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THERANOSCAN
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Traitement des CBNPC mutés EGFR
Quelle séquence?

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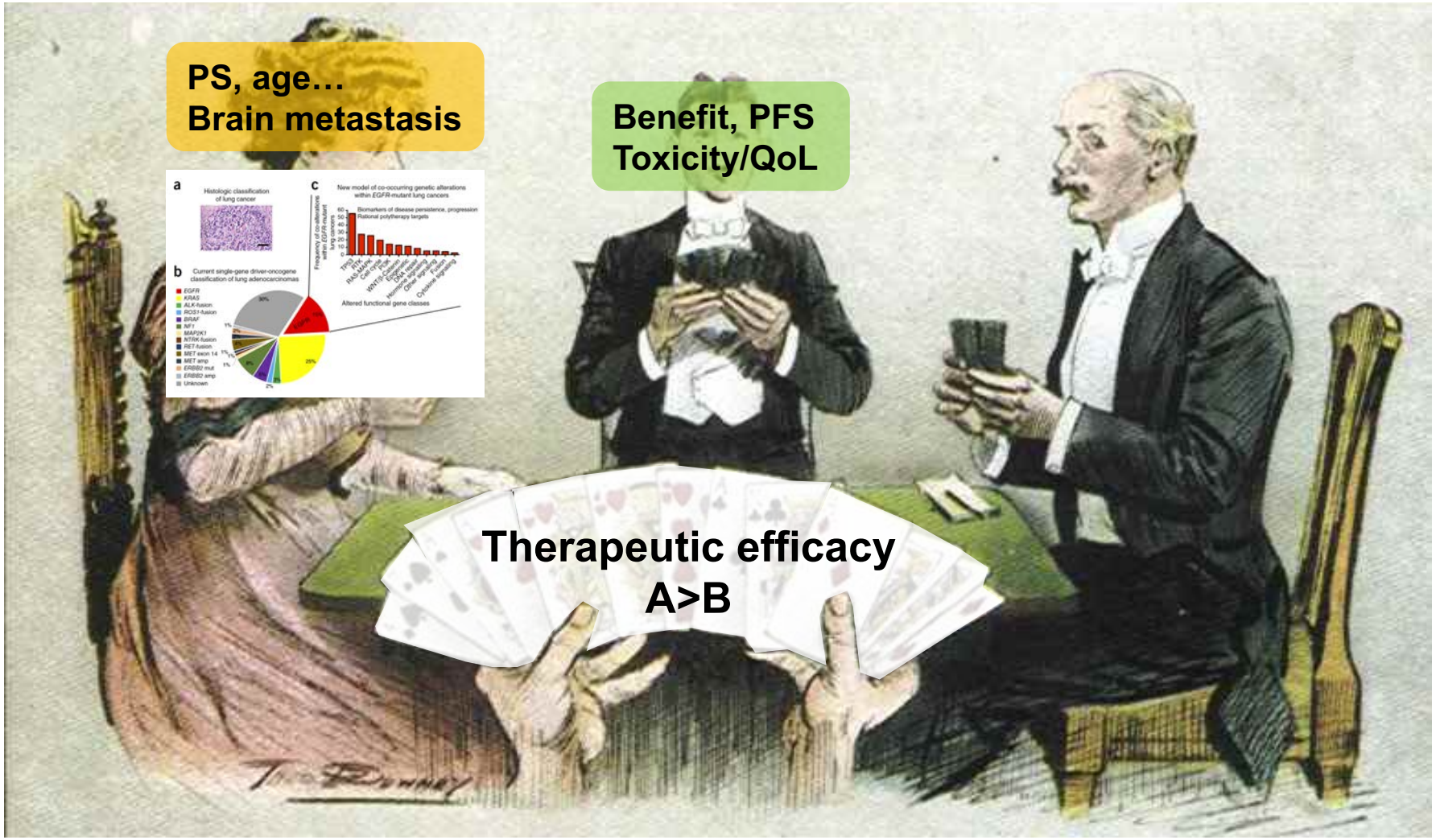
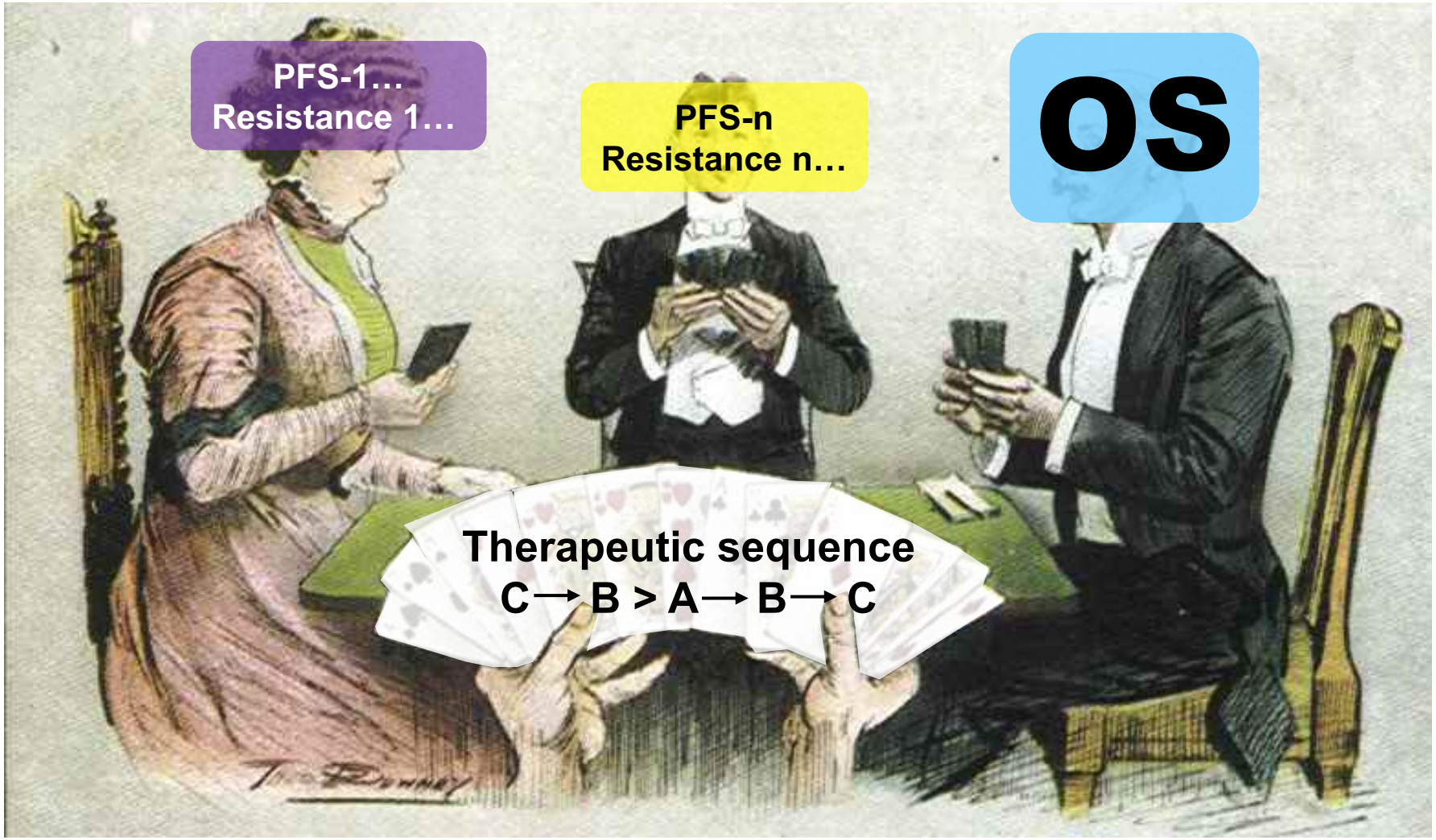
- Liens d’intérêt :
  - Honoraires pour la participation à des réunions d’experts : Abbvie, Astra-Zeneca, BMS, Boerhinger-Ingelheim, MSD, Novartis, Lilly, Pfizer, Takeda, Roche
  - Financement de projets de recherche : Astra-Zeneca, Novartis, Pfizer
- Liens d’intérêt en relation avec la présentation :
  - Honoraires pour la participation à des réunions d’experts : Astra-Zeneca, Boerhinger-Ingelheim, Roche

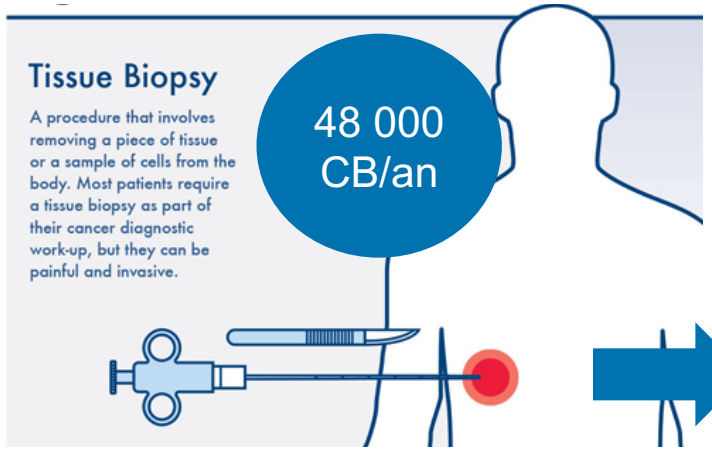
Traitement des CBNPC mutés EGFR



Traitement des CBNPC mutés EGFR

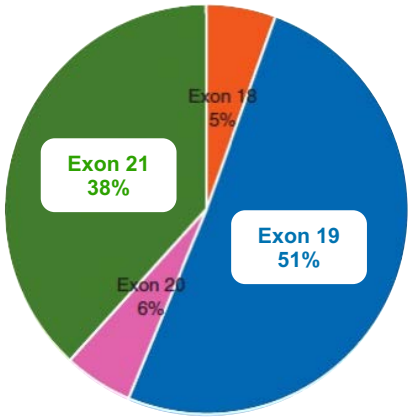


Les CBNPC mutés EGFR



IFCT
Biomarqueurs France

89%, exon 19/21
(n=1837)



Activité détaillée de génétique somatique dans le cancer du poumon en 2016

Plateformes hospitalières de génétique moléculaire des cancers

Localisation	Marqueur	Année	Nombre de patients	Pourcentage d'altérations moléculaires	Pourcentage de tests non interprétables
Poumon	Mutations BRAF				6.7
Poumon	Mutations EGFR				6.2
Poumon	Mutations HER2				6.8
Poumon	Mutations KRAS	2016	26889	28.7	6.2
Poumon	Mutations PI3KCA	2016			
Poumon	panel de mutations par NGS	2016	12987		
Poumon	panel de translocations par des techniques multiparamétriques	2016	466		
Poumon	Translocation ALK	2016	23434	3.1	1.6
Poumon	Translocation ROS1	2016	17680	1.0	1.2

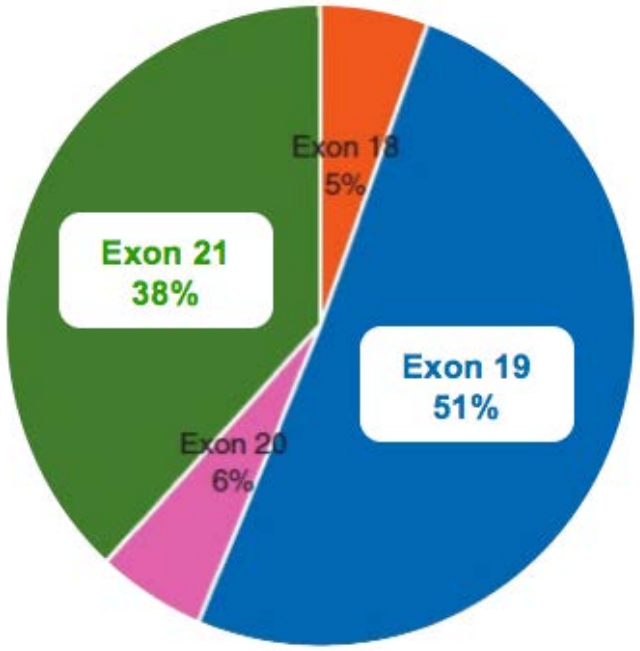
Common (classic) mutation
Rare mutation
Complex mutation
Co-mutations

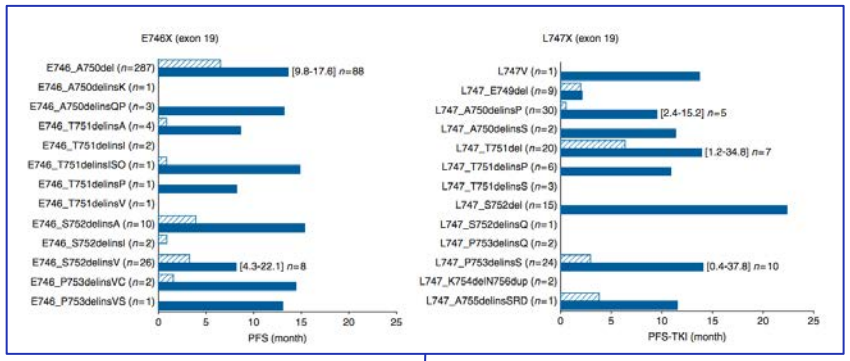
Données INCa 2016; Leduc C, Ann Oncol 2017, 28:2715

Les CBNPC mutés EGFR

IFCT Biomarqueurs France

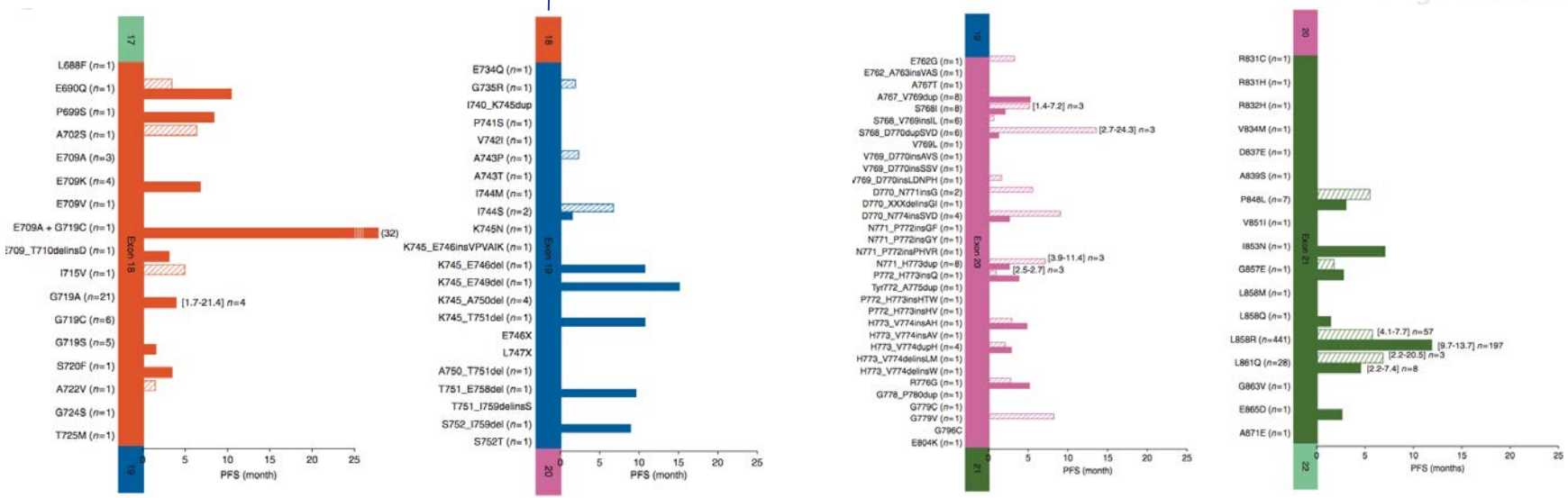
89%, exon 19/21
(n=1837)





TKI (erlotinib, gefitinib)

CT



Leduc C, Ann Oncol 2017, 28:2715

Les CBNPC mutés EGFR

EGFR WT

Baseline

Shin, Korea, n=176

10.2%

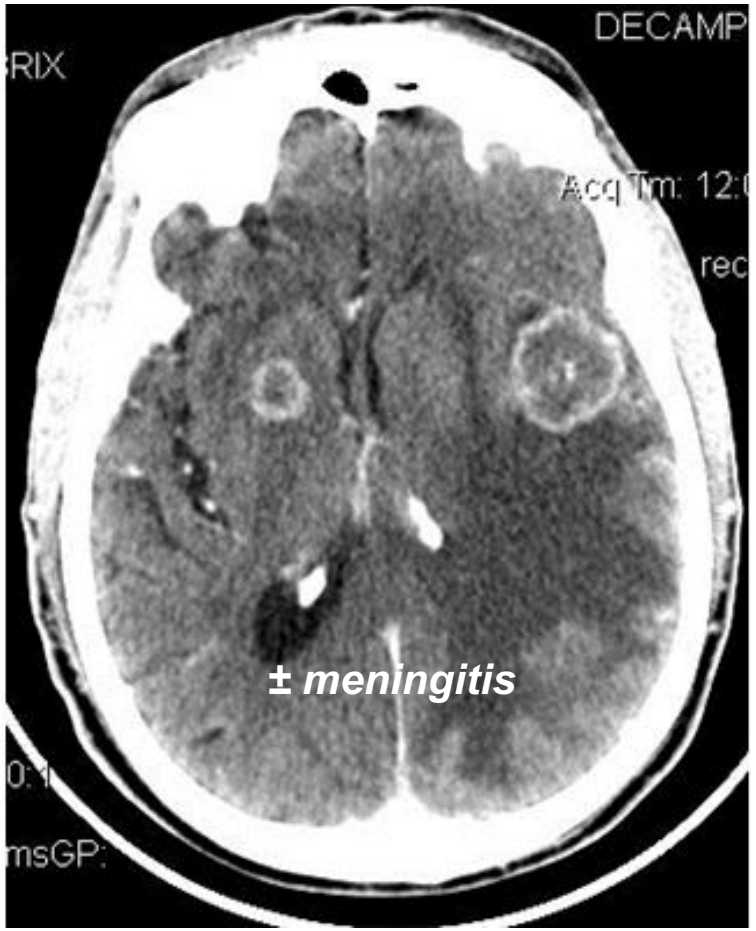
Han, China, n=126

11.0%

During progression

Han, China, n=126

22.0%



EGFR mutated

Baseline

Heon, USA, n=100

19.0%

Shin, Korea, n=138

More female and distant metastasis

27.5%

Han, China, n=108

More female and non smoker

27.0%

During progression

Heon, USA, n=100

35.0%

Han, China, n=108

44.0%

Heon S, Clin Cancer Res 2010, 16:5873Shin DY, JTO 2014, 9:195; Han G, Oncotarget 2016, 16:56998

Les CBNPC mutés EGFR

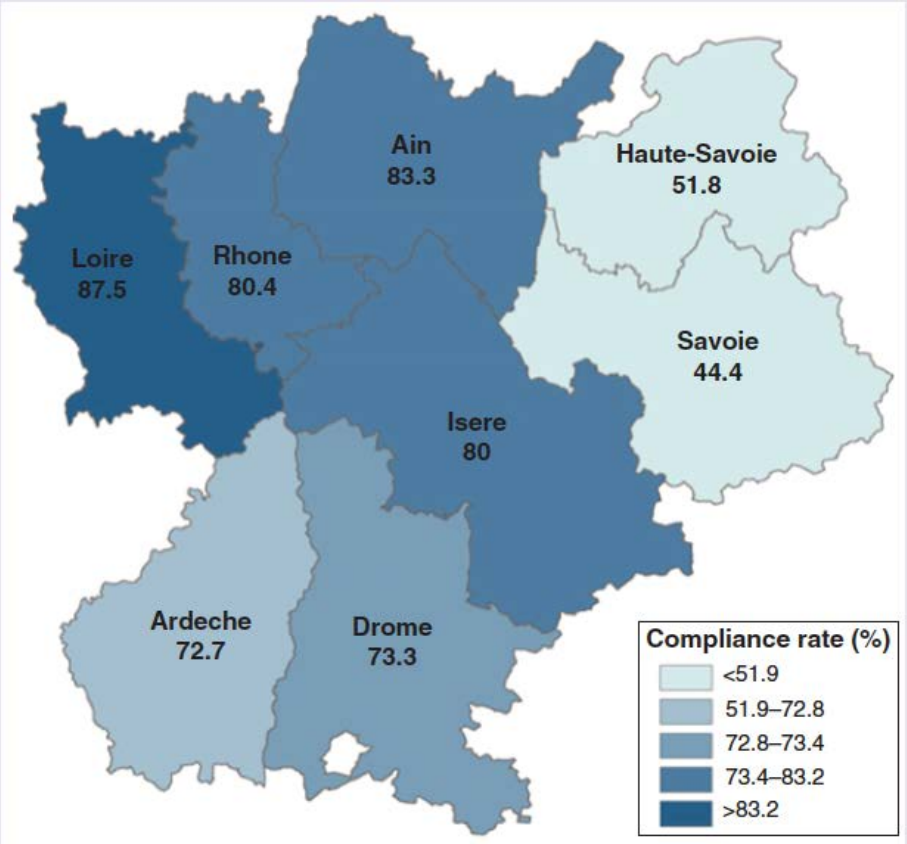
Research Article
For reprint orders, please contact: reprints@futuremedicine.com
Future ONCOLOGY

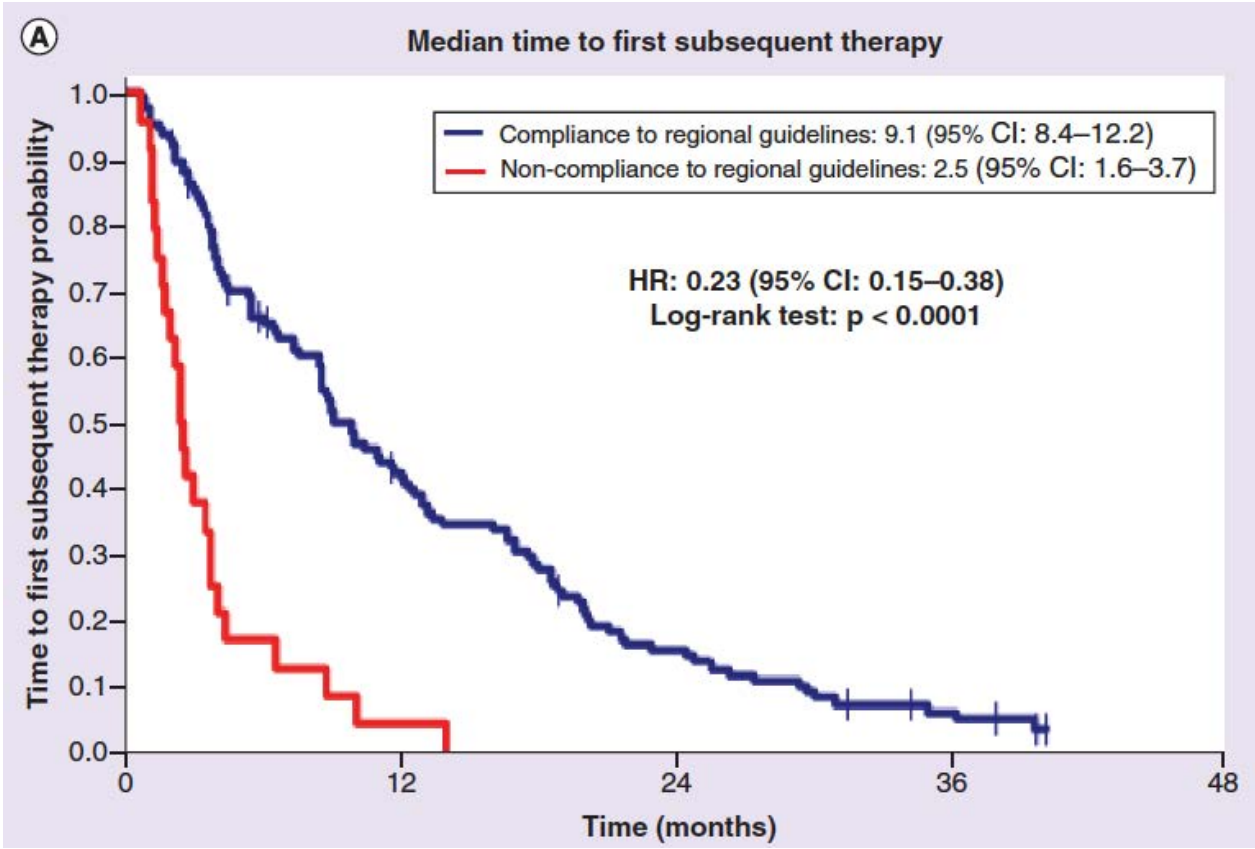
Compliance to regional recommendations for molecular analyses and management of advanced lung cancer patients

Aurélie Swalduz*[1,2], Pierre-Jean Souquet[3], Maurice Pérol[3], Denis Moro-Sibilot[4,5], Camille Schiffler[4], Sylvie Chabaud[6], Yohan Fayet[7], Muriel Rogasik[7], Hélène Labrosse[8], Fadila Farsi[8], Philippe Brun[9], Chantal Decroisette[10], Pierre Bombaron[11], Pierre-Paul Bringuier[12], Véronique Haddad[13], Fabien Forest[14], Michel Peoc'h[14], Sylvie Lantuejoul[5,13], Florence de Fraipont[15], Isabelle Ray-Coquard[2,16] & Pierre Fournel[17]

2012 Regional compliance to reflex EGFR testing and 1st line EGFR-TKI treatment

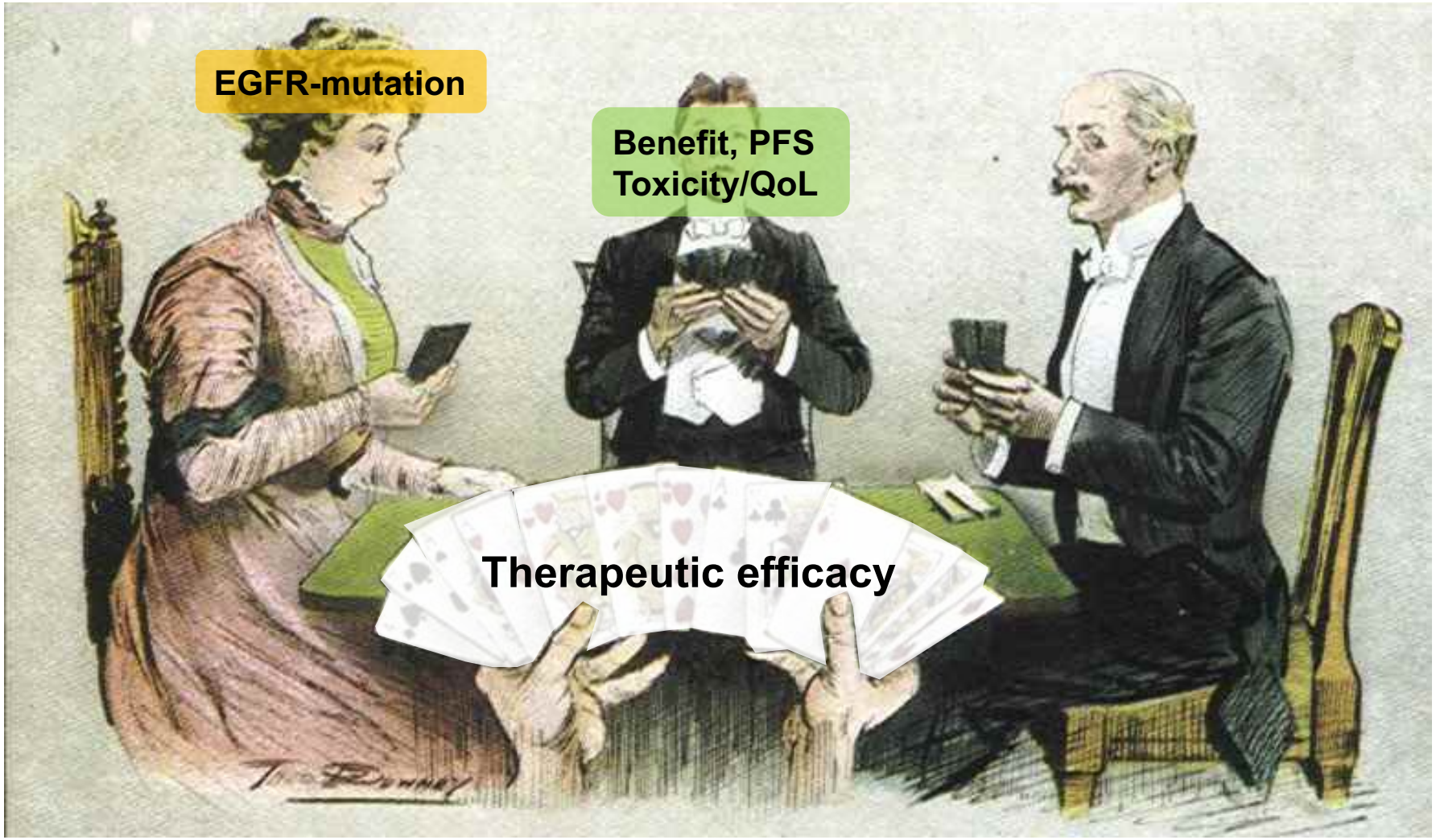
169 (11,3%) EGFR-driven NSCLC on 1850 advanced NSCLC tested





Swalduz A, Future Oncol 2019, 15:2139

ITK, puis chimiothérapie…



ITK, puis chimiothérapie…

1st generation TKIs

Afatinib

Trial	Trial design (phase, primary end point and treatment arms, including number of patients harbouring *EGFR* mutations)[a]	Median follow-up duration (months)	Outcomes (ORR, median PFS and median OS)
First generation			
IPASS	• III • PFS • Gefitinib (n = 1	17	• 71.2% versus 47.3% • 9.5 mo versus 6.3 mo (HR 0.48; P < 0.001) 21.9 mo (HR 1.00; P = 0.99)
First-SIGNAL	• III • OS • Ge (n		HR 0.54; P = 0.086) o (HR 1.04)
WJTOG3405	• III • PF • Ge		(HR 0.49; P < 0.0001) o (HR 1.25)
NEJ002	• III • PF • Ge (n		(HR 0.30; P < 0.001) o (HR 0.89; P = 0.48)
OPTIMAL (CTONG-0802)	• III • PF • Erl (n		(HR 0.16; P < 0.0001) o (HR 1.19; P = 0.27)
ENSURE	• III • PF • Erl (n		HR 0.34; P < 0.0001) o (HR 0.91; P = 0.61)
EURTAC	• III • PF • Erl pa		(HR 0.37; P < 0.0001) o (HR 1.04; P = 0.87)
Second generation			
LUX-Lung 3	• III • PFS • Afati (n = 11		o (HR 0.58: P = 0.001) mo versus 28.2 mo (HR etion: 33.3 mo versus 21.1 mo (HR 0.54; P = 0.002)
LUX-Lung 6	• III • PFS • Afatinib (n = 242) versus cisplatin + gemcitabine (n = 122)	33	• 66.9% versus 23% • 11.0 mo versus 5.6 mo (HR 0.28; P < 0.0001) • 23.1 mo versus 23.5 mo (HR 0.93; P = 0.61)

TKI-EGFR vs CT

- ORR: 56-85% vs 18-47%
- PFS: 9.2-13.1 vs 4.6-6.9 mo.

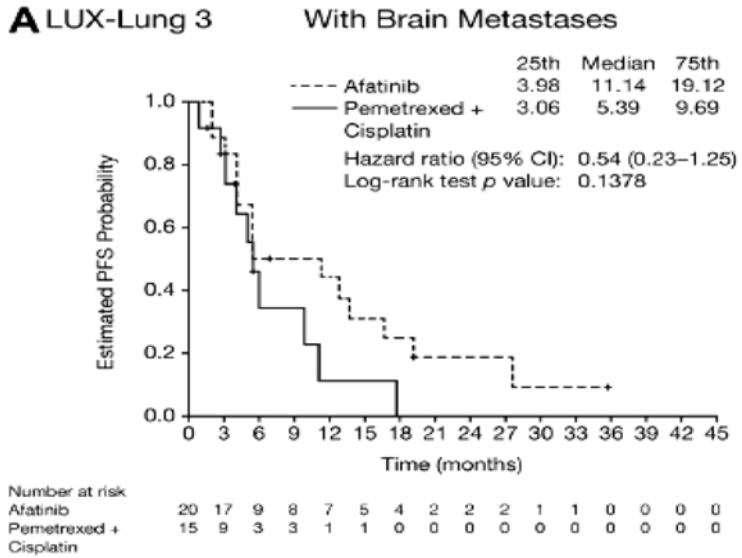
  HR: 0.16 to 0.58
- Better QoL and less toxicities
- Cost-effectiveness
- OS: 19.3-34.8 vs 19.5-37.3 mo.

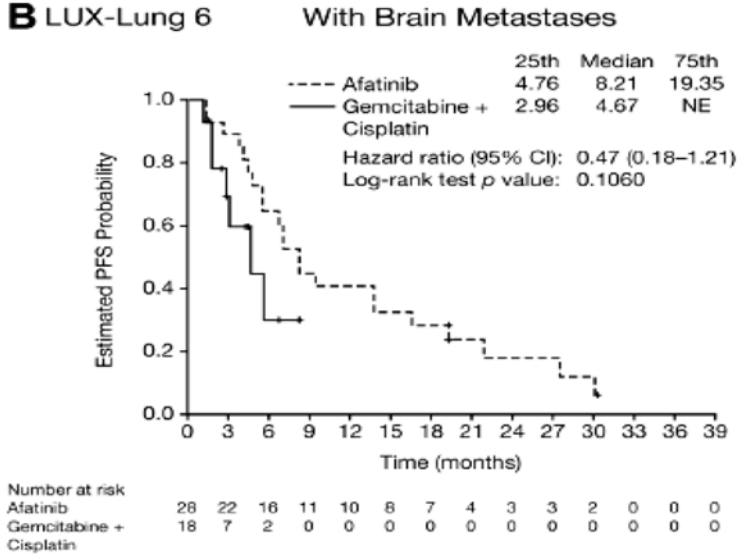
Recondo G, Nature Rev Clin Oncol 2018, 15:694

ITK, puis chimiothérapie…

LUX-Lung 3 and 6 brain metastasis efficacy by IRB

Outcome	With Brain Metastases		
LUX-Lung 3	Afatinib n = 20	Cisplatin-pemetrexed n = 15	*p* Value
ORR, *n* (%, 95% CI)	14 (70.0, 45.7-88.1)	3 (20.0, 4.3-48.1)	0.0058
DCR, *n* (%, 95% CI)	19 (95.0, 75.1-99.9)	12 (80.0, 51.9-95.7)	0.1986
LUX-Lung 6	Afatinib n = 28	Cisplatin-gemcitabine n = 18	*p* Value
ORR, n (%, 95% CI)	21 (75.0, 55.1-89.3)	5 (27.8, 9.7-53.5)	0.0027
DCR, n (%, 95% CI)	25 (89.3, 71.8-97.7)	13 (72.2, 46.5-90.3)	0.1486





Schuler M, JTO 2015, 11:380

ITK, puis chimiothérapie, pour les mutations communes…

1st generation TKIs

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First-SIGNAL	• III • OS • Ge (*n*		HR 0.54; *P* = 0 o (HR 1.0
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EGFR-mutations

- Only del19 and L858R mutations in almost all studies
- Except, IPASS and LUX-Lung 3 and 6 studies *(T790M; L861Q; G719X; S768I; Exon 20 ins)*

Recondo G, Nature Rev Clin Oncol 2018, 15:694

ITK ou chimiothérapie, pour les mutations rares…

Table 4
Response rates and survival outcomes from a post-hoc analysis of afatinib in patients with advanced lung adenoca

	ORR, %	DOR, months	Disease control rate, %	Median PFS, months[a]	M
Group 1: point mutations and deletions in exons 18–21 (n = 38)	71	11.1	84	10.7	
Group 2: T790M alone or in combination with other mutations (n = 14)	14	8.2	64	2.9	14.9
Group 3: exon 20 insertions (n = 23)	9	7.1	65	2.7	9.2

[a] Median follow-up 19.2 months.
[b] Median follow-up 34.7 months. DOR = duration of response; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Reproduced with permission from Yang JC, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015 Jul;16(7):830-8. doi:10.1016/S1470-2045(15)00026-1 [43].

- Afatinib better than CT (1)
- Afatinib better than 1st generation EGFR TKI (2)
- Osimertiinib efficacy (3)

- Osimertinib authorization to use or CT?

- Poziotinib (4)
- TAK 788 (5)

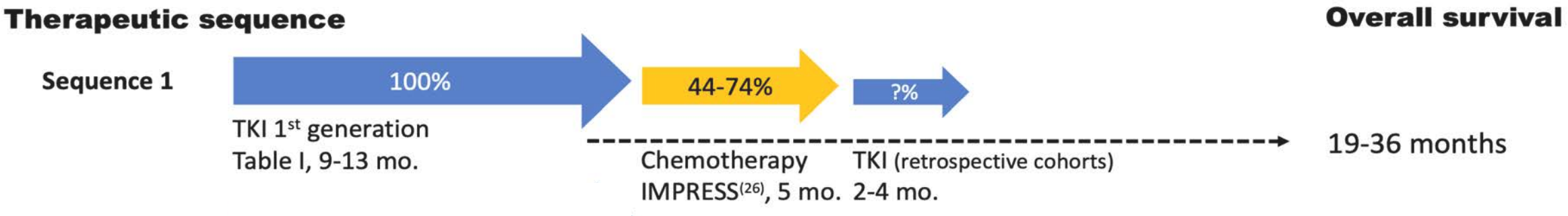
- The limited clinical activity seen in groups 2 and 3 is consistent with preclinical findings

Masood A, Seminars in Oncology Epub September 2019;

1) Yang JC Lancet Oncol 2015,16:830; 2) Shen Y, Lung Cancer 2017,110:56; 3) Cho JH, J Thorac Oncol 2018,13:S344

4) Heymach J, J Thorac Oncol 2018, WCLC; 5) Neal J, J Thorac Oncol 2018, WCLC

Erlotinib=gefitinib, puis CT…



Study name	Details of the study	PFS (months)	OS (months)	ORR (%)
CTONG 0901	Erlotinib [128] *vs.* gefitinib [128]; *EGFR*-mutant; 66% in 1st-line; phase III	13.0 (erlotinib) *vs.* 10.4 (gefitinib); ns	22.9 (erlotinib) *vs.* 20.1 (gefitinib); ns	56.3 (erlotinib) *vs.* 52.3 (gefitinib); ns

Cadranel J, Ann Transl Med 2018, 6:57

ITK de deuxième vs ITK de première génération, puis CT…

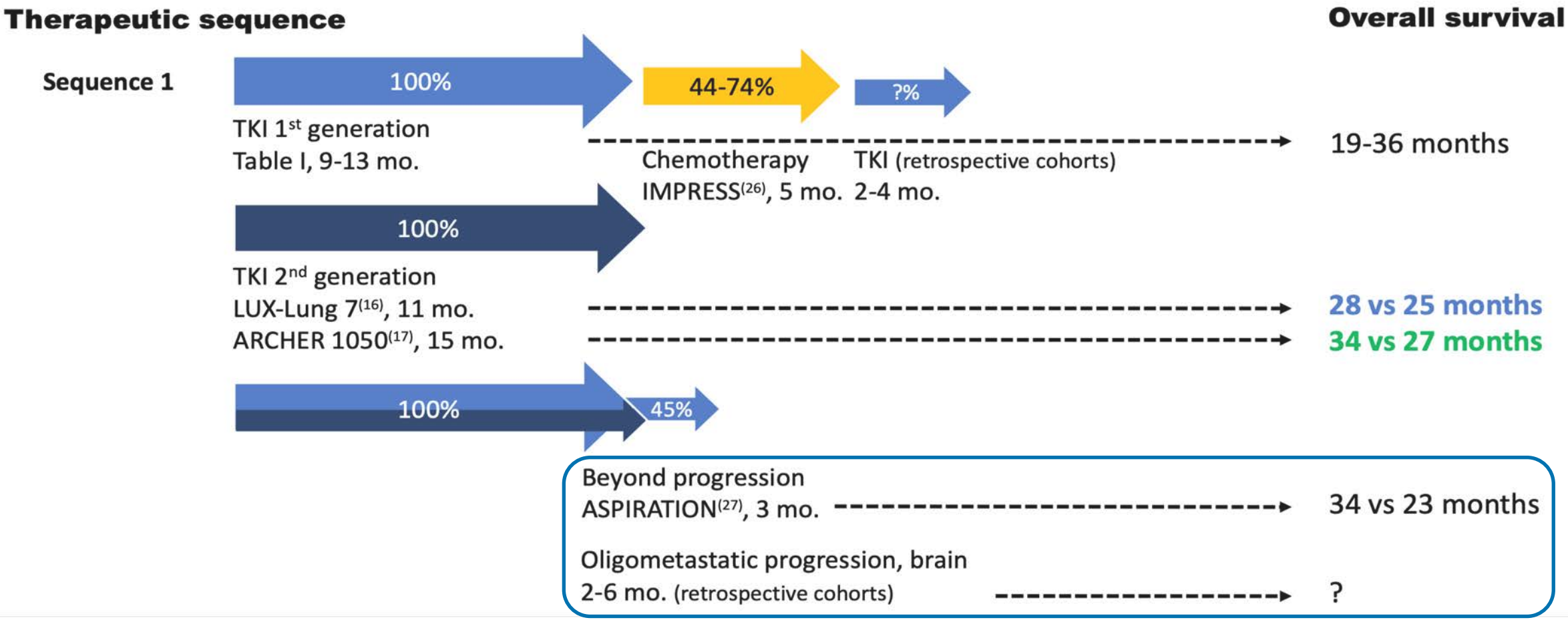
Phase III/IIb trials evaluating 1st vs 2nd generation EGFR TKIs in 1st line treatment

Study name	Details of the study	PFS (months)	OS (months)	ORR (%)
LUX-Lung 7	Afatinib [160] *vs.* gefitinib [159]; *EGFR*-mutant; 1st-line; phase IIb	11.0 (afatinib) *vs.* 10.9 (gefitinib); P=0.017	27.9 (afatinib) *vs.* 24.5 (gefitinib); ns	
ARCHER 1050	Dacomitinib [227] *vs.* gefitinib [225]; *EGFR*-mutant; 1st-line; phase III	14.7 (dacomitinib) *vs.* 9.2 (gefitinib); P<0.0001	34.1 (dacomitinib) *vs.* 26.8 (gefitinib); P=0.0438	(dacomitinib) *vs.* 72.0 (gefitinib); ns

- No brain metastasis
- No benefit for Caucasians
- 51% vs 30% grade 3 tox
- Detrimental QoL
- Which place in the context of osimertinib approval?

Karachaliou N, Transl Cancer Res 2019, 8:S23; Yang JJ, BJC, 2017, 116:568; Park K, Lancet Oncol 2016,17:577; Wu YL, Lancet Oncol 2017, 18:1454; Mok T, J Clin Oncol 2018, 36:2244

CBNPC mutés pour l'EGFR, quelle séquence thérapeutique?



*Cadranel J, Ann Transl Med 2018, 6:57; *Reck M, Lancet Respir Med 2019, Epub*

CBNPC mutés pour l'EGFR, quelle séquence thérapeutique?

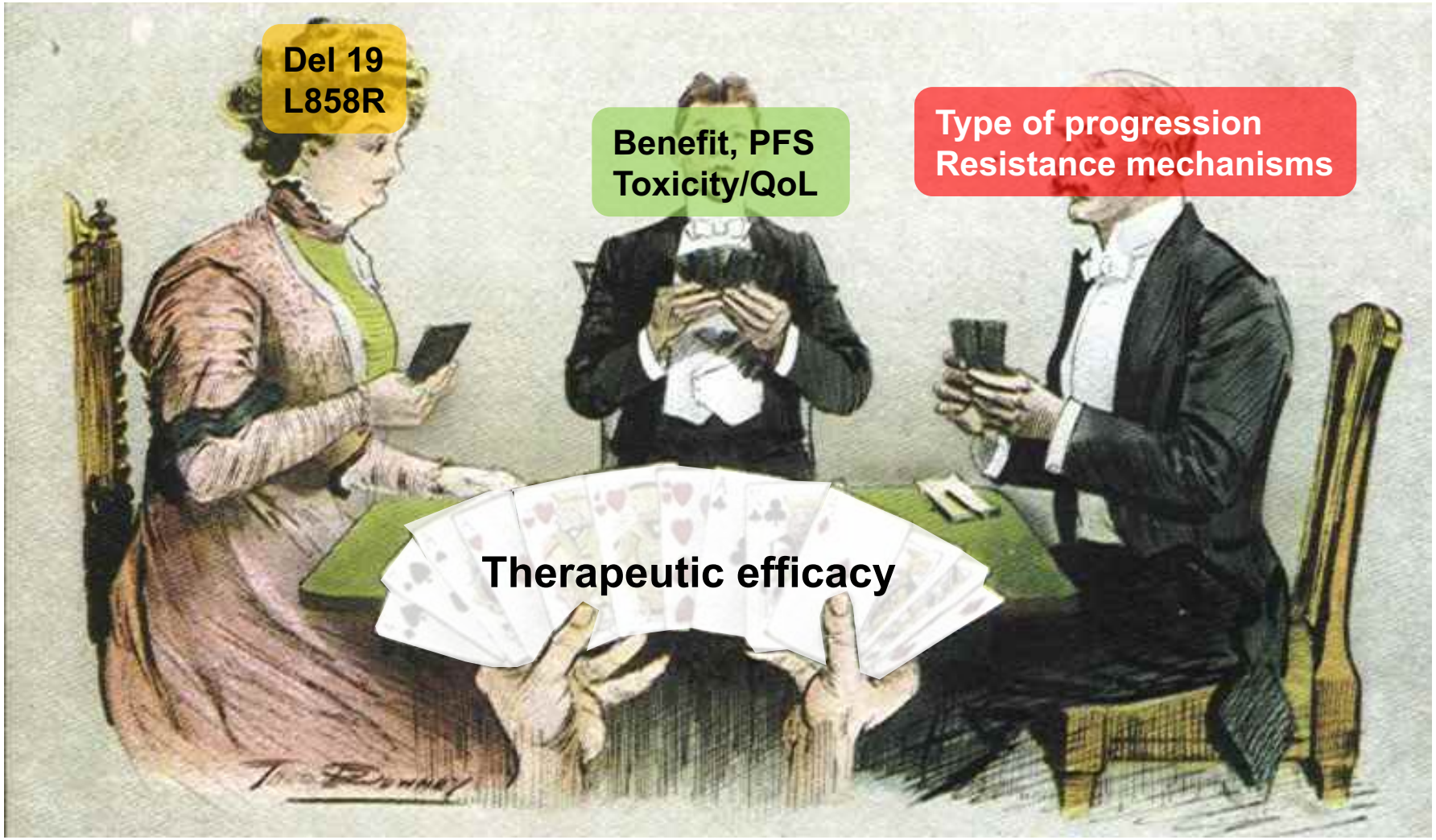
Comparison of pharmacokinetic characteristics of EGFR-TKI

Characteristics	Gefitinib	Erlotinib	Afatinib
Type	1st generation, reversible	1st generation, reversible	2nd generation, irreversible
Target	EGFR wt	EGFR wt	EGFR/HER2,4,(3) (and T790M)
MDT	800-1000 mg	150 mg	50 mg
Recommended dose	250 mg	150 mg	50 mg
Formulation	-	25, 100, 150 mg	20, 30, 40, 50 mg
Biodisponibility	59%	76%	45-70%
Impact of food intake	**No**	increased abs.	decreased abs.
Effect of gut pH	reduced abs.	reduced abs.	**No**
Pharmacologic interaction	CYP	CYP	**P-gp**
Smoking effect	No	**Yes**	No
Liver elimination	96%	90%	85%
≥grade 3 toxicity	**21-29%**	17-45%	36-49%
Skin toxicity	66-78%	71-80%	88-95%
Diarrhea	39-58%	26-57%	**81-89%**
Hepatitis	61%	6-41%	**20%**

Cost and availability

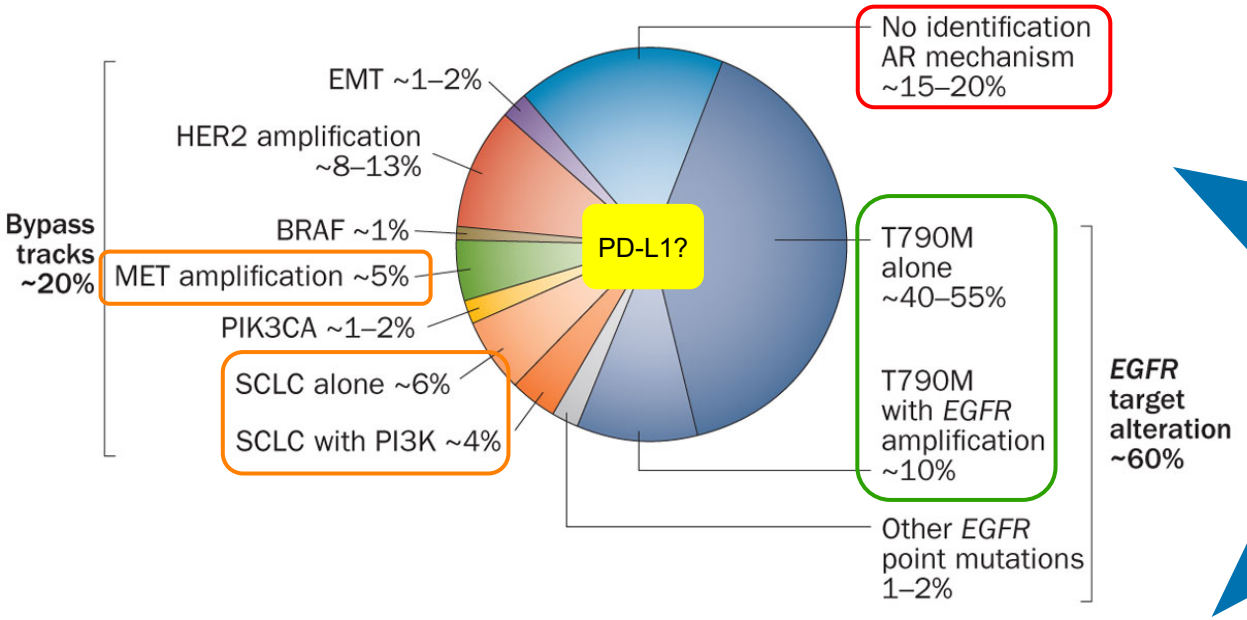
Adapted from Cadranel J, RMR 2018 cours du GOLF

ITK, puis rebiopsie à la progression…



ITK, puis rebiopsie à la progression…

Molecular resistance



Less frequent T790M selection in the CNS
More MET alterations (amplification, HGF expression)

How to detect (T790M) resistance mechanisms?

50% clinical sensitivity
(NGS, PD-L1)

Acquired resistance to EGFR TKI

→ All pts undergo biopsy, FDA-approved FFPE assay for T790M
- T790M+ → Third gen. EGFR TKI
- T790M– → Chemotherapy

70% clinical sensitivity
(NGS, gromagranine, enolase)

Acquired resistance to EGFR TKI

→ FDA-approved plasma assay for T790M and sensitizing mutations
- T790M+ → Skip biopsy, start third gen. EGFR TKI
- T790M– → Biopsy, FDA approved FFPE assay for T790M
  - T790M+ → Third gen. EGFR TKI
  - T790M– → Chemotherapy

Camidge R, Nat Rev Clin Oncol 2014, 11:473; Oxnard GR, J Clin Oncol 2016, 34:3375; Chouaid C, Lung Cancer 2014, 56:170

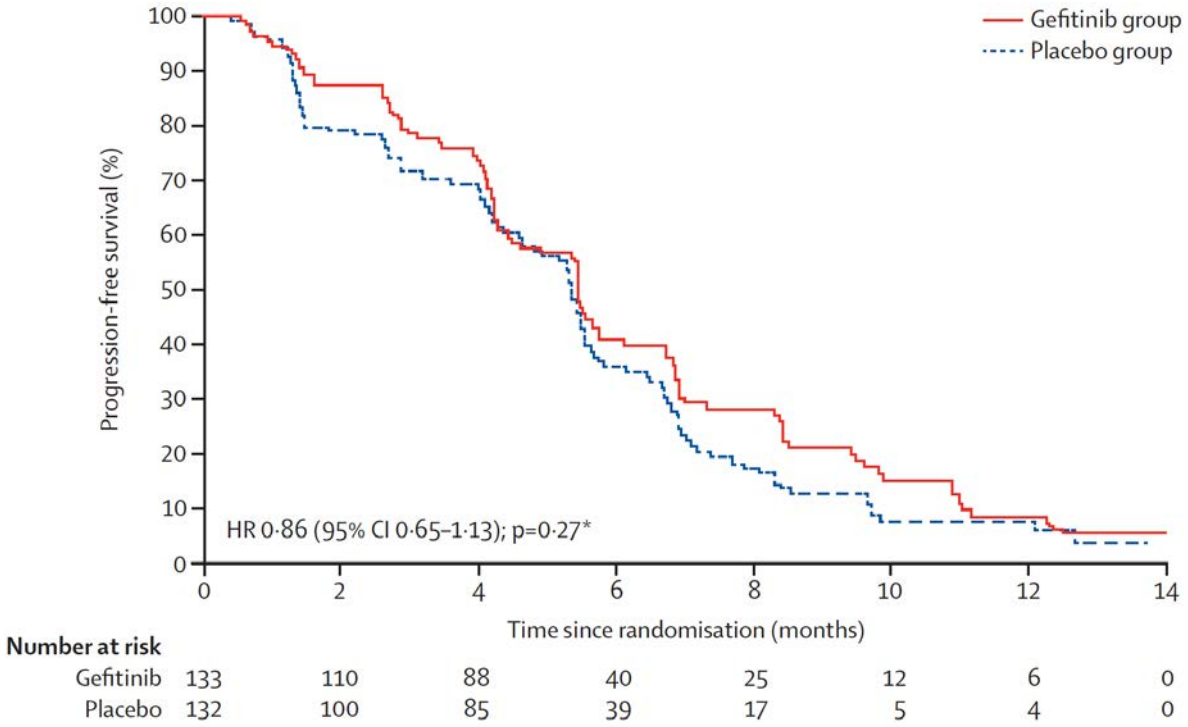
15-20%

Absence d'anomalie moléculaire, CT sans poursuite de l'ITK

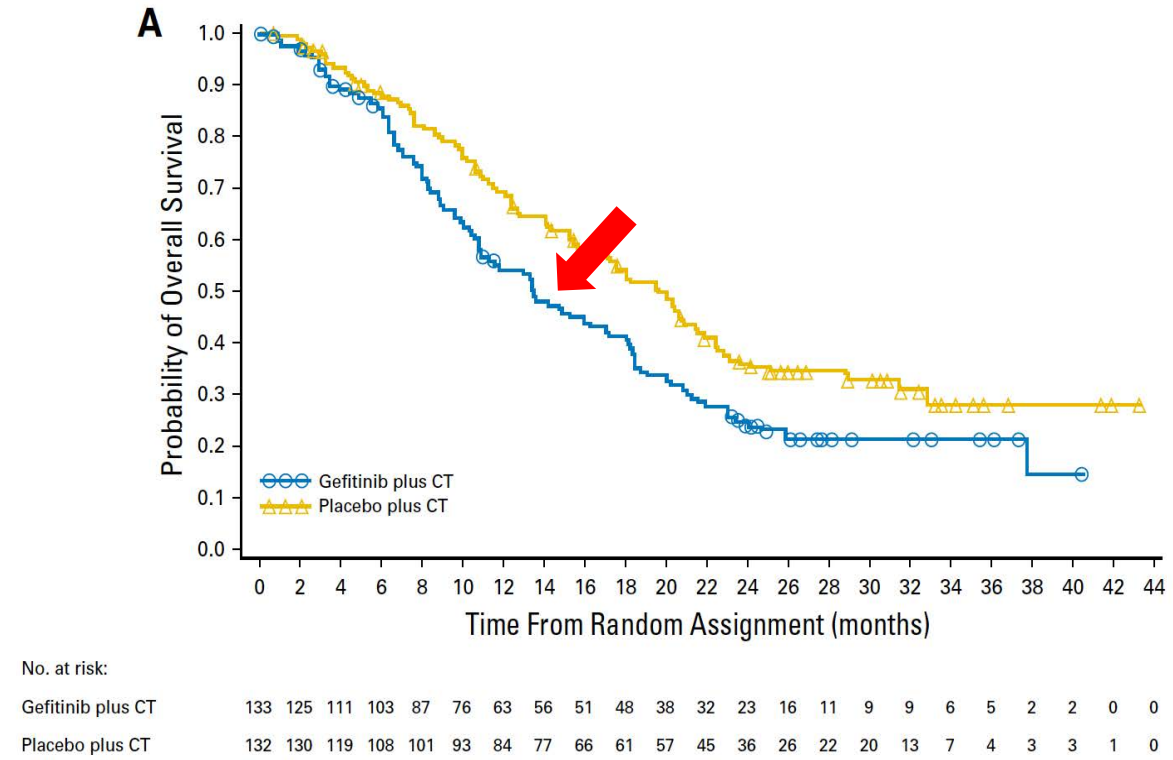
IMPRESS Phase III trial placebo controlled trial, 2nd line treatment of EGFR NSCLC

After progression on gefitinib, Cis-Pem/Pem ± Gefitinib, n=265

PFS



OS



Soria JC, Lancet Oncol 2015, 16:990; Mok T, J Clin Oncol 2017, 35:4025

Absence d'anomalie moléculaire, CT±bevacizumab et atezolizumab

IMpower 150 Phase III trial, 1st line treatment of all comers NSCLC

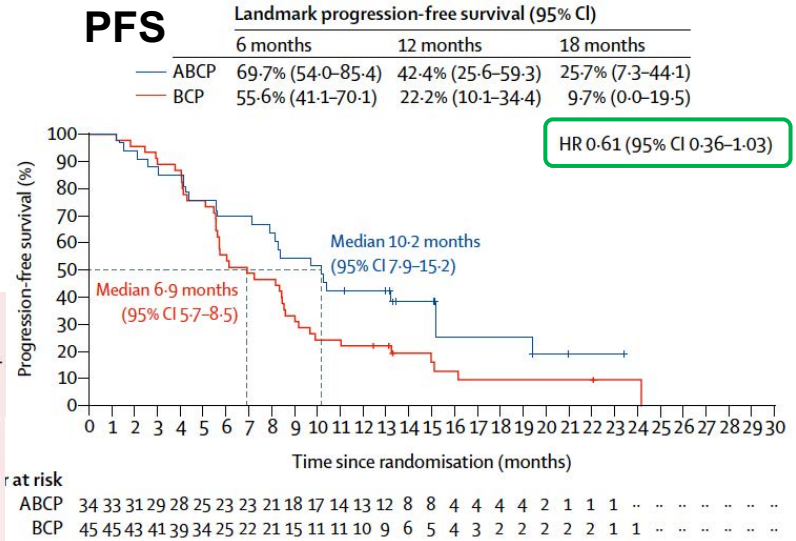
Carboplatin paclitaxel plus becacizumab (BCP) or atezolizumab (ACP) or atezolizumab plus bevacizumab (ABCP)

Subgroup analysis in EGFR driven NSCLC after EGFR-TKI (n=123)

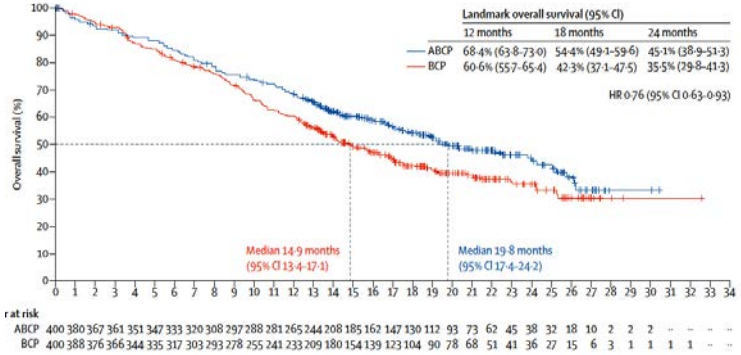
• Which proportion of T790M mutation after TKI progression?

	ACP group	BCP group	
Intention-to-treat population†			
EGFR-positive mutation§¶			
Number of patients	34	45	43
Proportion of patients with an objective response	24 (70·6%; 95% CI 52·5–84·9)	16 (35·6%; 95% CI 21·9–51·2)	18 (41·9%; 95% CI 27·0–57·9)
Complete response	2 (5·9%; 95% CI 0·7–19·7)	1 (2·2%; 95% CI 0·1–11·8)	0
Partial response	22 (64·7%; 95% CI 46·5–80·3)	15 (33·3%; 95% CI 20·0–49·0)	18 (41·9%; 95% CI 27·0–57·9)
Stable disease	5 (14·7%; 95% CI 5·0–31·1)	21 (46·7%; 95% CI 31·7–62·1)	19 (44·2%; 95% CI 29·1–60·1)
Progressive disease	2 (5·9%; 95% CI 0·7–19·7)	6 (13·3%; 95% CI 5·1–26·8)	3 (7·0%; 95% CI 1·5–19·1)
Median duration of response, months (range)	11·1 (2·8–18·0)	5·6 (2·6–15·2)	4·7 (2·6–13·5)
Number of patients with ongoing response at cutoff	9 (37·5%)	3 (18·8%)	0

PFS



OS



Similar frequency of ≥3 grade toxicities, with increased proportion of irAE in ABCP vs ACP arm

Reck M, Lancet Respir Med 2019, Epub

≈ 10%

Transformation en CBPC (±T790M), platine plus étoposide

Retrospective cohort of Small Cell Lung Carcinoma – post-EGFR TKI and *de novo*, in EGFR driven NSCLC

Characteristics	Total (n=67)
Age, years old	56 (27-87)
Female/Male, %	57/43
White/Asian/Others, %	49/42/9
Never smoker/smoker, %	73/27
Histology, % • ADC/others • *de novo* SCLC	 85/2 13
Del19/L858R/others, % *de novo* T790, %	67/24/12 3

TABLE 3. Frequency of Common Mutations Within Small-Cell Lung Cancer Cases, by Testing Method

Genotyping Platform	*TP53*	*RB1*	*PIK3CA*
All assays	38/48 (79)	18/31 (58)	14/52 (27)
Allele-specific PCR	2/8 (25)	—	3/8 (38)
NGS	32/35 (91)	15/26 (58)	11/39 (28)
Whole-exome sequencing	3/4 (75)	3/4 (75)	0/4 (0)
Unknown	1/1 (100)	0/1 (0)	0/1 (0)

ORIGINAL ARTICLE

Concurrent *RB1* and *TP53* Alterations Define a Subset of *EGFR*-Mutant Lung Cancers at risk for Histologic Transformation and Inferior Clinical Outcomes

Michael Offin, MD,[a] Joseph M. Chan, MD, PhD,[a] Megan Tenet,[a] Hira A. Rizvi

Therapy Received	No. (%)
Received before transformation to SCLC	n = 58
Checkpoint inhibitor	4 (7)
Cytotoxic chemotherapy	21 (36)
Platinum-doublet regimens	20 (34)
Bevacizumab	9 (16)

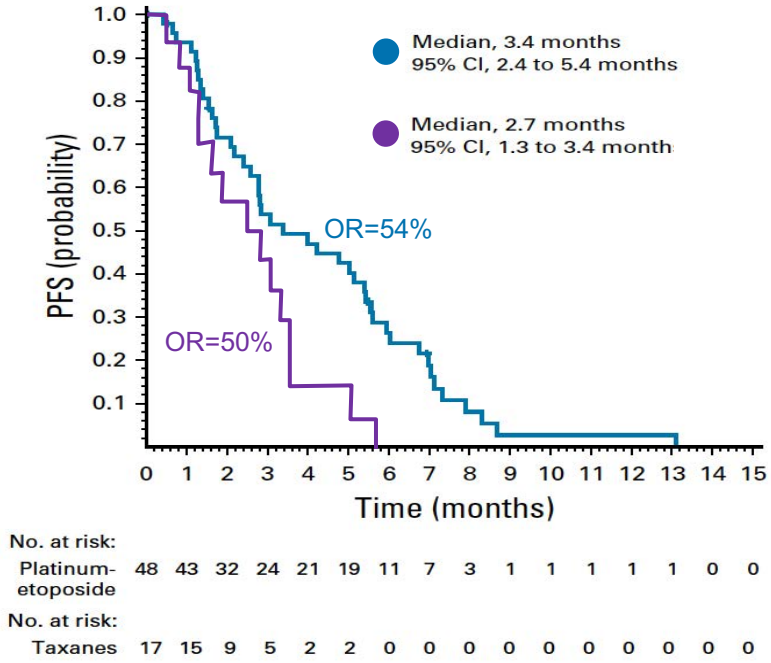
Lee JK, J Clin Oncol 2017, 35:3065; Marcoux N, J Clin Oncol 2018, 18:278; Offin M, JTO Epub May 2019

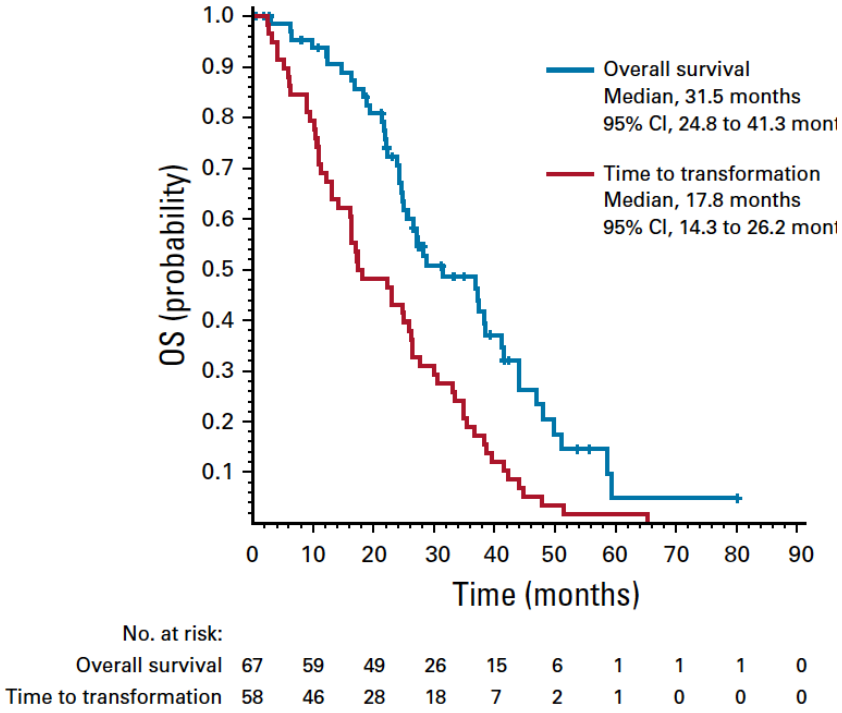
≈ 10%

Transformation en CBPC (±T790M), platine plus étoposide

Retrospective cohort of Small Cell Lung Carcinoma – post-EGFR TKI and *de novo*, in EGFR driven NSCLC

Therapy Received	(%)
Cytotoxic chemotherapy	63 (97)
● Platinum-etoposide	53 (82)
Other platinum-combination	7 (11)
● Taxane	21 (32)
Campthotecin (topotecan, irinotecan)	12 (18)
Temozolamide	4 (6)
EGFR TKI *(combined with CT)*	34 (52)
Checkpoint inhibitor	17 (26)
PD-1 or PD-L1 monotherapy	9 (14)
Ipilumumab plus nivolumab	8 (12)





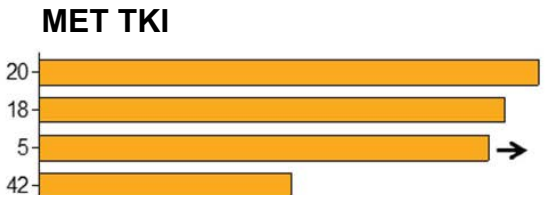
Jiang SY, Medicine 2016, 95:1; Lee JK, J Clin Oncol 2017, 35:3065; Marcoux N, J Clin Oncol 2018, 18:278

≈ 5%

Amplification de MET (±T790M)?

French retrospective cohort of EGFR NSCLC with MET alteration after TKI

Tested for MET IHC 3+ and/or FISH amplification



ClinicalTrials.gov identifier	Phase; population	Treatment	Status
NCT02468661	Phase I/II; EGFR TKI-pretreated; c-MET amplified	Erlotinib + INC280 (capmatinib; c-MET inhibitor) *vs.* chemotherapy (phase II)	Recruiting
NCT01610336	Phase IB/II; EGFR TKI-pretreated; c-MET amplified	Gefitinib + INC280	Ongoing, not recruiting
NCT02374645	Phase Ib; EGFR TKI-pretreated; c-MET amplified	Gefitinib + volitinib (c-MET inhibitor)	Ongoing, not recruiting
NCT01982955	Phase Ib/II; EGFR TKI-pretreated; c-MET amplified and T790M negative	Gefitinib + tepotinib (c-MET inhibitor)	Ongoing, not recruiting

MET, mesenchymal-to-epithelial transition; *MET*, MET proto-oncogene receptor tyrosine kinase; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; cfDNA, cell-free DNA.

Baldacci S, Oncotarget 2017, 8:107103; York E, JTO 2017, 12:e86; Kang J, JTO 2017, 13:e50; Deng L, JTO 2018 Epub September; Karachaliou N, Transl Cancer Res 2019, 8:S23

≈ 40-60%

Identification de la mutation T790M, osimertinib

Phase I and II trials of osimertinib in T790M resistant EGFR NSCLC after progression on EGFR-TKI

Efficacy (95% CI)	AURA (expansion phase I) (n=63) (8)	AURA (expansion phase II) (n=201) (8)	AURA 2 phase II (n=210) (65)	Pooled AURA I–II (n=411) (66)
RR (%)	61 [48–74]	61 [54–68]	71 [64–67]	66 [61–71]
DR (months)	9.7 [8.3–NR]	NR	7.8 [7.1–NR]	NR [8.3–NR]
DR up to 6 months (%)	72 [54–84]	83 [74–89]	75 [65–82]	78 [72–84]
DCR (%)	95 [86–99]	90 [85–94]	91 [87–95]	91 [88–94]
PFS (months)	11 [7–15]	NR [8.1–NR]	8.6 [8.2–9.7]	9.7 [8.3–NR]

Gonzalez-Larriba, TLCR 2017, 6:S21

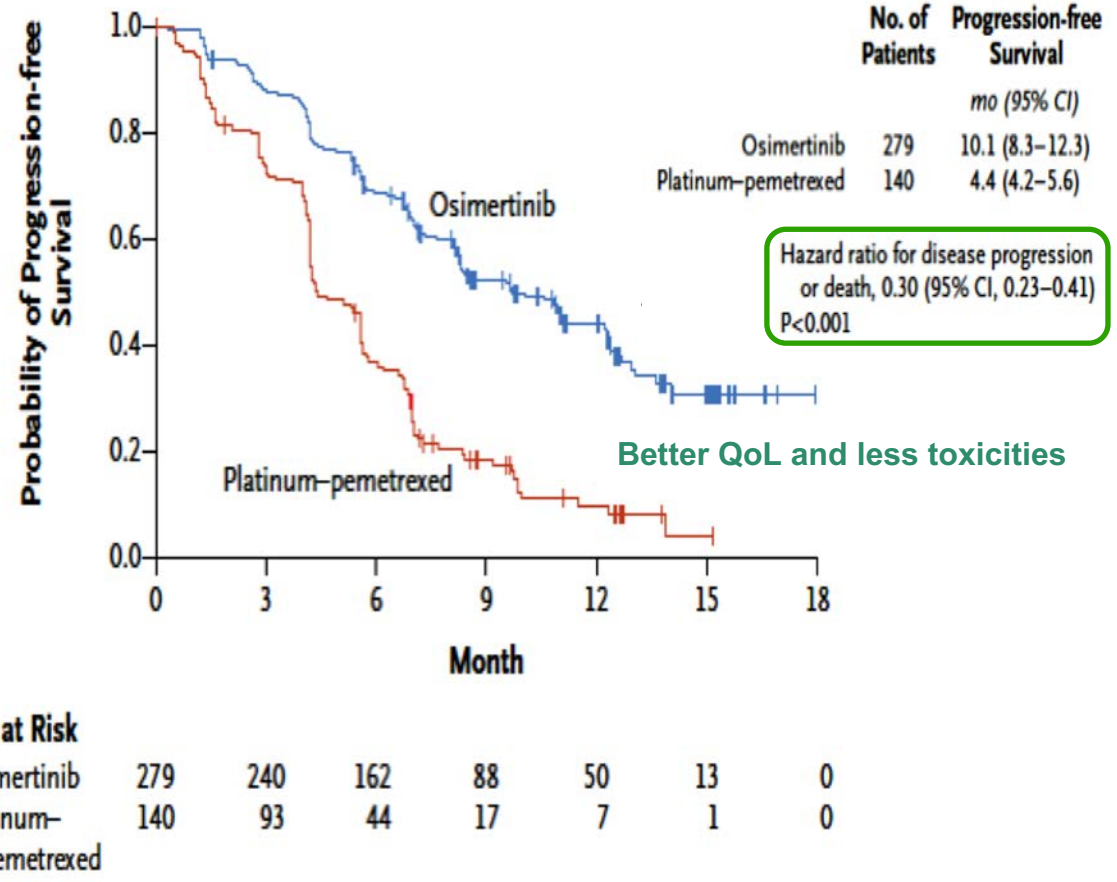
≈ 40-60%

Identification de la mutation T790M, osimertinib

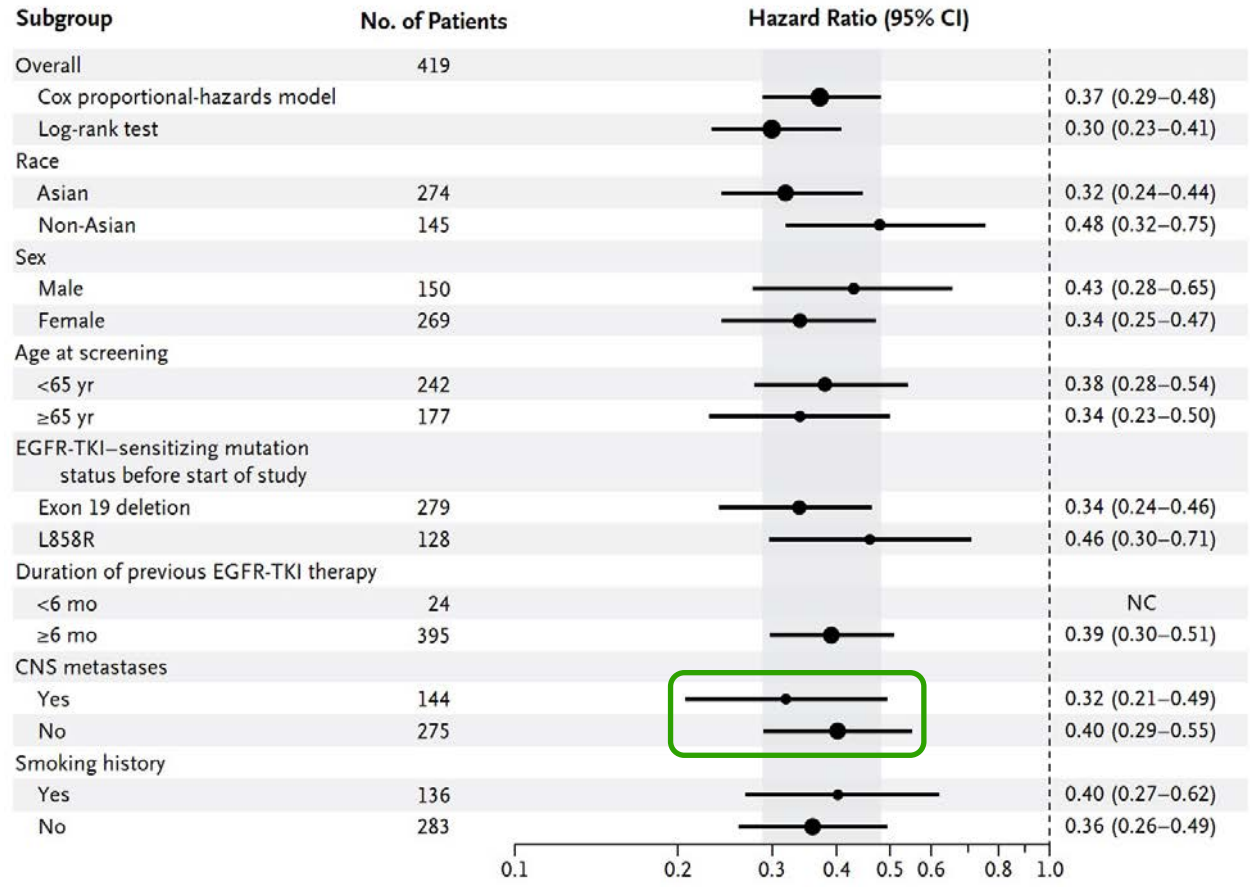
AURA 3 Phase III trial osimertinib vs platinum pemetrexed, 2nd line treatment of EGFR NSCLC

All patients with T790M mutation after 1st line EGFR TKI, amendment for osimertinib cross-over

A Patients in Intention-to-Treat Population



Better QoL and less toxicities



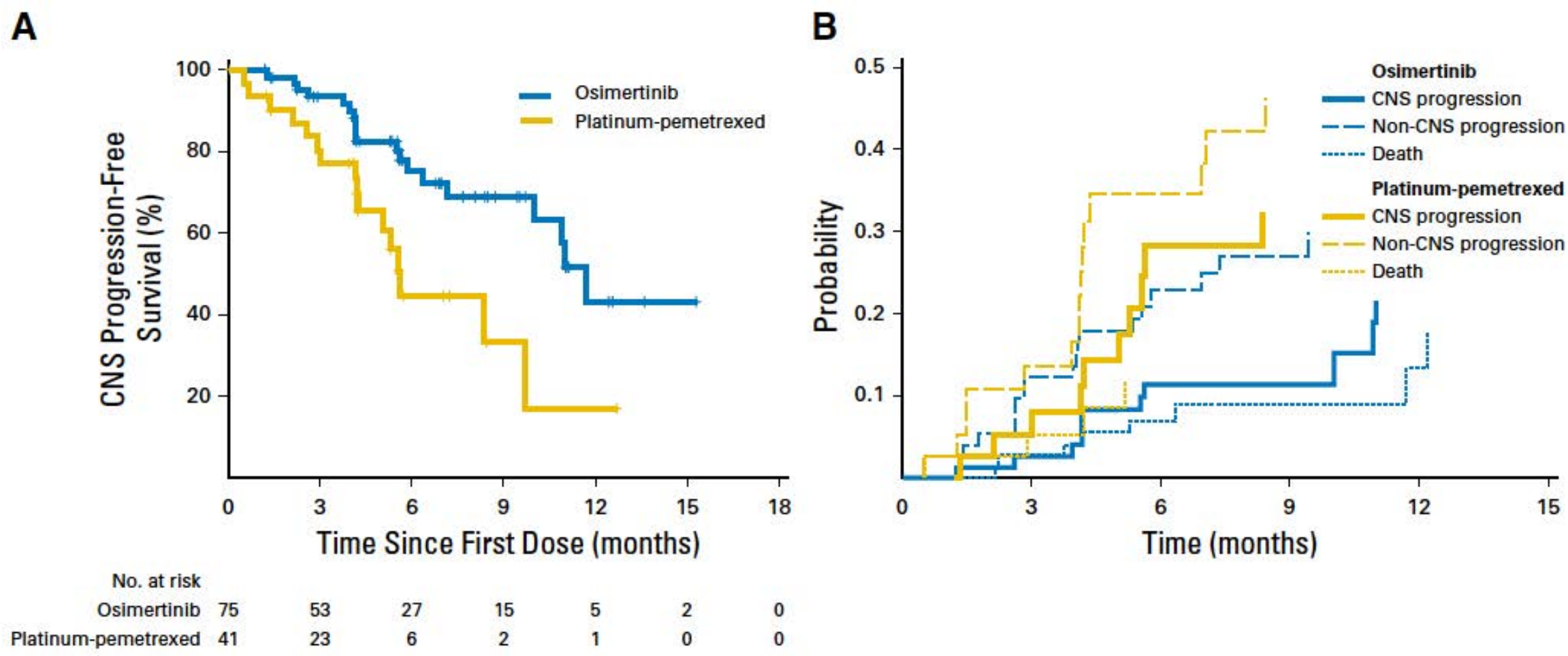
Mok TS, N Engl J Med 2017, 16:376

≈ 40-60%

Identification de la mutation T790M, osimertinib

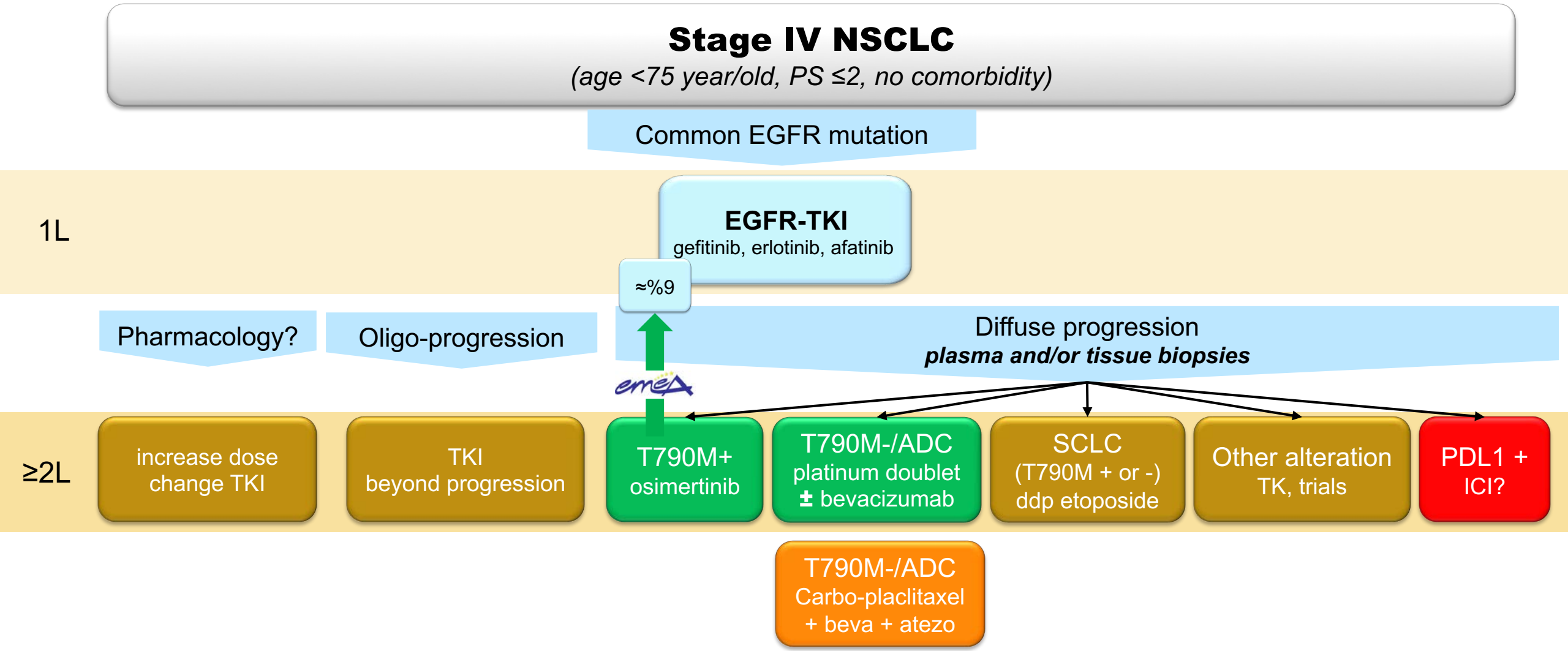
AURA 3 Phase III trial osimertinib vs platinum pemetrexed, 2nd line treatment of EGFR NSCLC

All patients with T790M mutation after 1st line EGFR TKI



Wu YL, J Clin Oncol 2018, epub July

CBNPC mutés pour l'EGFR, quelle séquence thérapeutique?



Planchard D, Annales Oncol 2018, 29:192; Planchard D, Annales Oncol 2019, Epub

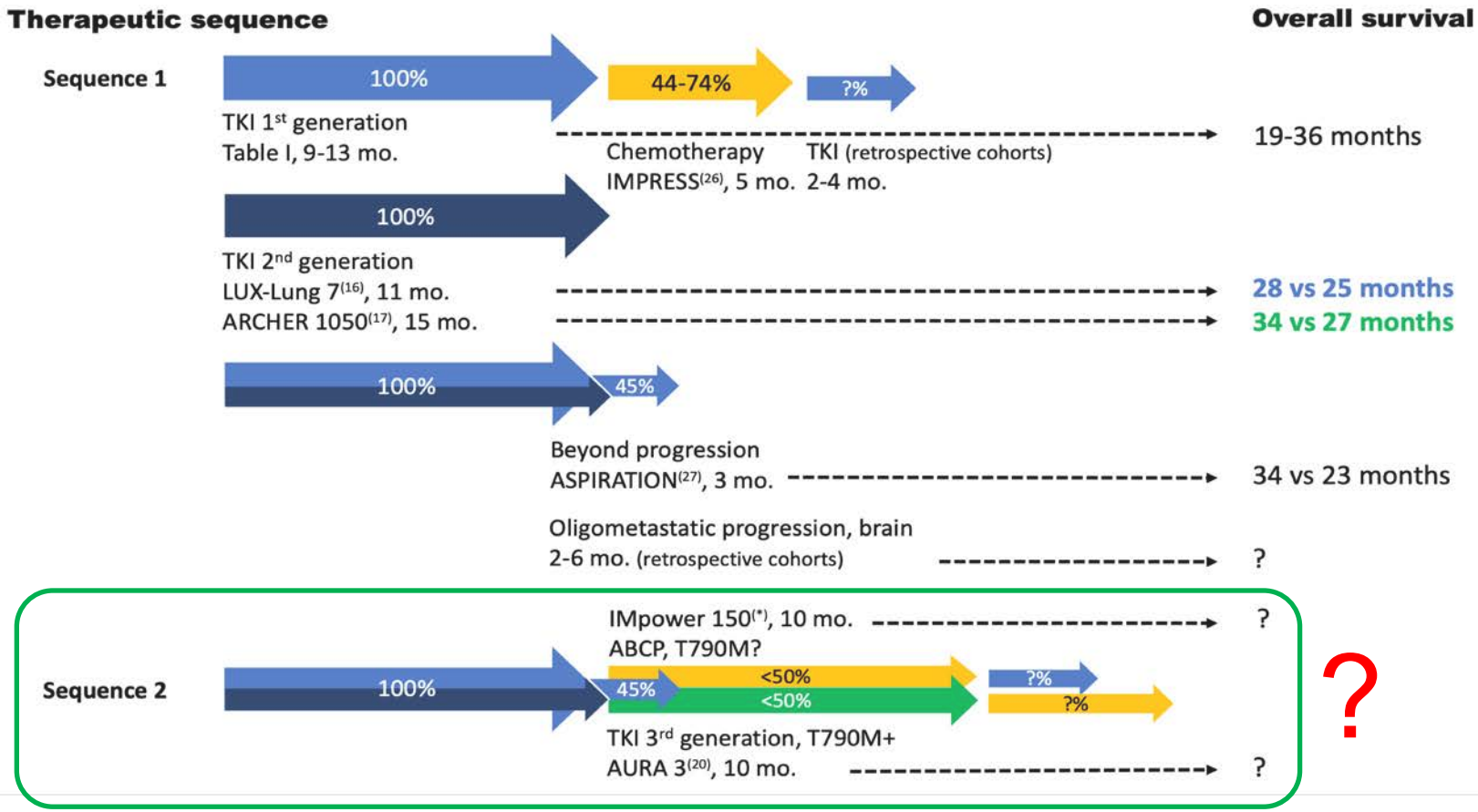
CBNPC mutés pour l'EGFR, quelle séquence thérapeutique?

TKI 1st generation

Chemotherapy

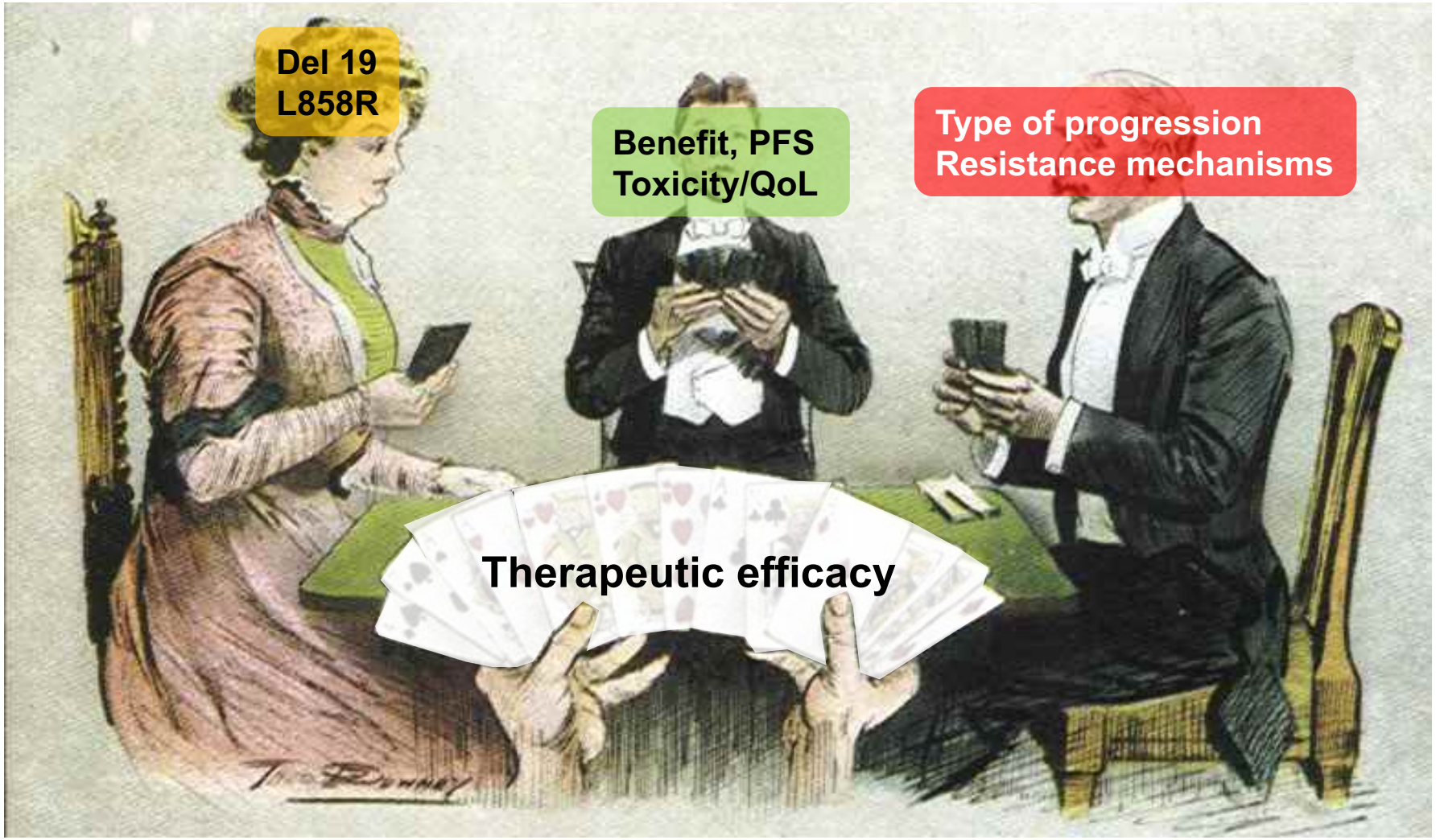
TKI 2nd generation

Osimertinib



*Cadranel J, Ann Transl Med 2018, 6:57; *Reck M, Lancet Respir Med 2019, Epub*

Osimertinib ou ITK 1ére génération en 1ère ligne?



Osimertinib ou ITK 1^{ére} génération en 1ère ligne?

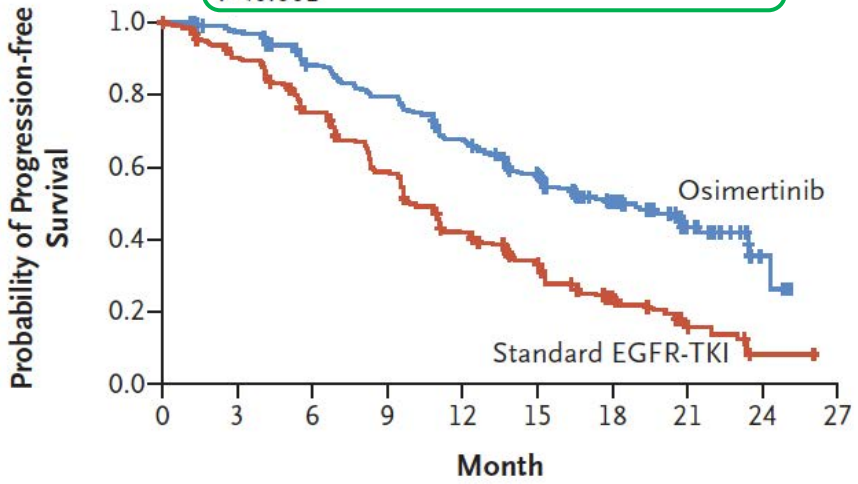
FLAURA Phase III 1st line treatment, osimertinib *vs* gefitinib/erlotinib

Advanced NSCLC, common EGFR mutation, double blind, amendment for osimertinib cross-over

A Progression-free Survival in Full Analysis Set

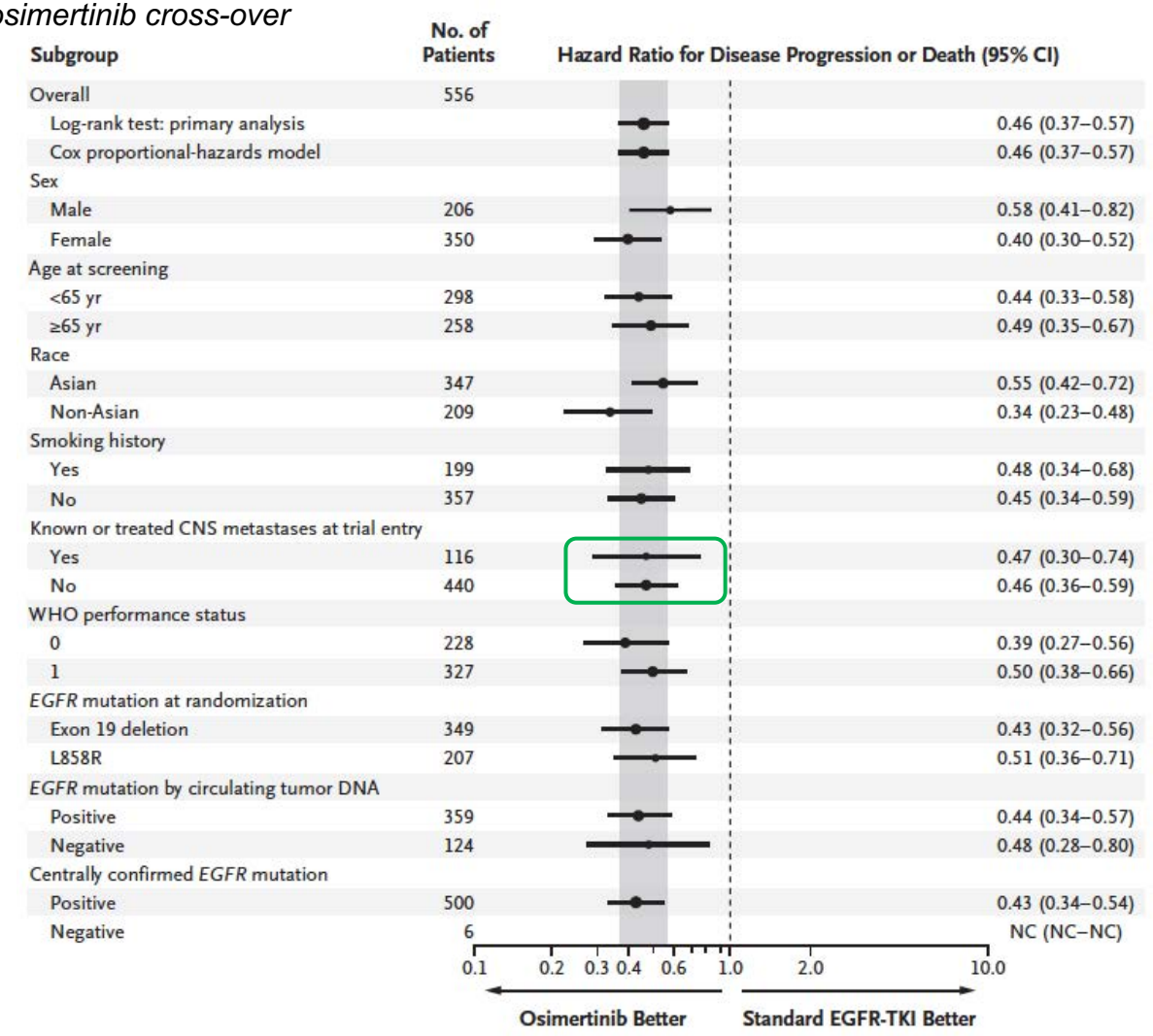
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

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



Soria JC, N Engl J Med 2018, 378:113

Osimertinib ou ITK 1^{ére} génération en 1ère ligne?

FLAURA Phase III 1st line treatment, osimertinib *vs* gefitinib/erlotinib

Advanced NSCLC, common EGFR mutation

Table S7. Most common possibly causally-related adverse events (as assessed by the investigator) reported in at least 10% of patients treated with osimertinib or standard EGFR-TKI

Adverse events by preferred term*	Osimertinib (n=279)					Standard EGFR-TKI (n=277)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
	Number (percent)									
Rashes and acnes†	152 (54)	125 (45)	24 (9)	3 (1)	0	205 (74)	105 (38)	81 (29)	19 (7)	0
Diarrhea	138 (49)	105 (38)	27 (10)	6 (2)	0	142 (51)	105 (38)	31 (11)	5 (2)	0
Dry Skin†	93 (33)	80 (29)	12 (4)	1 (<1)	0	92 (33)	70 (25)	19 (7)	3 (1)	0
Paronychia†	91 (33)	48 (17)	42 (15)	1 (<1)	0	84 (30)	52 (19)	30 (11)	2 (1)	0
Stomatitis	69 (25)	57 (20)	11 (4)	1 (<1)	0	45 (16)	36 (13)	8 (3)	1 (<1)	0
Decreased appetite	33 (12)	15 (5)	13 (5)	5 (2)	0	29 (10)	16 (6)	11 (4)	2 (1)	0
Pruritus	43 (15)	36 (13)	6 (2)	0	0	38 (14)	26 (9)	12 (4)	0	0
Aspartate aminotransferase elevation	22 (8)	15 (5)	5 (2)	2 (1)	0	57 (21)	31 (11)	16 (6)	10 (4)	0
Alanine aminotransferase elevation	17 (6)	11 (4)	5 (2)	1 (<1)	0	62 (22)	23 (8)	16 (6)	19 (7)	4 (1)

Soria JC, N Engl J Med 2018, 378:113; Ramalingam S, ESMO 2019

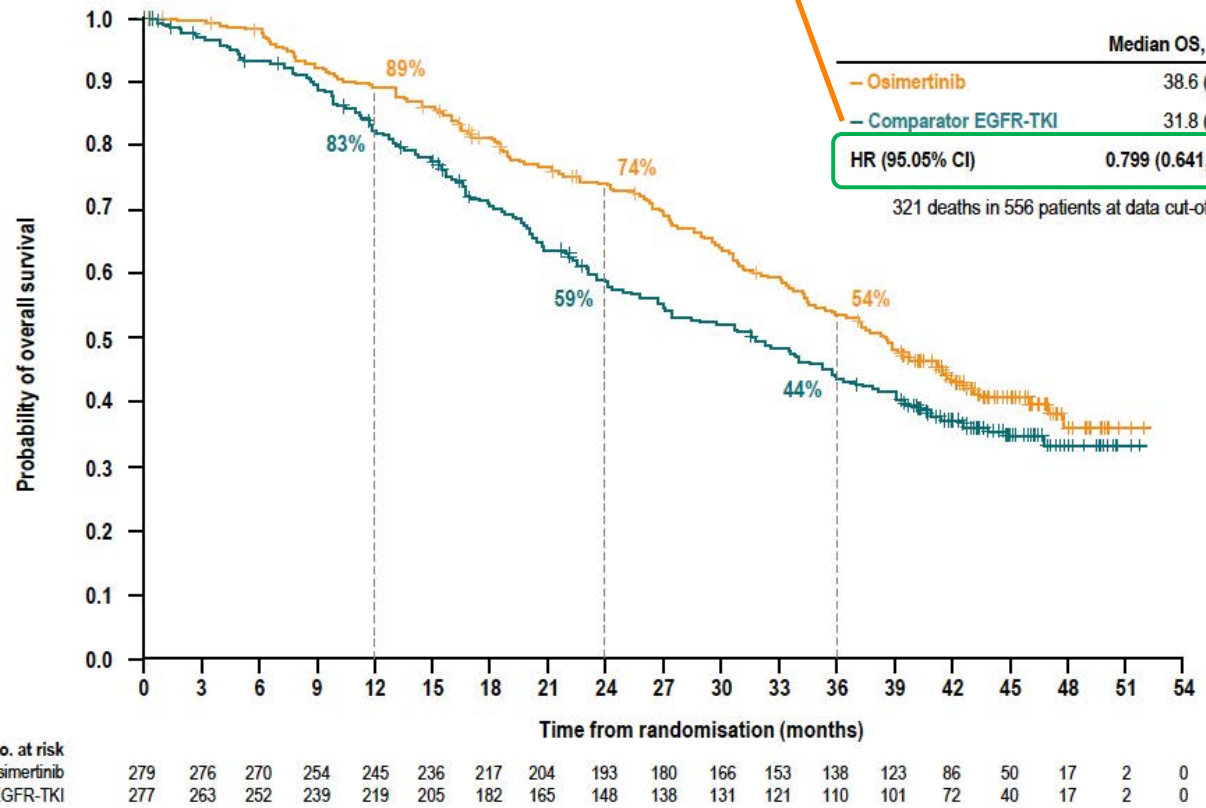
Osimertinib ou ITK 1ére génération en 1ère ligne?

FLAURA Phase III 1st line treatment, osimertinib *vs* gefitinib/erlotinib

Advanced NSCLC, common EGFR mutation

Overall survival

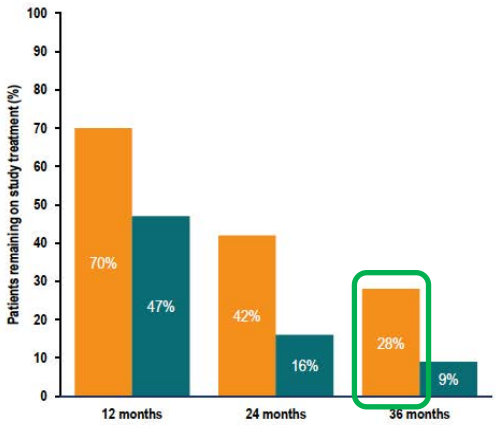
• What will be the results with afatinib or dacomitinib



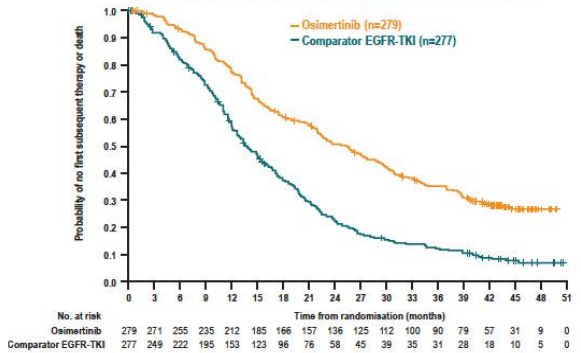
	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	0.799 (0.641, 0.997); p=0.0462

321 deaths in 556 patients at data cut-off: 58% maturity

Patients remaining on study treatment



Time to first subsequent treatment*



Time to first subsequent therapy or death	Events	Median, months (95% CI)
Osimertinib	194	25.5 (22.0, 29.1)
Comparator EGFR-TKI	242	13.7 (12.3, 15.7)
HR (95% CI)		0.478 (0.393, 0.581) p<0.0001

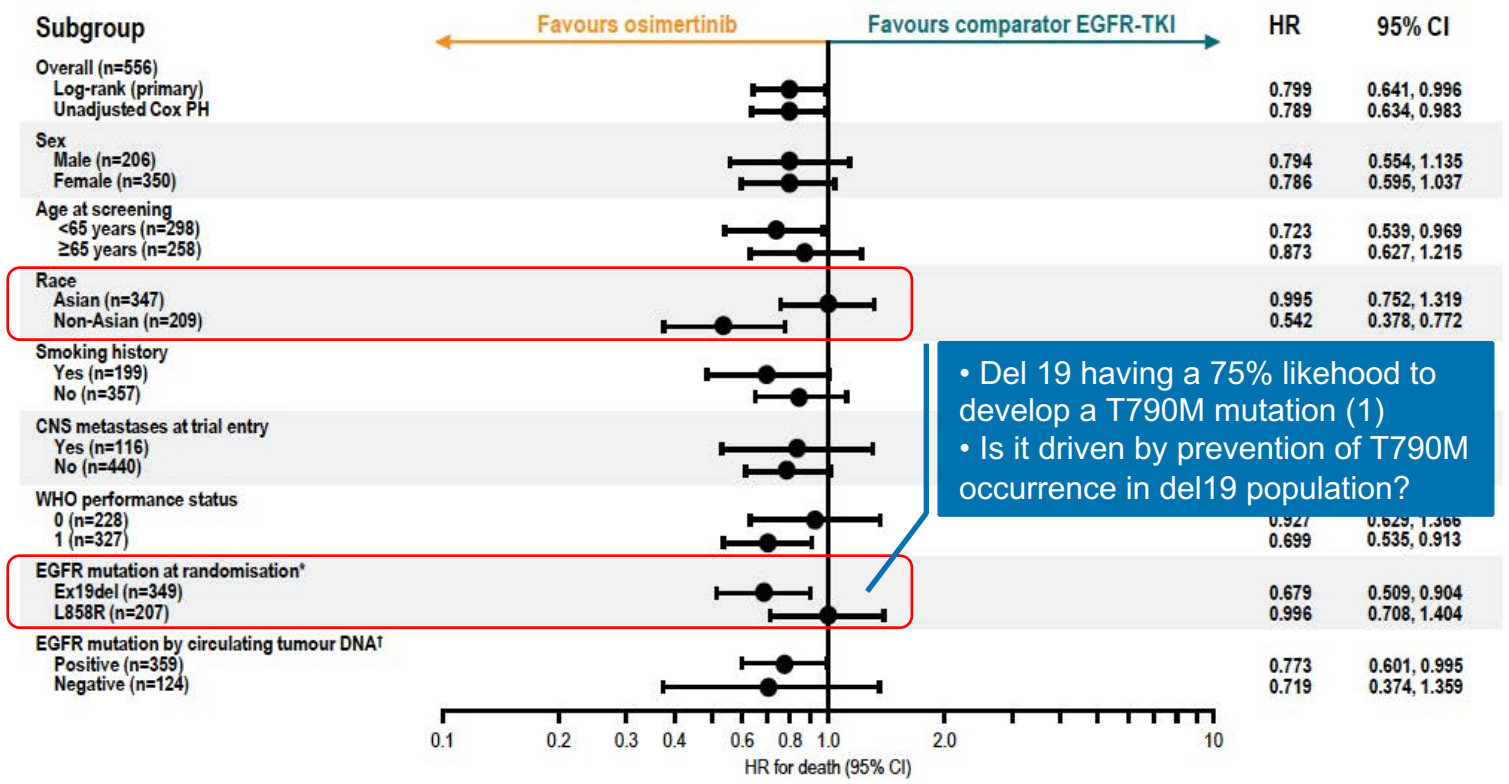
Ramalingam S, ESMO 2019

Osimertinib ou ITK 1^{ére} génération en 1ère ligne?

FLAURA Phase III 1st line treatment, osimertinib *vs* gefitinib/erlotinib
Advanced NSCLC, common EGFR mutation

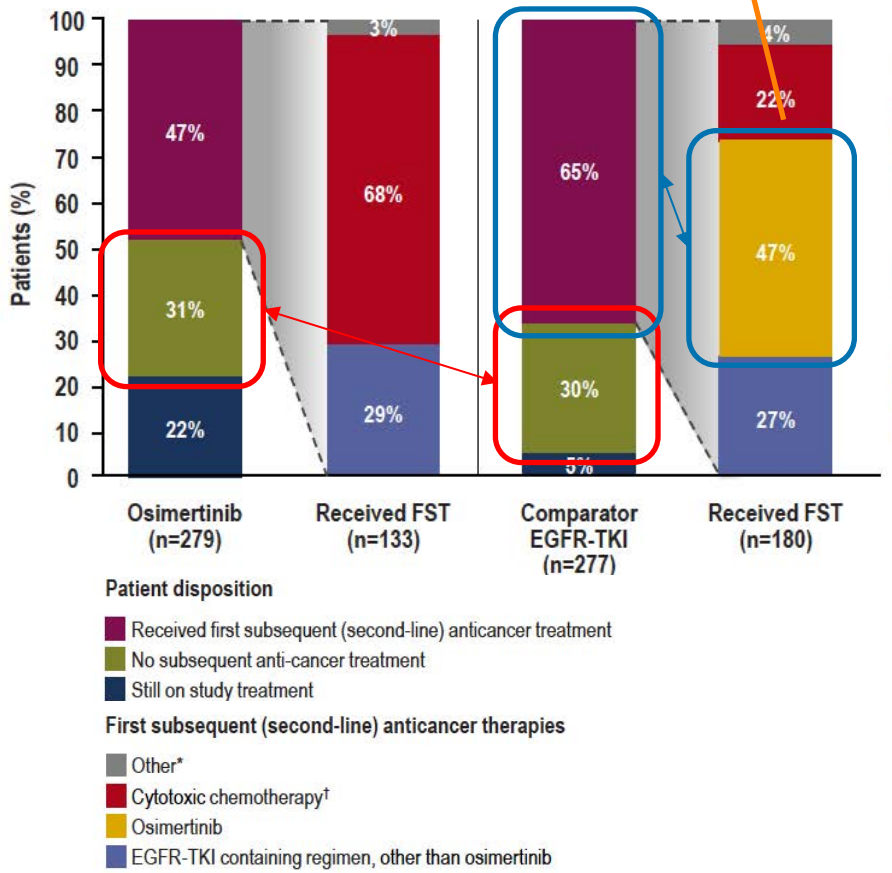
• only 31% of pts from SOC arm on osimertinib at progression
• while 47 to 74% T790M at progression (2,3)

Overall survival subgroups analysis



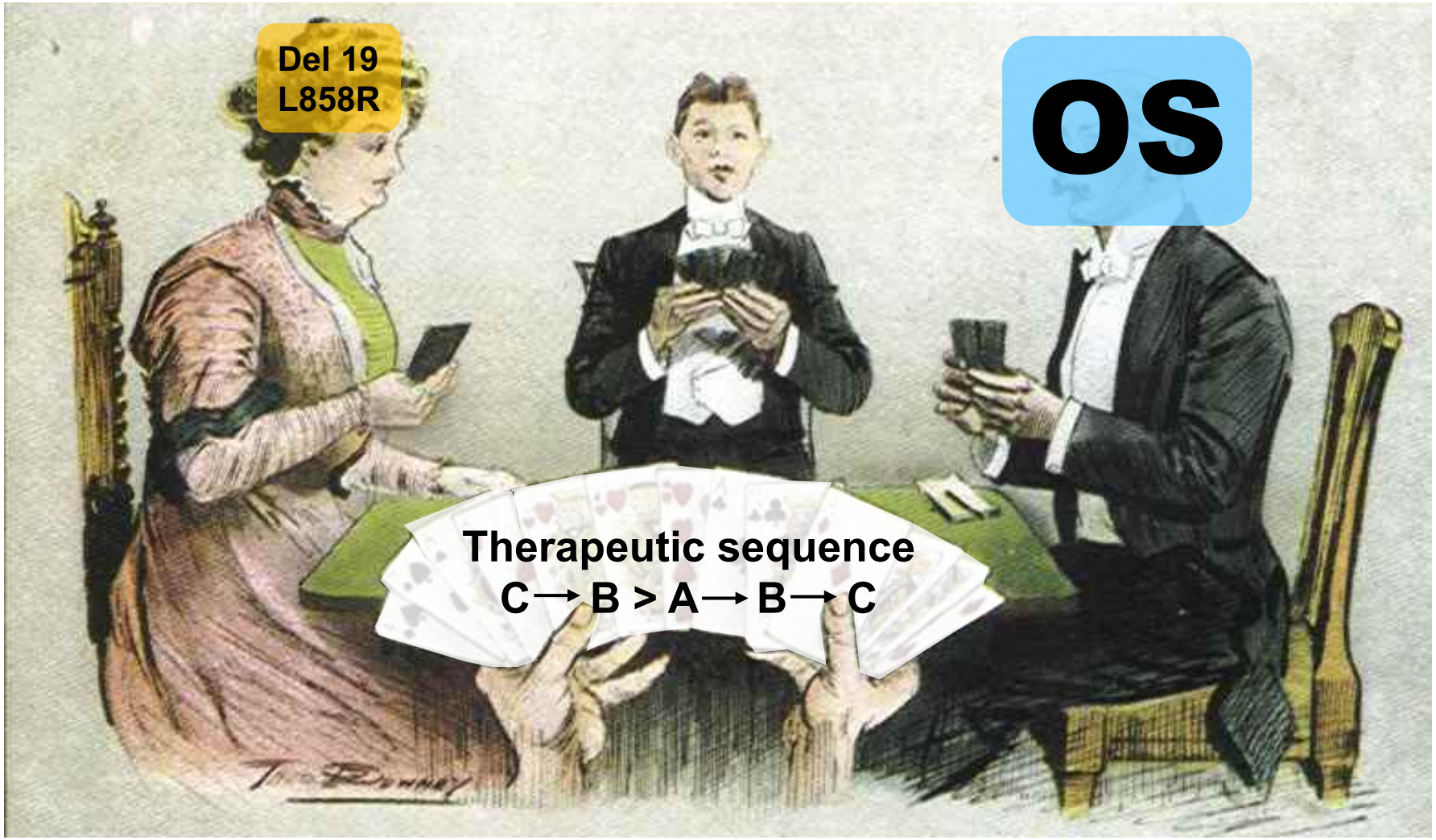
• Del 19 having a 75% likehood to develop a T790M mutation (1)
• Is it driven by prevention of T790M occurrence in del19 population?

Subsequent therapy after progression

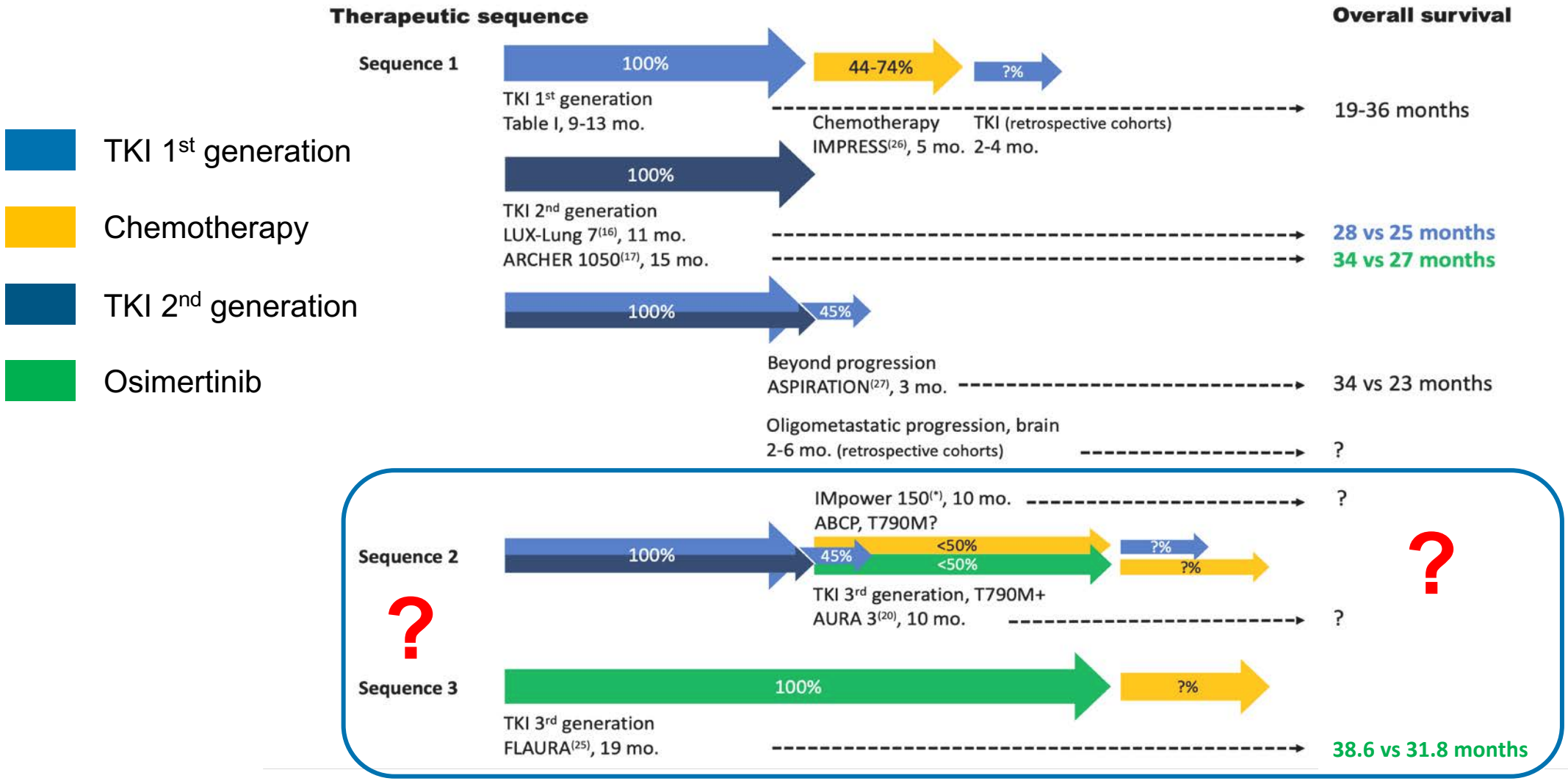


Ramalingam S, ESMO 2019; 1) Jenkins L, JTO 2017, 12:1247; 2) Ramalingam S, AACR 2018; 3) Gray JE, ESMO 2019

Traitement des CBNPC mutés EGFR



CBNPC mutés pour l'EGFR, quelle séquence thérapeutique?

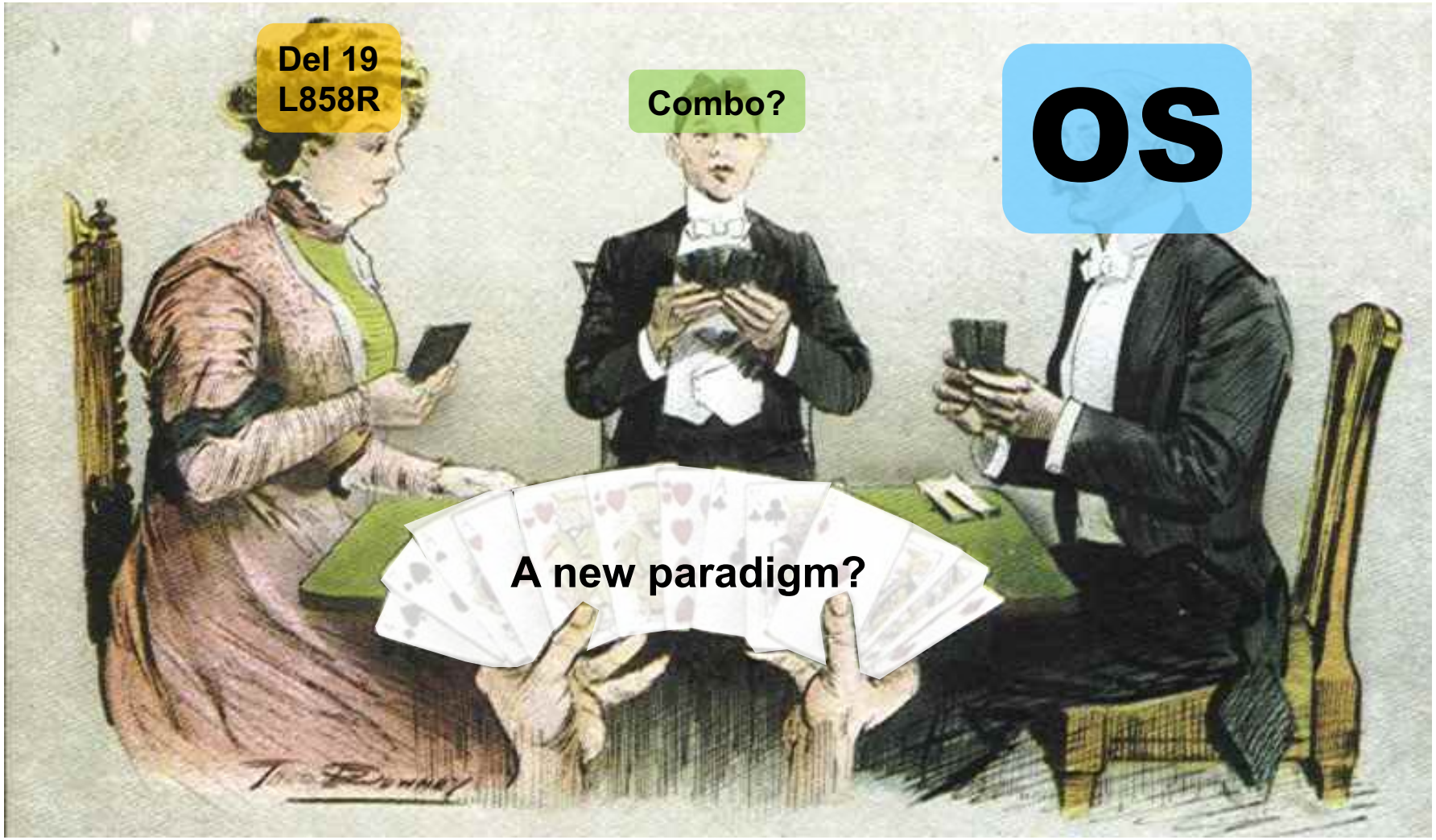


*Cadranel J, Ann Transl Med 2018, 6:57; *Reck M, Lancet Respir Med 2019, Epub*

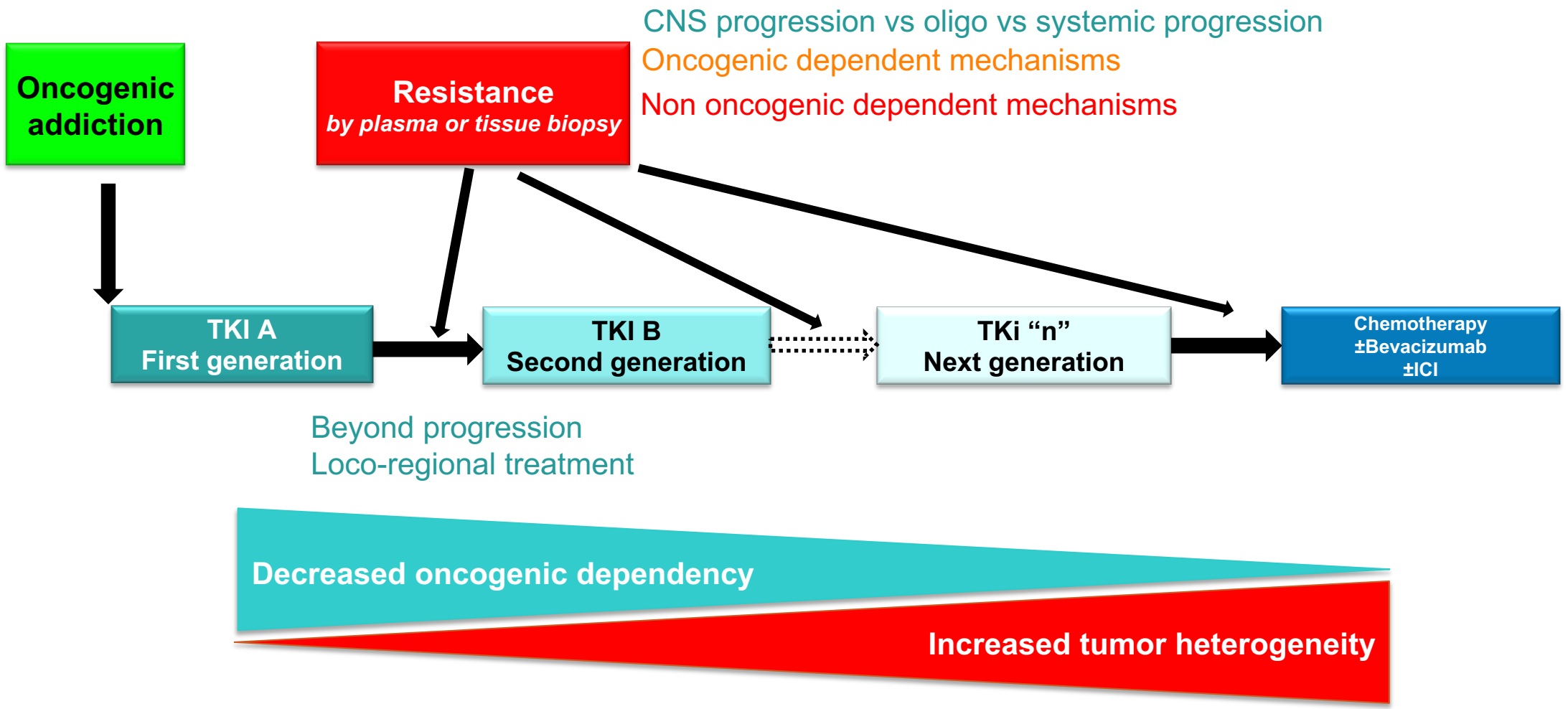
CBNPC mutés pour l'EGFR, quelle séquence thérapeutique?

Factor of choice	Sequential therapy	Osimertinib upfront
Availability and cost	**Favored**	Unfavored
Level of proof	Many trials/clinical experience	FLAURA phase III trial
PFS	Unfavored	**Favored**
OS	Unfavored	**Favored**
Brain efficacy	Unfavored	**Favored**
Tolerance	Unfavored	**Favored**
Need tissue/liquid rebiopsy	**Yes**	No
Resistance mechanisms	Complex	**Highly complex**
Futility of previous TKIs	No	**Yes**
Impact on compliance to recommandations	**Difficult**	**Easier?**

Traitement des CBNPC mutés EGFR



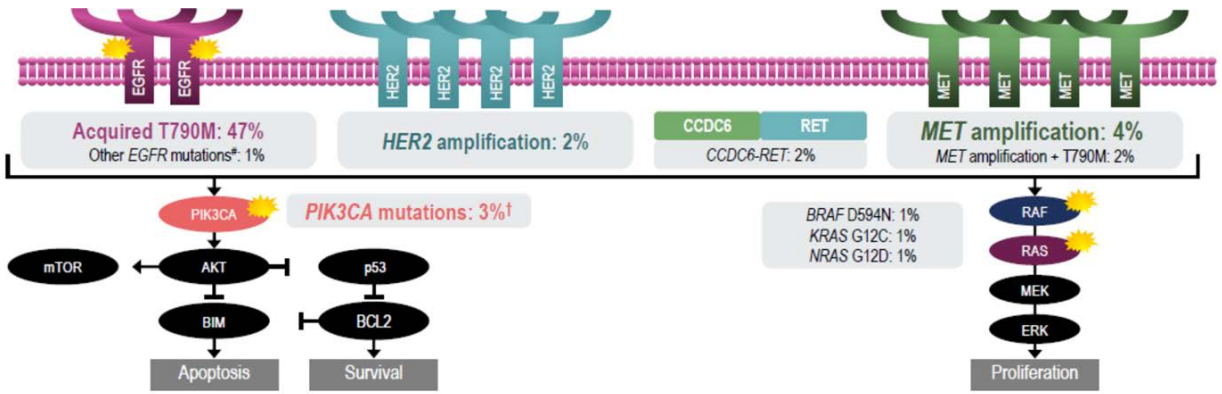
Traitement des CBNPC mutés EGFR



Traitement des CBNPC mutés EGFR

Osimertinib vs erlotinib/gefitinib post progression molecular alterations in pre- and post-TKI plasma specimens
FLAURA trial, NGS Guardiant360 assay (73 genes)

Erlotinib/gefitinib (n=129) : T790M≈50%

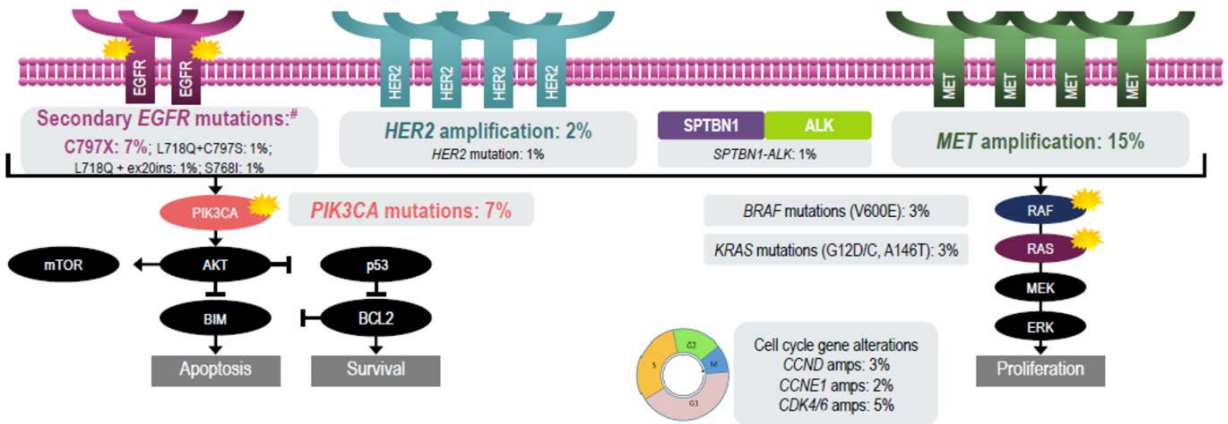


T790M predominant mechanism

T790M plasma monitoring
More indolent disease
Osimertinib effective in T790M resistance

VS.

Osimertinib (n=91) : unknown≈50%



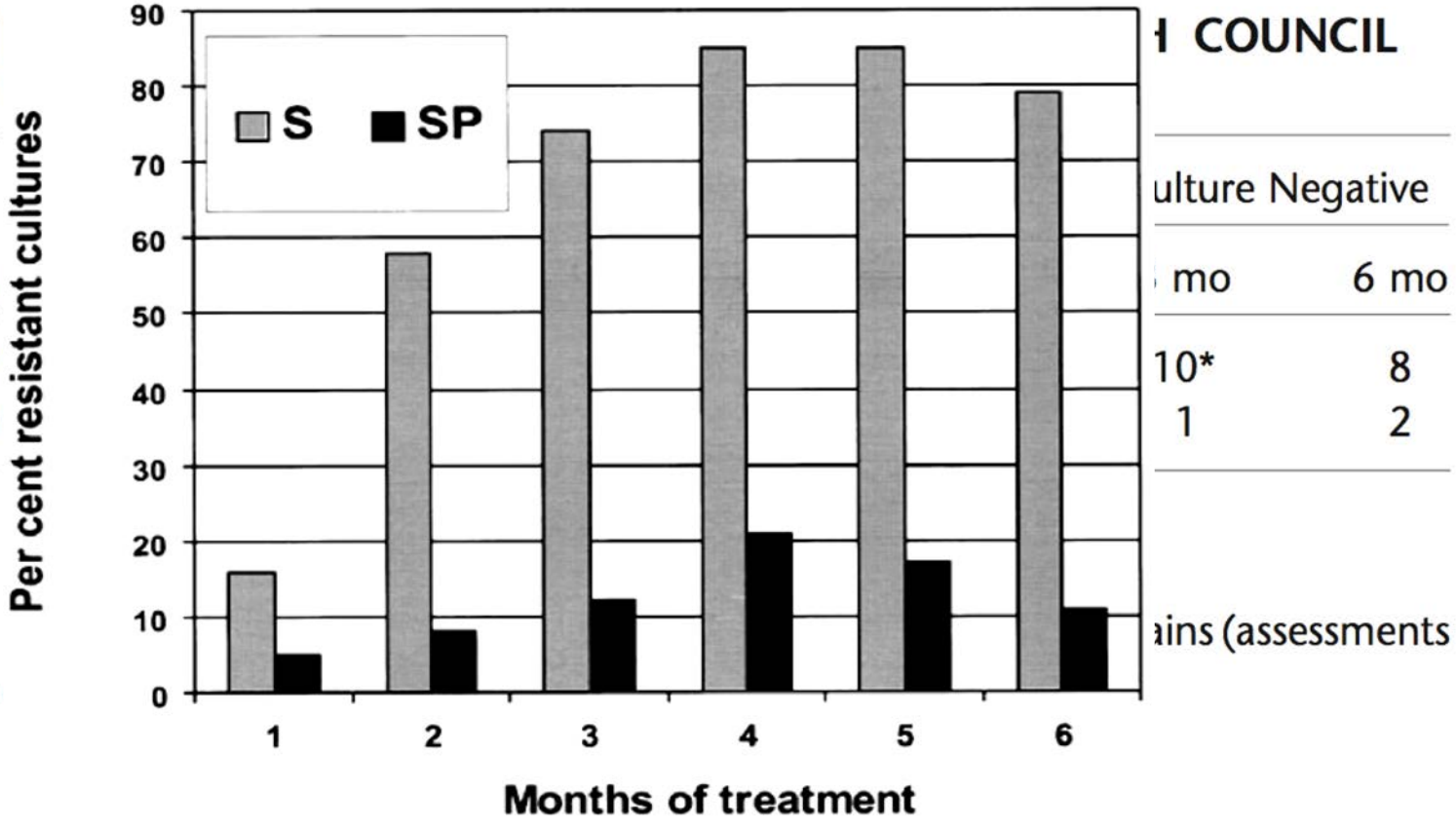
No predominant mechanism

No occurrence of T790M mutation
Complexity of resistance mechanisms
More aggressive disease?

Ramalingam, AACR 2018

Traitement des CBNPC mutés EGFR

1952 **Combotherapy to prevent or delay resistance**



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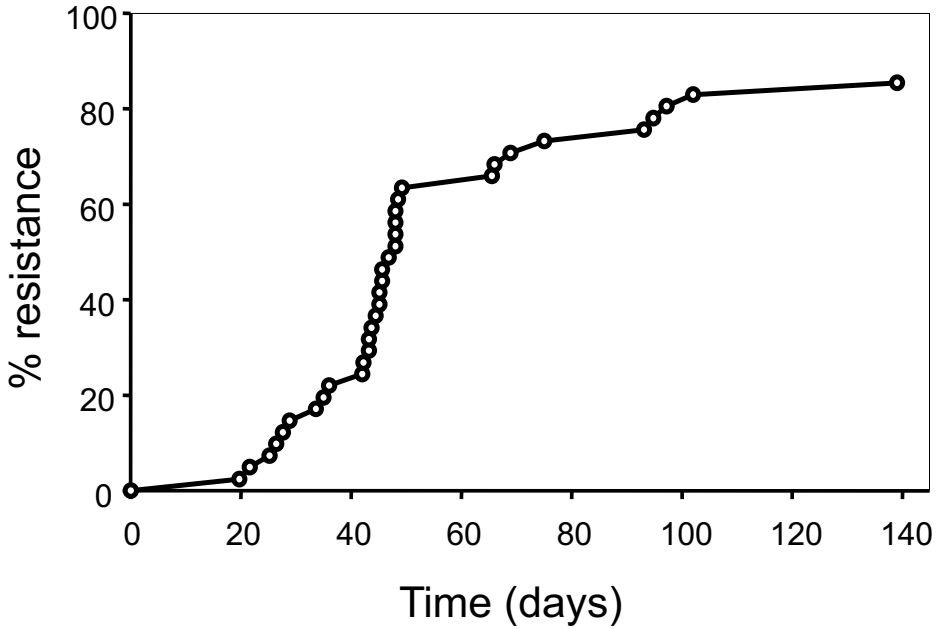
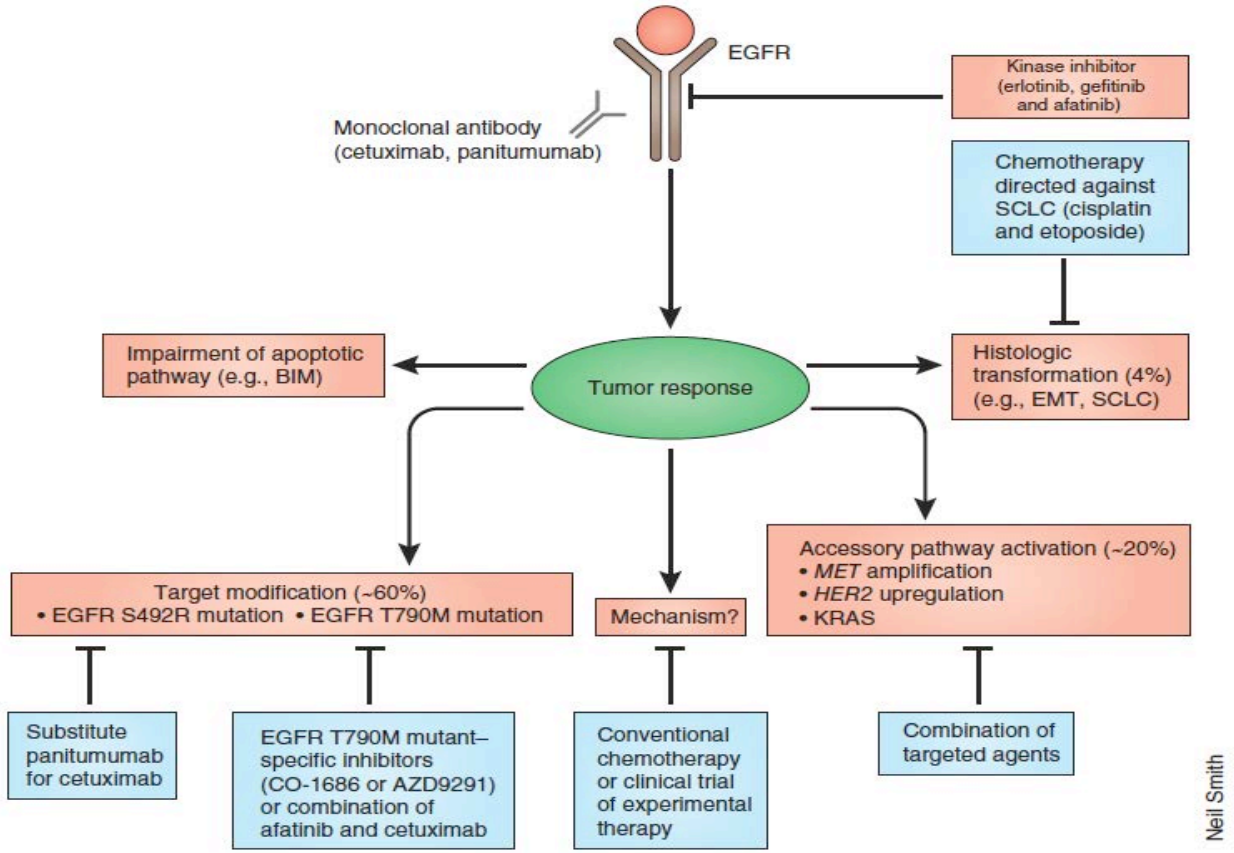
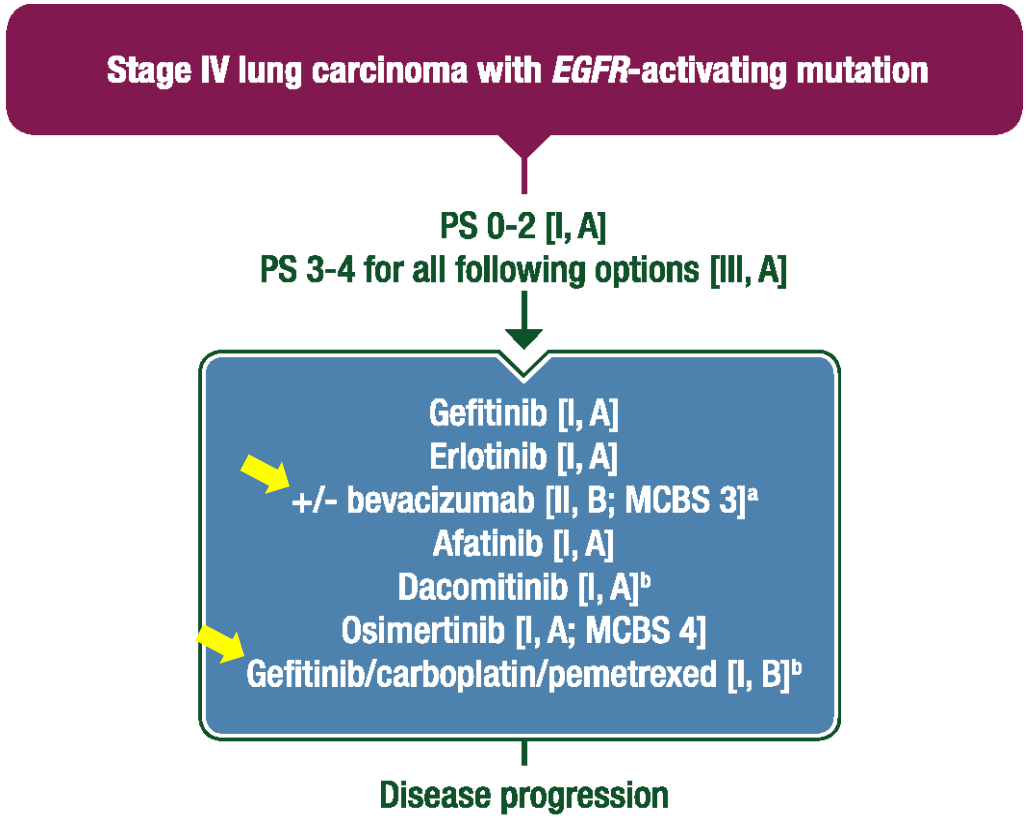


Mitchison DA, Am J Respir Crit Care Med 2005, 171:699-706; ATS/CDC, Am J Respir Crit Care Med 2003,167:603-662

Traitement des CBNPC mutés EGFR

Adaptated therapy to resistance mechanisms **vs.** **Combotherapy to prevent or delay resistance**





Chong CR Nature Med 2013, 19:1389; Planchard D, Annales Oncol 2018, 29:192; Planchard D, Annales Oncol 2019, Epub

Traitement des CBNPC mutés EGFR

- Patients fit for anti-angiogenic therapy
- Additional toxicity
- Preserve T790M emergence?

Phase IIb/III trials, 1st-line EGFR-TKI vs EGFR-TKI plus anti-angiogenic combination in EGFR NSCLC

Author	Population	Mutation	n	Combo	TKI	OR (%)	PFS (mo.)	HR [95% CI]	OS (mo.)	HR [95% CI]
Soria	All	common	553	**Osimertinib**	E/G	80/76	18.9/10.2	0.46 (0.37-0.57)	38.6/31.8	0.799 (0.64-0.99)
Yamamoto*	Asia	common	152	**E+Beva**	E	69/63	16.0/9.7	0.54 (0.36-0.79)	47.0/47.4	0.81 (0.53-1.23)
Saito	Asia	common	224	**E+Beva**	E	81/74	16.9/13.3	0.61 (0.42-0.88)	-	-
Nakagawa	All	common	449	**E+Ramu**	E	-/-	19.4/12.4	0.59 (0.46-0.76)	-	-

E: erlotinib; G: gefitinib; A: afatinib; Beva: bevacizumab; Ramu: ramucirumab; CaPm-PM: carboplatin pemetrexed and pemetrexed maintenance in eligible patients;. * Phase IIb trial.

Soria JC, N Engl J Med 2018, 378:113; Seto T, Lancet Oncol 2014, 15:1235; Yamamoto N, ASCO Chicago 2018; Saito H, Lancet Oncol 2019, Epub; Nakagawa K, Lancet Oncol 2019 Epub October; Ramalingam S, ESMO 2019

Traitement des CBNPC mutés EGFR

- Asian and Indian populations
- Additional toxicity of CT+TKI
- Combo first line should be considered

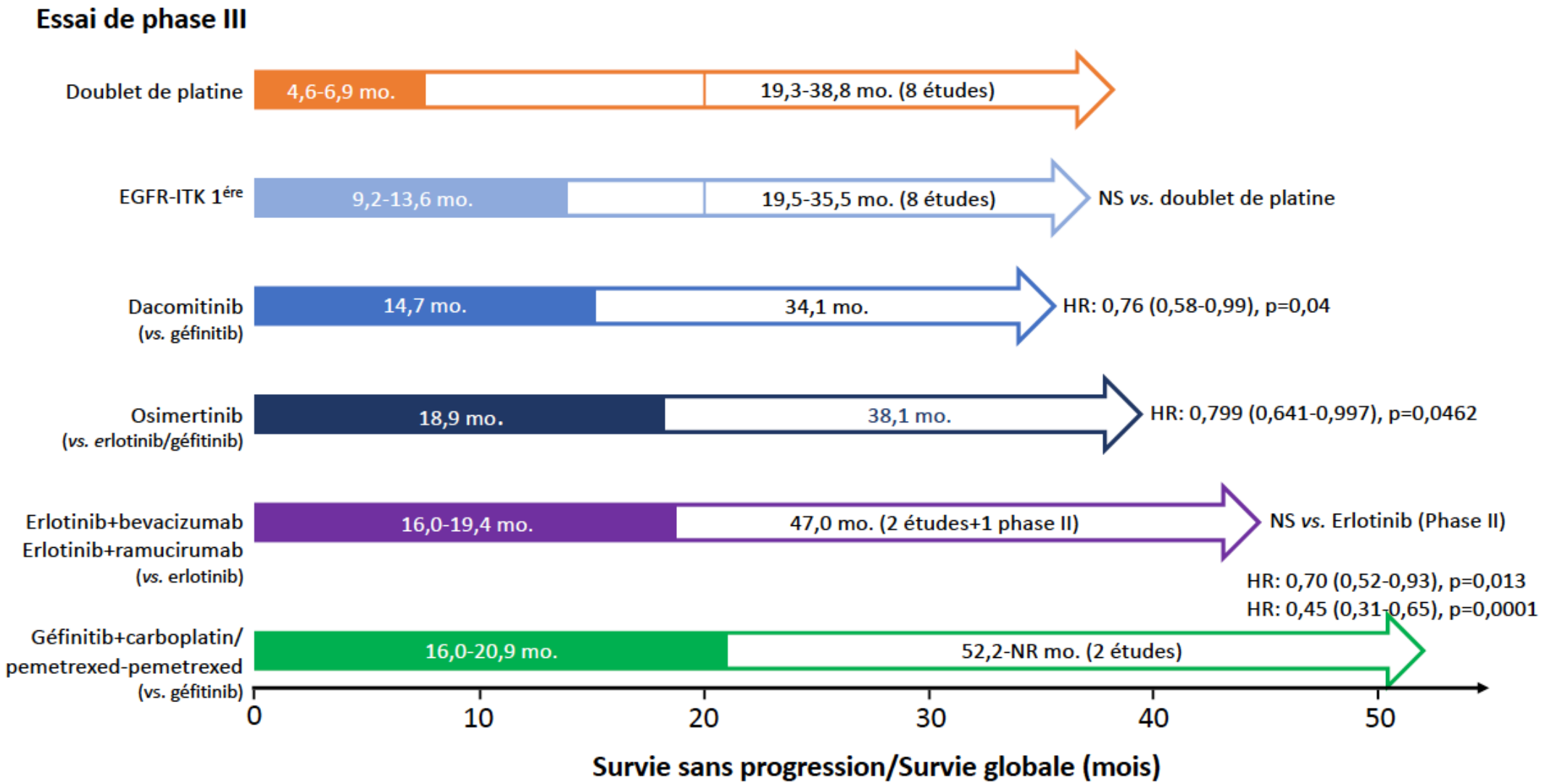
Phase IIb/III trials, 1st-line EGFR-TKI vs EGFR-TKI platinum-pemetrexed doublet in EGFR NSCLC

Author	Population	Mutation	n	Combo	TKI	OR (%)	PFS (mo.)	HR [95% CI]	OS (mo.)	HR [95% CI]
Soria	All	common	553	**Osimertinib**	E/G	80/76	18.9/10.2	0.46 (0.37-0.57)	38.6/31.8	0.799 (0.64-0.99)
Nakamura	Asie	common	342	**G+CaPm-Pm**	G	84/68	20.9/11.2	0.49 (0.39-0.63)	52.2/38.8	0.70 (0.52-0.93)
Noronha	India	common, PS0-2	350	**G+CaPm-Pm**	G	75/68	16.0/8.0	0.51 (0.39-66)	NR(24mo)-17	0.45 (0.31-0.65)

E: erlotinib; G: gefitinib; A: afatinib; Beva: bevacizumab; Ramu: ramucirumab; CaPm-PM: carboplatin pemetrexed and pemetrexed maintenance in eligible patients;. * Phase IIb trial.

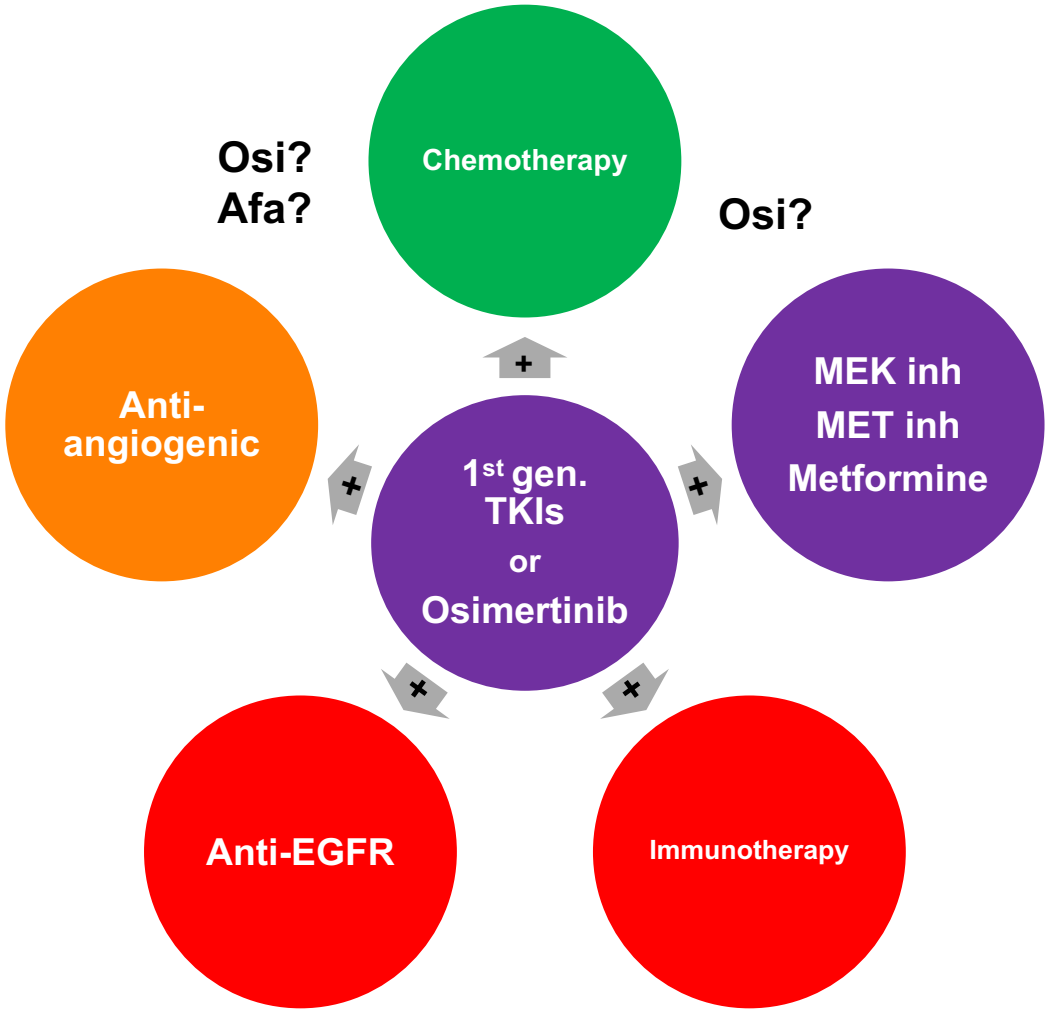
Soria JC, N Engl J Med 2018, 378:113; Nakamura A, ASCO Chicago 2018; Noronha V, J Clin Oncol 2019, Epub; Ramalingam S, ESMO 2019

Traitement des CBNPC mutés EGFR



Cadranel J, Cours du GOLF 2019

Traitement des CBNPC mutés EGFR



Traitement des CBNPC mutés EGFR

- Améliorer l'identification des CBNPC mutés EGFR
- La première ligne de traitement doit comporter un ITK-EGFR
- L'essai FLAURA positionne l'osimertinib en 1ère ligne de traitement
  - Les mécanismes de résistance de l'osimertinib en 1ère ligne doivent être mieux connus… biopsies liquides±tissu
- La place de l'association carboplatine, paclitaxel, bevacizumab, atezolizumab reste à définir
- La place des combinaisons thérapeutiques en première doit être définie