Thérapies ciblées : quel traitement pour quel patient ?

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Conflits d’intérêt

- Aucun conflit d’intérêt en relation avec le sujet traité

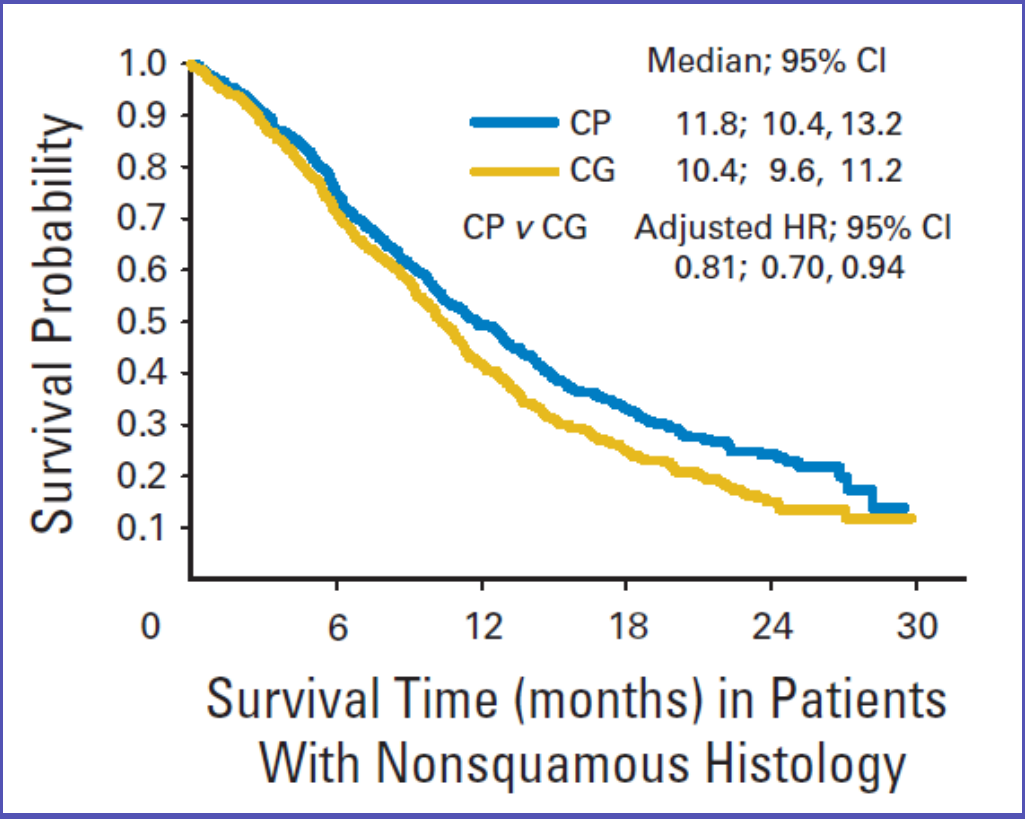
Plan du cours

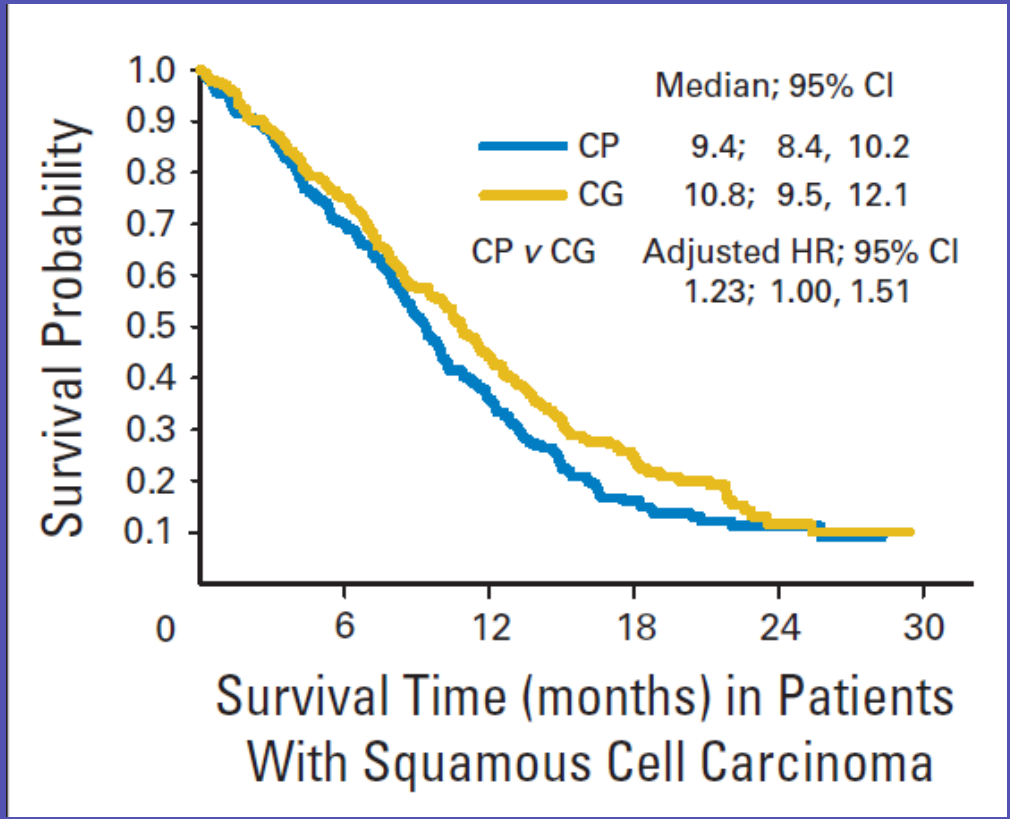
1. Qu'entend-on par thérapie ciblée?
2. Chez qui chercher une « cible »?
3. Place des traitements ciblés disponibles en routine: EGFR et ALK
4. Futur des thérapies ciblées
5. Quelques mots d'immunothérapie
6. Rôle des consultations multidisciplinaires

1. Qu’entend-on par thérapie ciblée?

Qu'est-ce qu'un traitement "ciblé" ?

- Groupe-Cible: population avec caractéristiques prédisposant à sensibilité au traitement = Population enrichie



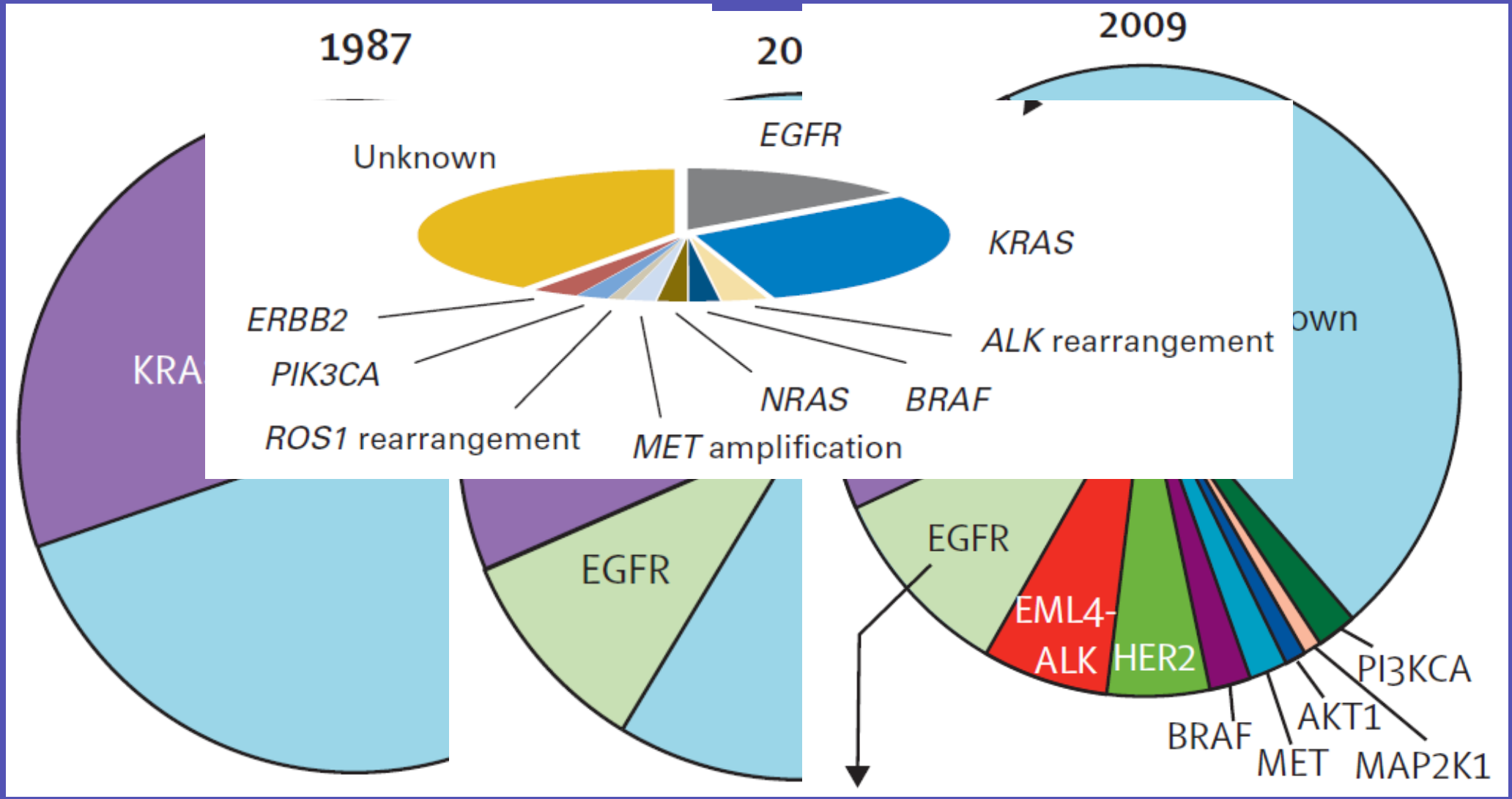


Scagliotti, JCO 2008;26:3543-3551

Qu'est-ce qu'un traitement "ciblé" ?

- Thérapies biologiques ciblées: ciblent de manière « spécifique » des voies métaboliques vitales pour la cellule cancéreuse
- Cibles:
  - récepteurs de facteur de croissance
  - médiateurs intracellulaires appartenant à une cascade signalétique
  - facteurs de néo-angiogenèse
  - gènes...

Evolution des connaissances et cibles moléculaires: adénocarcinomes



Cibles moléculaires: épidermoides

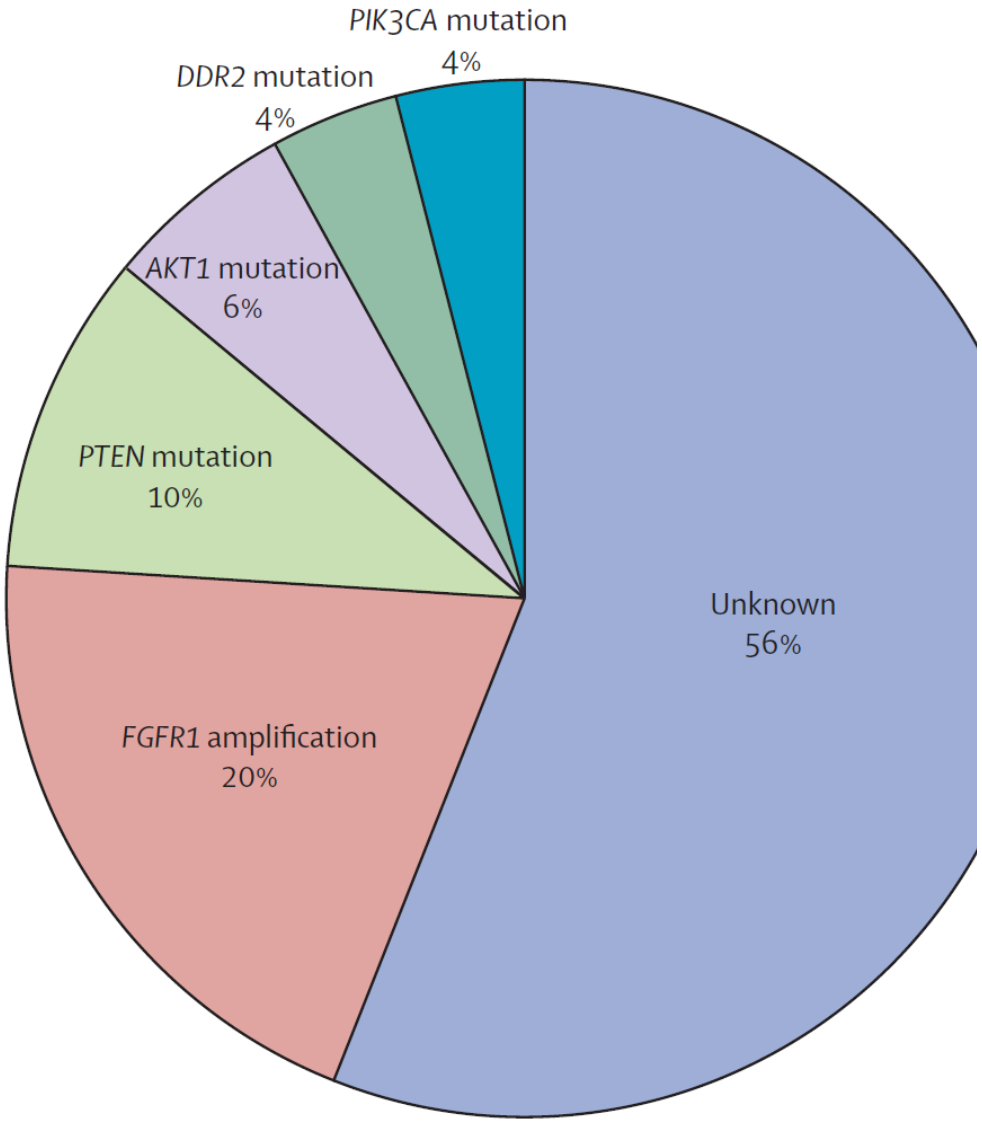


TABLE 1. Key Candidate Genes in Squamous Cell Lung Cancer

	Amplification		Mutation	
Gene	**Squamous**	**Adeno**	**Squamous**	**Adeno**
FGFR1	20%	1%		
SOX	20%	n.r.		
PIK3CA	20%	5%	6%	1.5%
MDM2	10%	5%		
PDGFRA	8–10%	3–7%		
MET	6%	<5%		
P53			65%	40%
NRF2			10–15%	1–2%
PTEN			10.2%	1.7%
EPHA2			7%	0
LKB1			5%	13%
AKT			5%	0
EGFR vIII			5%	0
DDR2			3–4%	n.r.
PTEN loss	IHC expression 70–75% hypermethylation 30–35% LOH 18–22% not significantly different by histology			

2. Chez qui chercher une « cible »?

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

Neal I. Lindeman,* Philip T. Cagle,† Mary Beth Beasley,‡ Dhananjay Arun Chitale,§ Sanja Dacic,¶ Giuseppe Giaccone,‖ Robert Brian Jenkins,** David J. Kwiatkowski,†† Juan-Sebastian Saldivar,‡‡ Jeremy Squire,§§ Erik Thunnissen,¶¶ and Marc Ladanyi‖‖

Question 1: Which Patients Should Be Tested for *EGFR* Mutations and *ALK* Rearrangements?

1.1a: Recommendation: *EGFR* molecular testing should be used to select patients for EGFR-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.1b: Recommendation: *ALK* molecular testing should be used to select patients for ALK-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

Question 2: When Should a Patient Specimen Be Tested for *EGFR* Mutation or *ALK* Rearrangement?

2.1a: Recommendation: *EGFR* mutation testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested.

2.1b: Suggestion: *ALK* rearrangement testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested.

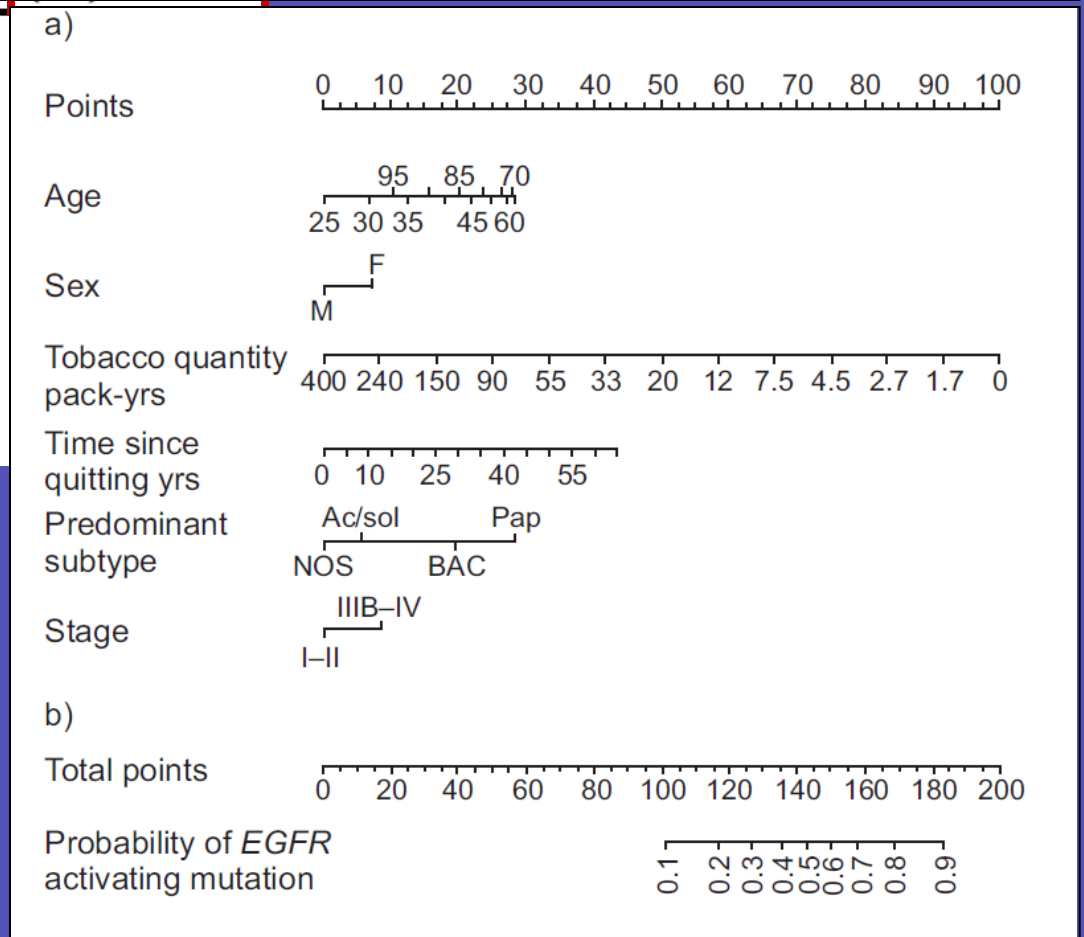
J Mol Diagnosis 2013: 415

Facteurs prédictifs de la présence d'une mutation activatrice d'EGFR

	Total (%)	Non-East Asian (%)
All subgroups	19	10
Smokers	11	4
Nonsmokers	54	35
Adenocarcinoma	42	16
Non-adenocarcinoma	3	1
Male	16	1
Female	46	20

Clin Cancer Res 2006: 4416S

Nomogram to predict the presence of *EGFR* activating mutation in lung adenocarcinoma



Girard et al, Eur Respir J, 2012

Reference	N pts	EML4-ALK+ n (%)	ADC (n+/n)	SCC (n+/n)	Test	Clinical characteristics associated with *EML4-ALK*
Soda (8), 2007	65	5 (7.7%)	4	1	PCR	-
Koivunen (17), 2008	305	8 (2.6%)	8/208 (3.8%)	0/88	FISH	Non/light smoking (p 0.049)
Inamura (15), 2008	221	5 (2.3%)	5/149 (3.4%)	0/72	PCR	-
Perner (57), 2008	603	16 (2.7%)	-	-	FISH	-
Wong (21), 2009	266					oking (p 0.009), age (p
Shaw (18), 2009	141					0.005), male (p 0.036), t smoking (p< 0.001)
Inamura (16), 2009	363					0.006), light smoking (p status (p 0.039), histological tiation (p 0.008)
Takahashi (20), 2010	313					noking (p<0.001), histological differentiation (p<0.001)
Sun (19), 2010	52	3 (5.8%)	3/52 (5.8%)	-	PCR	-
Martelli (29), 2009	120	9 (7.5%)	3/60 (5%)	4/48 (8.3%)	PCR	-
Zhang (22), 2010	103	12 (11.7%)	10/62 (16.1%)	2/29 (6.9%)	PCR	Non smoking (p 0.03)
Kwak (24), 2010	1500	82 (5.5%)	79	1	FISH	-

Facteurs prédictifs de ALK

Non fumeur/fumeur léger

Patients plus jeunes

Adénocarcinome

Berghmans et al; Lung Cancer: targets and Therapy; 2012

Autres exemples de facteurs prédictifs de la présence d'une cible moléculaire

Cible	Population
KRAS	Adénocarcinome, fumeur
HER-2	Adénocarcinome, non fumeur, sexe féminin
RET translocation	Adénocarcinome, non fumeur
ROS-1 translocation	Adénocarcinome, jeune, non fumeur
BRAF	Fumeur

3. Place des traitements ciblés disponibles en routine: EGFR et ALK

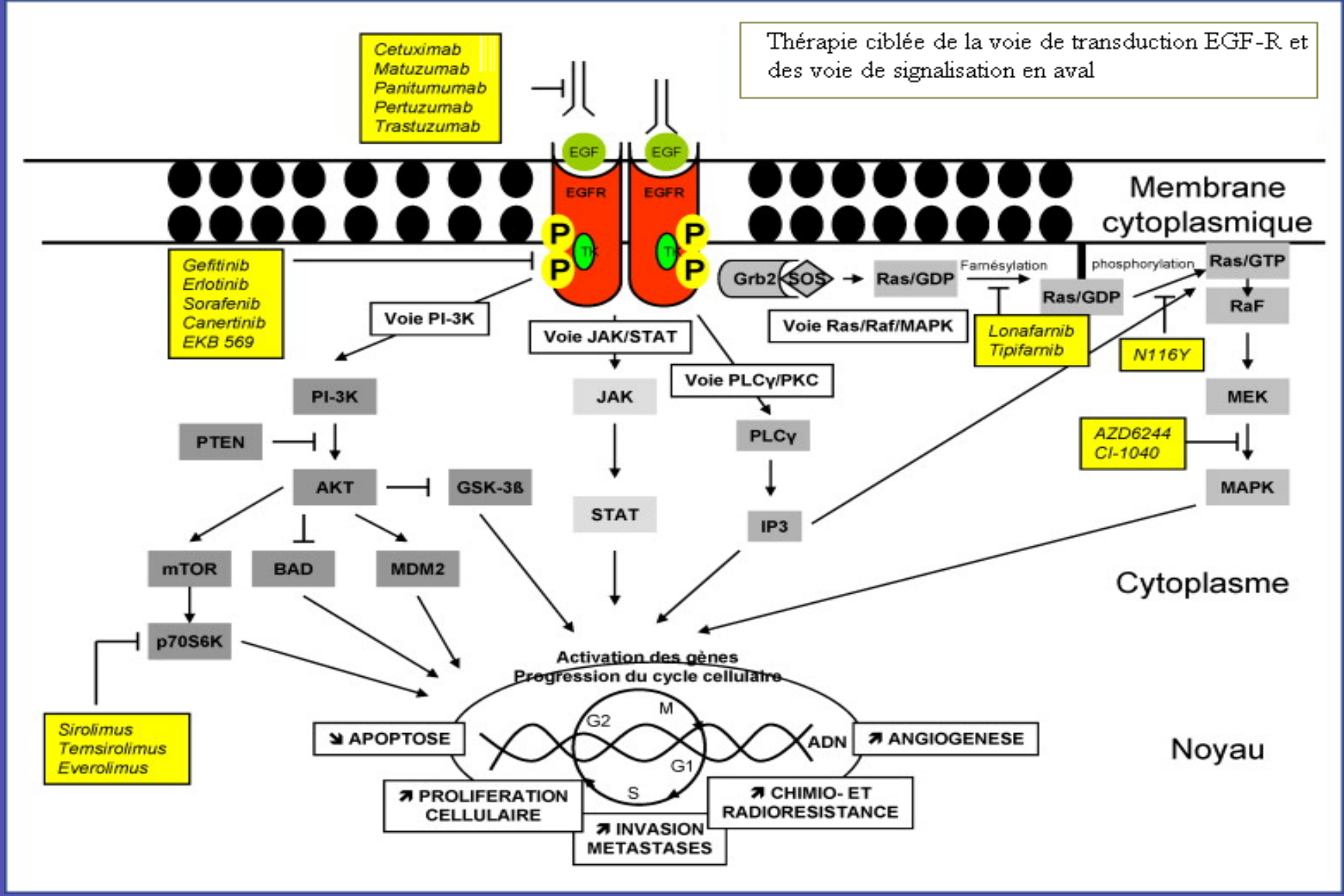
EGFR

Epidermal growth factor receptor

- Ubiquitaire mais présent en fortes quantités dans:
  - Tractus aérodigestif
  - Peau

→ TOXICITÉ

- Nombreux ligands:
  - EGF
  - TGFα, amphiréguline, α-celluline, épiréguline …



J Clin Oncol 2007: 587

Oncogene 2009: S24

Molécules disponibles

- Au moins 4 molécules sur le marché
  - Gefitinib
  - Erlotinib
  - Afatinib
  - Icotinib (Chine)
- Nouveaux agents prometteurs de 3ème génération
  - AZD9291
  - CO-1686
  - HM61713

Référence	Chimiothérapie	N pts	% RO	p	SM	p	Phase
1ère ligne en addition avec la chimiothérapie (population non sélectionnée)							
Giaccone (11)	Gemcitabine + CDDP + géfinitib 500 mg	365	50%	NS	9,9 m	NS	III
	Gemcitabine + CDDP + géfinitib 250 mg	365	51%		9,9 m		
	Gemcitabine + CDDP	363	47%		10,9 m		
Herbst (10)	Paclitaxel + CBDCA + géfinitib 500 mg	347	30%	NS	8,7 m	NS	III
	Paclitaxel + CBDCA + géfinitib 250 mg	345	30,4%		9,8 m		
	Paclitaxel + CBDCA	345	28,7%		9,9 m		
Herbst (12)	Paclitaxel + CBDCA	540	19,3%	NS	10,5 m	NS	III
	Paclitaxel + CBDCA + erlotinib	539	21,5%		10,6 m		
Gatzemeier (13)	Gemcitabine + CDDP + erlotinib	580	31,5%	NS	43 s	NS	III
	Gemcitabine + CDDP	579	29,9%		44,1 s		
En 1ère ligne, en traitement séquentiel (population non sélectionnée)							
Takeda (14)	Doublet de platine puis Gefitinib	300	34%	NS	13,7 m	NS	III
	Doublet de platine	298	29%		12,9 m		
En 1ère ligne, en comparaison à des soins de soutien chez des patients inéligibles pour une chimiothérapie conventionnelle							
Lee (18)	Erlotinib	350	4,3%		3,7m	0,46	III
	Soins de confort	320	2,2%		3,6m		
En maintenance, en l'absence de progression après 4 cycles à base de platine							
Cappuzzo (34)	Erlotinib	437	NA		12 m	S	III
	Placebo	447			11 m		
Gaafar (33)	Géfitinib	86	NA		10,9 m	NS	III
	Placebo	87			9,4 m		
Zhang (32)	Géfitinib	148	NA		18,7m	0,26	III
	Placebo	148			16,9m		
Pérol (31)	Gemcitabine	155	NA		?	NS	III
	Erlotinib	154			11,4 m		
	Observation	155			10,8m		
	Erlotinib + docétaxel ou pémétrexed	116	39%		7,8m		

- Pas de place pour un ITK d'EGFR en 1ère ligne dans des populations non sélectionnées ou en l'absence de mutation
- Rôle en traitement de maintenance??

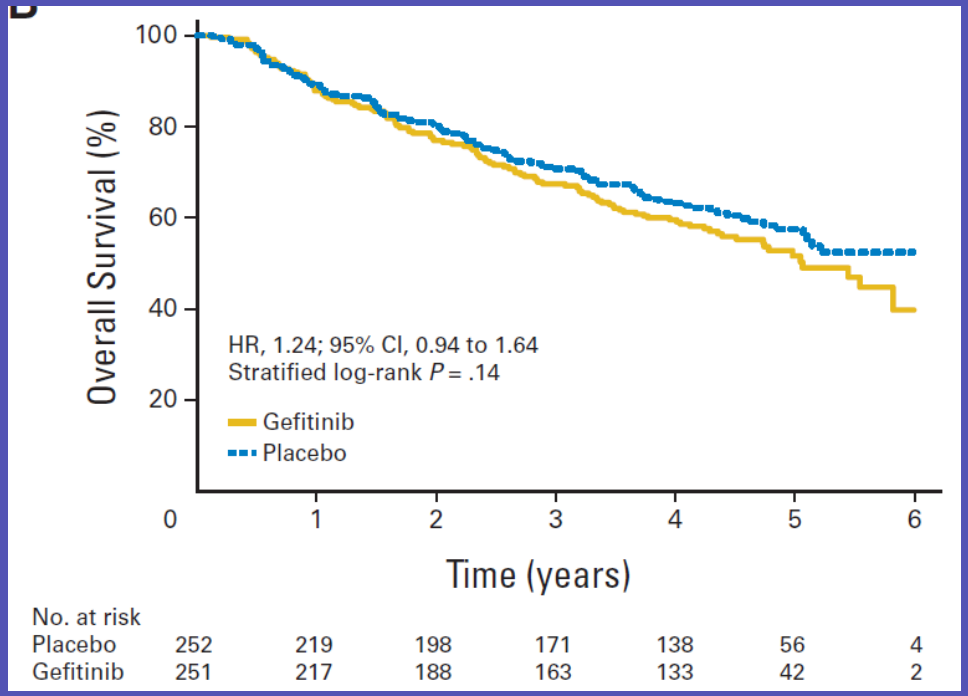
Référence	Chimiothérapie	N pts	% RO	p	SM	p	Phase
En rattrapage dans des populations non sélectionnées, versus soins de confort							
Shepherd (36)	Erlotinib	488	8,9%	S	6,7 m	S	III
	Placebo	243	1%		4,7 m		
Thatcher (37)	Géfitinib	1129	8%		5,6 m	0,09	III
	-	563	1,3%		5,1 m		
En rattrapage dans des populations non sélectionnées, versus chimiothérapie							
Maruyama (38)	Géfitinib	245	22,5%	0,009	11,5 m	0,33	III
	Docétaxel	244	12,8%		14 m		
Kim (39)	Géfitinib	723	9,1%	0,33	7,6m	NS	III
	Docétaxel	710	7,6%		8,0m		
Garassino (41)	Erlotinib	112	3%	0,001	5,4m	0,05	III
	Docétaxel	110	15,5%		8,2m		
Karampeazis (40)	Erlotinib	166	9%	0,47	10,1m	0,99	III
	Pémétrexed	166	11,4%		8,2m		
En rattrapage dans des populations « enrichies », versus chimiothérapie							
Sun (43)	Géfitinib	71	58,8%	<,001	22,2m	0,37	III
	Pémétrexed	70	22,4%		18,9m		
En rattrapage après échec d'un ITK d'EGFR							
Miller (42)	Afatinib	390	7%	0,007	10,8m	0,74	IIb/II
	Placebo	195	0,5%		12,0m		I

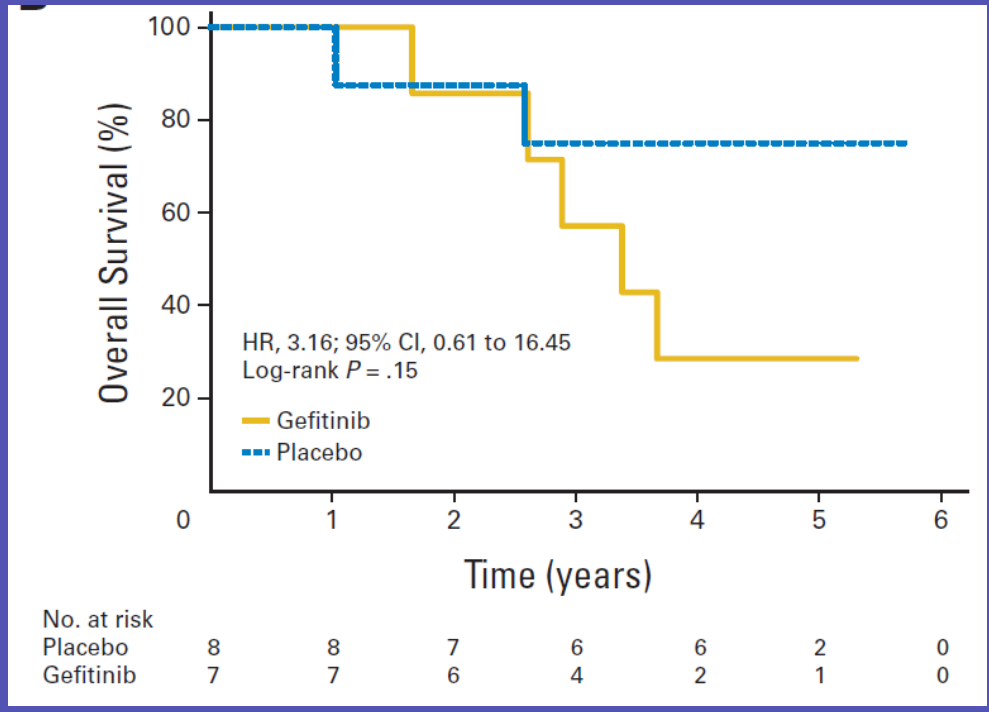
- Rôle limité pour un ITK d'EGFR en situation de rattrapage dans des populations non sélectionnées ou en l'absence de mutation

En cas de mutation activatrice d’EGFR

Stades chirurgicaux

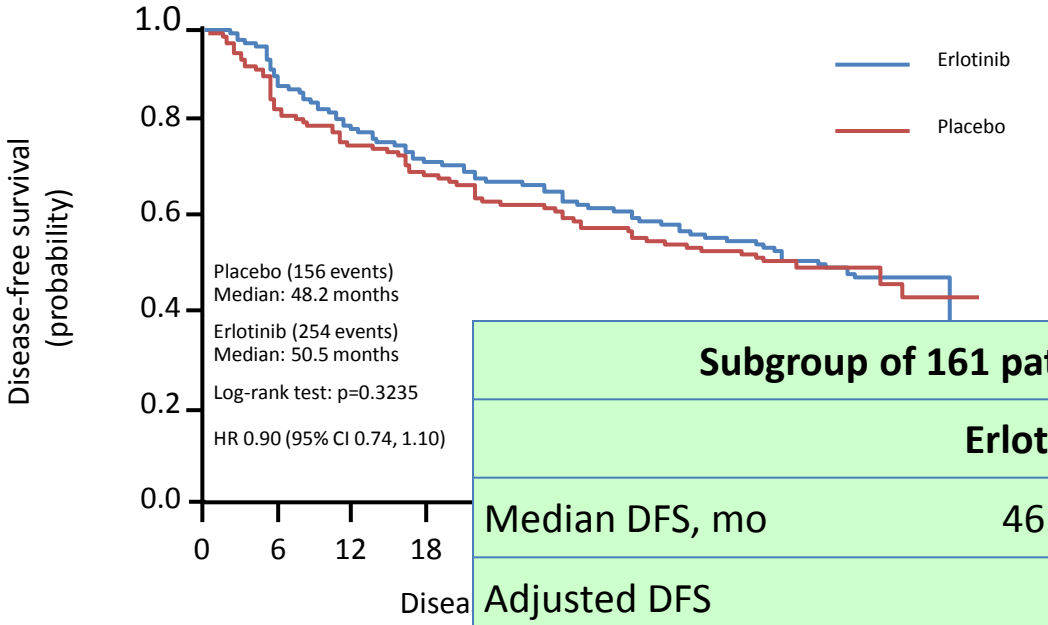
Gefitinib Versus Placebo in Completely Resected Non–Small-Cell Lung Cancer: Results of the NCIC CTG BR19 Study





Goss et al J Clin Oncol 2013

7501: A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results – Kelly K et al



Subgroup of 161 patients with EGFR activating mutation				
	Erlotinib	**Placebo**	**HR (95% CI)**	**p-value**
Median DFS, mo	46.4	28.5	0.61 (0.38, 0.98)	0.041†
Adjusted DFS			0.60 (0.36, 0.98)	0.041†
Patients relapsed, n (%)	35 (34.3)	31 (52.5)		
Brain relapses, %*	40.0	12.9		
Bone relapses, %*	14.3	29.0		
Median OS, mo	NR	NR	1.09 (0.56, 2.16)	0.815‡

Kelly et al. J Clin Oncol 2014; 32 (suppl 5; abstr 7501)

Stades locorégionaux

- Aucune donnée permettant de déterminer la place d'un ITK d'EGFR-TKI en cas de mutation activatrice chez les patients traités par CT-RT avec intention curative

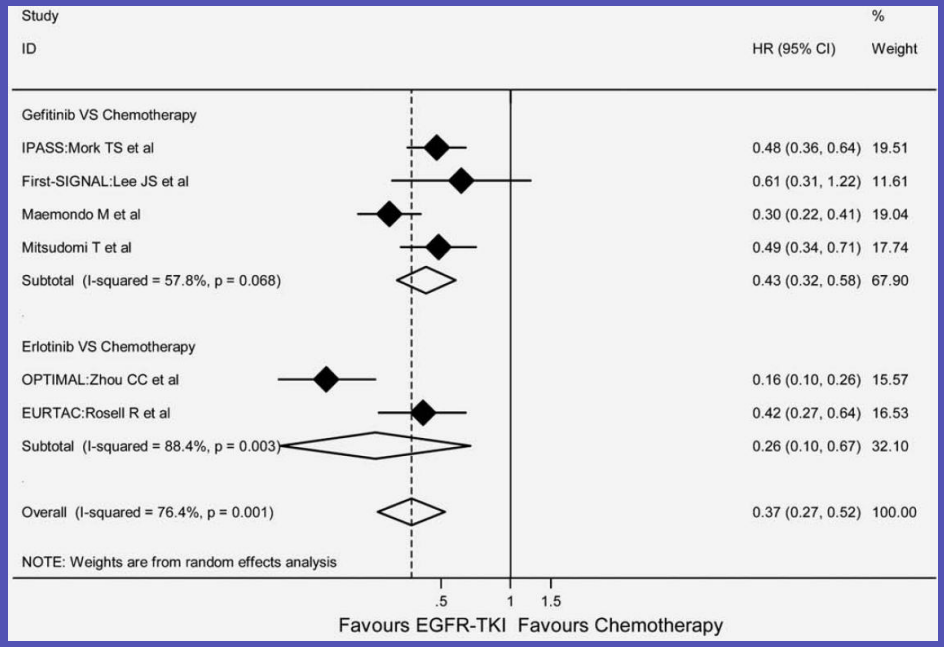
Maladies avancées: études randomisées en 1ère ligne comparant un ITK d'EGFR à CT

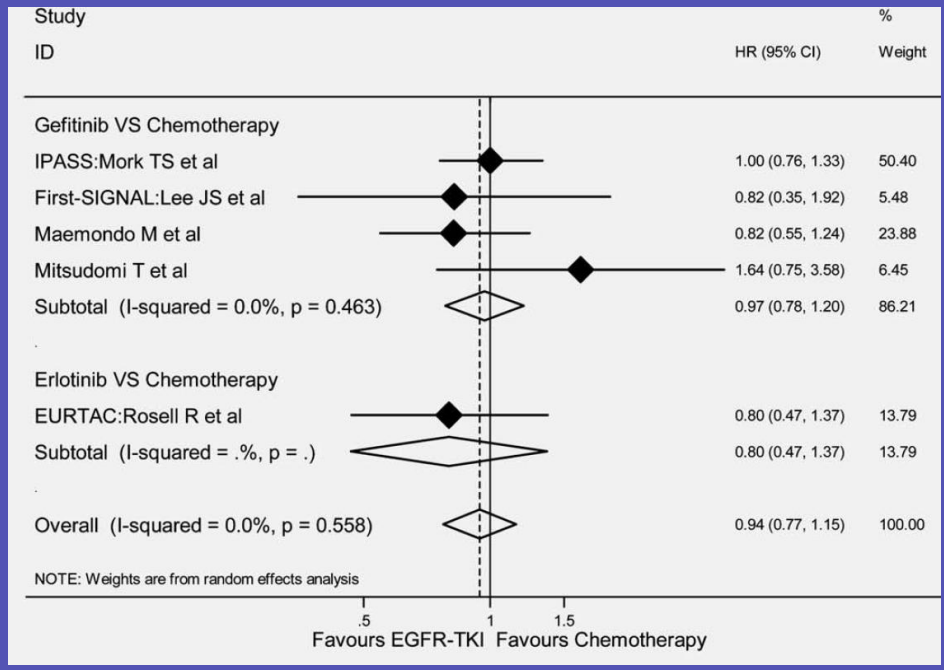
- Amélioration du taux de réponse et de la SSP
- Pas d'effet sur la survie (cross-over)

Maemondo, 2010 Inoue, 2013	Gefitinib	114	73,7%	S	27,7 m	0,48
	CBDCA + Pac	114	30,7%		26,6 m	
Mitsudomi, 2010	Gefitinib	86			Non atteint	0,21
	CDDP + Doc	86			30,9m	
Rosell, 2012	Erlotinib	86	58 %	S	19,3 m	NS
	Standard CT	87	15 %		19,5 m	
Zhou, 2011 (ASCO 2012)	Erlotinib	83	82 %	S	22,7m	0,69
	Gem + CBDCA	82	36 %		28,9m	
Sequist, 2013	Afatinib	230	56%	0,001	HR 1,12	0,60
	CDDP-PEM	115	23%			
Wu, 2014	Afatinib	242	67%	<0,001	22,1m	0,76
	CDDP-GEM	122	23%		22,2m	

Cross-over

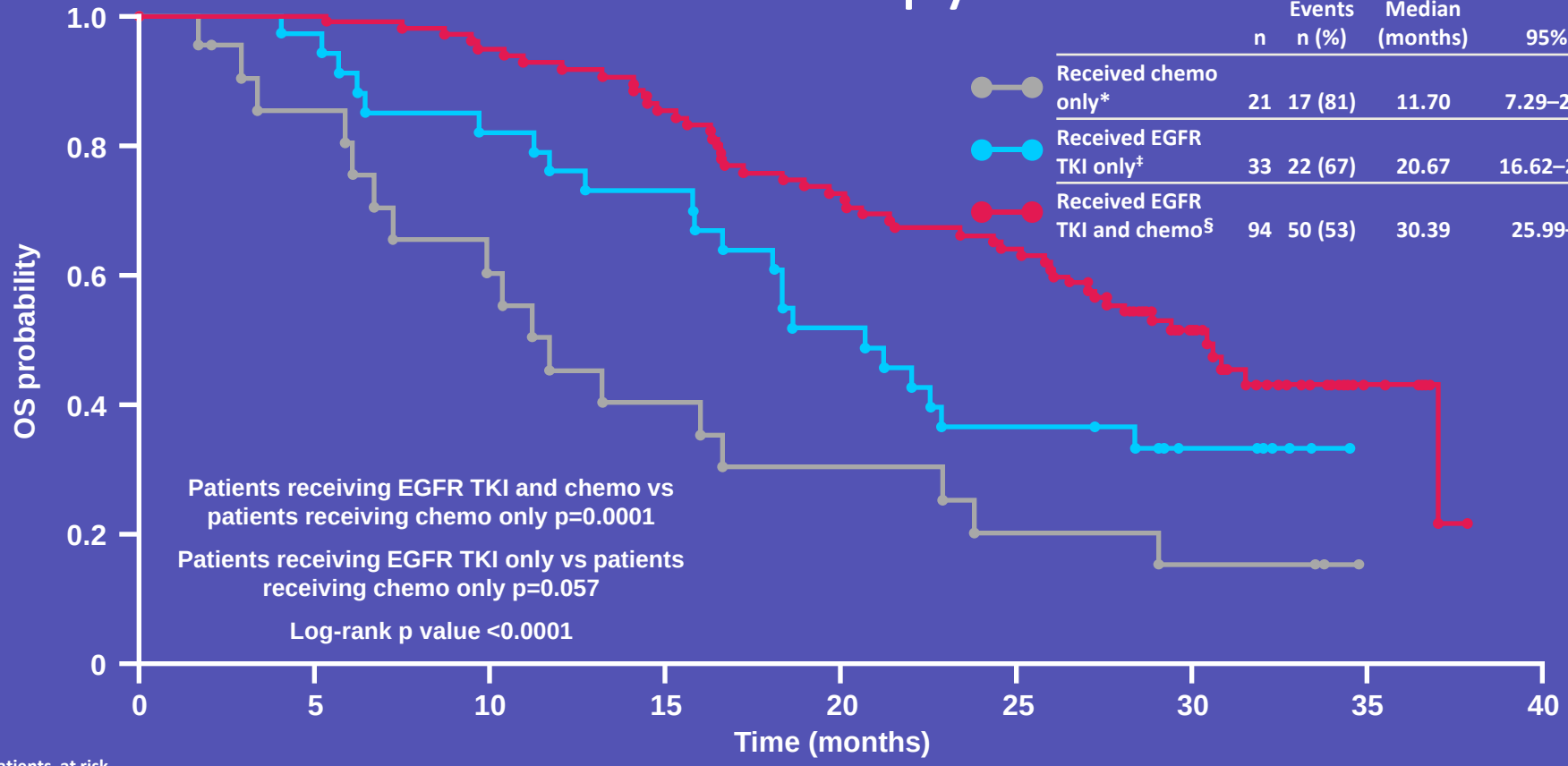
	ITK EGFR en rattrapage
Inoue	98.2%
Rosell	76%
Mitsudomi	59%
Lux Lung 3	75%
Lux Lung 6	56%





Int J Cancer 2012

Supplementary analysis: influence of EGFR TKI and chemotherapy on OS

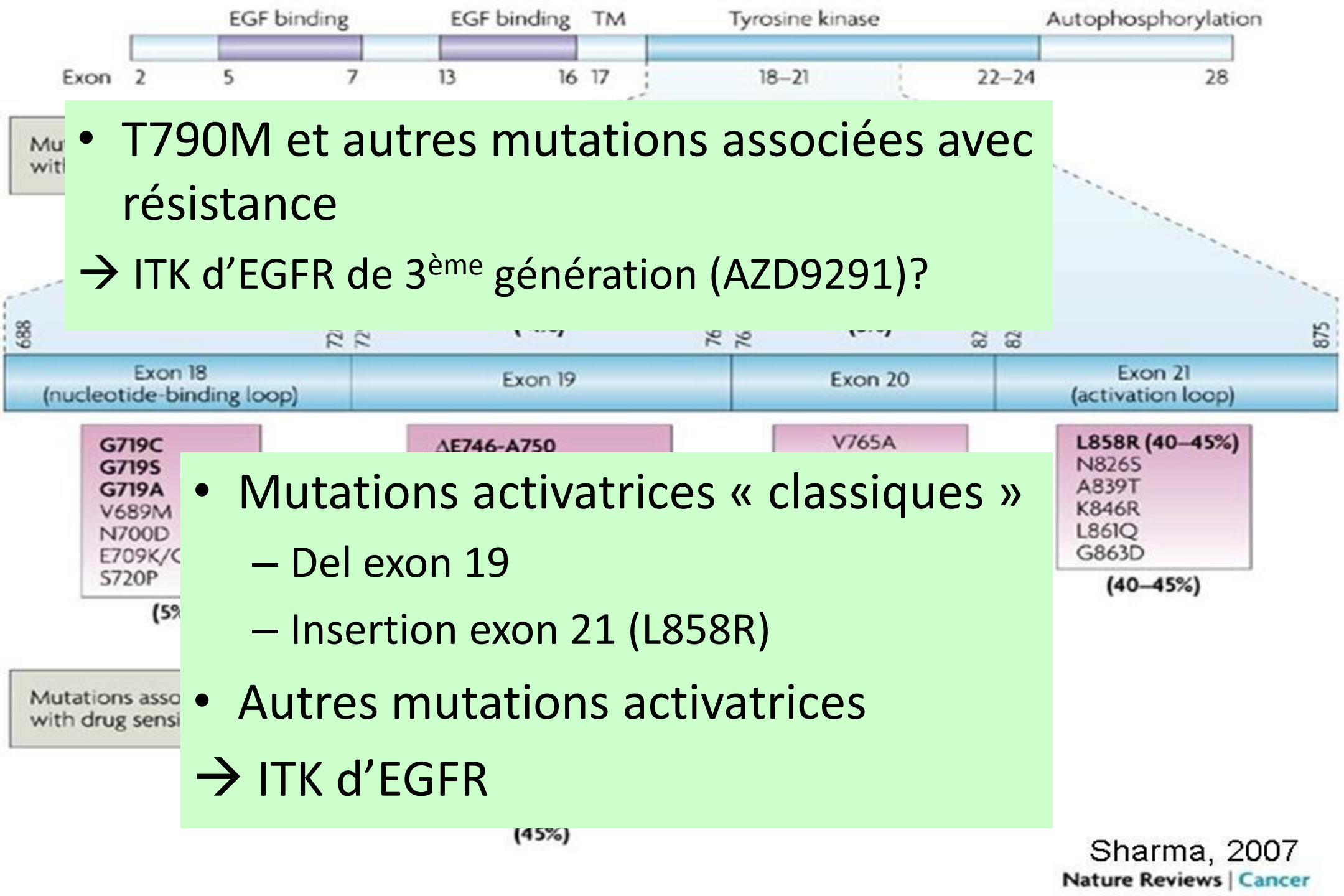


	n	Events n (%)	Median (months)	95% CI
Received chemo only*	21	17 (81)	11.70	7.29–22.87
Received EGFR TKI only‡	33	22 (67)	20.67	16.62–28.32
Received EGFR TKI and chemo§	94	50 (53)	30.39	25.99–NR

Patients at risk								
Patients receiving chemo only*	21	17	12	8	6	4	3	0
Patients receiving EGFR TKI only‡	33	32	27	24	17	12	7	0
Patients receiving EGFR TKI and chemo§	94	94	89	80	68	60	28	6

*Chemo only, no EGFR TKI: patients from the GC arm who had no further treatment (n=16) or further chemotherapy (n=5)
‡EGFR TKI only, no chemo: patients from the erlotinib arm who are still on treatment (n=7), had no further treatment (n=25) and who were re-challenged (n=1)
§EGFR TKI and chemo: patients from the erlotinib arm who switched to chemo (n=43), patients from the GC arm who switched to erlotinib in any line (n=51)

Zhou ASCO 2012.
Courtesy of Zhou



- T790M et autres mutations associées avec résistance

→ ITK d'EGFR de 3ème génération (AZD9291)?

- Mutations activatrices « classiques »
  - Del exon 19
  - Insertion exon 21 (L858R)
- Autres mutations activatrices

→ ITK d'EGFR

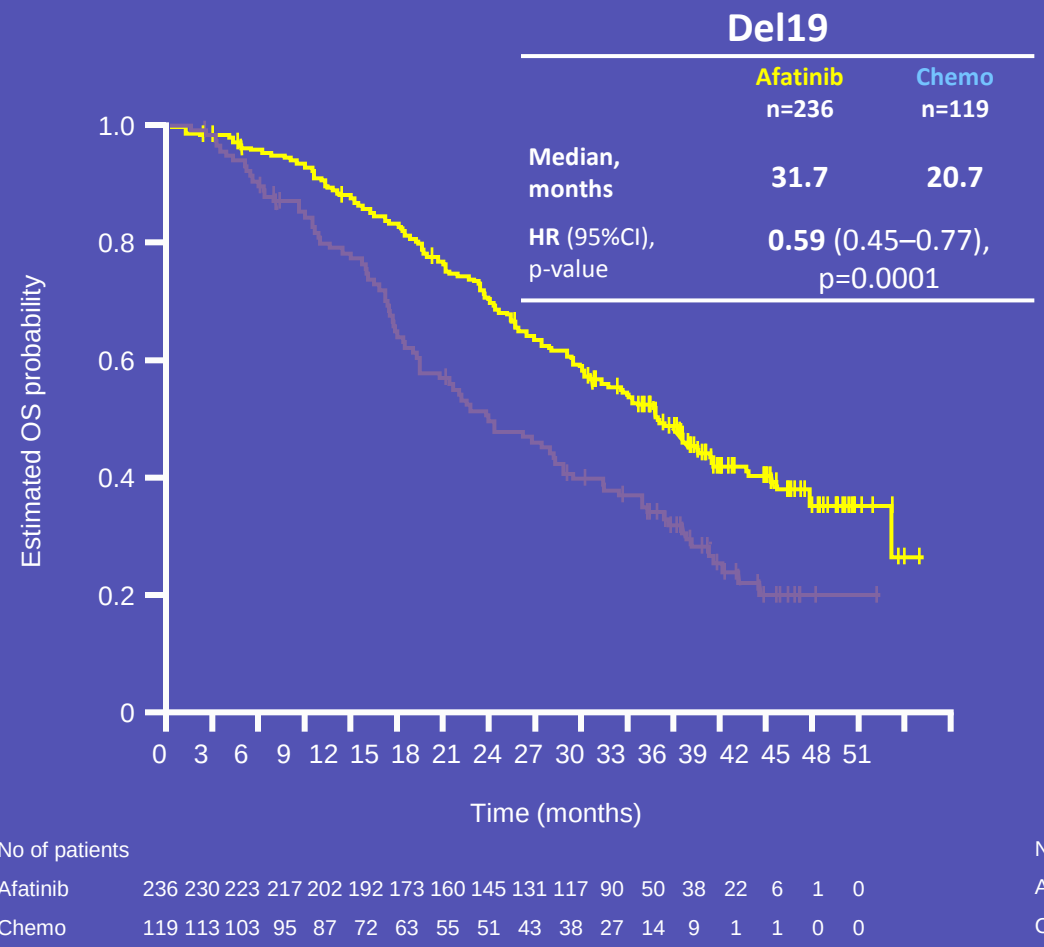
Sharma, 2007
Nature Reviews | Cancer

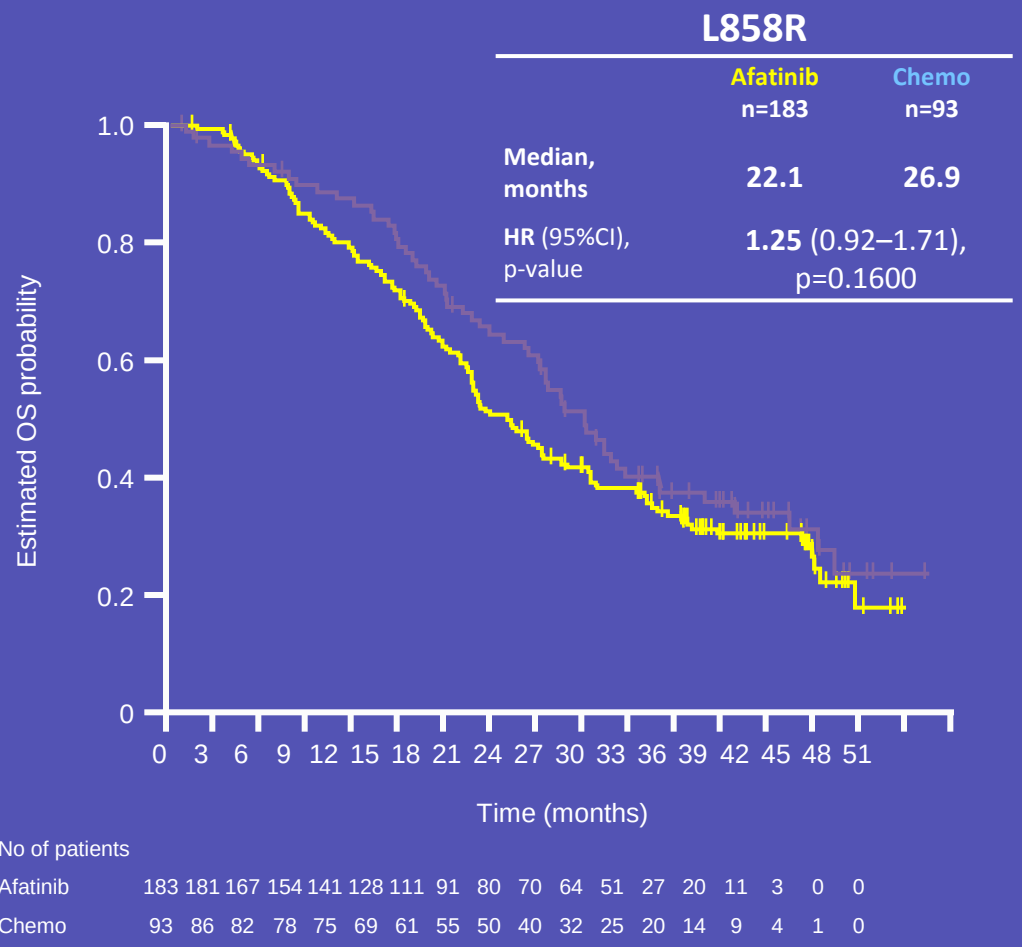
Mutations activatrices classique: Sensibilité différente aux ITK d'EGFR?

- Del exon 19 semble plus sensible aux ITK de 1ère-2de génération mais résultats conflictuels

Effet de l'ITK d'EGFR sur la SSP en fonction du statut Del exon19/L858R		
	TKI	p
Inoue	Gefitinib	0,181
Mitsudomi	Gefitinib	0,68
Rosell	Erlotinib	0,07
Zhou	Erlotinib	0,054
Sequist	Afatinib	0,01

Combined OS analysis: mutation categories
Lux Lung 3 and 6



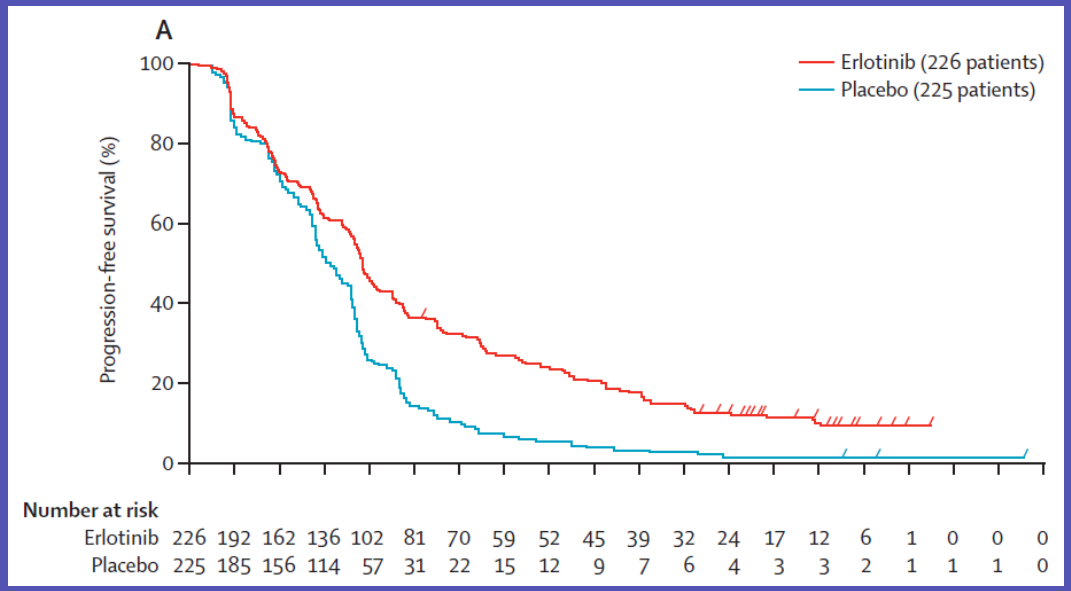


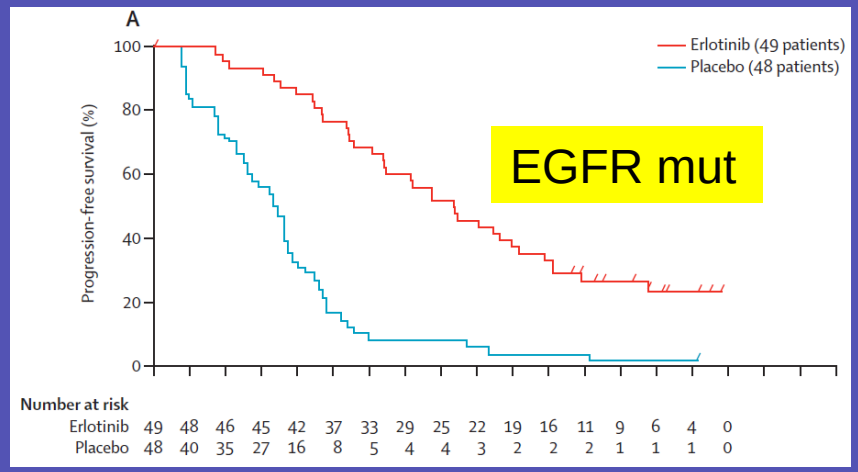
With the courtesy of Prof James Chih-Hsin Yang

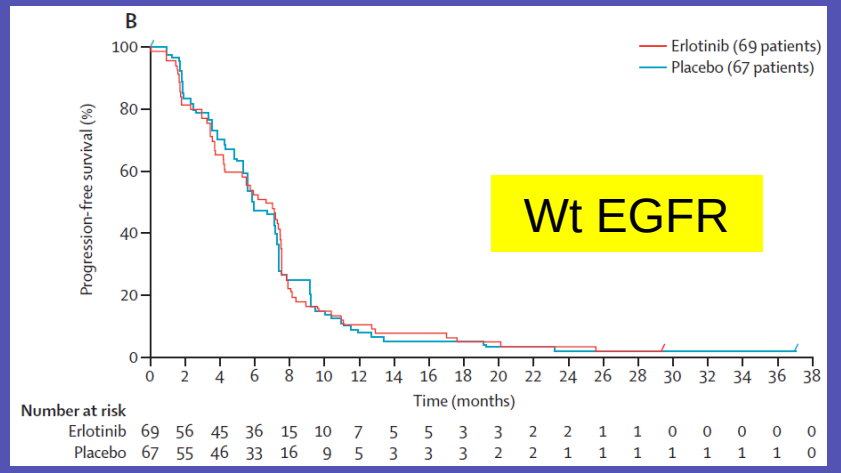
Y a-t-il un intérêt à combiner séquentiellement CT et ITK EGFR?

- Pas d'AMM!
- EGFR non muté: échec en concomitant en 1ère ligne
- CT et ITK intercalés: amélioration SSP

Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial

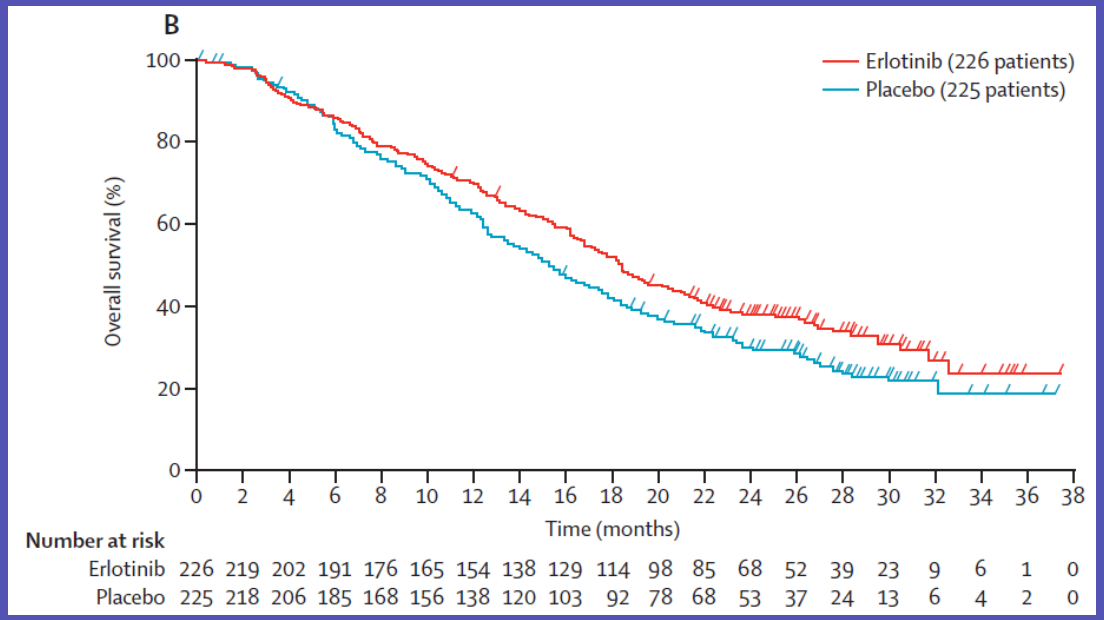


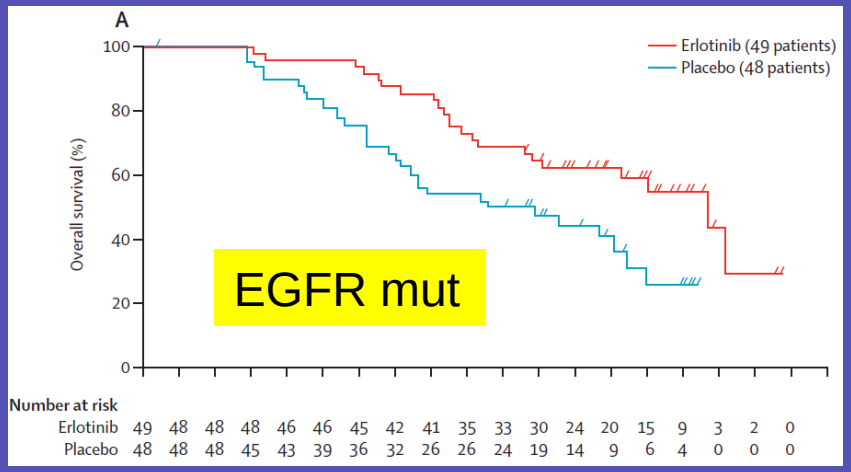


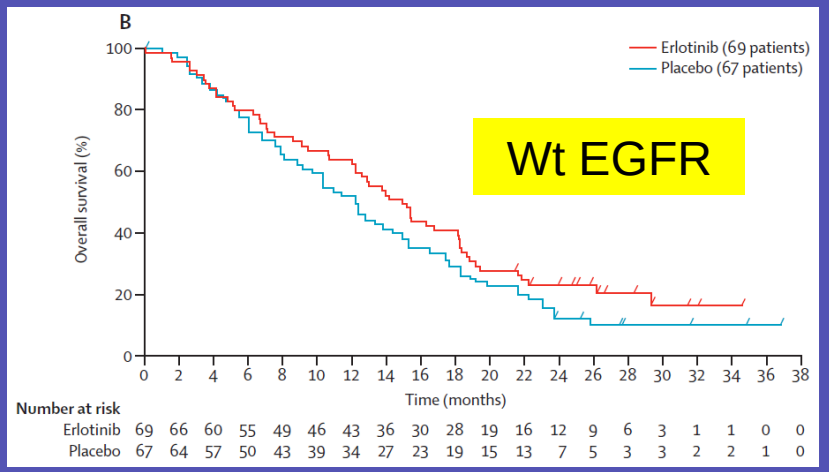


Wu et al, Lancet Oncol 2013

Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial

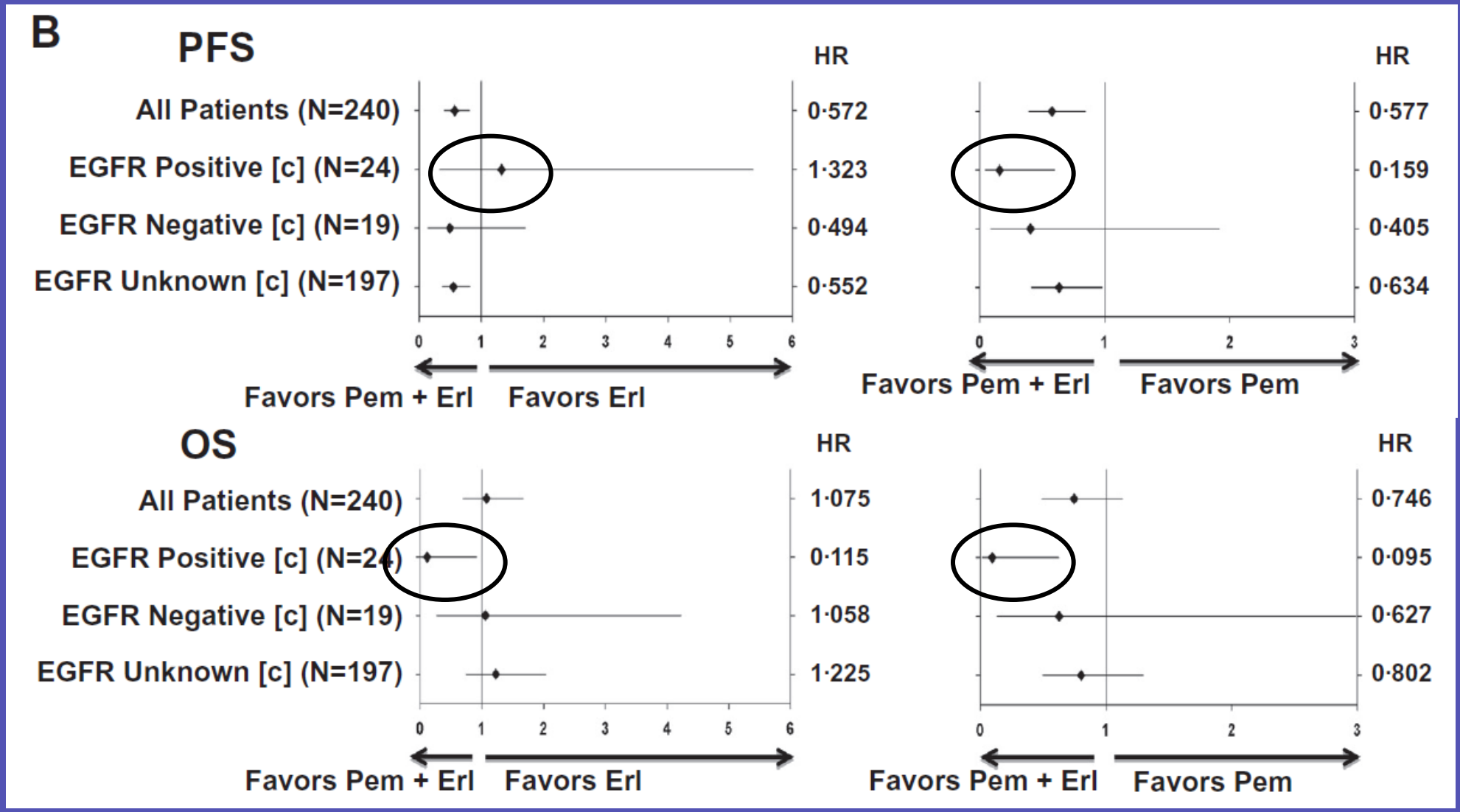






Wu et al, Lancet Oncol 2013

Three-arm randomised controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small cell lung cancer ☆

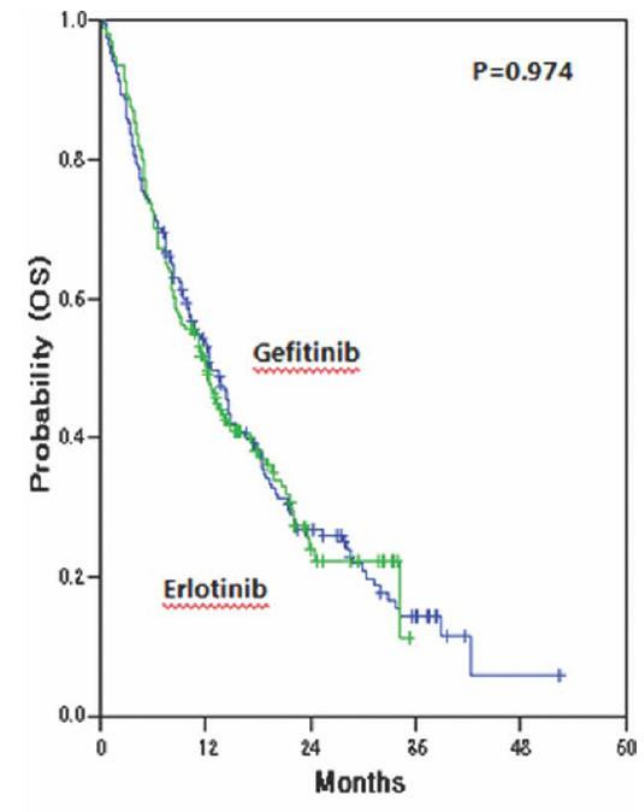


Lee et al, Eur J Cancer 2013

Quel ITK?

Comparison of Gefitinib Versus Erlotinib in Patients With Nonsmall Cell Lung Cancer Who Failed Previous Chemotherapy

Seung Tae Kim, MD; Jeeyun Lee, MD, PhD; Jeong-hoon Kim, MD; Young-Woong Won, MD; Jong-mu Sun, MD; Jina Yun, MD; Yeon Hee Park, MD, PhD; Jin Seok Ahn, MD, PhD; Keunchil Park, MD, PhD; and Myung-Ju Ahn, MD, PhD



Cancer 2010

Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations

Jenn-Yu Wu[a], Shang-Gin Wu[a], Chih-Hsin Yang[b], Yih-Leong Chang[c], Yeun-Chung Chang[d], Ya-Chieh Hsu[e], Jin-Yuan Shih[e,*], Pan-Chyr Yang[e]

	Réponse	p	Survie	p
Erlotinib	75,4%	0,07	15m	0,82
Géfitinib	61,9%		18,1m	

Lung Cancer 2011

Erlotinib has better efficacy than gefitinib in adenocarcinoma patients without *EGFR*-activating mutations, but similar efficacy in patients with *EGFR*-activating mutations

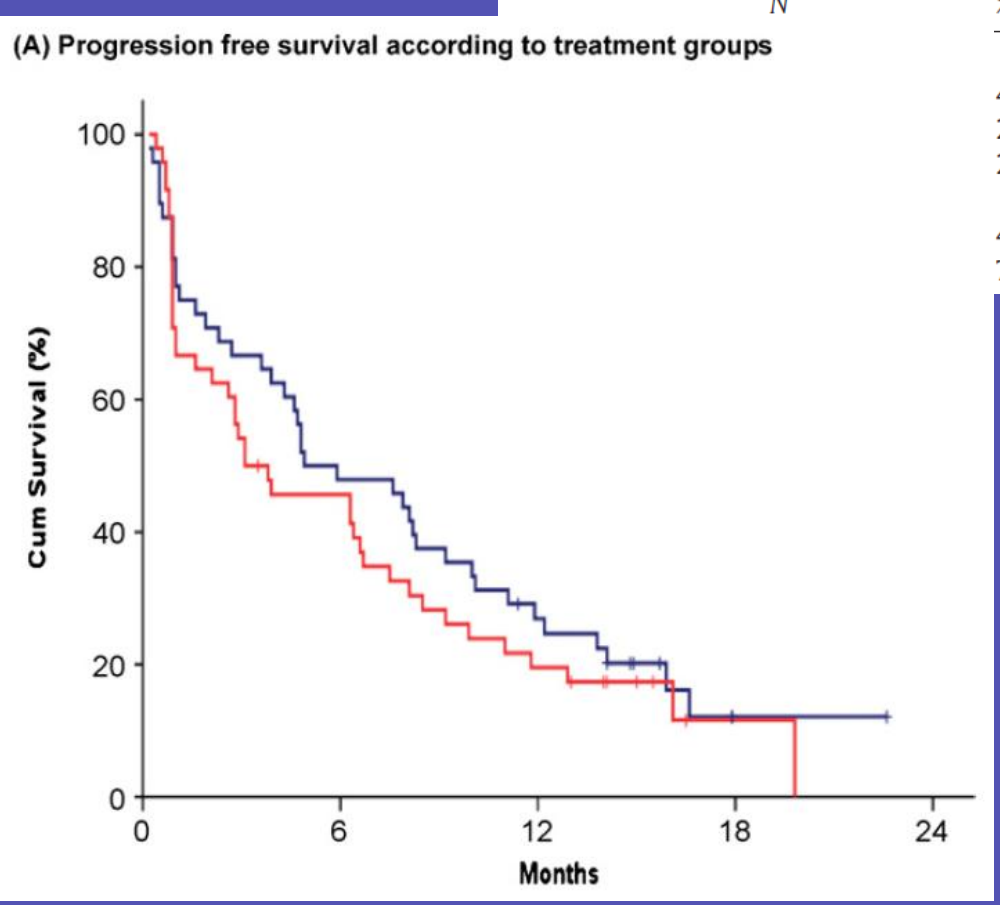
EXPERIMENTAL AND THERAPEUTIC MEDICINE 3: 207-213, 2012

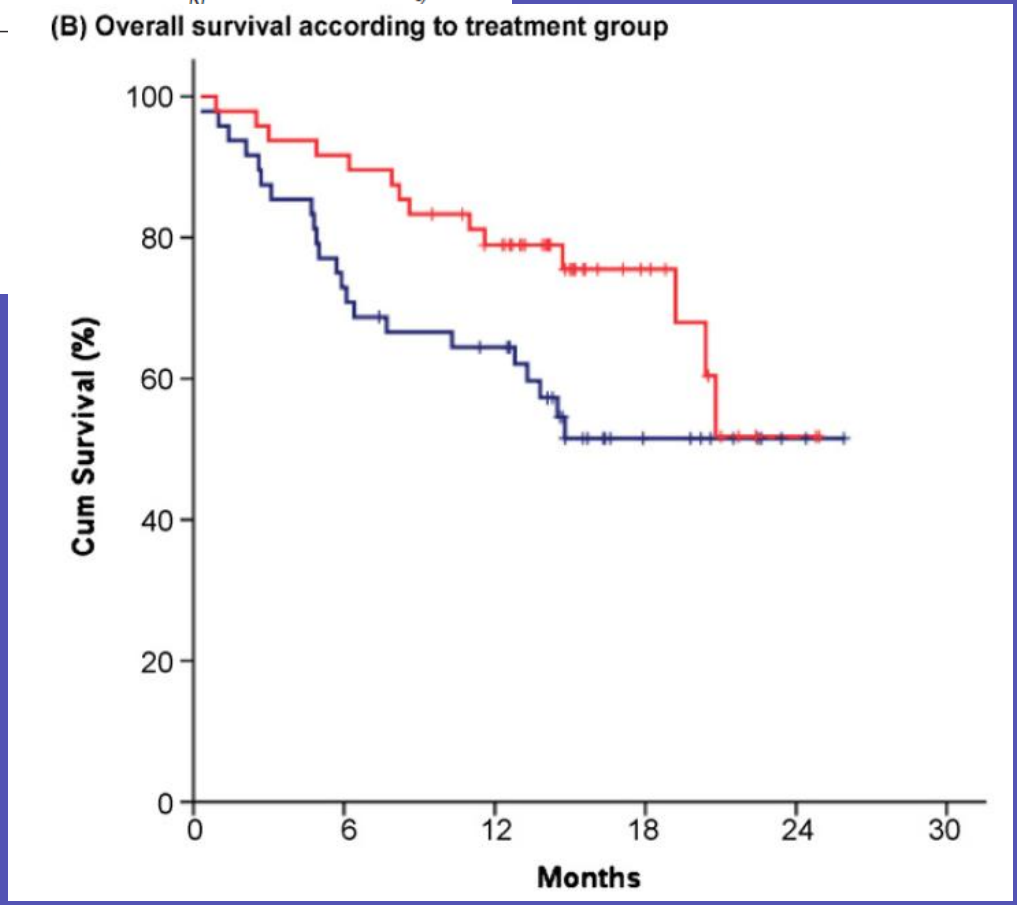
Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy☆

Seung Tae Kim[a,d,1], Ji Eun Uhm[a,1], Jeeyun Lee[a], Jong-mu Sun[a], Insuk Sohn[b], Seon Woo Kim[b], Sin-Ho Jung[c], Yeon Hee Park[a], Jin Seok Ahn[a], Keunchil Park[a], Myung-Ju Ahn[a,*]

Best response rate and disease control rate of treatment groups.

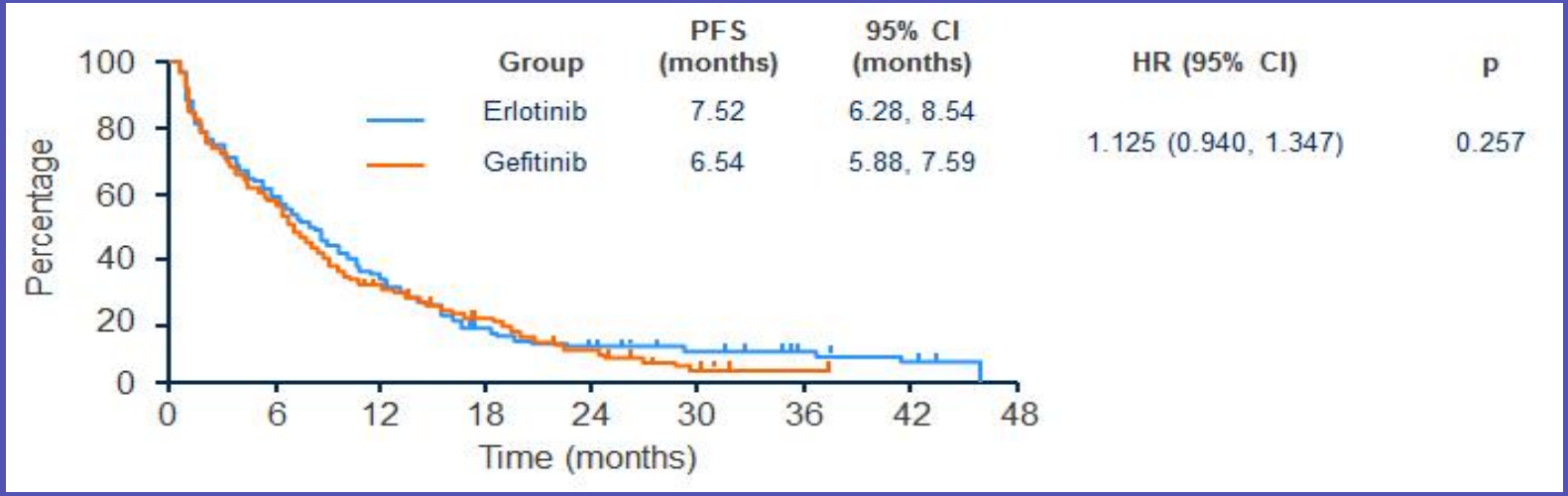
	Gefitinib ($n=48$)		Erlotinib ($n=48$)	
	N	%	*N*	%
		2.1		
		45.8		
		25.0		
		25.0		
		2.1		
		47.9		
		72.9		





Lung Cancer 2012

8041: Randomized phase III study comparing gefitinib (G) with erlotinib (E) in patients (pts) with previously treated advanced lung adenocarcinoma (LA): WJOG 5108L – Katakami N et al

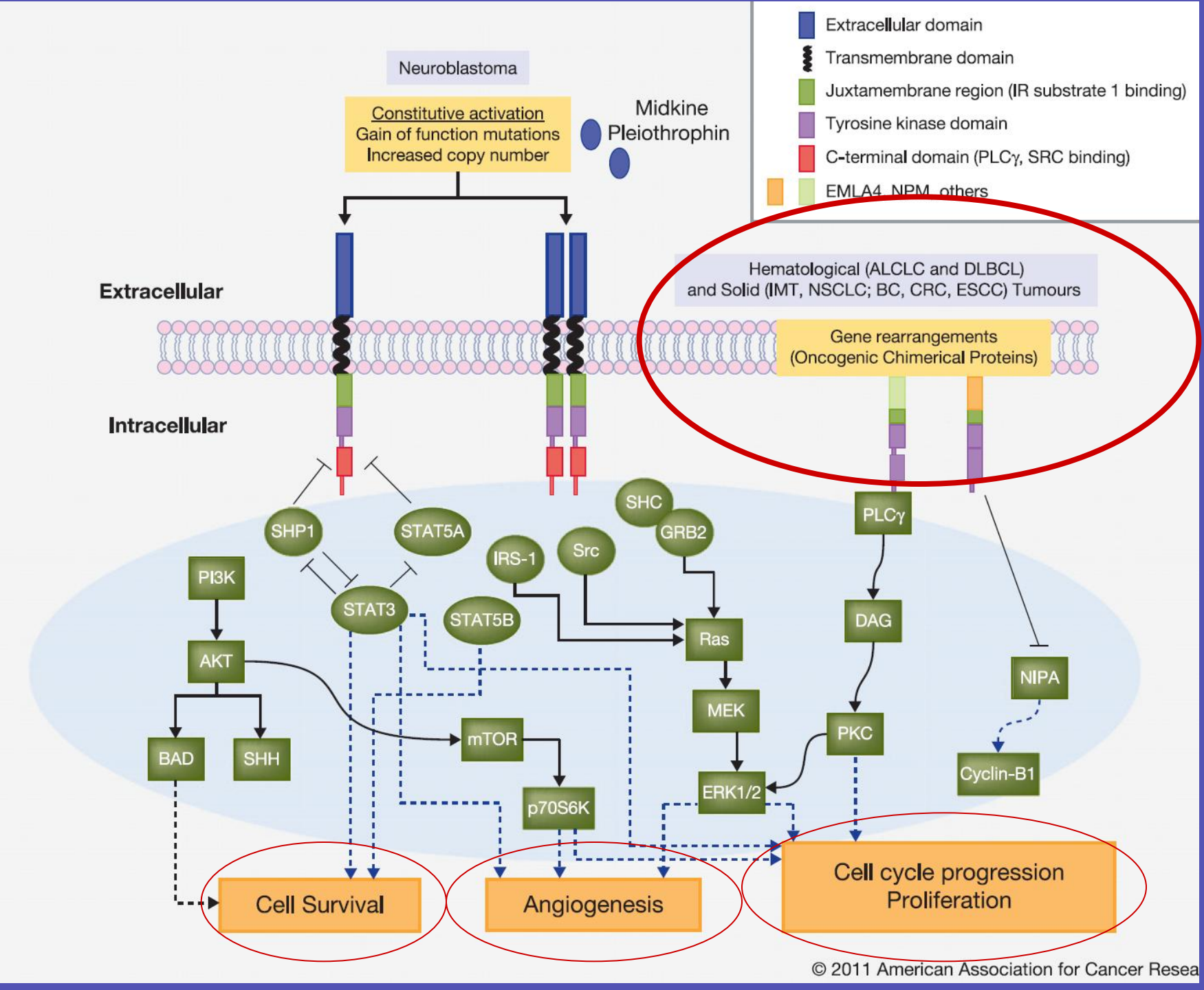


Group	PFS (months)	95% CI (months)	HR (95% CI)	p
Erlotinib	7.52	6.28, 8.54	1.125 (0.940, 1.347)	0.257
Gefitinib	6.54	5.88, 7.59		

- OS: 24,5 vs 22,8 m (HR 1,038, IC 95% 0,833-1,394)
- SSP et OS médianes en cas de mutation activatrice (erlotinib vs gefitinib)
  - SSP: 10,1 vs 8,9 m (p=0,532)
  - OS: 32,0 vs 26,6 m (p=0,111)

Katakami et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8041)

EML4-ALK



Prot aNle conserve domaine intracellulaire de ALK tandis que le partenaire intervient dans la dimérisation → dimérisation indépendante du ligand et activation constitutive de la kinase

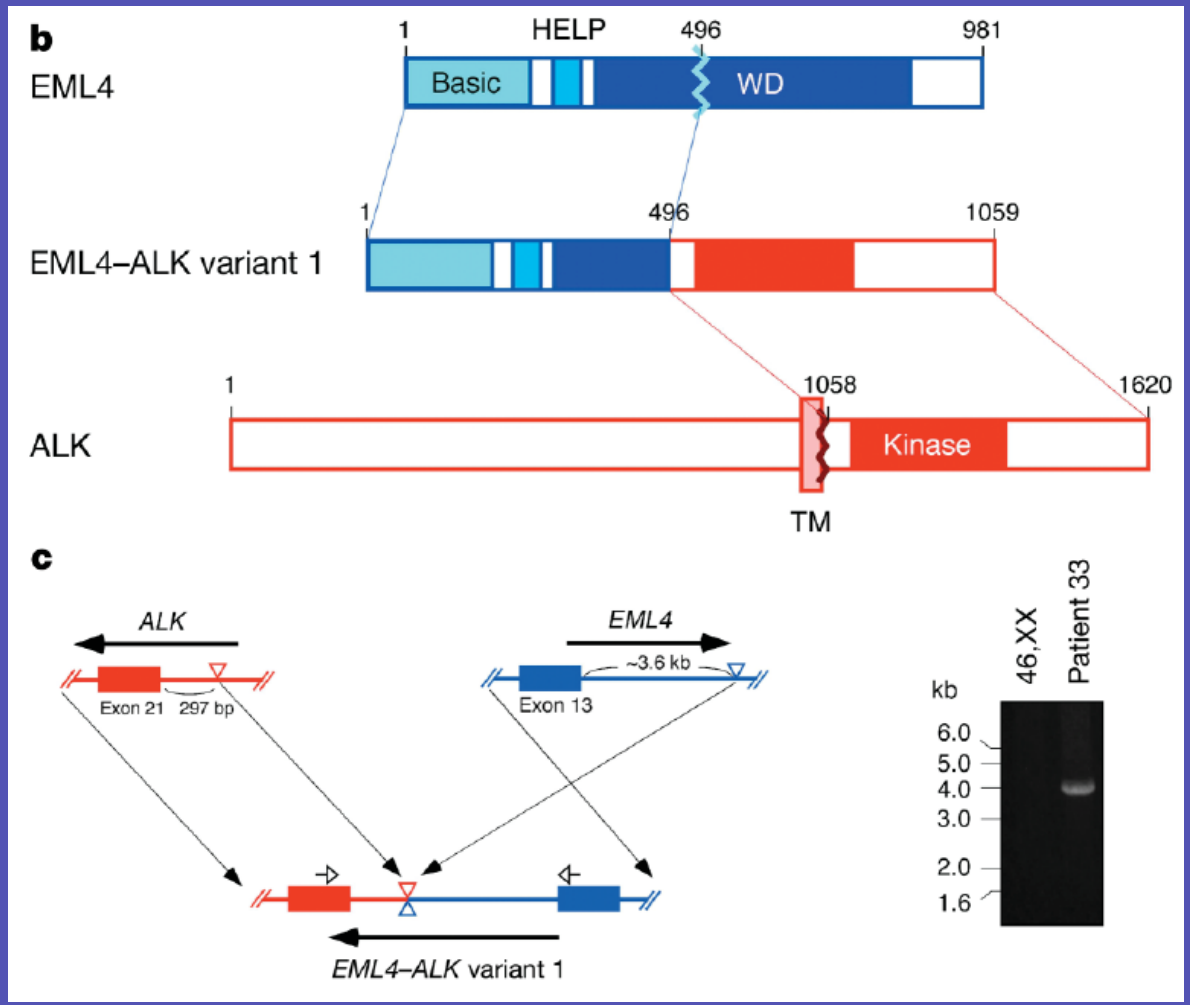
"ONCOGENE ADDICTION"

Grande et al; Mol Cancer Ther 2011

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

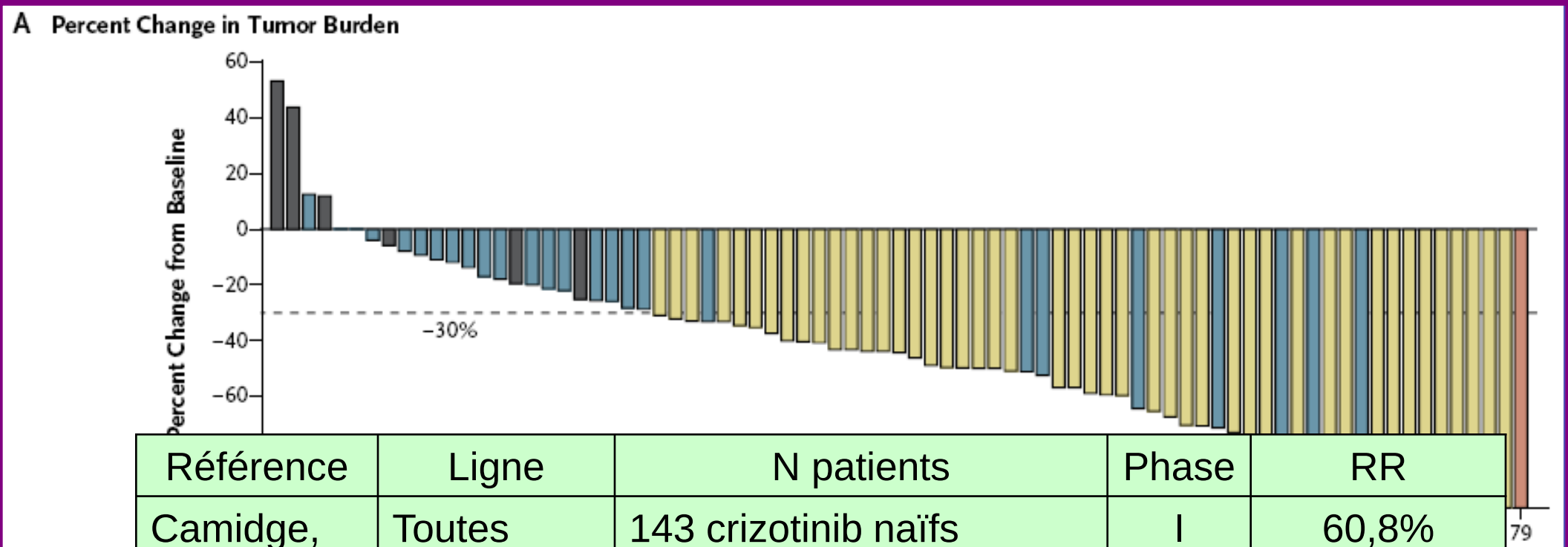
echinoderm microtubule-associated protein-like 4



Soda et al; Nature 2007

Crizotinib

Kwak, NEJM 2010



Référence	Ligne	N patients	Phase	RR
Camidge, 2012	Toutes	143 crizotinib naïfs 1ère ligne Rattrapage(2->3 lignes)	I	60,8% 63,6% 58,7-64,5%
Kim, 2012	Rattrapage	803 crizotinib naïfs 261 “population mature”	II	46% 60%

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Key patient inclusion criteria

- ALK+ by central FISH testing[a]
- Stage IIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0-2
- Measurable disease

(n=318)

R

Crizotinib 250 mg BID, 21-day cycle (n=159)

Stratification

- ECOG PS, brain metastases, prior EGFR TKI

Pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 IV, day 1, 21-day cycle (n=159)

Crossover to crizotinib on profile 1005

Secondary endpoints

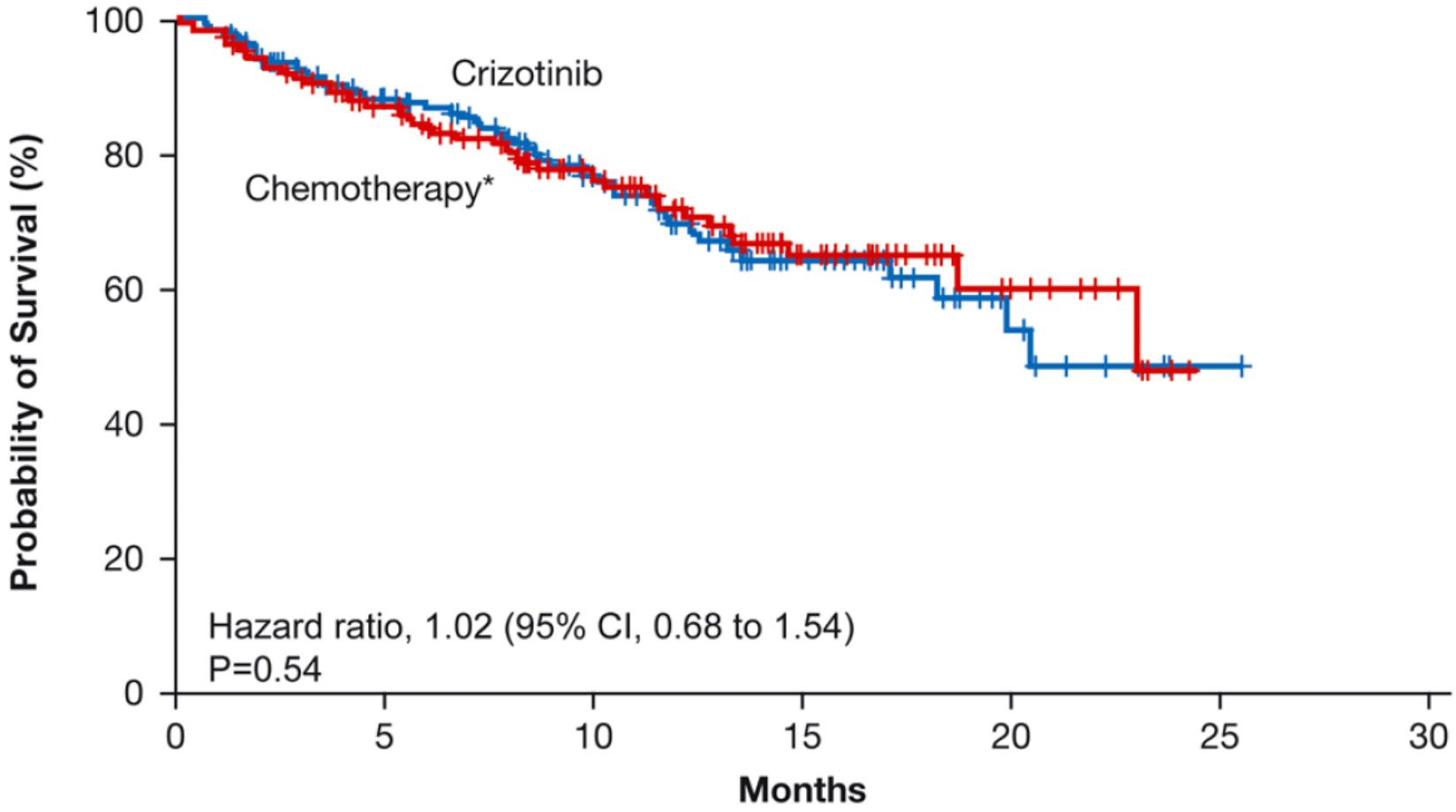
- ORR, DCR, DR, OS, safety, pt reported outcomes

Primary endpoint

- PFS (RECIST 1.1 by independent radiology review)

[a]ALK status determined using standard ALK break-apart FISH assay

Shaw et al. NEJM 2013



	Crizotinib (n=173)	Chemotherapy (n=174)

No. at Risk

Crizotinib	173	129	83	37	11	1	0
Chemotherapy	174	129	84	34	10	0	

No at risk

Crizotinib	172	93	38	11	2	0
Pemetrexed	99	36	12	3	1	0
Docetaxel	72	13	3	1	0	

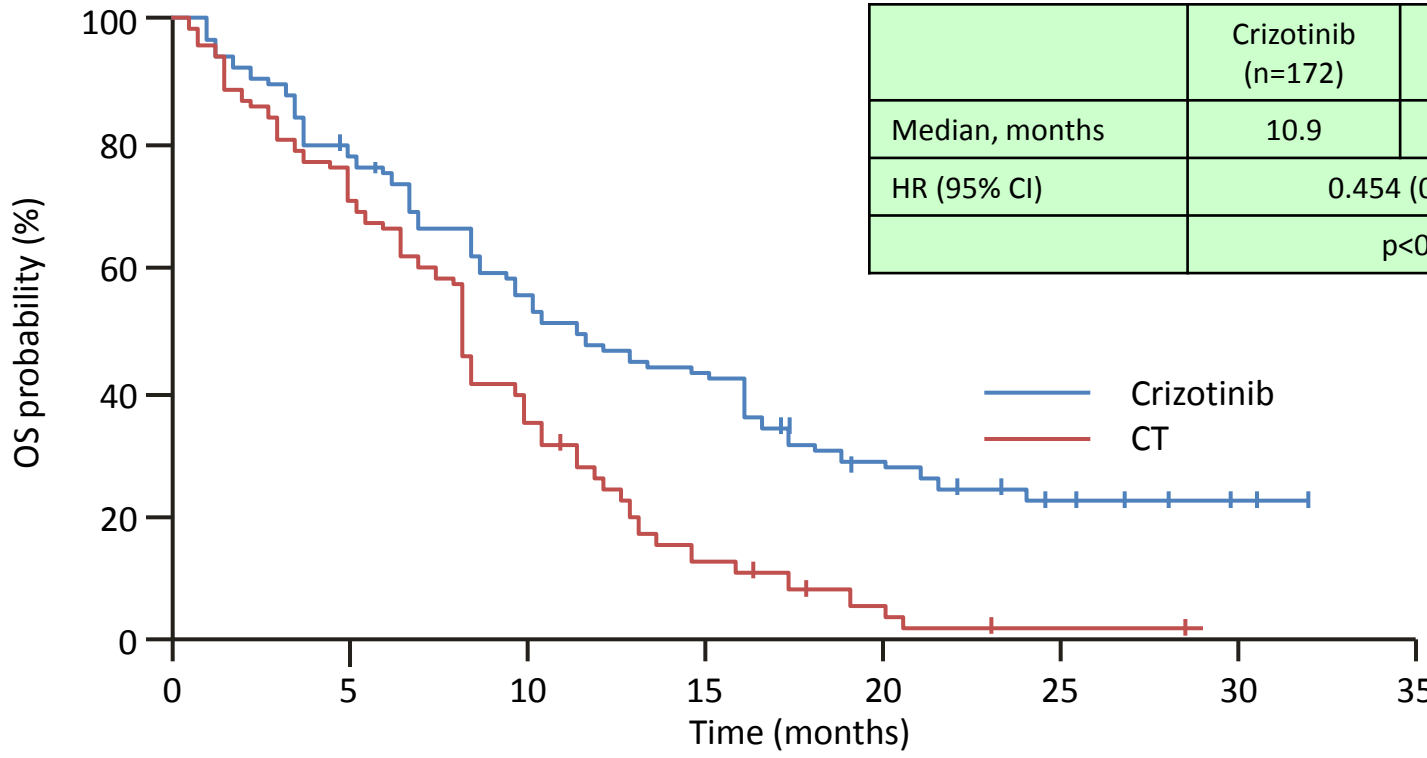
[a]vs crizotinib

Shaw et al. Ann Oncol 2012;Vol (suppl; abstr LBA1_PR)

8002: First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients (pts) with advanced *ALK*-positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014)

- **Key results**
  - Addition of crizotinib significantly improved PFS but not OS compared with CT alone

PFS



	Crizotinib (n=172)	CT (n=171)
Median, months	10.9	7.0
HR (95% CI)	0.454 (0.35, 0.60)	
	p<0.0001	

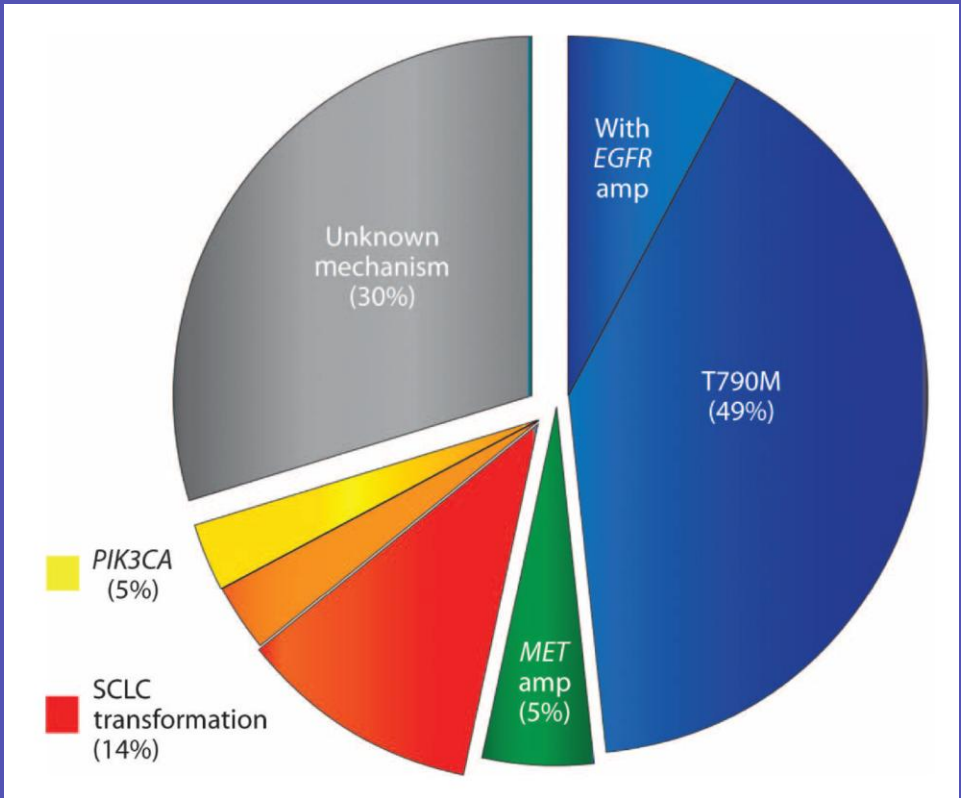
No. at risk								
Crizotinib	172	120	65	38	19	7	1	0
CT	171	105	36	12	2	1	0	0

Mok et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8002)

Nouveaux inhibiteurs de ALK

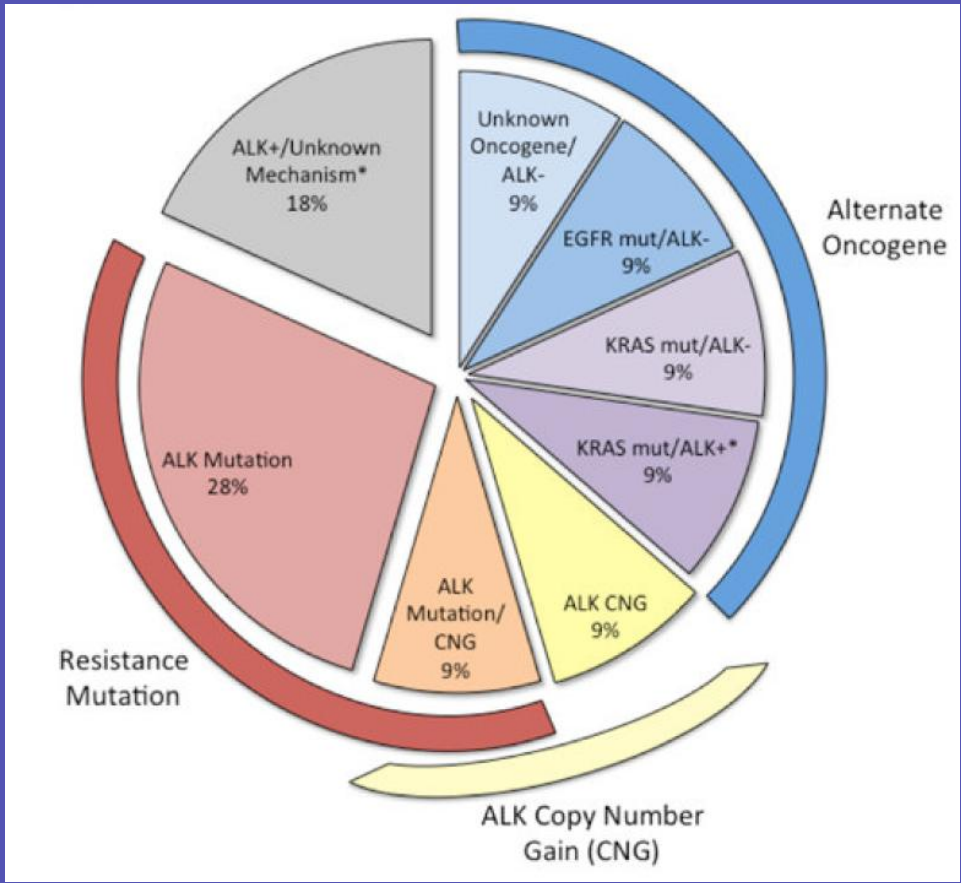
Référence	Molécule	Phase	RR
Kim, 2014	LDK378	I/II	58,5%
Kiura, 2012	CH5424802	I	85%
Nishio, 2012	CH5424802	II	85%
Gettinger, 2012	AP26113	I/II	73%
Felip, 2012	AUY922	II	32%

Problèmes des résistances



EGFR

Sequist et al, Sci Transl Med 2011



ALK

Doebele et al, Clin Cancer Res 2012

Quelle option à la progression ?

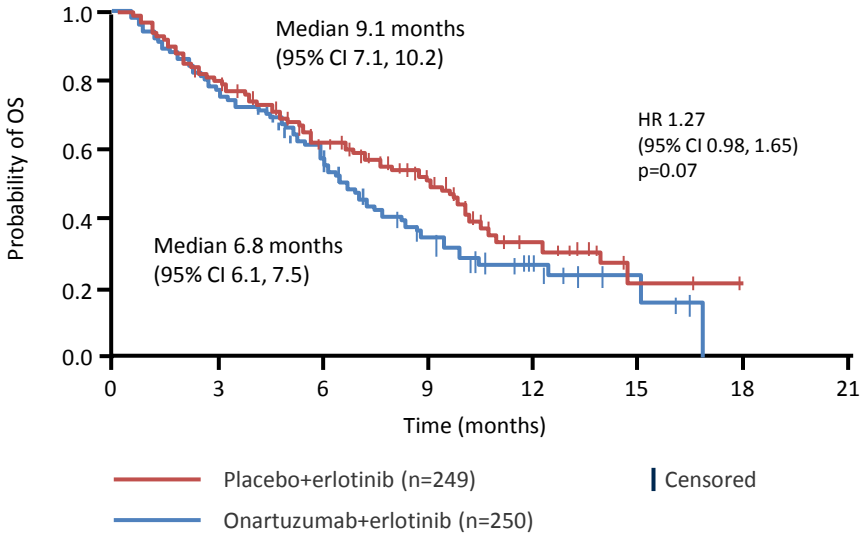
Biopsier site de progression pour objectiver type de résistance et adapter traitement

- EGFR
- ITK 3ème génération actif sur T790M
  - AZD9291
  - CO-1686
- Inhibiteur cMET
- …

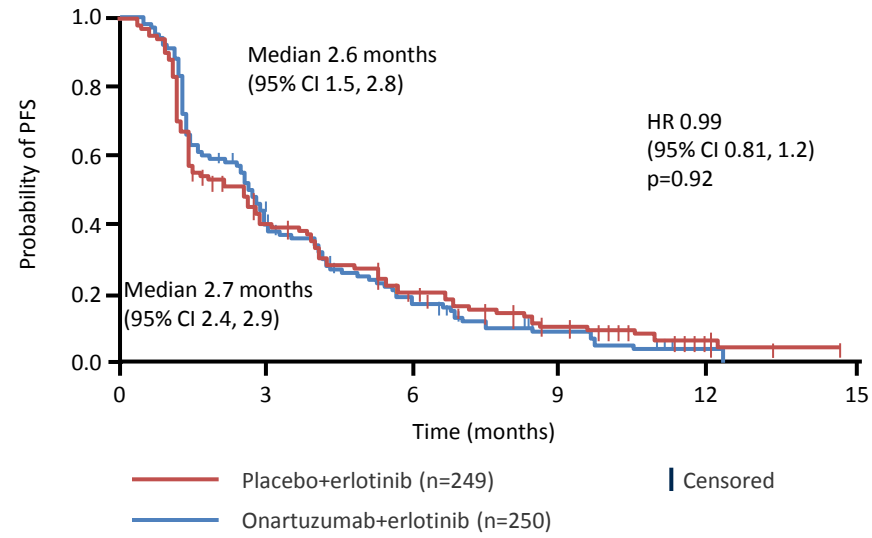
- ALK
- Inhibiteur 2de génération
  - Céritinib
  - CH5424802
  - AP26113
  - AUY922
- …

8000: Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial

OS



PFS

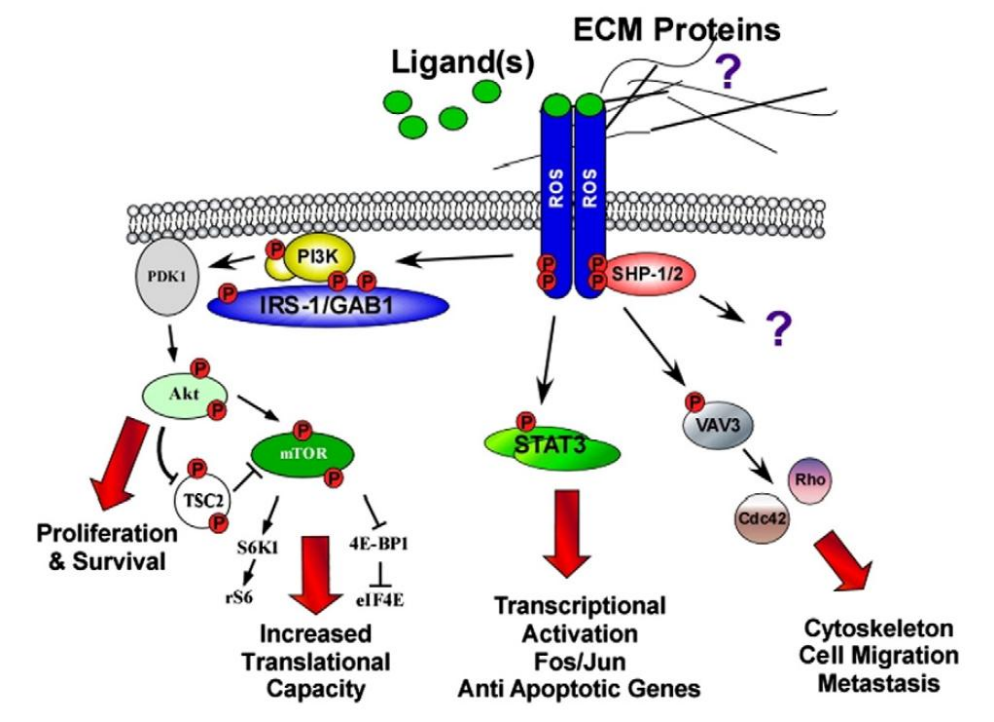


ORR 8.8% placebo+erlotinib vs. 6.4% onartzumab+erlotinib

Spigel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8000)

4. Futur des thérapies ciblées

ROS1



- Phase I
- 14 patients avec translocation ROS-1 translocation traitéspar crizotinib
- 9 (64%) réponse objective

Acquaviva et al Biochim Biophys Acta 2009

Shaw et al J Clin Oncol 30[Suppl]. 2012.

KRAS

Facteur prédictif de résistance aux ITK

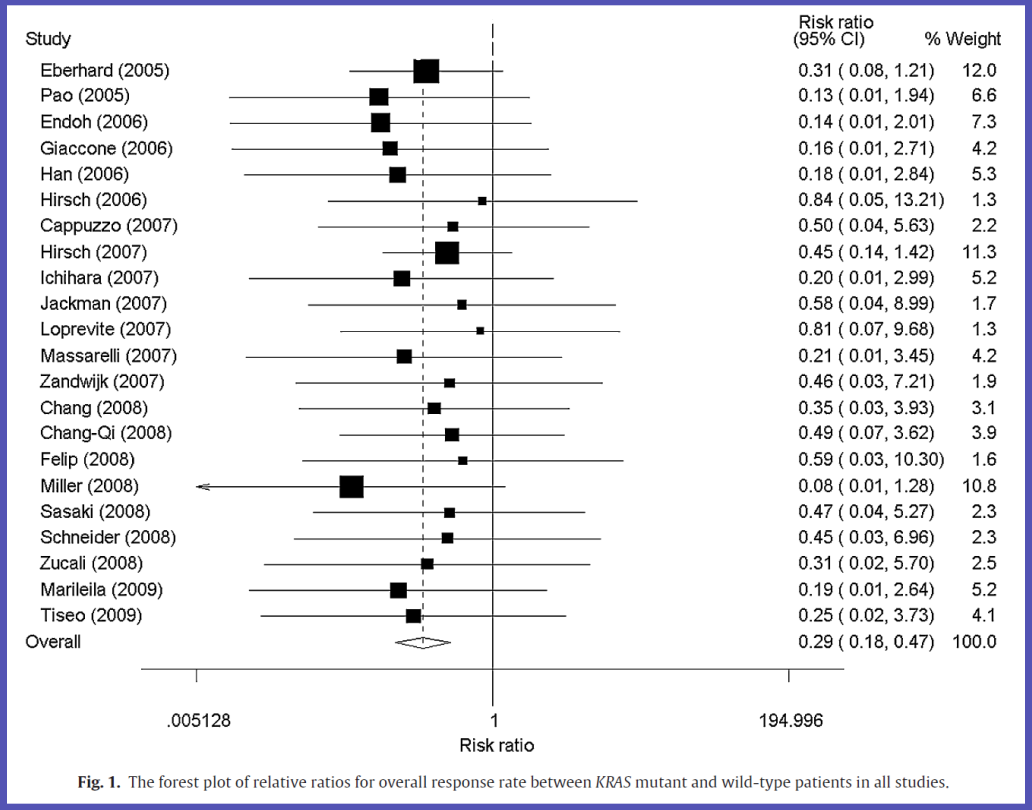
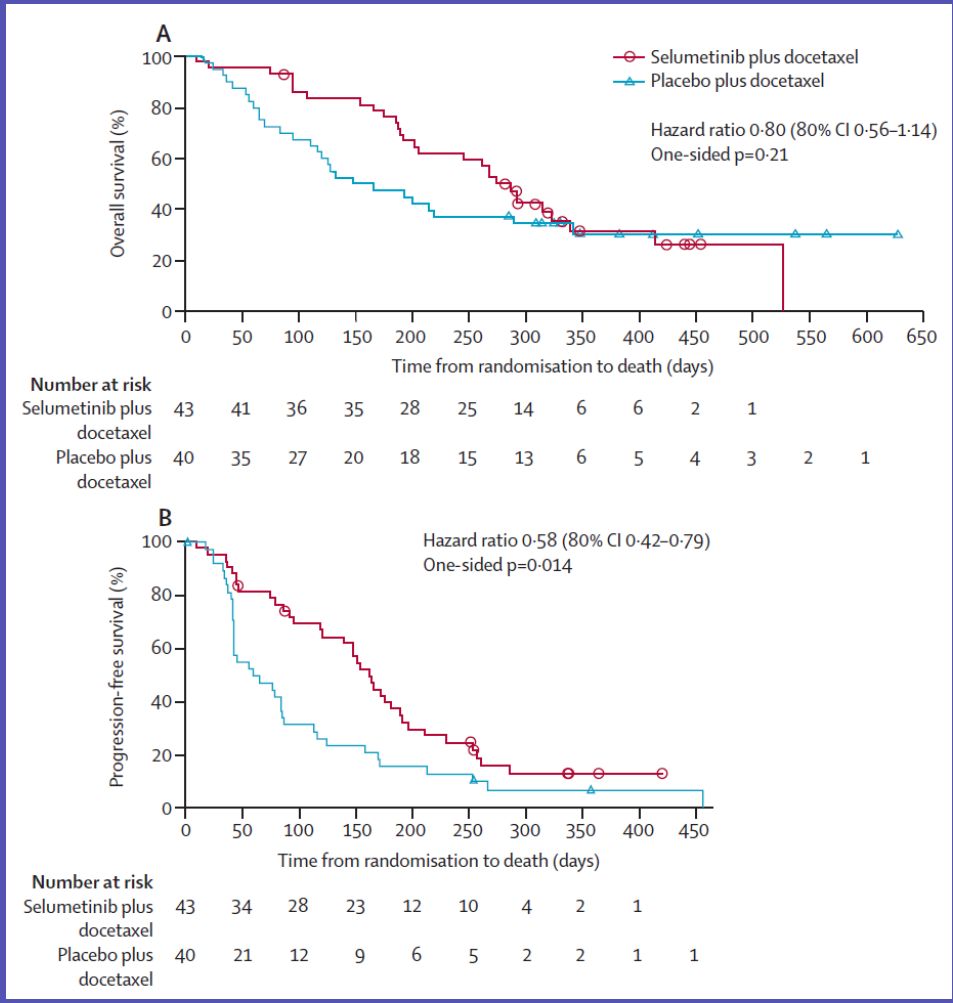


Fig. 1. The forest plot of relative ratios for overall response rate between *KRAS* mutant and wild-type patients in all studies.

Mao et al, Lung Cancer 2010

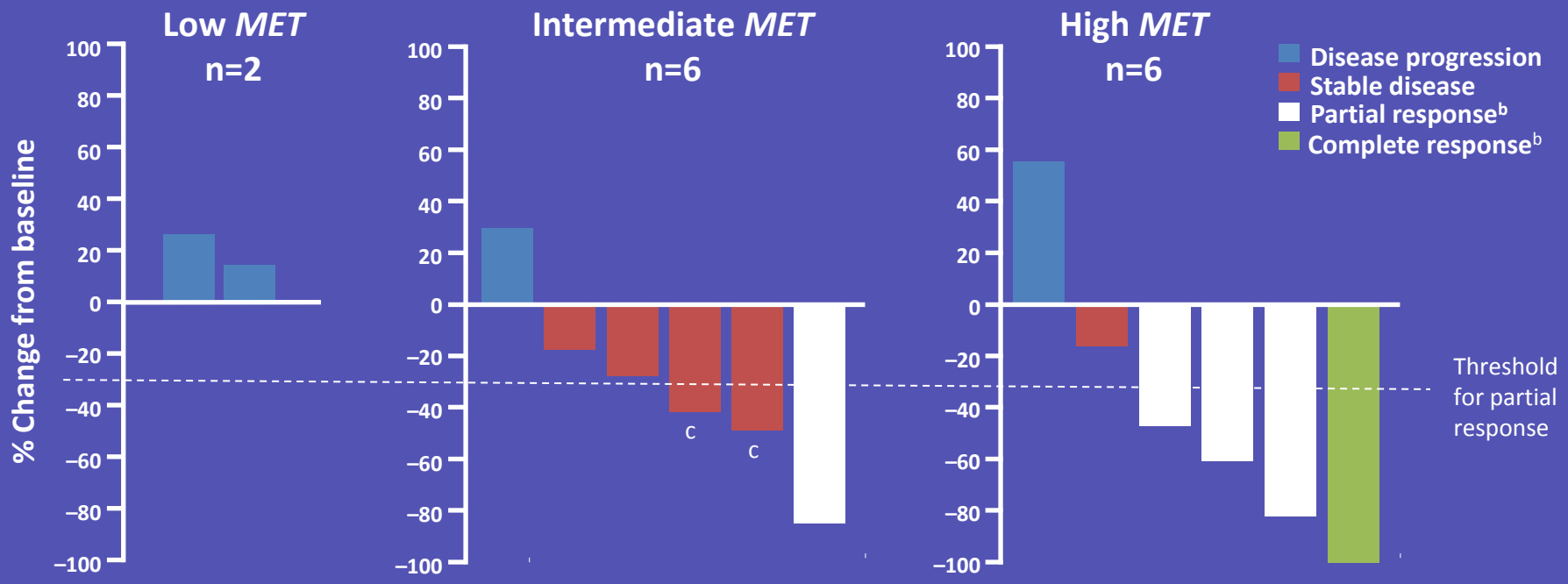
Selumetinib plus docetaxel for *KRAS*-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study



Janne et al, Lancet Oncol 2013

Amplification cMET

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



Camidge et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8001)

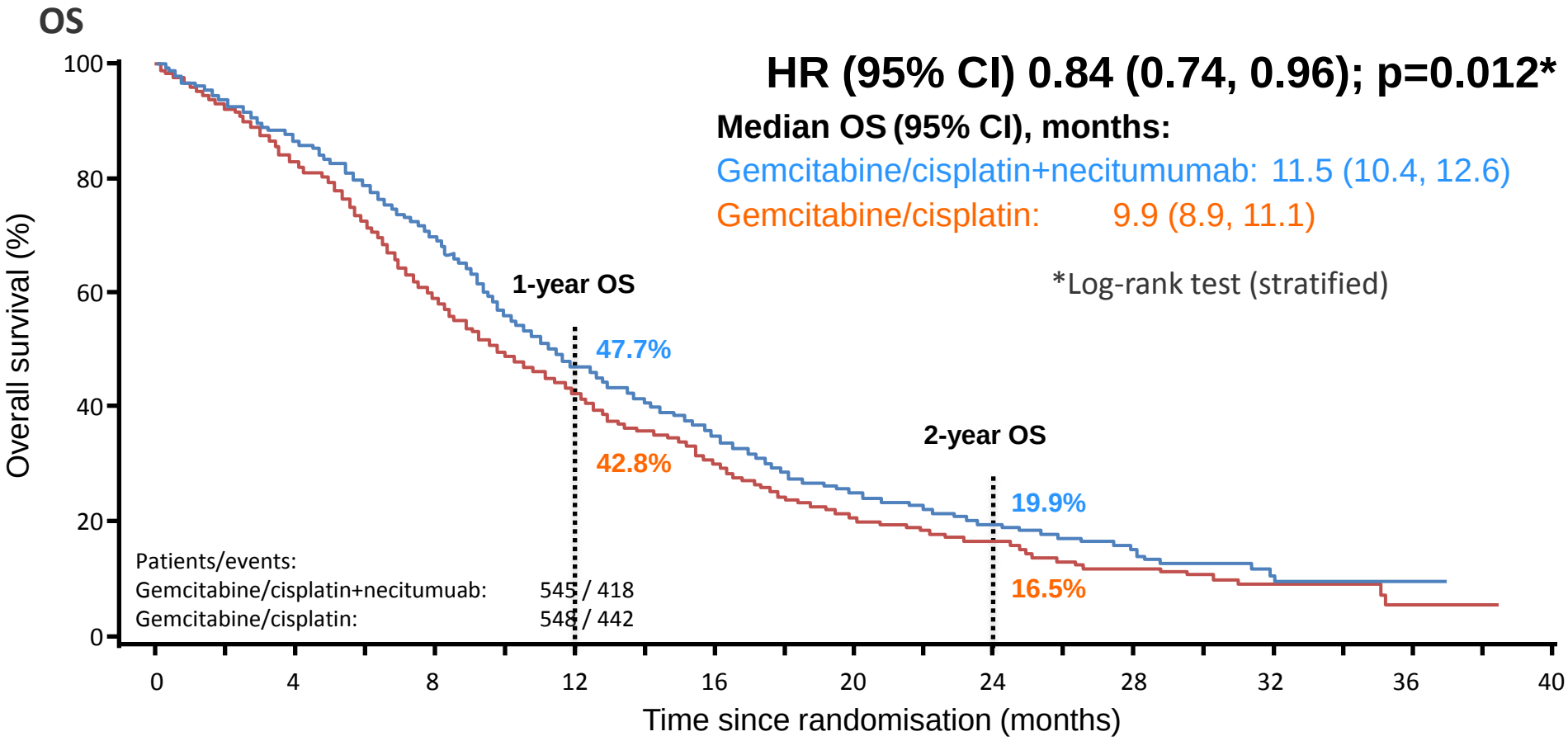
Autres examples de molécules intéressantes

- HER2: trastuzumab + CT, afatinib
- PI3K: inhibiteurs mTOR
- RET: cabozantinib, vandetanib, sunitinib, sorafenib
- BRAF (V600E): vemurafenib
- FGFR1: brivanib
- DDR2: activité *in vitro* imatinib, nilotinib, dasatinib

Quelle place pour les anticorps monoclonaux?

- Anti EGFR
  - Cible connue mais pas de sélection adéquate du groupe-cible
  - Pas d'AMM en Europe
- AntiVEGFR
  - Cible mal connue
  - Bévacizumab améliore un peu survie mais toxicité ++
  - Groupe-cible à définir

8008: A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC)

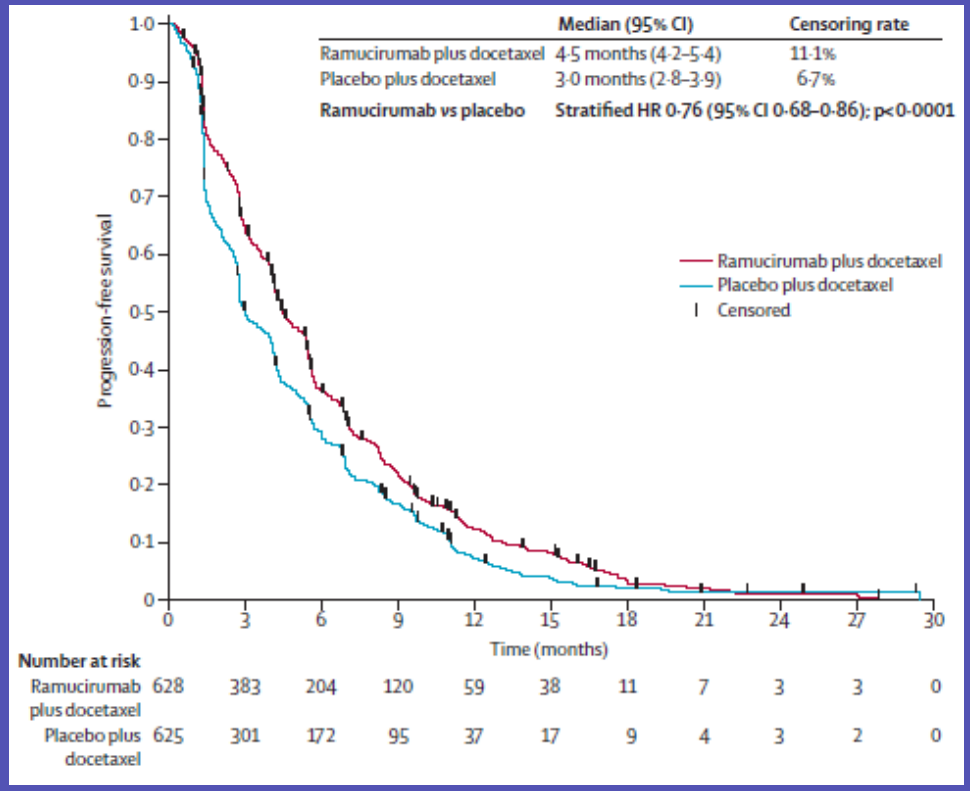


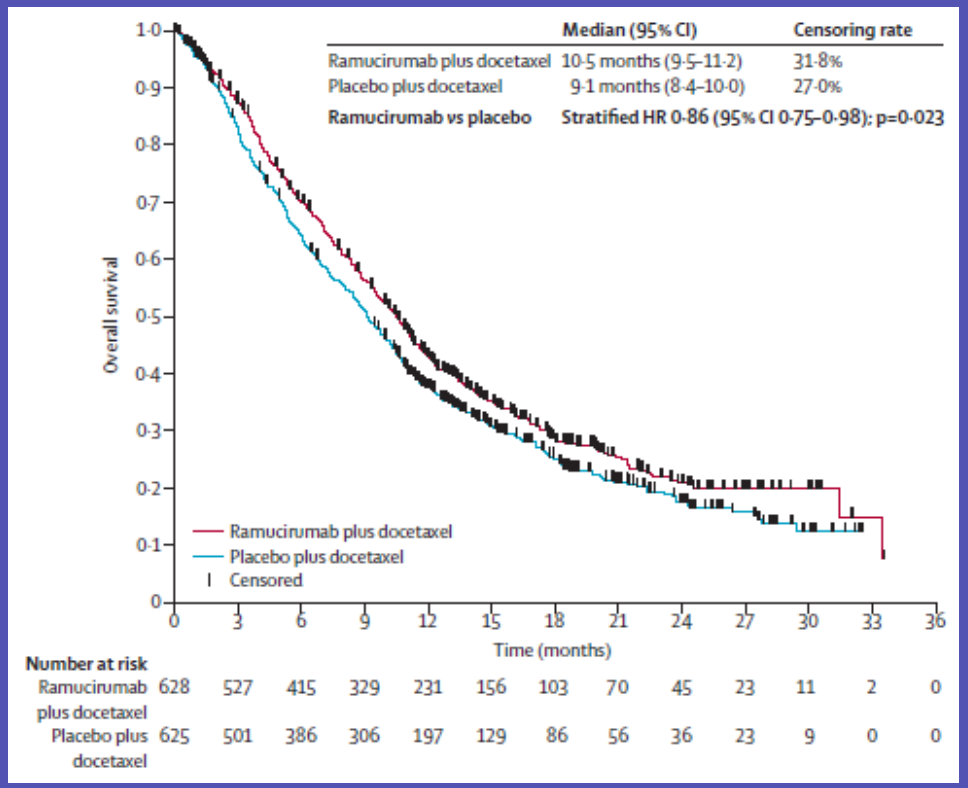
Follow-up time (median): Gemcitabine/cisplatin+necitumumab: 25.2 months; gemcitabine/cisplatin: 24.8 months

Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)

Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial

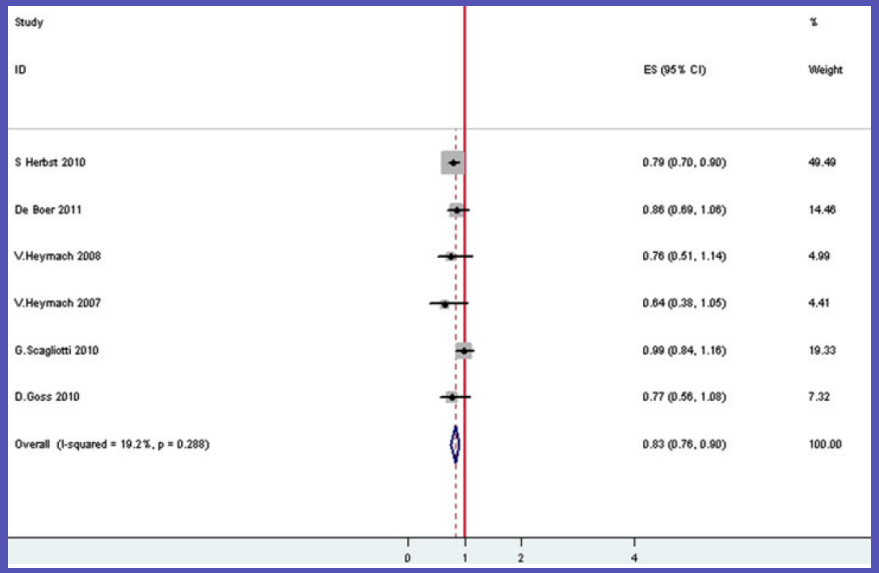
Edward B Garon, Tudor-Eliade Ciuleanu, Oscar Arrieta, Kumar Prabhash, Konstantinos N Syrigos, Tuncay Goksel, Keunchil Park, Vera Gorbunova, Ruben Dario Kowalyszyn, Joanna Pikiel, Grzegorz Czyzewicz, Sergey V Orlov, Conrad R Lewanski, Michael Thomas, Paolo Bidoli, Shaker Dakhil, Steven Gans, Joo-Hang Kim, Alexandru Grigorescu, Nina Karaseva, Martin Reck, Federico Cappuzzo, Ekaterine Alexandris, Andreas Sashegyi, Sergey Yurasov, Maurice Pérol

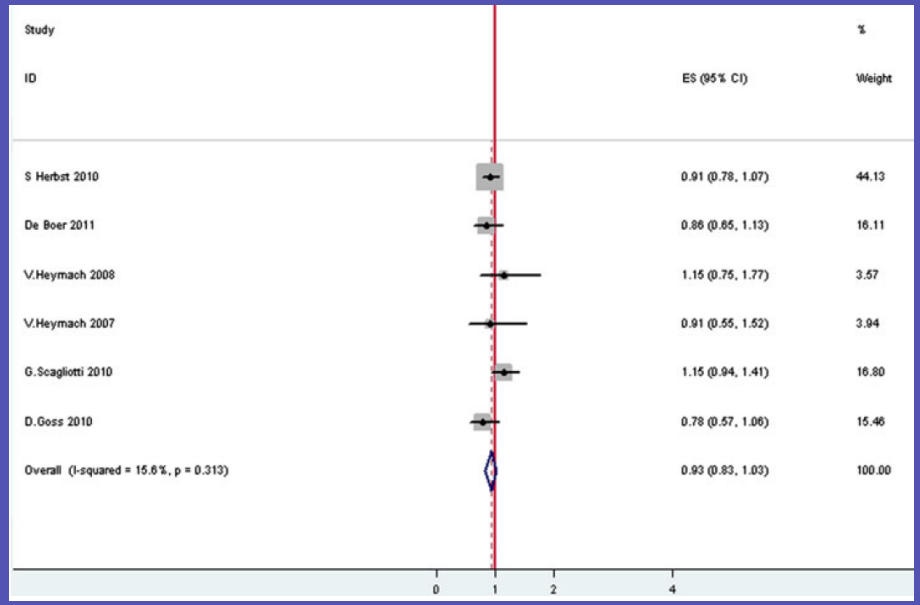


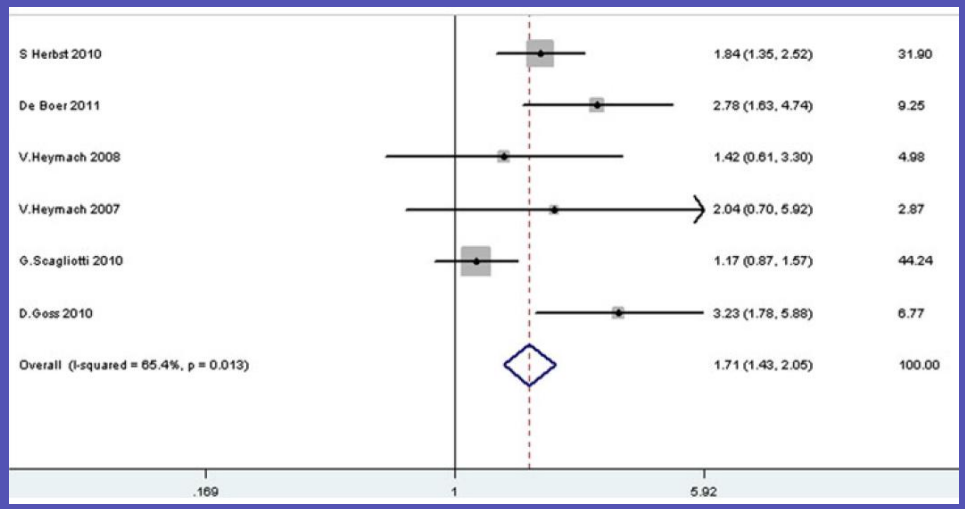


Lancet 2014: 665-73

Chemotherapy plus multitargeted antiangiogenic tyrosine kinase inhibitors or chemotherapy alone in advanced NSCLC: a meta-analysis of randomized controlled trials



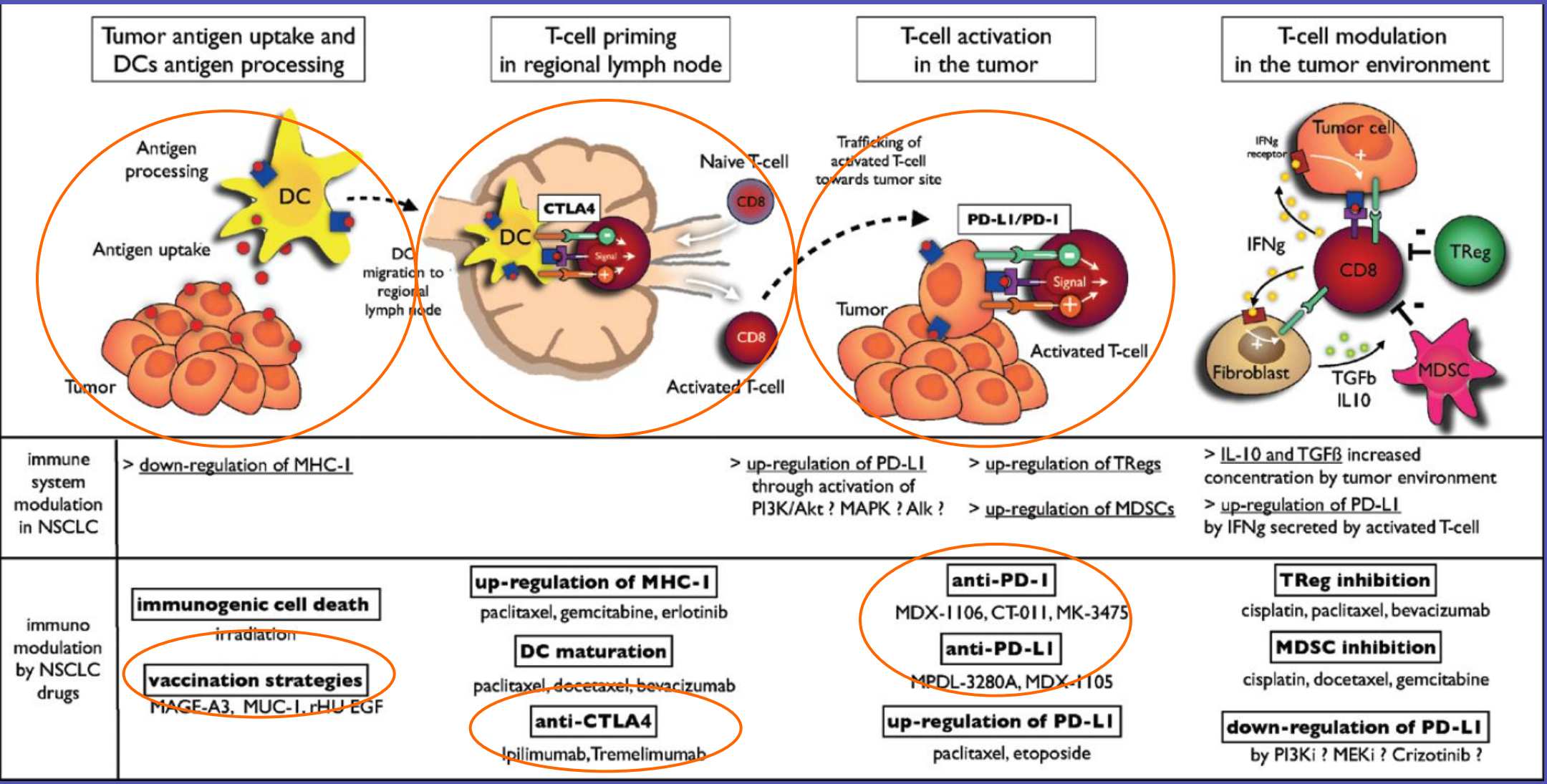




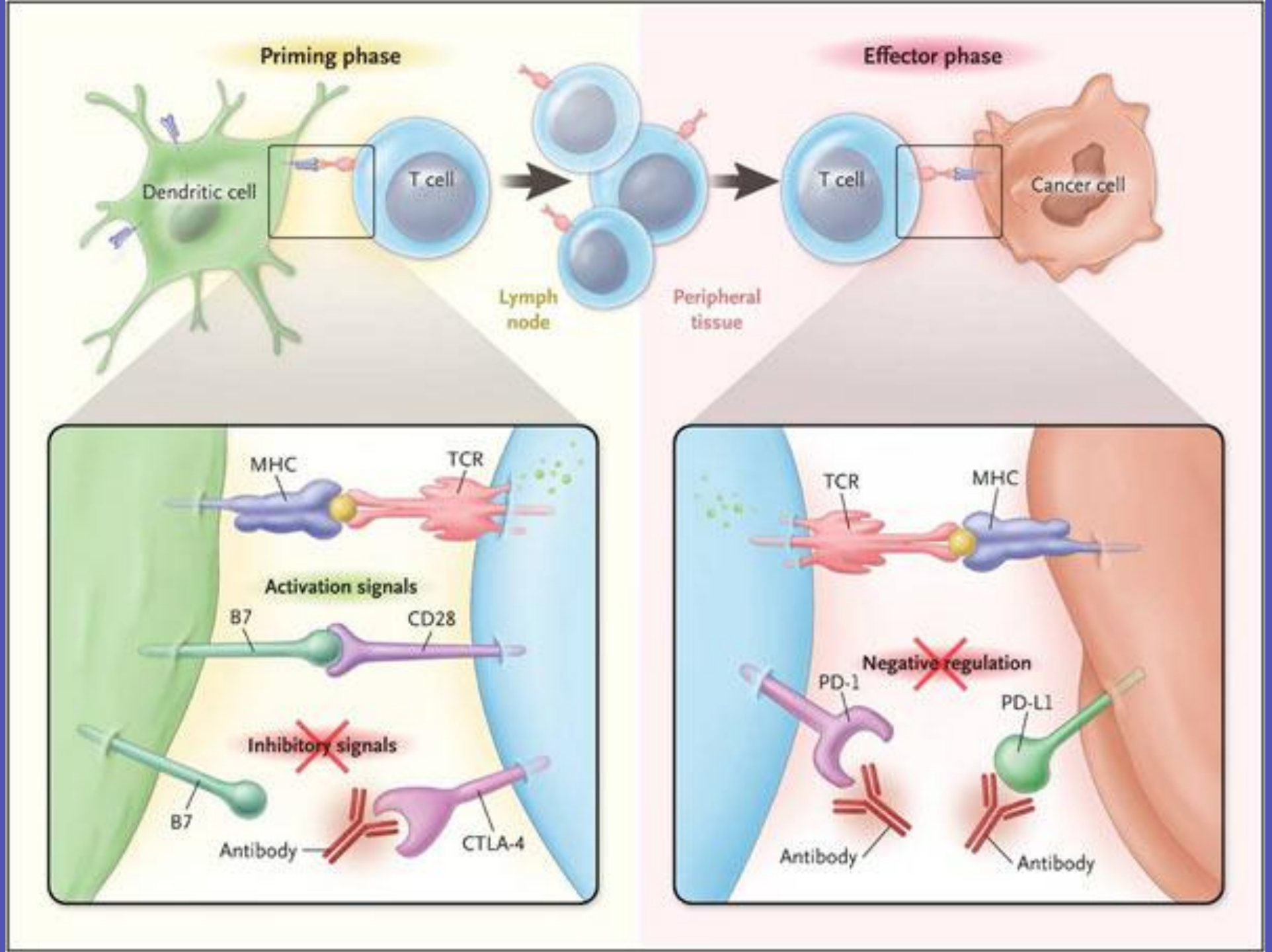
Toxicities	Chemotherapy plus multitargeted antiangiogenic TKI group (CMATKI)		Chemotherapy group ©)		CMATKI vs. C	
	n1	a1 (%)	n0	a0 (%)	OR (95% CI)	*p*
Rash	1,555	668 (43.0)	1,518	328 (21.6)	2.78 (2.37–3.26)	0
Diarrhoea	1,681	632 (37.6)	1,641	397 (24.2)	1.92 (1.65–2.24)	0.003
Hypertension	1,681	236 (14.0)	1,641	88 (5)	2.90 (2.19–3.84)	0.291
Nausea	1,555	350 (32.5)	1,518	236 (15.5)	0.71 (0.60–0.83)	0.201
Vomiting	1,469	199 (13.5)	1,477	254 (17.2)	0.75 (0.61–0.92)	0.206
Hemorrhage	1,681	222 (13.2)	1,641	179 (10.9)	1.27 (0.98–1.56)	0.025
Fatigue	1,681	551 (51.3)	1,641	552 (33.6)	0.95 (0.82–1.11)	0.321
Cough	1,091	247 (22.6)	1,056	206 (19.5)	1.08 (0.87–1.34)	0.772
Constipation	1,469	223 (15.2)	1,477	235 (15.9)	0.95 (0.78–1.17)	0.245
Anorexia	1,595	373 (23.4)	1,600	344 (21.5)	1.12 (0.95–1.33)	0.029
Alopecia	1,295	321 (24.8)	1,245	328 (26.3)	0.91 (0.75–1.10)	0.413

Xiao et al, Eur J Clin Pharmacol 2013

5. Quelques mots d’immunothérapie



Champiat et al, J Thorac Oncol 2014


Priming phase
Effector phase
Dendritic cell
T cell
Lymph node
Peripheral tissue
T cell
Cancer cell
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

8007: Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC)

	RECIST v1.1	**Immune-related response criteria**
ORR %(IC 95%)	26 (14-42)	47 (32-62)
SSP médiane (IC 95% CI), sem	27 (13,6-45,0)	37 (27-NR)

– Effets secondaires >5% patients: fatigue (22%), prurit (13%), hypothyroidisme (9%), dermatite acnéiforme (7%), diarrhée (7%), dyspnée (7%), rash (7%)

Rizvi et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8007)

8022: Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC

	Nivolumab+erlotinib (n=21)
ORR	19%
SSP	
SP (IC 95%) à 24 sem	51% (28-70)
SSP Médiane (range), sem	29,4 (4,6-81,7+)
OS	
Survie à 1 an (IC 95%)	73% (46-88)
Survie médiane (range), sem	Non atteinte (10,7+-86,9+)

Rizvi et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8022)

6. Rôle des consultations multidisciplinaires

O27.07 MOLECULAR MULTIDISCIPLINARY TUMOR BOARD (MMTB) FOR LUNG CANCER PATIENTS: 2-YEAR EXPERIENCE REPORT

- Cliniciens, unité phase I, pathologistes et biologistes.
- 245 pts
- Oncogenic drivers
  - ALK 10%
  - EGFR mut 24%
  - KRAS mut 30%
  - PI3KCA mut 0,4%
  - BRAF mut 3%
  - HER2 mut 1%
  - FGFR1 amplification 3%
  - Autres mutations 14%

- Recommendations
  - ✧ Inclusion étude 75 pts (31%)
  - ✧ Prescription selon AMM 49 pts (20%)
  - ✧ Prescription hors AMM 18 pts (7%)
  - ✧ Expanded access program 18 pts (7%).

- Ont reçu le traitement ciblé proposé
  - ✧ D'emblée 63 (42%)
  - ✧ A la progression 16 (11%)

J Thorac Oncol 8 Suppl 2, 2013

Quelle importance?

Table 2. Oncogenic Drivers Identified and Targeted Treatments Receive

Gene With Mutational or Structural Change	Genotyping, N Any (n = 1007)[a,b]
Any gene(s)	623 (62) [59-65]
Singletons[d]	
KRAS	245 (24) [22-27]
EGFR (sensitizing)[e]	175 (17) [15-20]
exon19 del	103 (10) [9-12]
L858R	64 (6) [5-8]
G719X	5 (0.5) [0.2-1]
L861Q	5 (0.5) [0.2-1]
ALK (rearrangement)	80 (8) [6-10]
EGFR (other)[f]	35 (4) [3-5]
ERBB2 (formerly *HER2*)	23 (2) [2-4]
BRAF	18 (2) [1-3]
V600E	14 (1) [0.8-2]
Non-*V600E*	4 (0.4) [0.1-1]
PIK3CA	7 (0.7) [0.3-2]
MET (amplification)	6 (0.6) [0.2-1]
NRAS	5 (0.5) [0.2-1]
MEK1	2 (0.2) [0.03-1]
AKT1	0 [0-1]
Doubletons	
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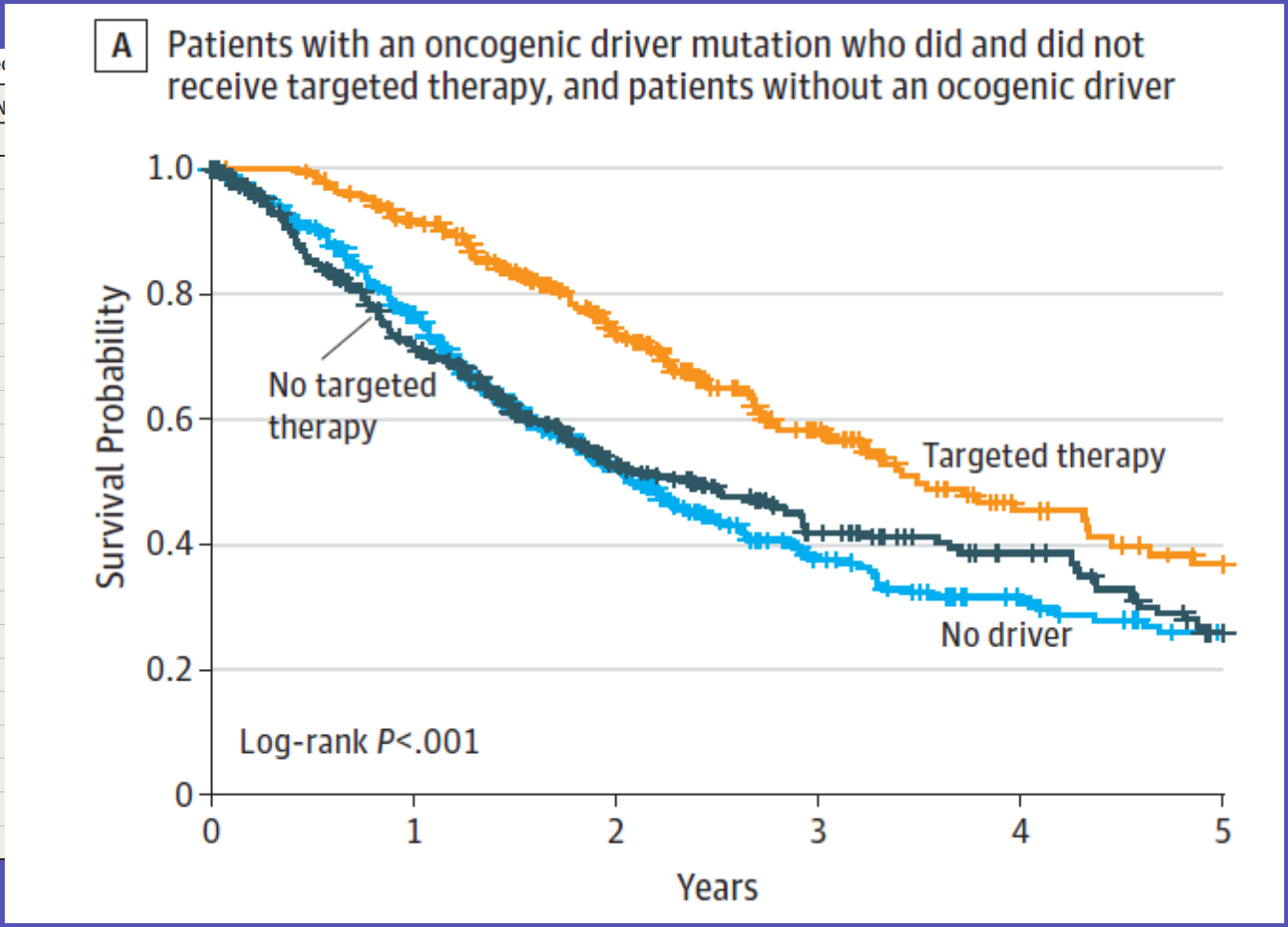
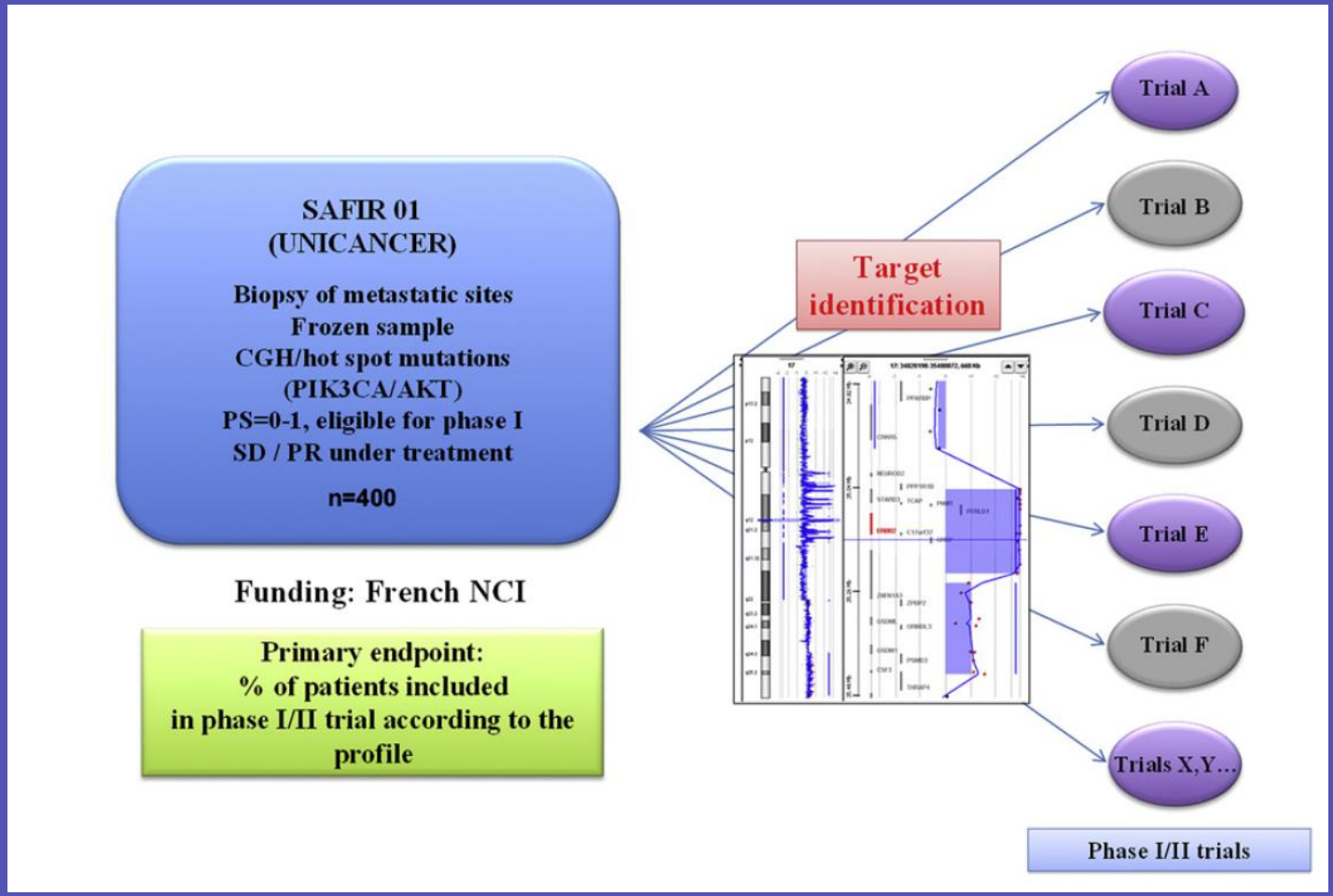


Kris et al, JAMA 2014

The challenge to bring personalized cancer medicine from clinical trials into routine clinical practice: The case of the Institut Gustave Roussy

Monica Arnedos[a,b], Fabrice André[a,b], Françoise Farace[b,c], Ludovic Lacroix[b,c], Benjamin Besse[a,b], Caroline Robert[a,b], Jean Charles Soria[a,b], Alexander M.M. Eggermont[d,]*



Mol Oncol 2012

Designs and challenges for personalized medicine studies in oncology: focus on the SHIVA trial

Christophe Le Tourneau · Maud Kamal · Olivier Trédan · Jean-Pierre Delord · Mario Campone · Anthony Goncalves · Nicolas Isambert · Thierry Conroy · David Gentien · Anne Vincent-Salomon · Anne-Lise Pouliquen · Nicolas Servant · Marc-Henri Stern · Anne-Gaëlle Le Corroller · Sébastien Armanet · Thomas Rio Frio · Xavier Paoletti

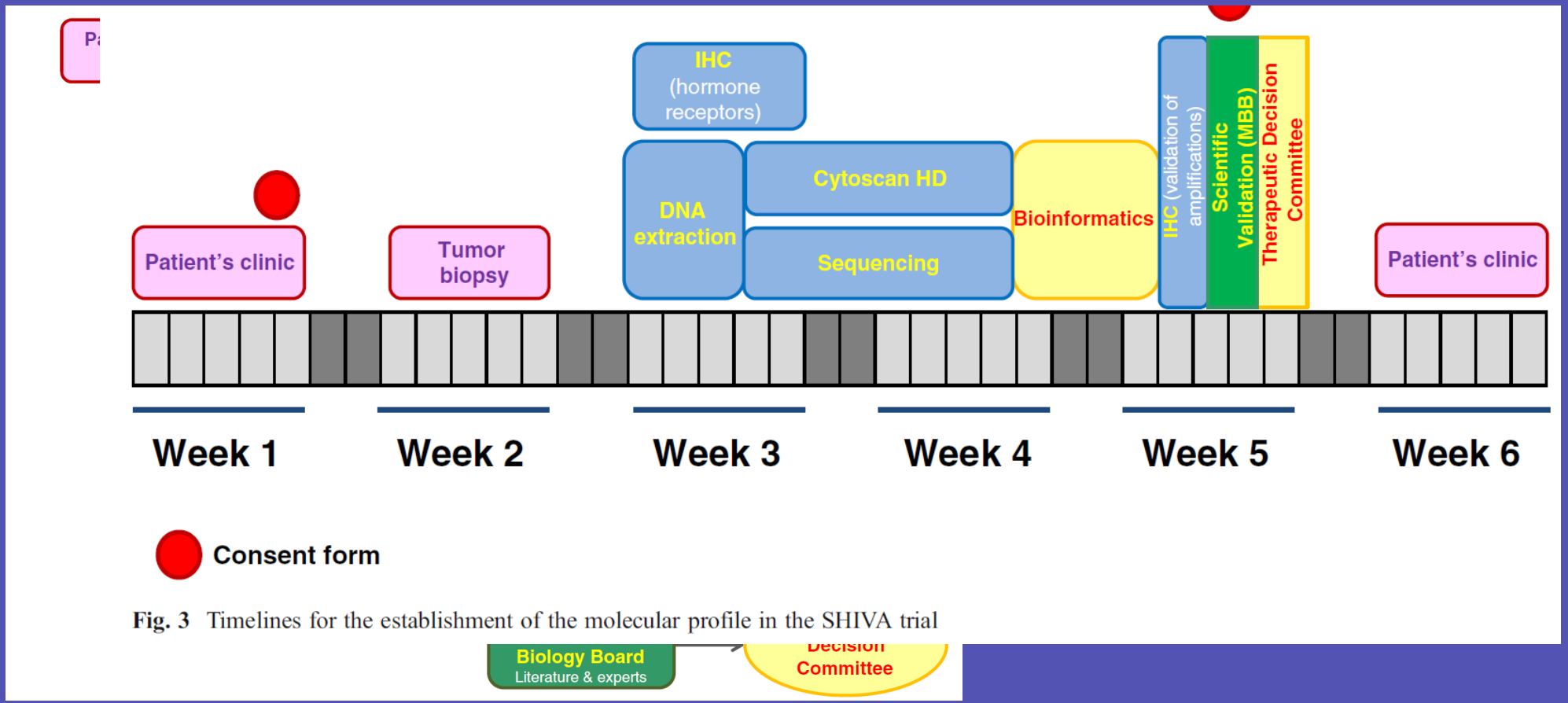


Fig. 3 Timelines for the establishment of the molecular profile in the SHIVA trial

Target Oncol 2012

Conclusions

- Les thérapies ciblées sont actives si la cible est connue!
- Les avancées en biologie moléculaire amènent à une complexification de la prise en charge des CBNPC qui d'une maladie fréquente évolue vers de nombreuses maladies rares

⇨ prise en charge multidisciplinaire (concertations multidisciplinaires moléculaires)