

Médecine de précision et thérapie ciblée

Cancers bronchiques non à petites cellules



Jeudi 10 mars 2022

Marc Denis / Elvire Pons-Tostivint

Quelques chiffres...

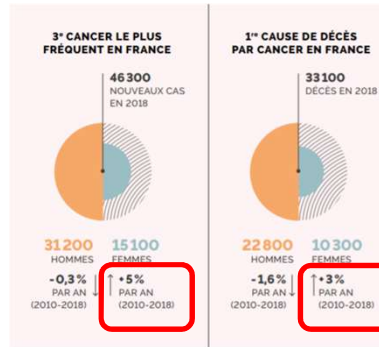
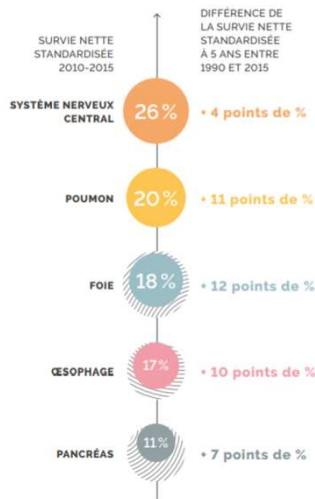
- Près de 400.000 nouveaux cas de cancer diagnostiqués en France en 2018 (204 000 hommes et 177 500 femmes)
- 157 000 décès en 2018
- 3.8 millions de patients avec un cancer en France
- Homme
 1. Cancers de la prostate
 2. Cancers du poumon (1)
 3. Cancers du côlon-rectum
- Femme
 1. Cancers du sein (1)
 2. Cancers du côlon-rectum
 3. Cancer du poumon (2)

Cancer = 1^{ère} cause de décès en France

Cancer du poumon = 1^{ère} cause de décès par cancer en France, en Europe et dans le Monde.



Un cancer grave et fréquent



ÂGE MÉDIAN AU DIAGNOSTIC
67 ans CHEZ LES HOMMES
65 ans CHEZ LES FEMMES

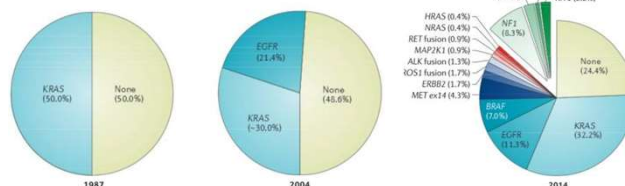
Majoritairement des hommes (67% des nouveaux cas)
 Mais l'incidence et la mortalité du nombre de cancers du poumon chez la femme augmente

Progrès dans le traitement des cancers bronchiques métastatiques



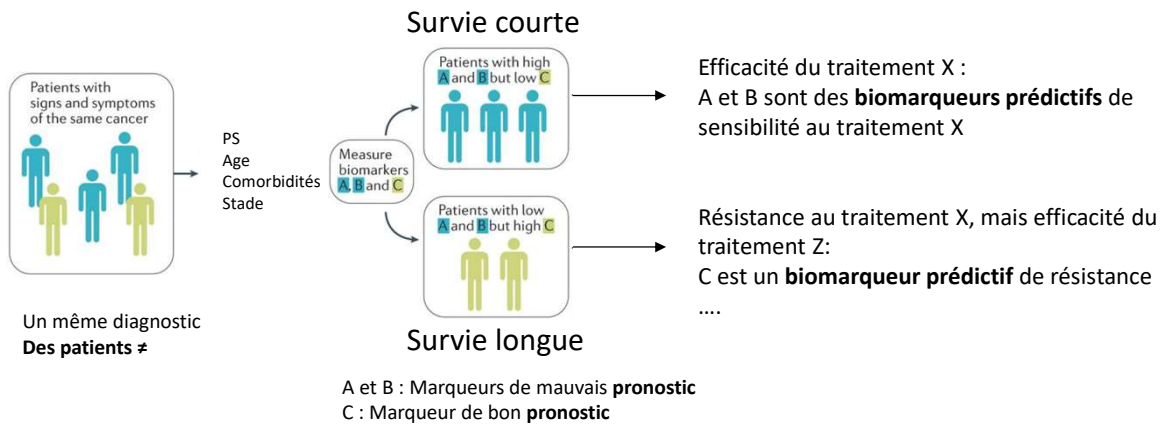
Cancer du poumon = une entité clinique

Cancer du poumon = des 10aines de maladies différentes
 = des 10aines de stratégies thérapeutiques



Pao et Chmielecki, Nat Rev Cancer 2010
 Vargas AJ, Harris CC. Nat Rev Cancer 2016

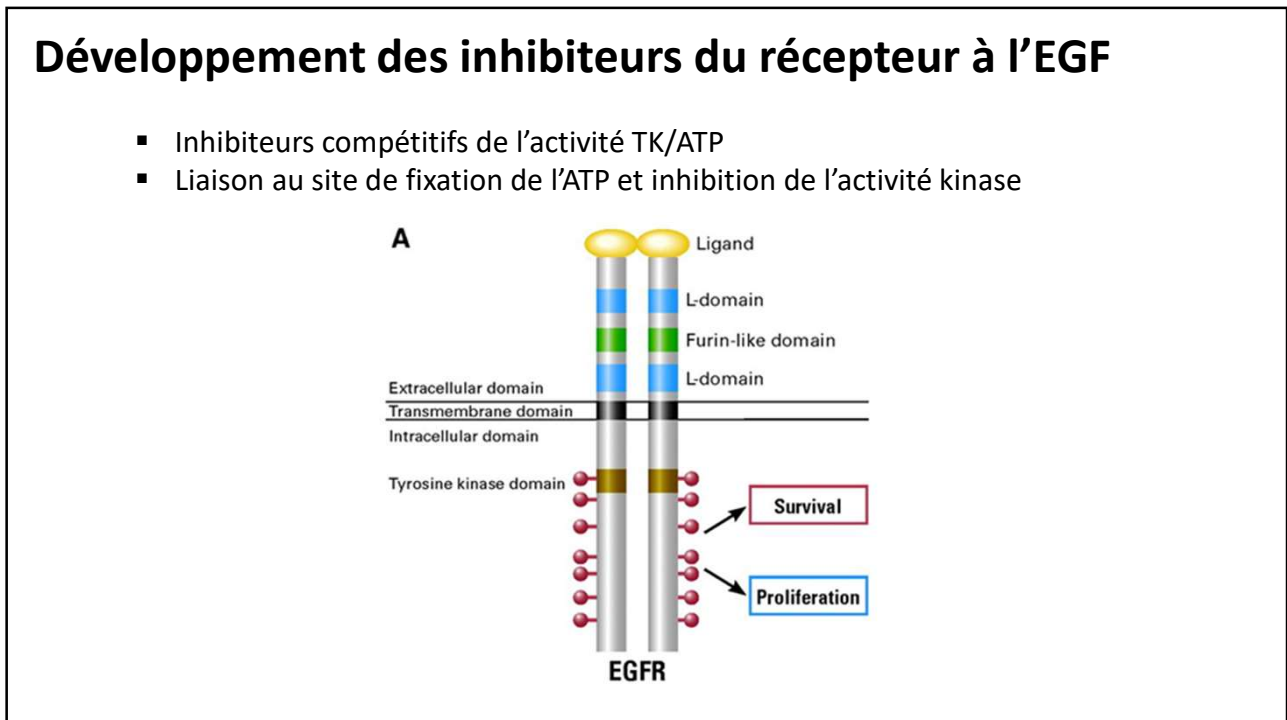
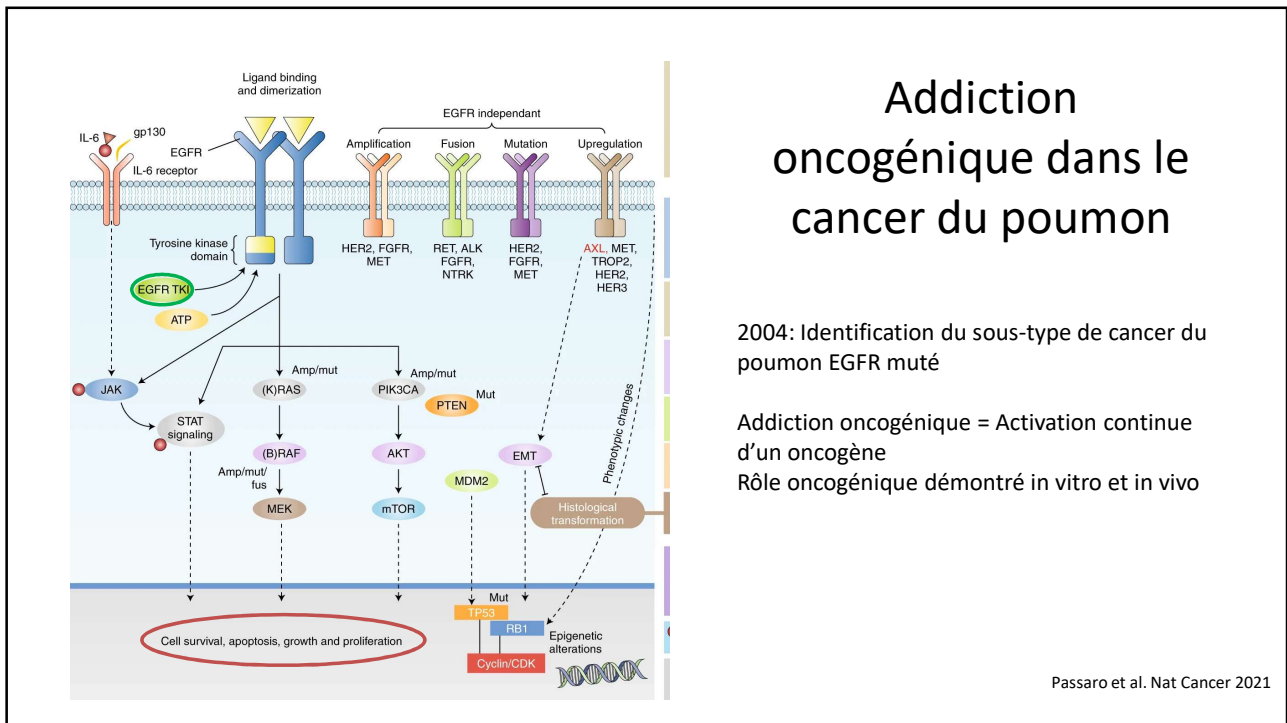
Qu'est ce qu'un biomarqueur?



Adapted from Vargas AJ, Harris CC. Nat Rev Cancer 2016 ;16:525-37.
Goossens N, et al. Transl Cancer Res 2015;4(3):256 – 269.

L'histoire d'un biomarqueur: EGFR

De l'identification de la population cible, aux ciblage des mutations de résistance



Etude BR.21

Etude randomisée contre placebo de phase III

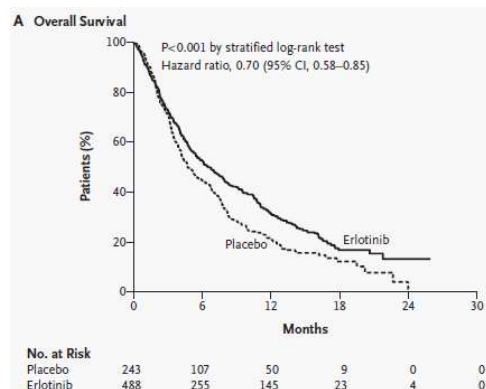
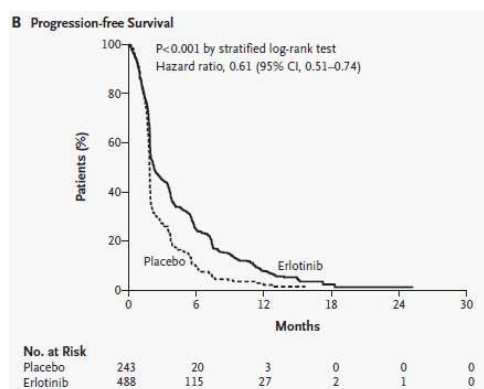
Les critères d'éligibilité

- Patients avec un Cancer Bronchopulmonaire Non à Petites Cellules avancés (stade IIIB ou IV)
- **En échec de traitement** après une ou deux lignes de chimiothérapie
- Stratification selon le centre, le performance status, la réponse à la chimiothérapie, le nombre de traitements reçus
- **Pas de sélection sur un biomarqueur**

- Randomisation avec un ratio 2:1 : erlotinib 150 mg/j ou placebo
- 731 patients randomisés

Shepherd FA, et al. N Engl J Med 2005

Etude BR.21 : paramètres d'efficacité



n	Traitement	Taux de R.O	mSSP	mSG
731	Erlotinib	8,9 %	2,2 mois	6,7 mois
	Placebo	< 1%	1,8 mois	4,7 mois

R.O = Réponses objectives

mSSP = médiane de Survie Sans Progression

mSG = médiane de Survie Globale

P<0.001 HR 0,61 (p<0,001) HR 0,70 (p<0,001)

Shepherd FA, et al. N Engl J Med 2005

Etude BR.21 : paramètres d'efficacité

Table 2. Analysis of Responses to the Study Treatment.*

Factor	No. of Cases Evaluated	No. of Responses (Complete and Partial)	Overall Response Rate (%)	P Value
Treatment				
Erlotinib	427	38	8.9	<0.001
Placebo	211	2	<1	
Age				
<60 yr	177	19	10.7	0.30
≥60 yr	250	19	7.6	
Sex				
Male	281	17	6.0	0.006
Female	146	21	14.4	
Pathological subtype				
Adenocarcinoma	209	29	13.9	<0.001
Other	218	9	4.1	
Performance status				
0 or 1	274	21	7.7	0.29
2 or 3	153	17	11.1	
Response to prior therapy				
Complete and partial responses	174	13	7.5	0.65
Progressive disease	87	9	10.3	
Stable disease	166	16	9.6	

Factor	No. of Cases Evaluated	No. of Responses (Complete and Partial)	Overall Response Rate (%)	P Value
Prior regimens				
1	214	19	8.9	1.00
2 or 3	213	19	8.9	
Prior platinum-based therapy				
Yes	396	36	9.1	1.00
No	31	2	6.5	
EGFR expression†				
Positive	106	12	11.3	0.10
Negative	80	3	3.8	
Unknown	241	23	9.5	
Smoking status				
Current smoker or ever smoked	311	12	3.9	<0.001
Never smoked	93	23	24.7	
Unknown	23	3	13.0	
Race or ethnic group				
Asian	53	10	18.9	0.02
Other	374	28	7.5	

Shepherd FA, et al. N Engl J Med 2005

Etude BR.21 :

→ A posteriori, identification de facteurs clinico-histologiques prédictifs de réponse à l'Erlotinib

- Femmes
- Adénocarcinomes
- Non fumeurs
- Asiatiques

Etude IPASS : paclitaxel + carboplatine vs gefitinib

→ Etude randomisée de phase III

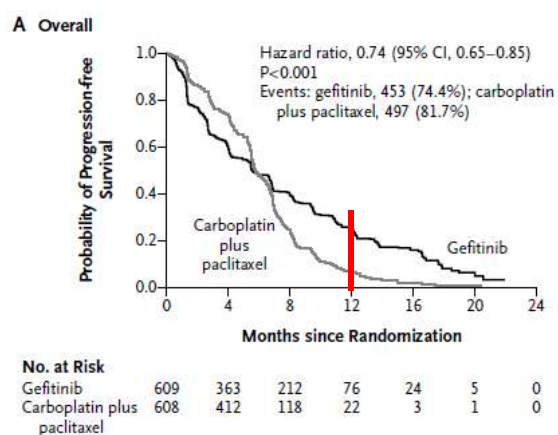
Les critères d'éligibilité: Sélection de la population sur les critères définis par les études précédentes

- Etude conduite en Asie du sud-est
- Histologie adénocarcinome
- Non fumeur ou très peu fumeurs
- En 1ère ligne de traitement : Chimiothérapie versus TKI

Mok T, et al. N Engl J Med 2009

Etude IPASS

→ Survie Sans Progression

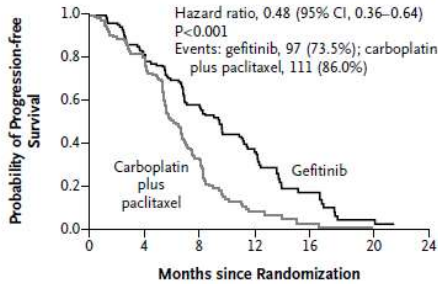


- Taux de Survie Sans Progression à 1 an
 - ✓ 24,9 % (gefitinib)
 - ✓ 6,7 % (paclitaxel + carboplatine)

Mok T, et al. N Engl J Med 2009

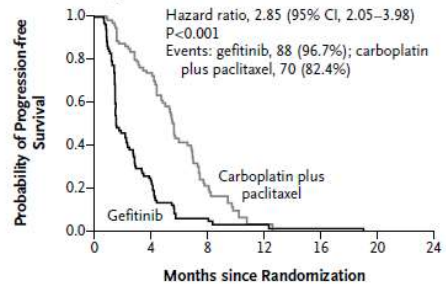
Etude IPASS → analyse selon statut EGFR (mutation ou absence de mutation)

B EGFR-Mutation-Positive



No. at Risk		0	4	8	12	16	20	24
Gefitinib	132	108	71	31	11	3	0	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0	0

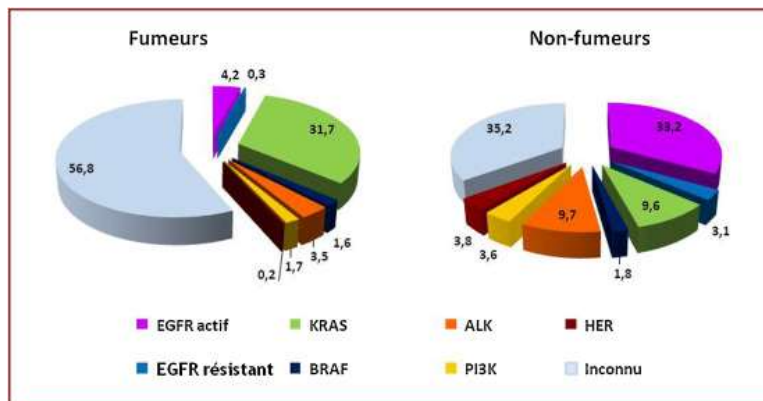
C EGFR-Mutation-Negative



No. at Risk		0	4	8	12	16	20	24
Gefitinib	91	21	4	2	1	0	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0	0

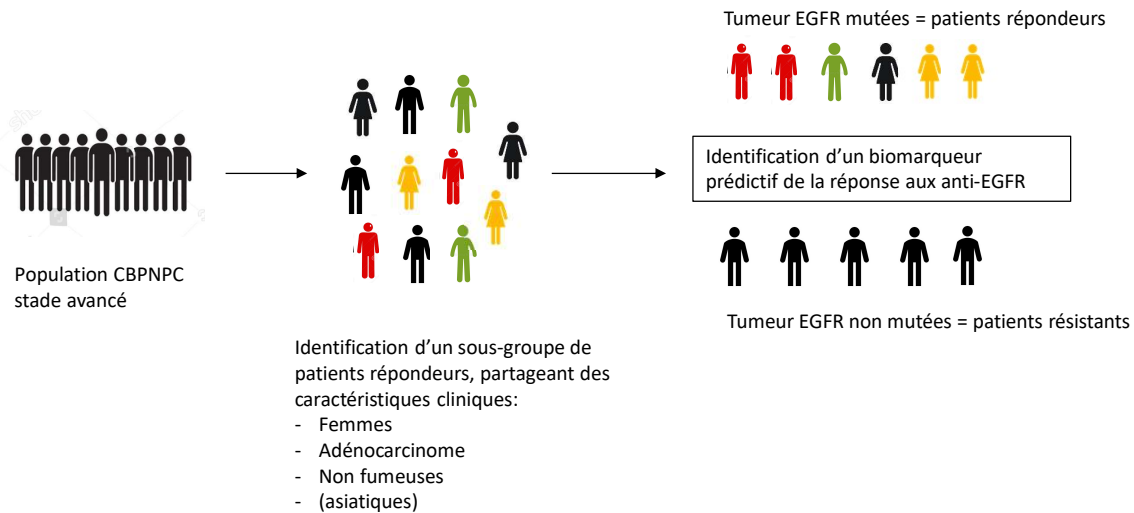
Mutation de EGFR : Biomarqueur prédictif de réponse aux TKI anti-EGFR

Mok T, et al. N Engl J Med 2009



- Cancer du poumon du fumeur ≠ non fumeur
- Non fumeur:
 - Adénocarcinome pulmonaire
 - Addiction oncogénique fréquente

Cancers du poumon EGFR muté → un modèle de thérapeutique de précision



Recommandations de l'ESMO → European Society of Medical Oncology

- La mutation de l'EGFR **doit être recherchée systématiquement dans les adénocarcinomes bronchopulmonaires**
- Le test de la mutation de l'EGFR n'est pas recommandé chez les patients avec un diagnostic histologique certain de cancer épidermoïde ; **excepté pour les patients non fumeurs ou peu fumeurs (< 15 PA).**

Table 2. Incidence of EGFR Mutations by Pack-Years of Cigarettes Smoked

Pack-Years	Stage I-III A			Stage III B/IV			All Stages			
	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI
Never smokers	131	228	57	171	352	49	302	580	52	48 to 56
1 to 5	22	57	39	20	68	29	42	125	34	25 to 43
6 to 10	11	47	23	29	69	42	40	116	34	26 to 44
11 to 15	10	59	17	9	49	18	19	108	18	11 to 26
16-25	13	129	10	13	110	12	26	239	11	7 to 16
26 to 50	16	294	5	27	246	11	43	540	8	6 to 11
51 to 75	10	148	7	11	95	12	21	243	9	5 to 13
> 75	3	116	3	4	66	6	7	183	4	2 to 8
P (trend test)	< .001 $\chi^2_{(df=1)} = 129$			< .001 $\chi^2_{(df=1)} = 90.2$			< .001 $\chi^2_{(df=1)} = 224$			

Novello S, et al. 2016
D'Angelo SP, et al. J Clin Oncol 2011

Chimiothérapie vs TKI – anti-EGFR

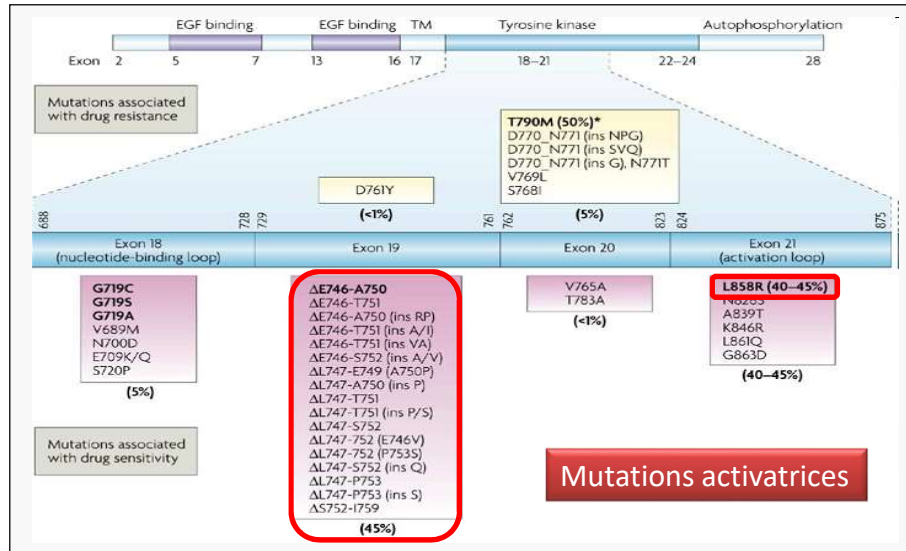
Studies	Treatment	n/mEGFR	ORR	mPFS	HR	mOS	HR
WJTOG3405 (Japan)	Gefitinib	604/177	62.1 %	9.2 mo.	0.489 (0.336 – 0.710)	34.8 mo.	1.252 (0.883 – 1.775)
	Doc + Cis		32.2 %	6.3 mo.		37.3 mo.	
NEJ002 (Japan)	Gefitinib	228	73.7 %	10.8 mo.	0.322 (0.236 – 0.438)	27.7 mo.	0.887 (0.634 – 1.241)
	Pacl/Cb		30.7 %	5.4 mo.		26.6 mo.	
IPASS (East-Asia)	Gefitinib	1217/261	71.2 %	9.5 mo.	0.48 (0.36 – 0.64)	21.6 mo.	0.91 (0.76 – 1.10)
	Pacl/Cb		47.3 %	6.3 mo.		21.9 mo.	
First-Signal (South Korea)	Gefitinib	313/42	84.6 %	8.0 mo.	0.544 (0.269 – 1.100)	27.2 mo.	1.043 (0.498 – 2.182)
	Gem-Cis		37.5 %	6.3 mo.		25.6 mo.	
OPTIMAL (China)	Erlotinib	165	83 %	13.1 mo.	0.16 (0.10 – 0.26)	-	-
	Gem-Cb		36 %	4.6 mo.		-	
EURTAC (Europe)	Erlotinib	173	58 %	9.7 mo.	0.37 (0.25 – 0.54)	19.3 mo.	1.04 (0.65 – 1.68)
	Pt-based CT		15 %	5.2 mo.		19.5 mo.	
LUX-Lung 6 (Asia)	Afatinib	364	66.9 %	11.0 mo.	0.28 (0.20 – 0.39)	23.1 mo.	0.93 p=0.6137
	Gem-cis		23 %	5.6 mo.		23.5 mo.	
LUX-Lung 3 (international)	Afatinib	345	56 %	11.1 mo.	0.58 (0.43 – 0.78)	28.2 mo.	0.88 p=0.358
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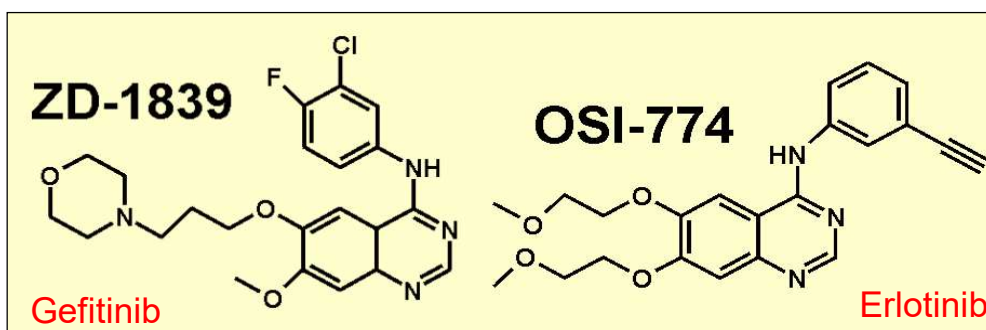
Pas de bénéfice démontré sur la survie globale du fait du Cross-over

Les altérations du gène EGFR

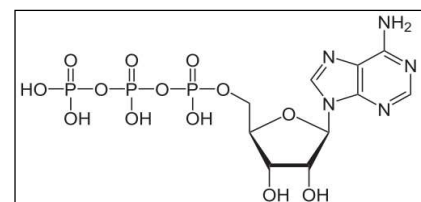


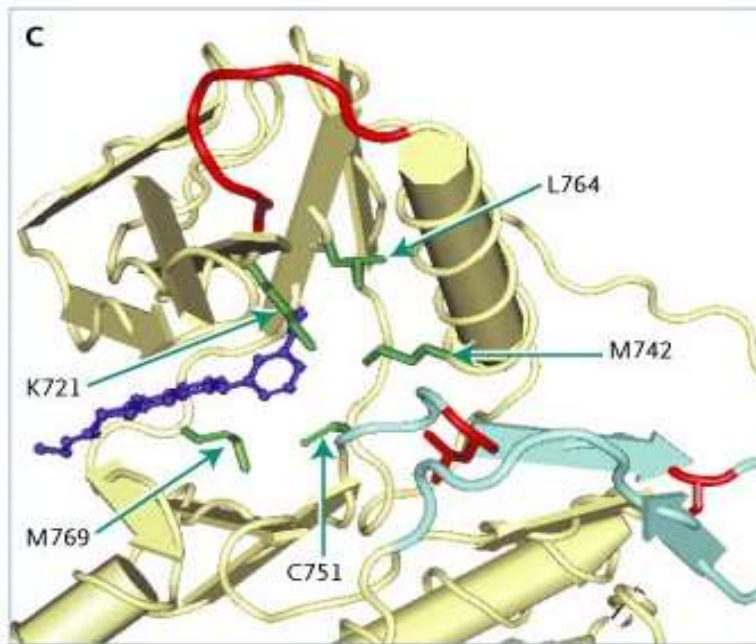
Nature Reviews Cancer 7 : 169-181, 2007

Quel lien entre mutation EGFR et efficacité thérapeutique ?



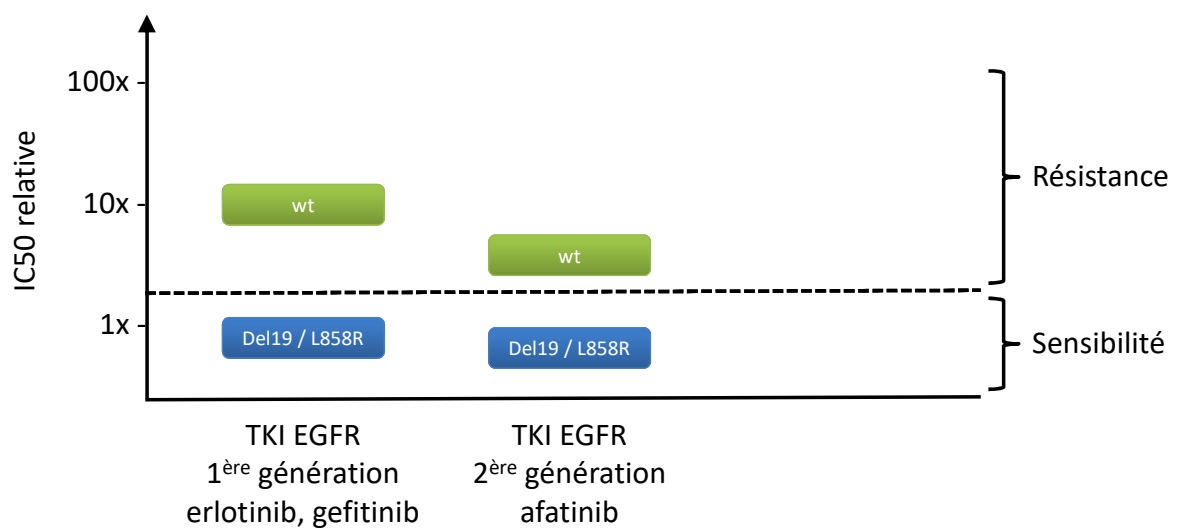
- Analogues structuraux de l'ATP
- Inhibiteurs compétitifs de l'activité TK d'EGFR





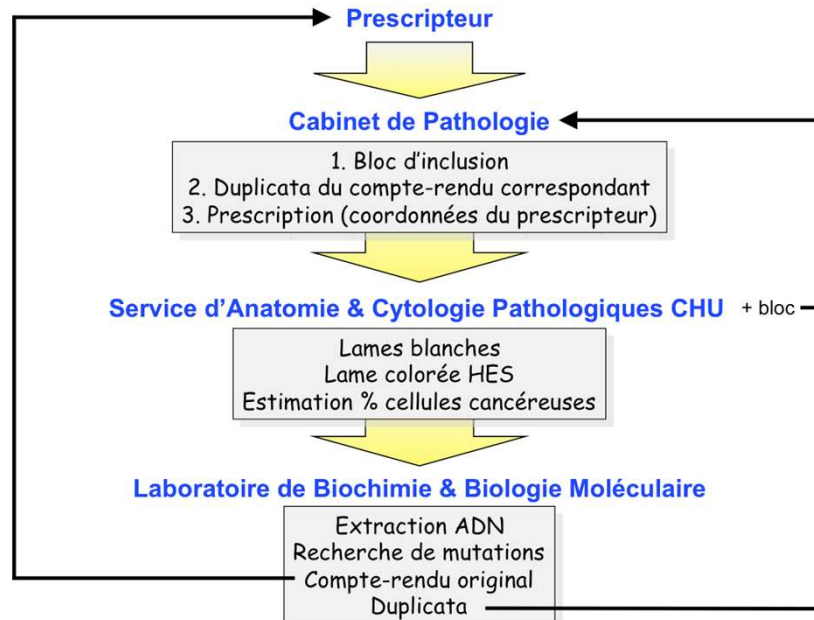
N Engl J Med 350:2129, 2004

Affinité relative des TKI de l'EGFR



Comment rechercher les altérations du gène EGFR ?

1. circuit

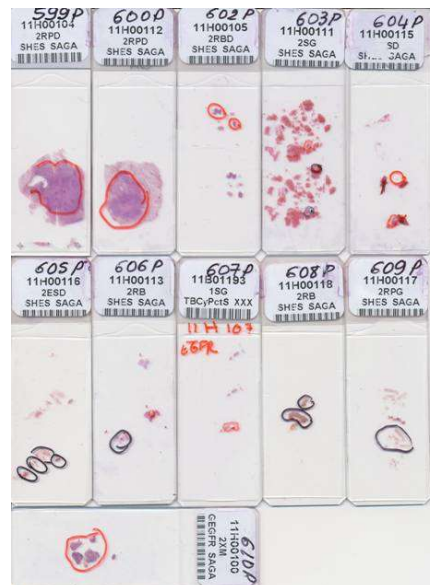


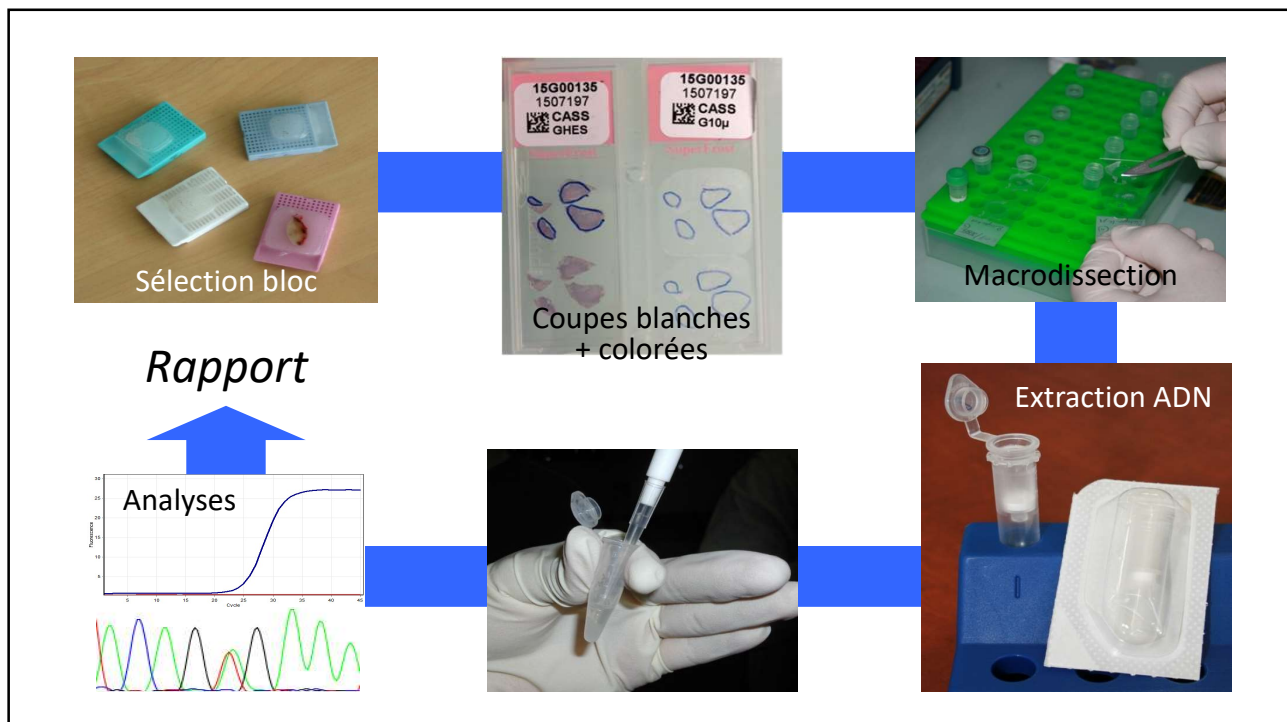
Comment rechercher les altérations du gène EGFR ?

2. Prélèvements

- Biopsies bronchiques
- Biopsies trans-thoraciques
- Biopsies à l'aiguille
- Pièce opératoire
- Liquide pleural
- Liquide Bronchiolo Alvéolaire

- Site primaire
- Site métastatique





Comment rechercher les altérations du gène EGFR ?

3. Techniques



Approches ciblées (PCR spécifique d'allèle)

Ne détectent que les mutations ciblées
Les mutations non recherchées ne sont pas détectées



Plus sensibles que techniques de criblage
Kits disponibles
Plus rapides (et moins chères)



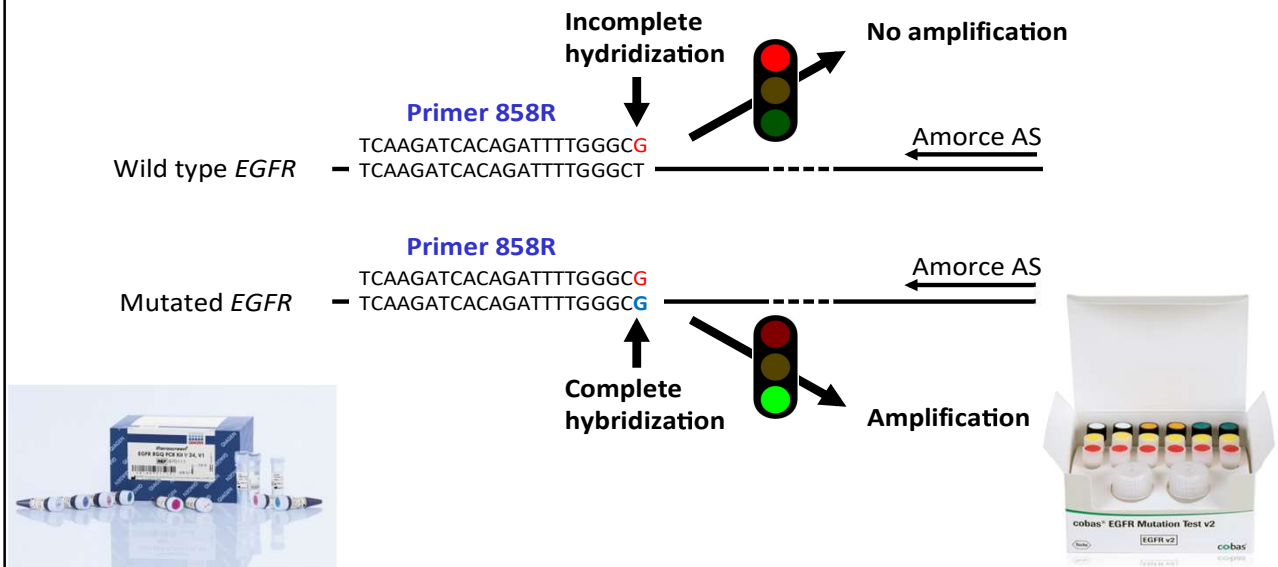
Techniques de criblage (séquençage - NGS)

Détectent toutes les mutations
Analyse de nombreux gènes simultanément



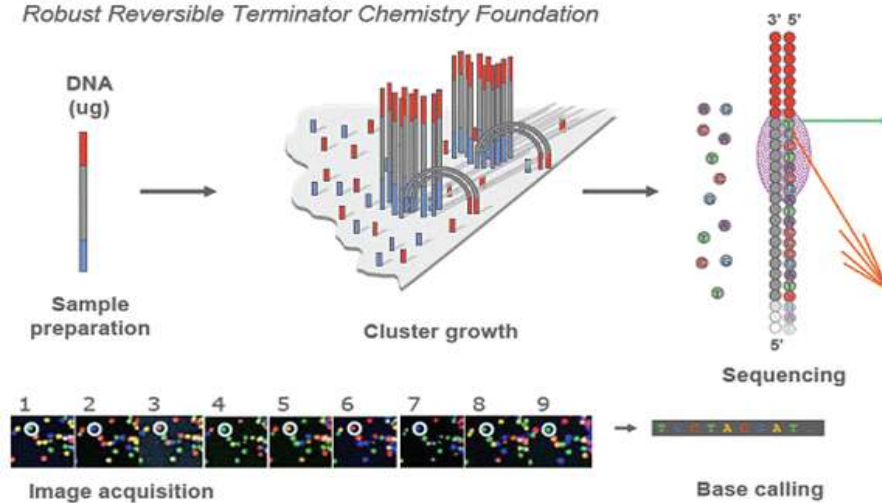
Moins sensibles que techniques ciblées
Plus longues, plus coûteuses

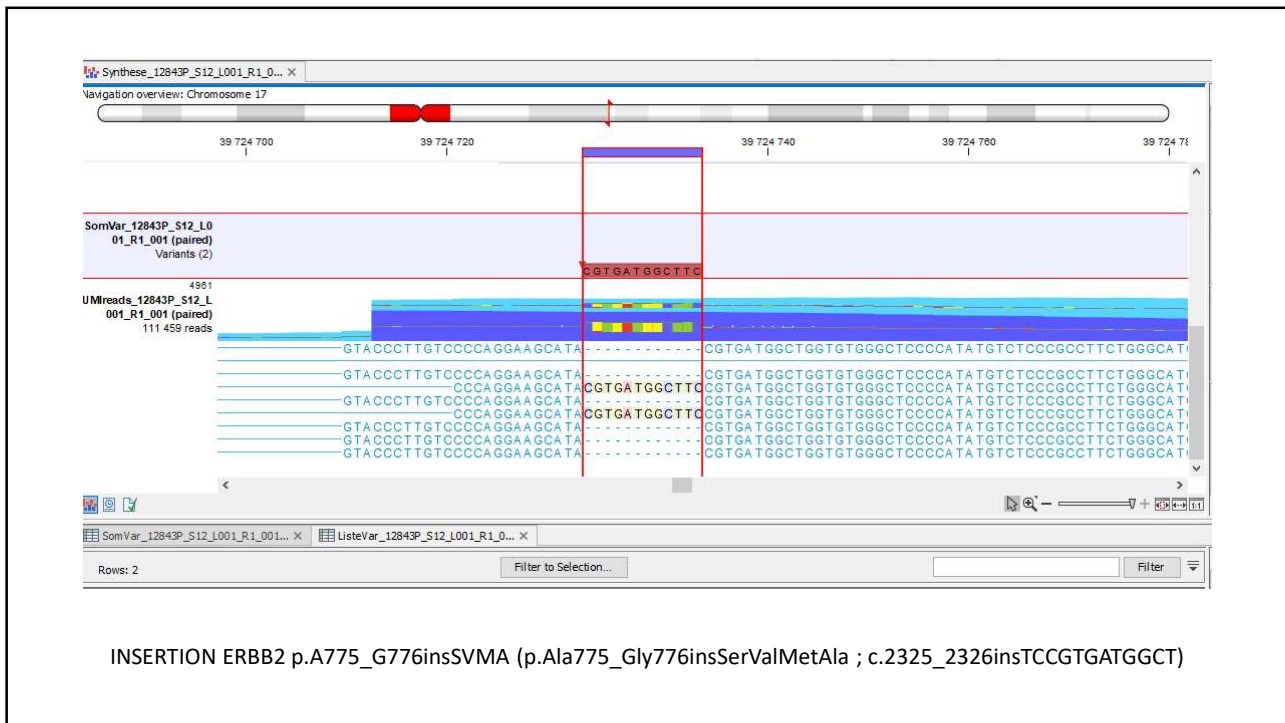
PCR spécifique d'allèle - principe



NGS – séquençage de nouvelle génération

Illumina Sequencing Technology Robust Reversible Terminator Chemistry Foundation





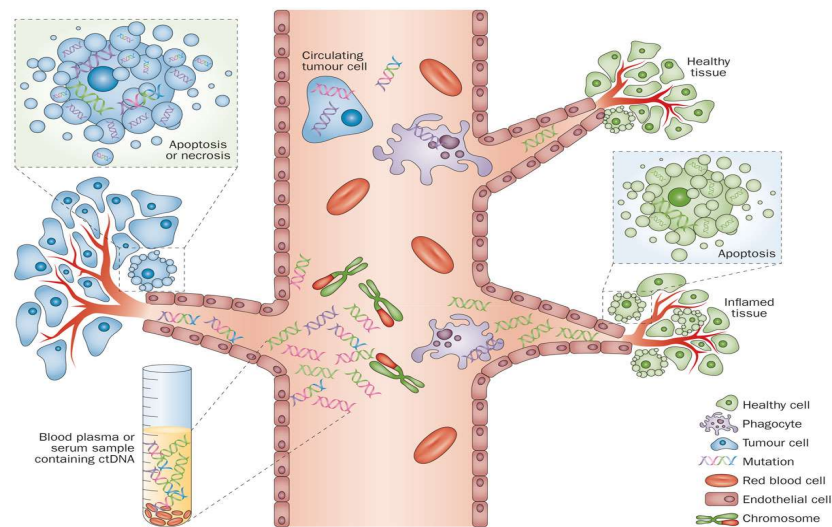
Mais...

- Test tissulaire non réalisable
 - ✓ Pas de prélèvement
 - ✓ Bloc épuisé
- Test non contributif
 - ✓ Faible cellularité
 - ✓ Mauvaise qualité ADN
- Suivi en cours de traitement
- Délai rendu résultat (TAT)



20-25%

ADN circulant – ADN tumoral circulant



Crowley, E. et al. Nat. Rev. Clin. Oncol. 2013

Comment détecter les altérations de la tumeur au niveau de l'ADN circulant ?

Technique :

- **Sensible**
- **Spécifique**

- Allele specific PCR (ARMS)
- PCR digitale
- Next-generation sequencing



IRESSA – EMA

When considering the use of IRESSA as a treatment for locally advanced or metastatic NSCLC, it is important that EGFR mutation assessment of the tumour tissue is attempted for all patients. If a tumour sample is not evaluable, then circulating tumour DNA (ctDNA) obtained from a blood (plasma) sample may be used.

Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status of tumours or ctDNA should be used to avoid false negative or false positive determinations (see section 5.1).

TAGRISSO – EMA

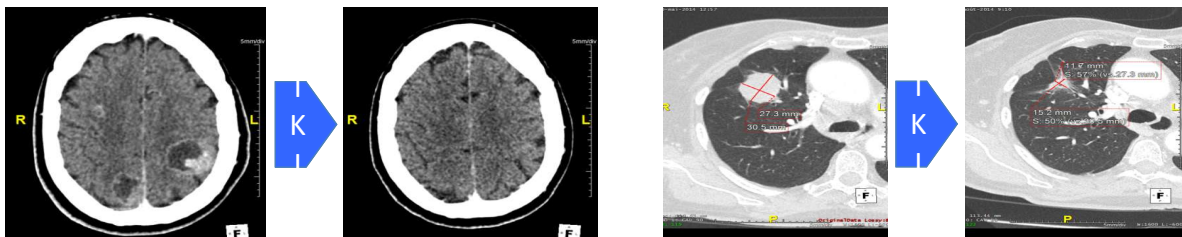
Assessment of EGFR T790M mutation status

When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR T790M mutation status is determined. A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Only robust, reliable and sensitive tests with demonstrated utility for the determination of T790M mutation status of tumour derived DNA (from a tissue or a plasma sample) should be used.

Et ça marche !!!

- Health degradation, dyspnea, neurological disorders
- Numerous brain metastases + bone lesions
- Lung biopsies : not contributive
- Pleural biopsies : adenocarcinoma, TTF1+
- Molecular testing : **long time to result** not compatible with neurological degradation
- Multidisciplinary staff decision : testing of circulating DNA >> **p.L858R**



Mais les patients rechutent !

Femme 63 ans, adénocarcinome, délétion exon 19 EGFR



Avant traitement

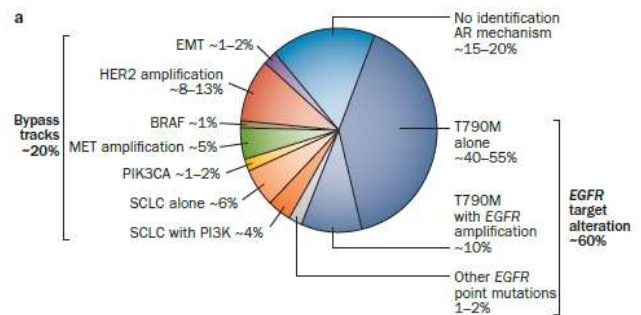
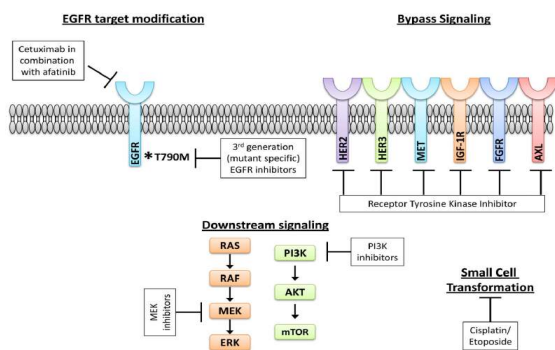


6 mois gefitinib



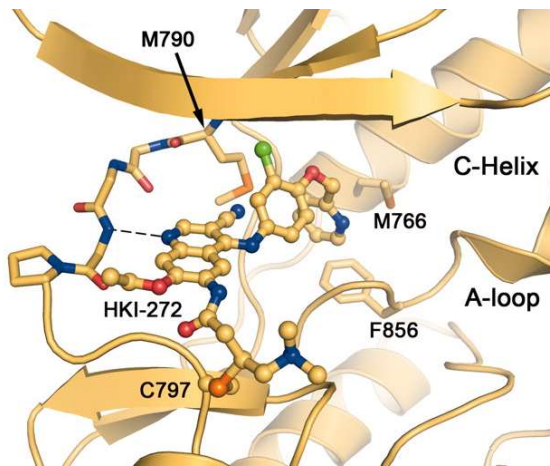
11 mois gefitinib

Résistance acquise aux TKI anti-EGFR



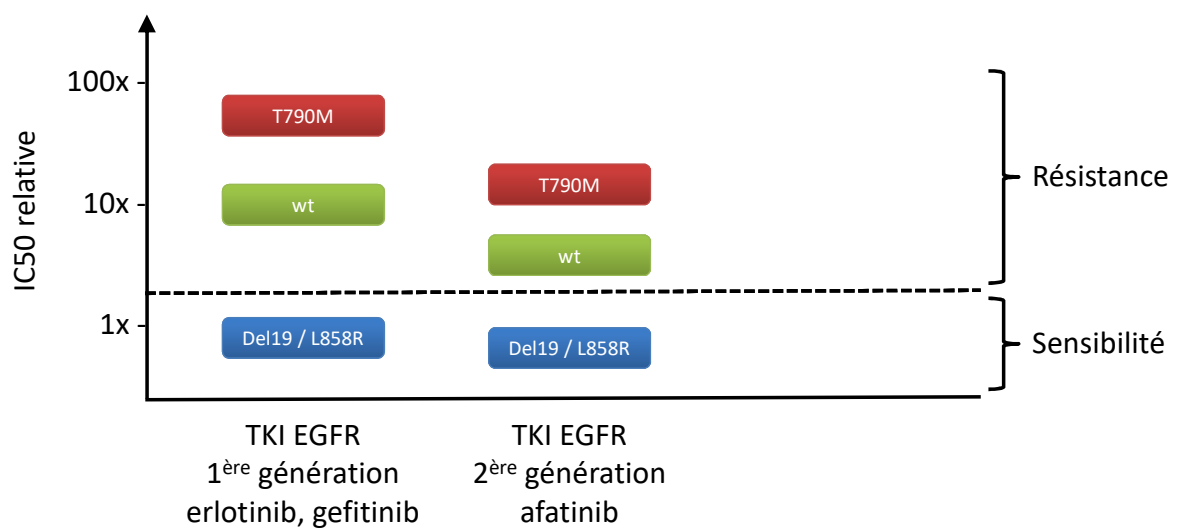
Sequist LV, et al. Sci Transl Med 2011
 Camidge DR, et al. Nat Rev Clin Oncol 2014
 Yu HA, et al. Clin Cancer Res 2013
 Lovly MC. Am Soc Clin Oncol Educ Book

La mutation T790M

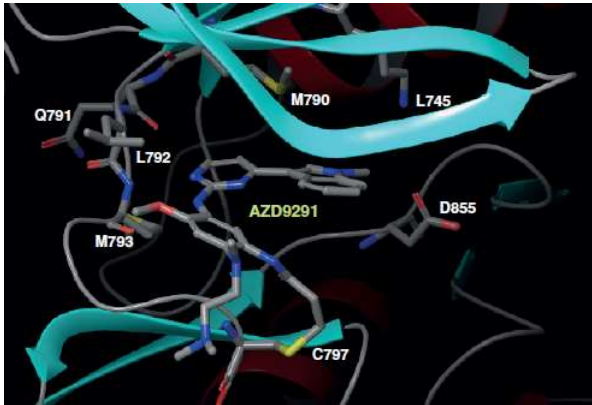


- Affinité augmentée pour ATP
- Inhibition stérique pour liaison TKI 1G/2G

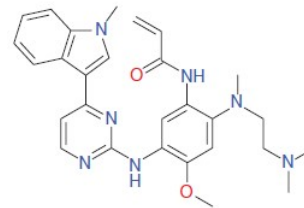
Affinité relative des TKI de l'EGFR



Osimertinib

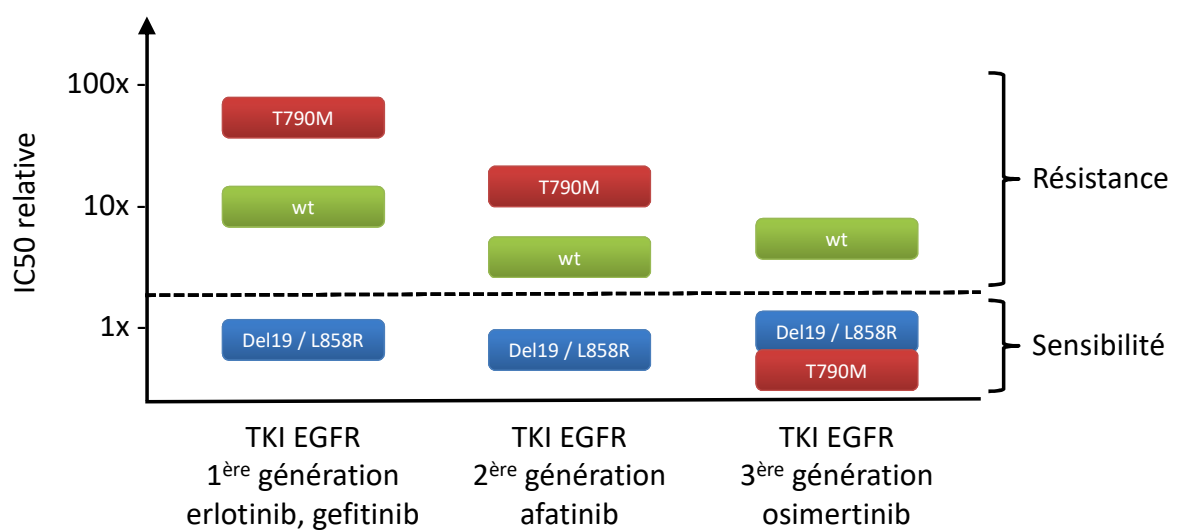


- 3^{ème} génération
- Structure de base différente
- Liaison covalente Cys 797

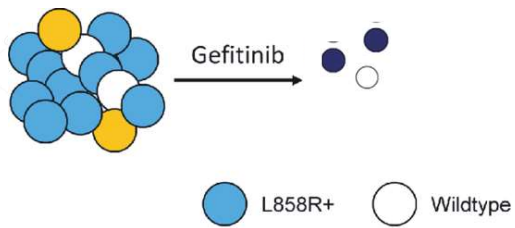


Cross DAE, et al. Cancer Discovery 2014

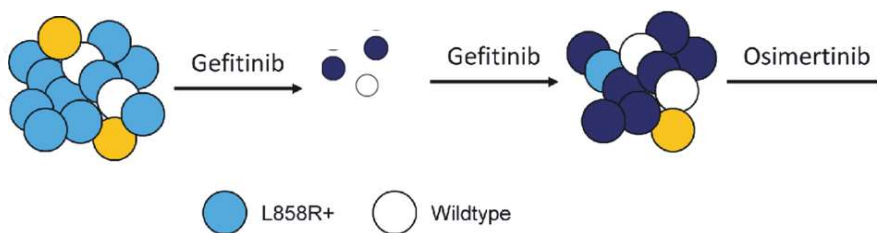
Affinité relative des TKI de l'EGFR



Stratégie de traitements séquentiels chez les patients avec addiction oncogénique

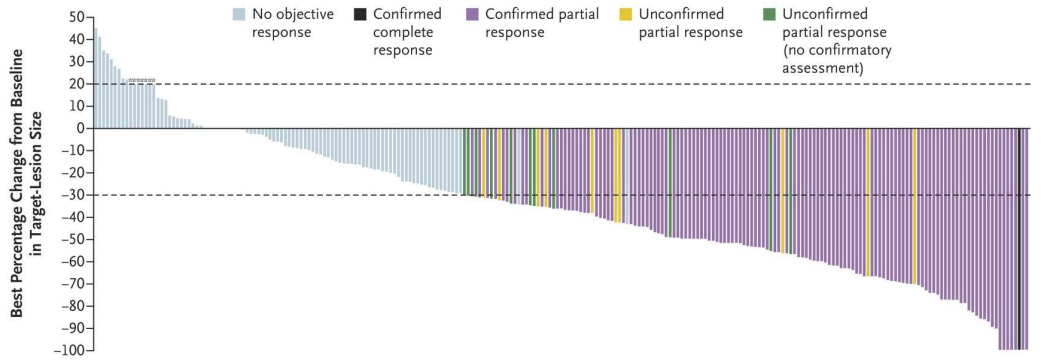


Stratégie de traitements séquentiels chez les patients avec addiction oncogénique



Osimertinib : phase I et phase II AURA chez patients ayant progressés sous TKI 1^{ère} G

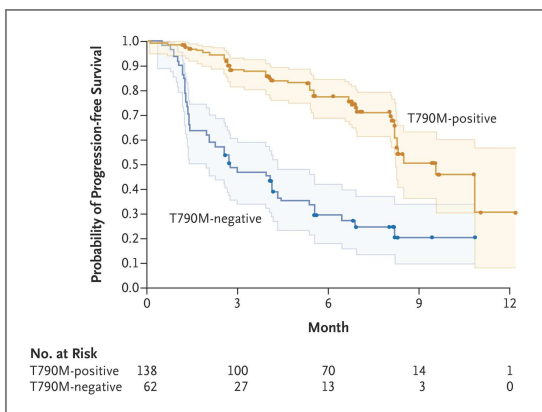
A All patients



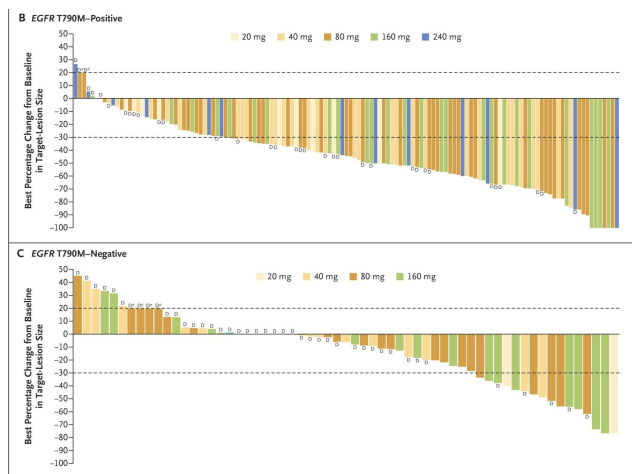
N=253 patients
Réponse objective : 51%

Jänne PA, et al. New Engl J Med 2015
Goss G, et al. Lancet Oncol 2016

Osimertinib : phase I et phase II AURA chez patients ayant progressés sous TKI 1^{ère} G



Réponse objective : 61% versus 21%

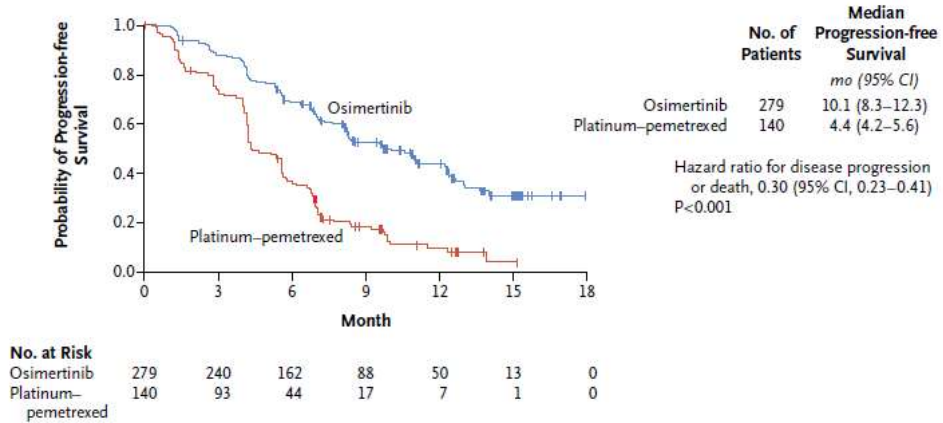


Jänne PA, et al. New Engl J Med 2015
Goss G, et al. Lancet Oncol 2016

Etude AURA 3: phase 3 dans la population EGFRm T790M +

n = 419 patients CBPNPC T790M + progressant après TKI-anti-EGFR (R 2:1)

A Patients in Intention-to-Treat Population



Mok T, et al. N Engl J Med 2016

Quelle stratégie de traitements chez les patients avec addiction oncogénique?

1) Stratégie séquentielle



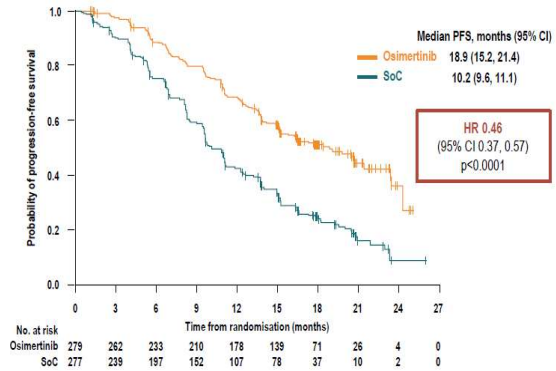
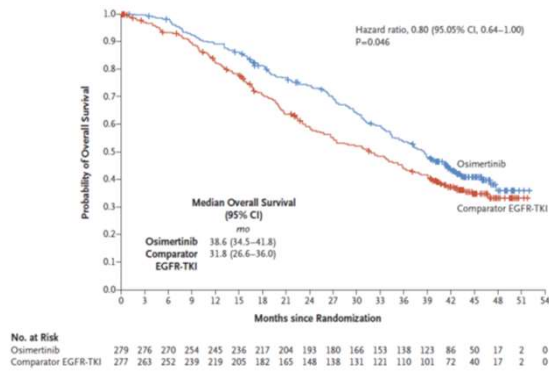
2) Next-generation upfront

Osimertinib en 1^{ère} ligne ?



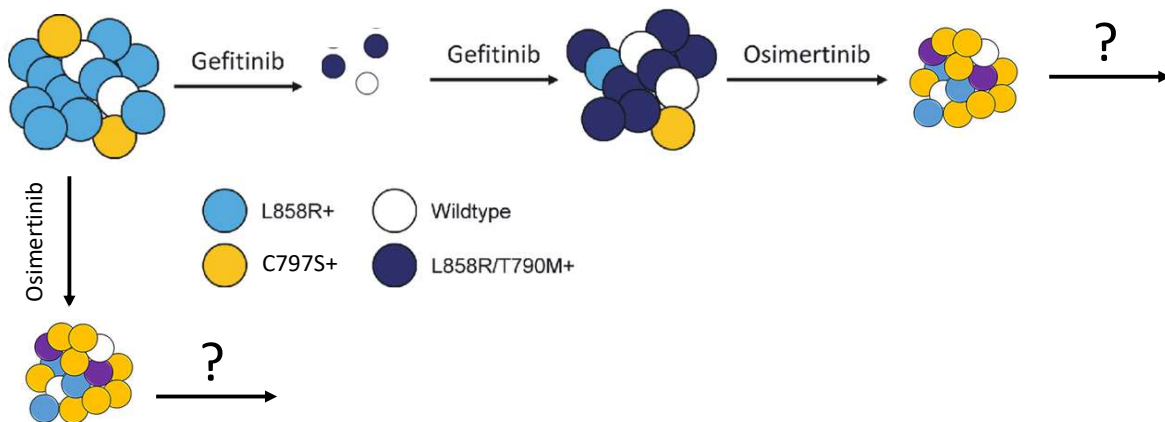
Etude FLAURA: EGFR mutés 1^{ère} ligne, pas de mutation T790M

n = 556 patients CBPNPC EGFR + avancés (del 19 ou L859) en 1^{ère} ligne

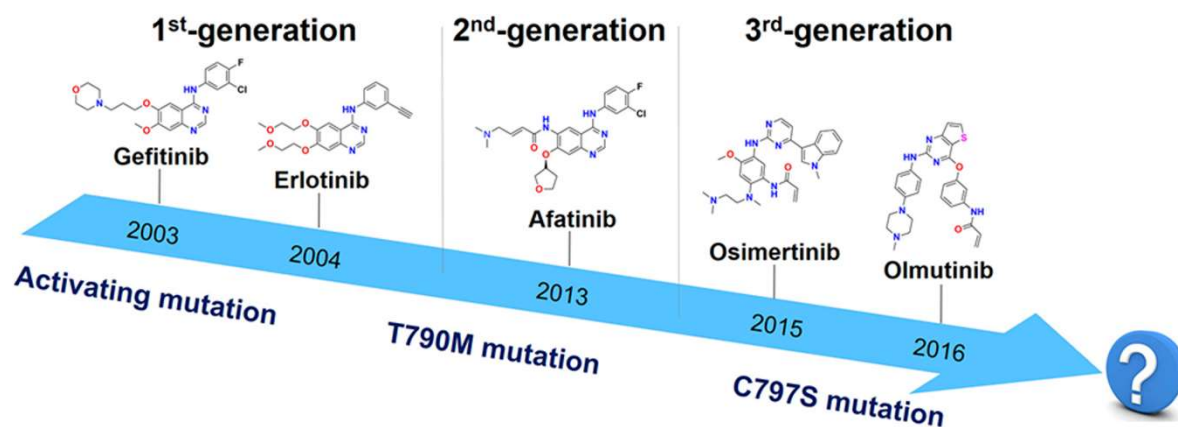
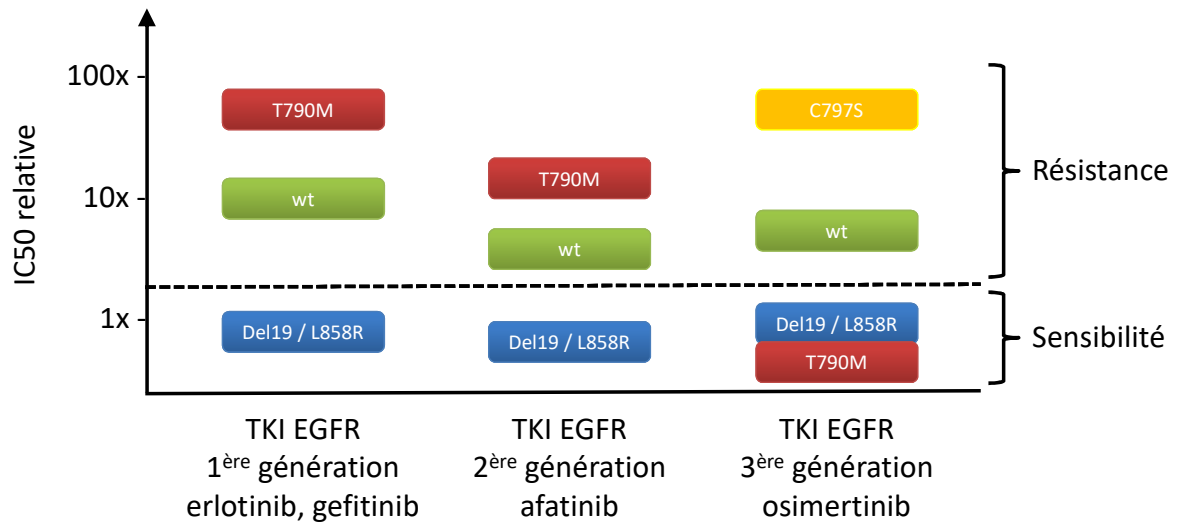


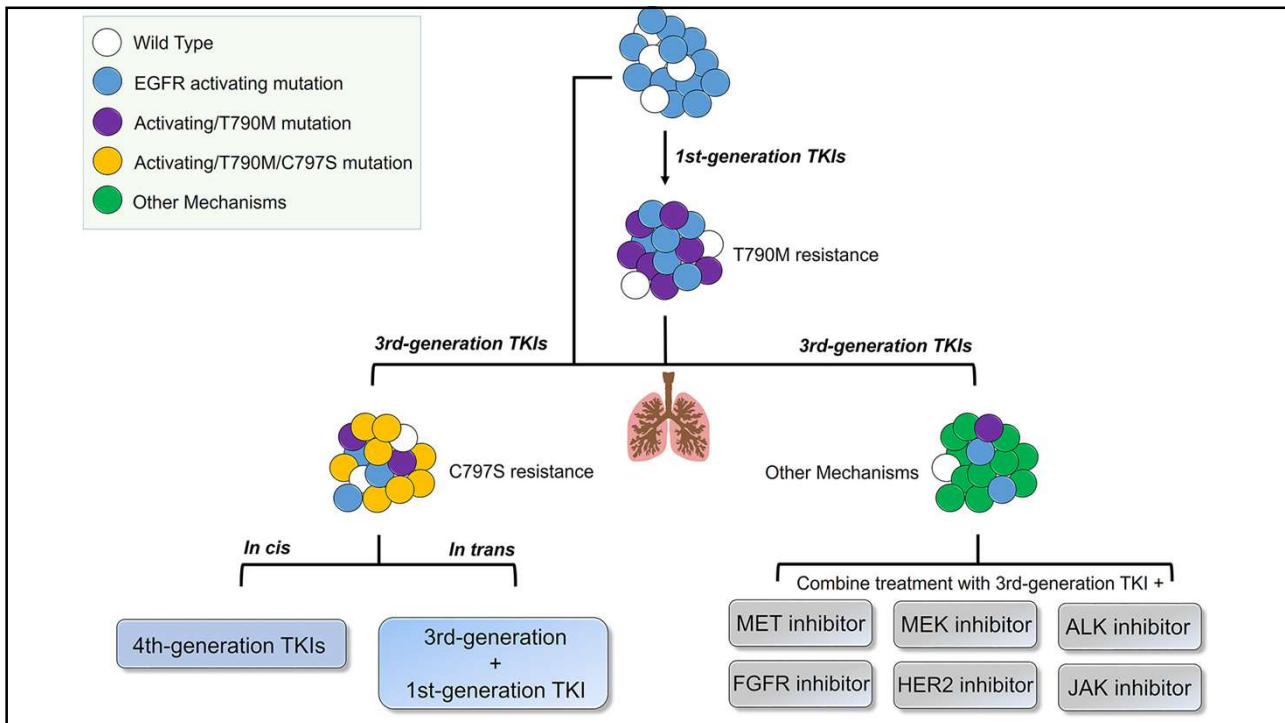
Soria JC, et al. N Engl J Med 2017; Ramaligam SS, et al. 2020

L'histoire continue....



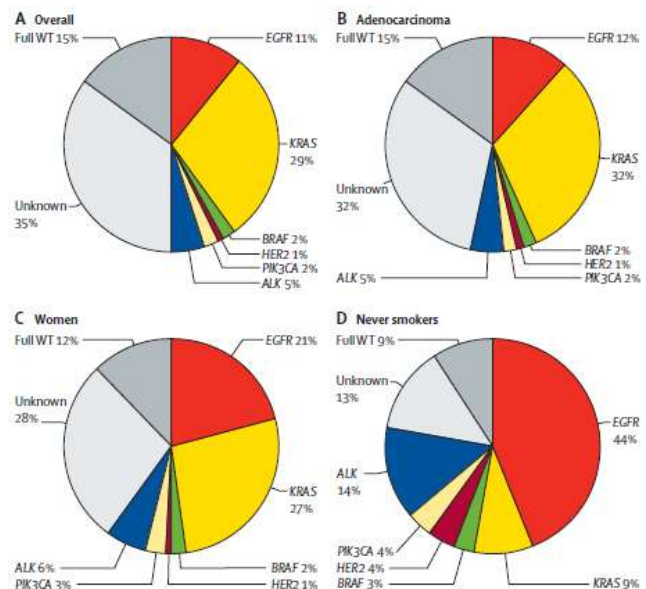
Affinité relative des TKI de l'EGFR





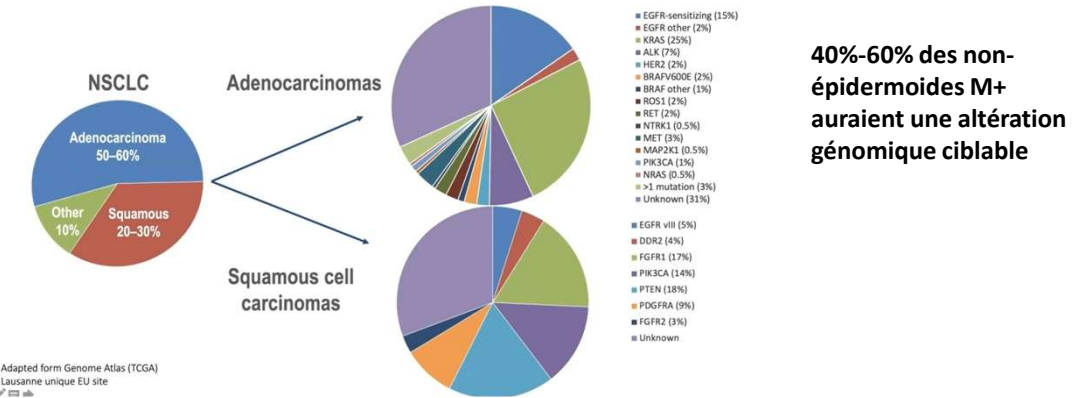
Autres altérations moléculaires Etude Biomarqueurs France

- Etude sur 1 an (2012-2013)
- Caractéristiques moléculaires et cliniques des CBPNPC
- 18 679 analyses moléculaires
- 17 664 patients avec un CBPNPC



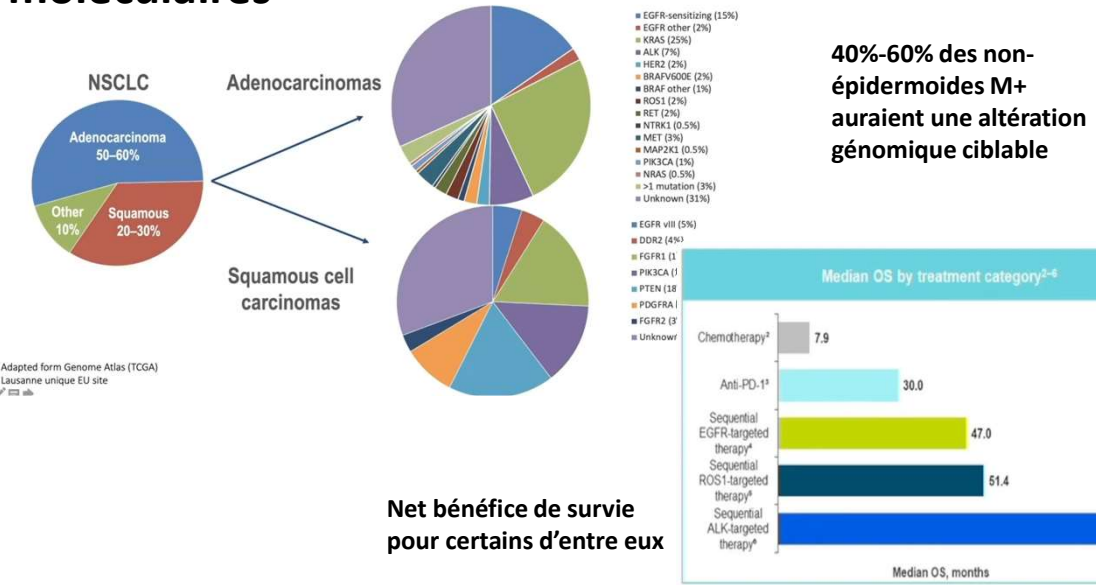
Barlési F, et al. Lancet 2016

Cancer du poumon: de nombreuses autres altérations moléculaires

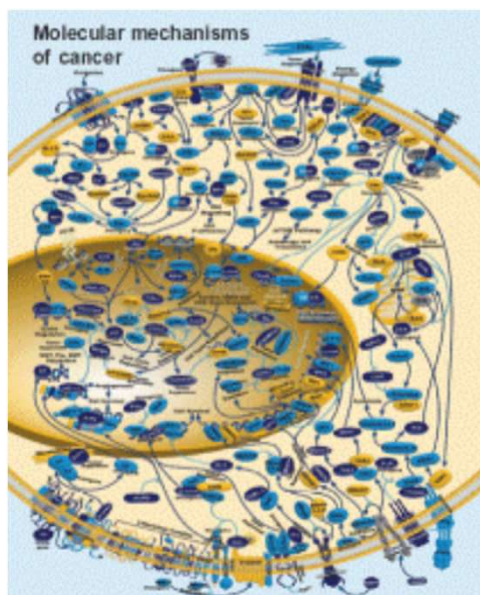


40%-60% des non-épidermoïdes M+ auraient une altération génomique ciblable

Cancer du poumon: de nombreuses autres altérations moléculaires



40%-60% des non-épidermoïdes M+ auraient une altération génomique ciblable



!!! Trouver un gène muté ≠ identifier une cible cliniquement pertinente

Oncogène driver:

In vitro: mutation capable de conférer à la cellule un phénotype cancéreux

In vivo: Oncogénèse dans un modèle murin immuno-tolérant

Les réarrangements ALK

Les propositions thérapeutiques

		Cibles
1 ^{ère} génération	Crizotinib	ALK, MET, ROS1
2 ^{ème} génération	Ceritinib	ALK, ROS1, IGF1
	Alectinib	ALK, RET
	Brigatinib	ALK, ROS1
	Ensartinib	ALK, TrkA, TrkC, ROS, EphA2, c-MET
3 ^{ème} génération	Lorlatinib	ALK, ROS1

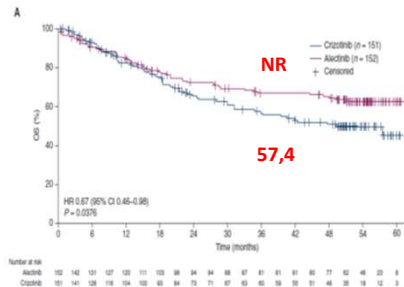
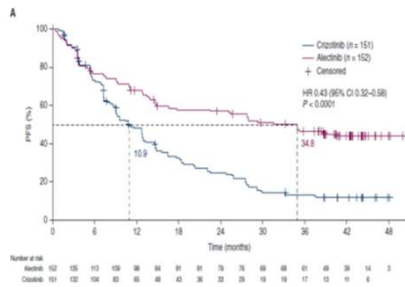
Et aussi Entrectinib, Repotrectinib (ROS1, NTRK)

Etude ALEX

Les paramètres d'efficacité

Toxicités tous grades

- nausées 14 %, vomissements 7 %
- diarrhée 12 %
- oedèmes périphériques 17%, vertiges 8 %, myalgies 16 %
- ALT 15 %, AST 14 %, Bili 15 %
- anémie 20 %



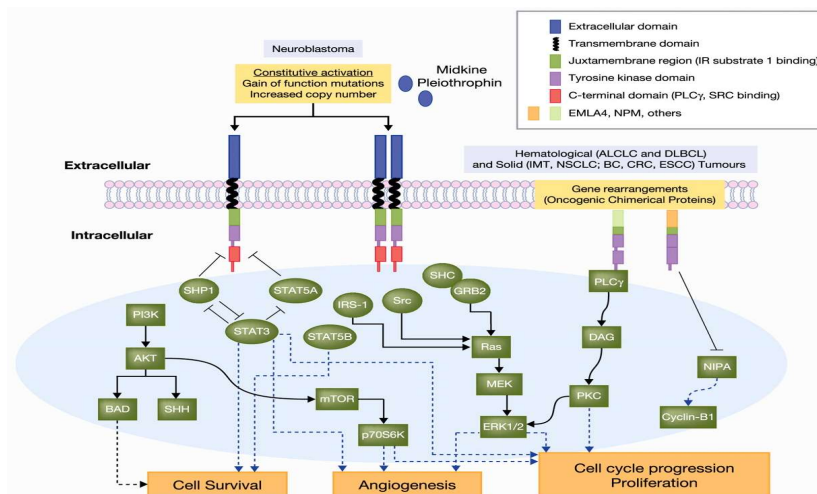
Alectinib 600 mg x 2 par jour
(1 cp = 150 mg)

Traitements à progression

- Bras alectinib : 60,7 % (dont ALKi 38,1 %)
- Crizotinib 63,2 % (dont ALKi 53,5 %, alectinib 21,1 %)

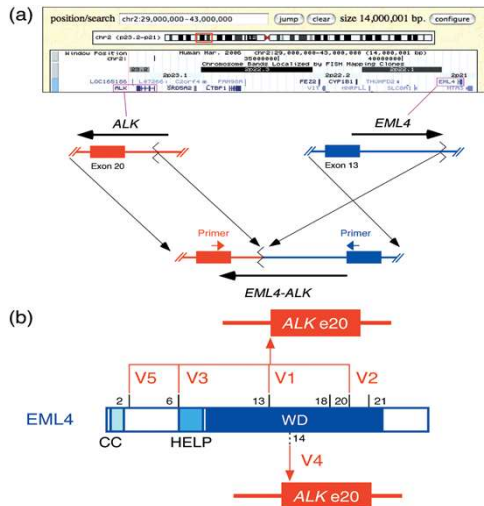
Peters S, et al N Engl J Med 2017 ; Mok T, et al. Ann Oncol 2020

Oncogenic ALK signaling pathway



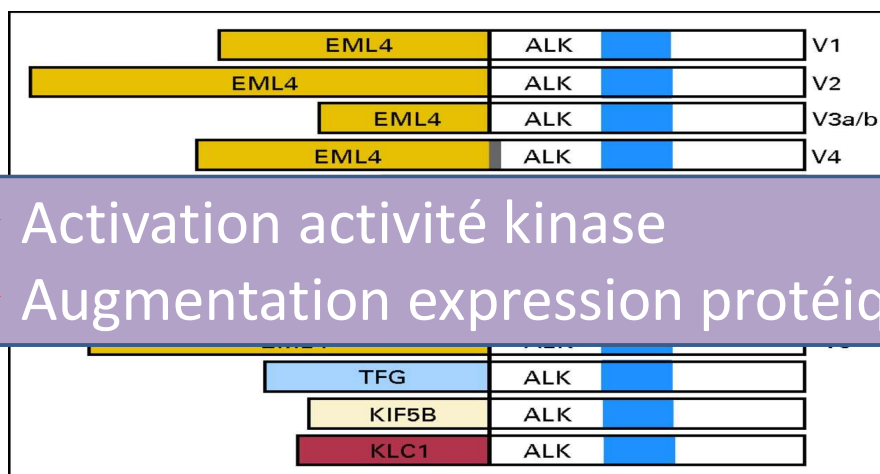
Grande et al., Mol. Cancer Ther. 2011

Translocation du gène ALK dans les CBNPC



Mano, Cancer Science 2008

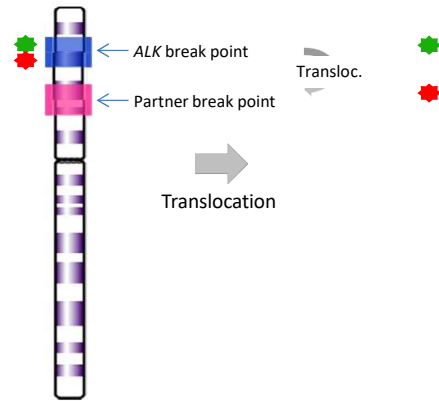
Les principaux transcrits de fusion du gène ALK



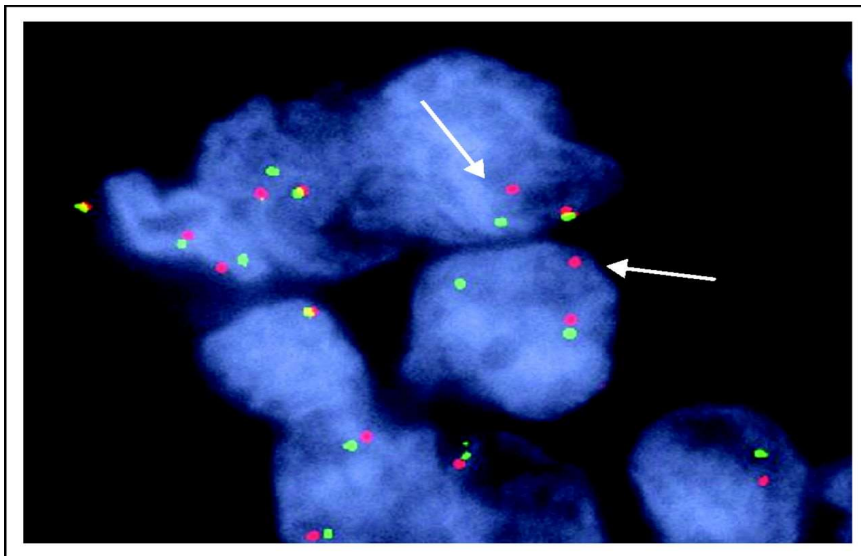
- Activation activité kinase
- Augmentation expression protéique

Shaw & Engelman, J. Clin. Oncol. 2013

Détection des transcrits de fusion par FISH

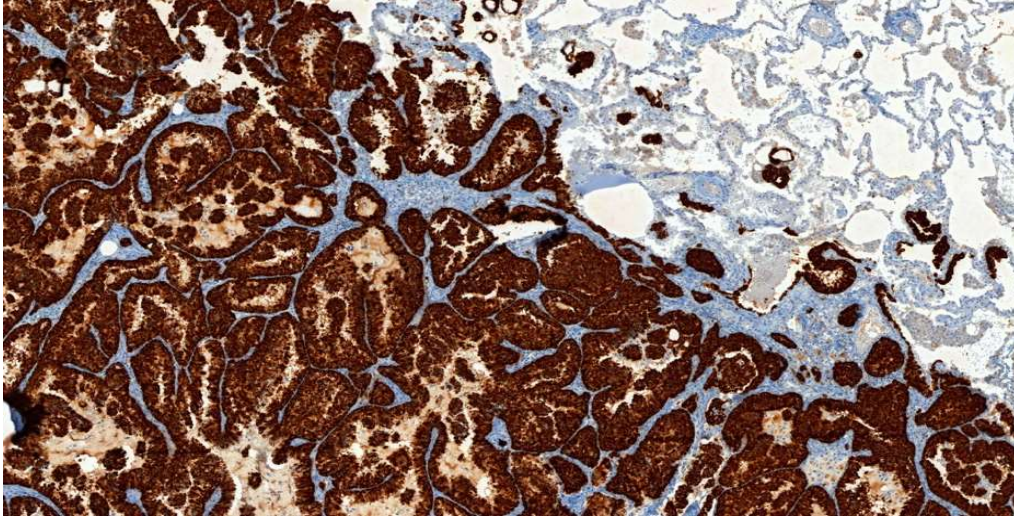


Détection des transcrits de fusion par FISH

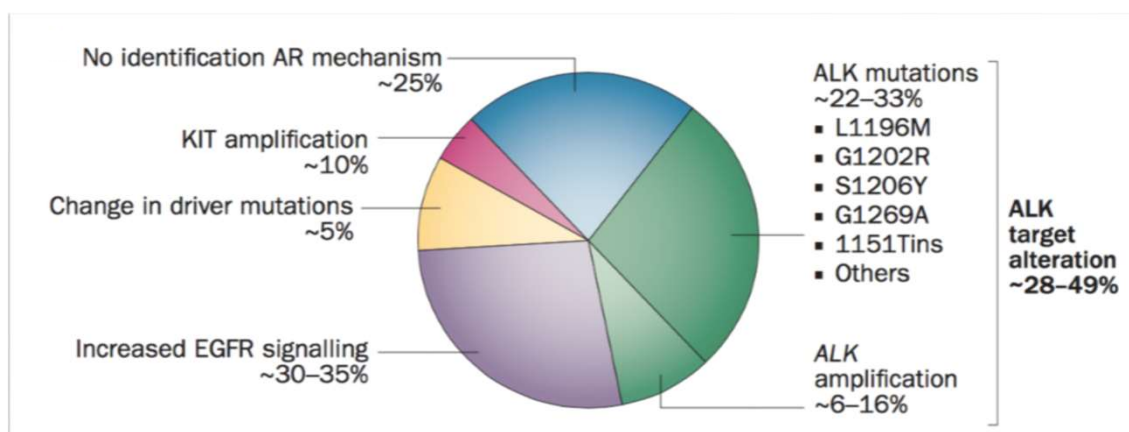


Shaw & Engelman, J. Clin. Oncol. 2013

Criblage par immunohistochimie ALK



Acquisition de mécanismes de résistance au crizotinib

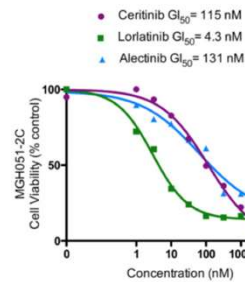


Camidge et al. Nat. Rev. Clin. Oncol. 2014

Mutations ALK et affinité inhibiteurs

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6 ^a	6.1	11.5
EML4-ALK F1174C	115.0	38.0 ^a	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1196F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G12029H	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1289A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N-F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N-E1210K	153.0	97.8	82.8	136.0	26.6

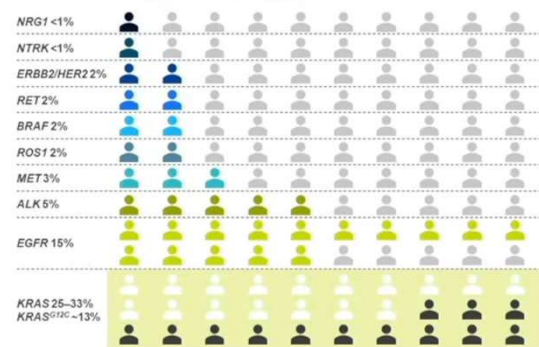
IC₅₀ ≤ 50 nmol/L
 IC₅₀ > 50 < 200 nmol/L
 IC₅₀ ≥ 200 nmol/L



Gainor et al., Cancer Discov 2016

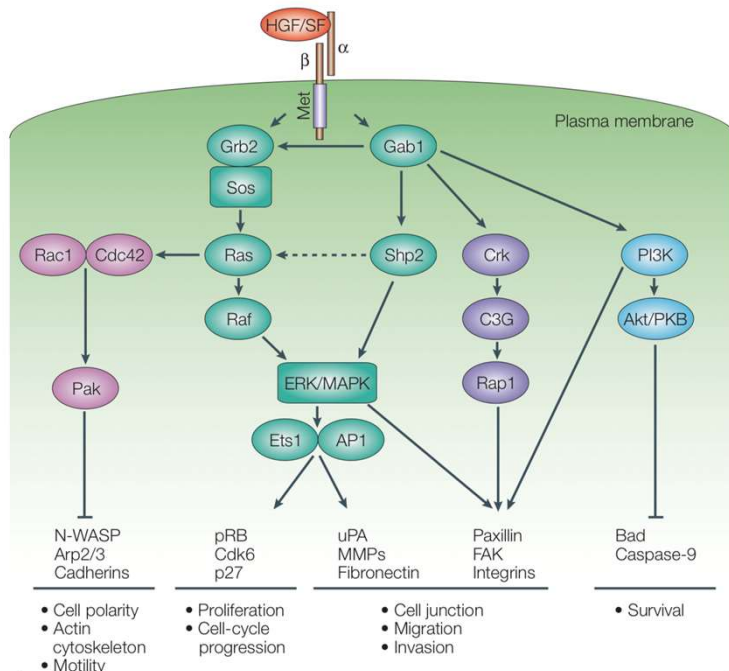
Conclusions

- Le CBPNPC de stade IV est une maladie très hétérogène sur le plan moléculaire.
- Les tests moléculaires sont le **standard** dans les prises en charges des patients avec un CBPNPC stade IV.
 - Réarrangement ALK: crizotinib, ceritinib, alectinib, lorlatinib
 - Mutation EGFR: afatinib, erlotinib, gefitinib, osimertinib
 - Réarrangement ROS: crizotinib, lorlatinib
- De nombreuses pistes ...

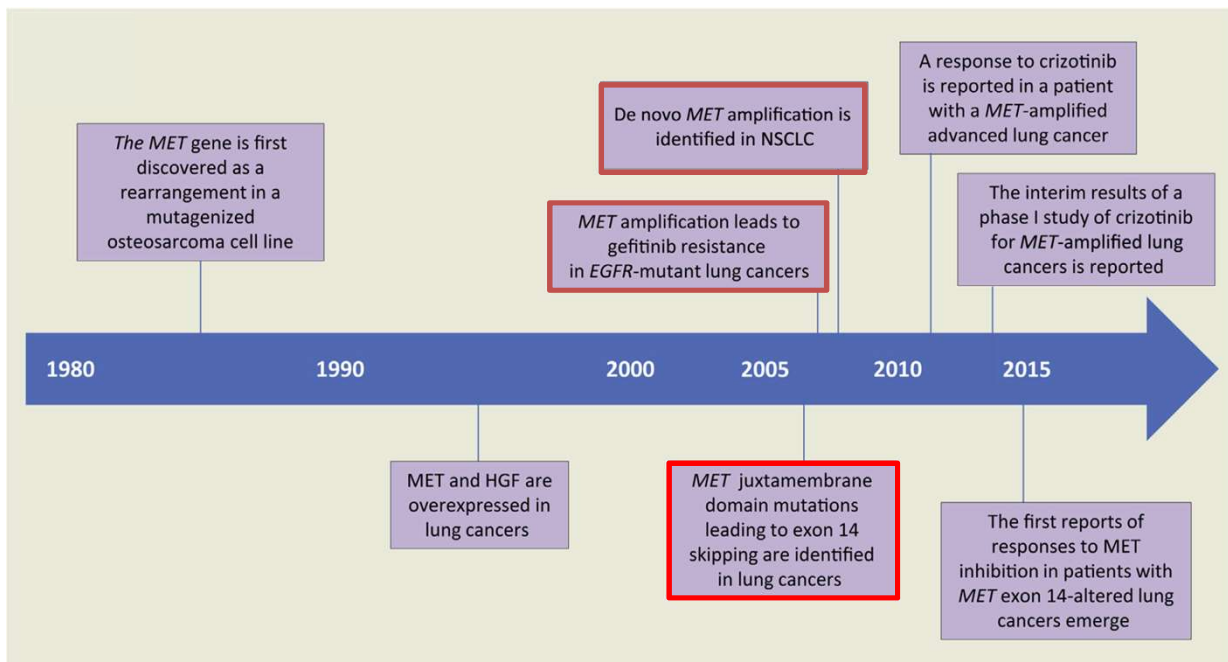


Modified from C. Lohy, presented at the International Lung Cancer Summit 2021

C-Met et voies de signalisation

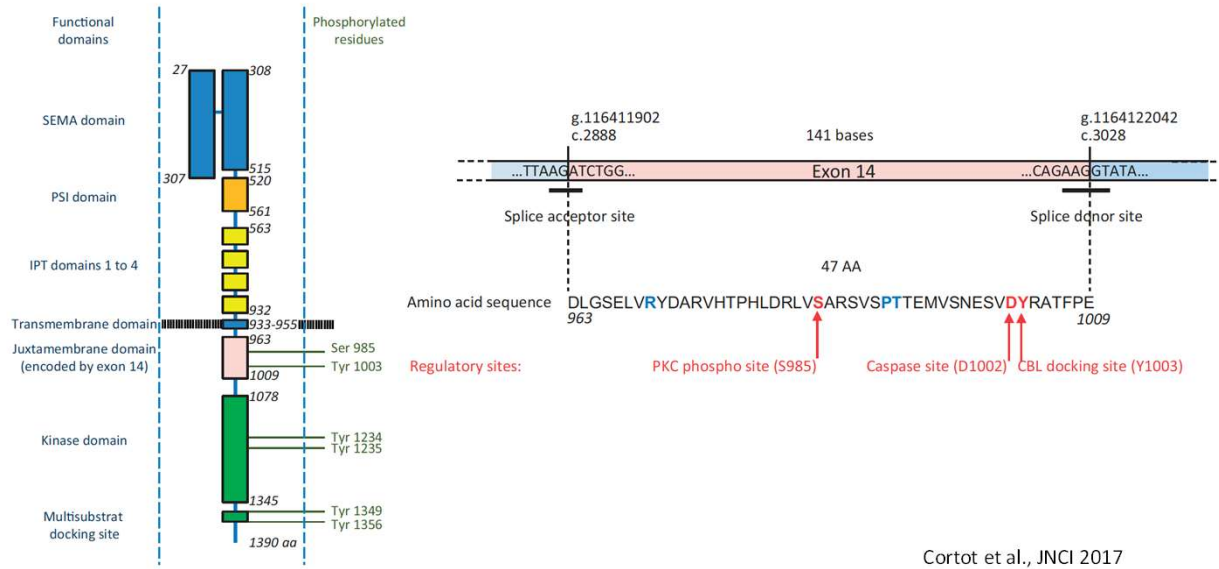


Birchmeier et al., Nature Reviews 2003

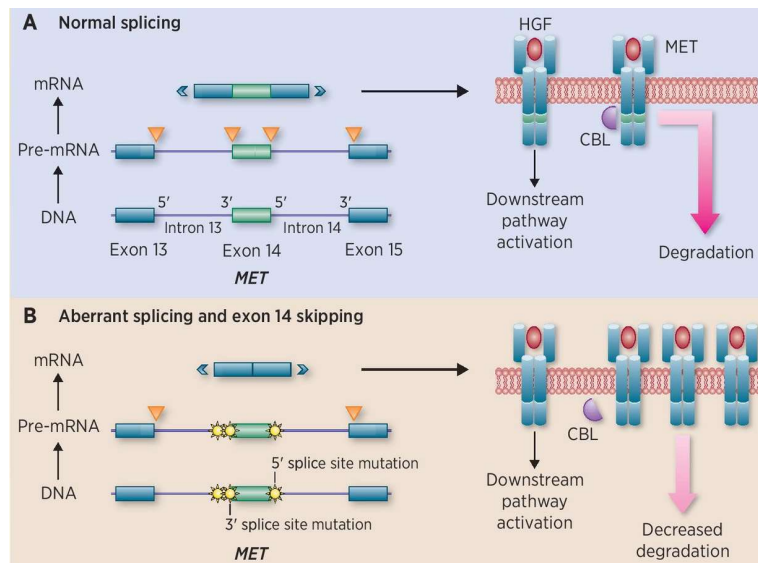


Drilon et al., JTO 2016

c-Met (hepatocyte growth factor receptor)



Saut de l'exon 14 de MET



Drilon, Clin Cancer Res 2016

PRECISION MEDICINE

Characterization of Non-Small-Cell Lung Cancers With MET Exon 14 Skipping Alterations Detected in Tissue or Liquid: Clinicogenomics and Real-World Treatment Patterns

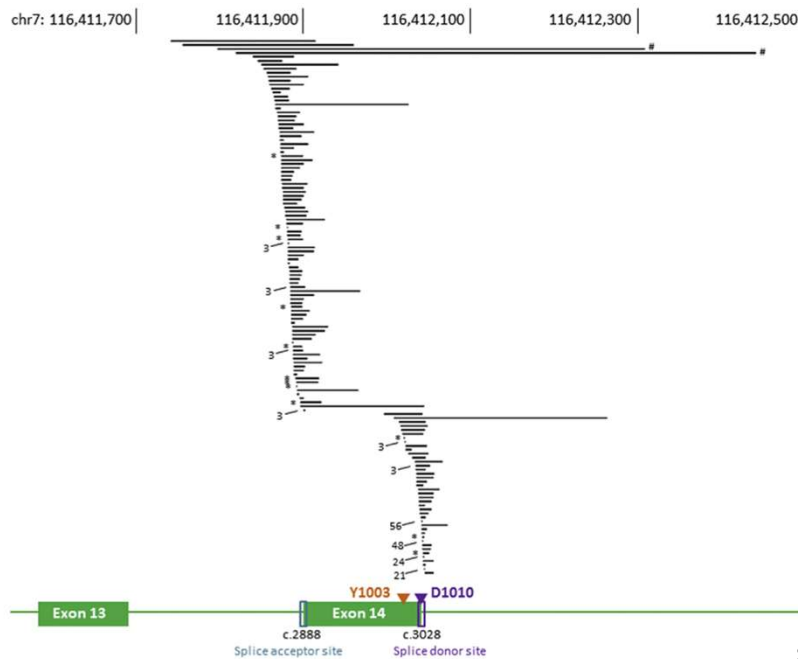
Jessica K. Lee, MS¹; Russell Madison, MS¹; Anthony Classon, MSc¹; Ole Gjoerup, PhD¹; Mark Rosenzweig, PhD¹; Garrett M. Frampton, PhD¹; Brian M. Alexander, MD, MPH¹; Geoffrey R. Oxnard, MD¹; Jeffrey M. Venstrom, MD¹; Mark M. Awad, MD, PhD²; and Alexa B. Schrock, PhD¹

TABLE 1. Clinical and Molecular Characteristics of Patients With NSCLC Harboring *MET* Exon 14 Alterations by Functional Site

Characteristics	<i>MET</i> Exon 14 WT NSCLC Patients	All <i>MET</i> Exon 14 Patients	PPT	Acceptor	Alters Multiple 5' Sites	Y1003	D1010	Donor	Alters Multiple 3' sites	Whole Exon Deletion
Total cases	67,627	1,592	276	36	208	36	353	496	187	7
Tissue cases, % (n)	87 (58,786)	92 (1,458)	91 (251)	92 (33)	94 (196)	100 (36)	91 (322)	91 (449)	91 (170)	100 (7)
ctDNA cases, % (n)	13 (8,841)	8.4 (134)	9.1 (25)	8.3 (3)	5.8 (12)	0.0 (0)	8.8 (31)	9.5 (47)	9.1 (17)	0.0 (0)
Sex (M:F), %	50:50	44:56	49:51	56:44	45:55	44:56	43:57	40:60	44:56	43:57
Median age, years, % (n)	67	75	76	78	75	76	75	73	73	79
< 65	42 (28,260)	15 (236)	16 (45)	11 (4)	17 (35)	14 (5)	12 (42)	16 (78)	15 (28)	0.0 (0)
≥ 65	58 (39,191)	85 (1,351)	84 (230)	89 (32)	83 (173)	86 (31)	88 (311)	83 (414)	85 (159)	100 (7)

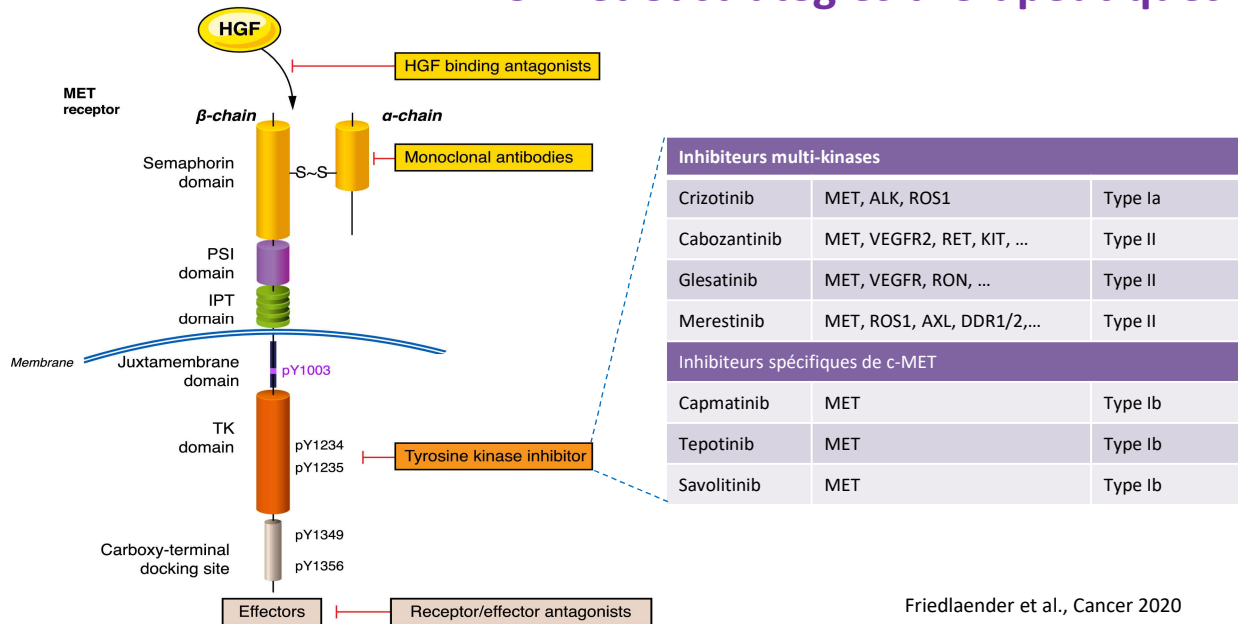
2,4%

JCO Precis Oncol 5:1354-1376. © 2021

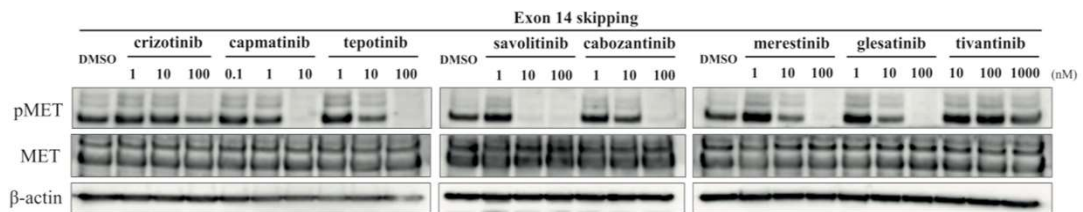


Schrock et al. JTO 2016

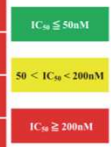
C-Met et stratégies thérapeutiques



Efficacité in vitro d'inhibiteurs de c-Met



Origin	Mutation	Type Ia		Type Ib		Type II			Type III
		crizotinib	capmatinib	tepotinib	savolitinib	cabozantinib	merestinib	glesatinib	tivantinib
Ba/F3	Wild type + IL3	> 1000	> 1000	> 1000	> 1000	> 1000	408	842	715
	Exon 14 skipping	22	0.6	3.0	2.1	7.8	8.1	21	206
	Y1003F	19	0.6	2.4	2.5	8.6	6.9	26	633
	D1010Y	20	0.4	1.3	2.0	7.5	6.4	18	609
	TPR-MET	68	2.2	24	8.8	86	28	189	736
Human gastric cancer	Hs746t (Exon 14 skipping)	47	1.6	2.2	119	46	191	331	92



Fujino et al., JTO 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeek, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griesinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van de T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. John, J. Scheele, J.V. Heymach, and X. Le

Best Response to Capmatinib — MET Exon 14 Skipping Mutation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capmatinib in MET Exon 14–Mutated or MET–Amplified Non–Small-Cell Lung Cancer

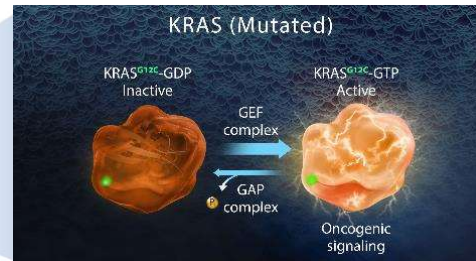
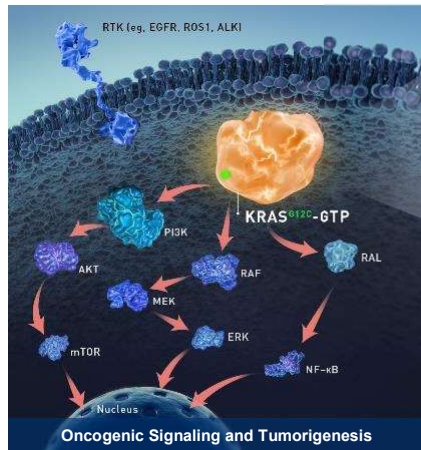
J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

KRAS

KRAS (Wild-Type)

KRAS cycles between active and inactive states, serving as an on/off molecular switch to regulate downstream signaling

KRAS Mutations Promote Oncogenic Signaling and Support Cancer Cell Growth and Survival

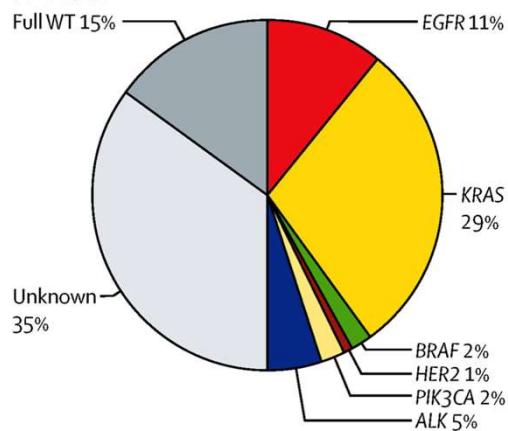


KRAS mutations favor the active form of the KRAS mutant protein and support oncogenic signaling

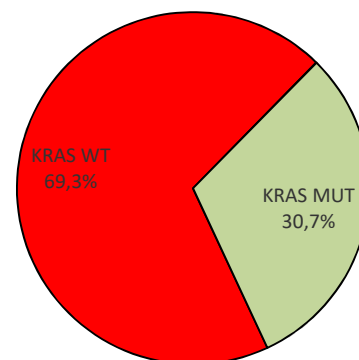
KRAS : altération fréquente dans les CBNPC

Etude Biomarqueurs France

A Overall



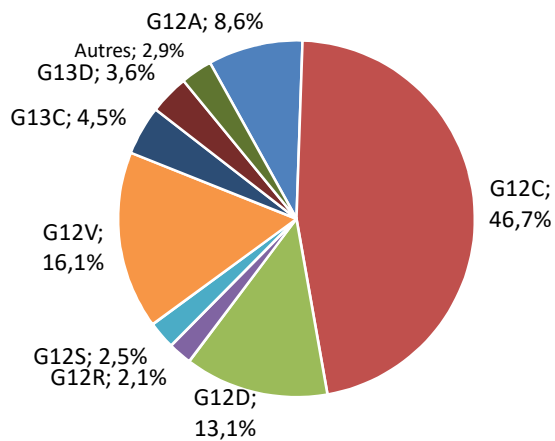
Activité Nantes (n=1821)



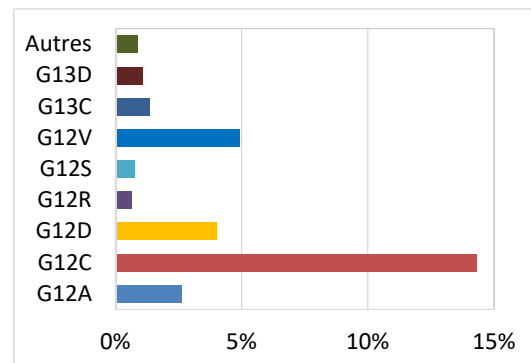
Barlesi et al., Lancet Oncol 2016

La mutation *KRAS* G12C est la plus fréquente

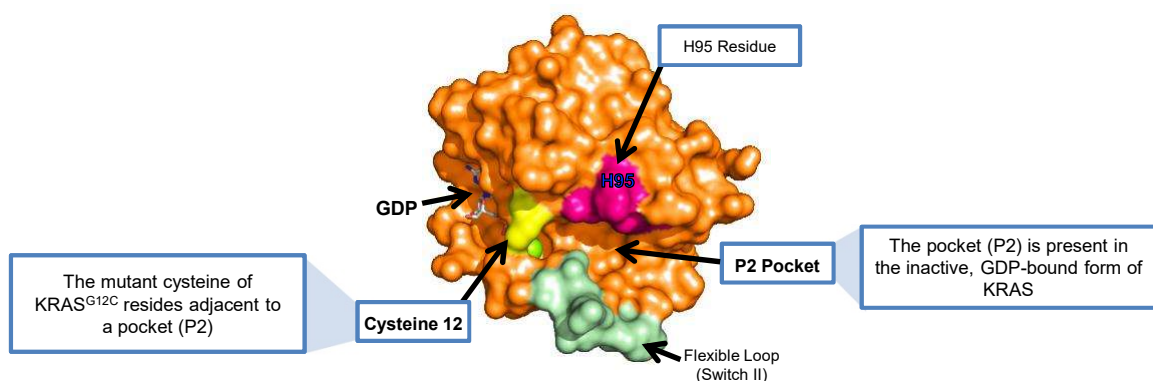
Répartition des mutations



Fréquences dans tumeurs testées (n=1821)

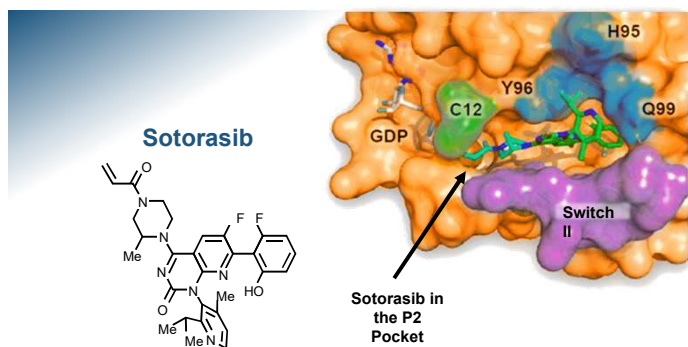


The G12C Mutation Creates a Narrow, Targetable Pocket on the Inactive Form of KRAS



Advances in understanding the structure of KRAS have prompted investigations of potential molecules to target KRAS

Discovery of a Binding Pocket on KRAS^{G12C} Provided a Path for Druggability

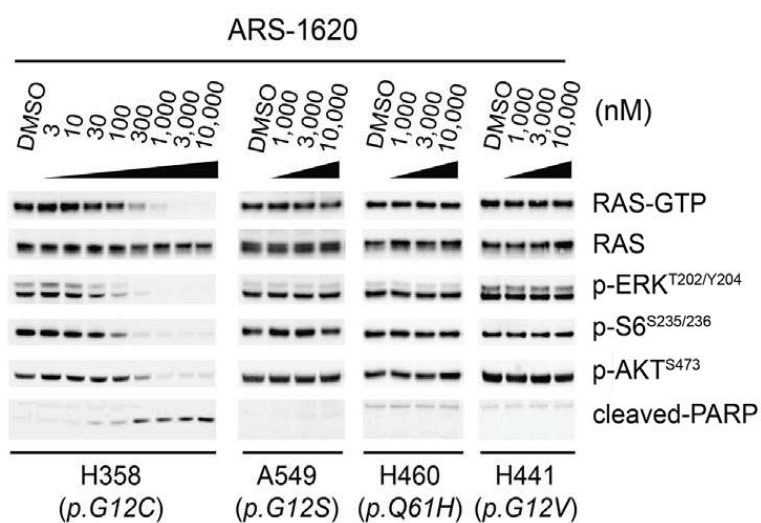


- Sotorasib is an oral, small molecule that selectively binds to the KRAS^{G12C} GDP-bound protein
- Sotorasib binds covalently to C12 and resides in a small pocket (P2) on the KRAS^{G12C} protein
- Sotorasib locks the KRAS G12C mutant protein in an inactive state, preventing oncogenic signaling without affecting wild-type KRAS signaling
- Sotorasib utilizes a surface groove and histidine (H95) to enhance binding, resulting in increased potency and selectivity

Sotorasib is a selective inhibitor of the KRAS^{G12C} protein

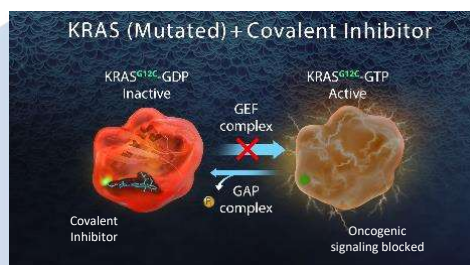
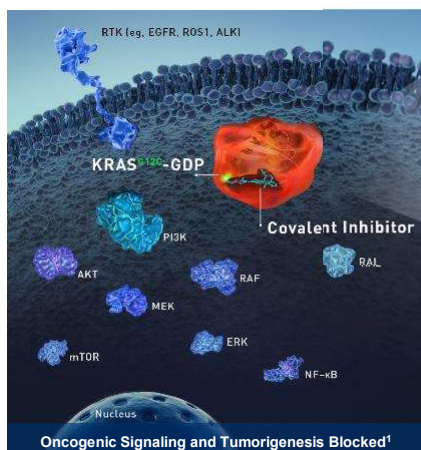
Ryan et al. Nat Rev Clin Oncol. 2018;15:709-720; Canon et al. Nature. 2019;575:217-223

Comment ça marche ?



Janes et al., Cell 2018

Inhibition of KRAS^{G12C} Represents an Important Therapeutic Approach in NSCLC



By utilizing the KRAS^{G12C} binding pocket, covalent inhibitors can lock KRAS^{G12C} in the inactive state, blocking cancer cell proliferation and survival, without affecting wild-type KRAS signaling

Inhibiteurs disponibles dans le cadre d'ATU

Molécule	Laboratoire	Tumeurs ciblées	Ligne	Essai
Mobocertinib (TAK788)	Takeda	CBNPC avancé/métastatique	2L après platine	NCT02716116
Poziotinib	Spectrum Pharmaceuticals	EGFR ins20	2L	ZENITH20
Capmatinib	Novartis		2L	GEOMETRY Mono-1
Tepotinib	Merck	CBNPC avancé/métastatique	2L	VISION
Crizotinib	Pfizer	MET exon 14	2L après platine (RTU)	A8081001 PROFILE1001
Pralsetinib (BLU667)	BluePrint Medicines	CBNPC avancé/métastatique	2L après platine	ARROW
Selpercatinib (LOXO292)	Lilly	RET réarrangé	2L après platine	LIBRETTO 001
Sotorasib (AMG510)	AMGEN	CBNPC avancé/métastatique KRAS G12C	2L	FLATIRON

Conclusions

- De nombreuses pistes :
 - Identifier les “bonnes” cibles,
 - et développer les “bons” inhibiteurs

