	<5%
AKT1	0	<5%
MAP2K1	<5%	0
MET	<5%	<5%

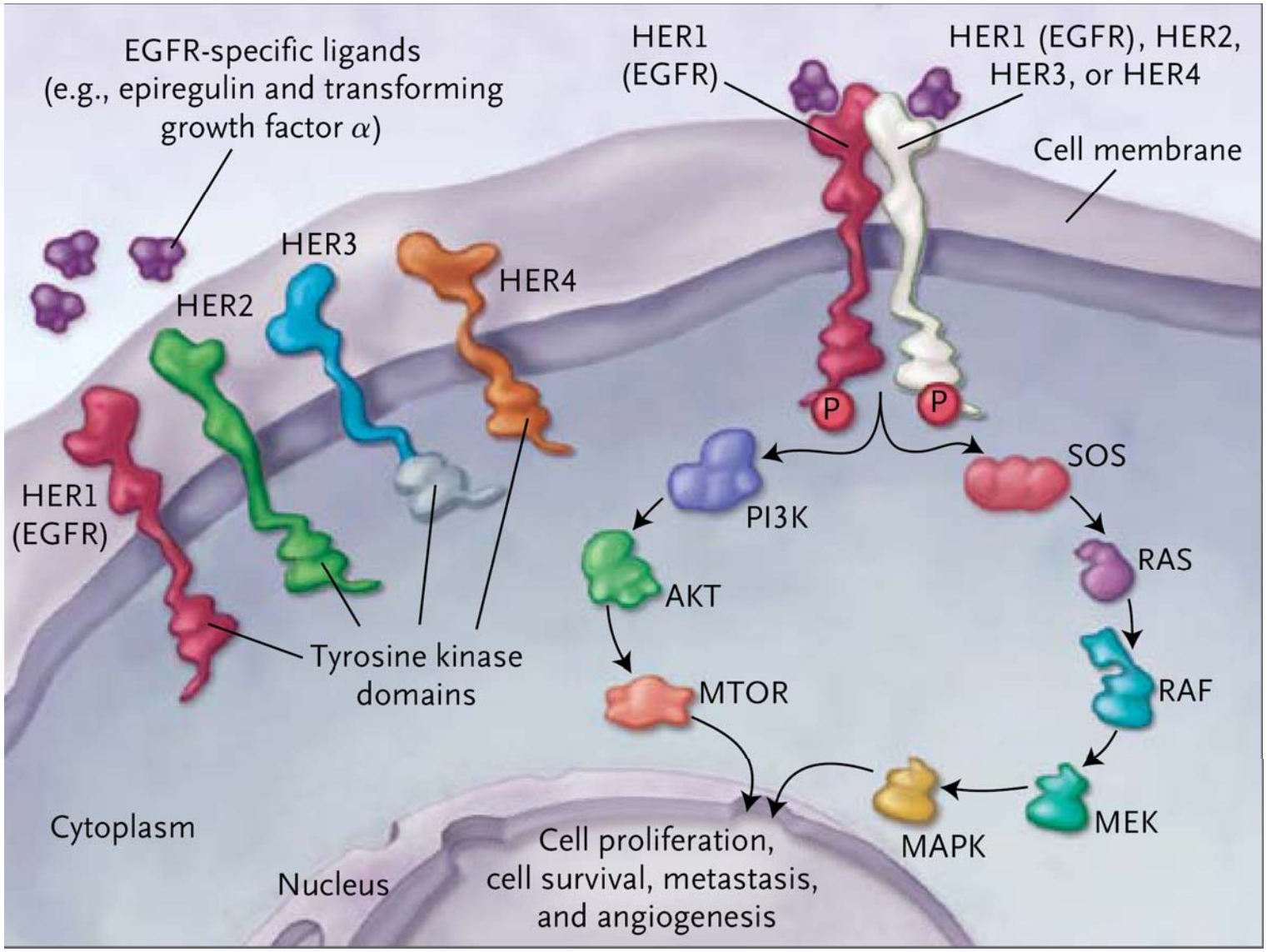
Data based on our literature search of Jan 31, 2010. *Mainly EGFR kinase domain mutations. †Mainly EGFR 'VIII' mutations, which result from deletion of exons 2–7.

Table 1: **Frequency of driver mutations in non-small-cell lung cancers**

Tableau 1. Association possible entre le type d'altération génétique et le sous-type d'adénocarcinome pulmonaire

Type de mutation/ altération	Sous-type histologique d'adénocarcinome
EGFR	Adénocarcinome bien différencié, avec composante bronchioloalvéolaire non mucineuse, papillaire et/ou micro-papillaire
KRAS	Adénocarcinome (bronchioloalvéolaire ou non) de type mucineux
BRAF	Adénocarcinome papillaire
ELM4-ALK	Adénocarcinome de type solide et/ou avec composante à cellules isolées
CTNNB1 (Bêtacaténine)	Adénocarcinome à cellules claires ou de type fœtal

Pusztaszeri M et al 2011 Revue Medicale Suisse


EGFR-specific ligands
(e.g., epiregulin and transforming
growth factor α)
HER1
(EGFR)
HER1 (EGFR), HER2,
HER3, or HER4
Cell membrane
HER3
HER4
HER2
HER1
(EGFR)
P
P
SOS
PI3K
RAS
AKT
RAF
Tyrosine kinase
domains
MTOR
MEK
MAPK
Cytoplasm
Nucleus
Cell proliferation,
cell survival, metastasis,
and angiogenesis

Les thérapies ciblées en développement clinique pour NSCLC

	Study phase	Selected population*
ALK		
PF-02341066	1, 2, 3	Yes
HER2		
HKI-272	1, 2	No
BIBW 2992	1, 2, 3	Yes
Lapatinib	1, 2	No
Pertuzumab	1, 2	No
Trastuzumab	2, 3	Yes
PI3K		
BEZ2235	1	No
GDC-0941	1	No
XL147	1, 2	No
AKT		
MK2206	1	No
BRAF		
Sorafenib	1, 2	No
GSK2118436	1	Yes
XL281	1	No
MAP2K1		
CI-1040	1, 2	
AZD6244	1, 2	No
TAK-733	1	No
AS703026	1	No
GSK1120212	1	No
PD-325901	1, 2	No
GDC-0973/XL518	1	No
RO4987655	1	No
RO5126766	1	No
MET		
PF-02341066	1, 2	Yes
GSK1363089, formerly known as XL880	1	No
XL184	1, 2	Yes
AMG 102	1, 2	No
MetMAb	1, 2	No
ARQ 197	1, 2	No
SCH 900105	1, 2	No

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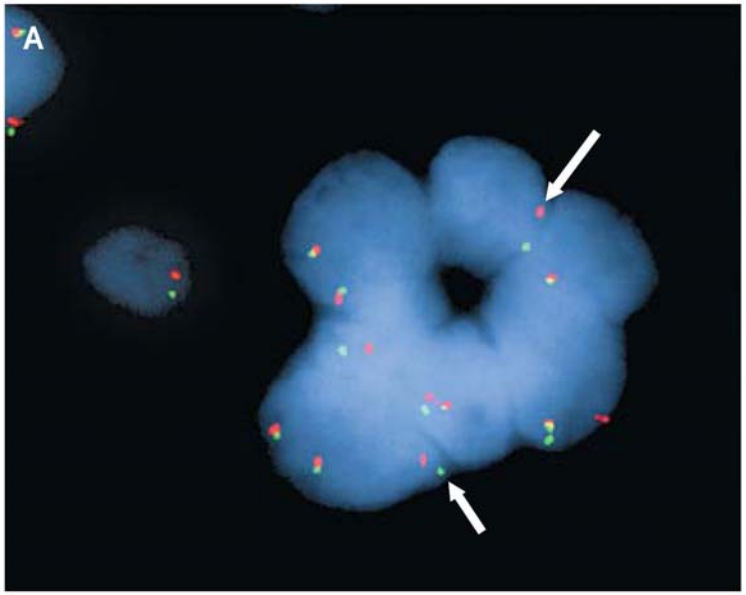
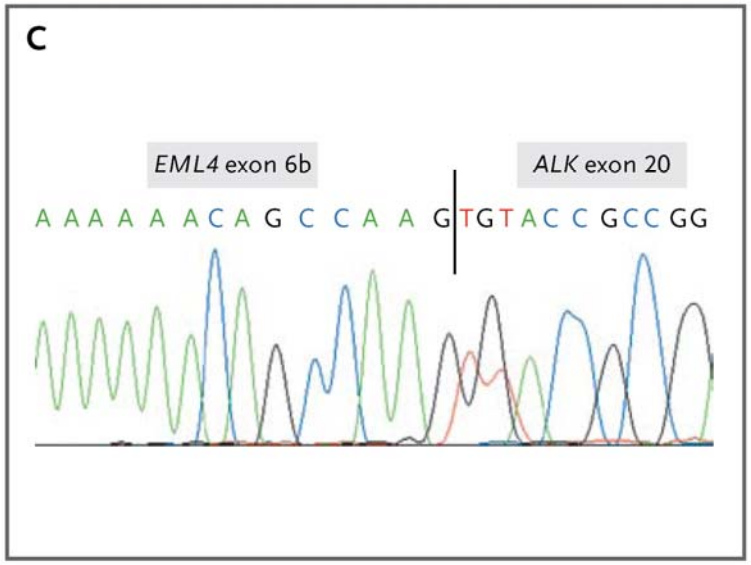
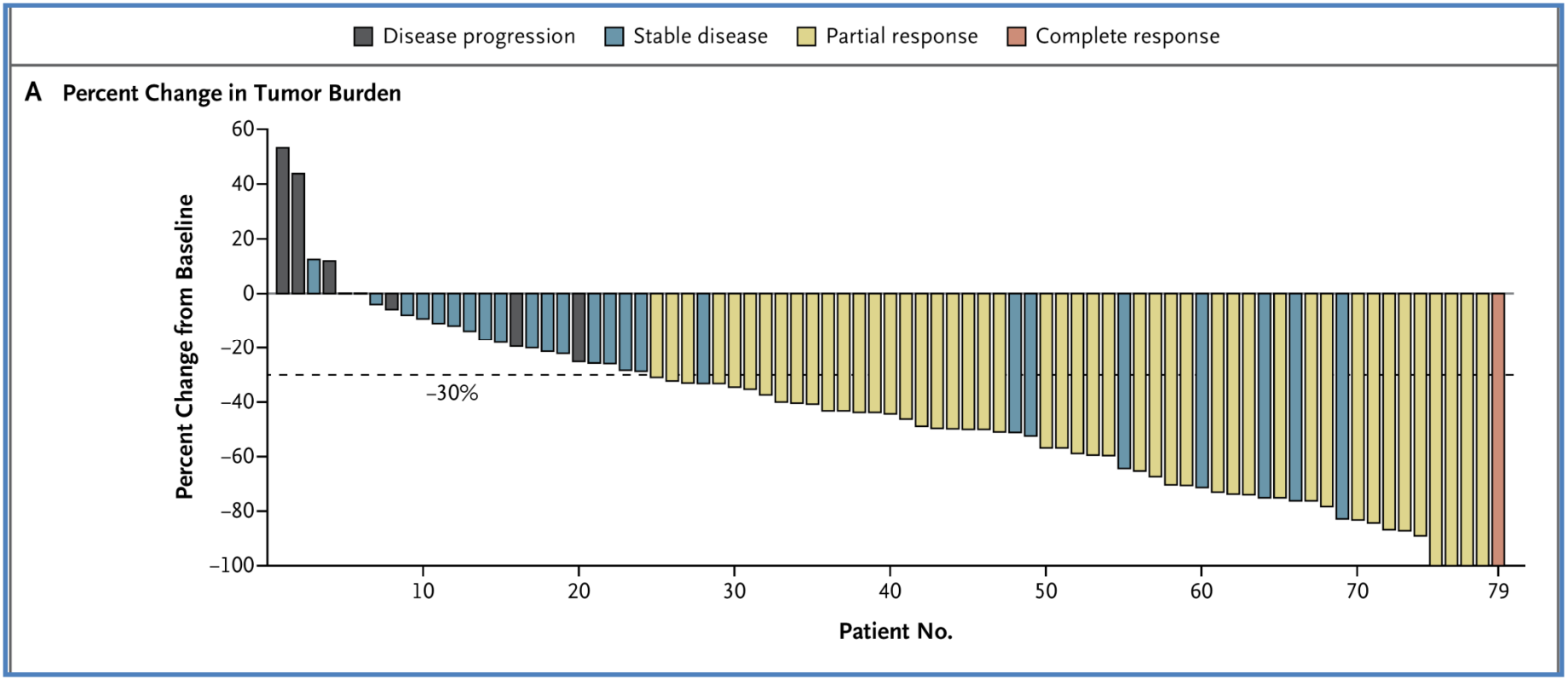
Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.


A


C
EML4 exon 6b
ALK exon 20
A A A A A A C A G C C A A G T G T A C C G C C G G

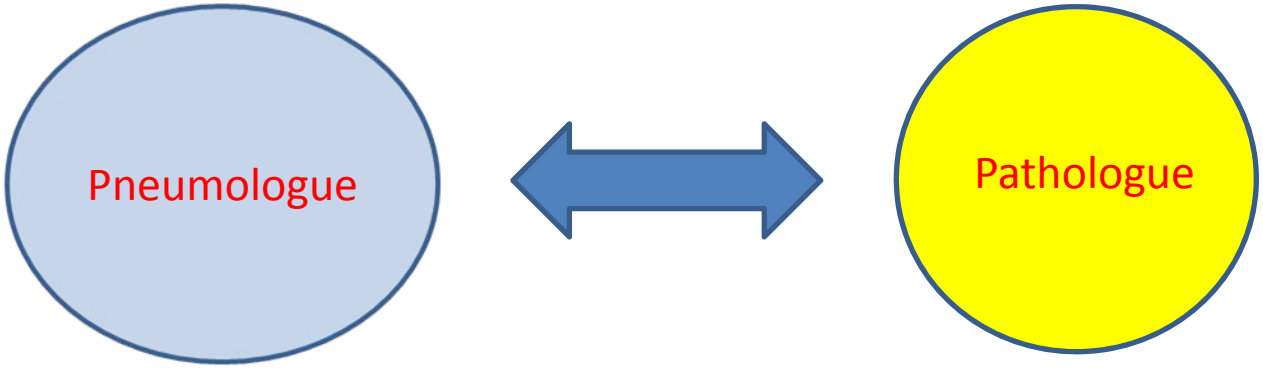


Crizotinib is an oral ATP competitive selective inhibitor of the ALK and MET tyrosine kinases that inhibits tyrosine phosphorylation of activated ALK at nanomolar concentrations.

Conclusions I

Réflexion sur le matériel de biopsie adéquat

Information pour le pathologue



?? Cytologie d'un épanchement pleural:
cellules tumorale compatible avec une origine pulmonaire

Résultats prélèvement par EBUS: + pour NSCLC

Conclusions II

Traitement personnalisé en fonction d'anomalie moléculaire

Nouvelles molécules disponible dans futur proche

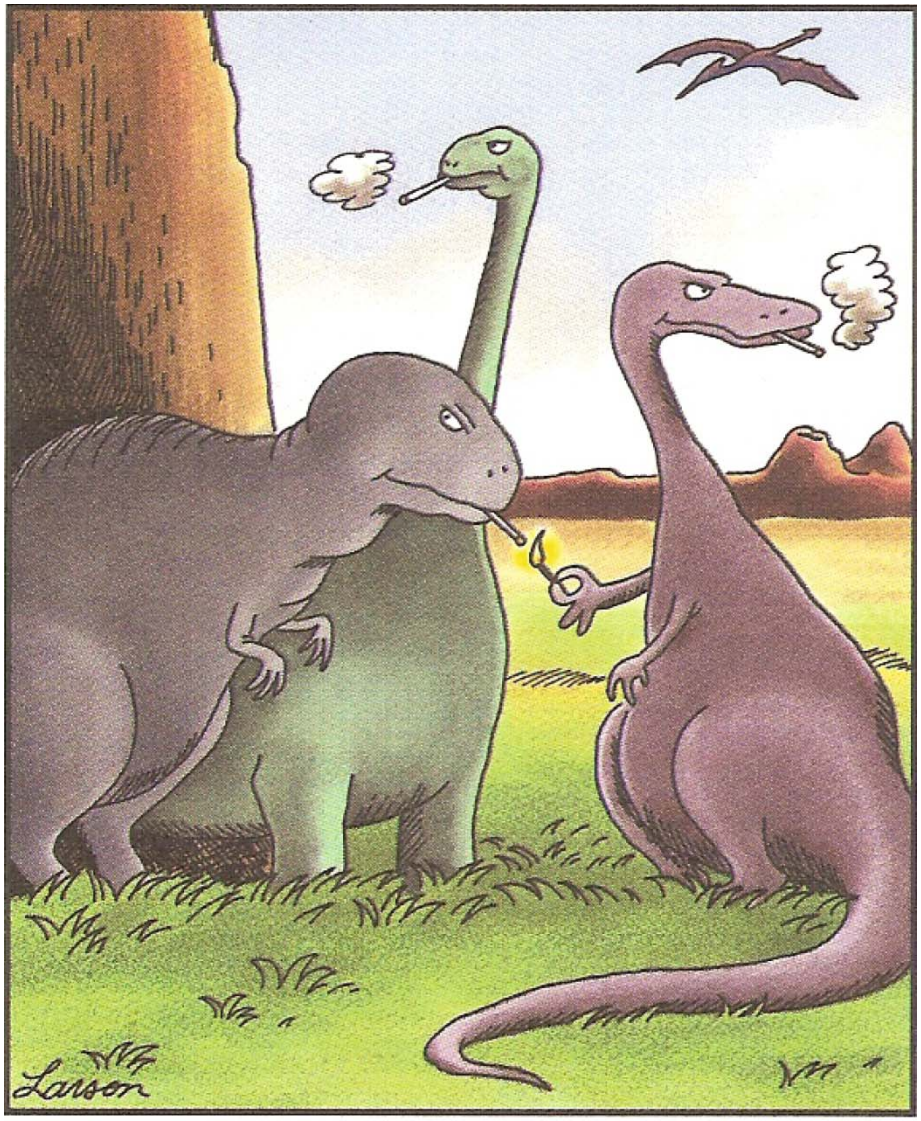
Guidelines du groupe suisse de pathologie pulmonaire

histologie- Immunohistologie à minima (epi-non epi)

status mutationnel EGFR chez tous les non-epi

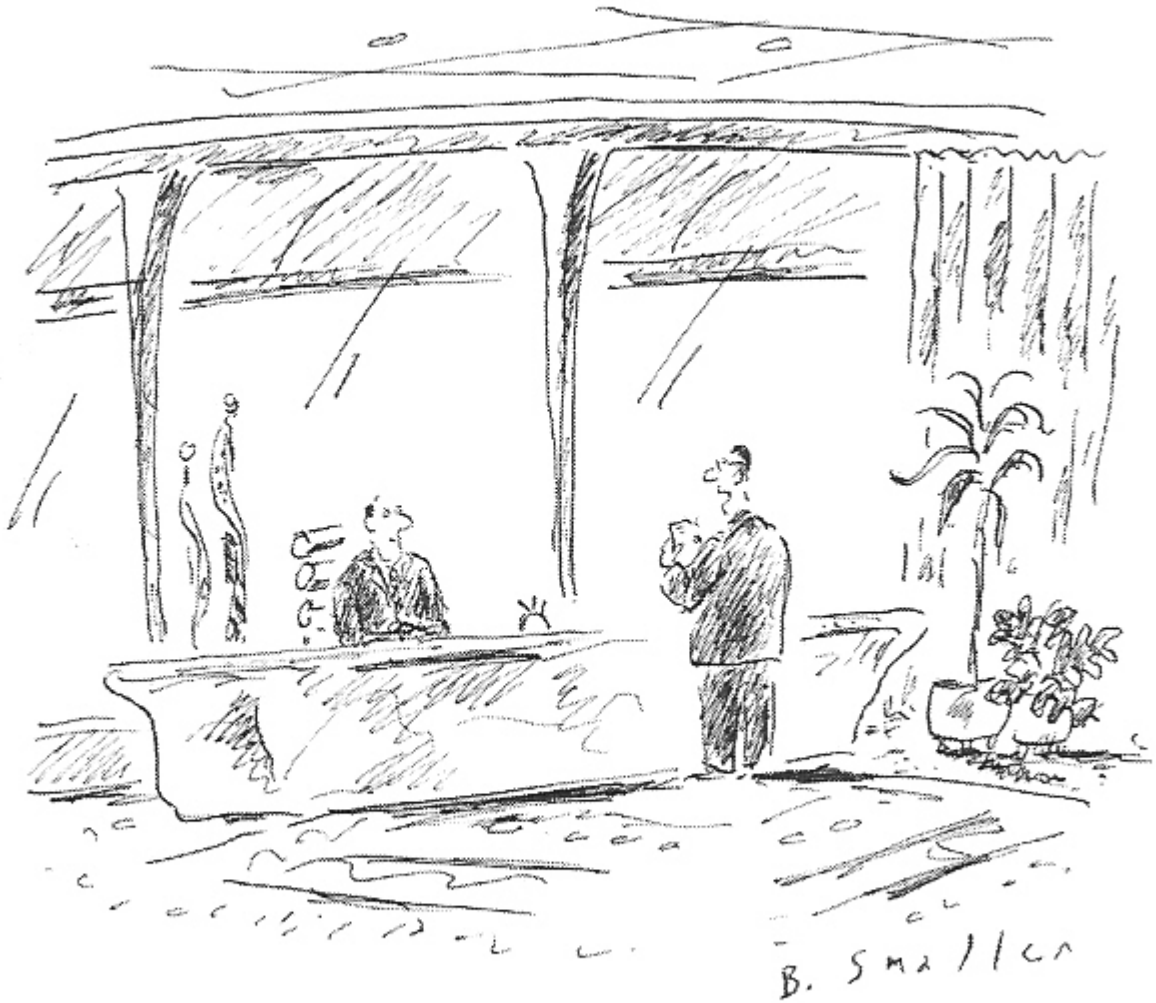
Si EGFR – ad analyse de ALK

Privilégier des prélèvements suffisants pour permettre un diagnostic précis et un traitement ciblé



The real reason dinosaurs became extinct

THE NEW YORKER



"You can't please all the people all the time, so you might as well please the pharmaceutical lobby."