Groupe d'Oncologie de Langue Française

CBNPC, les autres cibles:
KRAS, HER2, BRAF, MET

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Tobacco-industry and tobacco corporate affiliate related conflict of interest	**NO**
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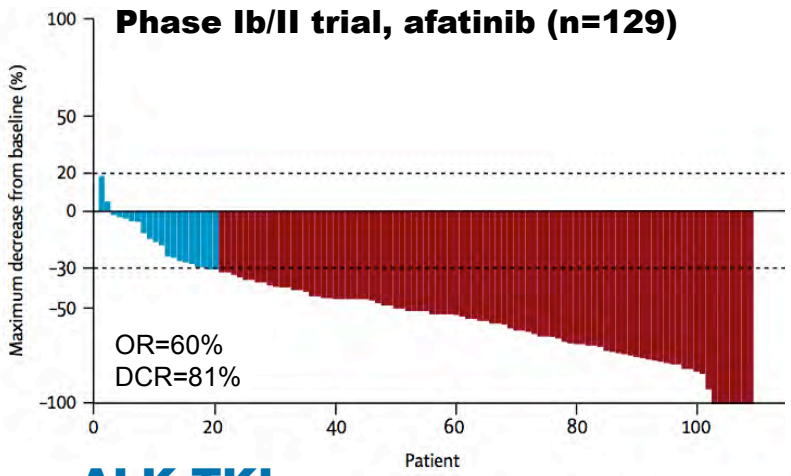
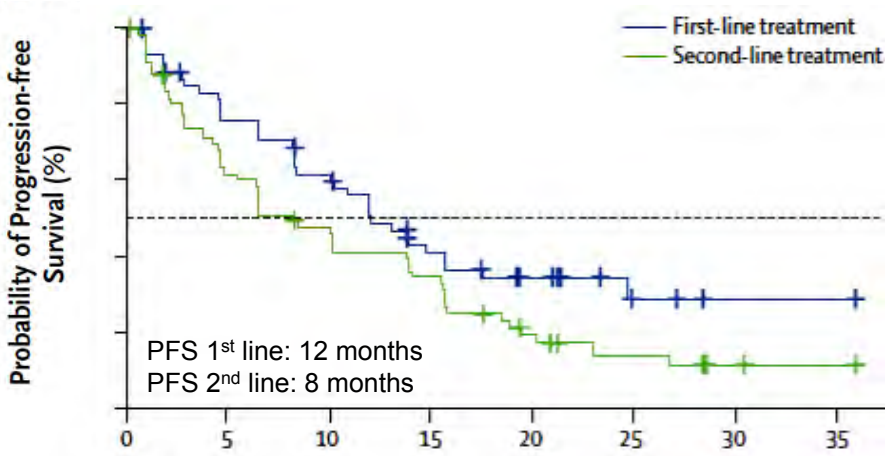
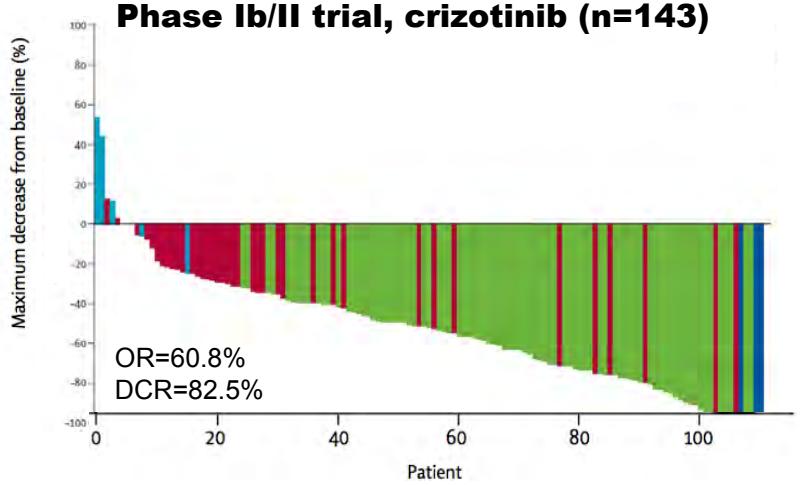
Qu'a t-on appris des premières cibles?

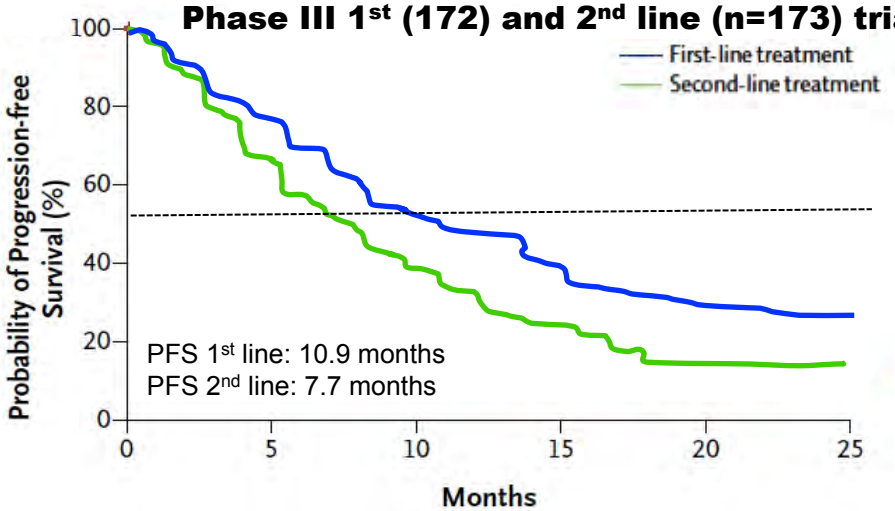
EGFR TKIs





ALK TKIs

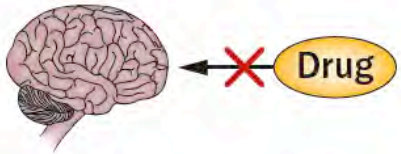




Yang JC, Lancet Oncol 2012, 13:539; Camidge DR, Lancet Oncol, 2012,13:1011; Shaw AT, N Eng J Med 2013, 368:2385; Solomon BJ, N Engl J Med 2014, 371:2167

Qu'a t-on appris des premières cibles?

1 Pharmacological/ biological resistance

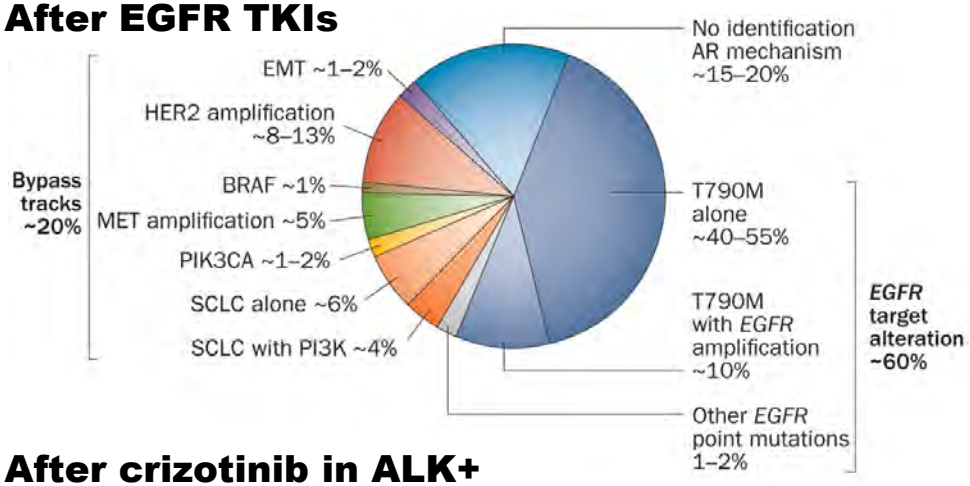


Inadequate CNS penetration

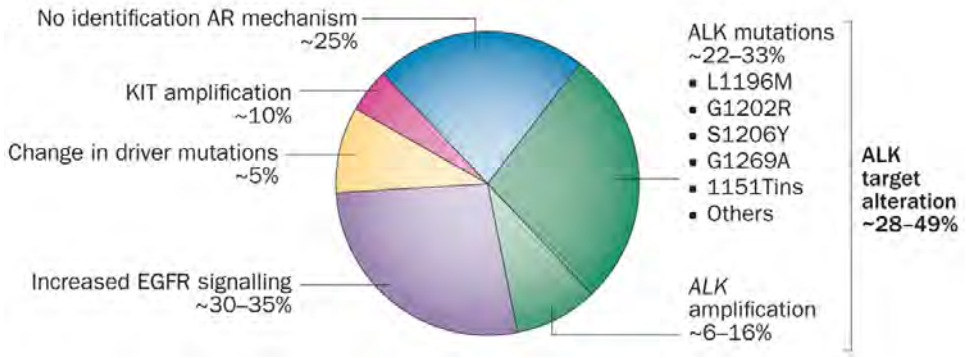
T790M mutation (60%)

2 Biological resistance

After EGFR TKIs



After crizotinib in ALK+



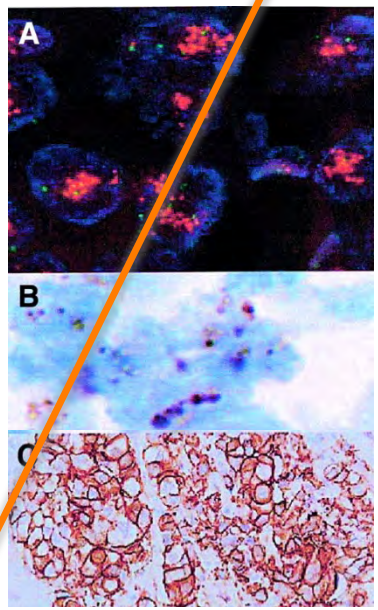
Several mutations (35%)

Camidge R, Nat Rev Clin Oncol 2014, 11:473

Qu’a t-on appris des premières cibles?

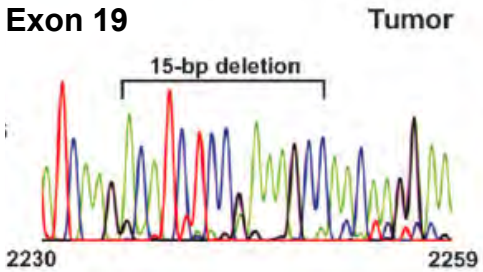
Amplification génique
Surexpression protéique

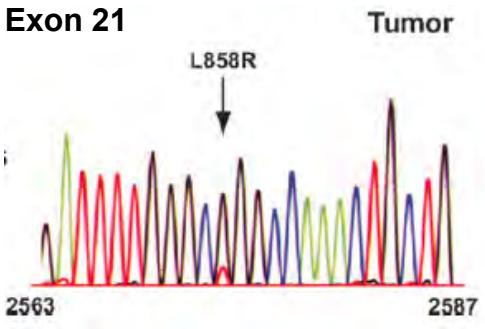
EGFR



Gain de fonction
Mutation dans la kinase

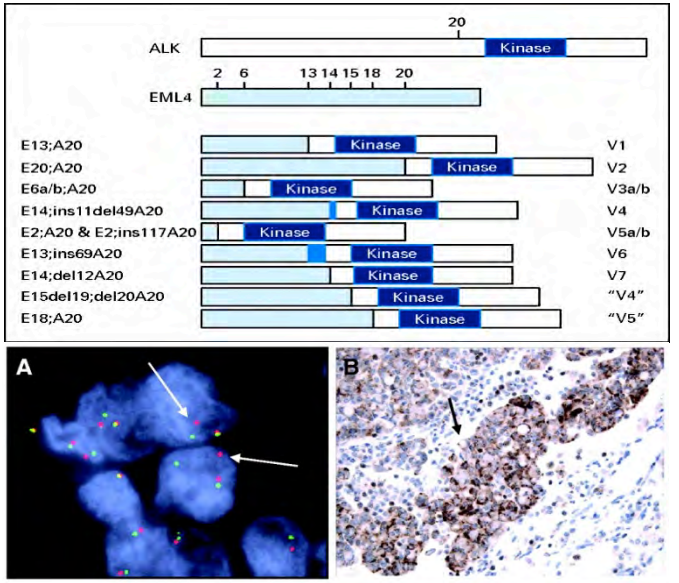
EGFR





Réarrangement chromosomique
Protéine de fusion oncogénique

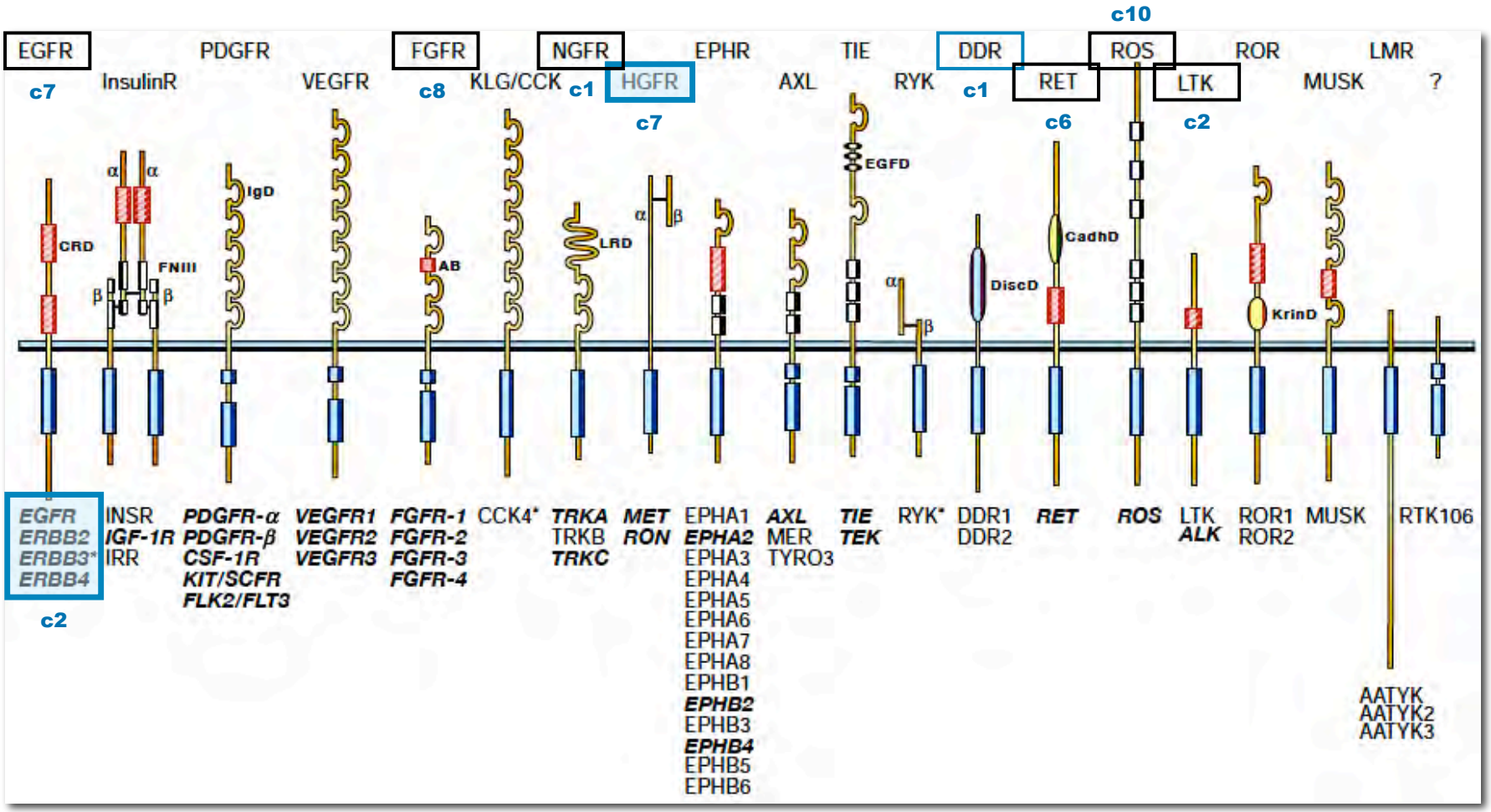
ALK



Blume-Jensen P, Nature 2001, 411:355

Quelles sont les autres cibles?

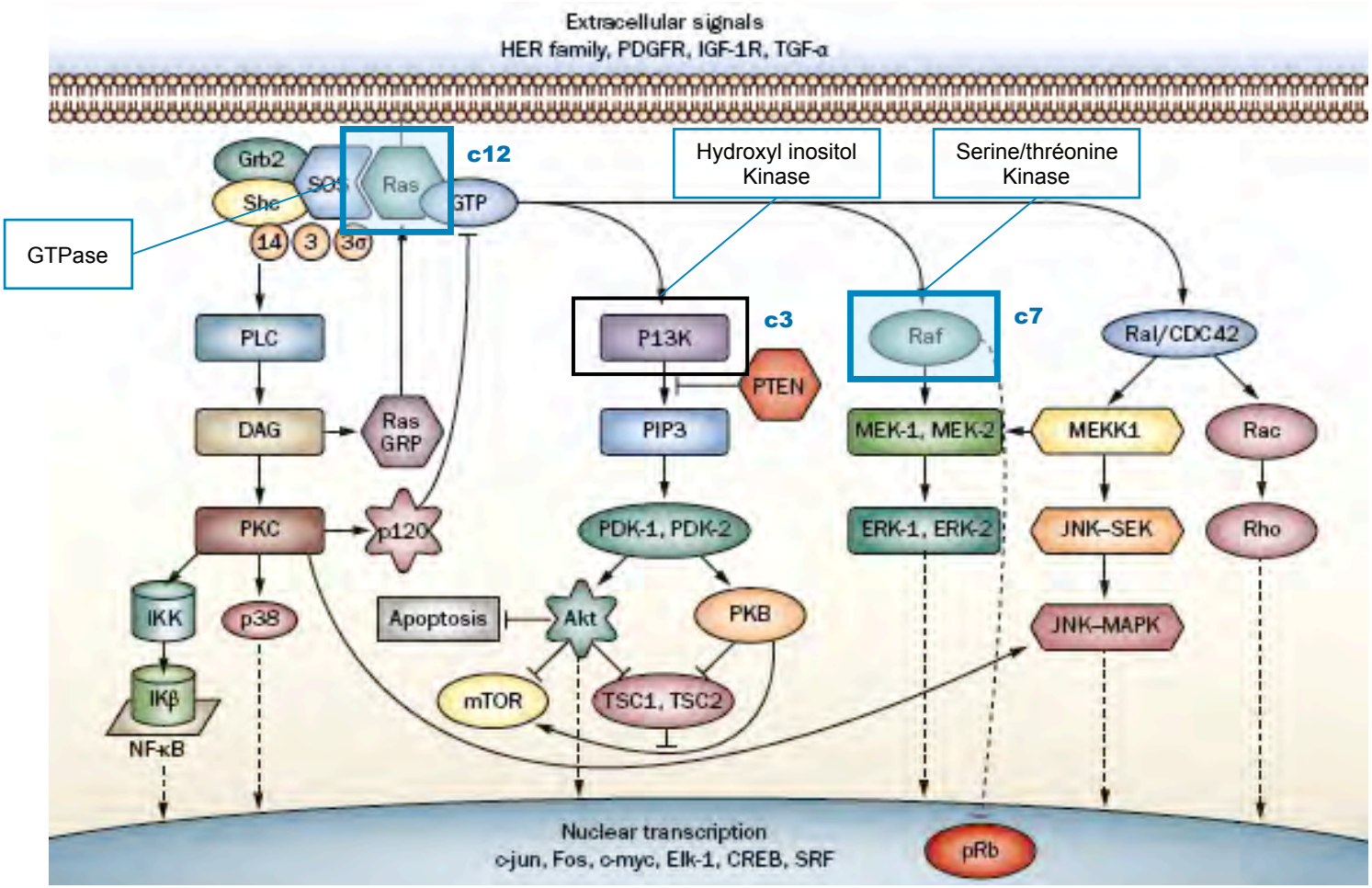
Récepteurs transmembranaires à tyrosine kinase



Blume-Jensen P, Nature 2001, 411:355

Quelles sont les autres cibles?

Voies de signalisation en aval des RTK, kinase cytosolique



Linardou H, Nat Rev Clin Oncol 2009, 6:352

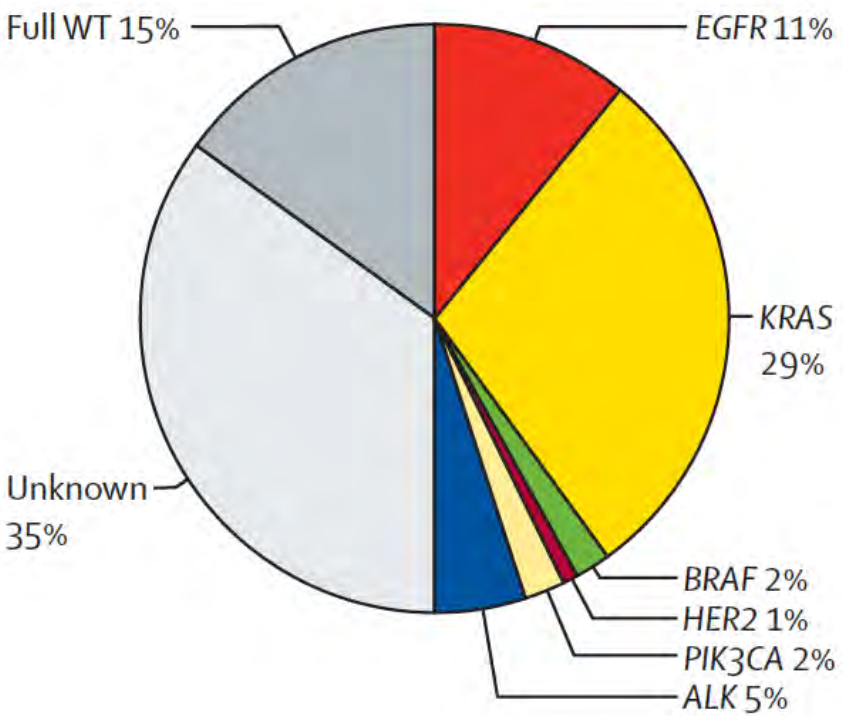
Quelles sont les autres cibles?

Gene	Alteration	Frequency	Drugs	ORR
AKT1	mutation	1%		
ALK	rearrangement	3-7%	crizo; 2nd line: ceritinib, alectinib	74%; 2nd line: 40-70%
BRAF	mutation	1-3%	vemurafenib, dabra, dabra+trametinib	33-63%
DDR2	mutation	≈4% (SC)	dasatinib	?
EGFR	mutation	10-40%	gef, erlo, afa; 2nd line: osi (T790M)	60%; 2nd line: 65%
FGFR1	amplification	20% (SC)		
HER2	mutation/ampli	2-4%	afa, lapa, dacomitinib; trastuzumab, TDM1	12-33%
KRAS	mutation	15-25%		
MEK1	mutation	1%		
MET	skip mut/ampl	0.3-4%	crizotinib, cabozantinib, capmatinib	65%?
NRAS	mutation	1%		
PI3KCA	mutation	1-3%		
PTEN	mutation	4-8%		
RET	rearrangement	1%	cabozantinib, vande, vande+evero	17-80%
ROS1	rearrangement	1%	crizotinib, ceritinib	70%
TRK	rearrangement	1%	entrectinib	?

MacConaill LE, J Clin Oncol 2012, 31:1815; Hirsch F, Lancet 2016, 388:1012

Epidémiologie, pronostic, traitements

BIOMARQUEURS France (n=18 679)



KRAS mutations: 30% of NSCLC (ADC)

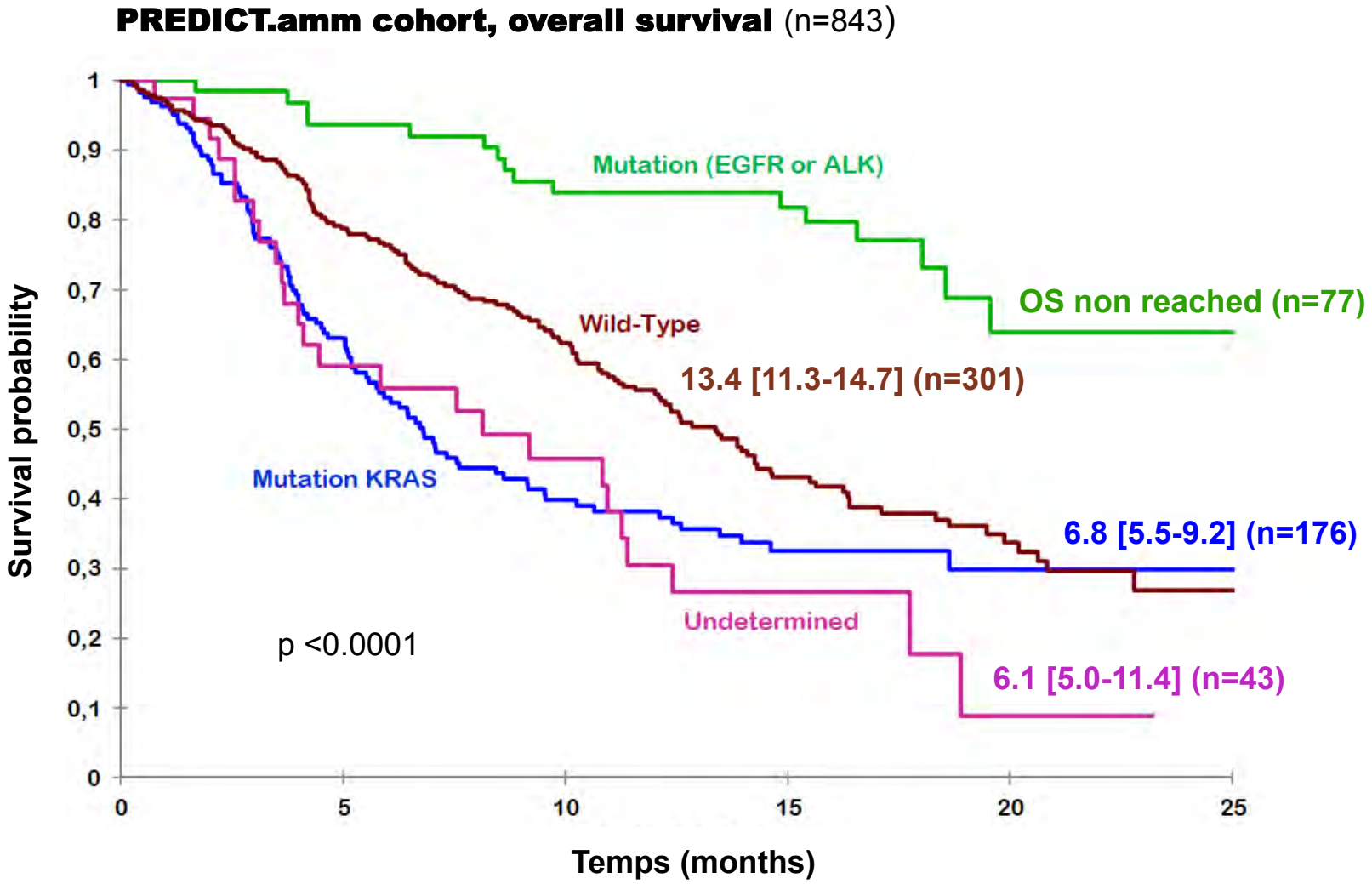
G12C 42%
G12V 21%
G12D 17% *(non smoker; mucinous)*
G12A 7%

KRAS mutations correlated with:
Higher exonic mutation rate
Smoking genomic signature
STK11 mutation
P53 mutation

10- to 100-fold higher mutation rate than *EGFR*-mutated or *KRAS* wild-type tumours

Barlési F, Lancet 2016, 387:1414; Kemps E, Eur Resp Rev 2016, 25:71

Epidémiologie, pronostic, traitements

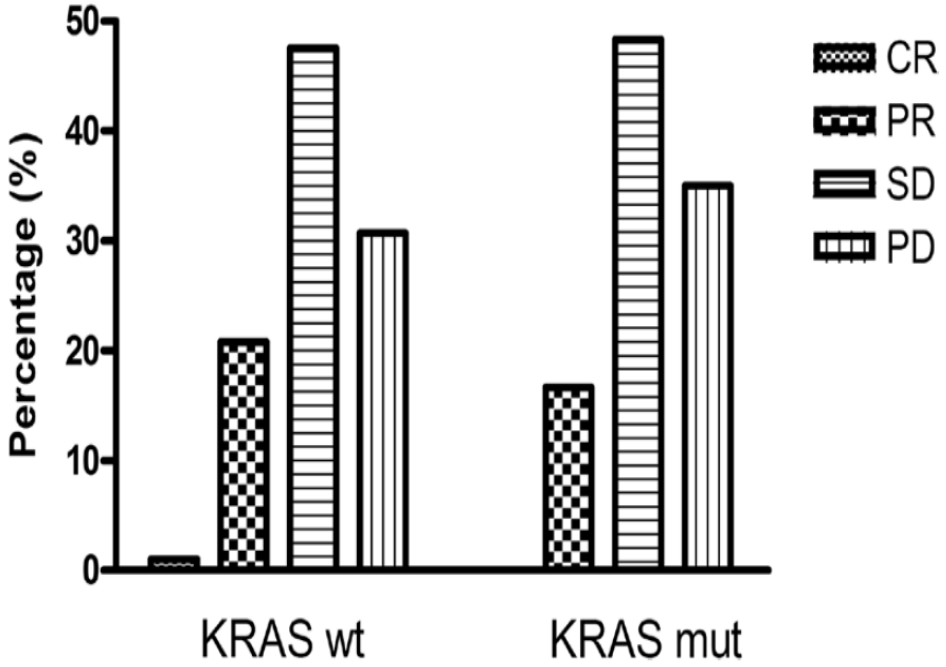


Cadranel J, ESMO 2015

Epidémiologie, pronostic, traitements

Retrospective cohort (n=161)
1st line doublet platinum; advanced non squamous
KRAS: 37%

	KRAS Wild-Type	*KRAS* Mutation
Chemotherapy regimen		
Gemcitabine	51.5	51.7
Pemetrexed	30.7	31.7
Docetaxel	16.8%	16.7
Vinorelbine	1.0	0.0



Mellema W, J Thorac Oncol 2013, 8:1190

Epidémiologie, pronostic, traitements

Retrospective cohort (n=484)
1st line doublet platinum; advanced NSCLC
KRAS: 8%; EGFR:38%

Table 3. Response Rates and Progression-free Survival by KRAS Mutation Status.

	Total No.		KRAS mutation	KRAS WT	P
Pemetrexed plus platinum	155	No.	15	140	
		Response rate	27%	38%	0.39
		PFS (months)	3.9	4.9	0.004
Gemcitabine plus platinum	237	No.	16	221	
		Response rate	25%	39%	0.25
		PFS (months)	2.4	4.3	0.03
Taxane plus platinum	64	No.	6	58	
		Response rate	33%	41%	0.7
		PFS (months)	1.4	3.9	0.04

Sun JM, PLOS ONE 2013, 8:e64816

KRAS

Epidémiologie, pronostic, traitements

Taux de réponse aux TKI-EGFR rapportés chez les malades KRAS mutés

Study	Drugs	No. of Patients Tested for *KRAS* Mutation	No. of Patients With *KRAS* Mutation	Response Rate (%)
Pao et al[12]	Gefitinib/erlotinib	59	9	0
Jackman et al[82]	Erlotinib	41	6	0
Massarelli et al[81]	Gefitinib/erlotinib	70	16	0
Miller et al[80]	Erlotinib	86	18	0
Han et al[86]	Gefitinib	69	9	0
Hirsch et al[83]	Gefitinib	138	36	7
Schneider et al[79]	Erlotinib	195	17	0
Felip et al[85]	Erlotinib	39	7	0
Van Zandwijk et al[78]	Gefitinib	15	3	0

Abbreviations: PFS, progression-free survival; OS, overall survival; NR, not reported.

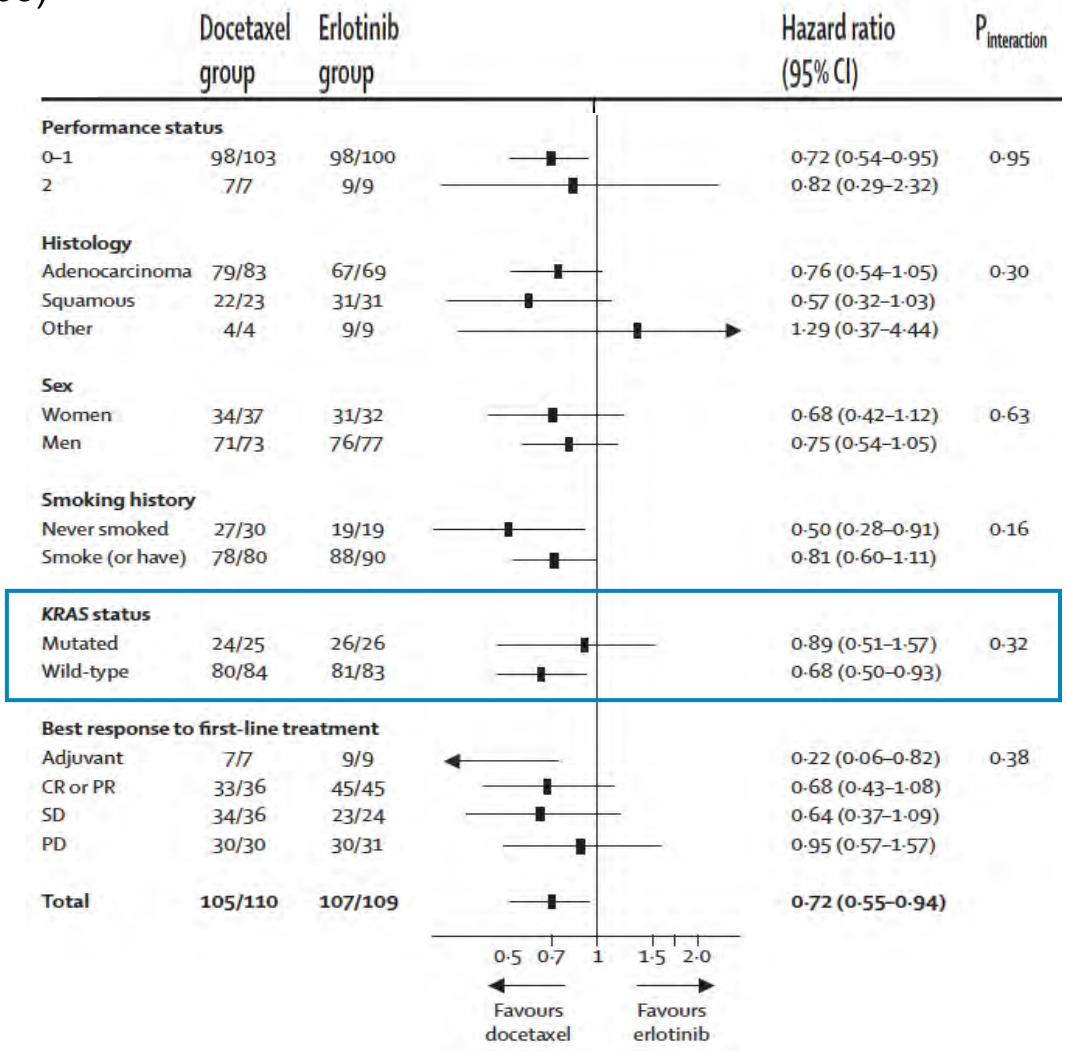
Roberts PJ, J Clin Oncol 2010, 28:4869

Epidémiologie, pronostic, traitements

Tailor Phase III Trial (n=203)

2nd line EGFR wt NSCLC EGFR wt

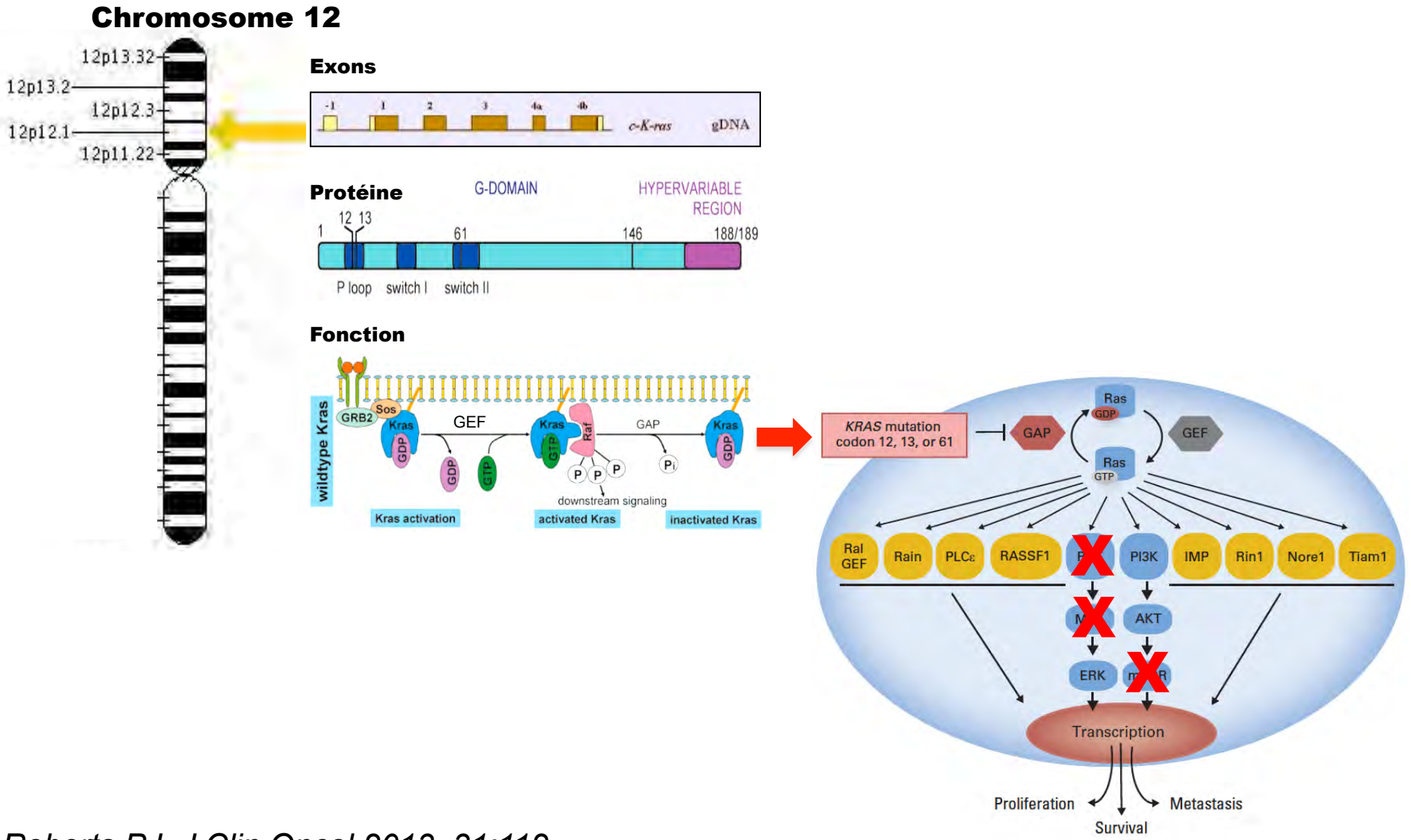
Docetaxel vs erlotinib



Garassino MC, Lancet Oncol 2013, 14:981

KRAS

Du gène à la voie de signalisation



Roberts PJ, J Clin Oncol 2013, 31:112

KRAS

Du gène à la voie de signalisation

TABLE 1 Clinical outcomes related to evaluated drugs in *KRAS*-mutated nonsmall cell lung cancer patients

Trial arm [ref.]	Patients	Previous lines	ORR %	DCR %	Median PFS months	Median OS months
MAPK pathway						
Salirasib [24]	33	Any	0	33.3		
Sorafenib [25]	10	⩾1	33.3	60	3	
Sorafenib [26]	59	⩾1	8.5	50.8	2.3	5.3
Sorafenib	34	⩾2	2.9	44.1	2.6	6.4
versus placebo [27]	34	⩾2	0	7.6	1.7 (HR 0.46, 95% CI 0.25–0.82; p=0.007)	5.1 (HR 0.76, 95% CI 0.45–1.26; p=0.279)
Sorafenib	14	⩾1		79		
versus erlotinib	7	⩾1		14		
versus erlotinib + bexarotene	3	⩾1		33		
versus vandetanib [28]	14	⩾1		0		
Selumetinib	9	⩾1	0		3.9	
versus selumetinib + erlotinib [29]	30	⩾1	6.7		4.5	
Selumetinib + docetaxel	44	⩾1	36.4	80	5.3	9.4
versus docetaxel + placebo [30]	43	⩾1	0	46.5	2.1 (HR 0.58, 95% CI 0.42–0.79; p=0.014)	5.2 (HR 0.8, 95% CI 0.56–1.14; p=0.21)
Trametinib	86	1	11.6	90.7	3	8
versus docetaxel [31]	43	1	11.6	74.4	2.8 (HR 1.23, 95% CI 0.81–1.87; p=0.316)	Unreached (HR 0.97, 95% CI 0.52–1.83; p=0.934)
Trametinib + docetaxel [32]	22	⩾1	13.6	61		
Trametinib + pemetrexed [33]	20	⩾1	75	65		
mTOR inhibitors						
Ridaforolimus [34]	79	⩾1		35.4		
Ridaforolimus	14	⩾1 SD after 8 weeks ridaforolimus			4	18
versus placebo [34]	14	⩾1 SD after 8 weeks ridaforolimus			2 (HR 0.36, p=0.013)	5 (HR 0.46, p=0.09)
Hsp90 inhibitor						
Ganetespib [35]	17	⩾1	0	35	1.9	11.0

Kemps E, Eur Resp Rev 2016, 25:71

KRAS

Du gène à la voie de signalisation

ICI?

TABLE 2 Ongoing clinical trials performed in … tients

			Tumour type
MEK inhibitors			
Selumetinib + docetaxel (*versus* docetaxel)			NSCLC
Trametinib + chemoradiation			Unresectable NSCLC
PD-0325901 + palbociclib			NSCLC and other solid tumours
MEK162 + BYL719			All solid tumours
MEK162			l solid and haematological malignancies
MEK162 + RAF265			All solid tumours
MEK162 + erlotinib			NSCLC
PD-0325901 + dacomitinib	NCT02039336	I	NSCLC
Other			
BIND-014	NCT02283320	II	NSCLC
Bortezomib	NCT01833143	II	NSCLC
Retaspimycin HCl (IPI-504) + everolimus	NCT01427946	Ib/II	NSCLC
VS-6063 (defactinib)	NCT01951690	II	NSCLC
Wild-type reovirus + paclitaxel + carboplatin	NCT00861627	II	NSCLC
Abemaciclib (LY2835219)	NCT02152631	III	NSCLC

News Release AstraZeneca

ASTRAZENECA PROVIDES UPDATE ON PHASE III TRIAL OF SELUMETINIB IN NON-SMALL CELL LUNG CANCER

Selumetinib did not meet trial endpoint of progression-free survival in KRASm NSCLC patients

09 August 2016

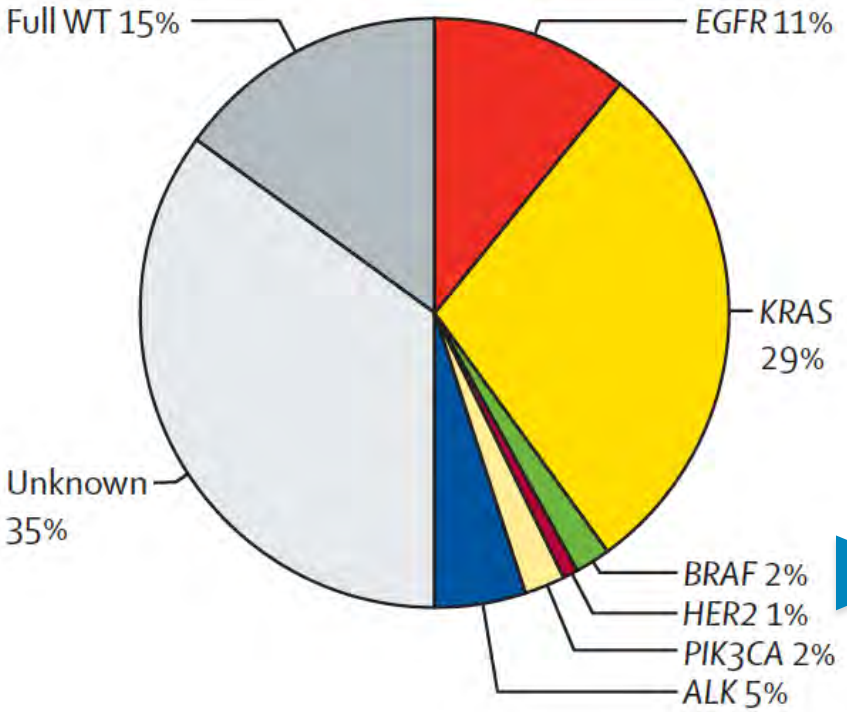
AstraZeneca today announced results from the Phase III SELECT-1 trial of the MEK 1/2 inhibitor, selumetinib, in combination with docetaxel chemotherapy as 2nd-line treatment in patients with *KRAS* mutation-positive (*KRAS*m) locally-advanced or metastatic non-small cell lung cancer (NSCLC).

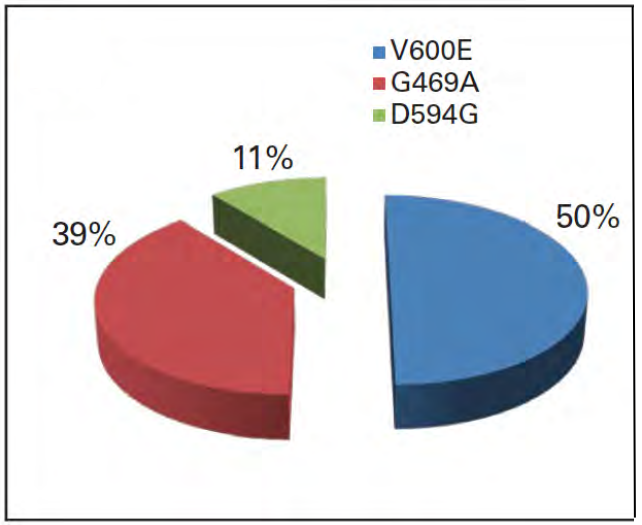
The results showed that the trial did not meet its primary endpoint of progression-free survival (PFS), and selumetinib did not have a significant effect on overall survival (OS). The adverse event profiles for selumetinib and docetaxel were consistent with those seen previously.

Kemps E, Eur Resp Rev 2016, 25:71

Epidémiologie, pronostic, traitements

BIOMARQUEURS France *(n=18 679)*





BRAF mutation: 1-3% of NSCLC (ADC, µpapillaire)

BRAF V600E (≈50%); non V600E (≈50%) (exclusive)

V600E associated with: non smoking, female, older(?)
non V600E associated with: smoking

Barlési F, Lancet 2016, 387:1414; Litvak AM, JTO 2014, 9:1669; Marchetti A, J Clin Oncol 2011, 29: 3574; Caparica R, Crit Rev Onco Hematol 2016, 101:32; Chen D, PLOS One 2014, 9:e101354

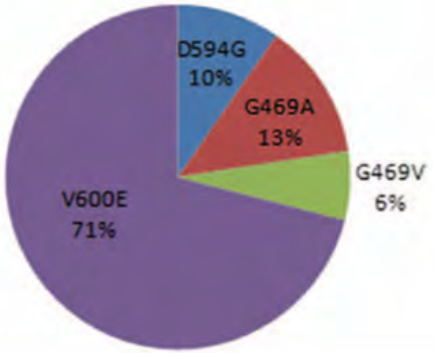
Epidémiologie, pronostic, traitements

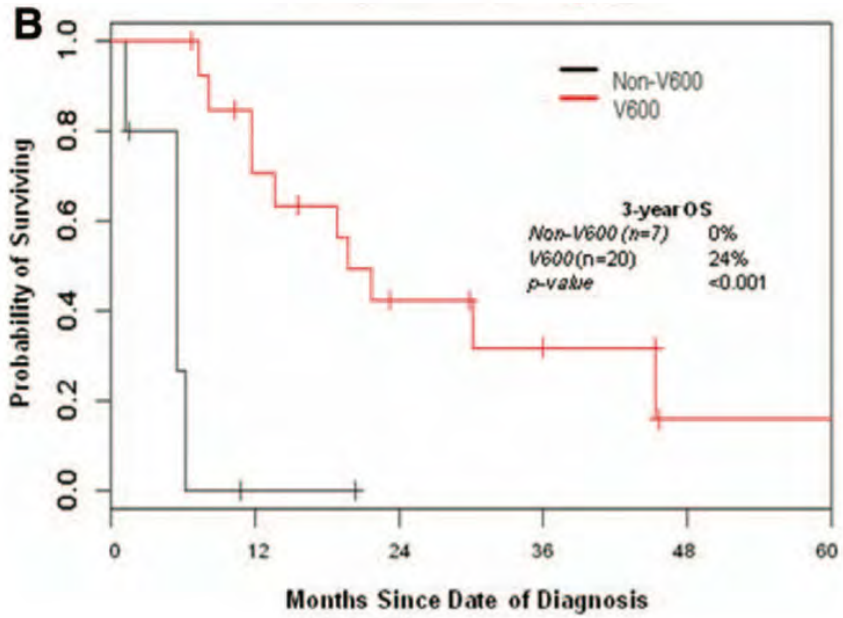
BRAF retrospective cohort (n=63)

Mutant *BRAF*	All (*n* = 63)	V600 (*n* = 36)	Non-V600 (*n* = 27)
Median age, years	65	64	66
Range	(33–85)	(48–79)	(33–85)
Sex			
Female	34 (54%)	19 (53%)	15 (56%)
Male	29 (46%)	17 (47%)	12 (44%)
Smoking history			
Never-smokers	5 (8%)	3 (8%)	2 (7%)
≤15 pack-years	13 (21%)	12 (33%)	1 (4%)
>15 pack-years	45 (71%)	21 (58%)	24 (89%)
Histology			
Adenocarcinoma	100%	100%	100%
Stage[a]			
I	17 (27%)	9 (25%)	8 (30%)
II	4 (6%)	2 (6%)	2 (7%)
IIIa	11 (17%)	3 (8%)	8 (30%)
IIIb	4 (6%)	2 (6%)	2 (7%)
IV	27 (43%)	20 (56%)	7 (26%)
Race			
White, non-Hispanic	55 (87%)	30 (83%)	25 (93%)

Litvak AM, JTO 2014, 9:1669

BRAF mutation and prognosis in Stage IIIb/IV





BRAF

Epidémiologie, pronostic, traitements

Advanced BRAF NSCLC retrospective cohort (n=14)

Table 3. Treatments and clinical outcomes for advanced NSCLC patients by genotype

	Genotype			
	Mutant *BRAF*			
Characteristic	All ($n = 14$) *N* (%)	V600E ($n = 7$) *N* (%)	Non-V600E ($n = 7$) *N* (%)	Wild-type ($n = 79$) *N* (%)
Median no. of treatment regimens	3	3	3	2
Range	(1–6)	(1–4)	(1–6)	(1–7)
Best response to chemotherapy[a]				
CR	0 (0)	0 (0)	0 (0)	0 (0)
PR	7[b] (50)	2 (29)	5 (71)	38[c] (48)
Stable disease	5 (36)	3 (43)	2 (29)	36[d] (46)
PD	2 (14)	2 (29)	0 (0)	5 (6)
Response rate, %	50	29	71	48
Median PFS, mo	5.2	4.1	8.9	6.7
(95% CI)	(3.9–9.4)	(2.2–13.9)	(5.2–11.7)	(5.0–8.5)

a. 1st line doublet platinum

Cardarella S, Clin Cancer Res 2013, 19:4532

Epidémiologie, pronostic, traitements

Advanced BRAF NSCLC retrospective cohort (n=35)

TABLE 3. Drug Exposure

Sample size (N)	35
BRAF inhibitor therapy	35 (100%)
BRAF inhibitors and lines (tota	
Vemurafenib	
Dabrafenib	
Sorafenib	
Sequential BRAF inhibitors	
No	
Yes	
BRAF inhibitor used in	
First line	
Further lines	

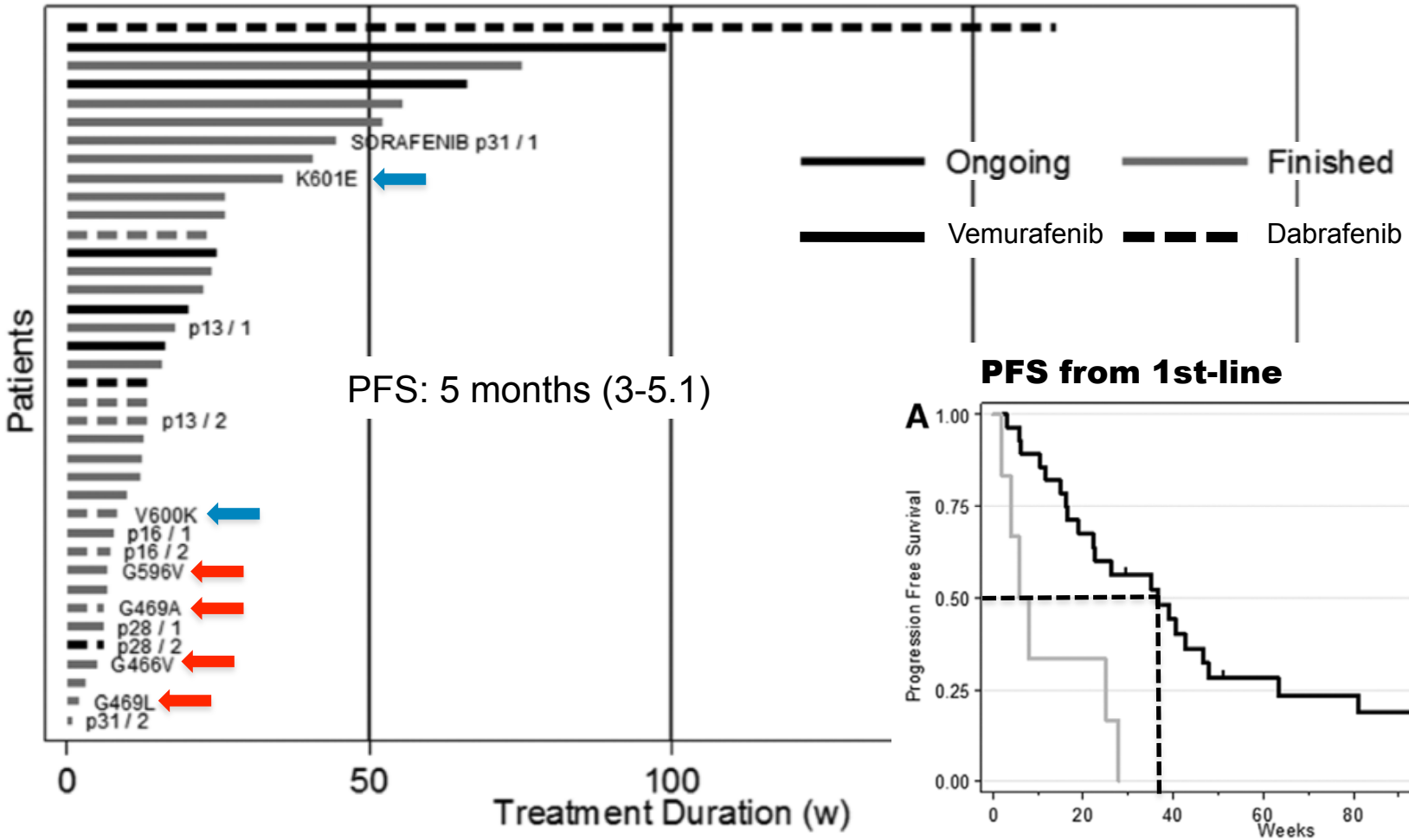
TABLE 4. Best Response with BRAF Inhibitor

	All Patients (N = 35)	V600E and Vemurafenib Subgroup (N = 25)
Data missing	1	1
Not measurable	1 (3%)	1 (4%)
CR	2 (6%)	2 (8%)
PR	16 (47%)	11 (46%)
SD	11 (32%)	10 (42%)
PD	4 (12%)	0
ORR	18 (53%; 95% CI: 35–70)	13 (54%; 95% CI: 33–74)
DCR	29 (85%; 95% CI: 69–95)	23 (96%; 95% CI: 79–100)

Gautschi O, JTO 2015, 10:1451

Epidémiologie, pronostic, traitements

Advanced BRAF NSCLC retrospective cohort (n=35)



PFS: 5 months (3-5.1)

PFS from 1st-line

Gautschi O, JTO 2015, 10:1451

Du gène à la voie de signalisation

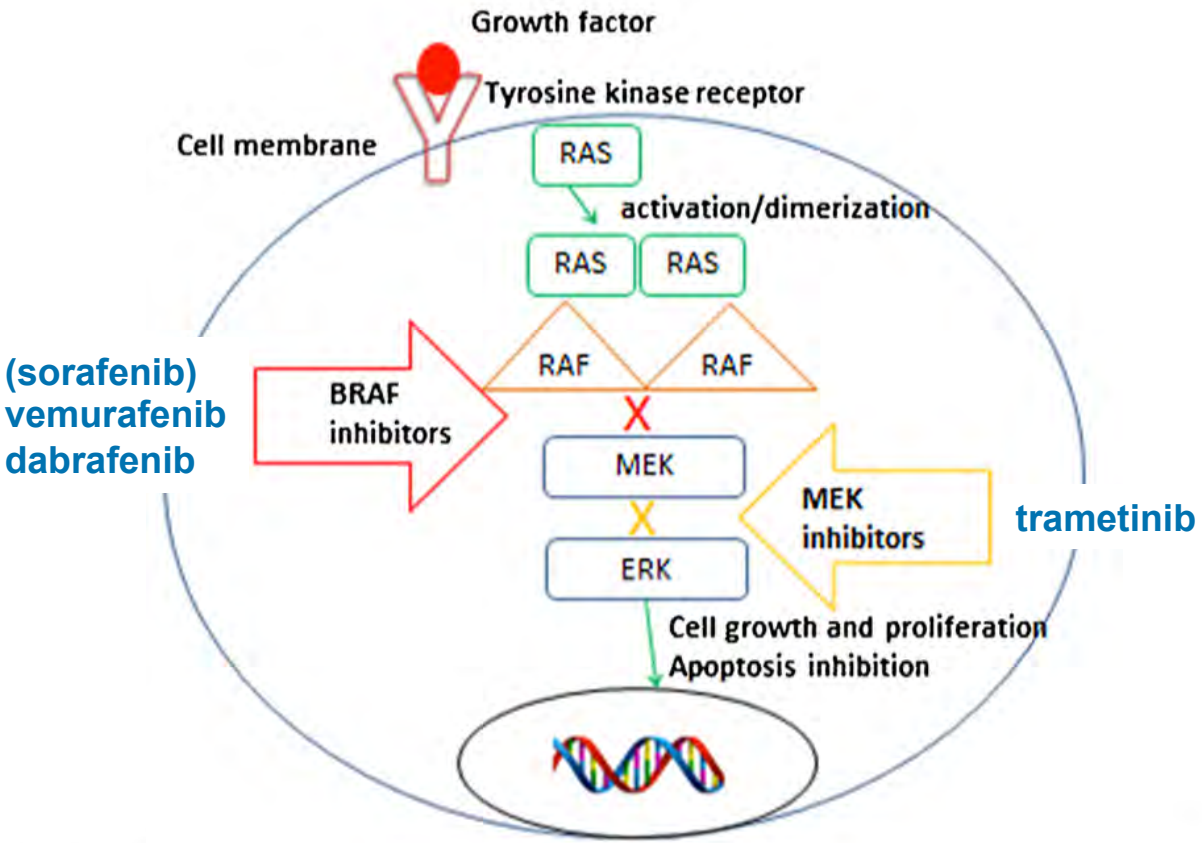


Table 2
New *B-Raf* inhibitors.

BRAF inhibitor	Phase of development	Mechanism of action
LGX818	Phase 1 trial currently recruiting patients (Wu and Zhu, 2011)	Mutant BRAF selective inhibitor
ARQ736	Phase 1 trial currently recruiting patients (Chapman et al., 2011; Hauschild et al., 2013)	Pan-RAF inhibitor
RAF265	Phase 1 trial presented in 2011; Phase 2 trial currently recruiting patients (Hyman et al., 2015; Larkin et al., 2014)	Multi-kinase inhibitor (BRAF, RET)
GDC0879	Pre-clinical data (Long et al., 2014)	Mutant BRAF selective inhibitor
XL281	Phase 1 trial presented in 2009 (Planchard et al., 2013)	Mutant BRAF selective inhibitor

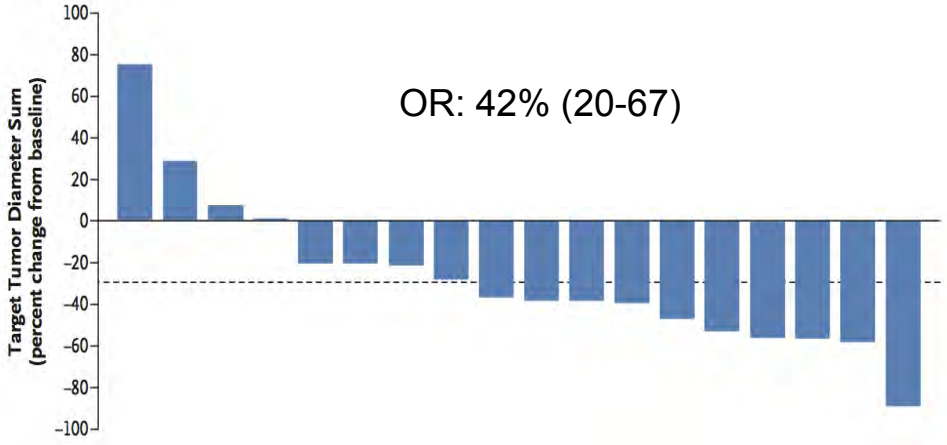
Caparica R, Crit Rev Onco Hematol 2016, 101:32

Du gène à la voie de signalisation

ORIGINAL ARTICLE

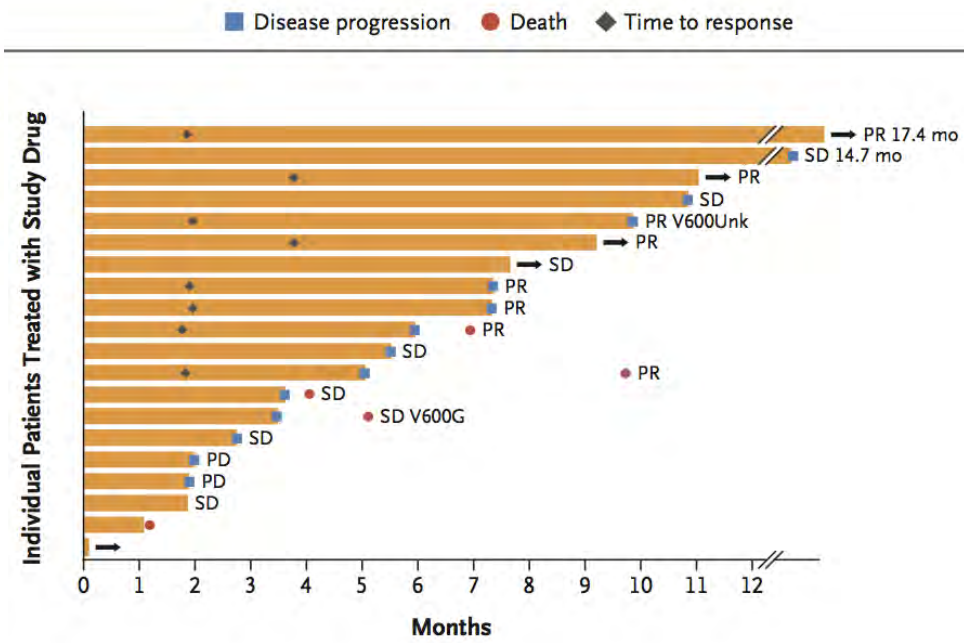
Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

NSCLC Cohort (n=20)
Vemurafenib: 960 mg bid
Advanced disease, mutation V600, all lines



OR: 42% (20-67)

PFS: 7.3 months (3.5-10.8)

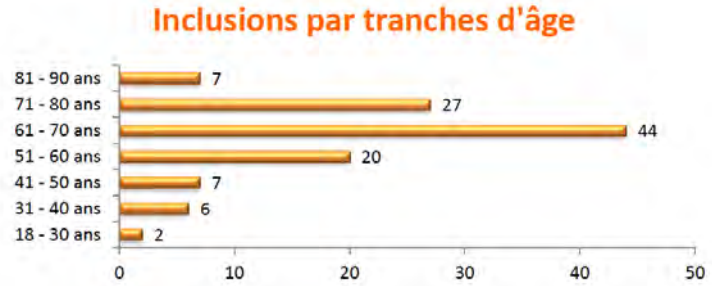


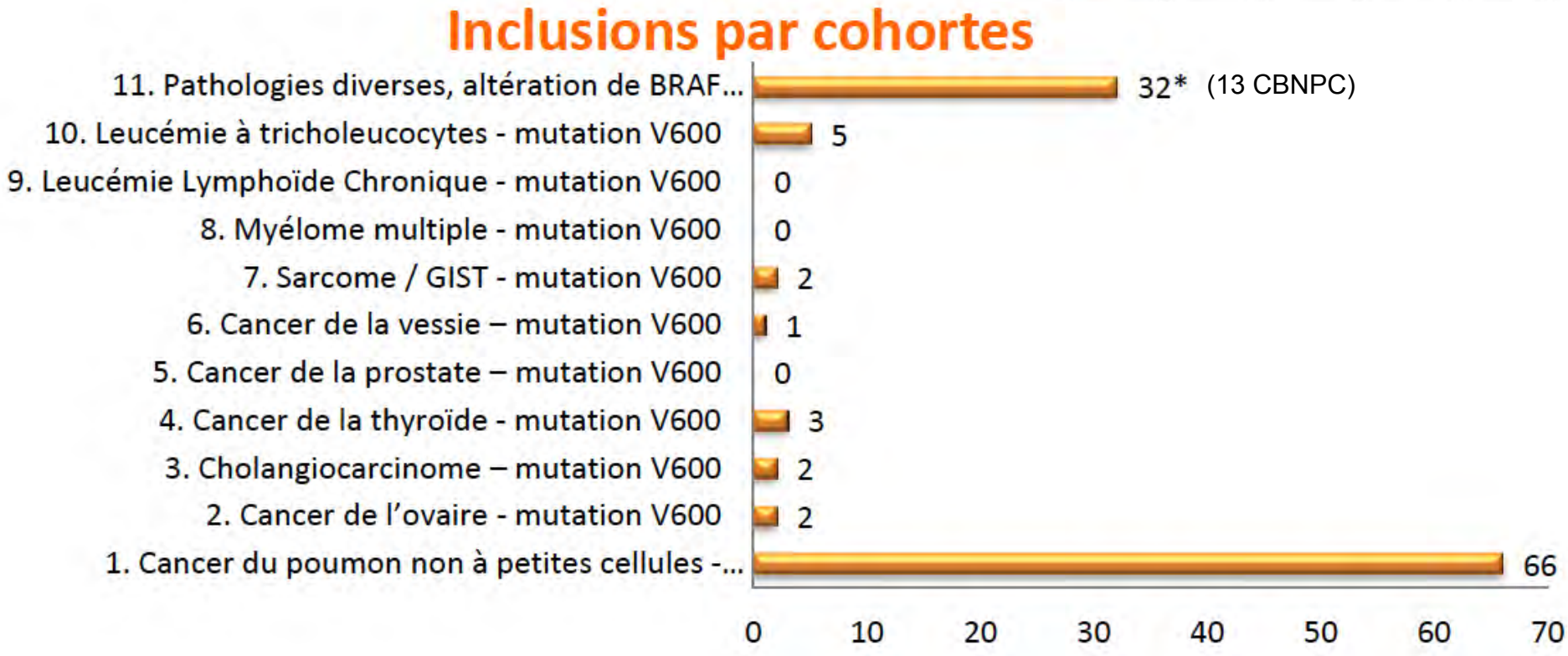
SAFETY, ≈ 20% adverse events
- Rash, 68%
- Fatigue, 56%
- Arthralgia, 40%

Hyman DM, N Engl J Med 2015, 373:726

Du gène à la voie de signalisation

AcSe Vemurafenib UNICANCER/IFCT



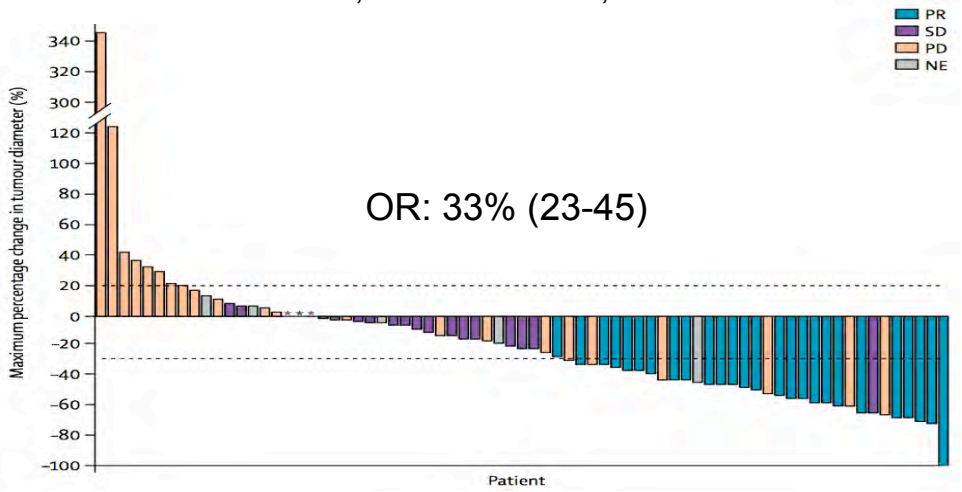


www.unicancer.fr ; données 09/2016

Du gène à la voie de signalisation

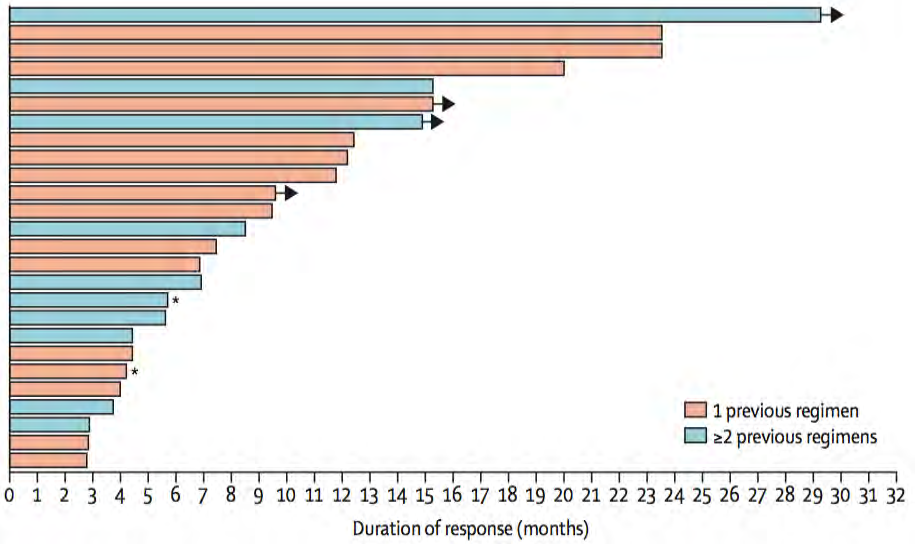
Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

Phase II trial (n=78)
Dabrafenib: 150 mg bid
Advanced disease, mutation V600E, all lines



OR: 33% (23-45)

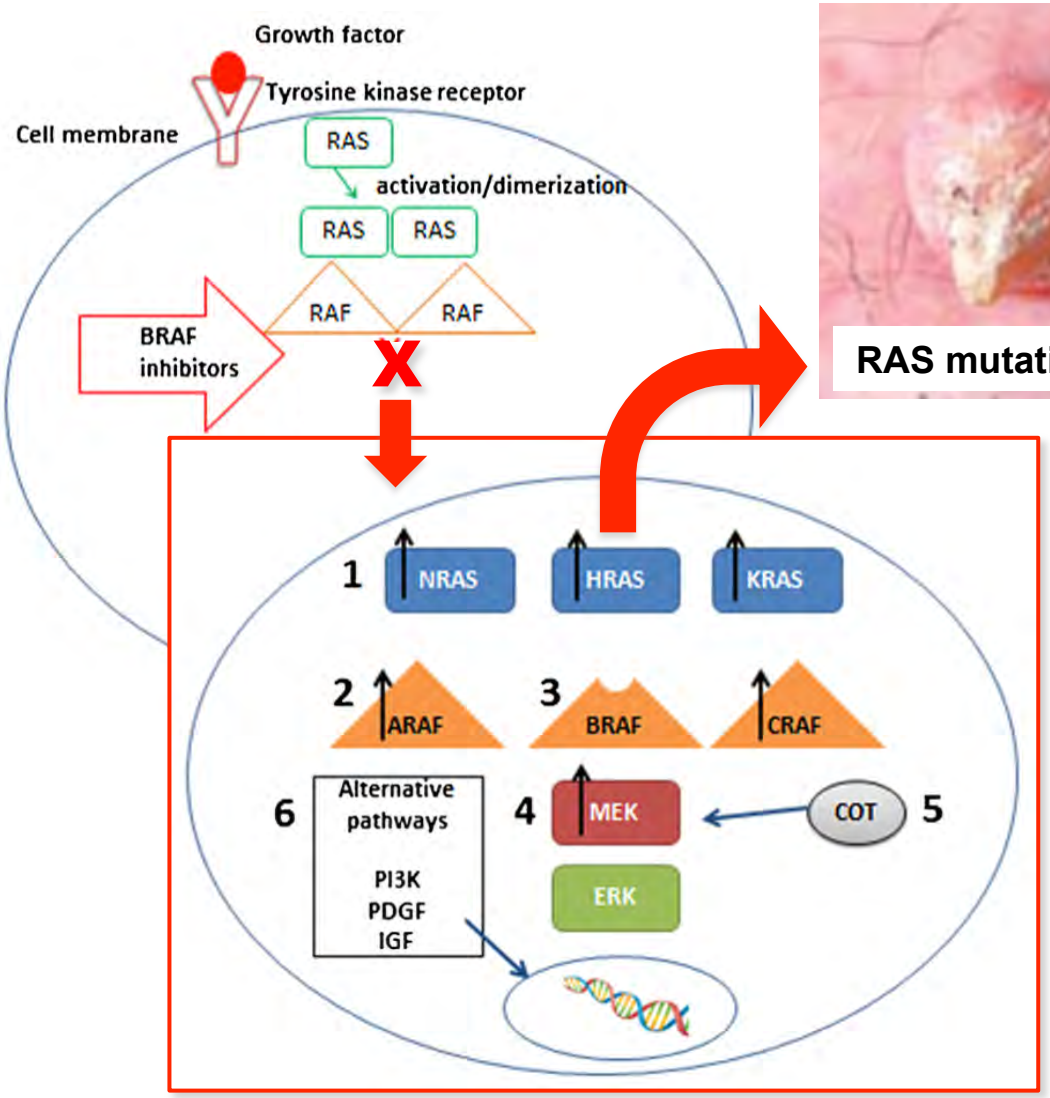
PFS: 5.5 months (3.4-7.3)

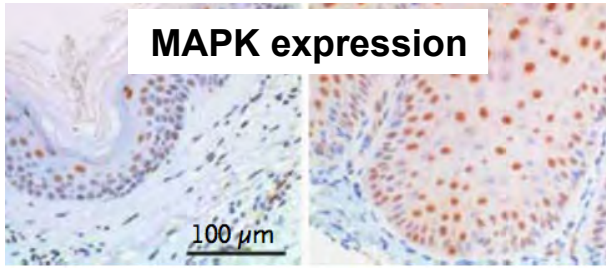


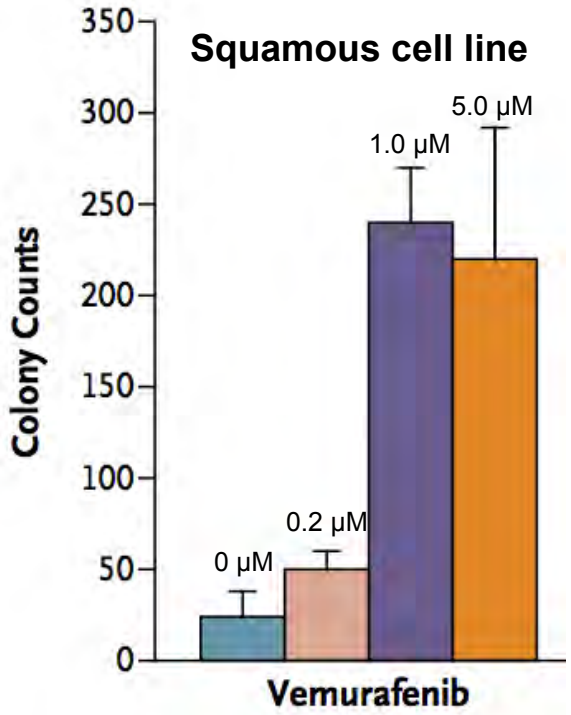
SAFETY, ≈ 42% SAE
- grade 3, cutaneous squamous carcinoma, 12%
- grade 3, cutaneous basal cell carcinoma, 5%
- grade 3, asthenia, 5%

Planchard D, Lancet Oncol 2016, 17:642

Du gène à la voie de signalisation





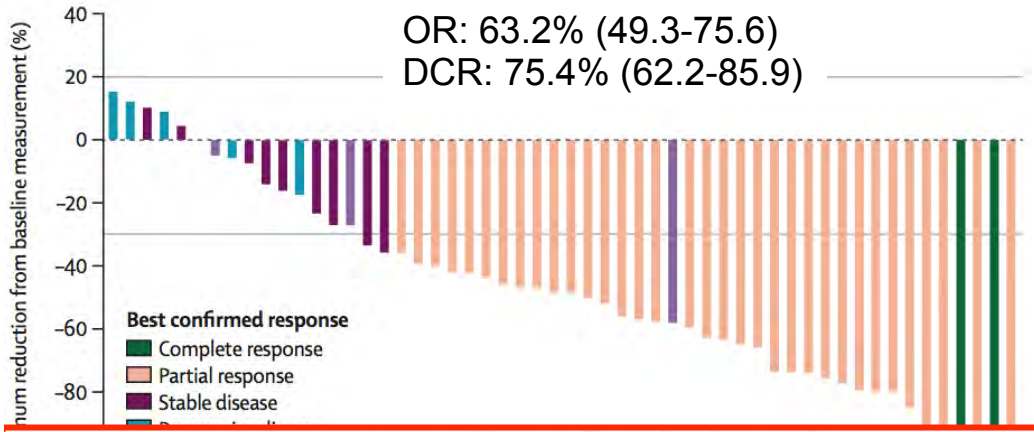


Caparica R, Crit Rev Onco Hematol 2016, 101:32; Su F, N Engl J Med 2012, 366:207

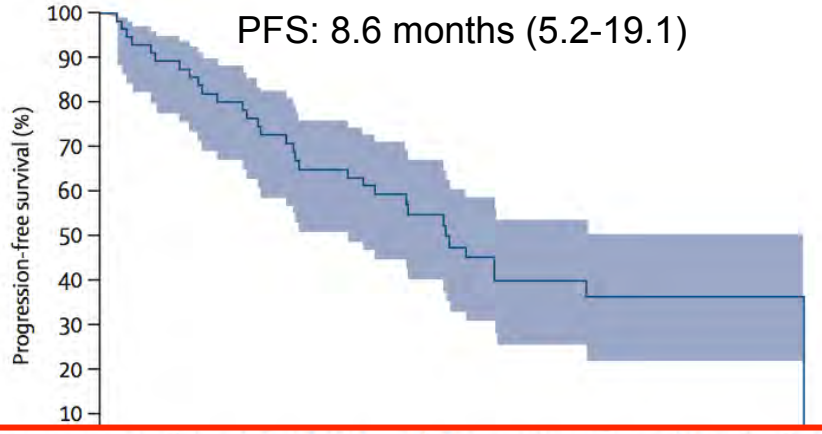
Du gène à la voie de signalisation

Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

Phase II trial (n=57)
Dabrafenib: 150 mg bid plus trametinib: 2 mg qd
Advanced disease, mutation V600E, ≥ 1 line



OR: 63.2% (49.3-75.6)
DCR: 75.4% (62.2-85.9)



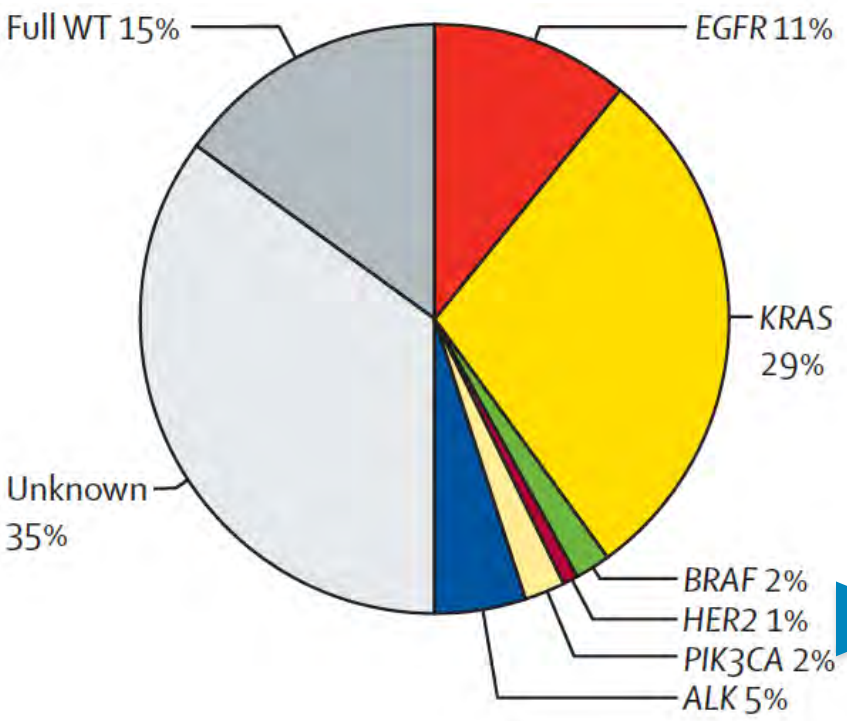
PFS: 8.6 months (5.2-19.1)

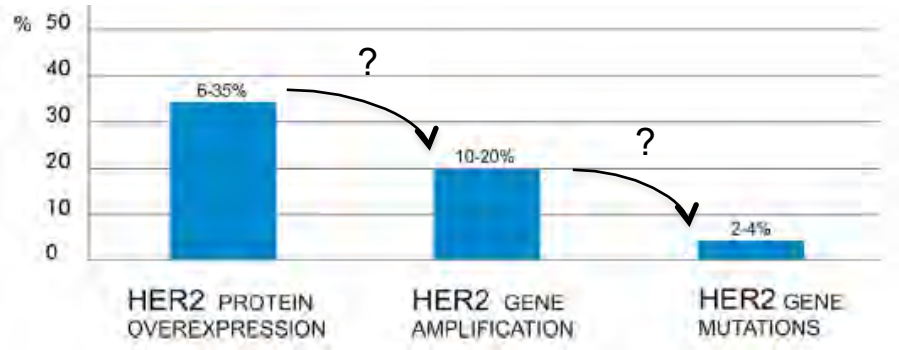
SAFETY: Serious adverse events were reported in 32 (56%) of 57 patients and included pyrexia in nine (16%), anaemia in three (5%), confusional state in two (4%), decreased appetite in two (4%), haemoptysis in two (4%), hypercalcaemia in two (4%), nausea in two (4%), and cutaneous squamous cell carcinoma in two (4%). The most common grade 3–4 adverse events were neutropenia in five patients (9%), hyponatraemia in four (7%), and anaemia in three (5%).

Planchard D, Lancet Oncol 2016, 17:984

Epidémiologie, pronostic, traitements

BIOMARQUEURS France (n=18 679)





HER2 mutation: 2-4% of NSCLC (ADC)

↓

HER2 exon 20 insertion: 85%; exclusive

↓

HER2 mutation associated with:
non smoking, female(?)

Barlési F, Lancet 2016, 387:1414; Arcila ME, Clin Cancer Res 2012, 18:4910; Mazières J, J Clin Oncol 2013, 31:1997

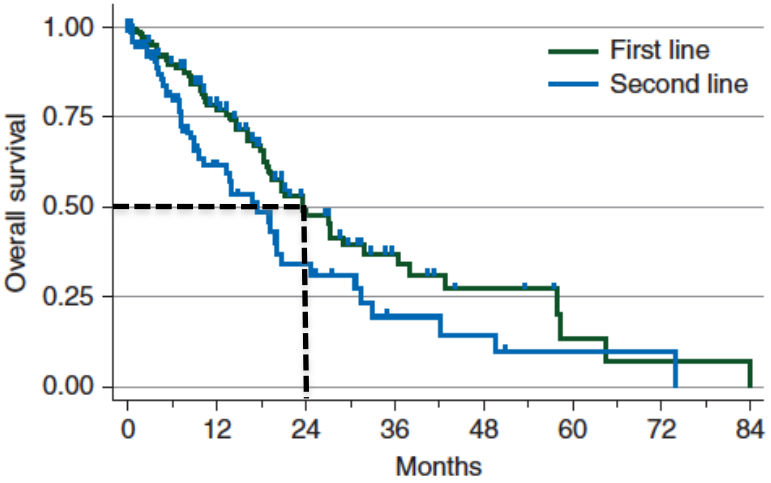
Epidémiologie, pronostic, traitements

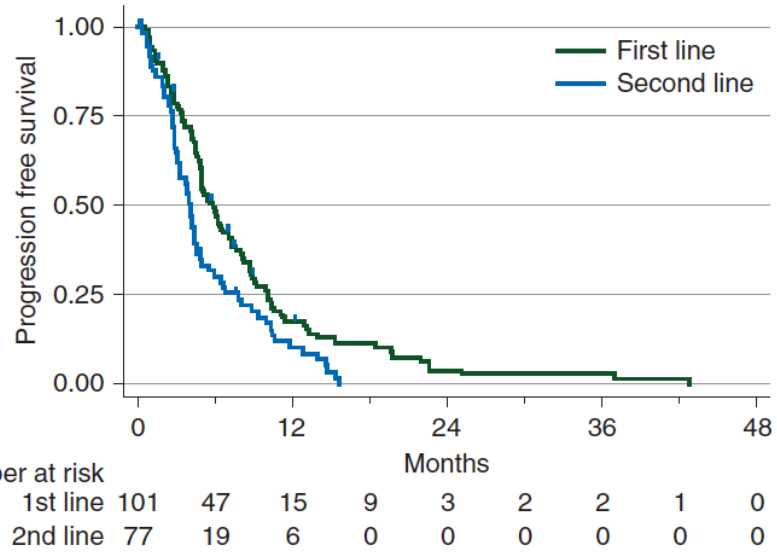
European EUHER2 cohort (n=101)

HER2 mutation

Table 1. Clinical and biological characteristics of patients with an *HER2* mutation ($n = 101$)

	Number	Value
Age at initial diagnosis, years ($n = 101$)		
Median		61
Range		30–87 years
Gender		
Male	38	37.6%
Female	63	62.4%
Tobacco use		
Never	61	60.4%
Former	36	35.6%
Current	4	4%
Median pack-years consumption (current and former)		15 (3–48)
Range		
Tumor stage		
I	4	4%
II	2	2%
III	14	13.9%
IV	81	80.2%
Metastatic sites of stage IV		
Lung	22	22%
Brain	6	6%
Bone	10	10%
Multiple organs	33	33%
Other	7	7%
None	15	15%
Unknown	8	8%
Concomitant mutations		
EGFR mutations	5	5%
ALK translocation	1	1%
ROS translocation	1	1%





Mazières J, Annales Oncol 2016, 27:281

Epidémiologie, pronostic, traitements

European EUHER2 cohort (n=101)

Table 2. Overall response rate (ORR), disease control (DC), progression-free survival (PFS, weeks), and overall survival (OS, weeks) according to drug type

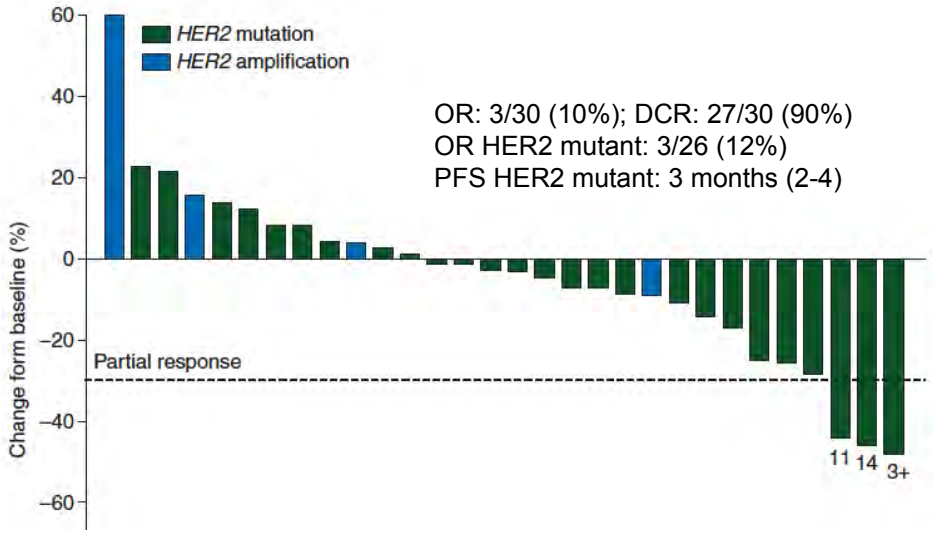
Treatment	*n*	ORR	DC	PFS median (95% CI)	OS median (95% CI)
First-line: without HER2-targeting treatment	93	43.5%	70.7%	6 (5; 7.1)	24 (19.1; 36.4)
Second-line: without HER2-targeting treatment	52	10%	36%	4.3 (3.1; 5)	19.4 (9.6; 24.7)
EGFR-TKI[a]	26	7.6%	26.8%	2.99 (1.87; 4.47)	20.14 (7.14; 32.95)
Trastuzumab combination, T-DM1[a]	58	50.9%	75.5%	4.8 (3.4; 6.5)	13.3 (8.1; 15)
Neratinib, lapatinib, and afatinib[a]	29	7.4%	55.5%	3.4 (2.4; 4)	6.5 (4.7; 30.6)

Mazières J, Annales Oncol 2016, 27:281

Epidémiologie, pronostic, traitements

Phase II trial (n=30)
HER2 molecular alteration
Dacomitinib all lines

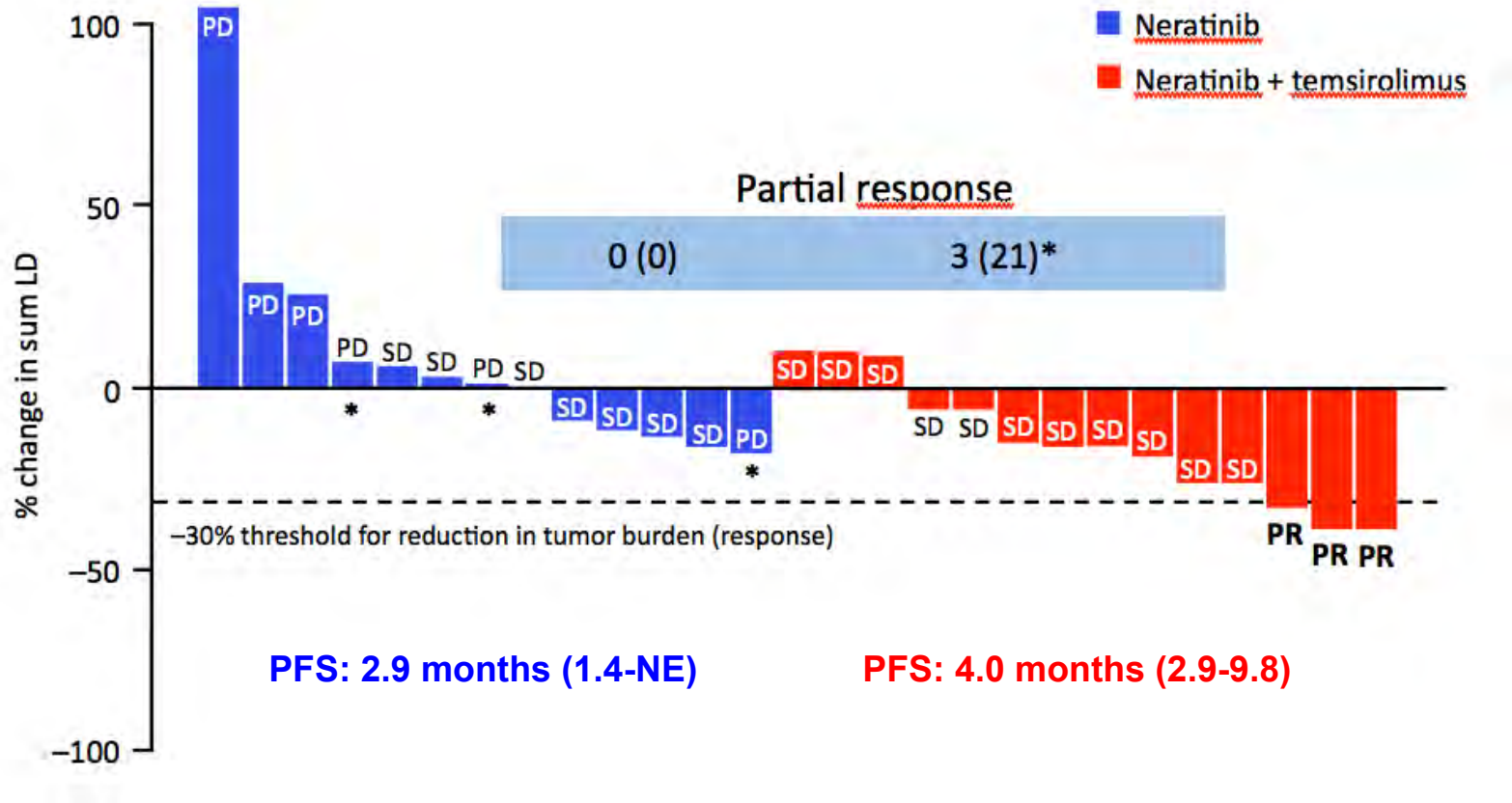
	HER2-Mutant exon 20 insYVMA (*n*=13)	*HER2*-Mutant exon 20 others (*n*=13)	*HER2*-Amplified (*n*=4)
Median Age (range)	60 (43-75)	58 (33-73)	50 (42-72)
ECOG PS			
0	2 (15%)	7 (54%)	1 (25%)
1	11 (85%)	6 (46%)	3 (75%)
Women	9 (69%)	6 (46%)	0 (0%)
Stage IIIB ADC	0 (0%)	2 (15%)	0 (0%)
Stage IV ADC	13 (100%)	11 (85%)	4 (100%)
Never Smoker	9 (69%)	8 (62%)	1 (25%)
Caucasian	9 (69%)	12 (92%)	3 (75%)
African American	0 (0%)	0 (0%)	1 (25%)
Asian	3 (23%)	1 (8%)	0 (0%)
Other	1 (8%)	0 (0%)	0 (0%)
Prior Therapies			
0	1 (8%)	4 (31%)	0 (0%)
1	6 (46%)	5 (38%)	1 (25%)
2	2 (15%)	1 (8%)	0 (0%)
≥3	4 (31%)	3 (23%)	3 (75%)
Trastuzumab	1 (8%)	1 (8%)	0 (0%)
Dacomitinib 30 mg	1 (8%)	4 (31%)	0 (0%)
Dacomitinib 45 mg	12 (92%)	9 (69%)	4 (100%)



Kris MG, Annales Oncol 2015, 26:1421

Epidémiologie, pronostic, traitements

Phase I/II trial (n=30)
HER2 mutant
Neratinib vs neratinib plus temsirolimus



Besse B, ESMO 2014

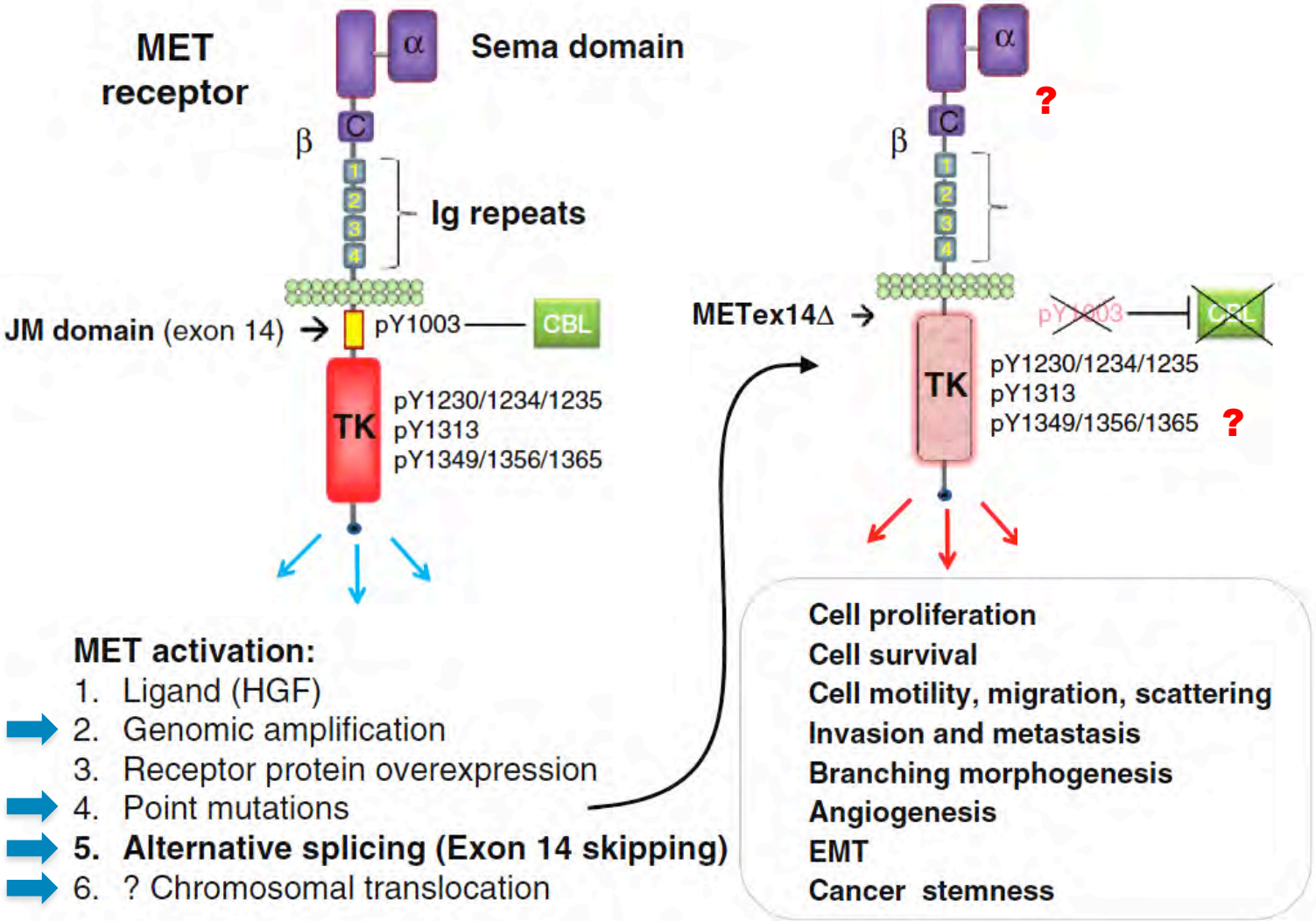
Du gène à la voie de signalisation

Table 1
Targeted drug therapies, their mechanisms, and available clinical trials in HER2 positive NSCLC.

Drug class	Representative drug	Mechanism	Available data in NSCLC
Antibodies targeting HER2	*Trastuzumab*	Targets extracellular domain IV of HER2 receptor, prevents dimerization	[43–46]
	Pertuzumab	Targets extracellular domain II of HER2 receptor, prevents dimerization	None
	Trastuzumab-emtansine (TDM1)	A cytotoxic microtubule inhibitor, DM-1, is conjugated to trastuzumab, which delivers it to HER2 labeled tumor cells	Ongoing (NCT02289833)
HER-family tyrosine kinase inhibitors	*Lapatinib*	Inhibits EGFR/HER1 and HER2	None
	Afatinib	Inhibits EGFR/HER1, HER2, and HER4	[50]
	Neratinib	Inhibits EGFR/HER1 and HER2	[57]
	Dacomitinib	Inhibits EGFR/HER1, HER2, and HER4	[56]
Mammalian target of rapamycin (mTOR) inhibitors	*Temsirolimus*	Binds to FKBP-12 protein with the resulting complex inhibiting mTOR, causes G1 growth arrest of tumor cells	Ongoing (NCT01827267)
Phosphoinositide-3 kinase (PI3K) inhibitors	*Buparlisib*	Inhibits four isosomes of class I PI3K (α, β, γ, δ)	None
Heat shock protein 90 (HSP90) inhibitors	*Ganetespib*	Inhibits hsp90 molecular chaperone, leads to simultaneous degradation of critical oncoproteins including HER2	None
Insulin growth factor 1 receptor (IGF-1R) Inhibitors	*Cixutumumab*	Prevents natural ligand binding to IGF-1R, prevents activation of PI3K/AKT signaling pathway	None
Fc-modified chimeric monoclonal antibody	*Margetuximab*	Binds the HER2 receptor, mediates antibody-dependent cellular cytotoxicity via recruitment of immune cells	Ongoing (NCT01148849)

Mar N, Lung Cancer 2015, 87:220

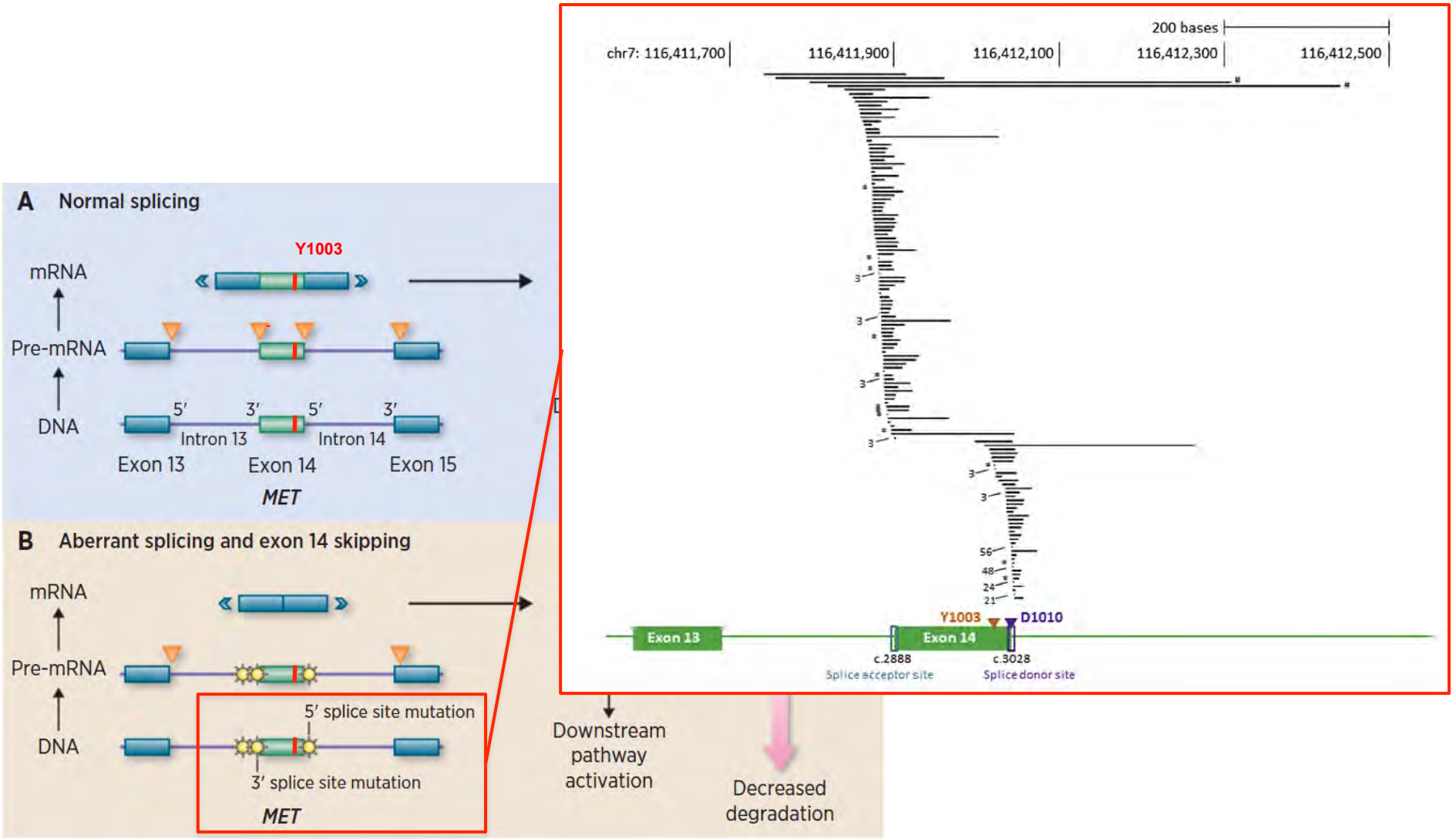
Du gène à la voie de signalisation



Ma PC, Cancer Discov 2015, 5:802

MET

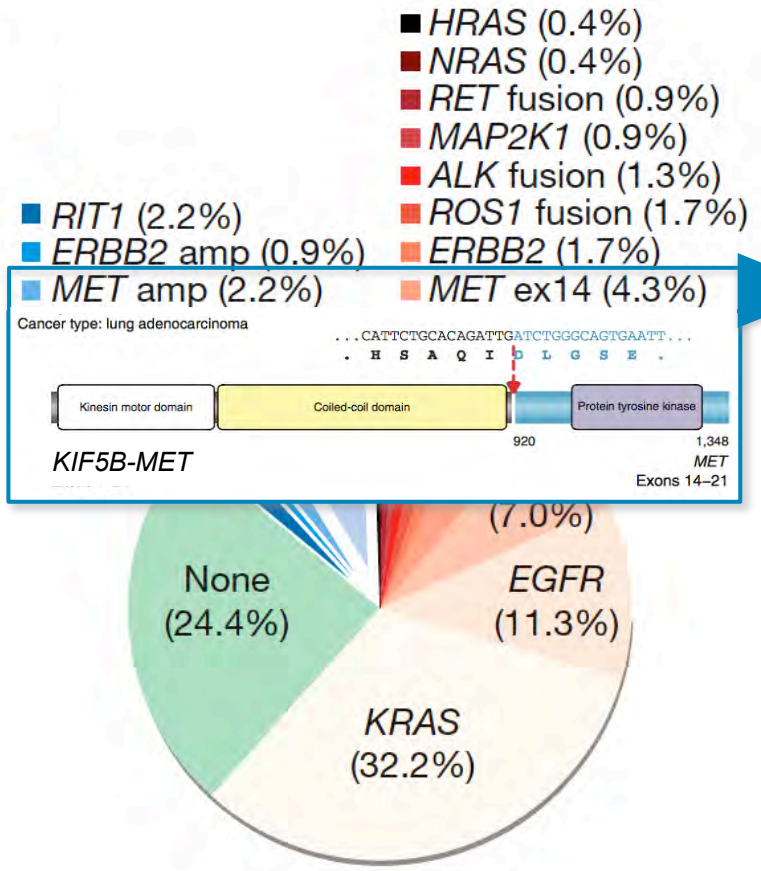
Du gène à la voie de signalisation



Drilon A, Clin Cancer Res 2016, 22:2832; Schrock AB, JTO 2016, 11:1493

Epidémiologie, pronostic, traitements

ADC Genome Atlas *(n=230)*



MET alterations: ≈2-4% of NSCLC

↓

MET ampli (≈2%); MET exon 14 (≈4%);
KIF5B-MET (?) (exclusive)

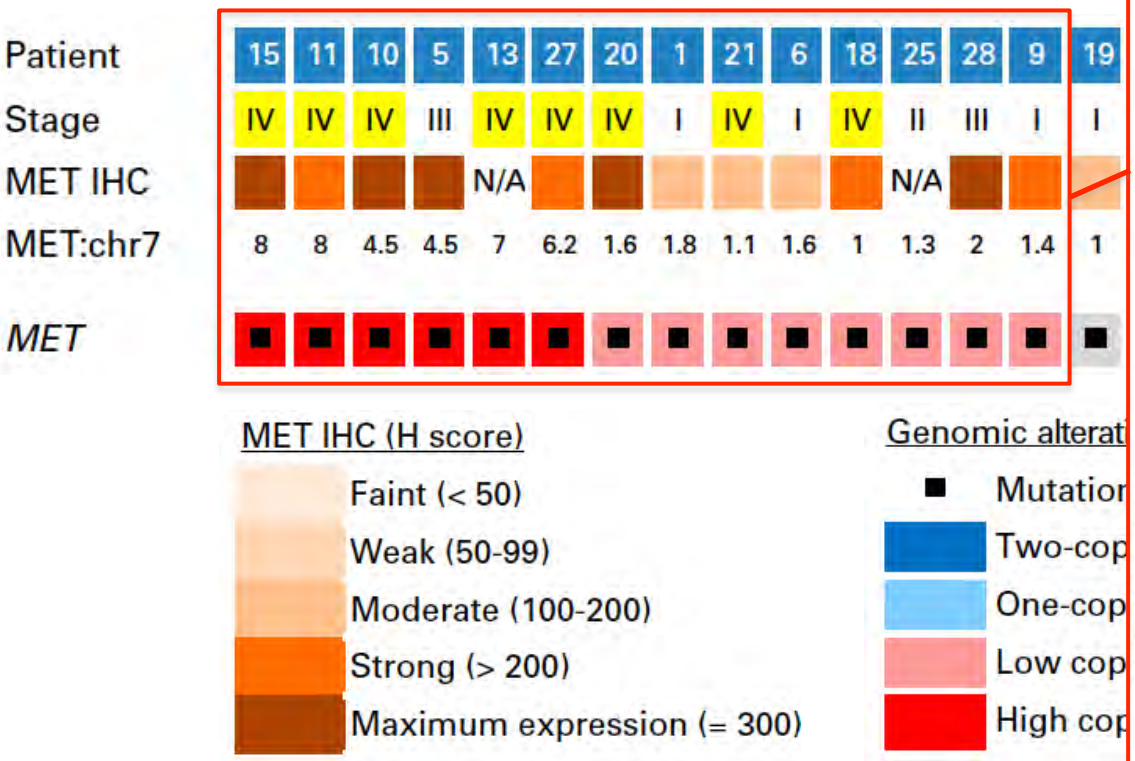
↓

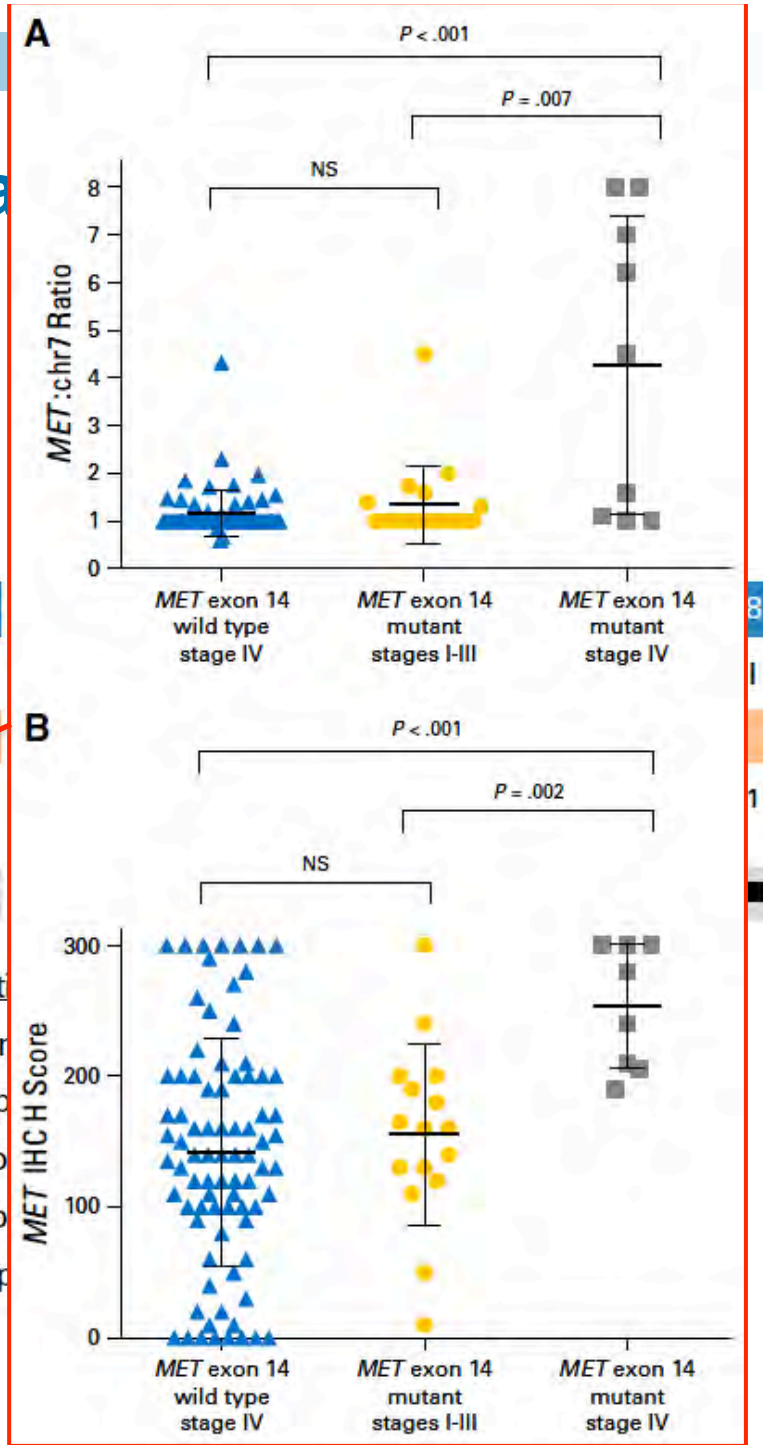
MET alterations associated with:
ADC, sarcomatoide/ADS; smoking; older

Cancer Genome Atlas Nature 2014, 511:543; Stransky N, Nat Commun 2014,5:4846

Epidémiologie, pronostic, tra

MET exon 14 mutation cohort (n=28/933)





Awad M, J Clin Oncol 2016, 34:721

Epidémiologie, pronostic, traitements

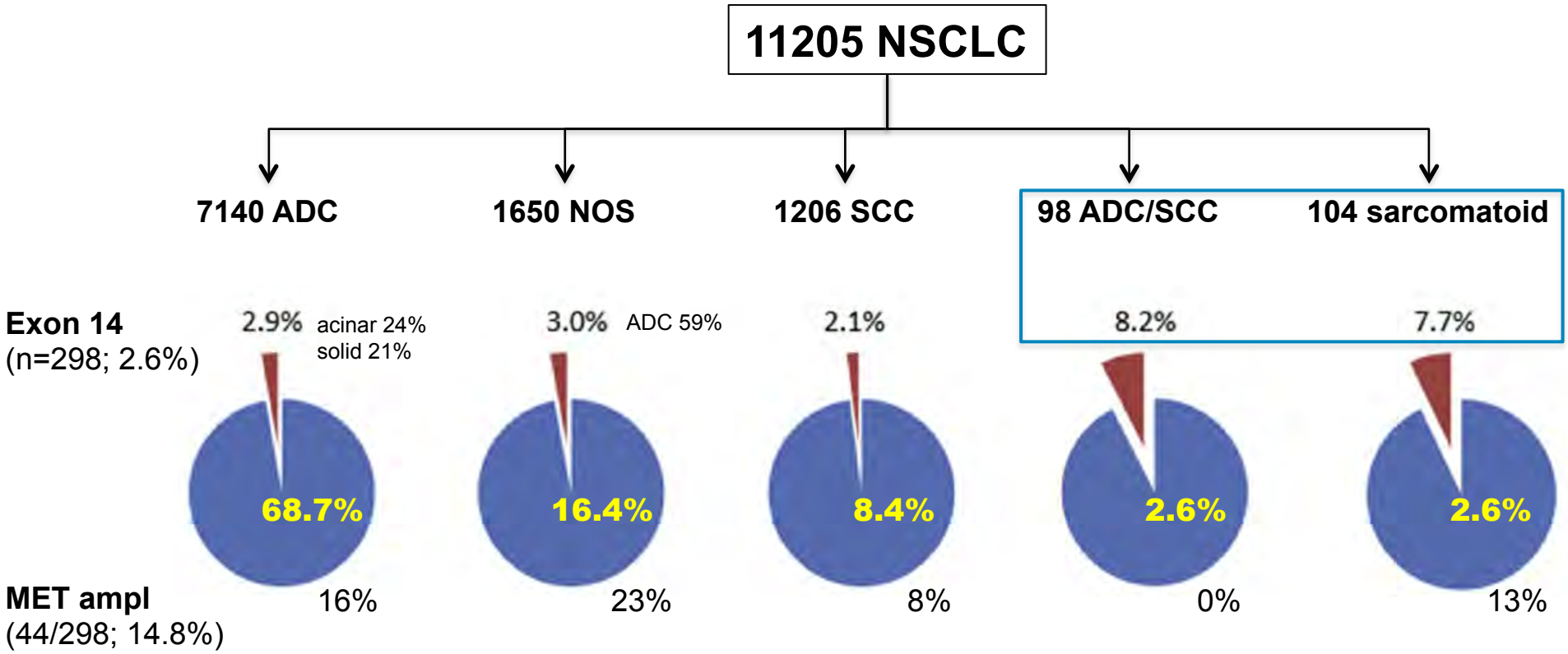
1. Tumors with ≥5 *MET* signals per cell were classified as FISH$^+$ according to Capuzzo scoring system (13).
2. Tumor with *MET*/CEP7 ratio ≥2 were defined as FISH$^+$ by PathVysion (14, 15).
3. High-level amplification (H-Amp) was defined as clustered *MET* signals or *MET*/CEP7 ratio ≥5 (6).

Characte					
Histology					
AD					
SCC					
LCC					
ADSQ					
LELC					
PSC					
METΔ14					
Positive	18	18	0	0%	<0.001
Negative	669	212	457		
Cappuzzo					
Positive	20	16	4	25%	<0.001
Negative	667	214	453		
PathVysion					
Positive	8	8	0	0%	<0.001
Negative	679	222	457		
High-level amplification					
Positive	24	23	1	4%	<0.001
Negative	663	207	456		
MET FISH$^+$					
Positive	29	25	4	16%	<0.001
Negative	658	205	453		
H-Amp	8	8	0	0%	
Polysomy	9	9	0		
L-Amp/H-GCN	7	6	1		
L-Amp/L-GCA	5	2	3		

Tong JH, Clin Cancer Res 2016, 22:3048

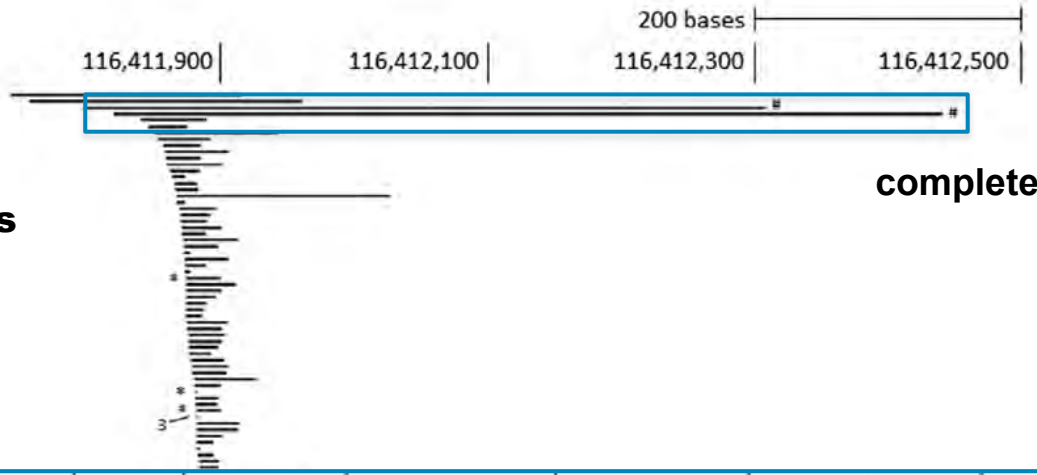
Epidémiologie, pronostic, traitements

MET exon 14 mutation cohort (n=298/11205)



Schrock AB, JTO 2016, 11:1493

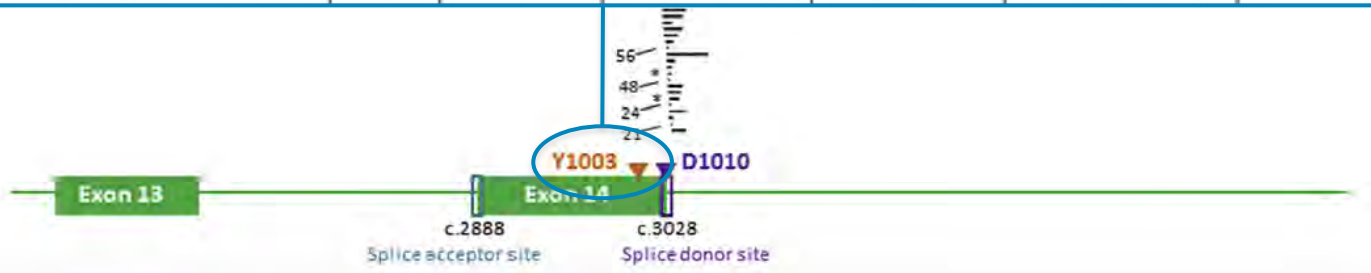
Epidémiologie, pronostic, traitements



complete deletion

165 different variants

Case	Specific Y1003 mutation	Age	Gender	Histology	*MET*amp	*MDM2*amp	*CDK4*amp
1	Y1003F	79	Female	AdenoCA	No	No	No
2	Y1003F	92	Female	SqCC	No	No	No
3	Y1003fs*1	74	Female	AdenoCA	Yes	No	No
4	Y1003N	78	Female	AdenoCA	No	No	Yes
5	Y1003N	92	Female	NOS	No	Yes	Yes
6	Y1003S	76	Female	AdenoCA	No	Yes	Yes



Schrock AB, JTO 2016, 11:1493

Epidémiologie, pronostic, traitements

MET exon 14 mutation cohort (n=298/11205)

Table 3. Response of Patients with NSCLC with *METex14* to a MET TKI (Crizotinib)

Patient Case	Histologic Subtype	*METex14* Alteration	*MET* Amp	*MDM2* Amp	*CDK4* Amp	Biopsy Timing	Response to Crizotinib[a]
1	AdenoCA	3028+1_3028+1delG	Yes	No	Yes	After crizotinib	PR, 24 mo
2	AdenoCA	D1010Y	No	No	No	Before crizotinib	PR, 7 mo, ongoing
3	AdenoCA	3028+1delG	Yes	Yes	No	Before crizotinib	CR, 7 mo, ongoing
4	AdenoCA	D1010H	No	No	No	Before crizotinib	Stable disease, 4 mo, ongoing
5	AdenoCA	2888-16_2888-3del14	Yes	Yes	No	Before crizotinib	PR, 10 mo, ongoing
6	SqCC	2888-11_2904del28	No	No	No	Before crizotinib	PR
7	AdenoCA	2888-16_2888-13delTTCT	No	No	No	Before crizotinib	CR, 3 mo, ongoing
8	AdenoCA	3028 + 1G>A	No	No	No	Before crizotinib	Unresectable to resectable and NED after resection

Schrock AB, JTO 2016, 11:1493

Epidémiologie, pronostic, traitements

MET exon 14 mutation review

Table 1. Overview cMET Exon 14 Skipping Patients Who Received Anti-cMET Therapy: An Overview of the Characteristics of the Patients Described Thus Far Who Presented with cMET Exon 14 Skipping and Were Treated with cMET Small Molecule Inhibitors

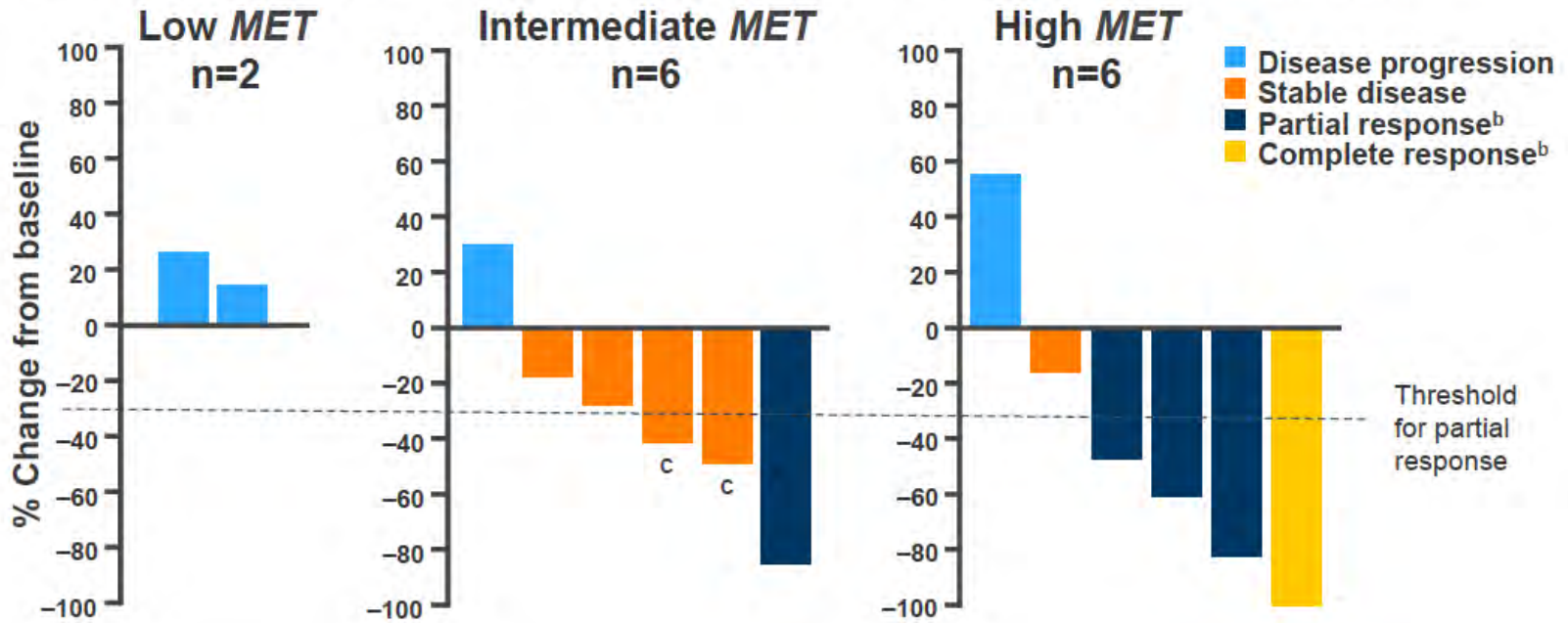
Age	Sex	Smoker	Cancer Type	Previous Treatments	cMET ex14 Splice Mutation	Other Genetic Information	cMET Inhibitor	Response	Ref
84	Female	Never	Stage III histiocytic sarcoma	None	c2888-5_2944del62	*TP53* pR175H *ZMYM3* c3008-1G>A	Crizotinib	-60% progression after 11 mo	7
82	Female	25 PY	Stage IV large cell lung cancer	Resection	c3028G>C	*TP53* pN30fs*14	Capmatinib	-53%	7
66	Female	4 PY	Stage I squamous carcinoma lung	Resection Gemcitabine + carboplatin Palliative radiotherapy Paclitaxel + carboplatin CHK1 inhibitor	c3028+1G>T	NA	Capmatinib	-61%	7
80	Female	Never	Stage Ia lung adenocarcinoma	Docetaxel Pemetrexed Radiotherapy	c3028G>C	*cMET* amplification	Cabozantinib	Stable disease	6
78	Male	Yes	Stage IV adenocarcinoma lung	Carboplatin + pemetrexed + bevacizumab Pemetrexed + bevacizumab Albumin-bound paclitaxel	c3024_3028delAGAAGGT ATATT	*CDKN2A* deletion *CDKN2B* deletion	Crizotinib	-30%	6
65	Male	Yes	Stage IV adenocarcinoma lung	Cisplatin + pemetrexed + bevacizumab Pemetrexed + bevacizumab Gemcitabine	c3028+1G>T	*EGFR* WT *ALK* WT	Crizotinib	-31%	6
90	Female	Never	Metastatic adenocarcinoma lung	Pemetrexed Gemcitabine	c3028G>T	*CDK4* amplification *MDM2* amplification	Crizotinib	-47%	6
64	Female	Never	Metastatic poorly differentiated adenocarcinoma	Chemotherapy (not specified)	c3028G>A	*EGFR, KRAS, BRAF, ALK, ROS1* WT cMET amplification	Crizotinib	Ongoing response at 8 mo	74
71	Male	15 PY	Metastatic lung adenocarcinoma	Radiotherapy (3000 cGy) Carboplatin + pemetrexed	c3082G>C	No *cMET* amplification	Crizotinib	Ongoing response at 6 mo	75
86	Male	Never	Metastatic lung adenocarcinoma	Radiotherapy Pemetrexed	c2887-18_2887-7del12	NA	Crizotinib	Response, but discontinued because of pneumonitis	76
61	Male	Never	Sarcomatoïd NSCLC	Radiotherapy Carboplatin + paclitaxel + bevacizumab	c2888-5_2890TTAAGATC>A c3028+2T>G c3280C>T	NA	Crizotinib	Partial response Progression after 5 mo	77

Van Der Steen N, JTO 2016, 9:1423; Heist RS, The Oncologist, 2016,21:481; Zheng D, Oncotarget 2016, 7:41791

Epidémiologie, pronostic, traitements

8001: Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC) – Camidge DR et al

- **Key results**
  - 1 CR and 4 PRs have been observed with crizotinib among 12 patients to date

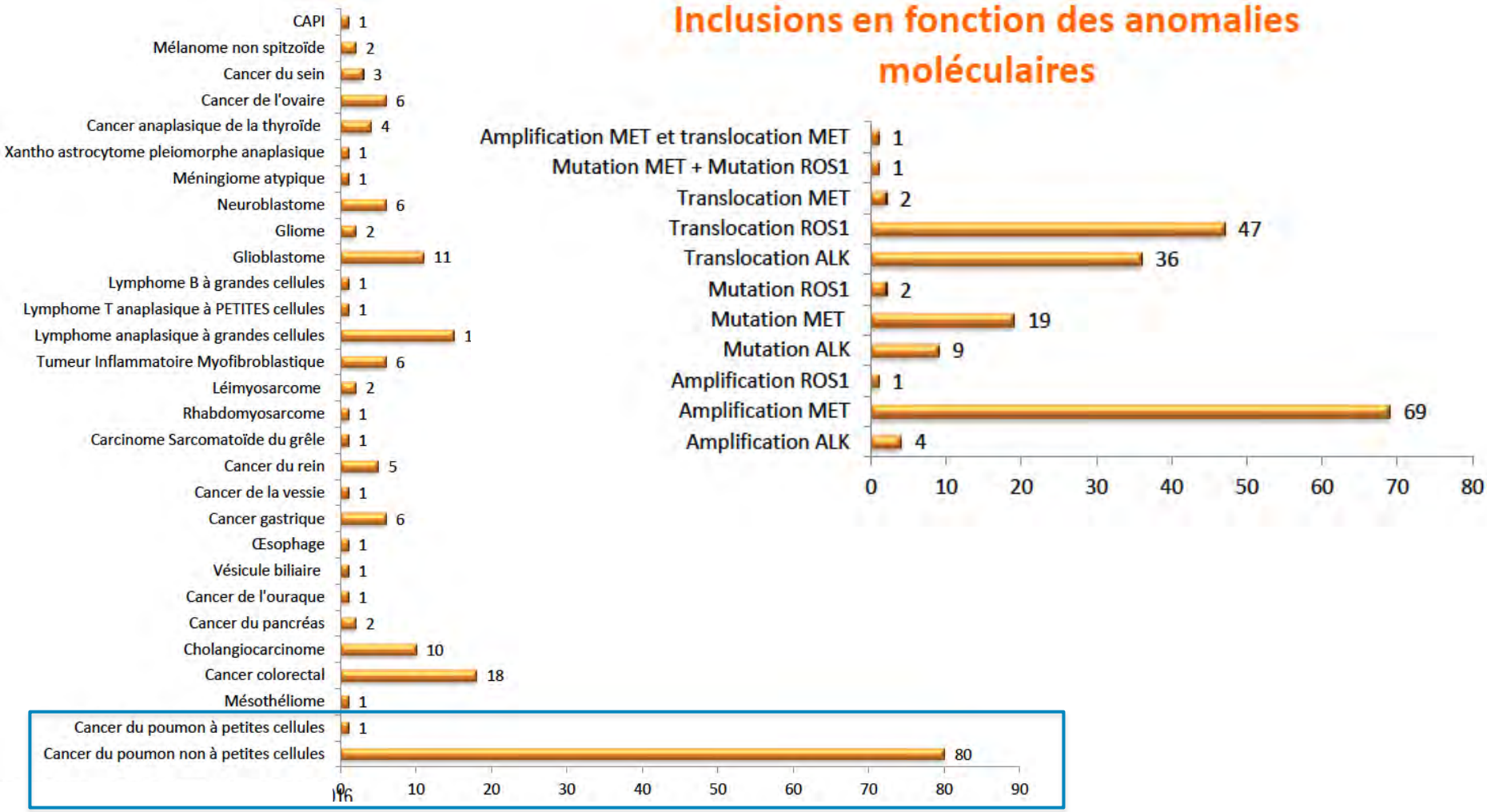


- **Conclusion**
  - Crizotinib seemed to have anti-tumour activity and was generally well tolerated which warrants further study of crizotinib in advanced *c-MET*-amplified NSCLC

Camidge R, ASCO 2014

Epidémiologie, pronostic, traitements

ACSE Crizotinib UNICANCER/IFCT



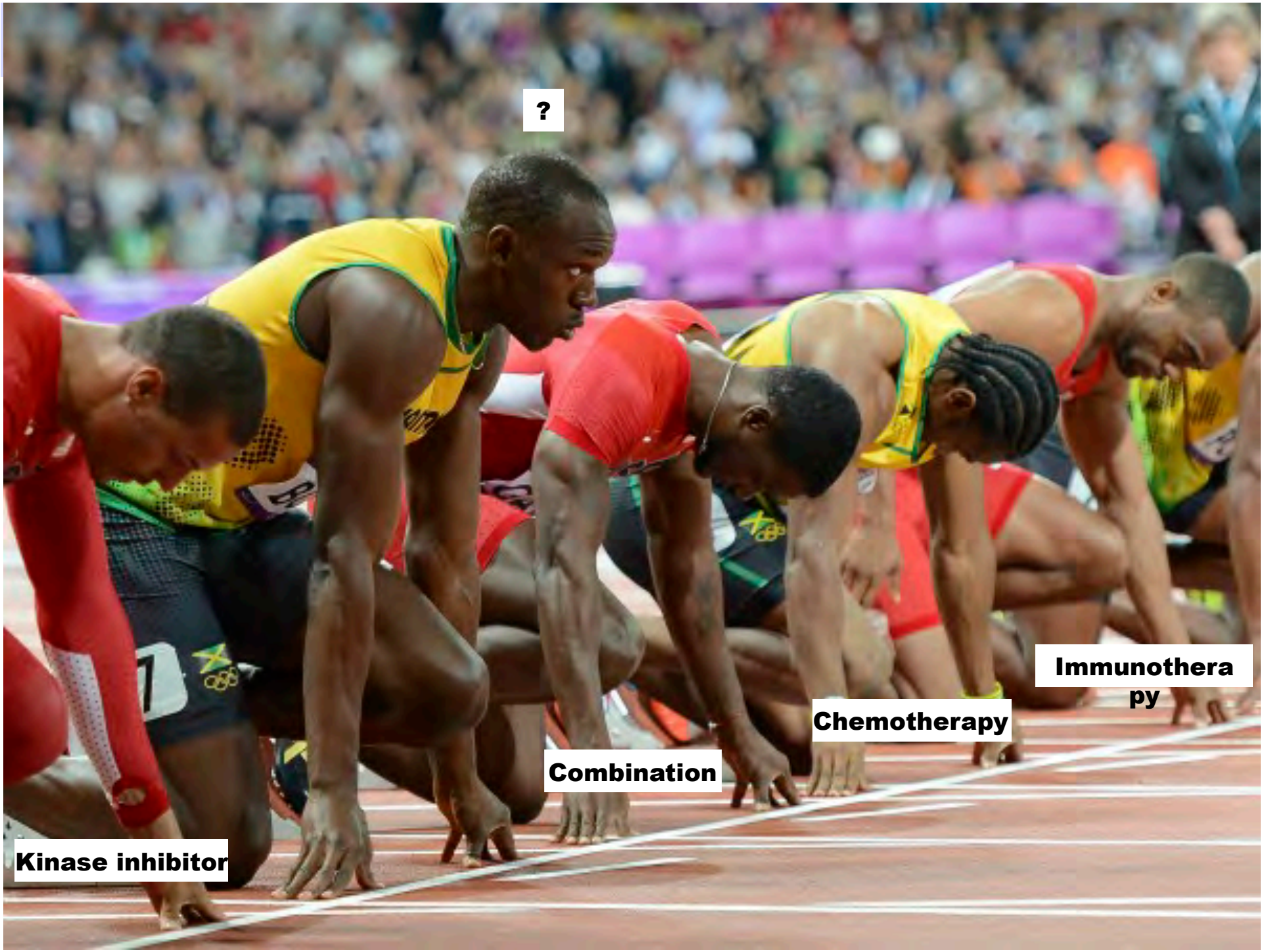
www.unicancer.fr ; données 09/2016

Epidémiologie, pronostic, traitements

Drug in development for MET alteration in NSCLC

Drug	Company	Target	Trials	Comment
Crizotinib	Pfizer	MET, ALK, ROS	AcSe, CREATE, METROS	
Capmatinib	Novartis	MET, (EGFR)	Phase I/II	EGFR resistance
Cabozantinib	Ipsen	RET, MET, ROS, AKL, Kit, fms	Phase I/II	RET, EGFR resistance
MGCD265	Mirati	MET, AXL	Phase I/II	
Onartuzumab	Roche	MET	Stop	
ARGX-111	Argenx	MET	Phase I	

Van Der Steen N, JTO 2016, 9:1423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Chemotherapy
Combination
Kinase inhibitor


OLT
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