Les nouvelles cibles thérapeutiques en oncologie thoracique

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INSERM UMR1037 CRCT

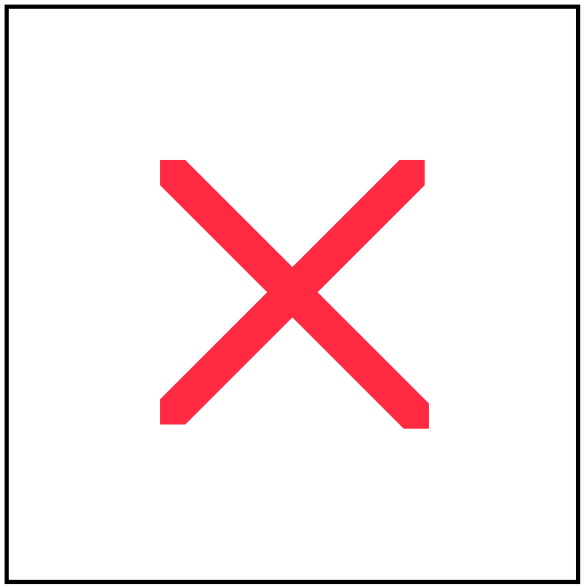
Thérapies ciblées

- Quelques généralités

Quizz

Parmi ces molécules quelles sont celles qui sont des thérapies ciblées?

1. Erlotinib
2. Nivolumab
3. Pemetrexed
4. Dabrafenib
5. Crizotinib



Quizz

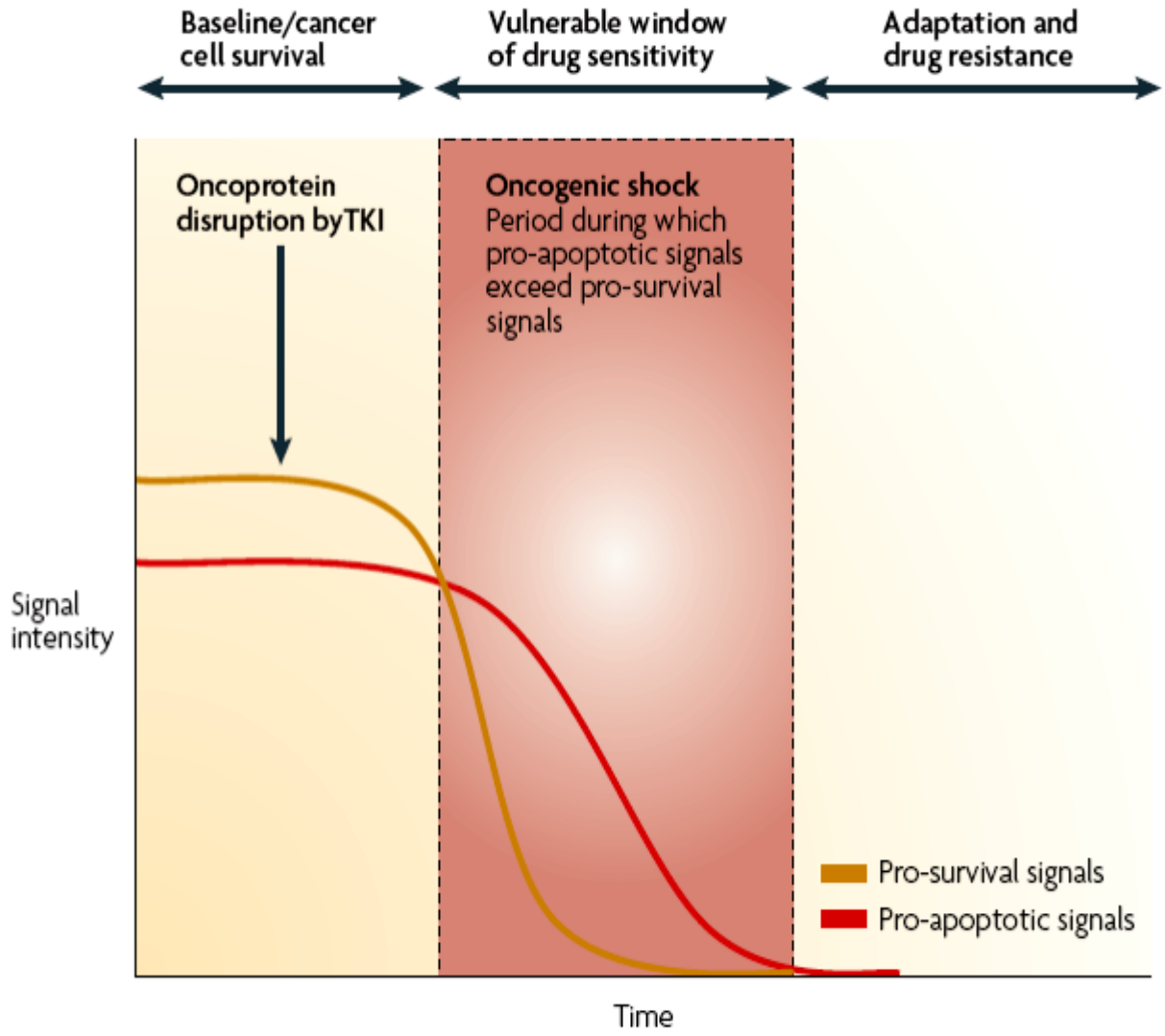
Parmi ces molécules quelles sont celles qui sont des thérapies ciblées?

1. **Erlotinib** — **EGFR** 
2. **Nivolumab** — ~~**PD1**~~
3. **Pemetrexed** — ~~**TS**~~
4. **Dabrafenib** — **BRAF** 
5. **Crizotinib** — **ALK** 

Les thérapies ciblées bloquent des oncogènes moteurs.

Généralités

- **Choc Oncogenique**



Généralités

Quels sont les événements moléculaires qui peuvent conduire à une addiction oncogénique ?

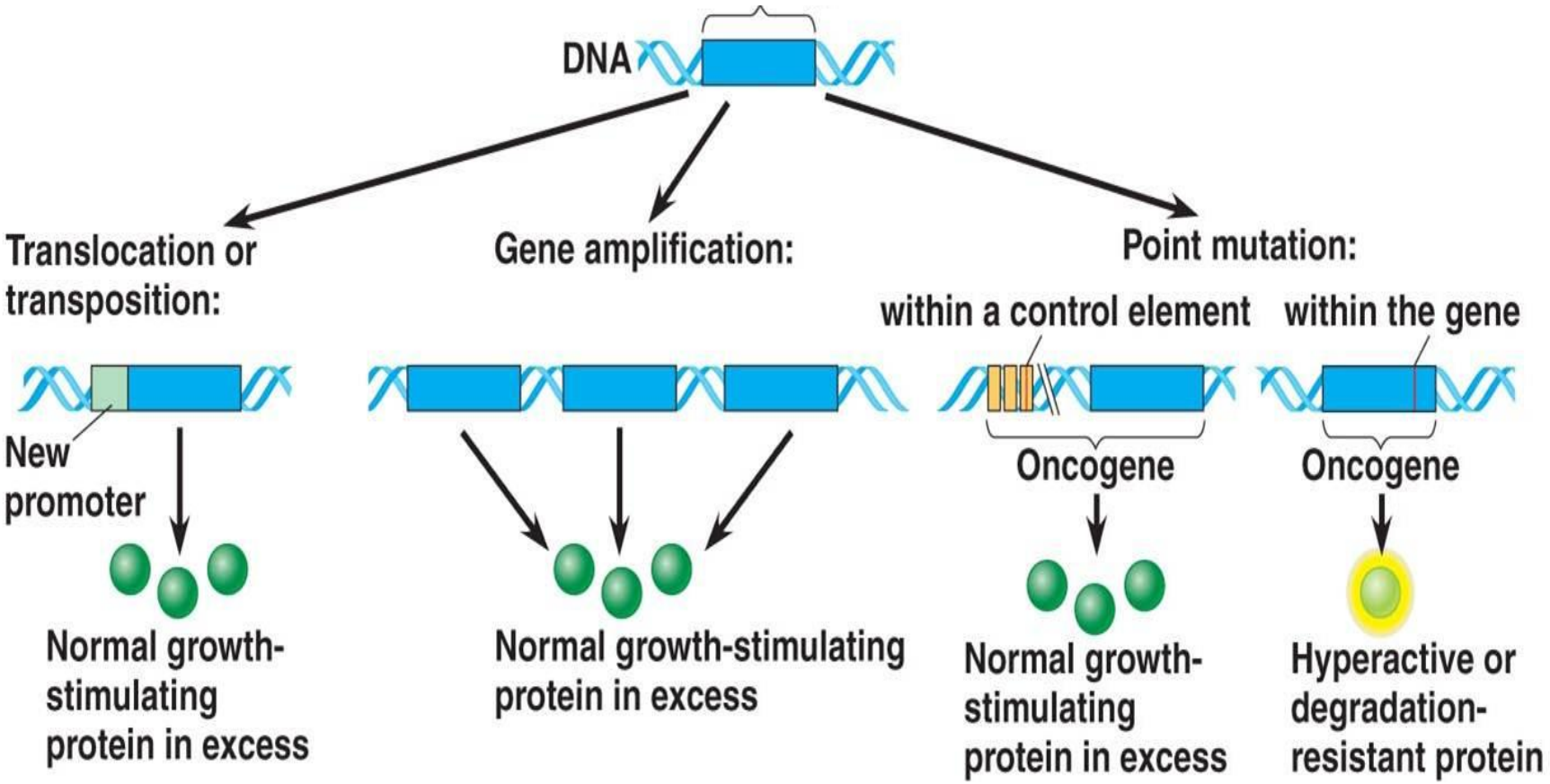
1. Surexpression
2. Mutation ponctuelle
3. Amplification
4. Polyploïdie
5. Translocation chromosomique

Généralités

Quels sont les événements moléculaires qui peuvent conduire à une addiction oncogénique ?

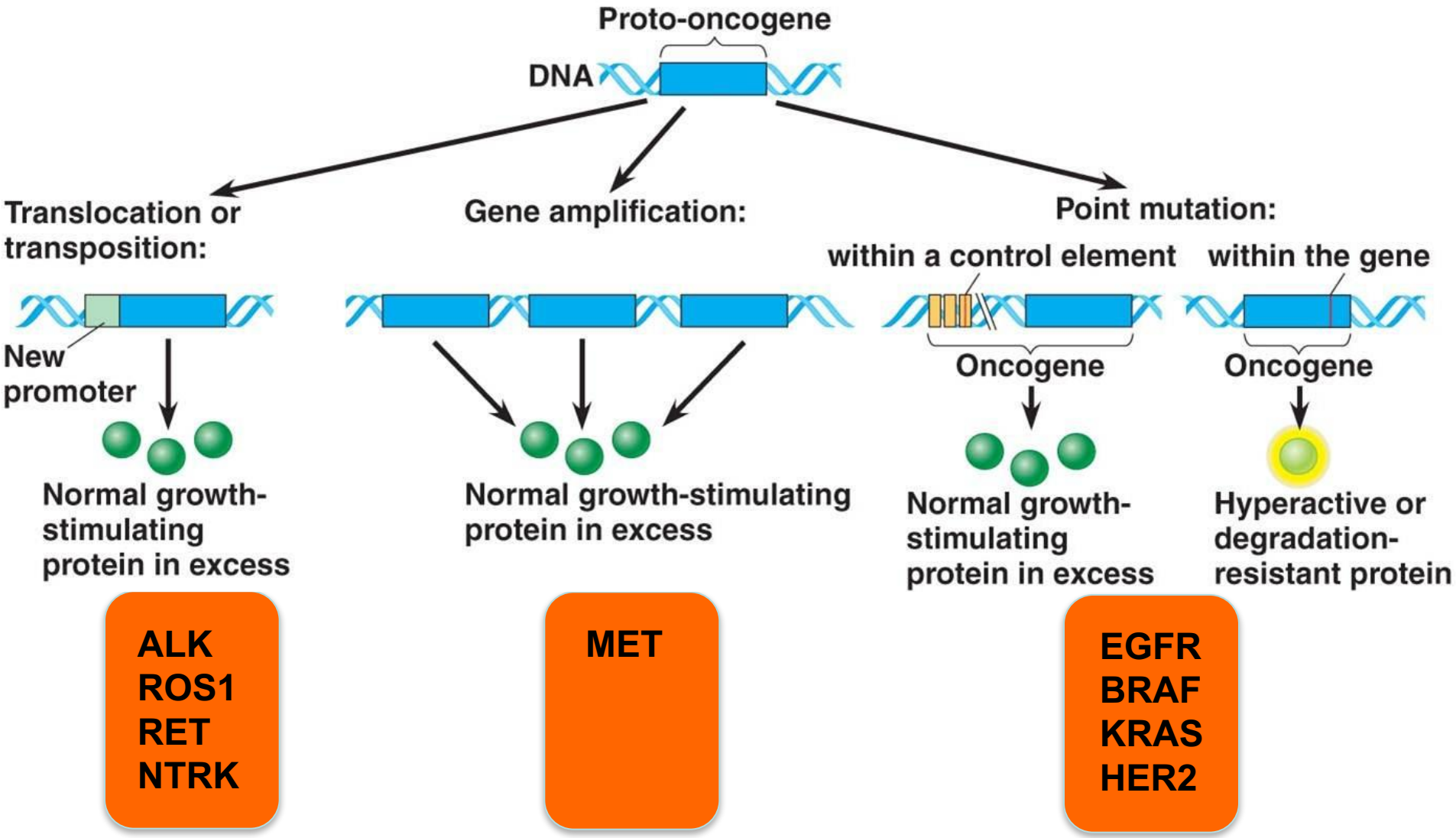
1. Surexpression
2. **Mutation ponctuelle** ☒
3. **Amplification** ☒
4. Polyploïdie
5. **Translocation chromosomique** ☒

Généralités

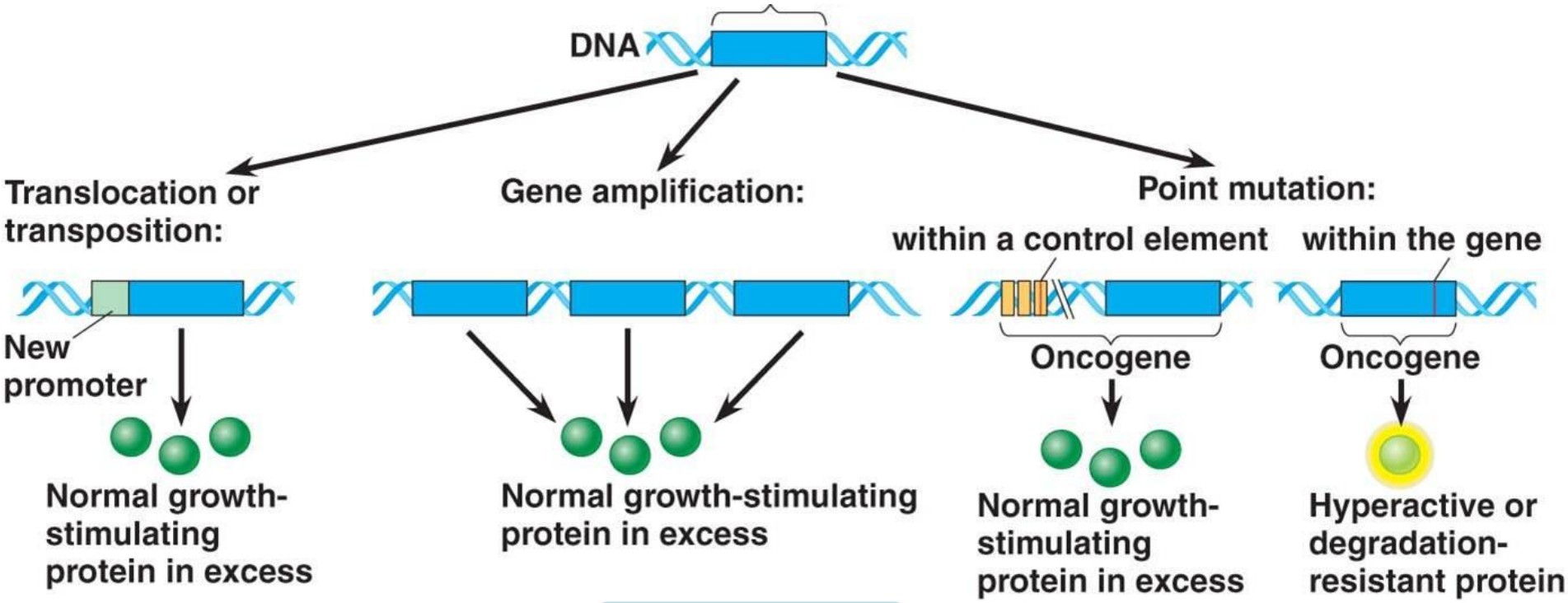


Généralités

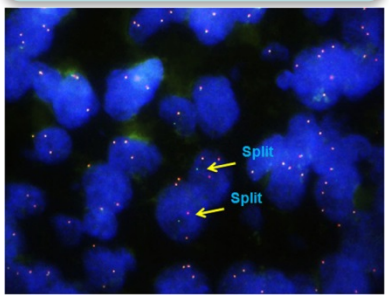
Main molecular abnomalities



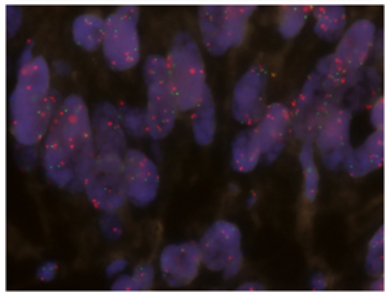
Généralités



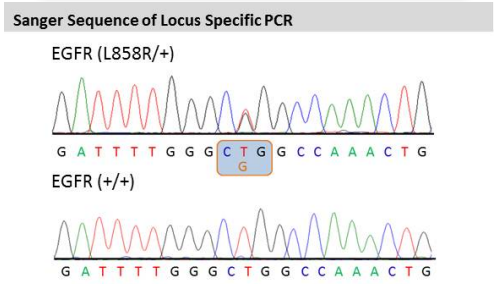
IHC, FISH, PCR



FISH, CISH



Sequencing



Next Generation Sequencing

Thérapies ciblées

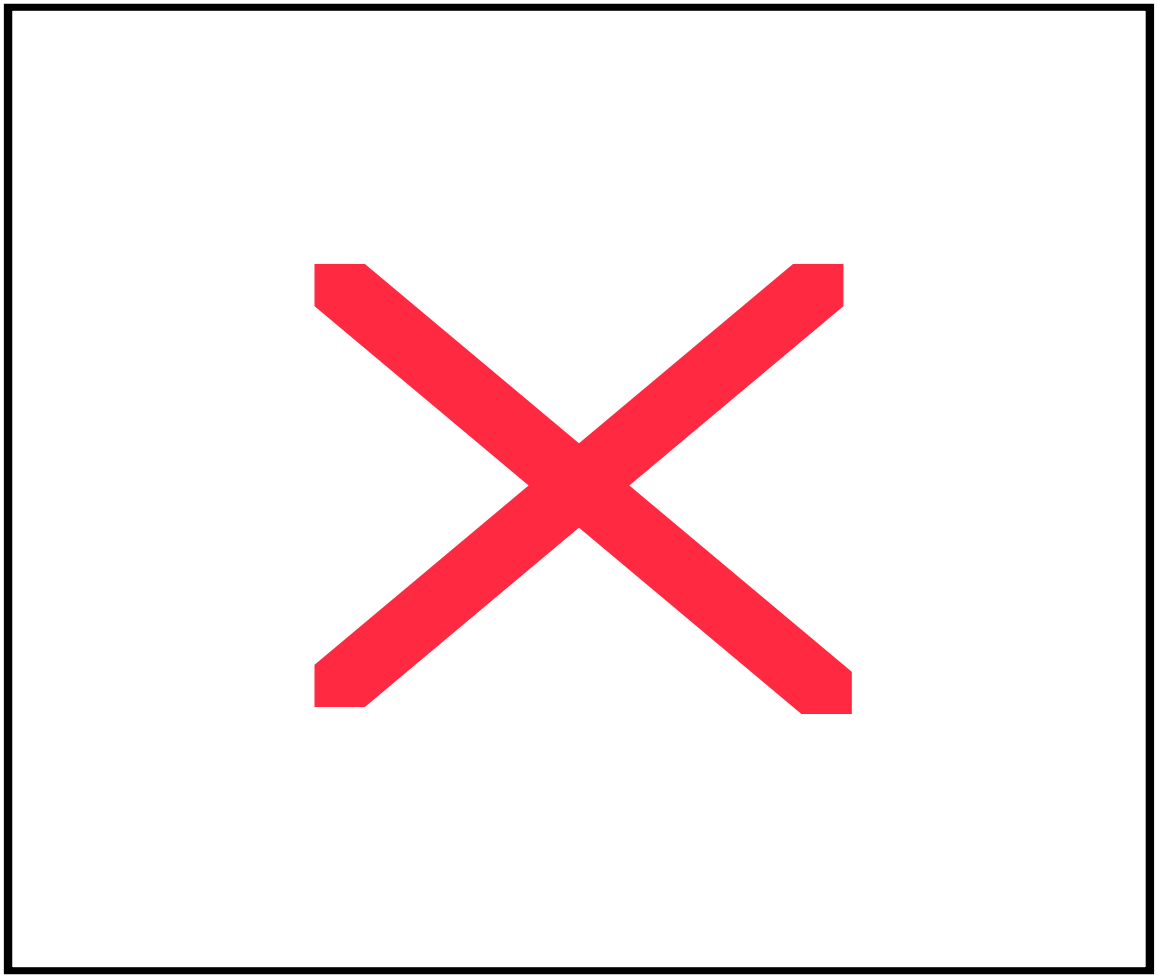
- Les biomarqueurs validés

Les biomarqueurs validés

EGFR

ALK

K-Ras



BRaf

Her2

ROS1

EGFR

Patiente non-fumeuse de 72 ans. PS1. Adénocarcinome bronchique T2N2M1c (os, foie). Mutation EGFR L858R exon 21. Quelles molécules ont l'AMM pour débuter ?

1. Erlotinib
2. Crizotinib
3. Afatinib
4. Pembrolizumab si PDL1 > 50%
5. Osimertinib

EGFR

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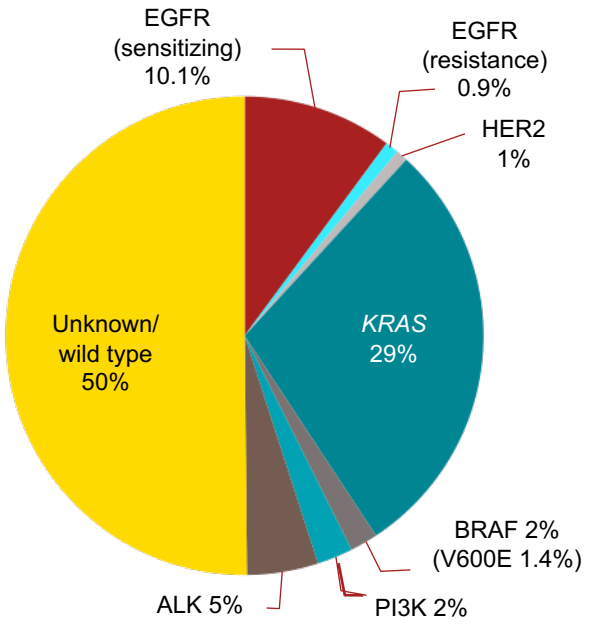
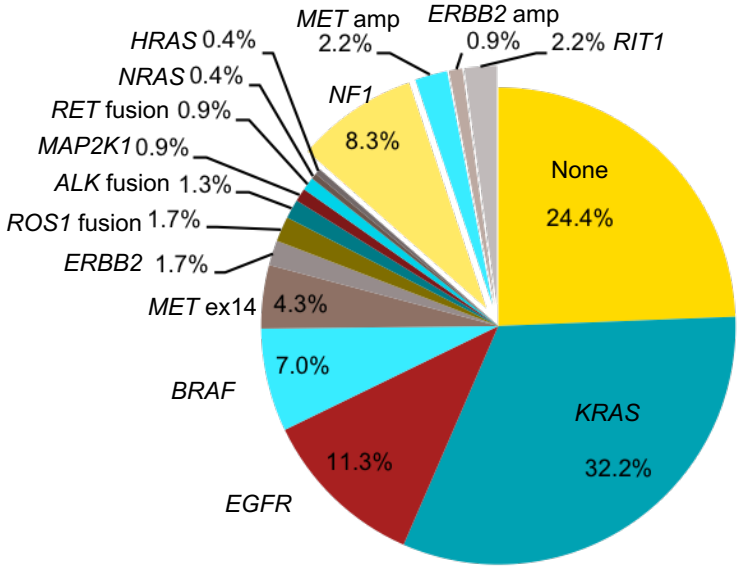
5. **Osimertinib**

Les biomarqueurs validés

Biomarker France (IFCT)



Cancer Genome Atlas Research Network

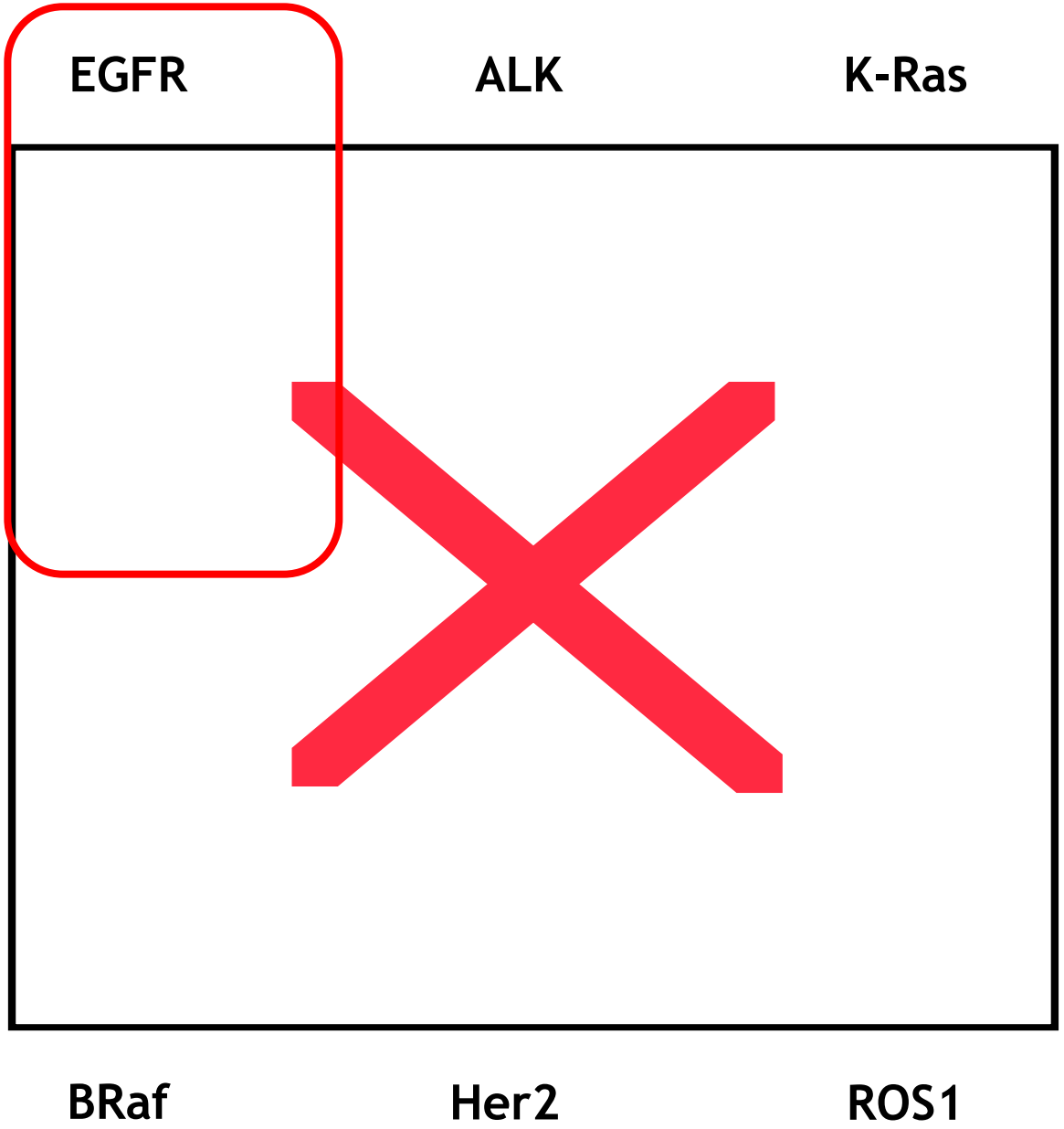


By including amplification of MET and ERBB2, MET exon 14 splicing mutations, RIT1 mutations, and NF1 loss-of-function mutations, the driver-positive group increases to ~75% of cases

IFCT, French Cooperative Thoracic Intergroup.

Barlesi F, et al. Lancet. 2016;387:1415-26.
Cancer Genome Atlas Research Network. Nature. 2014;511:543-50.

Les biomarqueurs validés



EGFR

Author	Study	Agent	N (EGFR mutant)	RR (%)	Median PFS (months)	Median OS (months)
Mok	IPASS	Gefitinib	261	71.2 vs 47.3	9.8 vs 6.4	21.6 vs 21.9
Han	First-SIGNAL		142	84.6 vs 37.5	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi	WJTOG3405		177	62.1 vs 32.2	9.2 vs 6.3	35.5 vs 38.8
Maemondo	NEJGSG002		230	73.7 vs 30.7	10.8 vs 5.4	30.0 vs 23.6
Zhou	OPTIMAL	Erlotinib	154	83 vs 36	13.1 vs 4.6	22.6 vs 28.8
Rosell	EURTAC		174	54.5 vs 10.5	9.2 vs 5.4	19.3 vs 19.5
Yang	LUX-Lung 3	Afatinib	345	56 vs 23	13.6 vs 6.9	31.6 vs 28.2
Wu	LUX-Lung 6		364	67 vs 23	11.0 vs 5.6	23.6 vs 23.5

EGFR

	Exon 18	Exon 19	Exon 20	Exon 21
classic		Del E746-T750 Gefitinib Erlotinib Afatinib		L858R Gefitinib Erlotinib Afatinib
rare	G719X Afatinib		T790M Osimertinib Poziotinib	L861Q Gefitinib Erlotinib Afatinib
Very rare	E709X V700D G720P	D761Y	insertion V769X N771T	G863D N826S A839T
	Complex mutations : poziotinib, afatinib, osimertinib + cetuximab ?			

EGFR : progression

- **Comment gérer la progression sous EGFR-TKI ?**

EGFR-TKI

Resistance ?	Vérifier observance, PK ? Attention avec les M+ os
Primaire < 3 mois	Chimoitherapie +/- bevacizumab
M+ cérébrales	Continuer TKI + RT (stereotaxie)
Oligometastatique	Continuer TKI +traitement local
Rebiopsie	
Progression lente	Continuer TKI and surveillance
Rebiopsie	
Vraie progression	Changement (TKI 3G, cMET inh, chimio)

EGFR première ligne

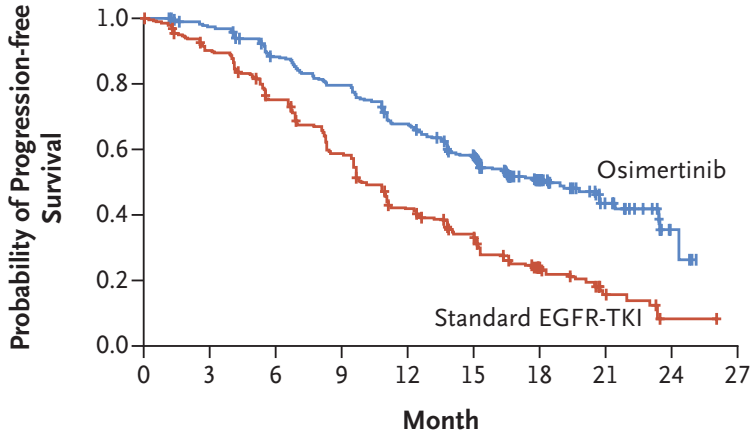
FLAURA trial

- PFS in the global population and in patients with brain mets (osimertinib vs standard EGFR-TKIs)

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

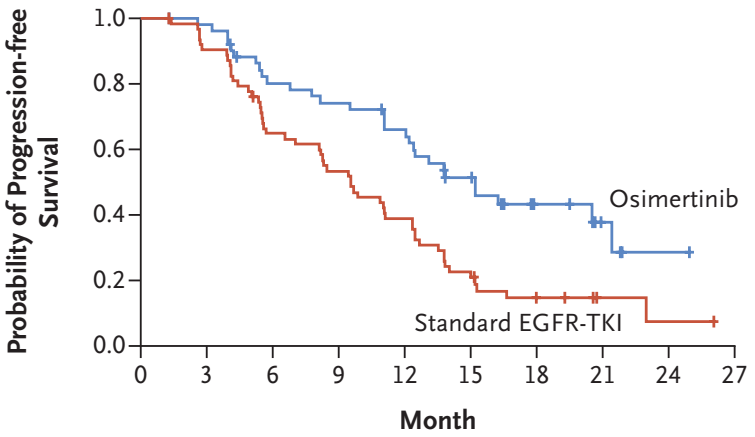


No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

B Progression-free Survival in Patients with CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

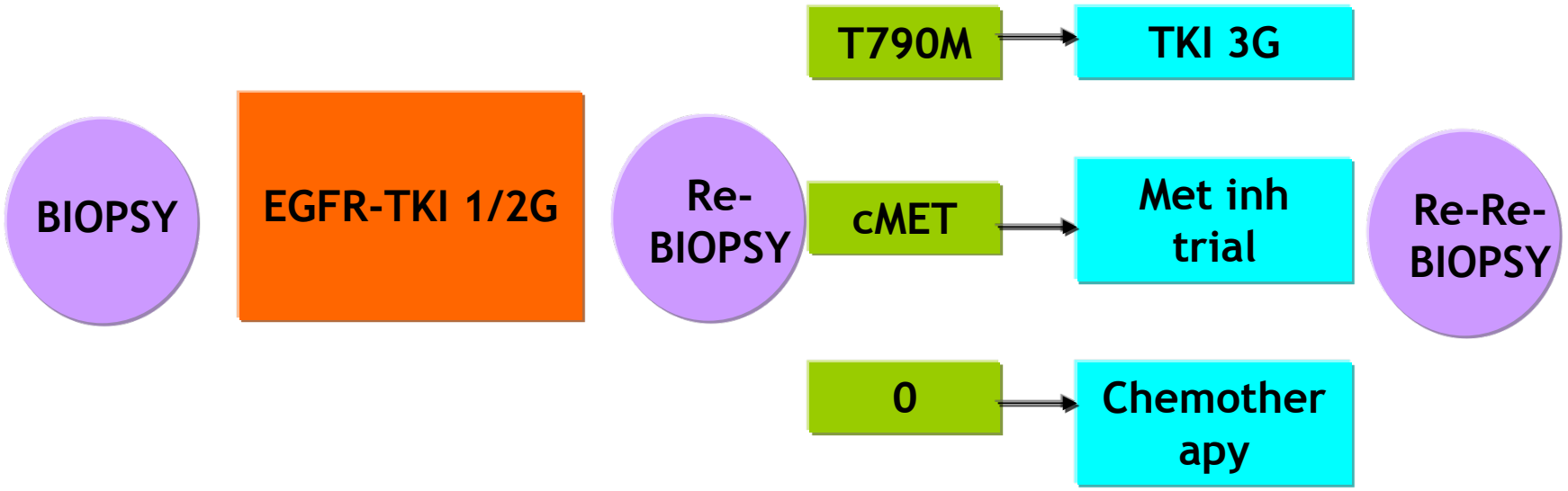
Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001



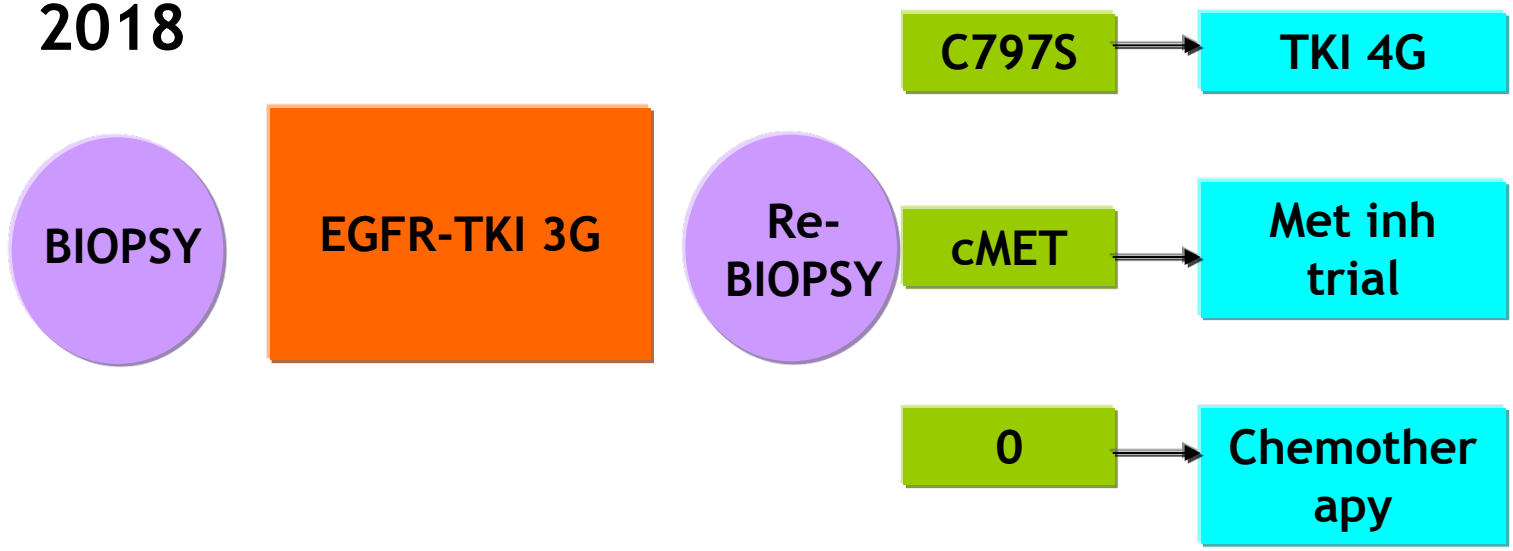
No. at Risk										
Osimertinib	53	51	40	37	32	22	9	4	1	0
Standard EGFR-TKI	63	57	40	33	24	13	6	2	1	0

Soria JC, NEJM 2017

Que faire si j'ai un patient EGFR ?



2018



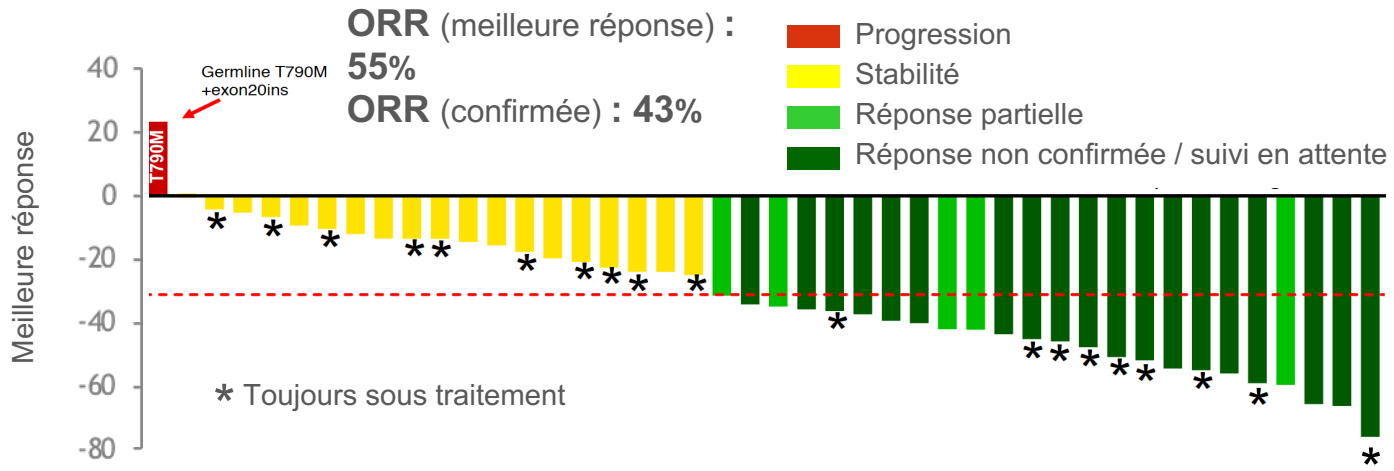
Mutations rares de l'EGFR : exon 20

Poziotinib

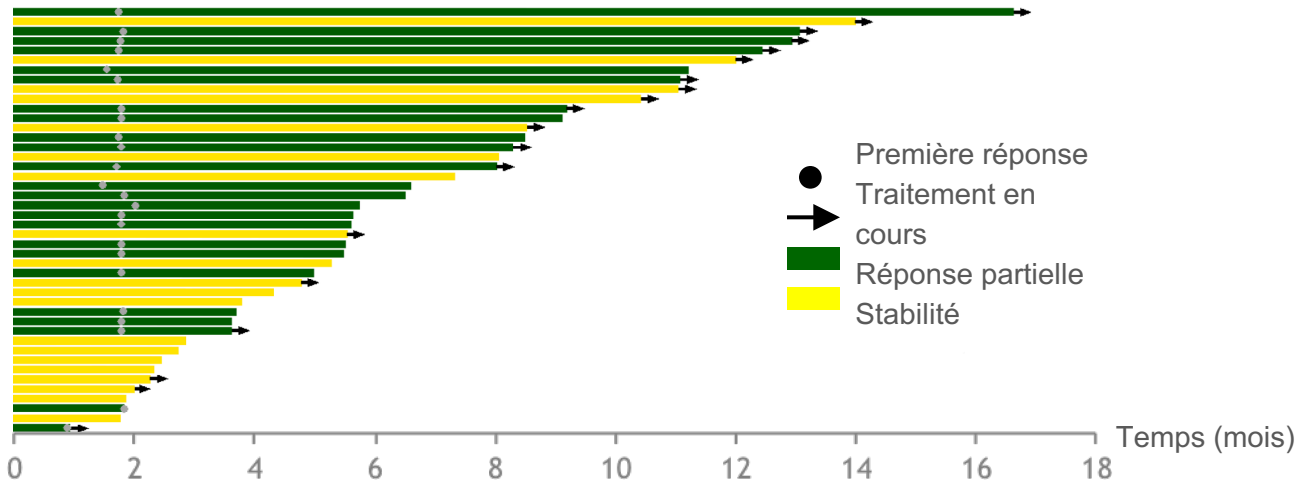
- **Design : monocentrique** (MD Anderson Cancer Center)
  - → ***Cohort 1*** **: CBNPC *EGFR* exon 20 mutant (N=50)**
  - → ***Cohort 2*** **: CBNPC *HER2* exon 20 mutant (N=30 prévus)**
- **Objectif principal :**
  - → **Taux de réponse objectif (RECIST 1.1).**
- **Objectifs secondaires :**
  - → **SSP, SG, taux de contrôle, durée de réponse, tolérance et toxicité**
- **Critères d'inclusion :**
  - → **1. *EGFR* ou *HER2* insertion de l'exon 20 ou mutation ponctuelle à l'exclusion des T790M acquises.**
  - → **2. Au moins un traitement systémique.**
  - → **3. Métastases cérébrales incluables si asymptomatiques et stables, sans augmentation d'un traitement par stéroïdes ou d'anti-épileptiques.**

Efficacité du Poziotinib, *EGFR* Exon 20+ NSCLC

Efficacité du Poziotinib *CBNPC EGFR* Exon 20 muté
(patients évaluables n=44)

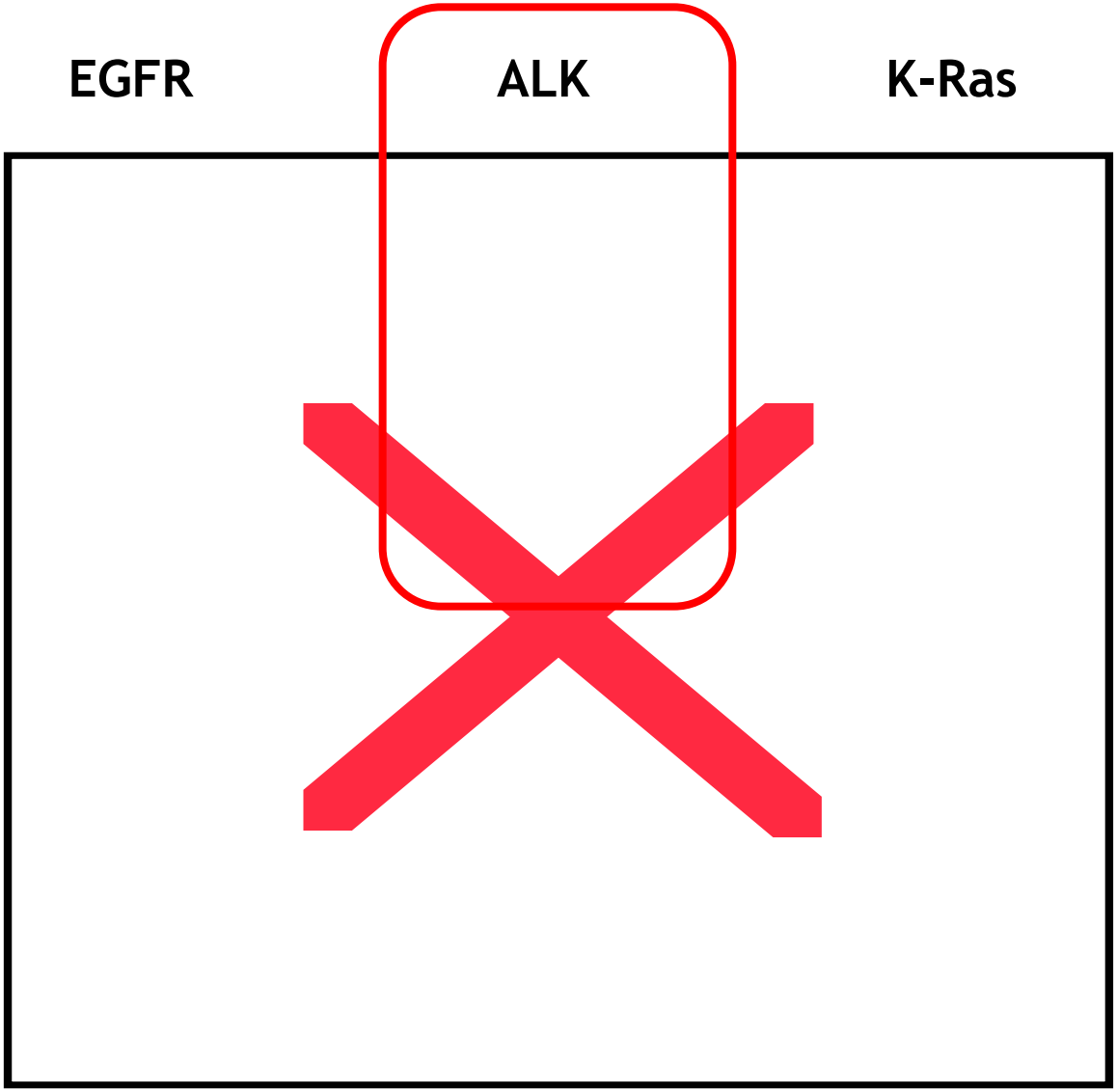


Durée de traitement individuelle



Heymach JV. et al.- WCLC® 2018 – Abs.# OA02.06

Les biomarqueurs validés



ALK

Patient non-fumeur de 40 ans. PS0. Adénocarcinome bronchique T1N3M1c (cérébral asymptomatique, surrénales). Translocation de ALK.
Quel est votre traitement de choix ?

1. Chimiothérapie
2. Crizotinib
3. Radiothérapie cérébrale
4. Alectinib
5. Ceritinib

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ALK

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
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 L1198F	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 G1202del	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 G1269A	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

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

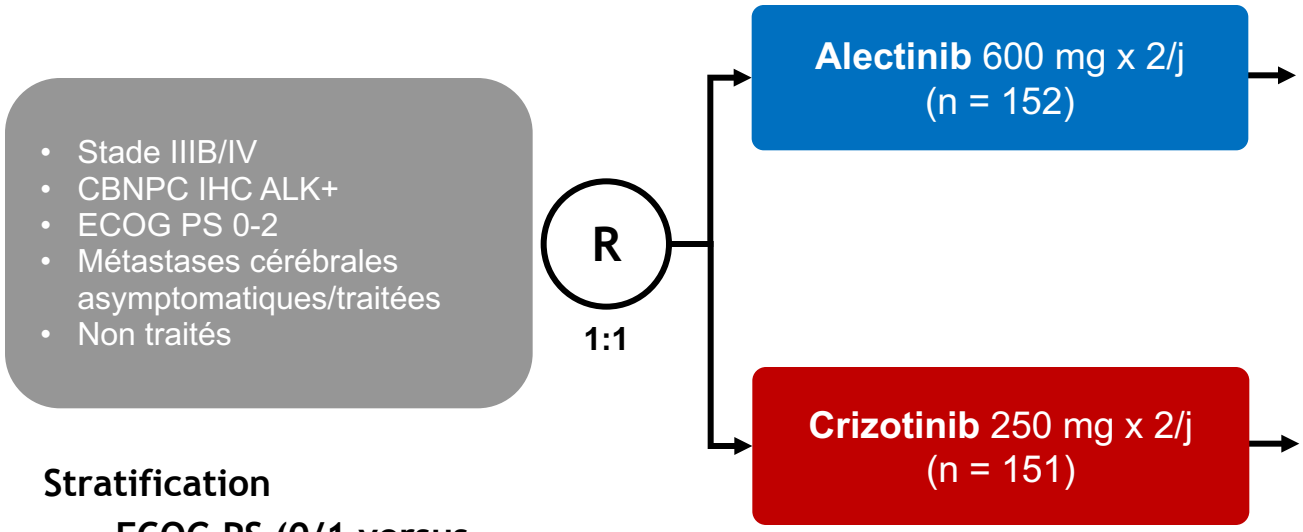
$IC_{50} \geq 200$ nmol/L

Gainor, Cancer Discovery 2016

ALK

ALEX trial : alectinib vs crizotinib en première ligne.

- *Phase III testant alectinib versus crizotinib*



Critères de jugement

•Principal
- SSP (évaluée par les investigateurs)

•Secondaires
- SSP par comité indépendant
- Délai d'apparition des métastases cérébrales
- Taux de RO
- SG
- Durée de réponse
- Taux de réponse cérébrale
- Durée de la réponse cérébrale
- Profil de tolérance

Stratification

- **ECOG PS (0/1 versus 2)**
- **Asiatiques versus autres**
- **Présence ou non de métastases cérébrales**

Peters S, NEJM 2017

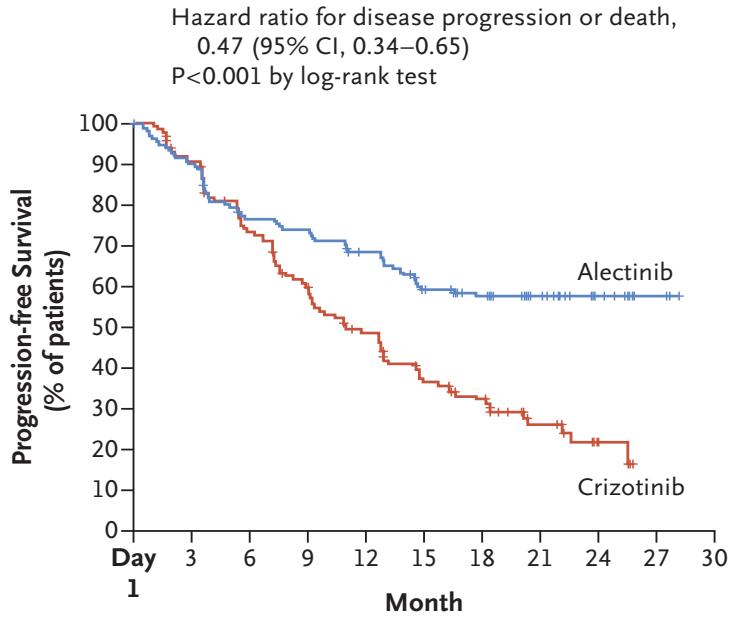
ALK

ALEX trial : alectinib vs crizotinib en première ligne.

- PFS dans la population globale
- Incidence cumulative des M+ cérébrales

A Progression-free Survival

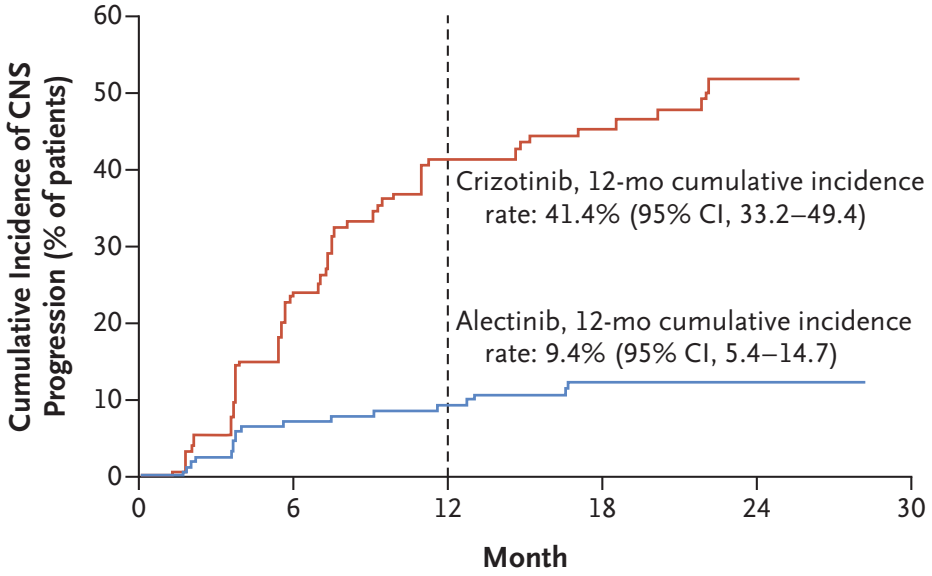
10.9 mois vs 34.8 mois



No. at Risk

Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

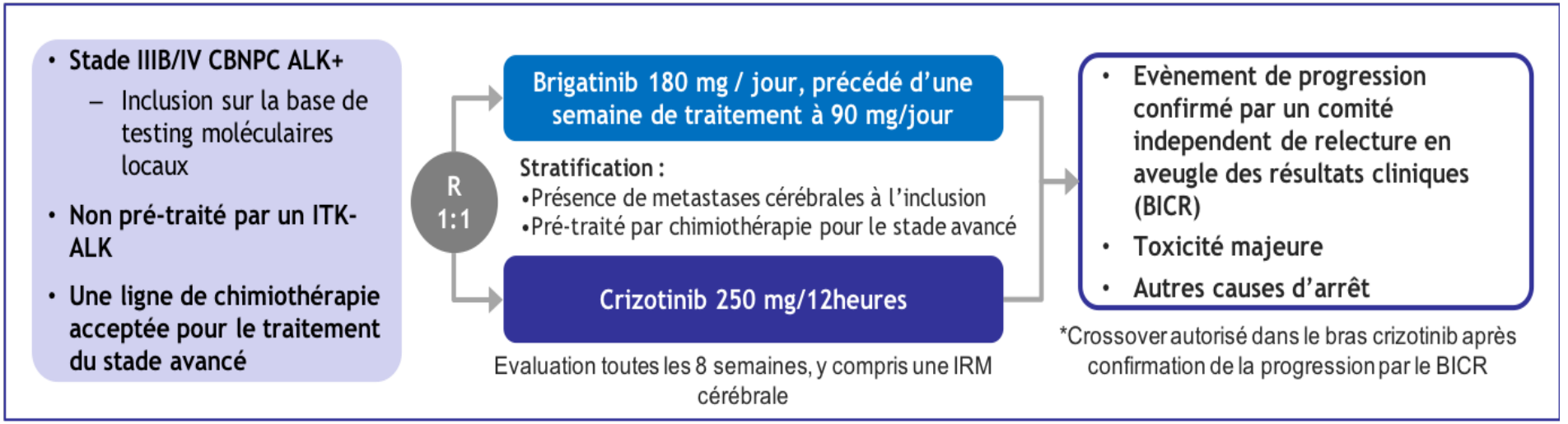
C Cumulative Incidence of CNS Progression



Peters S, NEJM 2017

ALK

ALTA1 trial : brigatinib vs crizotinib en première ligne.



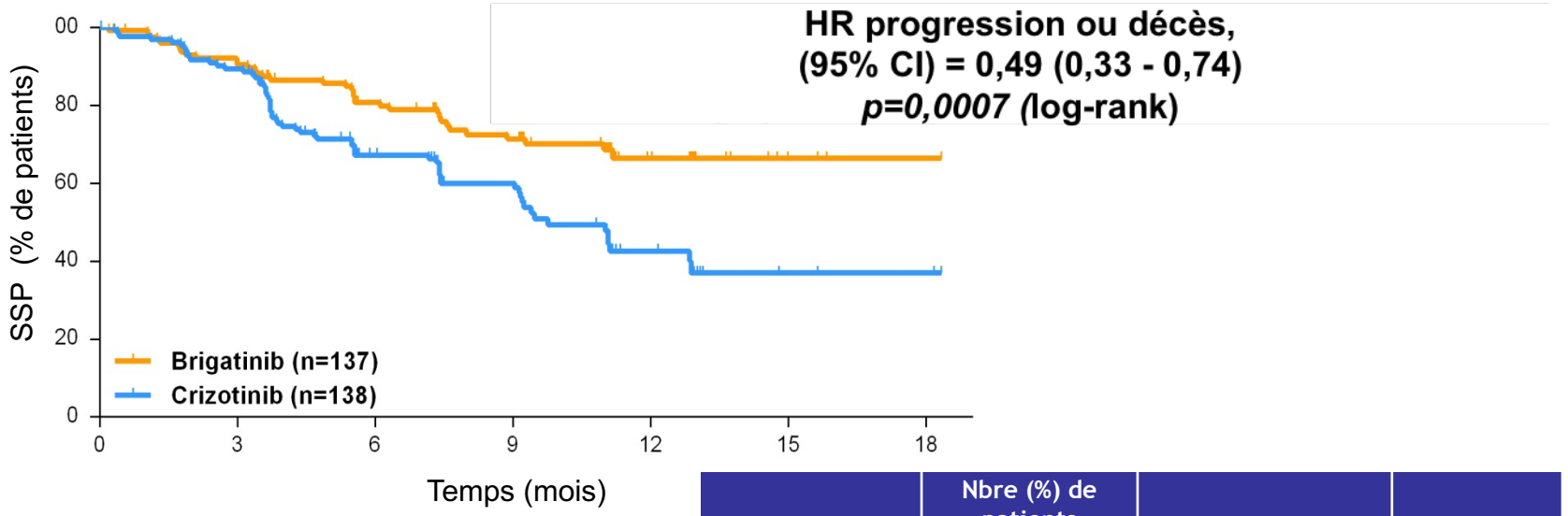
- **Objectif principal :** Survie sans progression (SSP) évaluée par un comité de relecture indépendant en aveugle selon les critères RECIST v1.1
- **Objectifs secondaires :** Taux de réponse objectif confirmé, Taux de réponse SNC confirmé, SSP SNC, Survie globale, Toxicité, et tolérance

Camidge R, NEJM 2018

ALK

ALTA1 trial : brigatinib vs crizotinib en première ligne.

- Le brigatinib est supérieur au crizotinib en termes de SSP.

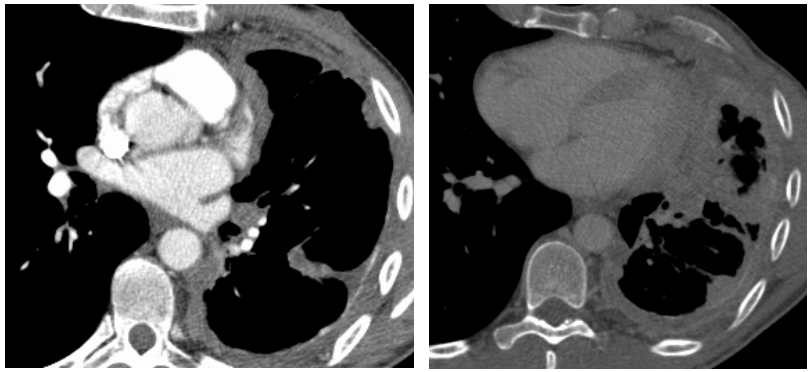


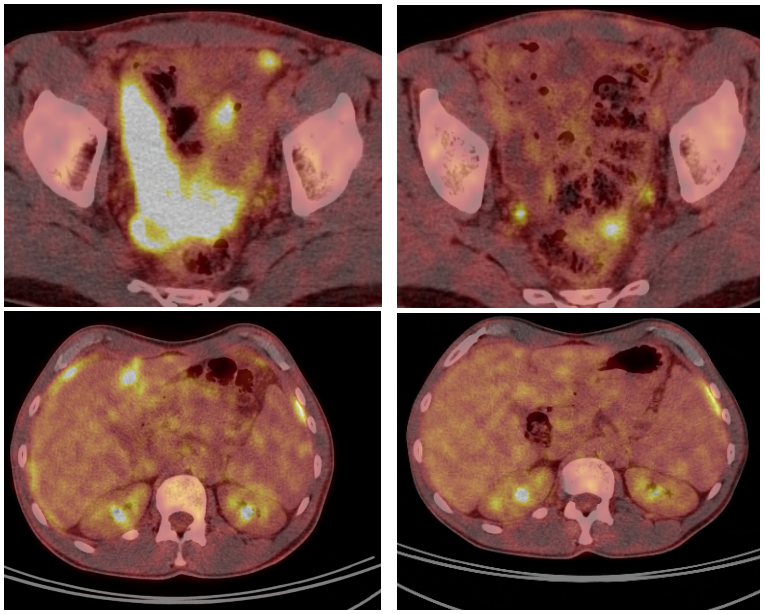
Traitement	Nbre (%) de patients présentant un évènement	Médiane SSP (IC95%)	SSP à 1 an, % (IC95%)
Brigatinib (n=137)	36 (26)	NA (NA-NA)	67 (56-75)
Crizotinib (n=138)	63 (46)	9,8 mois (9,0-12,9)	43 (32-53)

- Probabilité de survie à 1 an :
  - brigatinib, 85% (IC 95%, 76% - 91%) ; crizotinib, 86% (77% - 91%)

Camidge R, NEJM 2018

Exemple d'un patient ALK





2010 2011 2012 2013 2014 2015 2016 2017

Carbo-taxol-CT322

Alimta 6 C.

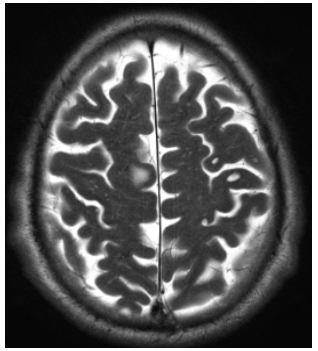
crizotinib

alectinib

ceritinib

Lorlatinib

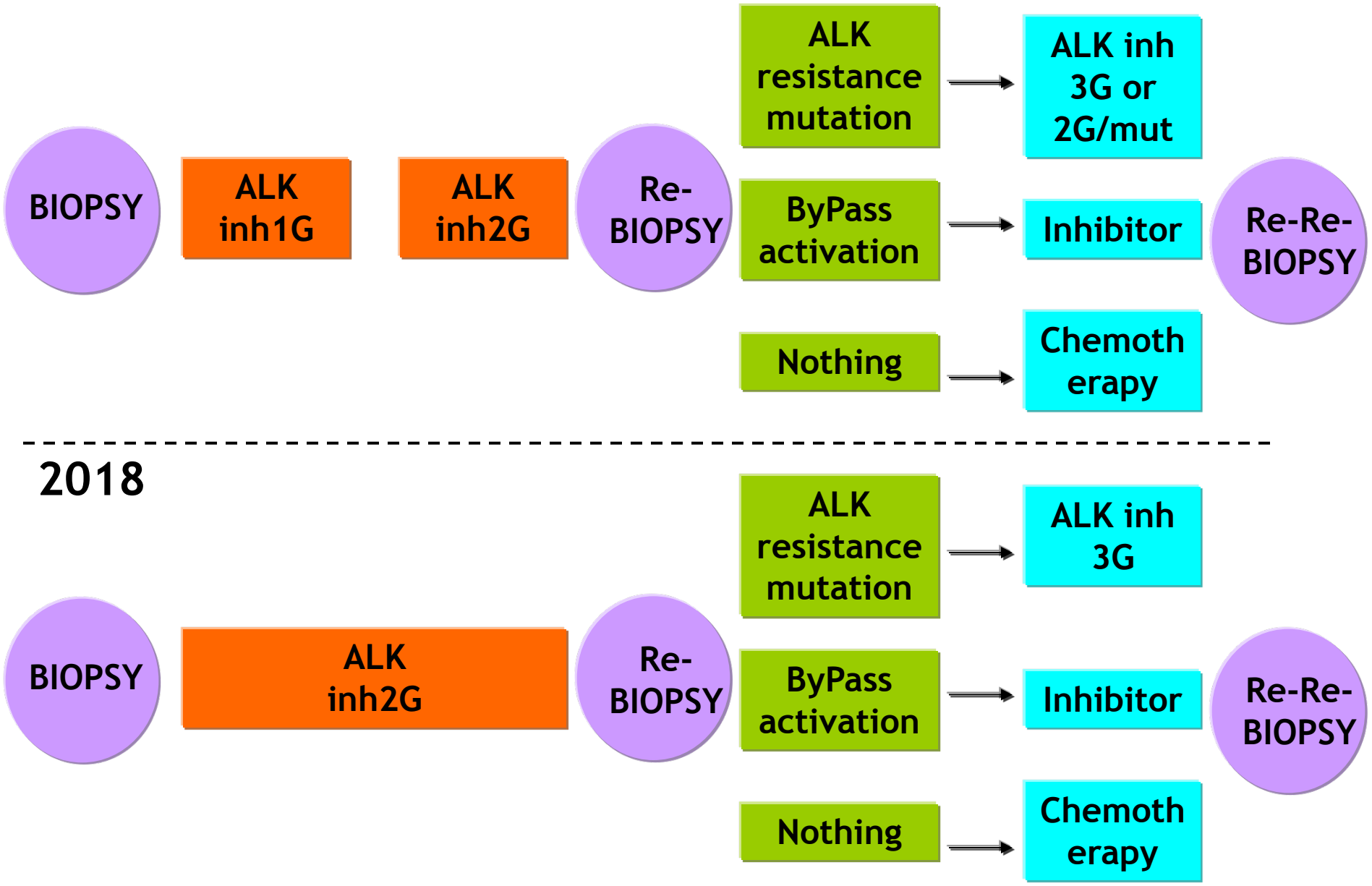
Thoracic RT



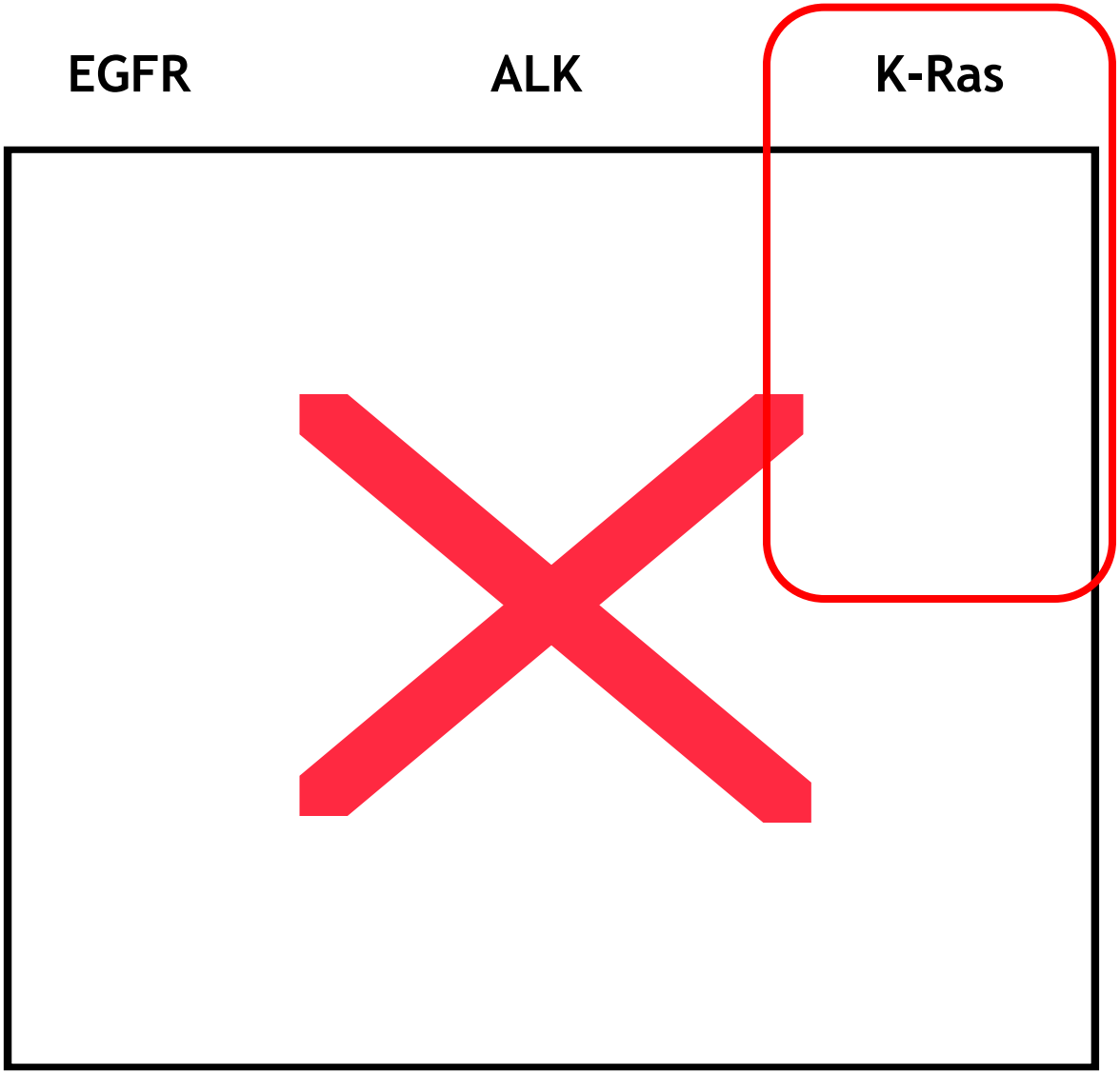
Stereotactic brain RT

G1202R

Que faire si j'ai un patient ALK ?



Les biomarqueurs validés



KRAS

Patient fumeur de 65 ans. PS1. Adénocarcinome bronchique T1N3M1a (plévre). Mutation de KRAS G12C
Quel est votre traitement de choix ?

1. Chimiothérapie
2. Chimiothérapie + immunothérapie
3. Inhibiteur de CDK4
4. Immunothérapie si PDL1 > 50%
5. Inhibiteur de MEK

KRAS

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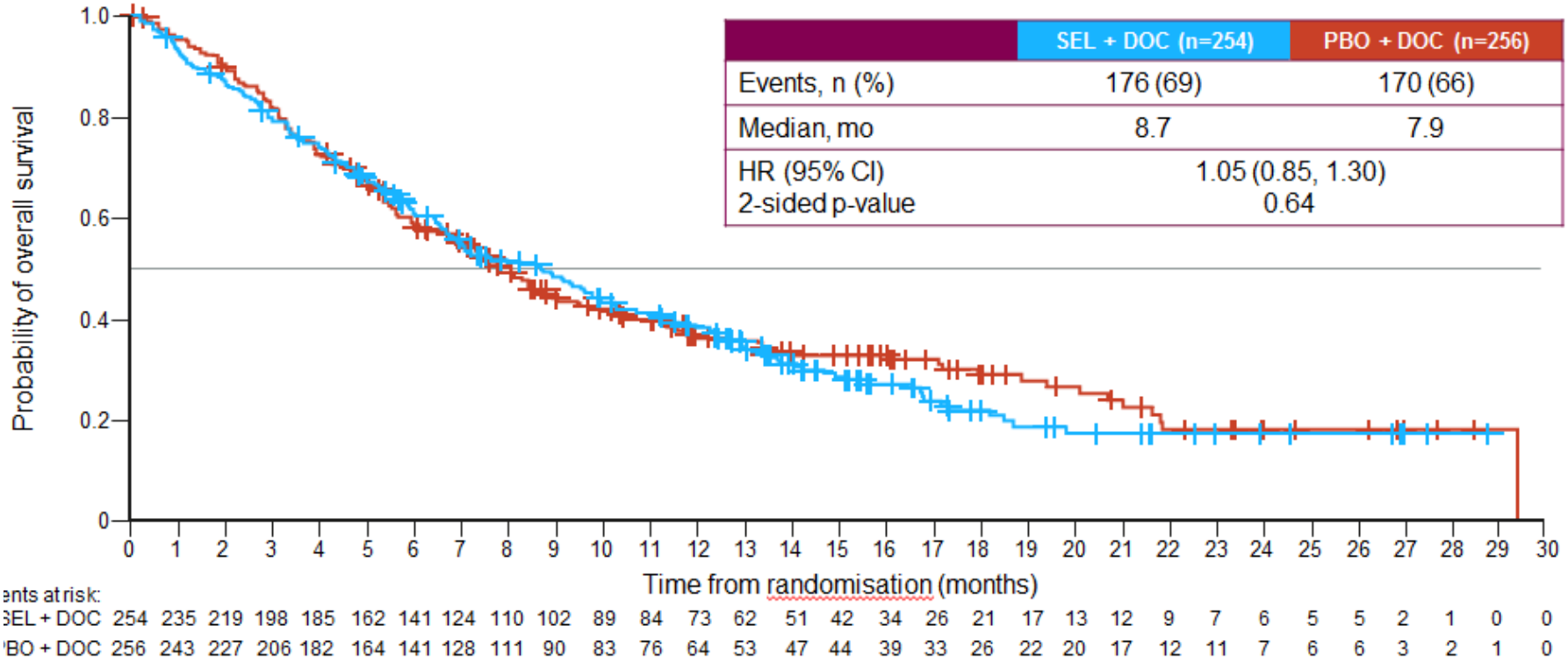
3. **Inhibiteur de CDK4**
4. **Immunothérapie si PDL1 > 50%**
5. **Inhibiteur de MEK**

KRAS

- **SELECT-1 phase 3 trial (selumetinib)**

Overall survival

OS was not significantly improved with selumetinib + DOC compared with PBO + DOC



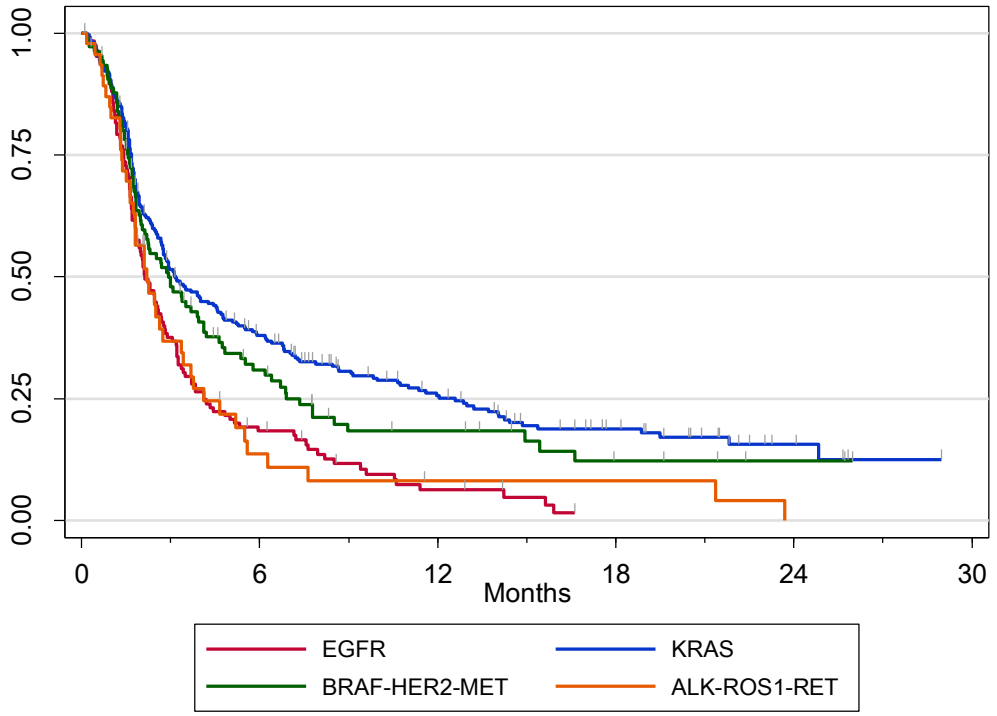
	SEL + DOC (n=254)	PBO + DOC (n=256)
Events, n (%)	176 (69)	170 (66)
Median, mo	8.7	7.9
HR (95% CI) 2-sided p-value	1.05 (0.85, 1.30) 0.64	

KRAS

IMMUNOTARGET COHORT: PFS

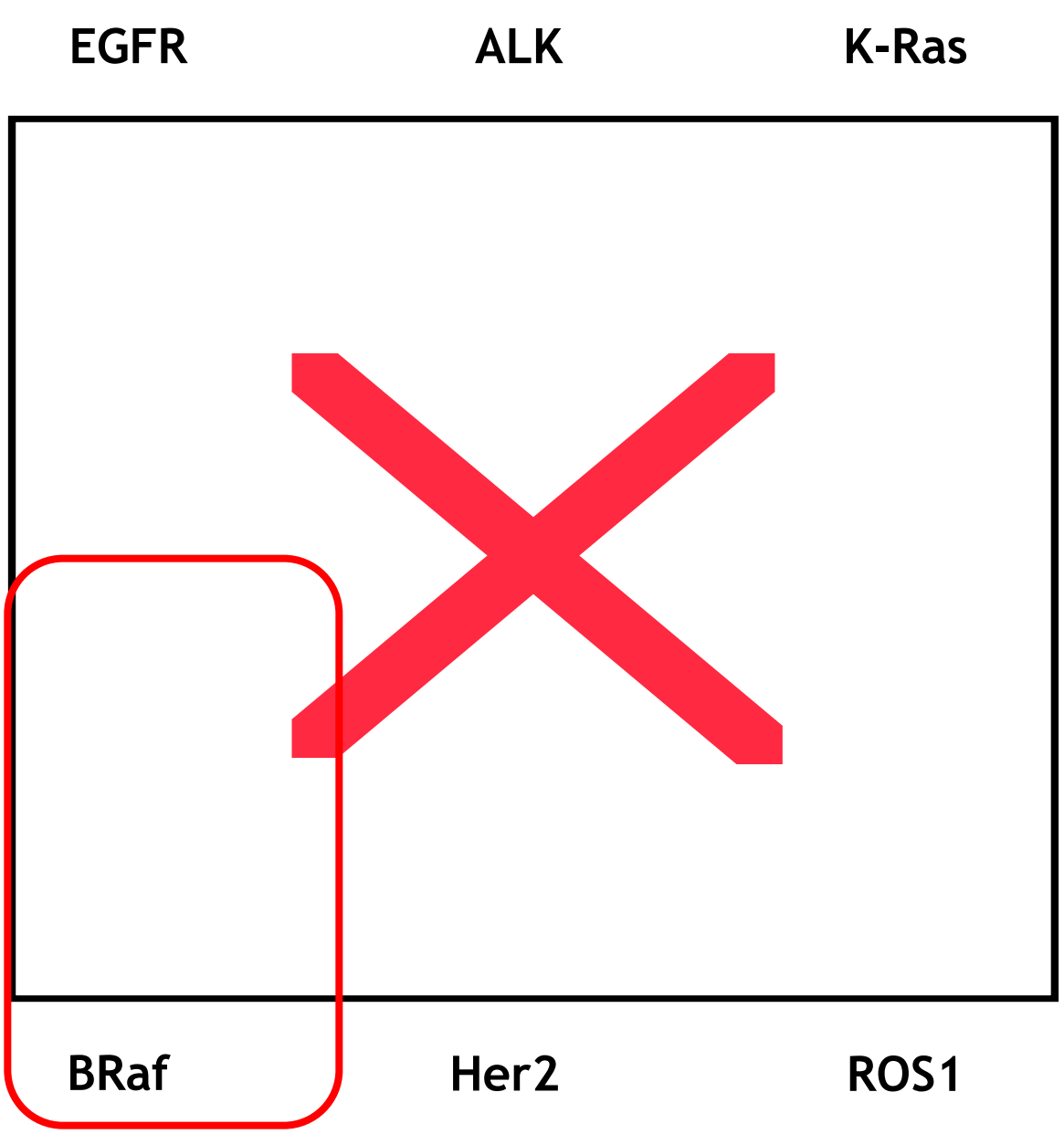
Driver	PFS (months)	
KRAS	3.2	3.2
EGFR	2.1	2.1
BRAF	3.1	2.9
MET	3.4	
HER2	2.5	
ALK	2.5	2.2
RET	2.1	
ROS1	-	
TOTAL	2.8	

PFS according to driver alteration (p < 0.001)



Median follow-up 16.1 months

Les biomarqueurs validés



BRAF

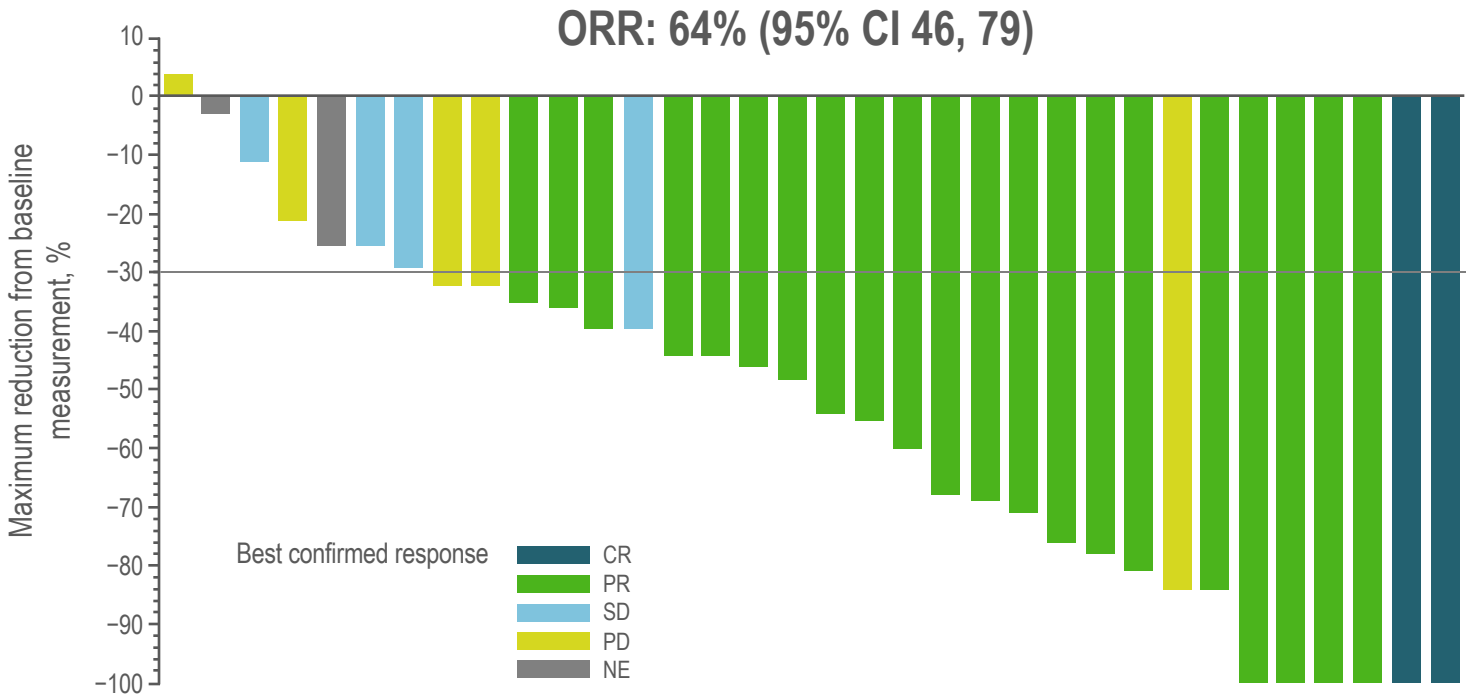
- Overview of BRAF inhibitors

Author	n	Drug	Response rate	PFS (months)	OS (months)
Hyman (BASKET-trial)	20	Vemurafenib	42%	7.3	NR
Mazières (AcSé vemu)	101	Vemurafenib	44%	5.2	9.1
Gautschi (EU-RAF)	35	Vemurafenib	53%	5	10.8
Planchard (BRF cohort A)	78	Dabrafenib	33%	5.5	12.7
Planchard (BRF cohort B)	57	Dabrafenib + trametinib	63%	9.7	12.7
Planchard (BRF cohort C)	36	Dabrafenib + trametinib 1L	64%	14.6	24.6

BRAF

MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

Cohort C

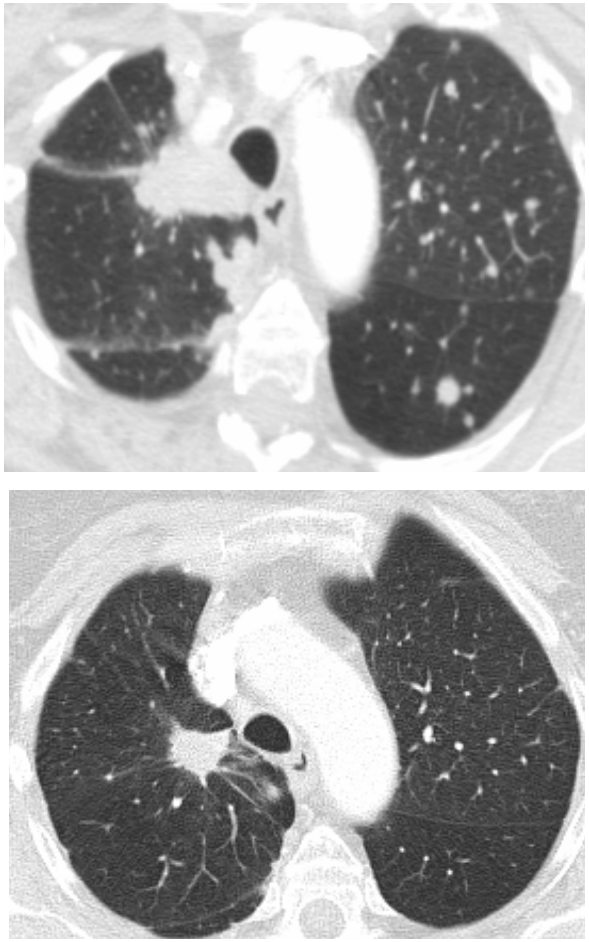


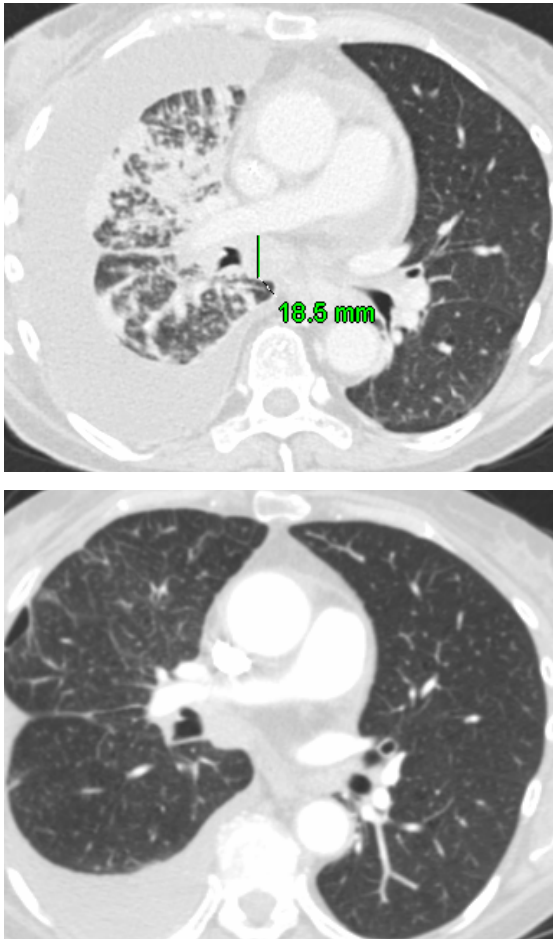
Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

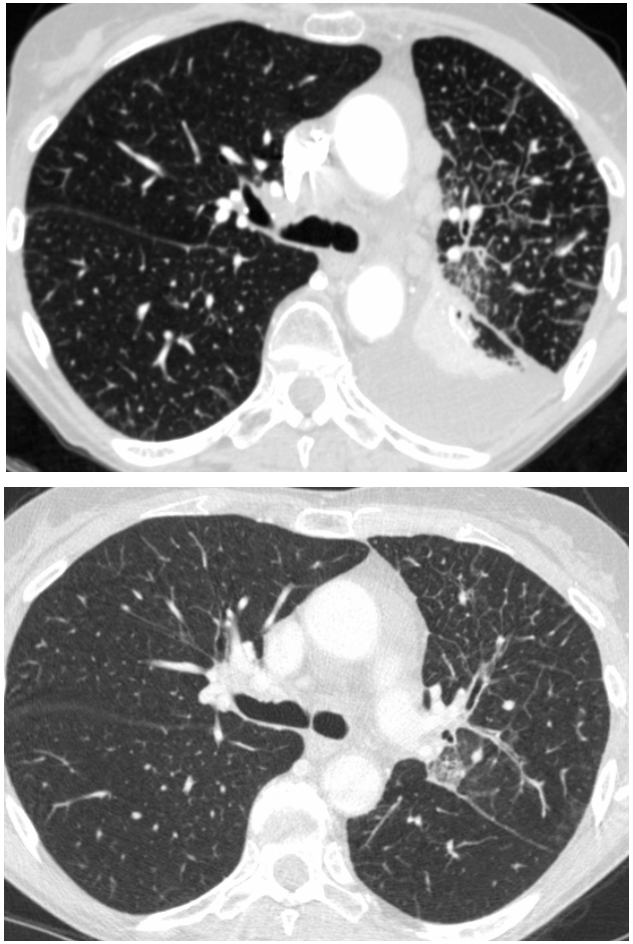
NOTE: Dabrafenib + trametinib is not approved for the treatment of *BRAF*+ NSCLC in Japan

BRAF

Stage IV patients treated with Dabrafenib (GSK 113928 trial).







Starting15/03/2012

Still under treatment

Starting15/09/2012

Stopped in 2016

Starting 04/10/2012

Stopped in 2017

BRAF

Use of dabrafenib + trametinib

- 22 Jun 2017: FDA has been granting regular approval to dabrafenib and trametinib combination for metastatic NSCLC with BRAF V600E mutation
- 23 Feb 2017: EMEA. Trametinib combined with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.
- 19 Mar 2018 : Negative response from the French Transparence Committee (asking for a comparative clinical trial)

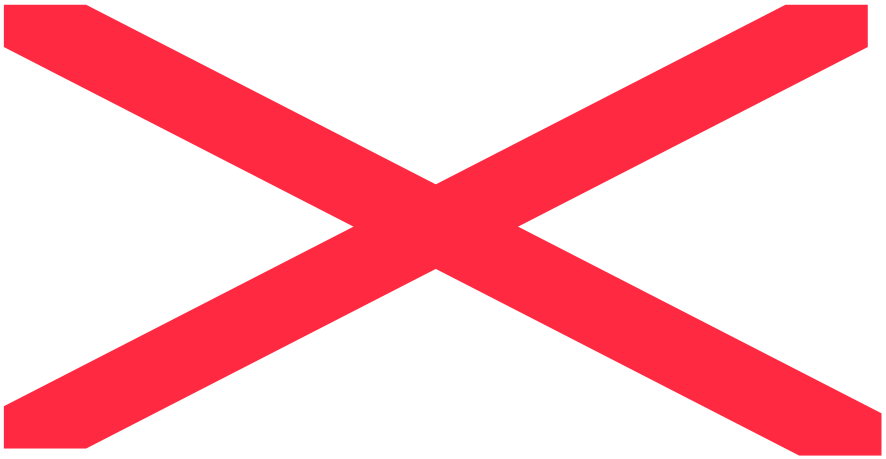
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Vemurafenib in Patients Harboring V600 and Non V600 BRAF Mutations: Final Results of the NSCLC Cohort from the AcSé Trial.

J Mazieres[1], L Montané[2], F Barlesi[3], B Coudert[4], PJ Souquet[5], J Otto[6], R Gervais[7], D Moro-Sibilot[8], I Monnet[9], E Brain[10], O Huillard[11], G Quéré[12], D Debieuvre[13], E Fabre[14], M Jaffro[1], SCollot[1], G Ferretti[8], C Tiffon[15], C Mahier - Ait Oukhatar[16], JY Blay[2]

[1]Centre Hospitalier Universitaire, Toulouse, [2]Centre Léon Bérard, Lyon, [3]Assistance Publique Hôpitaux de Marseille, Marseille, [4]Centre Georges François Leclerc, Dijon, [5]Centre Hospitalier Lyon Sud, Lyon, [6]Centre Antoine Lacassagne, Nice [7]Centre François Baclesse, Caen [8]Centre Hospitalier Universitaire de Grenoble, Grenoble, [9]Centre Hospitalier Intercommunal Créteil, Creteil, [10]Institut Curie, Hôpital René Huguenin, Saint Cloud, [11]Hôpitaux Universitaires Paris Centre, Hôpital Cochin, Paris, [12]CHRU de Brest, Brest, [13]Centre Hospitalier de Mulhouse, Mulhouse [14] Hôpital Européen Georges Pompidou, Paris, [15]Institut National du Cancer, Boulogne Billancourt, [16]UNICANCER, Paris, France

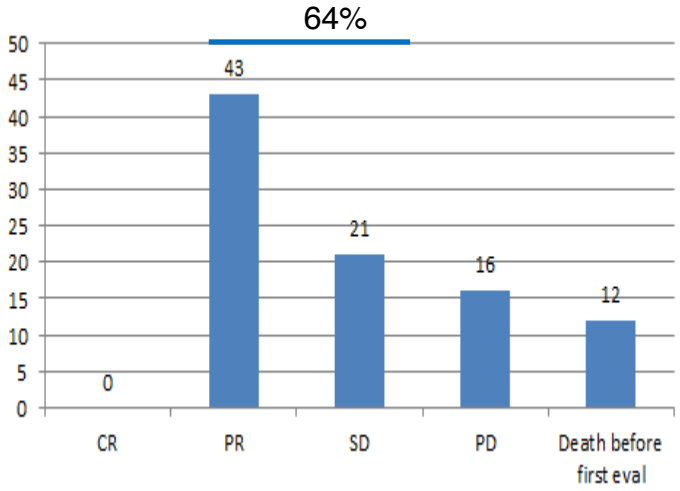
WCLC 2018

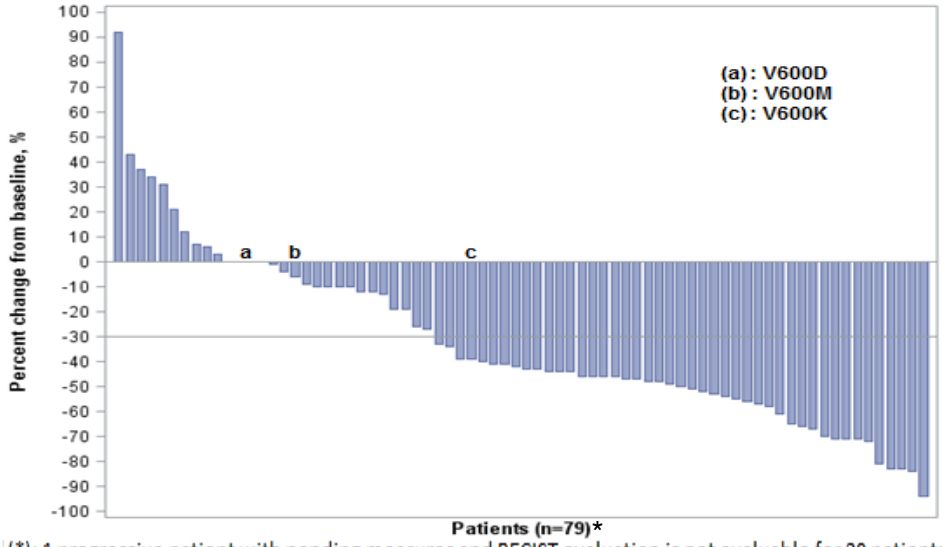


BRAF V600 cohort (n= 100)

Primary objective : Objective Response Rate (CR + PR)

- Mean Bayesian Estimated Success rate: **44.9%** credibility 95%CI : [35.2;54.8]
- Prob ORR > efficacy bound (30%): 99.9%
- Median response duration: **6.4 months**



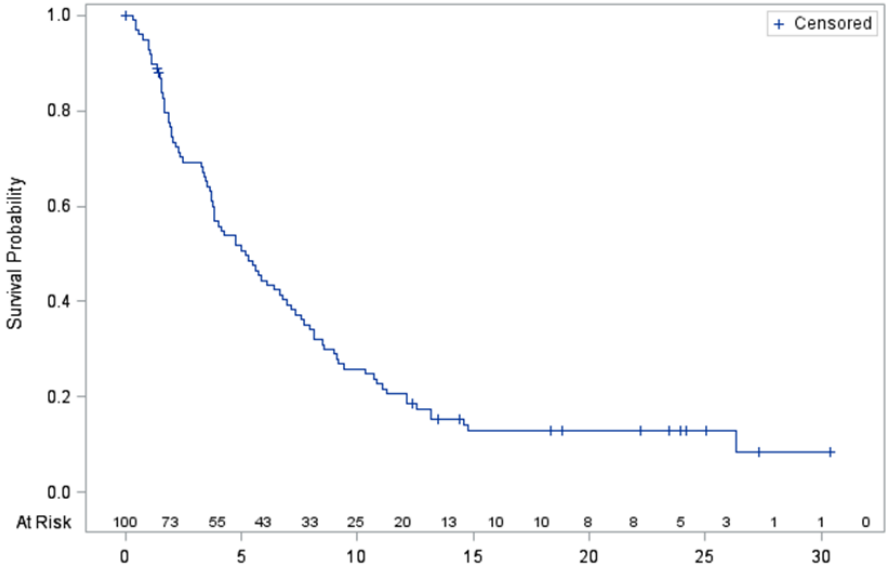


(*): 1 progressive patient with pending measures and RECIST evaluation is not evaluable for 20 patients : 12 deaths before first evaluation, 7 treatment stop before first evaluation, 1 clinic progression.

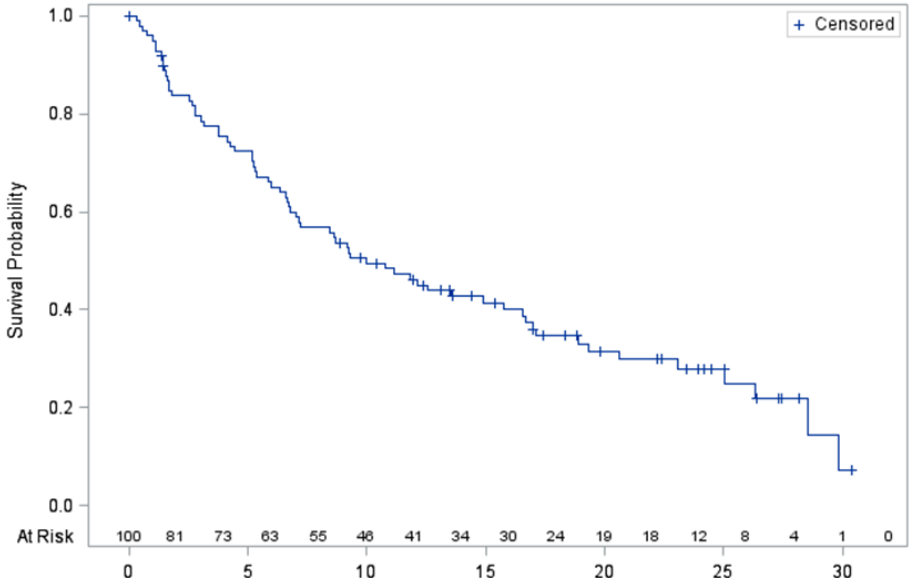
WCLC 2018

BRAF V600 cohort (n= 100)

Secondary objectives : PFS and OS



PFS: **5.2 months** [3.8;6.9]

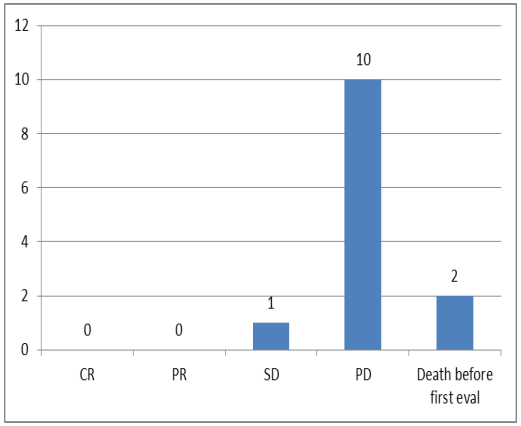


OS: **9.3 months** [6.8;14.9]

BRAF non V600 cohort (n= 15)

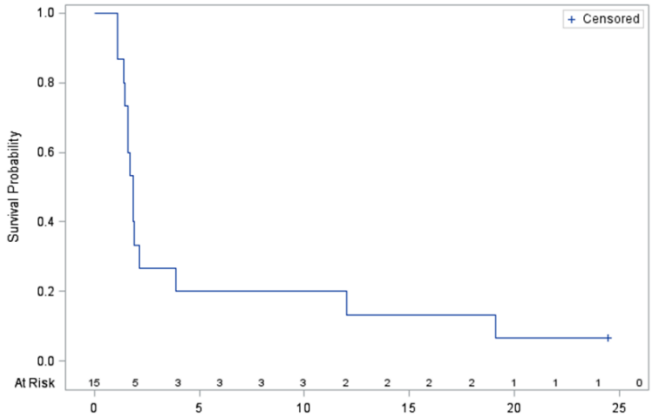
- Mean Bayesian Estimated Success rate : **5.9%** ; credibility 95%CI : [0.2%; 20.6%]
- Prob ORR < futility bound (10%): 81.5% - **study stopped**

Response rate: 0

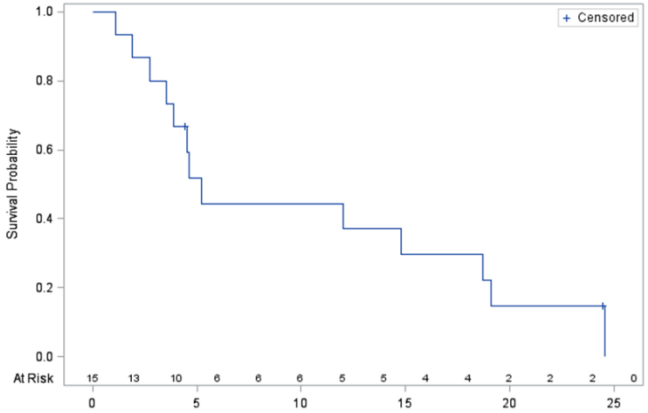


RECIST evaluation is not evaluable for 2 patients (treatment stop before first evaluation).

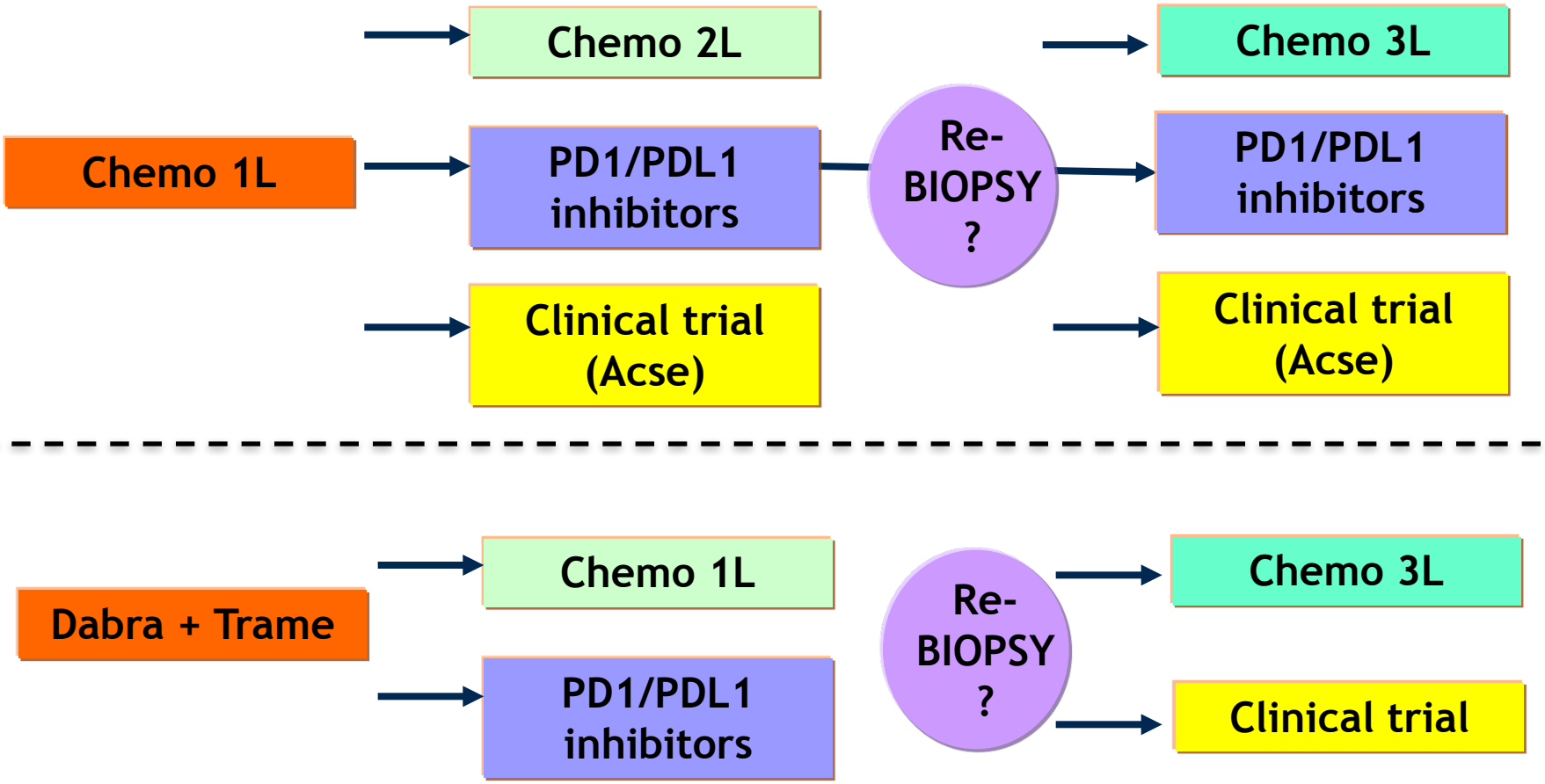
PFS: **1.8 m**. [1.4;2.1]



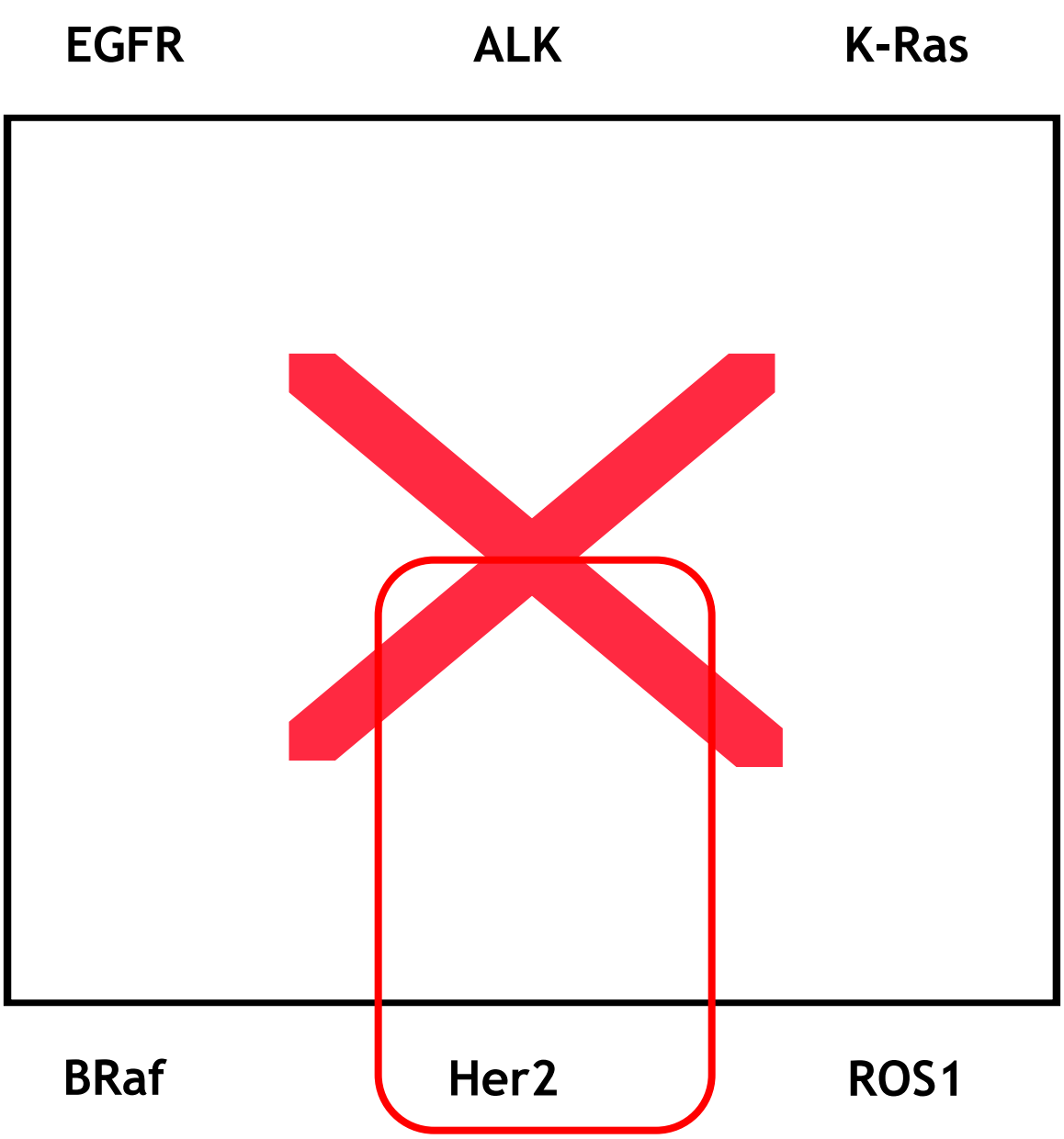
OS: **5.2 m**. [2.8; 18.7]



Que faire si j'ai un patient BRAF ?

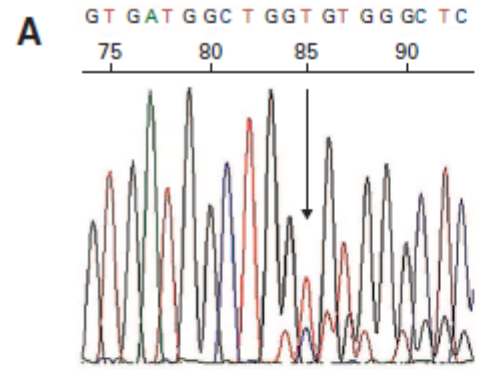


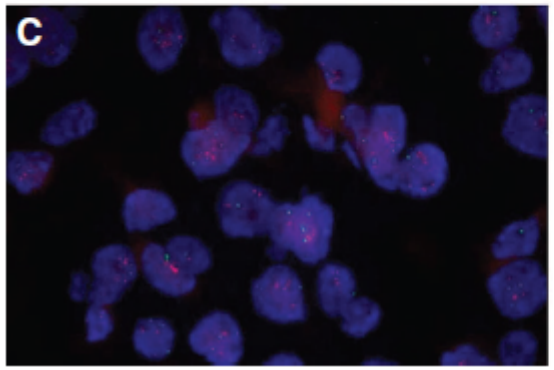
Les biomarqueurs validés

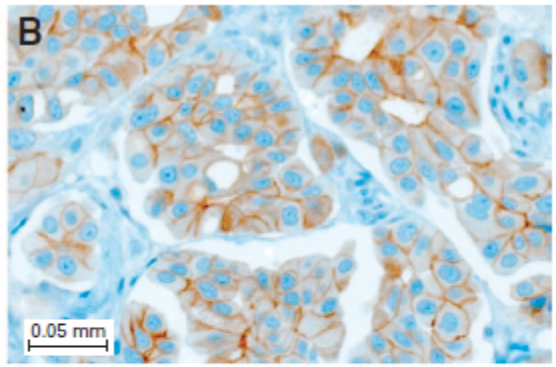


HER2

Characteristics of HER2 mutated patients, n=65.







		No	value
Age at diagnosis, years		65	
	Mean		61.1
	SD		11.6
	Median		60.4
		No	%
Gender			
	Women	45	69
	men	20	31
Tobacco			
	never	34	52,3
	former	11	16,9
	current	12	18,5
	unknown	8	12,3
Tumor stage			
	I	11	16,9
	II	3	4,6
	III	15	23.1
	IV	33	50.8
	unknown	3	4,6

Mazières J, JCO 2013

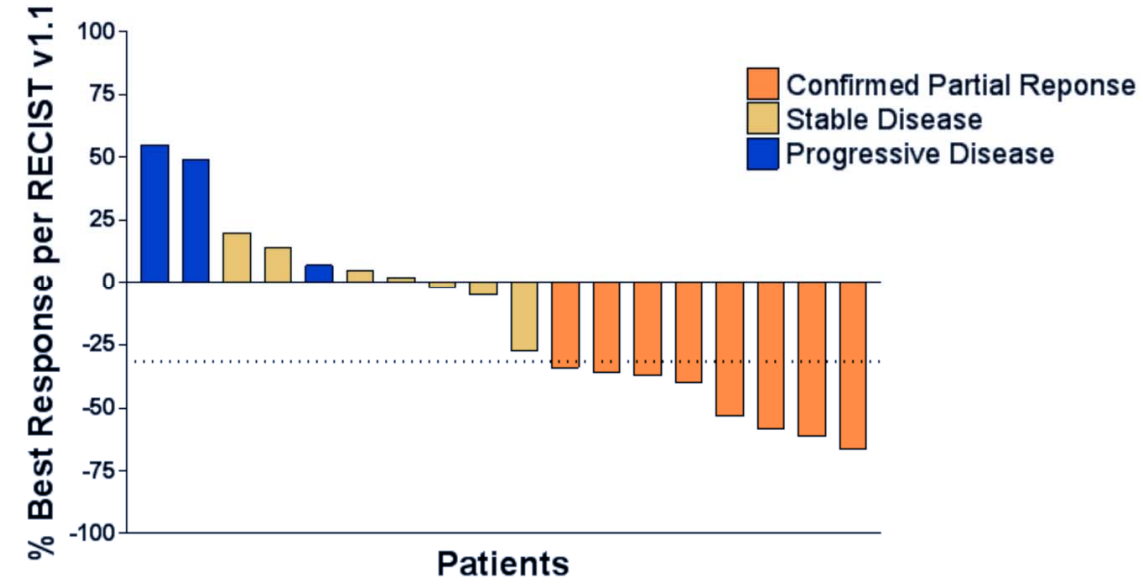
HER2

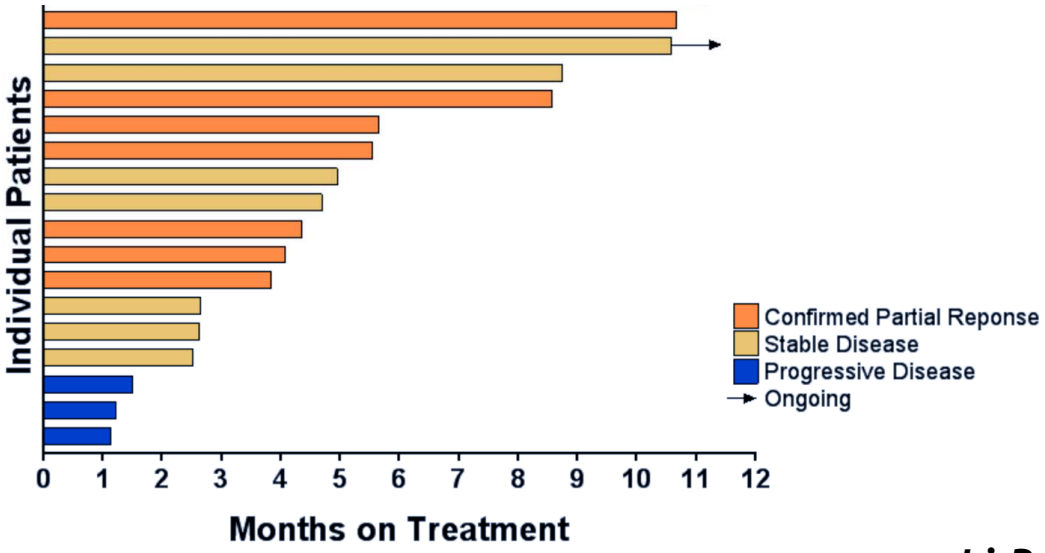
Treatment	*n*	ORR	DC	PFS median [CI95%]	OS median [CI95%]
First-line: without HER2 targeting treatment	93	43.5%	70.7%	6 [5;7.1]	24[19.1;36.4]
Second-line: without HER2 targeting treatment	52	10%	36%	4.3 [3.1;5]	19.4 [9.6;24.7]
EGFR-TKI *	26	7.6%	26.8%	2.99[1.87;4.47]	20.14[7.14;32.95]
Trastuzumab combination, T-DM1 *	58	50.9%	75.5%	4.8[3.4;6.5]	13.3[8.1;15]
Neratinib, Lapatinib and Afatinib *	29	7.4%	55.5%	3.4[2.4;4]	6.5[4.7;30.6]

Mazieres J, Annals of Oncology 2015

T-DM1 et mutation de HER2

Ado-trastuzumab emtansine for patients with *HER2* mutant lung cancers: Results from a phase II basket trial





Li B, JCO 2018

Essai IFCT-1703

Phase II single arm trial of trastuzumab in combination with pertuzumab in pretreated patients with non-small cell lung cancer (NSCLC) harboring a Her2 mutation and receiving docetaxel

R2D2 trial (HER2-positive lung cancer treated with Dedicated Drug)

N° EUDRACT : 2015-004475-75

Sponsor

IFCT Intergroupe Francophone de Cancérologie Thoracique

10 rue de la Grange-Batelière 75009 PARIS – France

STUDY CHAIR

JULIEN MAZIERES, M.D. PHD.

STUDY CO-CHAIR

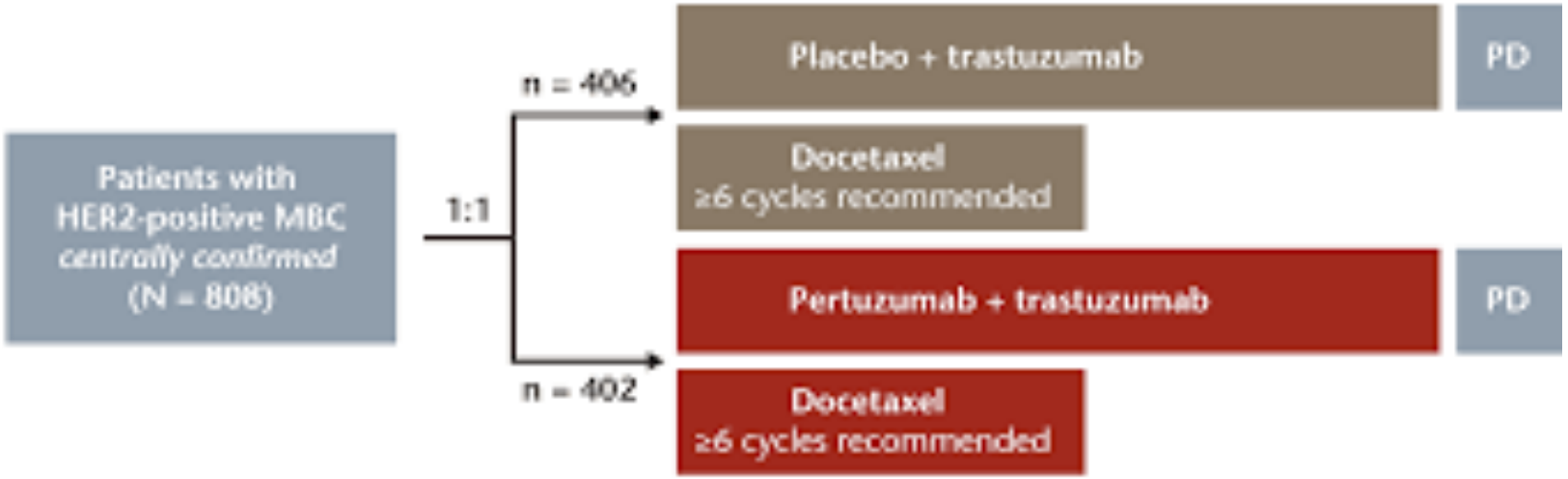
DR BENJAMIN BESSE (GUSTAVE ROUSSY, VILLEJUIF)

Trastuzumab + pertuzumab (K sein)

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

Study design

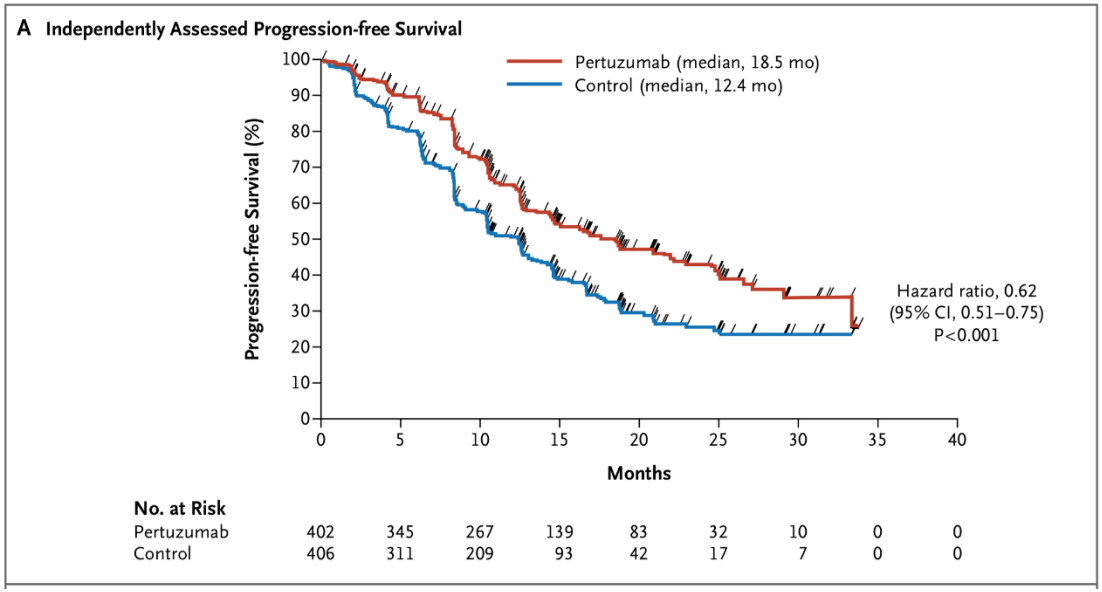


Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

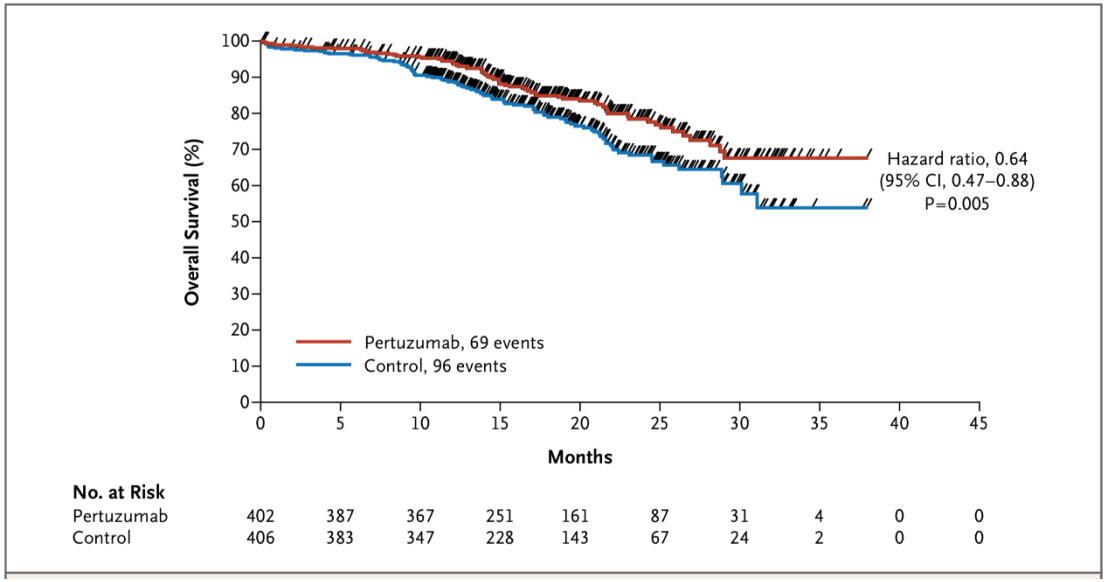
HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; N/n = number of patients; PD = progressive disease

Trastuzumab + pertuzumab (K sein)

PFS 12.4 mois vs 18.5 mois HR 0.62

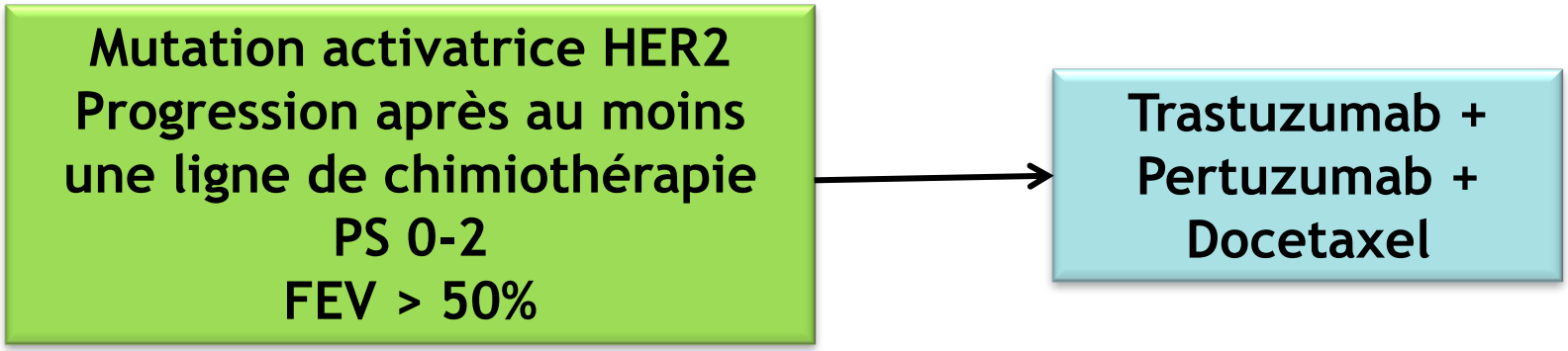


OS 37 mois vs NR HR 0.66



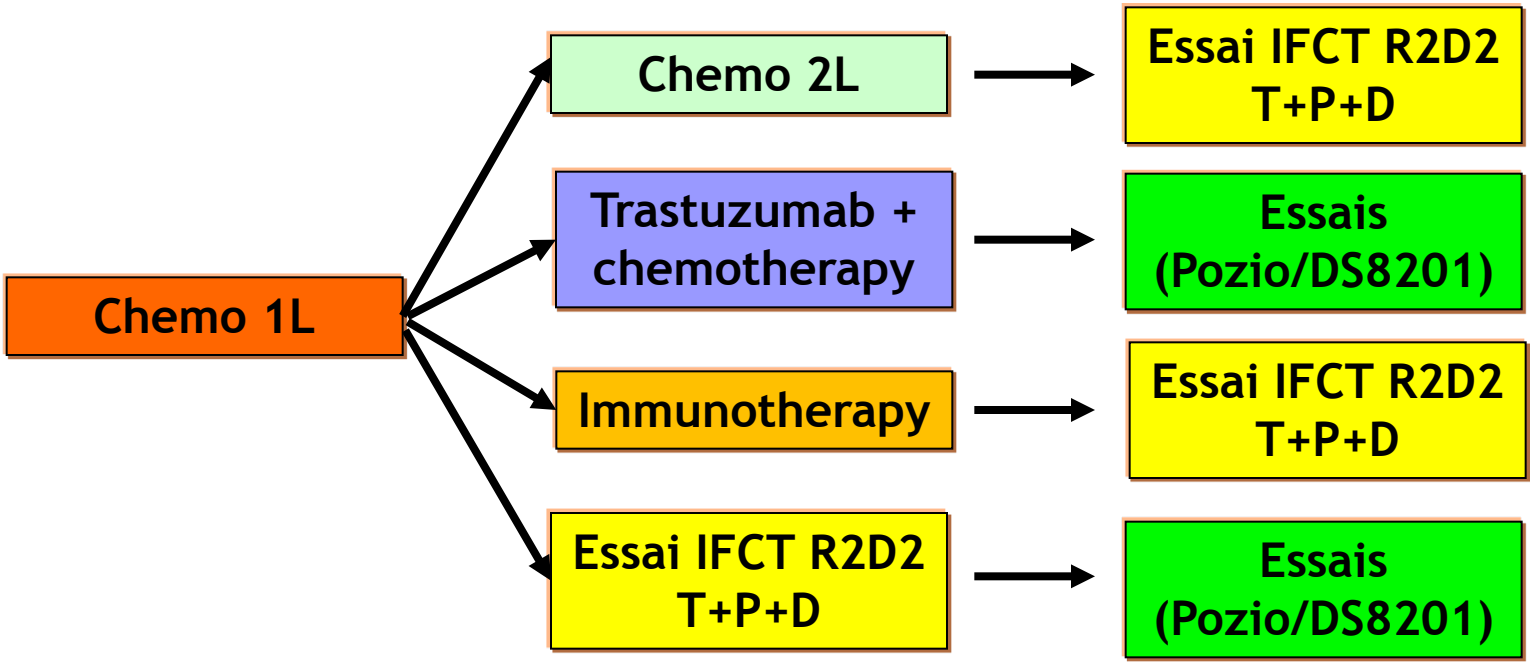
Design R2D2

- Etude de phase 2



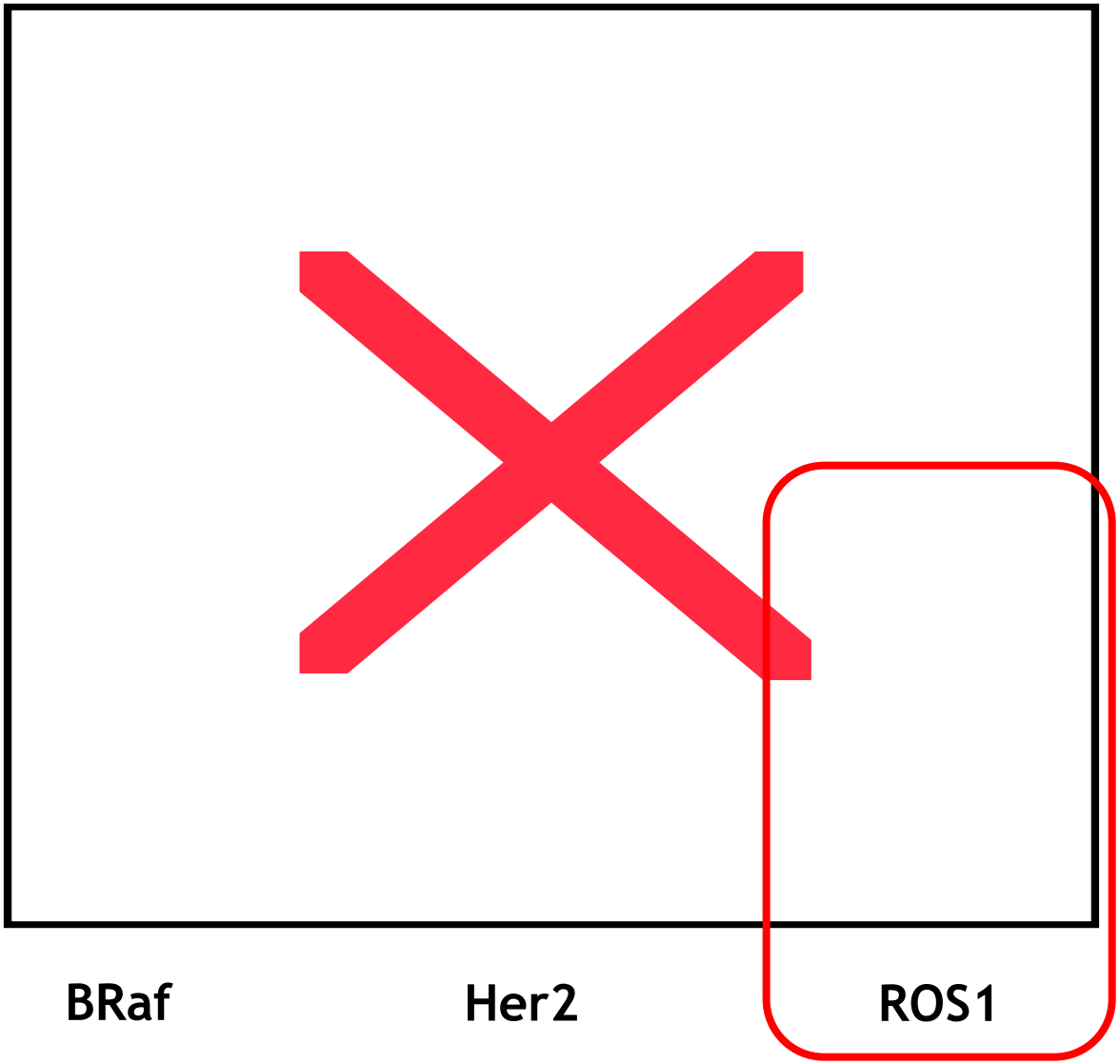
- Two stage design and O'Brien-Fleming (OF) stopping rules.
- P0 = .20; Pa = .40; statistical power of 0.90; type I error rate (one-sided) of 0.05.
- N = 22 (stage 1). Si < 4 réponses: arrêt.
- Puis n 21. n = 43. (+5%, n = 45)

Que faire si j'ai un patient HER2 ?



Les biomarqueurs validés

EGFR ALK K-Ras

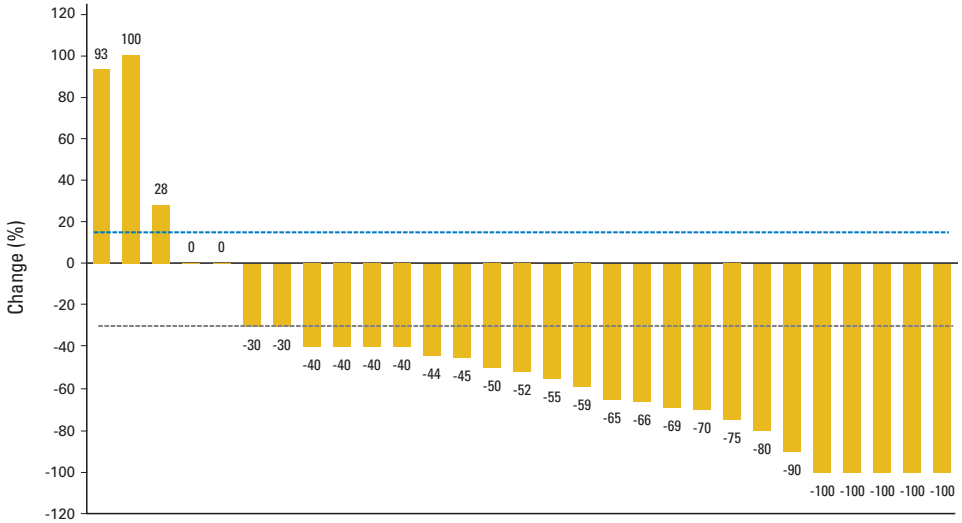


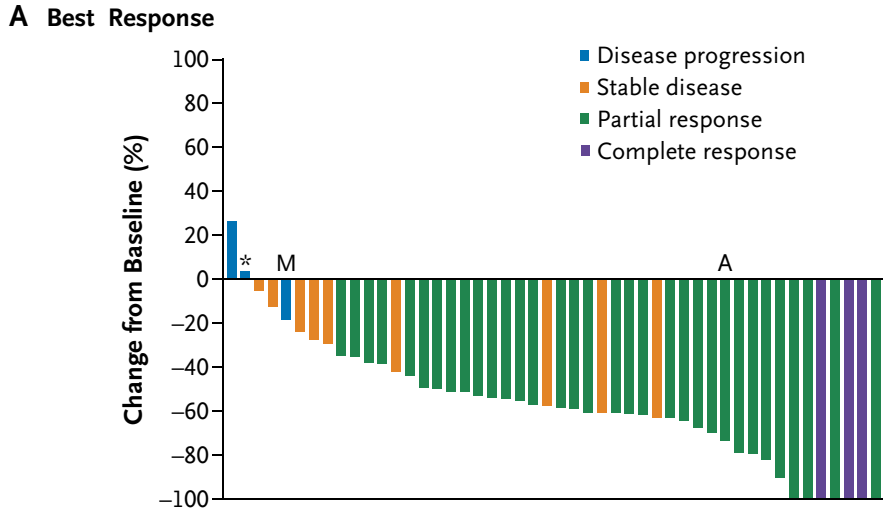
BRaf Her2 ROS1

ROS1

- European series 2013-2014.
- N = 31 patients ROS1+ (FISH)
- Treated with crizotinib
- TR = 80%, PFS = 9.1 m

- Expansion of a phase 1 trial
- N = 50 ROS1+ (FISH)
- Treated with crizotinib
- TR = 72%, PFS = 19.2 m





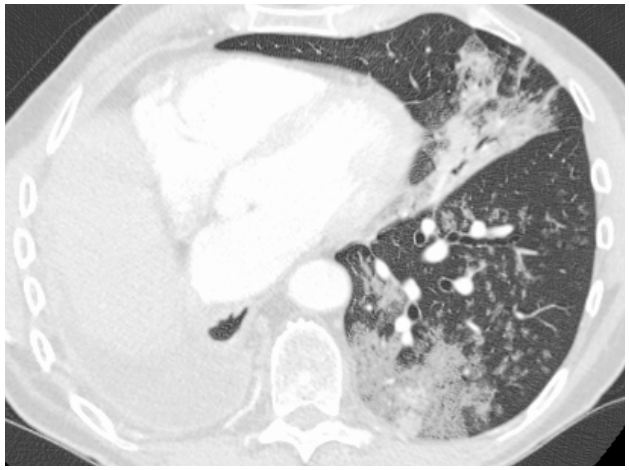
Mazieres J, JCO 2015

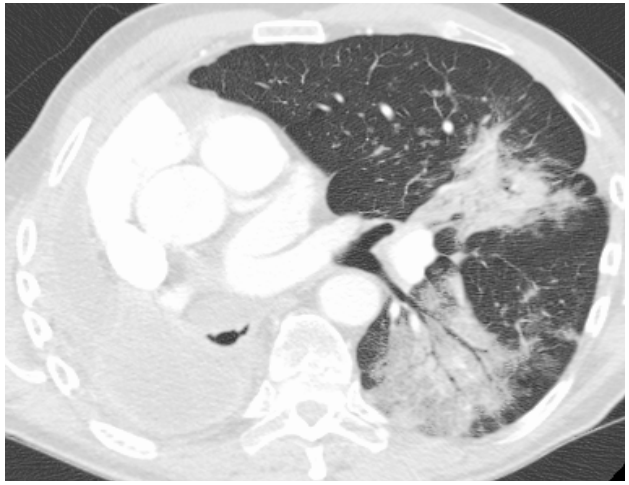
Shaw A, NEJM 2015

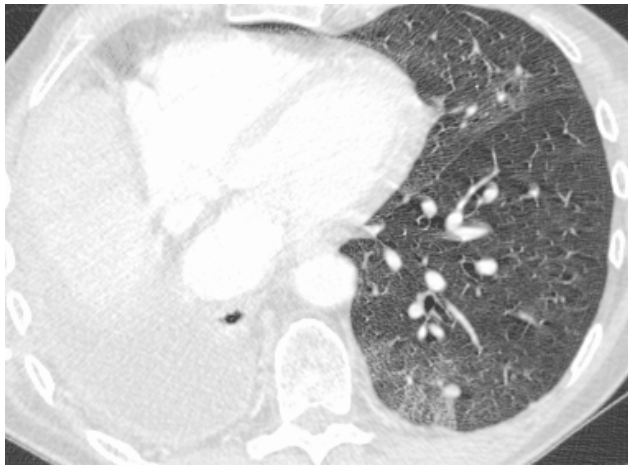
ROS1

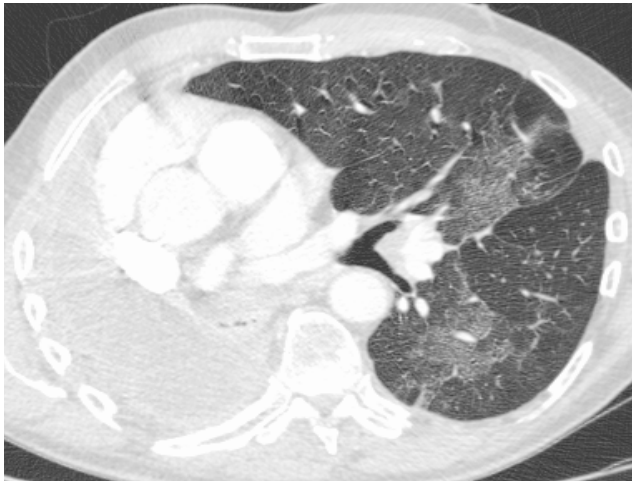
62 ys old male, non-smoker, lepidic adenocarcinoma
Recurrence after right pneumonectomy and 2 chemos
Treatment with crizotinib (AcSé trial)

08/13



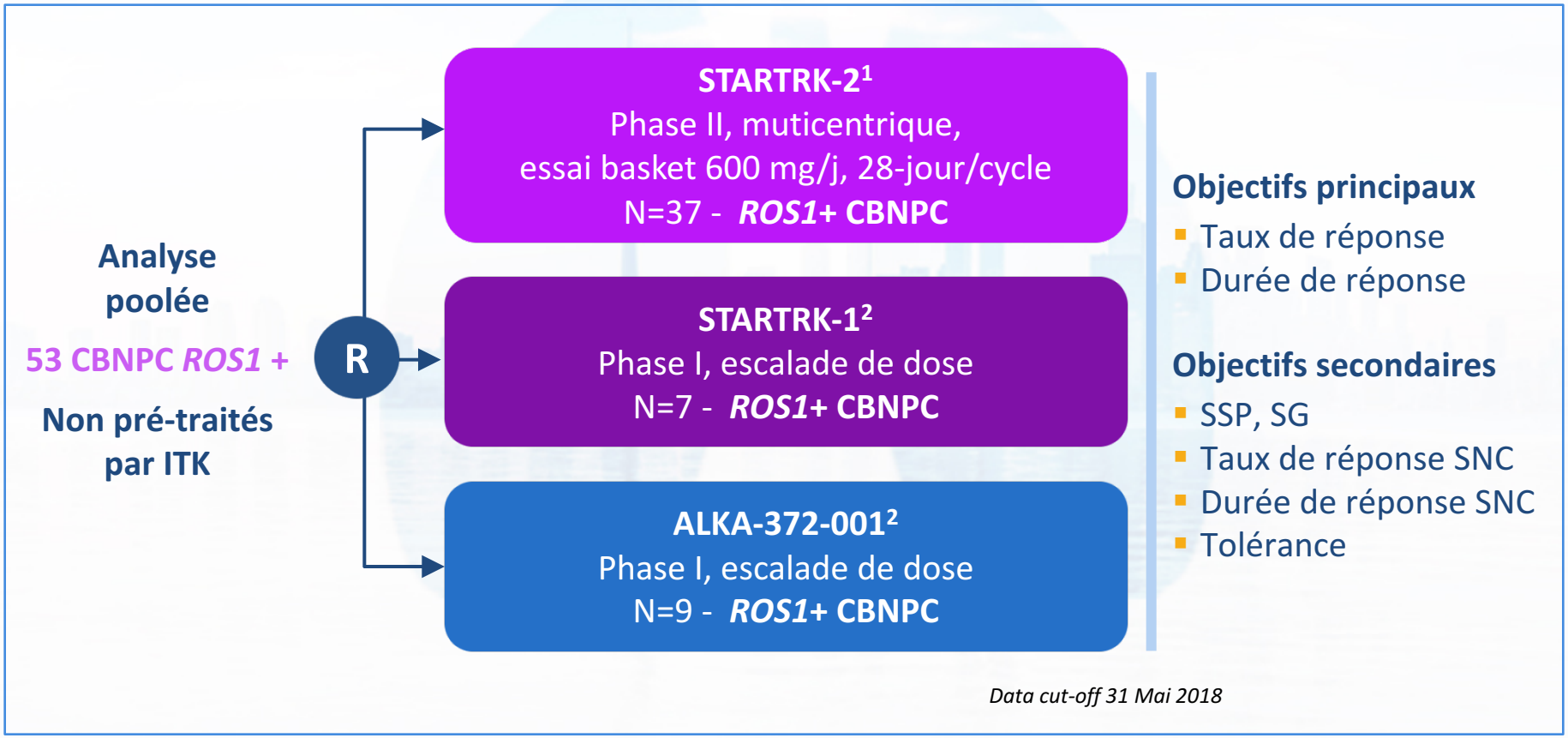






09/18

ENTRECTINIB
Analyse poolée de 3 essais thérapeutiques

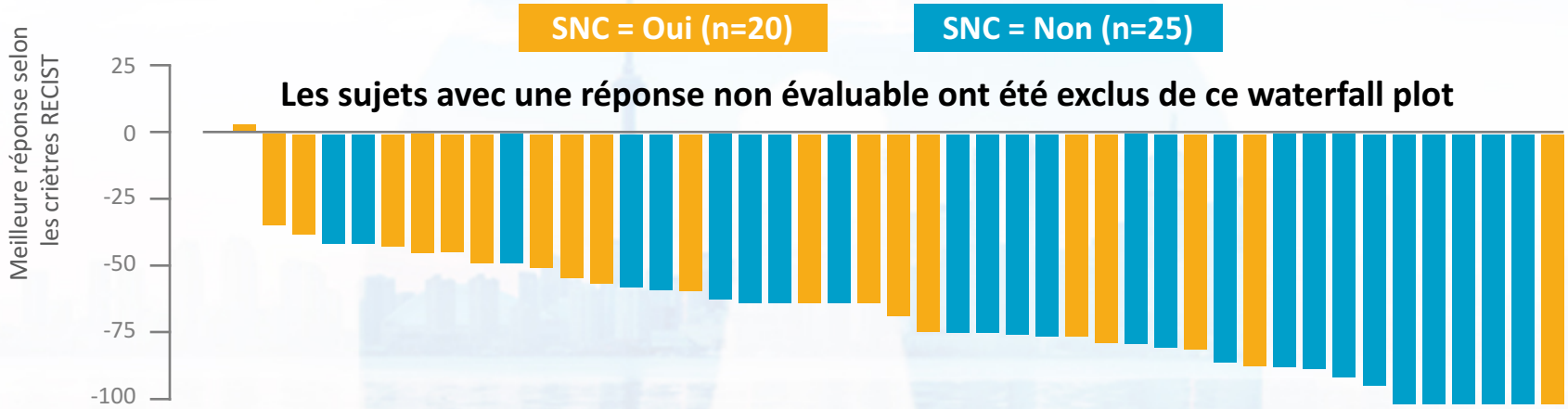


1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017

Analyse de la réponse tumorale

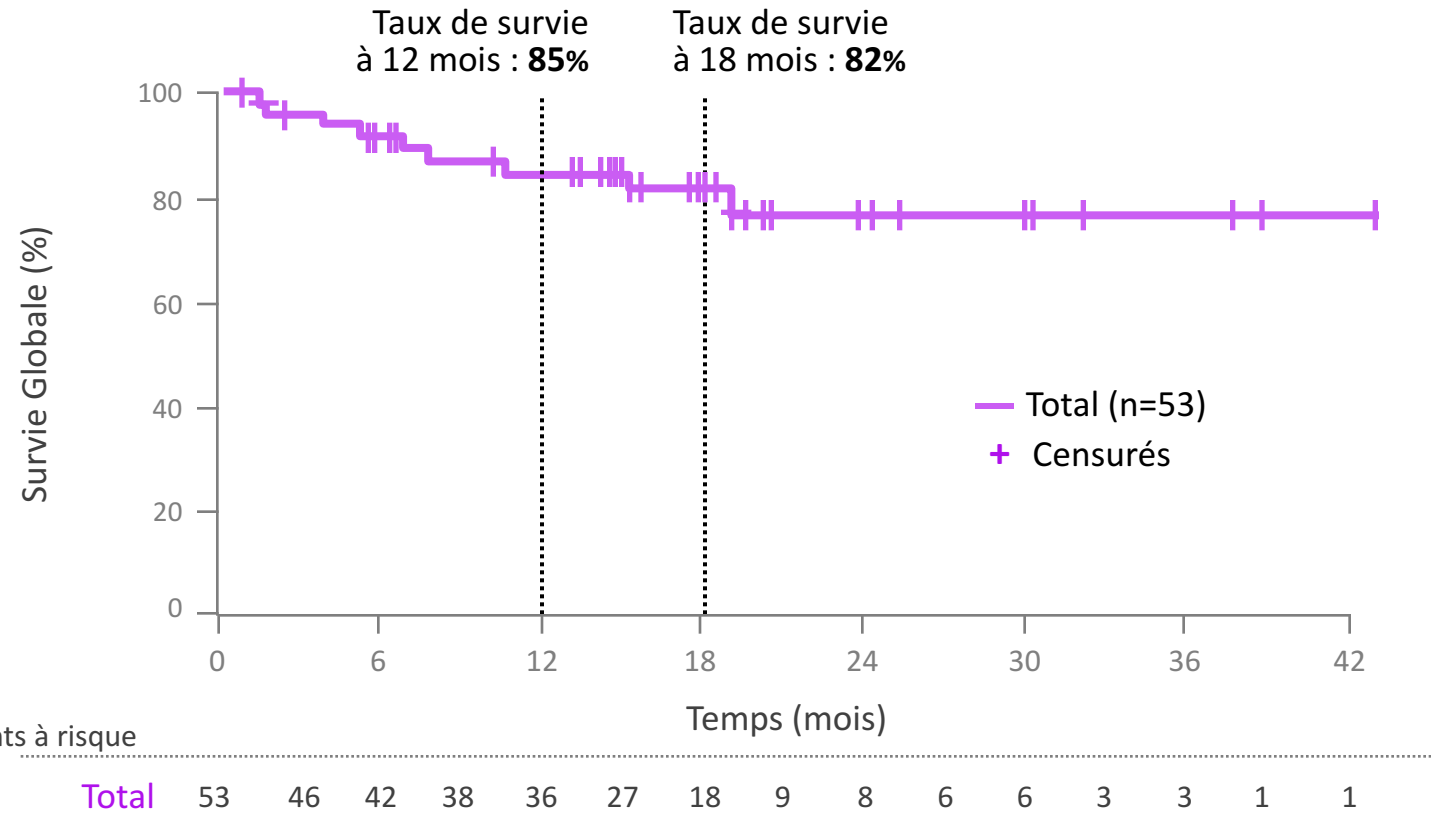
Variation de la taille tumorale : CBNPC *ROS1+* (n=53) (évaluation BICR)

Meilleure réponse (BICR), présence de métastases cérébrales à l'inclusion (Investigateur)



n (%)	Total N=53	Métastases du SNC à l'inclusion N=23	Pas métastases du SNC à l'inclusion N=30
Taux de réponse **objectif** IC95% (%)	**41 (77,4)** (63,7 – 87,7)	**17 (73,9)** (51,5 – 89,7)	**24 (80,0)** (61,4 - 92,2)
Réponse complète	3 (5,7)	0	3 (10,0)
Réponse Partielle	38 (71,7)	17 (73,9)	21 (70,0)
Stabilité	1 (1,9)	0	1 (3,3)
Progression	4 (7,5)	4 (17,4)	0

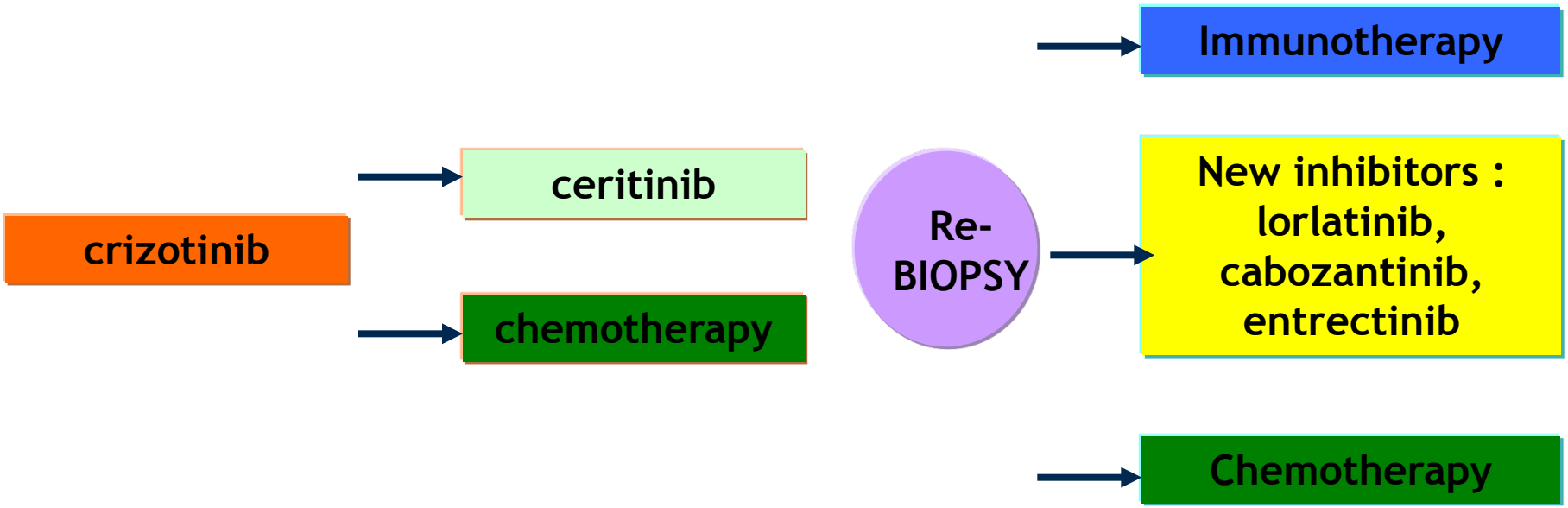
Survie globale



Survie globale médiane non atteinte

Durée de suivi médian : **15,5 mois**

Que faire si j'ai un patient ROS1 ?



Nouvelles cibles

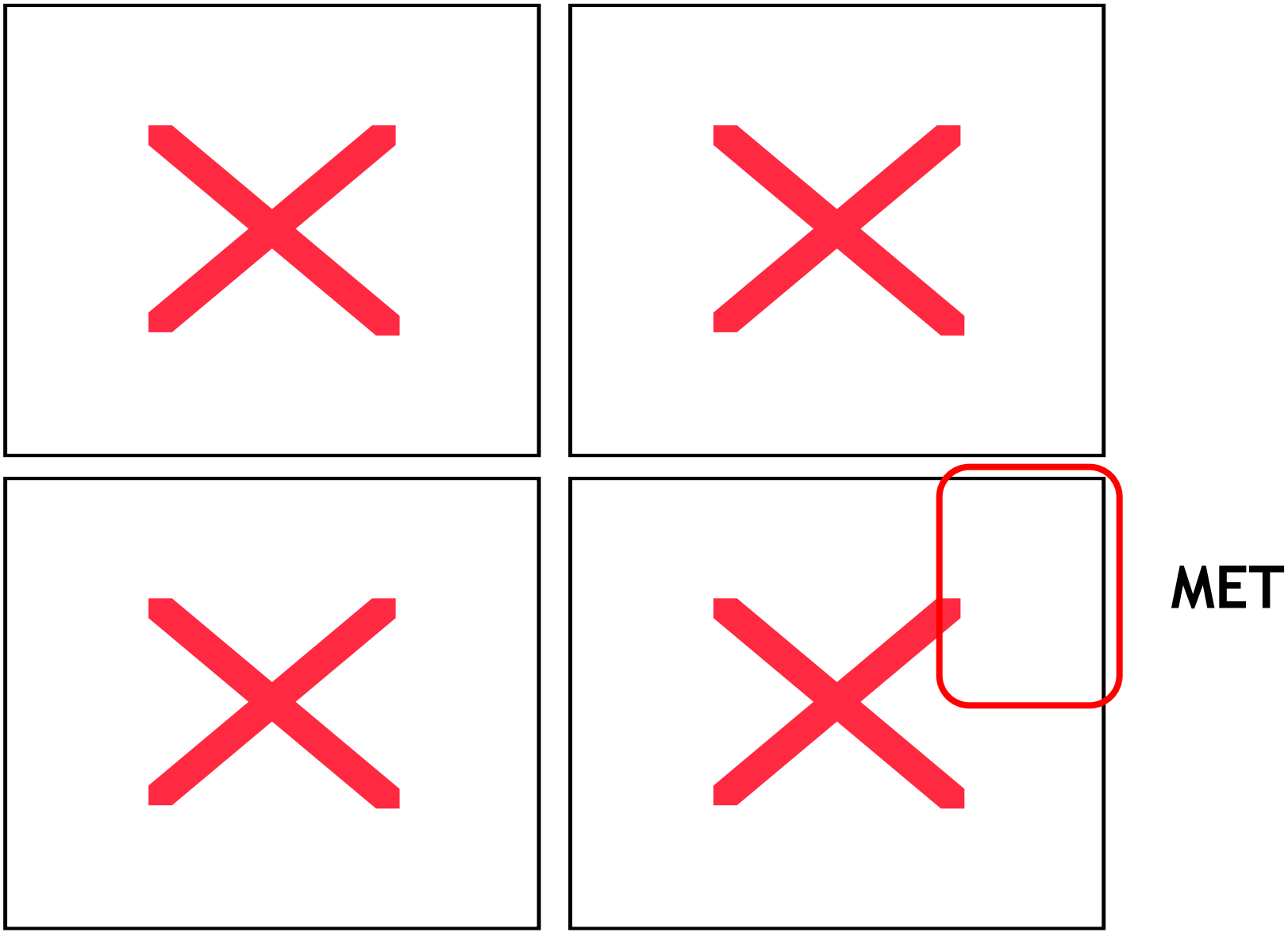
New targets (NGS routinely used in France)

Panel tumeurs solides			
gène	**Exons / hotspots**	**Molécule associée**	**utilité clinique**
AKT1	3	AKT inhibitors	essais cliniques
ALK	23+24+25	crizotinib, ALK inhibitors	AcSé, essais cliniques
BRAF	11+15	vemurafenib, dabrafenib	AMM
EGFR	18+19+20+21	anti EGFR	AMM
ERBB2 (HER2)	20	trastuzumab, neratinib	essais cliniques
ERBB4	E452K et R393W	Afatinib	essais cliniques
FGFR2	S252, N549, K659	FGFR inhibitors	essais cliniques
FGFR3	7+9+14 (R248 àS249 et G370 à Y	FGFR inhibitors	essais cliniques
HRAS	2+3+4	inhibiteurs de MEK	essais cliniques
KIT	8+9+11+13+17+18	imatinib	AMM
KRAS	2+3+4	panitumumab et cetuximab	AMM
MAP2K1 (MEK1)	2	inhibiteurs de MEK	essais cliniques
MET	2 + 14 à 20	crizotinib	AcSé
NRAS	2+3+4	panitumumab, MEK inhibitors, BRAF inhibitors	pré-AMM, essais cliniques
PDGFRA	12+14+18	imatinib	AMM
PIK3CA	9 + 20	PI3K inhibitors	essais cliniques

Thérapies ciblées

- Les nouvelles cibles

Les nouvelles cibles



Etude de Phase II évaluant le Tepotinib dans les CBNPC avec saut de l'exon 14 de MET : VISION

- CBNPC avancé ou métastatique
  - Toutes histologies
- Saut de l'exon 14 de *MET* par NGS
  - Sur tissue ou sang
- En 1ère, 2ème ou 3ème ligne de traitement
- N = jusqu'à 120
- Regions: UE, USA, Japon

→ **Tepotinib 500 mg/jour** →

Objectif principal

- Taux de réponse objectif;

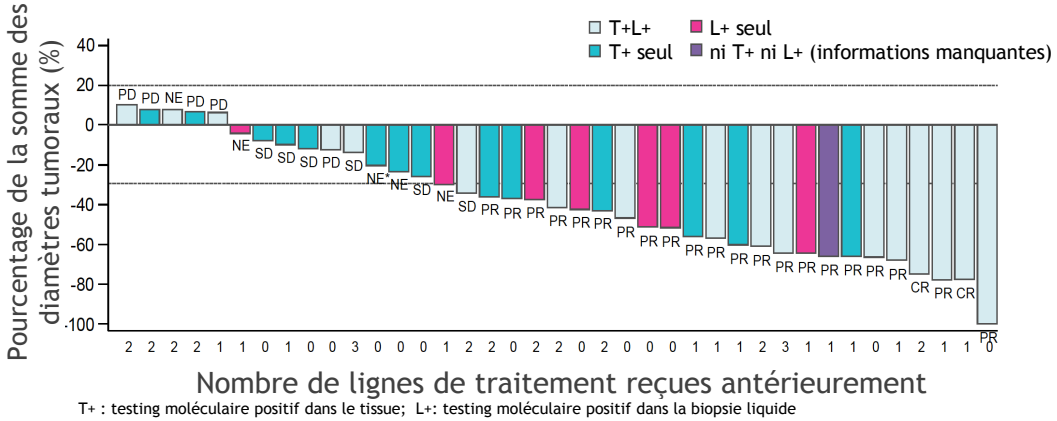
RECIST v1.1
(Revue indépendante centralisée, IRC)

Objectifs secondaires

- Taux de réponse objectif (investigateur)
- Tolérance
- Durée de réponse
- Survie sans progression
- Survie globale

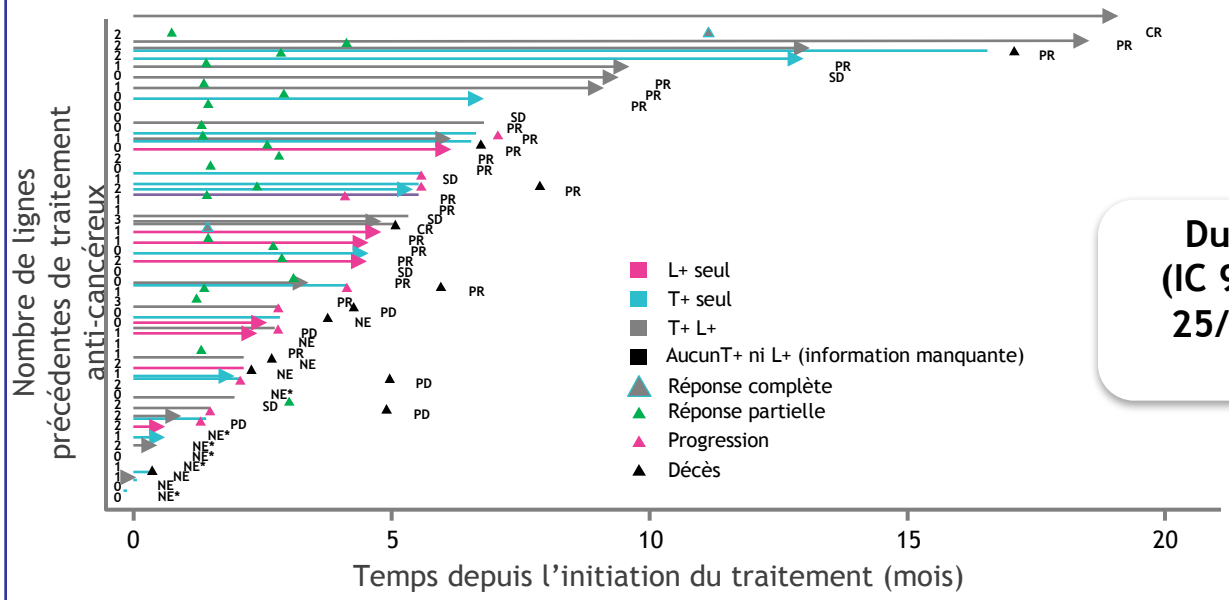
MET

Variation du diamètre tumoral (investigateur)



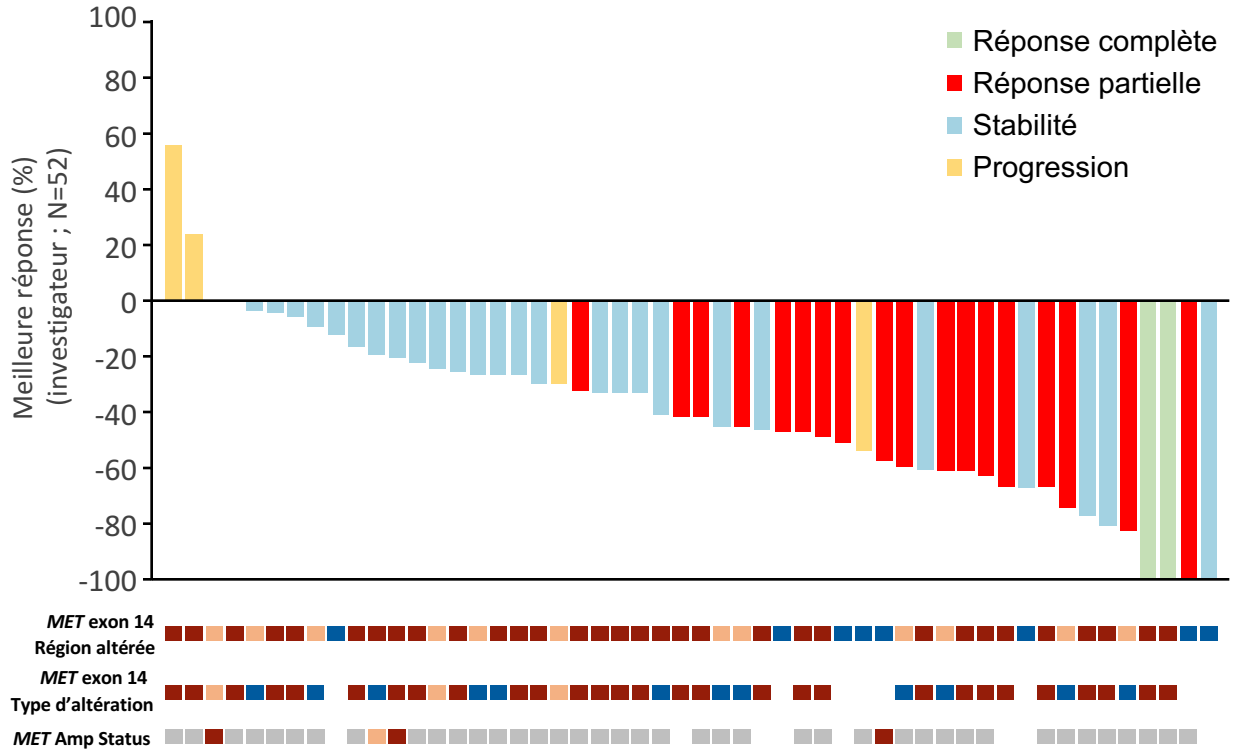
T+ : testing moléculaire positif dans le tissue; L+: testing moléculaire positif dans la biopsie liquide

Tepotinib 500 mg	(n=28)
Meilleure réponse RECIST 1.1, n (%)	
Réponse complète	0 (0)
Réponse partielle	12 (42,9)
Stabilité	6 (21,4)
Progression	5 (17,9)
Non-évaluable	5 (17,9)
Taux de réponse objectif, n (%) [IC95%]	**12 (42,9) [24,5 ; 62,8]**
Taux de contrôle de la maladie, n (%) [IC95%]	**18 (64,3) [44,1 ; 81,4]**



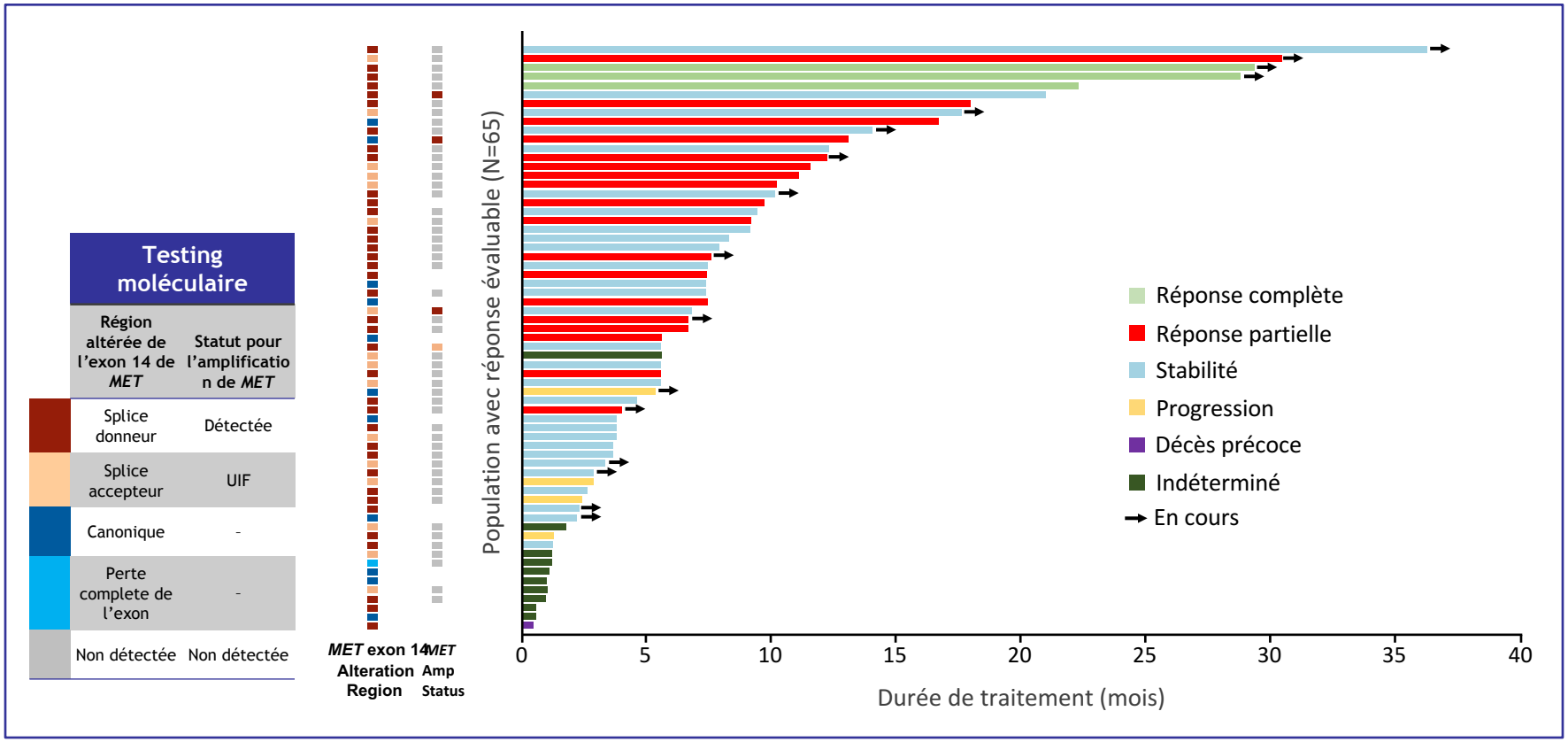
Durée médiane de réponse (IC 95%) : 14,3 (3,7, ND) mois
25/46 patients sont toujours traités

Analyse de l'efficacité du crizotinib dans la cohorte *MET* exon 14 de l'essai de phase I PROFILE 1001



Testing moléculaire			
	Région altérée de l'exon 14 de MET	Type d'altération *MET* exon 14	Statut pour l'amplification de *MET*
	Splice donneur	substitution de base	détectée
	Splice accepteur†	Large indel (>35 bp)	
	Canonique	Indel	-
	Non détectée	-	non détectée

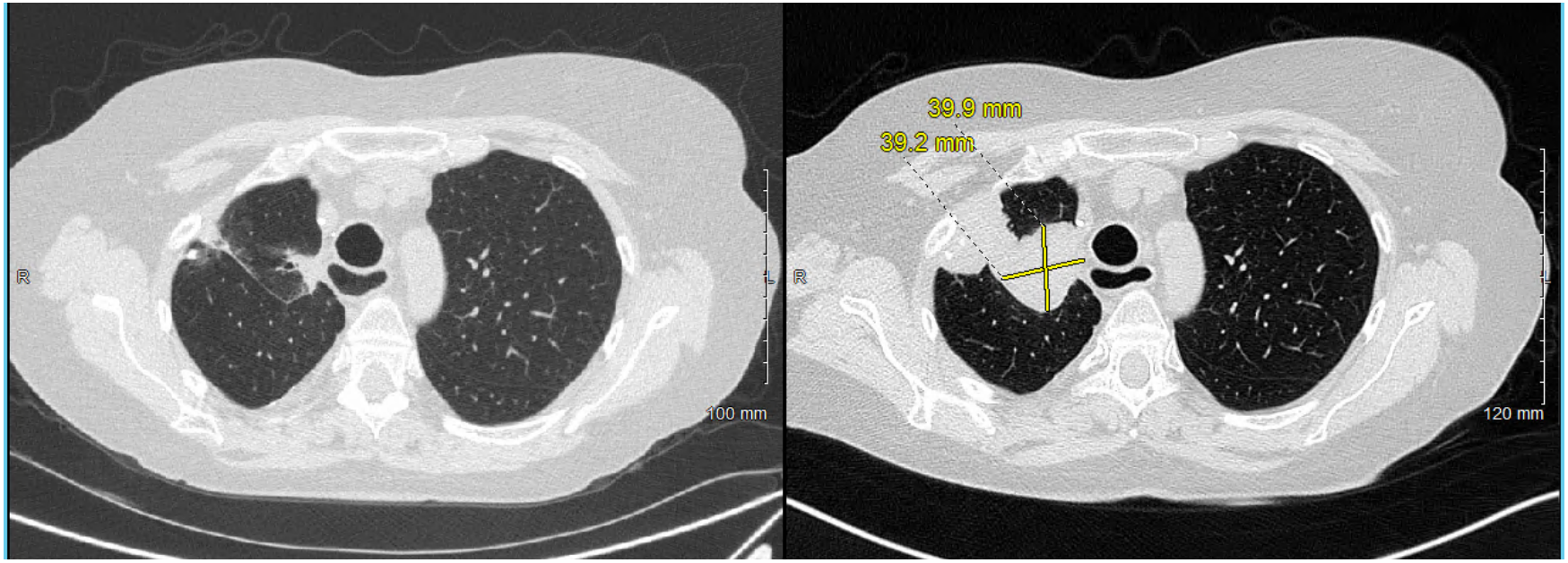
Analyse de l'efficacité du crizotinib dans la cohorte MET exon 14 de l'essai de phase I PROFILE 1001



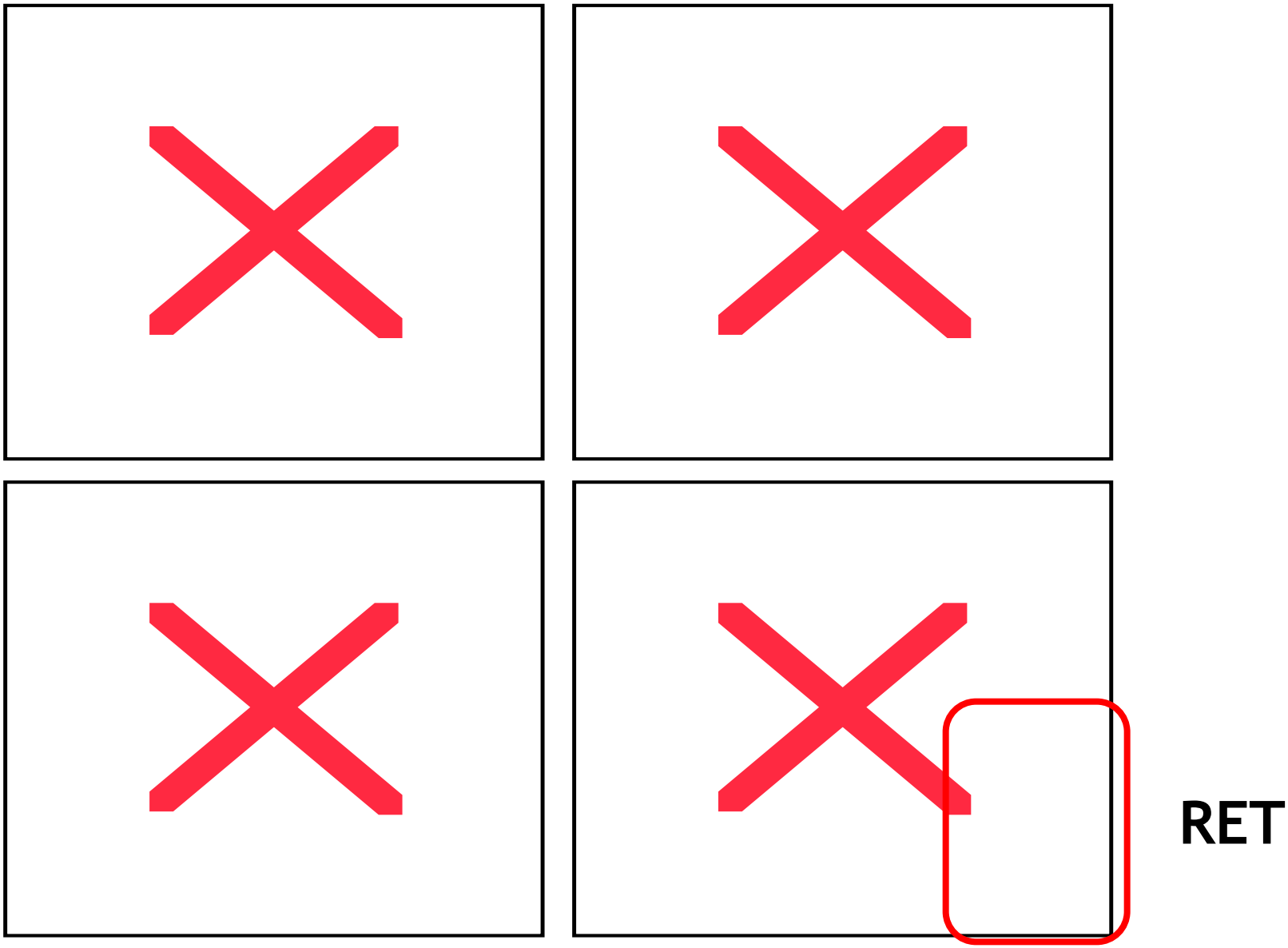
La médiane de SSP est estimée à 7,3 mois (IC95%, 5,4 ; 9,1)

MET exon 14 mutation

- 65 yr old female with stage IV NSCLC already treated with 7 lines of treatment (chemo and IO)
- Never smoker but negative for major oncogenic drivers
- Screened in the SPECTALUNG european program
- MET exon 14 mutation D1028H
- Treated with crizotinib outside a clinical trial (due to renal impairment)



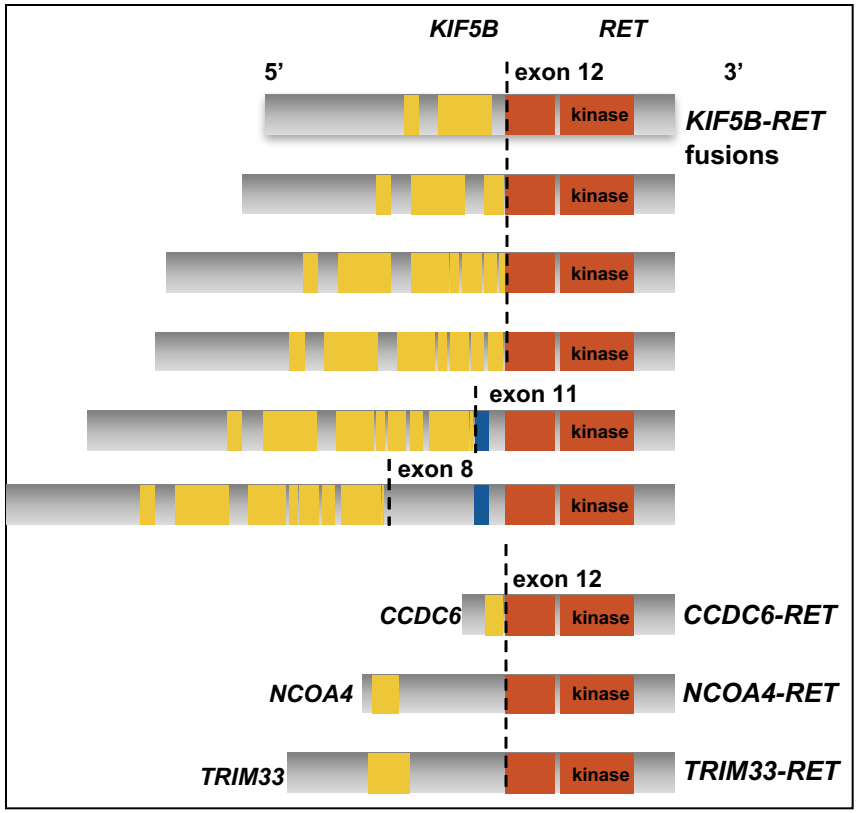
Les nouvelles cibles



RET

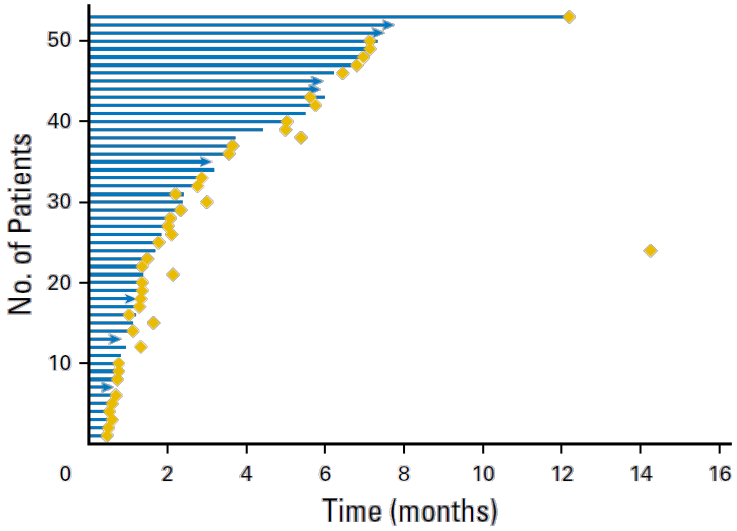
- 1–2% of unselected NSCLCs
- Clinical features: young, never or former light cigarette smokers

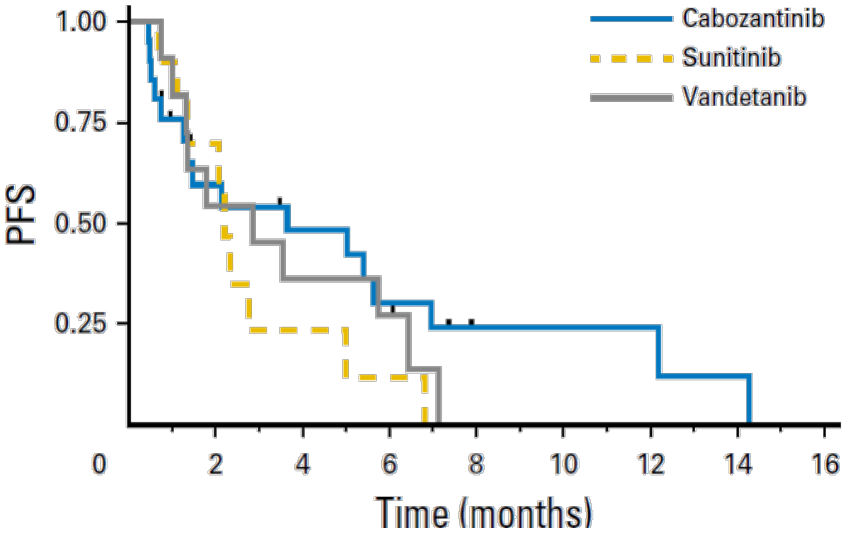
- Intact tyrosine kinase domain fused to an upstream gene partner
  - most common: KIF5B
  - others: CCDC6, NCOA4, TRIM33, KIAA1468
- Result in ligand-independent dimerization and downstream growth pathway activation
- Oncogenic in vitro and in vivo
- diagnosis
  - FISH, DNA-based NGS, RNAseq (IHC not helpful)



Drilon A, et al. Cancer Discov. 2013;3:630-5. Kohno T, et al. Nat Med. 2012;18:375-7. Lipson D, et al. Nat Med. 2012;18:382-4. Saito M, et al. Carcinogenesis. 2014;35:2452-6. Suehara Y, et al. Clin Cancer Res. 2012;18:6599-608. Takeuchi K, et al. Nat Med. 2012;18:378-81.

Global RET Registry





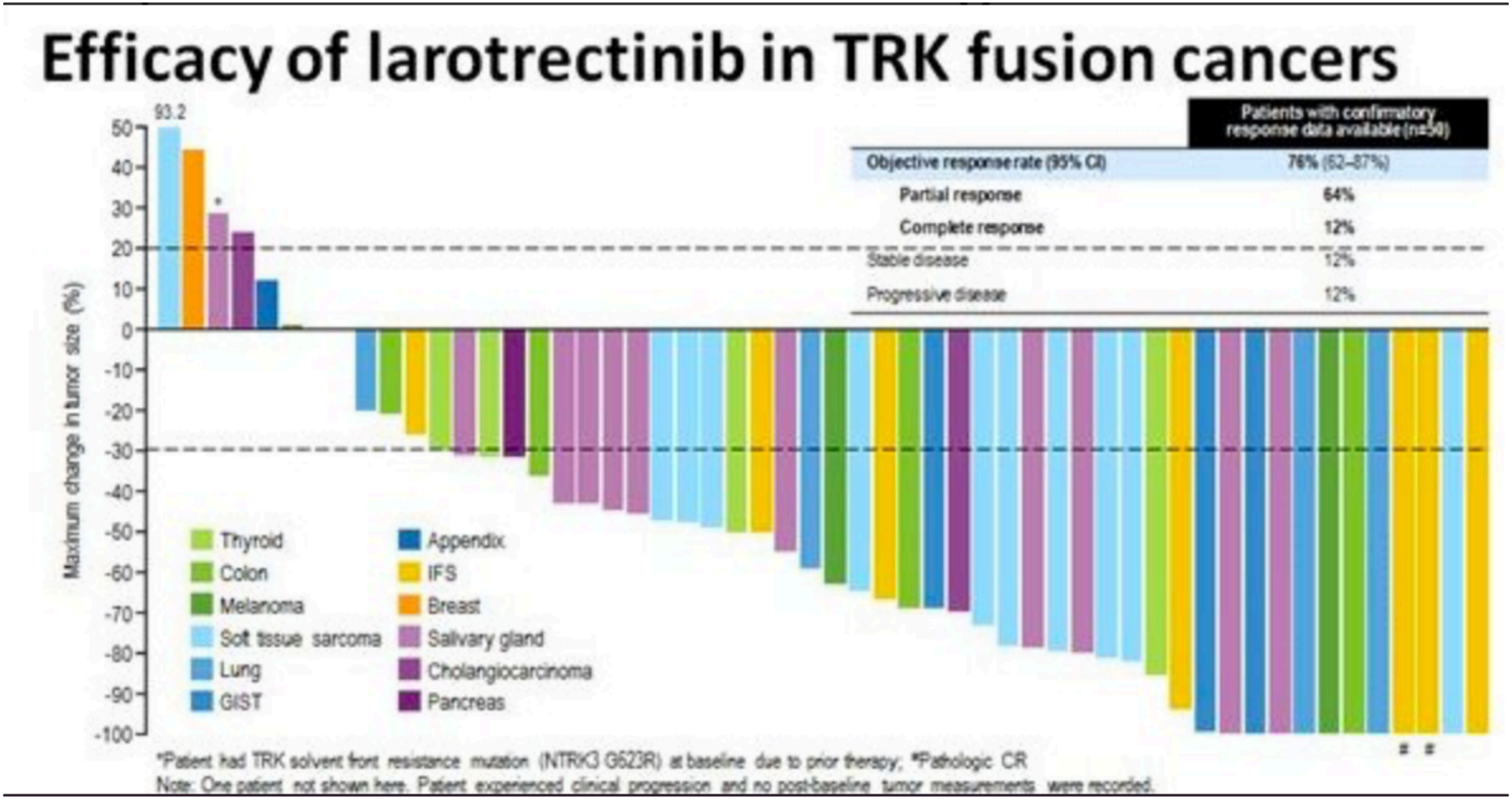
RET inhibitor	Best response (% ; 95 % CI)	Median DoT (range	Median PFS (95% CI)	Median OS (95% CI)
Cabozantinib	7 of 19 evaluable (37%; 16.3 to 61.6)	1.6 months (0.5 to 12.2 months)	**3.6 months (1.3 to 7.0 months)**	4.9 months (1.9 to 14.3 months)
Vandetanib	2 of 11 evaluable (18%; 2.3 to 51.8)	2.9 months (0.8 to 7.1 months)	**2.9 months (1.0 to 6.4 months)**	10.2 months (2.4 to NR)
Sunitinib	2 of 9 evaluable (22%; 2.8 to 60.0)	2.2 months (0.7 to 6.6 months)	**2.2 months (0.7 to 5.0 months)**	6.8 months (1.1 to NR)

Gautschi et al, JCO 2017

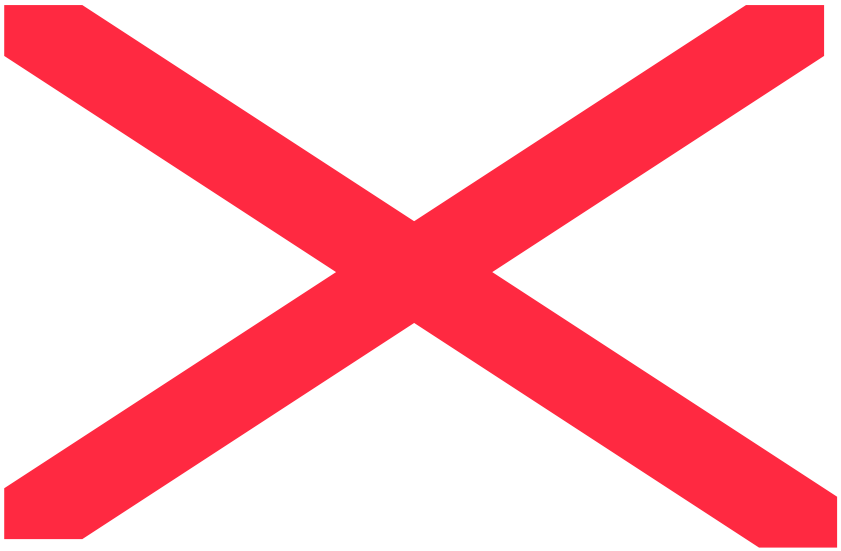
Traitements anti-RET (état des lieux en 09/2018)

Agent	auteur	N	Ligne de traitement	Partenaire de fusion RET	RO	SSP mois	SG mois	Toxicité
Cabozantinib	Drilon	26	L1 : 23% L2 : 50% ≥L3 : 27%	KIF5B 62% Autre 15% Inconnu 23%	28%	5.5	9.9	Gr3 lipase 15% Gr4/5 0%
Lenvatinib	Velcheti	25	L1 : 8% L2 : 32% ≥L3 : 60%	KIF5B 52% Autre 48%	16%	7.3	NA	Gr3 92% Gr HTA 68% Gr5 12%
Vandetanib	Lee	17	L1 : 0% L2 : 28% ≥L3 : 72%	KIF5B 29% Autre 18% Inconnu 53%	18%	4.5	11.6	Gr3 HTA 18% Gr3 QT 11% Gr 4/5 0%
	Yoh	17	L1 : 0% L2 : 37% ≥L3 : 63%	KIF5B 62% CCDC6 31%	47%	4.7	11.1	Gr3 HTA 58% Gr4 pneumonie, rash, QT
LOXO-292	Oxnard	38	L1 : 13% L2 : 87%	KIF5B 60% Autre 40%	68%	NA	NA	Gr3 diarrhée 1% Gr3 céphalées 1% Gr4/5 0%
BLU-667	Subbiah	14	Ph 1 escalade L1 : 23% L2 : 77%	KIF5B CCDC6 KIAA1468	50%	NA	NA	Gr3 15% Gr3 HTA 8% Gr4/5 0%
RXDX-105	Drilon	21	Ph 1 escalade	KIF5B inactif autre	29%	NA	NA	Gr3 rash 10% Gr3 neutropénie 7% Gr3 anémie 7%
LOXO-292	Oxnard	38	Ph 1b escalade L1 : 13% ≥L2 : 87%	KIF5B CCDC6 CLIP1	68%	NA	9.9	Gr3 diarrhée 1% Gr3 céphalées 1% Gr4/5 0%

NTRK


Efficacy of larotrectinib in TRK fusion cancers
Patients with confirmatory response data available (n=58)
Objective response rate (95% CI) 76% (62–87%)
Partial response 64%
Complete response 12%
Stable disease 12%
Progressive disease 12%
93.2
Maximum change in tumor size (%)
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Thyroid
Colon
Melanoma
Soft tissue sarcoma
Lung
GIST
Appendix
IFS
Breast
Salivary gland
Cholangiocarcinoma
Pancreas
*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Les nouvelles cibles



Nouvelles cibles

New targets (NGS from Foundation One)

DNA Gene List: Entire Coding Sequence for the Detection of Base Substitutions, Insertion/Deletions, and Copy Number Alterations

ABL1	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*
BCORL1	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTK*	*C11orf30 (EMSY)*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CD274*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHD2*	*CHD4*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*
DOT1L	*EGFR*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*
FLT4	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*	*GATA1*	*GATA2*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*
GSK3B	*H3F3A*	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*
IGF2	*IKBKE*	*IKZF1*	*IL7R*	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*
JAK2	*JAK3*	*JUN*	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*
KIT	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEN1	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*	*MTOR*	*MUTYH*
MYC	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*
NOTCH2	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*PAK3*
PALB2	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*
PIK3CB	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PLCG2*	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*
PREX2	*PRKAR1A*	*PRKCI*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*
RAD50	*RAD51*	*RAF1*	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX10*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*	*STAT4*	*STK11*
SUFU	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (promoter only)*	*TET2*	*TGFBR2*	*TNFAIP3*	*TNFRSF14*
TOP1	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WISP3*
WT1	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*					

DNA Gene List: For the Detection of Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*	*ETV4*
ETV5	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*	*MYC*	*NOTCH2*
NTRK1	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*		

Nouvelles cibles

FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
1504586146, FR	08 November 2017	Lung adenocarcinoma

Date of Birth	19 March 1943	**Medical Facility**	Inst Claudius Regaud		
Sex	Female	**Ordering Physician**	Philippe, Rochaix	**Specimen Received**	26 October 2017
FMI Case #	TRF283526	**Additional Recipient**	Carlos Gomez-Roca	**Specimen Site**	Spine
Medical Record #	Not Given	**Medical Facility ID #**	206738	**Date of Collection**	29 May 2017
Specimen ID	17T25326	**Pathologist**	Not Provided	**Specimen Type**	Slide

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

12 genomic findings

9 therapies associated with potential clinical benefit

0 therapies associated with lack of response

22 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

ERBB3 amplification
NF1 loss exons 31-24
CDK4 amplification
MDM2 amplification
APC S1068fs*57
CDKN2A/B loss
FRS2 amplification
GLI1 amplification – equivocal‡
NKX2-1 amplification – equivocal‡
RPTOR amplification

Additional Findings†

Microsatellite status MS-Stable

Tumor Mutation Burden TMB-Low; 5 Muts/Mb

Nouvelles cibles

PATIENT RESULTS

- 12 genomic findings
- 9 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 22 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified[†]

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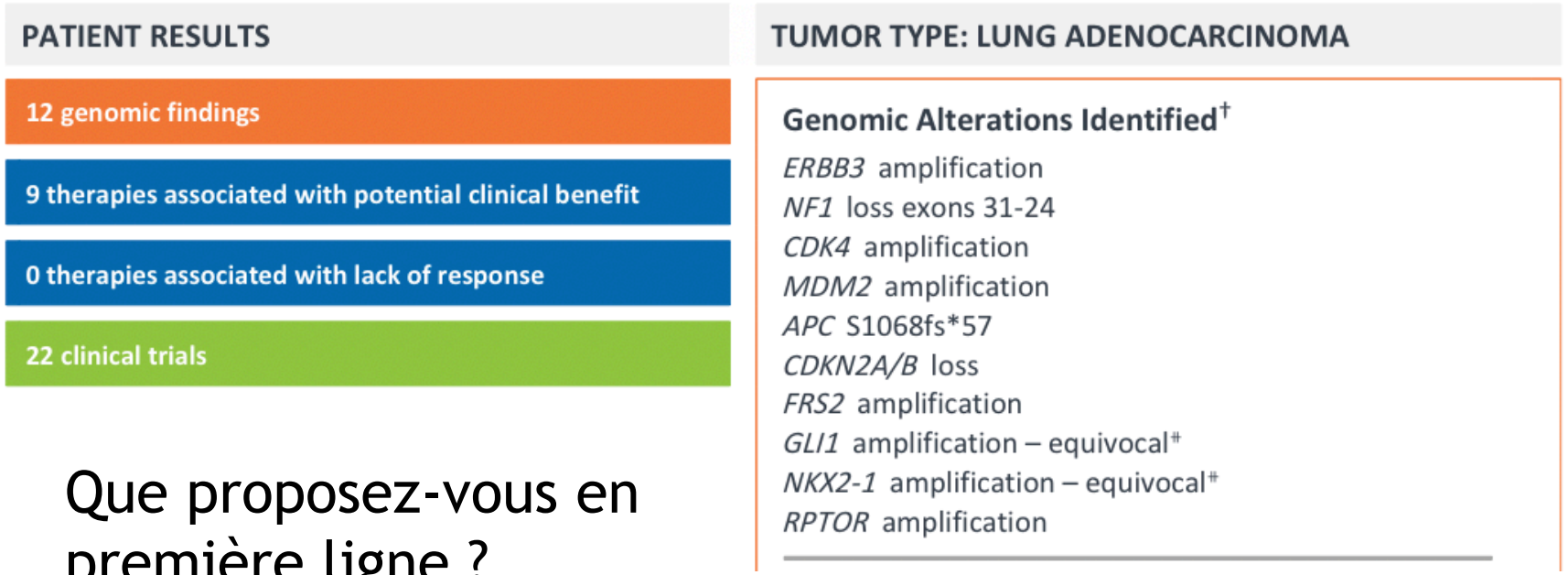
MDM2 amplification
APC S1068fs*57
CDKN2A/B loss
FRS2 amplification
GLI1 amplification – equivocal[#]
NKX2-1 amplification – equivocal[#]
RPTOR amplification

Que proposez-vous en première ligne ?

1. Chimiothérapie
2. Inhibiteur de CDK4
3. Pan-HER inhibiteur
4. Immunothérapie
5. Inhibiteur de MEK

Nouvelles cibles



Que proposez-vous en première ligne ?

1. Chimiothérapie
2. Inhibiteur de CDK4
3. Pan-HER inhibiteur
4. Immunothérapie
5. Inhibiteur de MEK

Synthèse des thérapies ciblées en 2018

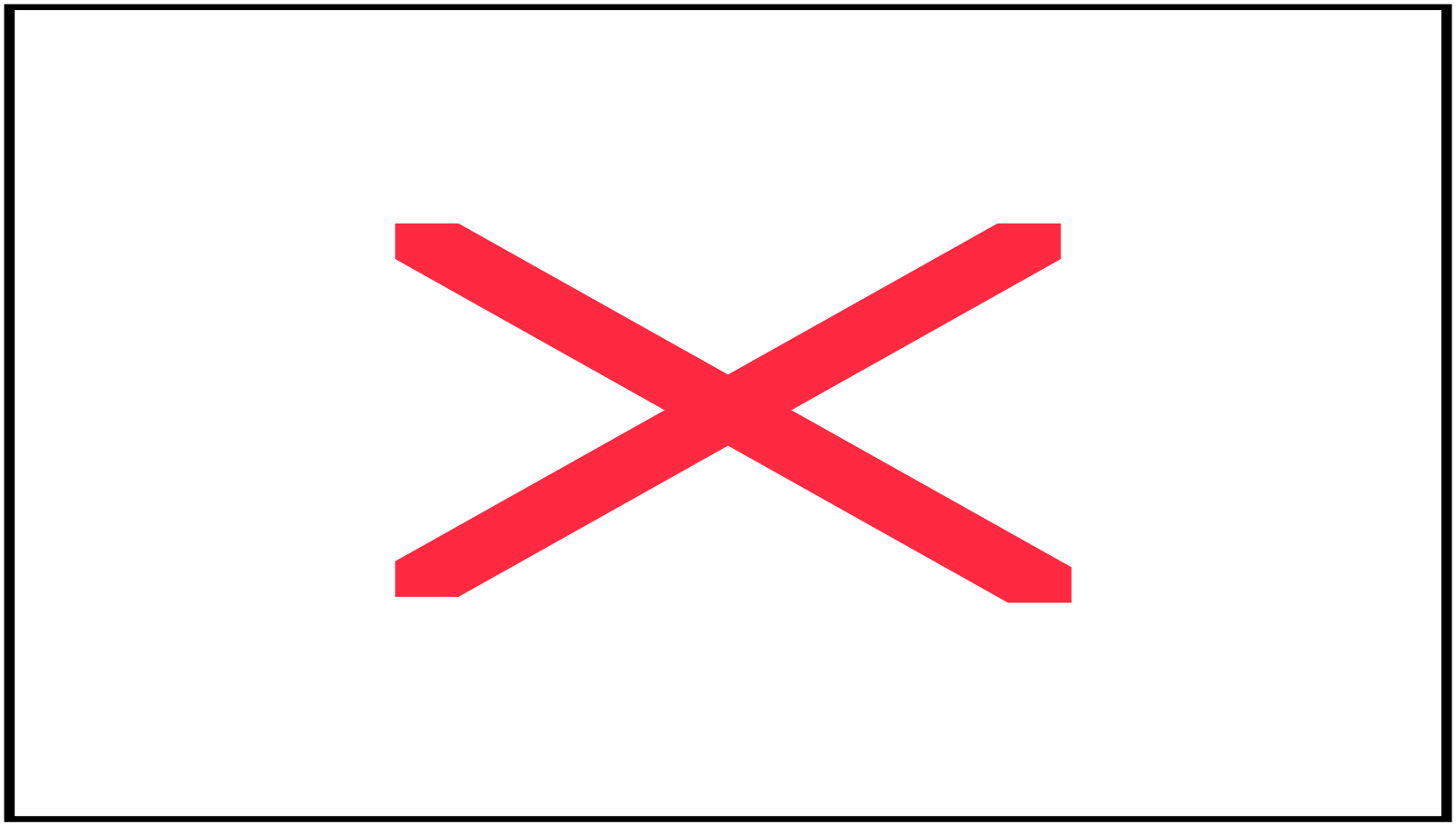
Cible	Biologie	%	Molécules approuvées	A venir	
EGFR	Mutation	11%	Gefitinib, Erlotinib Afatinib, Osimertinib	Poziotinib	
ALK	Translocation	4%	Crizotinib, Ceritinib, Alectinib,	Lorlatinib, Brigatinib	
BRaf	Mutation	2%	Dabrafenib + trametinib	Encorafenib	
ROS1	Translocation	1%	Crizotinib	Lorlatinib, Entrectinib	
HER2	Mutation	1%		Trastuzumab, DS-8201, T-DM1	
KRas	Mutation	25%		Abemaciclib, antiMEK	
MET	Amplif. mutation	2-5%		Crizotinib, Tepotinib	
RET	Translocation	2%		Alectinib, Caboz, BLU-667, LOXO 292	
NTRK	Translocation	1%		Larotrectinib	

Thérapies ciblées

- **Les freins et délais**

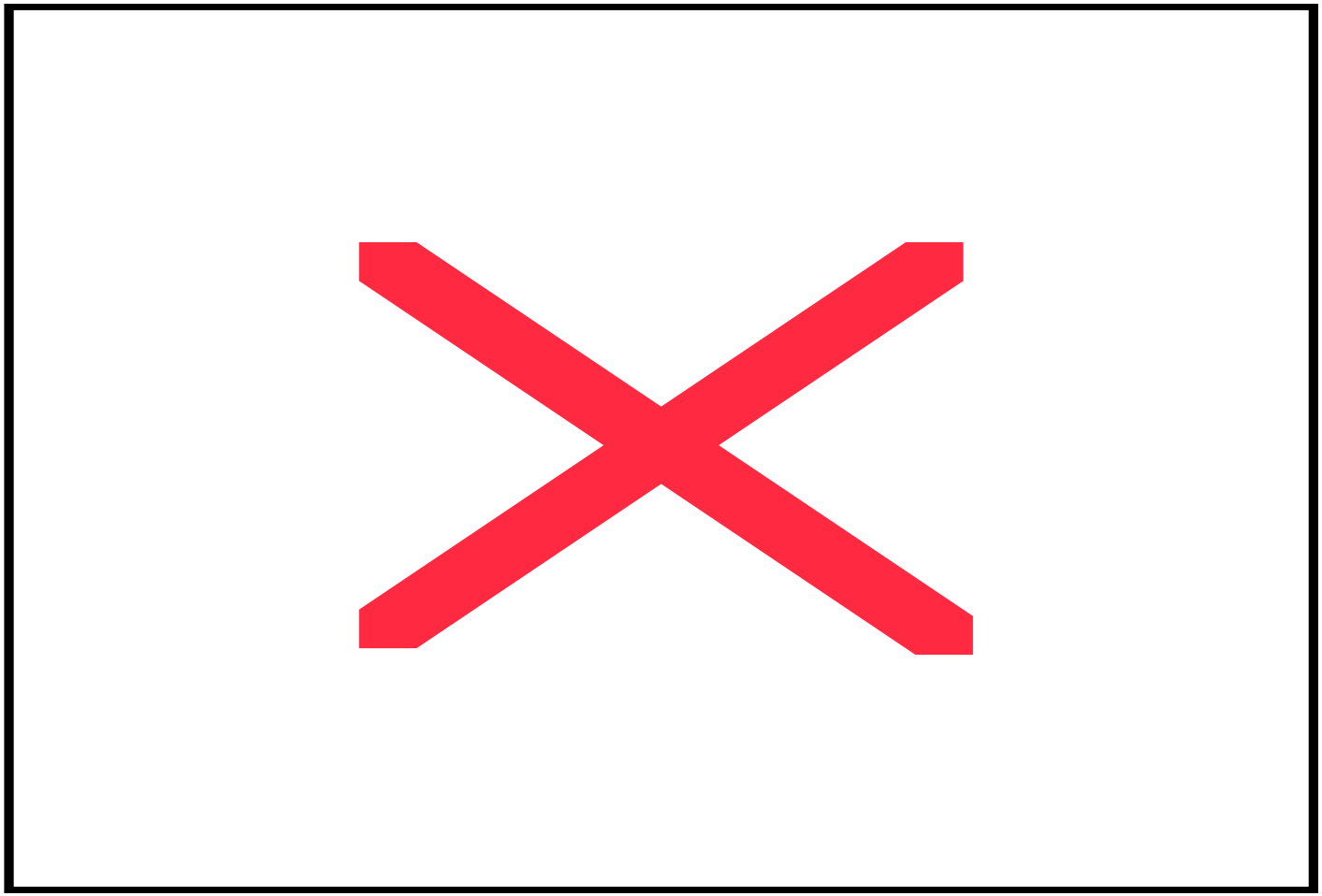
Les délais

Delay between drug approval and reimbursement (Europe)



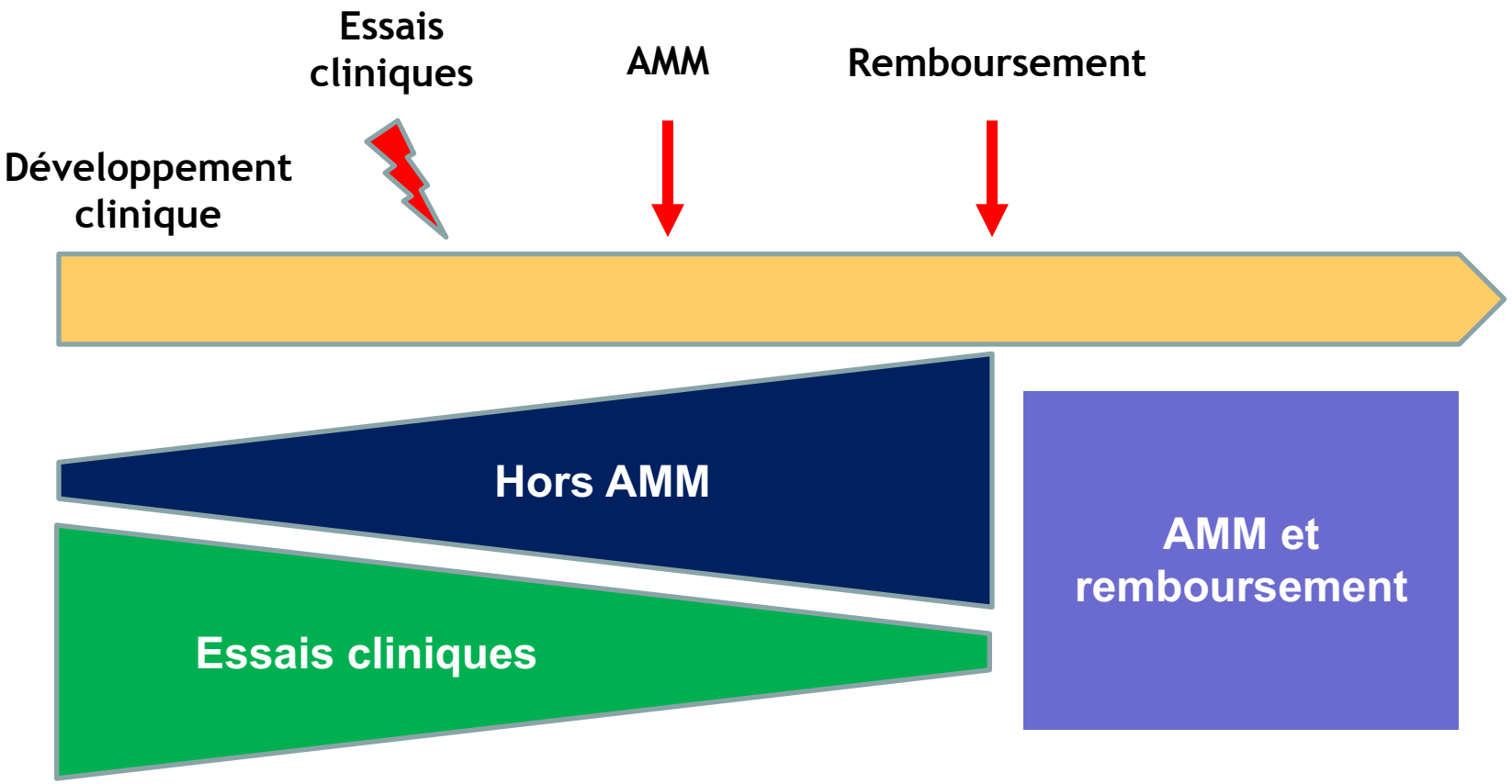
Les délais

Approval speed in FDA and EMEA



Waiting for approval

Utilisation hors AMM ?



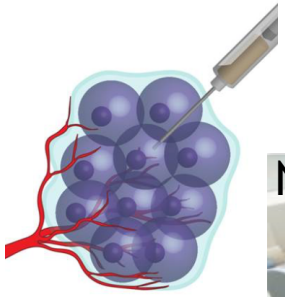
Thérapies ciblées

- **La RCP moléculaire**

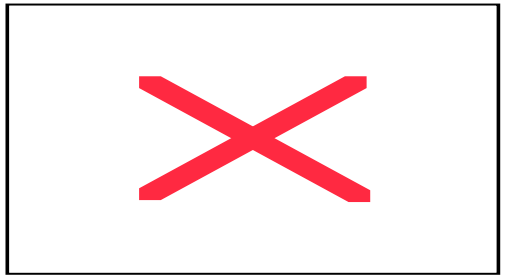
RCP moléculaire

Patients | Biology | Treatments

Tissue



NGS



Blood

PDX

MTB

Weekly
Clinicians
Pathologists
Biostats
Researcher
Biologists

Phase 1 trial

Phase 2 - 3

Conventional treatment

Research-based trials

Rebiopsy (tissue, liquid)

CRCT Translational projects
Early resistance to targeted drugs and immunotherapy

Conclusion

Algorithm pour les CBNPC stade IV (2018)