



Prise en charges des patients avec CBNPC EGFR mutés

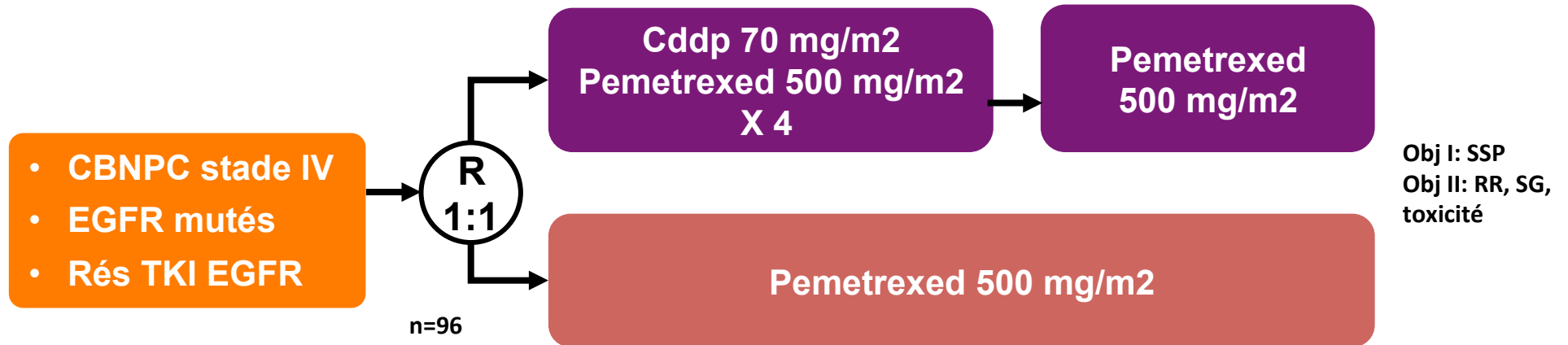
Cours du GOLF
Limoges, 19 Septembre 2017

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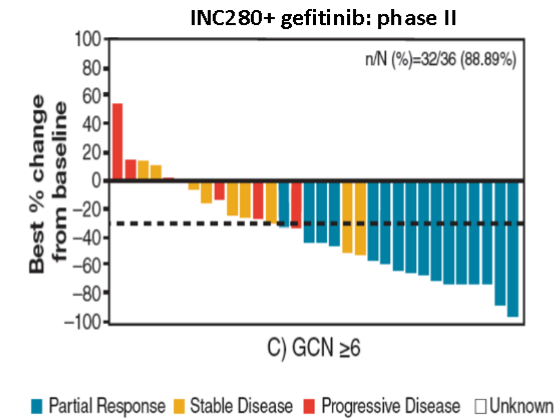
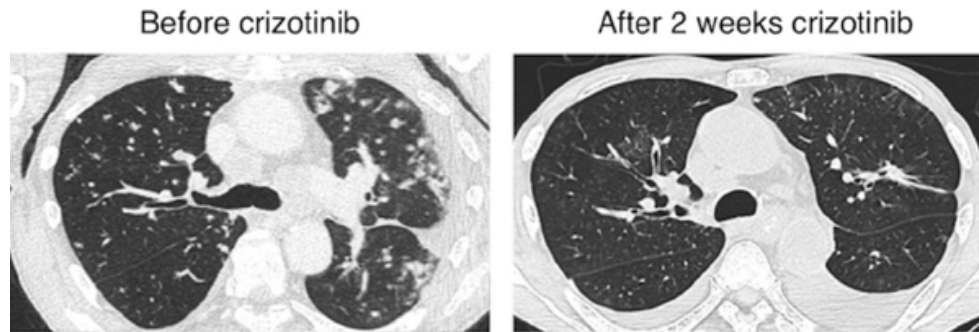


Quelle chimiothérapie après les TKI EGFR?



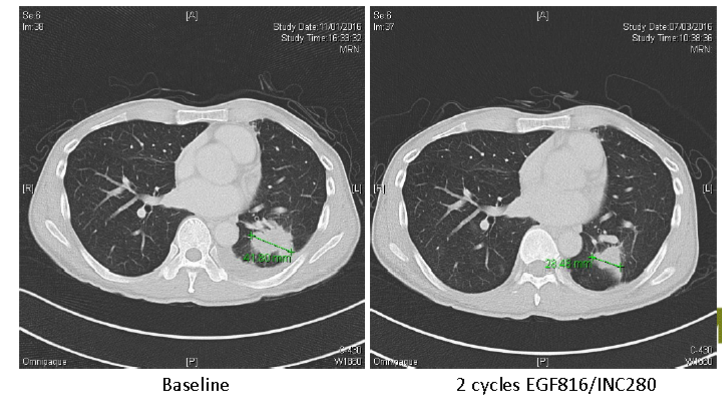
	Cis Pem	Pem
RR	34%	17%
SSP p = 0.313	5,4	6,4

cMet



- Met amplif et/ou hyper expression (+++)
- N=43
- T790M+ (29%)
- 1/12 réponse avec TKI cmet (monothérapie)

INC280+ EGF816: phase I/II
Acquired resistance: exon 19 del, T790M+, MET IHC+2



Yoshimura et al, *Respir Med Case Rep* 2017;20:160-3

Baldacci et al, *WCLC* 2016;P3.02B-051

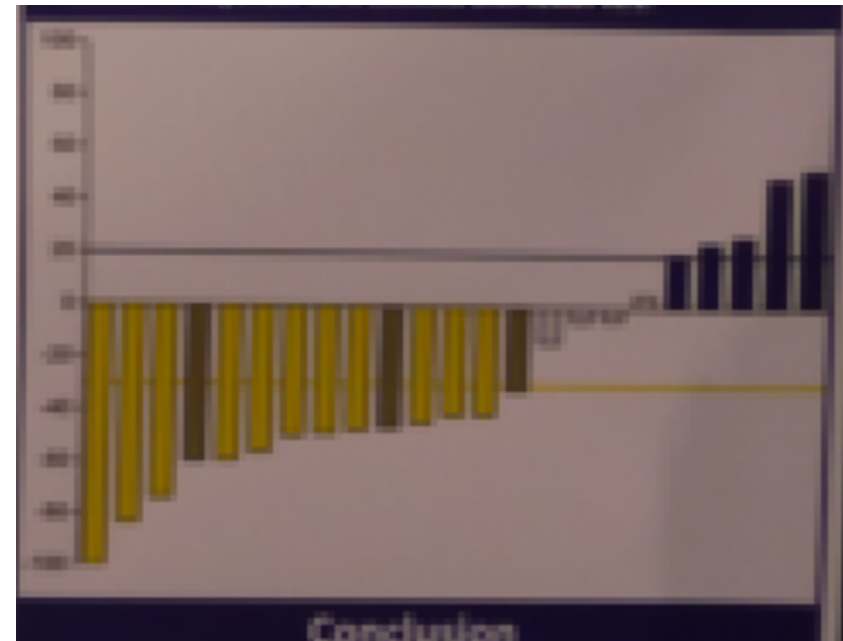
Wu et al, *ASCO* 2016, Abstr 9020

Her2

17% des patients avec résistance secondaire aux TKI EGFR
 Trastuzumab 4 mg/kg puis 2 mg/kg, Paclitaxel 60 mg/kg hebdo
 RR extra cérébral 58%, RR global 47%

Her2 IHC	n (%)
1	3(12)
2	9(38)
3	12(50)
Her2 GCN n	
<5	9(43)
5-10	8(38)
>10	4(19)

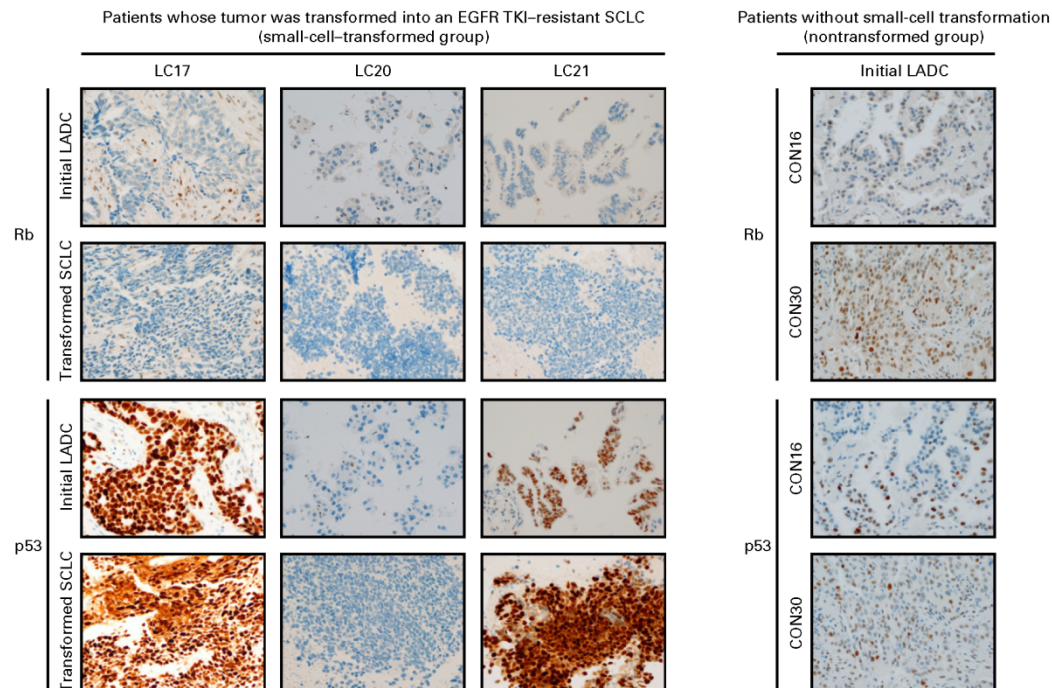
Réponse	All	IHC +	IHC ++	IHC +++	GCN < 5	GCN 5-10	GCN > 10
CR	1	0	0	1	0	0	1
PR	10	0	3	7	2	4	3
SD	4	1	2	1	3	0	0
PD	9	1	4	3	3	4	0
Décès	1	1	0	0	1	0	0
RR(%)	46	0	33	67	22	50	100



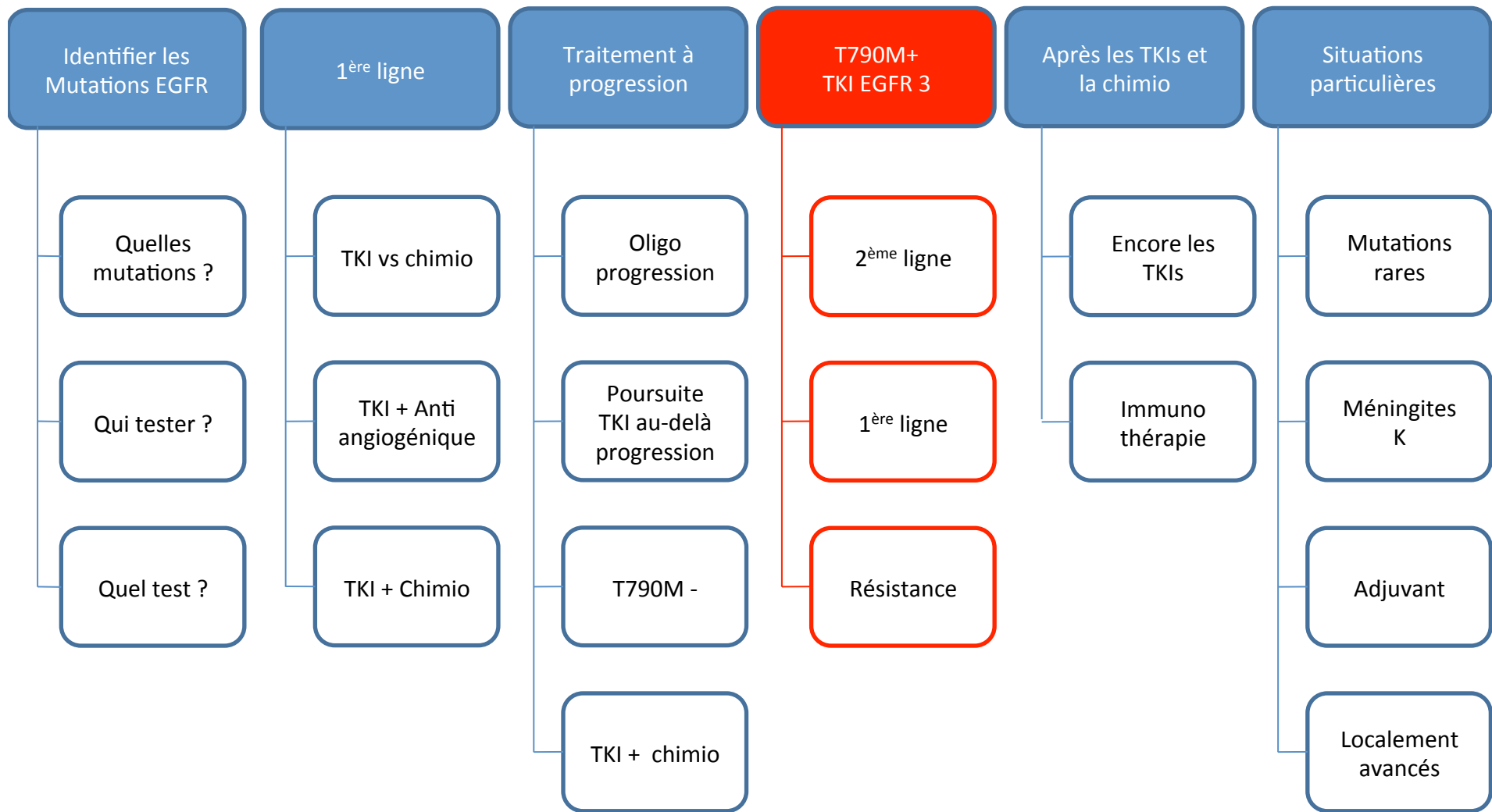
De Langen et al, ASCO 2017; Abstr 9042

Transformation histologique CPC

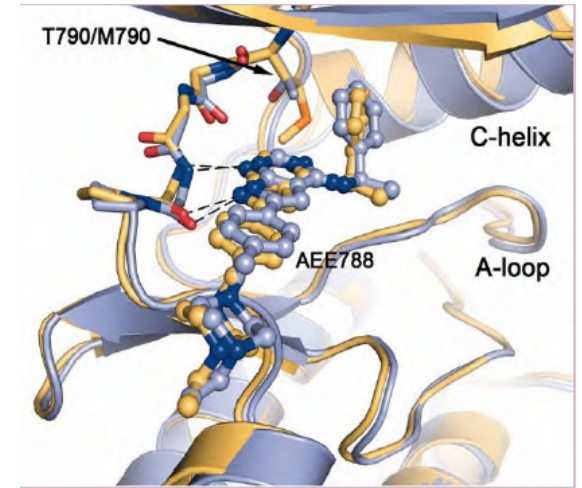
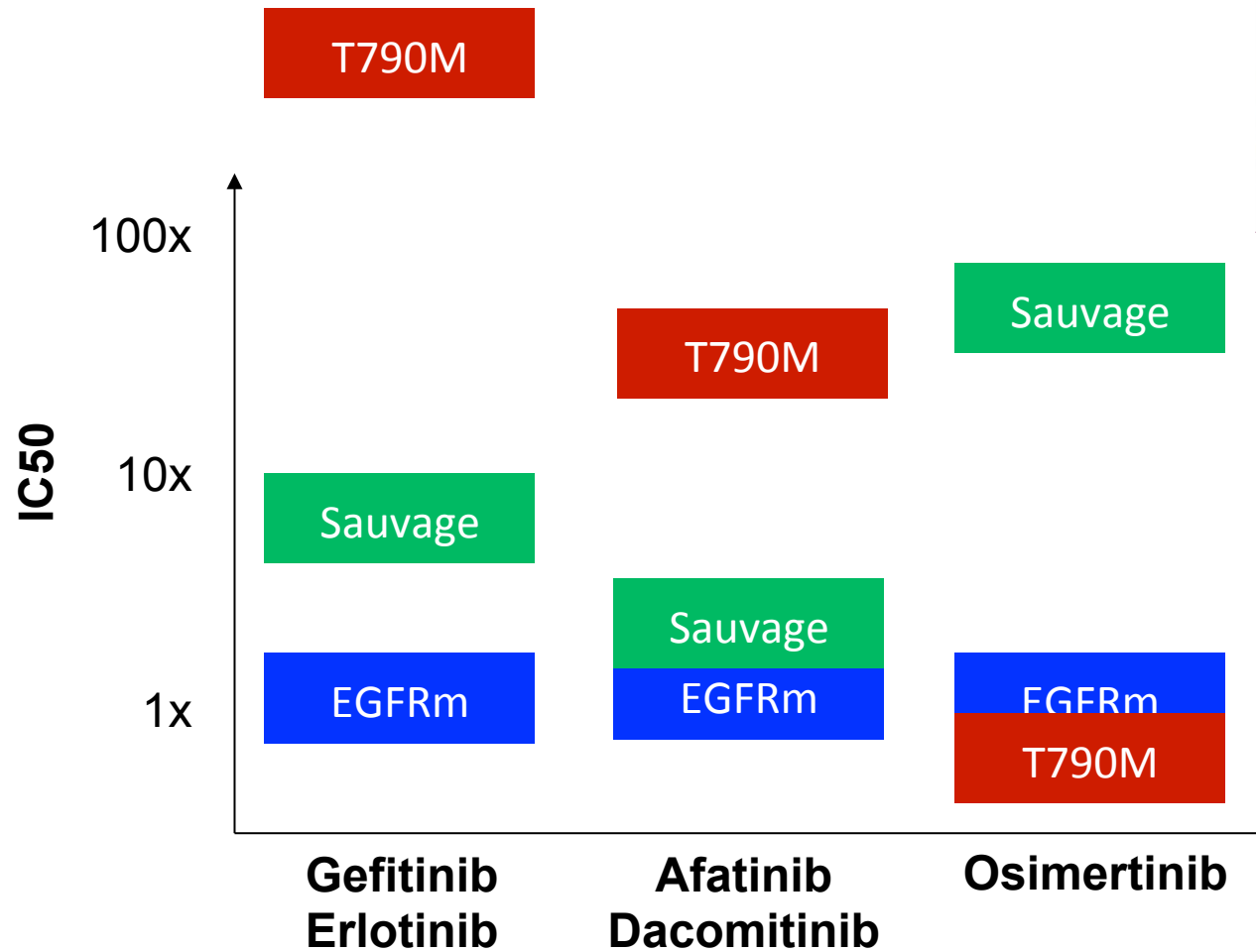
- Taux de réponse à la chimio: 70% (n=34)



- Inactivation complète de Rb et p53 (IHC) est présente avant la transformation histologique
- 82% vs 3%
- Risque multiplié par 43



T790M



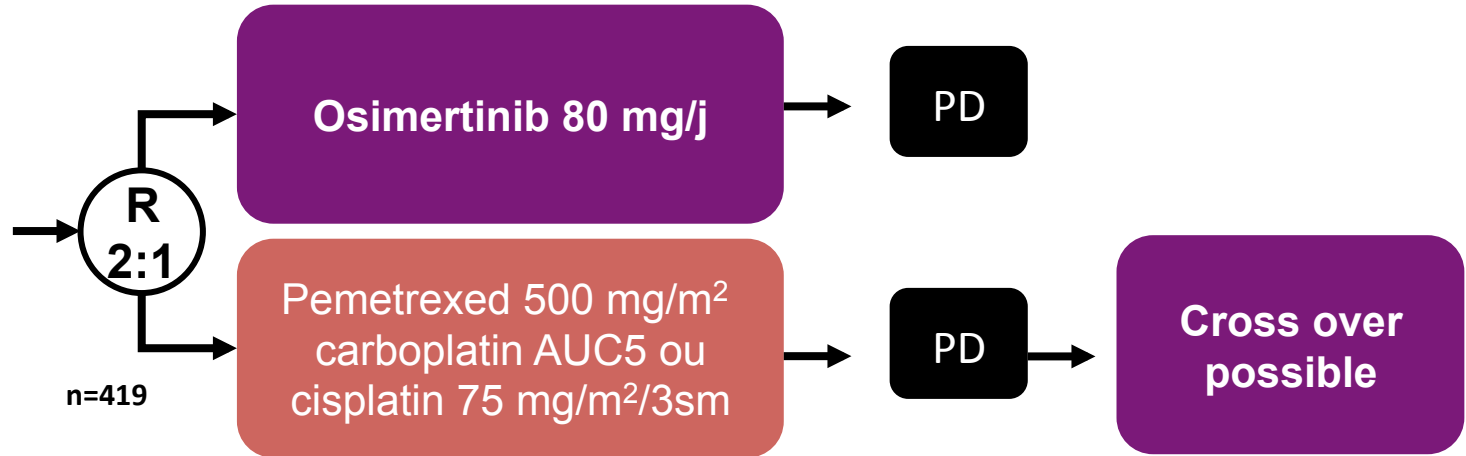
■ Récepteurs EGFR sauvages

■ Récepteur avec mutation T790M de résistance

■ Mutation activatrice de l'EGFR

AURA 3

- CBNPC localement avancé ou stade IV
- Progression après TKI EGFR
- T790M+
- PS 0 ou 1
- Métas SNC non symptomatiques

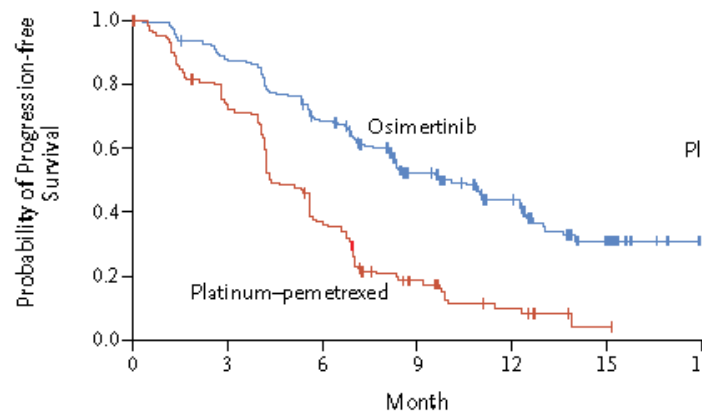


Stratification

- Ethnie (Asian vs. non-Asian)

Obj I: SSP
Obj II: RR, SG, toxicité

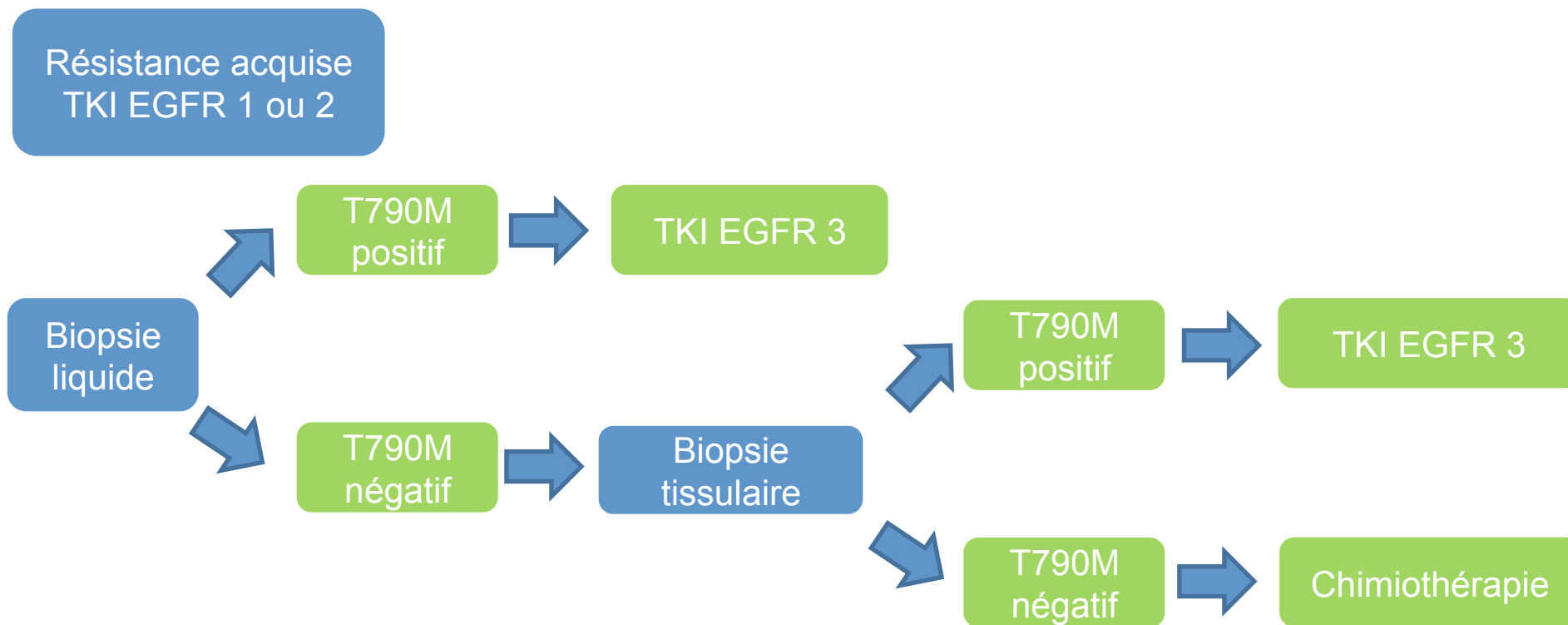
Patients in Intention-to-Treat Population



	No. of Patients	Median Progression-free Survival mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum-pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

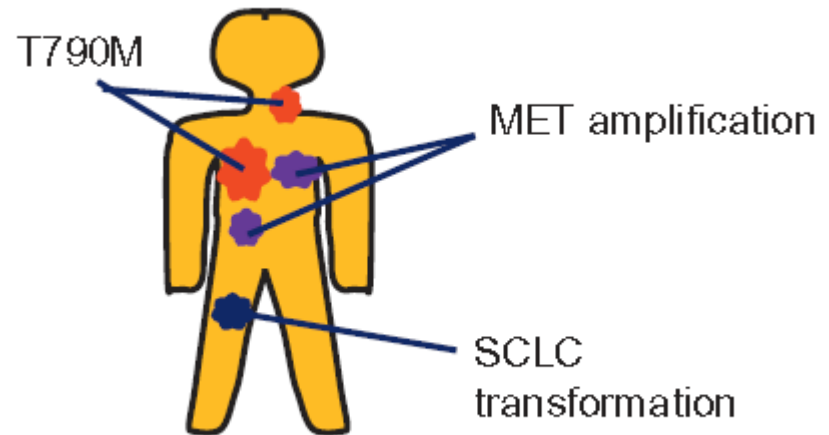
No. at Risk	0	3	6	9	12	15	18
Osimertinib	279	240	162	88	50	13	0
Platinum-pemetrexed	140	93	44	17	7	1	0



Discordance spatiale



T790M for all lesions

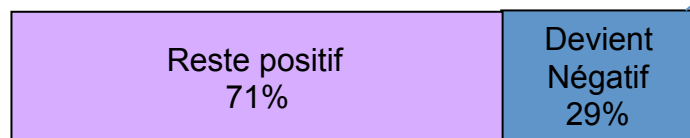


Discordance temporelle

Première
rebiopsie

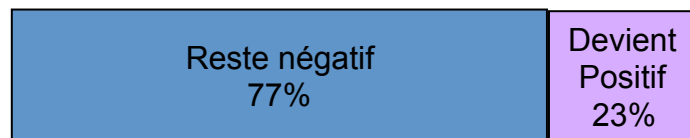
Rebiopsies ultérieures

T790M
positif
(n=31)

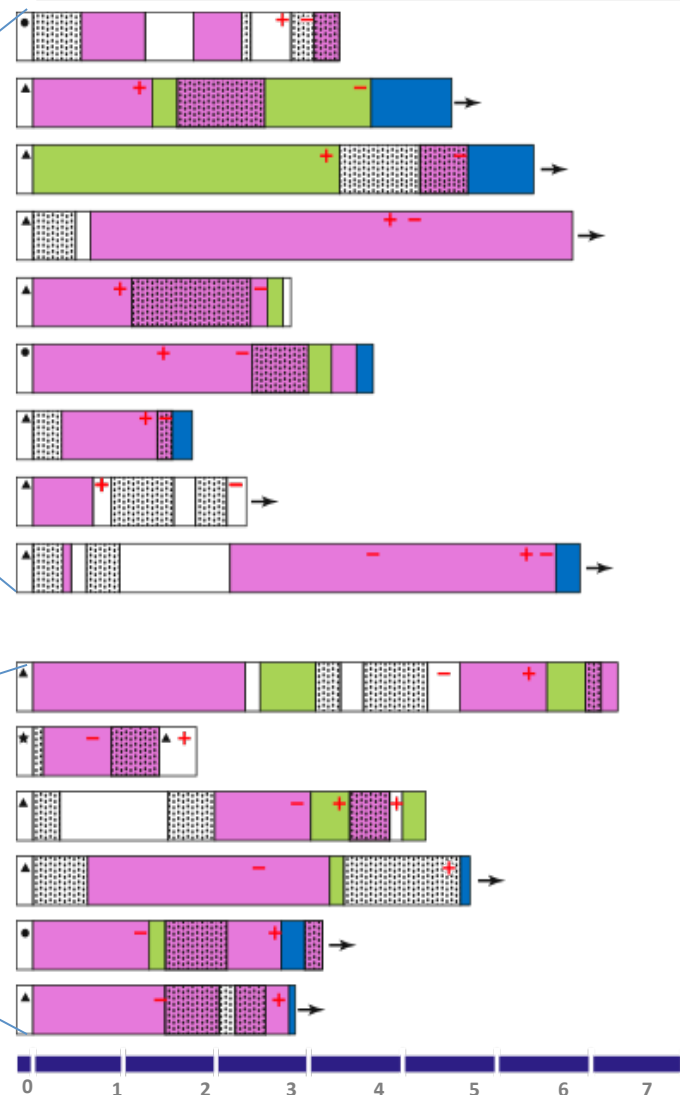
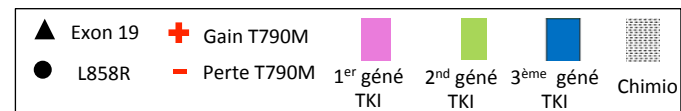


Perte T790M

T790M
négatif
(n=26)

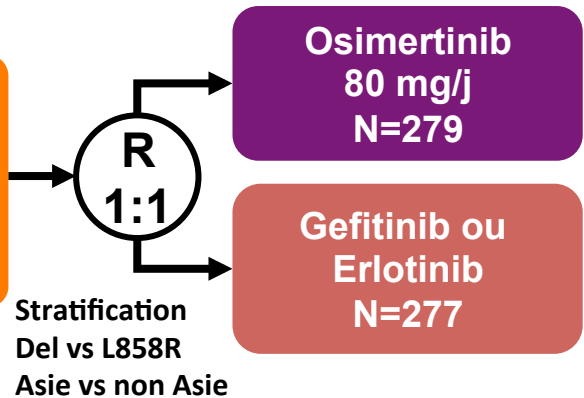


Gain T790M



FLAURA

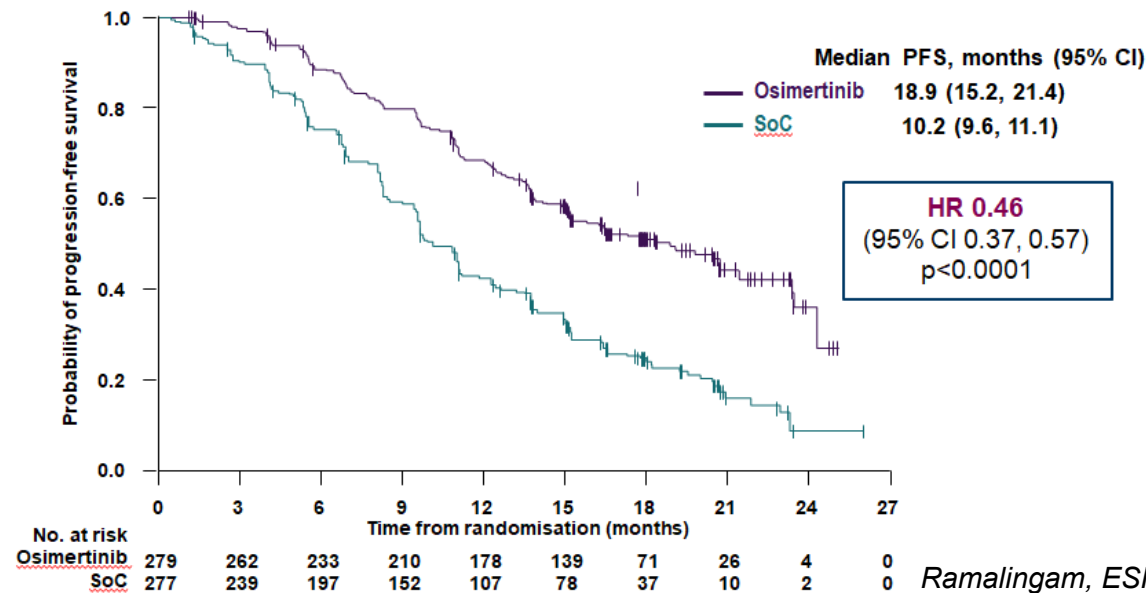
- CBNPC localement avancé ou IV
- PS 0-1
- EGFR+ (exon19/21)
- Métas SNC stables



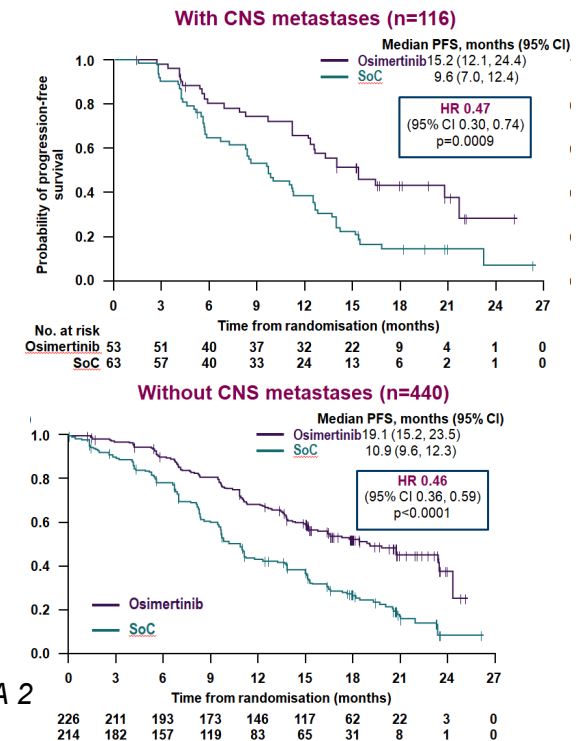
Obj I: SSP et SG
(investigateur)

Toxicité

Moins d'acné et d'hépatites

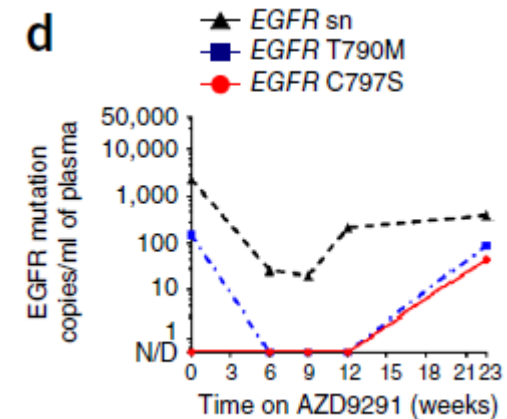
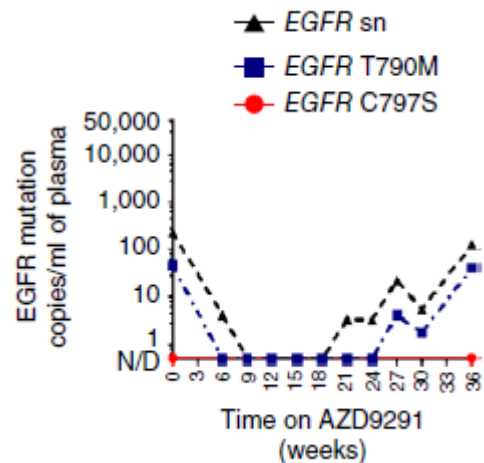
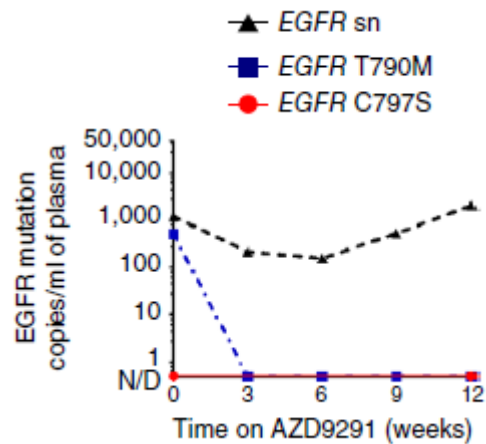
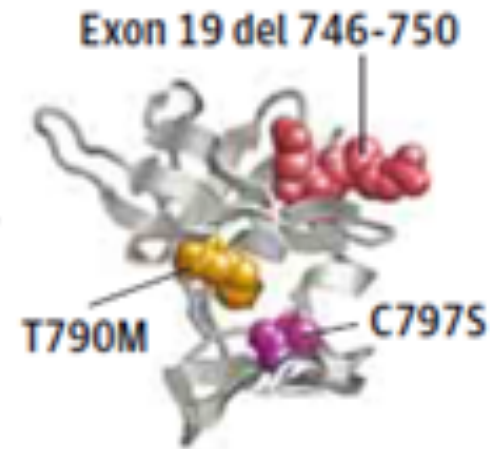


Ramalingam, ESMO 2017; LBA 2

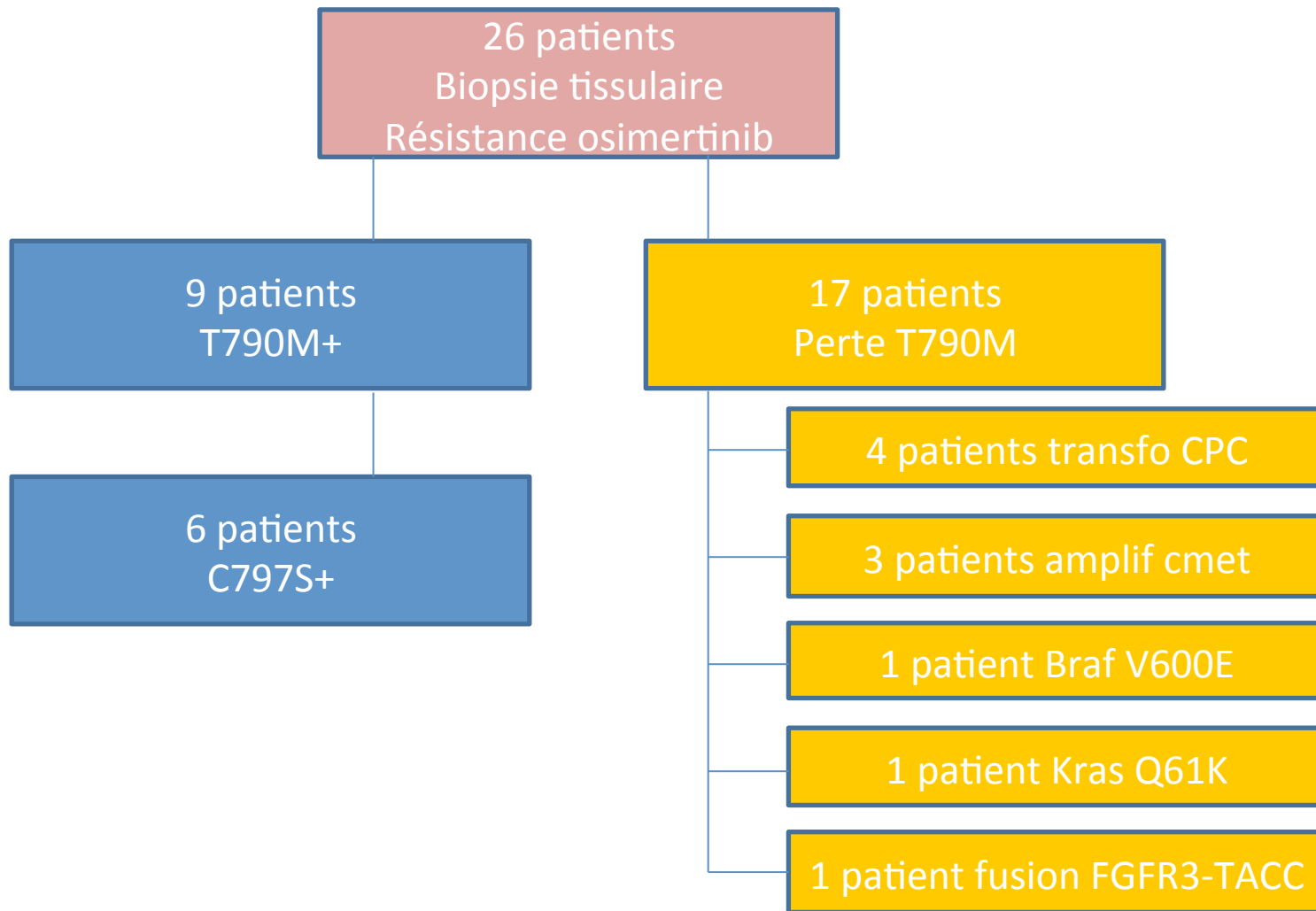


Résistance à l'osimertinib (1)

- C797S

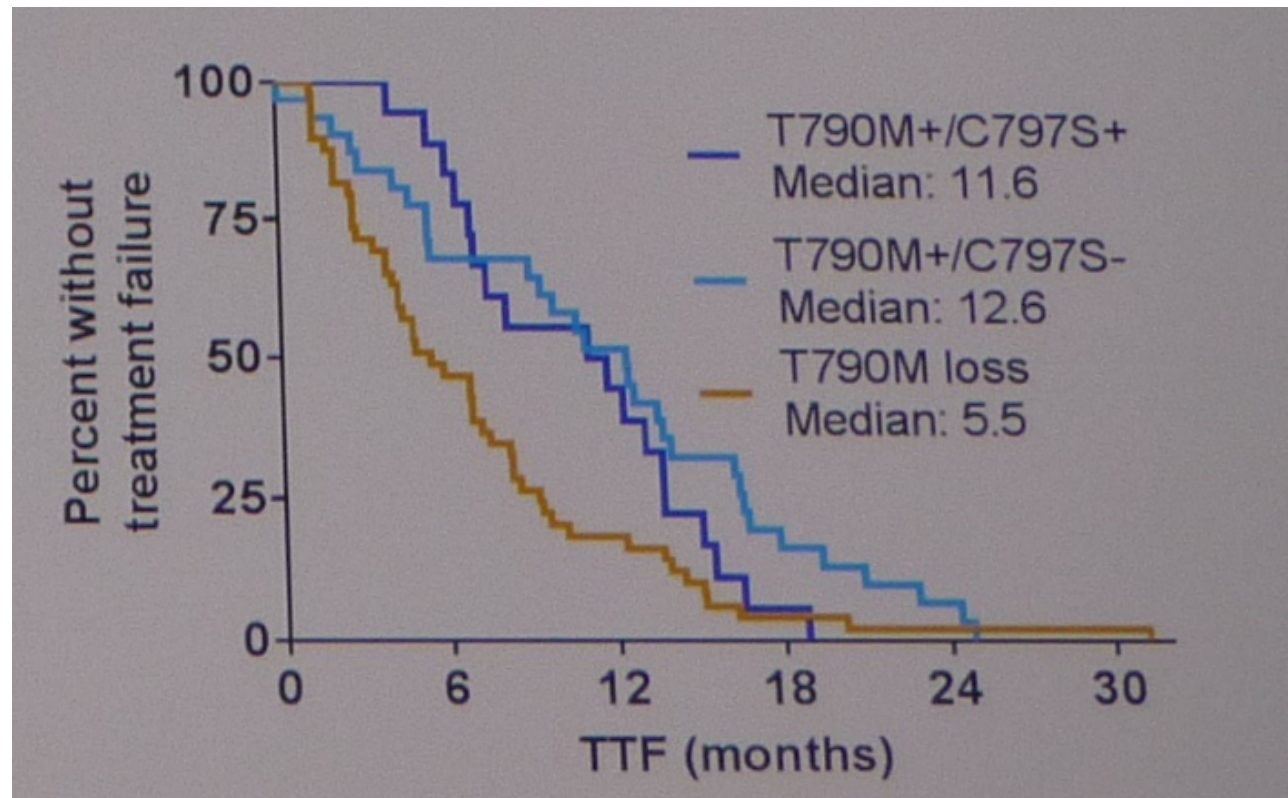


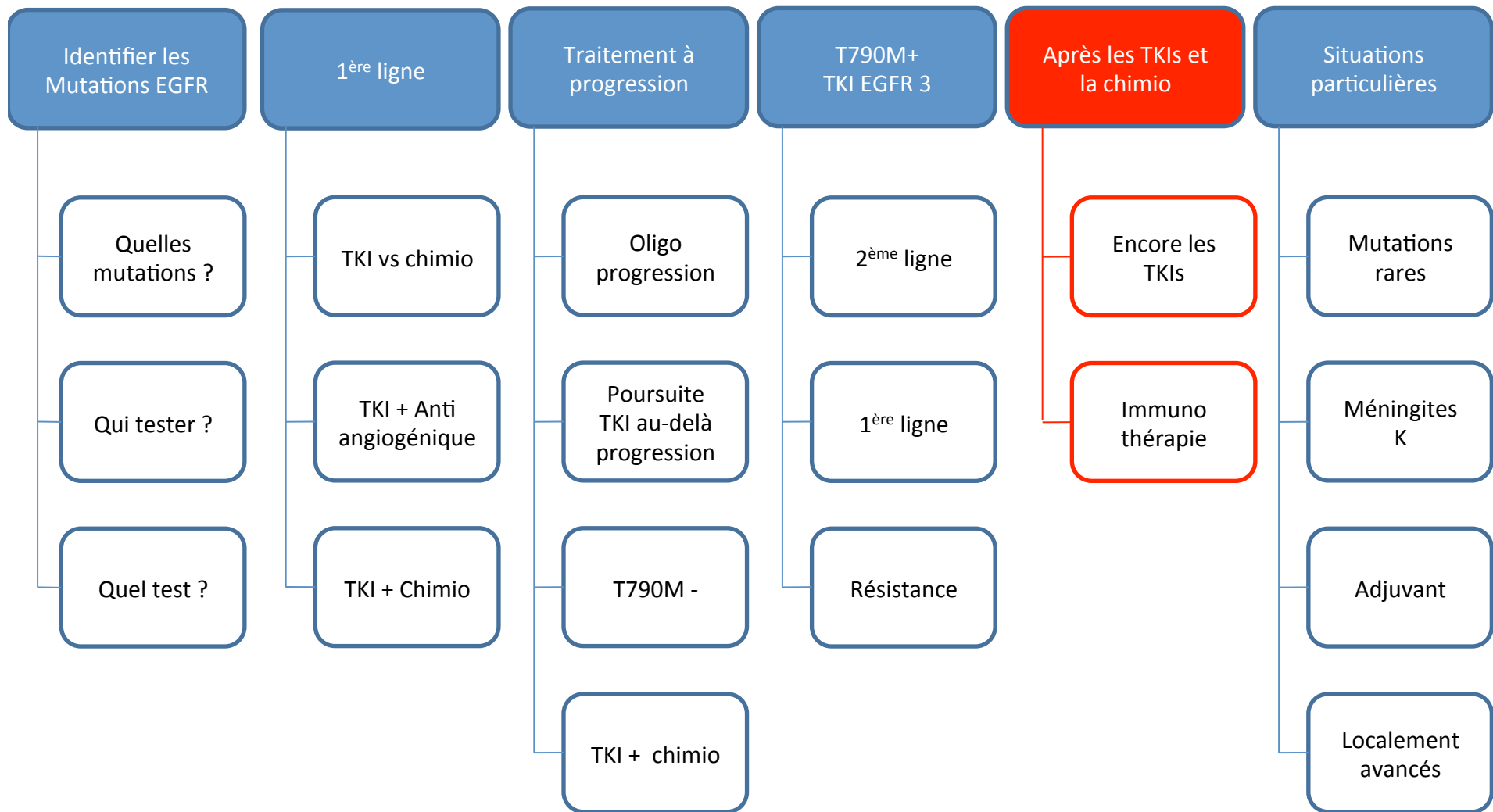
Résistance à l'osimertinib (2)



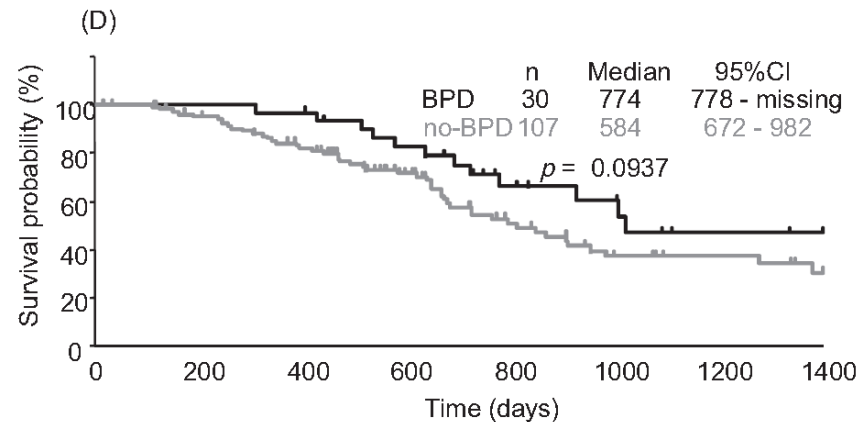
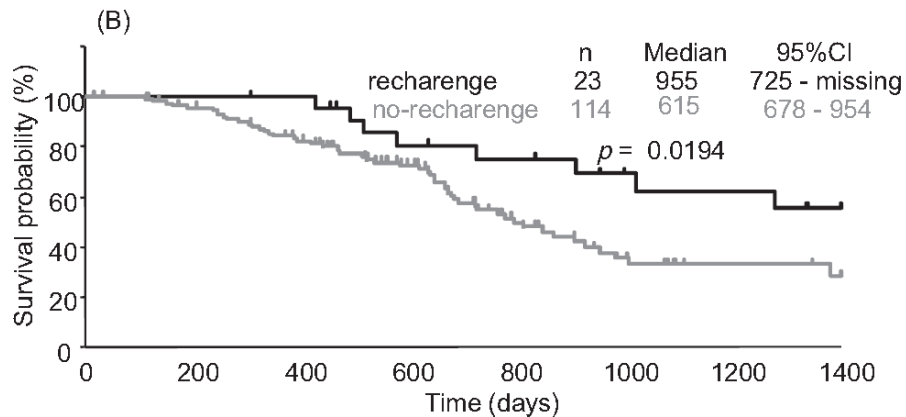
Résistance à l'osimertinib (3)

- n=98 biopsies liquides





Rechallenge



- Critères prédictifs d'une réponse au rechallenge
 - Sensibilité initiale? Oui¹⁻⁴
 - Durée de l'intervalle libre sans TKI EGFR? Oui¹ et non²
 - Présence de la T790M? Non³
 - Lésions cérébrales plus sensibles? oui⁴

Nishino et al, *Lung Cancer* 2013; 82: 299-304

(1) Tang et al, *J Cancer Res Clin Oncol* 2014; 140: 427-433

(2) Kwon et al, *Tuberc Res Dis* 2017; 80: 187-193

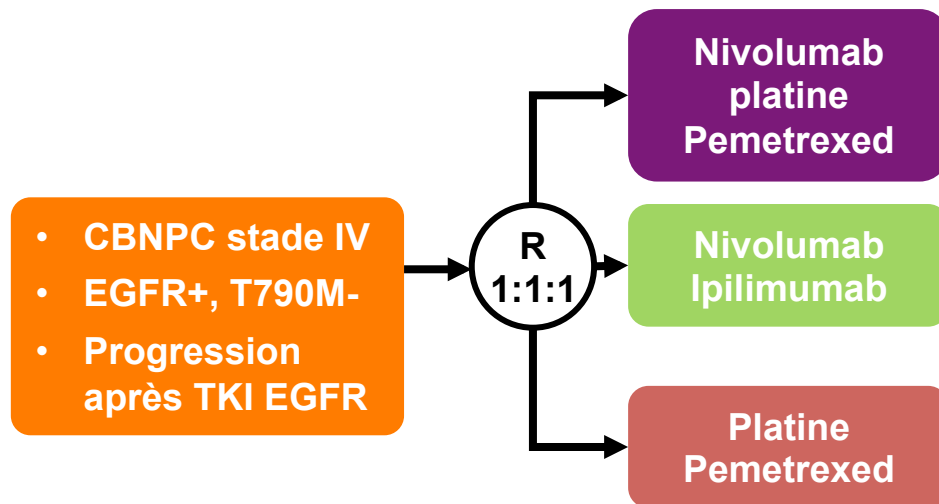
(3) Zhang et al, *Oncotarget* 2017; 8: 4994-5002

(4) Lee et al, *Clin Lung Cancer* 2014; 15: 145-151

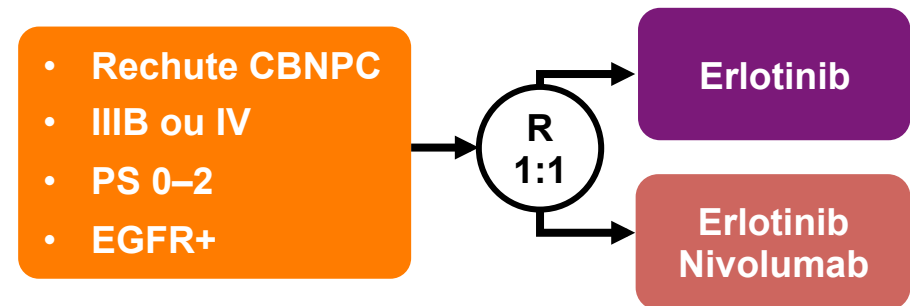
Immunothérapie

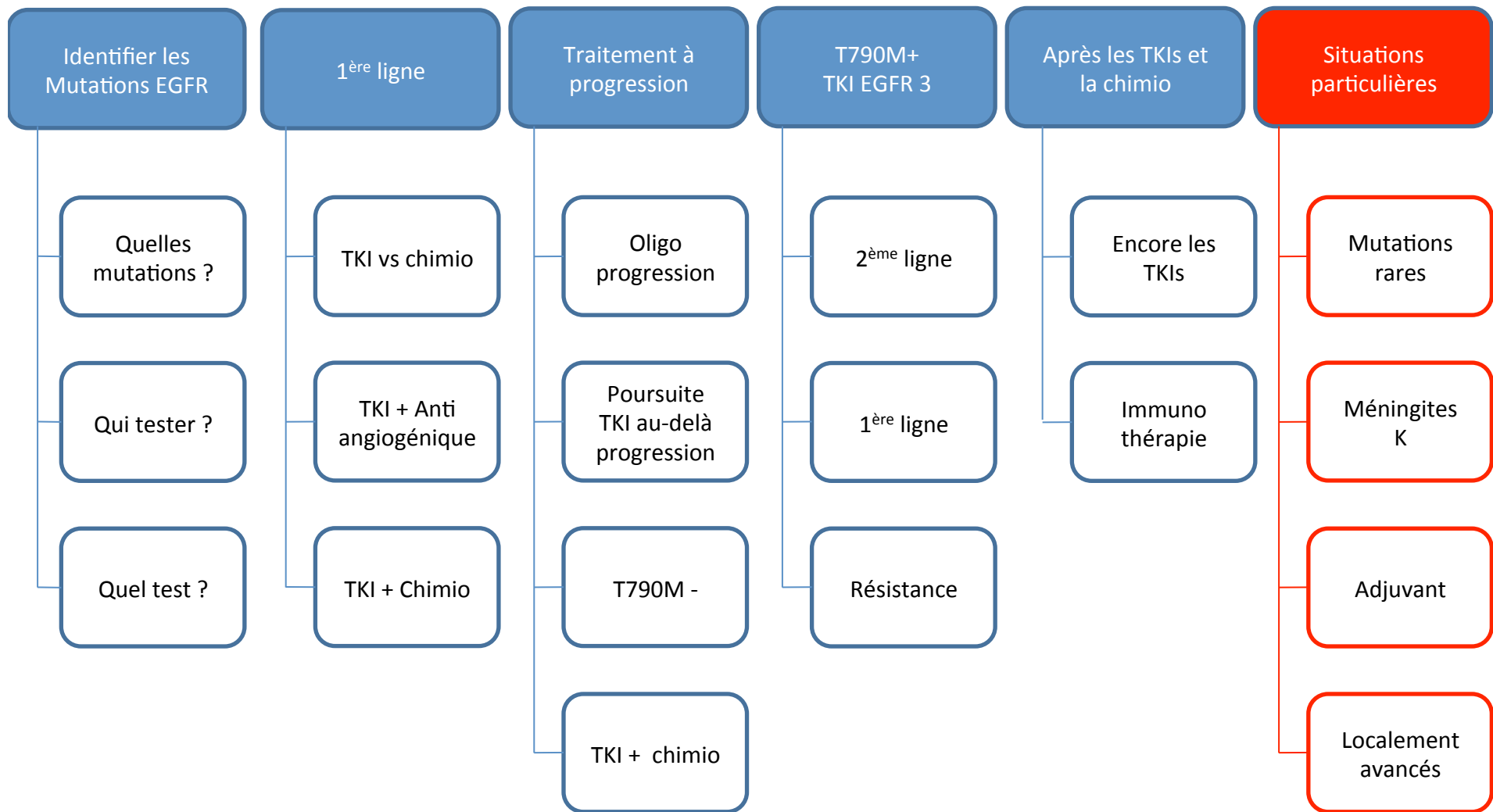
- Après les TKI EGFR et la chimiothérapie (1^{ère} et 2^{ème} ligne)
- Après la réinduction?
- Mutations mineures, fumeurs, PDL1+

Checkmate 722

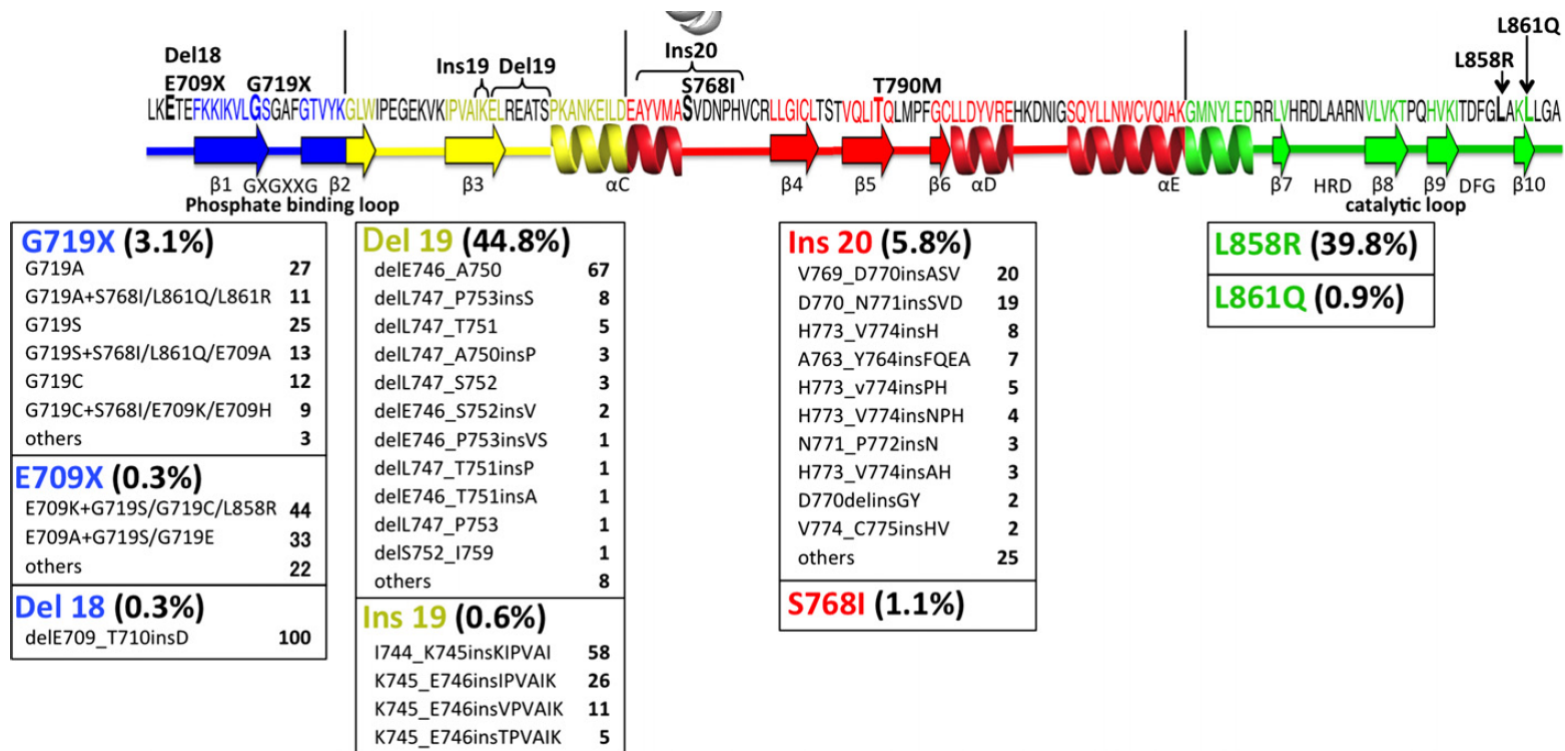


Checkmate 370





Mutations rares (1)



Mutations rares (2)

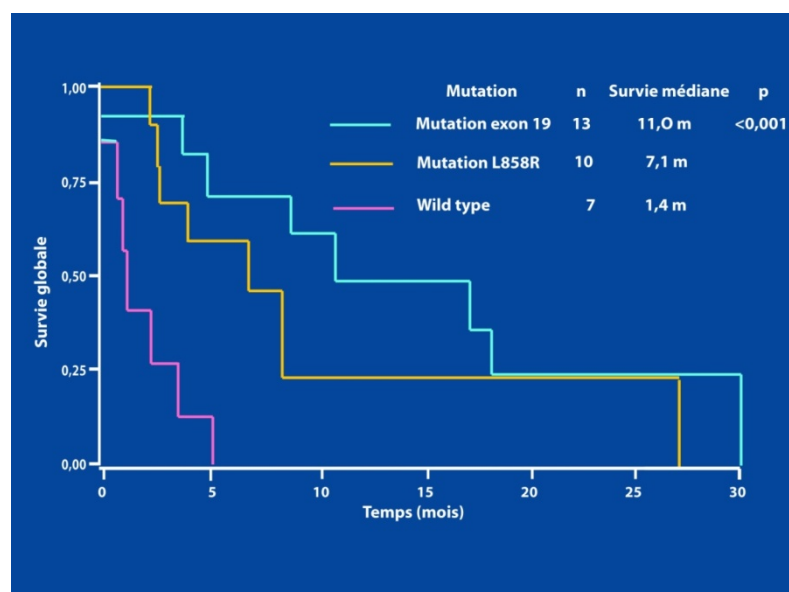
Table 2. Summary of the *in vitro* sensitivities of Ba/F3 cells expressing each EGFR mutation to various TKI

Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750	4.8	4.9	0.9	<1	60	1.1	19
	Del19	delE746_S752insV	306	14	0.2	1.4	86		
	Del19	delL747_A750insP	7.4	13	1	1.6	30		
	Del19	delL747_P753insS	4.1	5.4	2	1.9	38		
	Del19	delS752_I759	35	7.9	0.2	2	6.7		
	Ins19	I744_K745insKIPVAI	400		7				
	Ins19	K745_E746insTPVAIK	100		0.9				
20	Ins20	A763_Y764insFQEA	174	48	3.7			44	673
	Ins20	Y764_V765insHH	>1000	3845	79			237	1730
	Ins20	M766_A767insAI		3403	79				
	Ins20	V769_D770insASV	3100	4400	72	230	48	333	5290
	Ins20	D770_N771insNPG	3356	3700	72		230	42	262
	Ins20	D770_N771insSVD		3187	86				
	Ins20	H773_V774insH		>10 000	268		550		
	S768I	S768I	315	250	0.7			49	
	T790M	T790M+delE746_A750	8300	>10 000	64	140		3	28
	T790M	T790M+L858R	>10 000	>10 000	119	300		21	13
21	L858R	L858R	26	16	4	2.6	1.4	9	140
	L861Q	L861Q	170	103	0.5		3.3	9	
EGFR wild type with interleukin-3			9350	>10 000	>100	>1000	>1000	3078	1549
Plasma drug concentration			(448–2717)	(2717–4040)	(69–130)	(166–238)	(N/A–132)	(400–600)	N/A–N/A

IC50 values (nM) of <10, 10–99, 100–999 and ≥1000 are shown in blue, light blue, yellow and red, respectively. When the exact value was not described in the literature, the approximate number was estimated from each figure. IC90 values are described in del709_T710insD, E709K, G719A and wild type. EGFR, epidermal growth factor receptor; N/A, not available TKI, tyrosine kinase inhibitors.

Méningites carcinomateuses (1)

Etude rétrospective de la survie
en fonction du statut EGFR



	T790M+
LCR	21% (6/28)

	Cmet ampl+
LCR	39% (11/28)

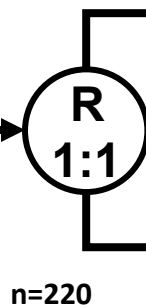
Méningites carcinomateuses (2)

- 1. Sous-dosage relatif ?
- 2. Dilatation ventriculaire ?
- 3. Cible irradiable ?
- 4. Quelle mutation activatrice?
- 5. Mécanisme moléculaire de la résistance méningée?

Adjuvant

- Stade II/IIIA résection complète
- PS 0–1
- EGFR+ (exon19/21)

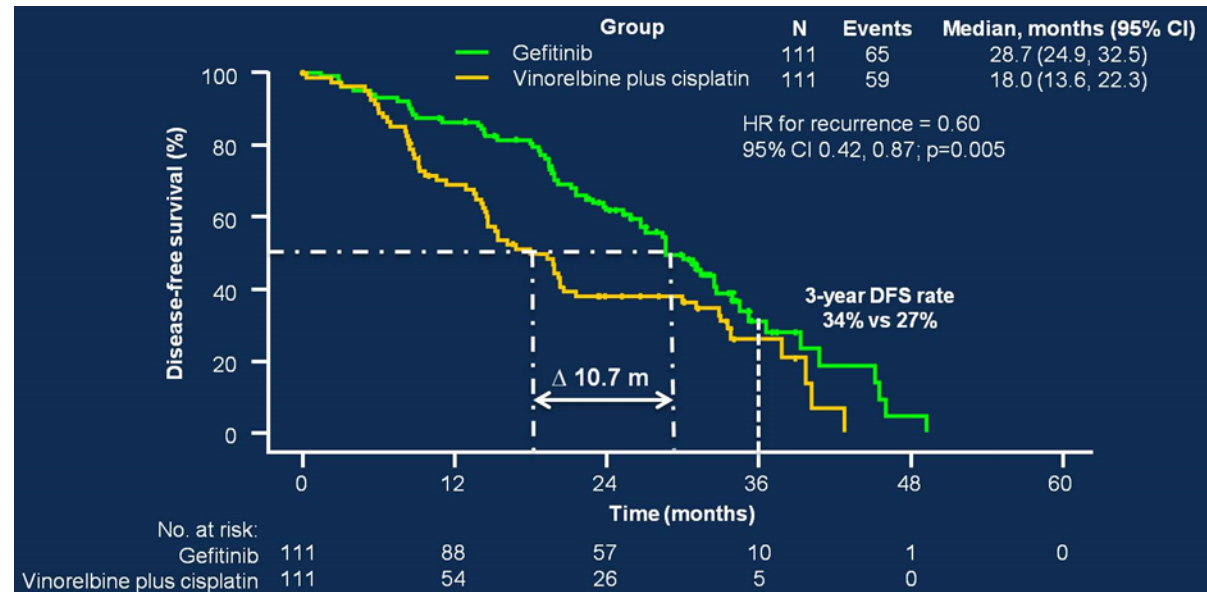
Stratification
Del vs L858R
N0 vs N1



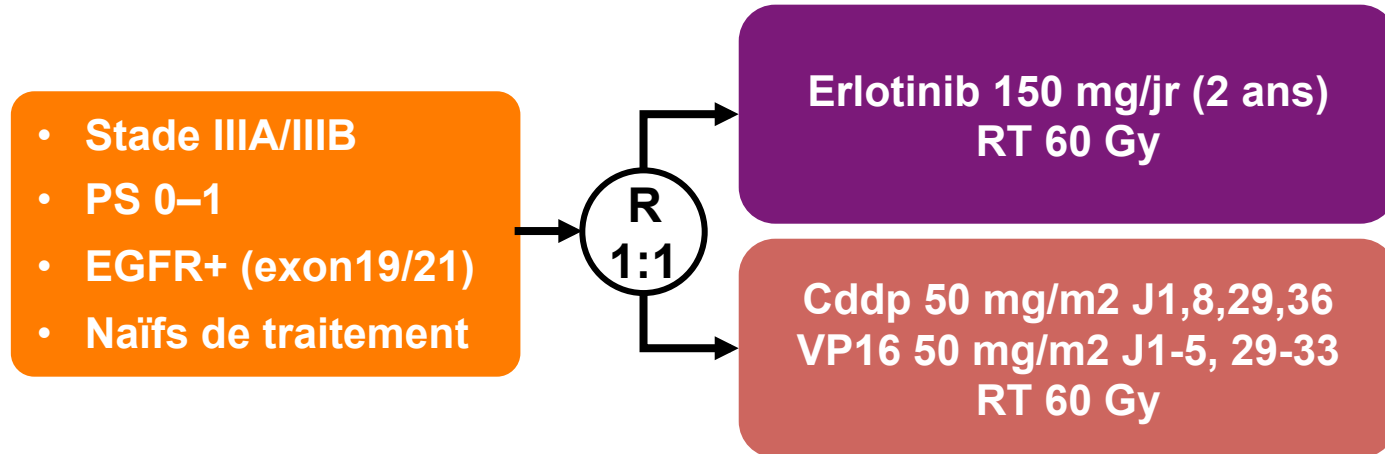
Gefitinib 250 mg/jr (2 ans)
Jusqu'à progression ou toxicité

Cddp 75 mg/m2
Vinorelbine 25 mg/m2 J1 J8
x 4

Obj I: SSP

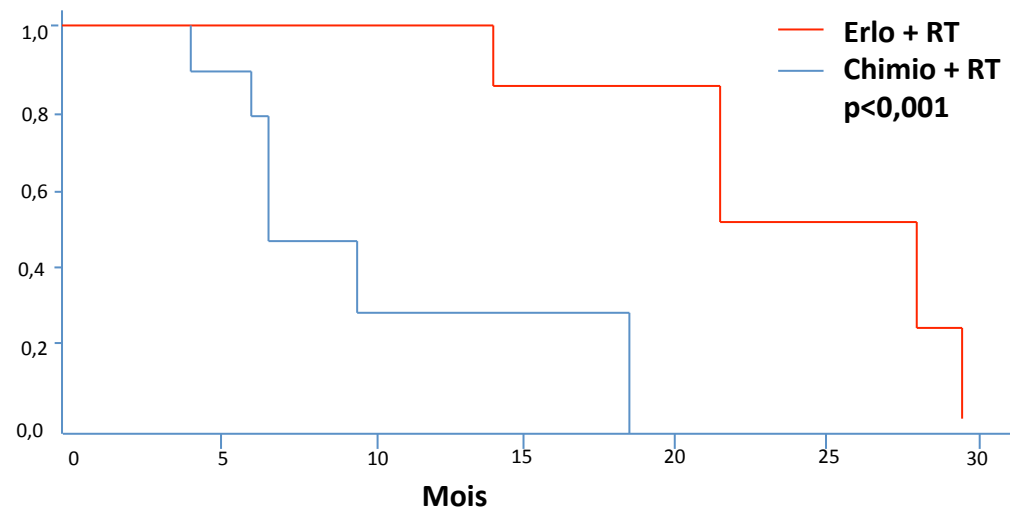


Localement avancés



Obj I: SSP
Obj II: RR, SG,
QOL, tox, ...

n=41



Take home message

- Chez tout CBNPC avancés non épidermoïde, quelque soit le statut tabagique, rechercher les mutations EGFR
- Ne pas arrêter trop tôt les TKI EGFR
- Répéter recherche T790M (hétérogénéité spatiale et temporelle)

Quelle est la séquence optimale ?

