Update nel trattamento del paziente con driver molecolare

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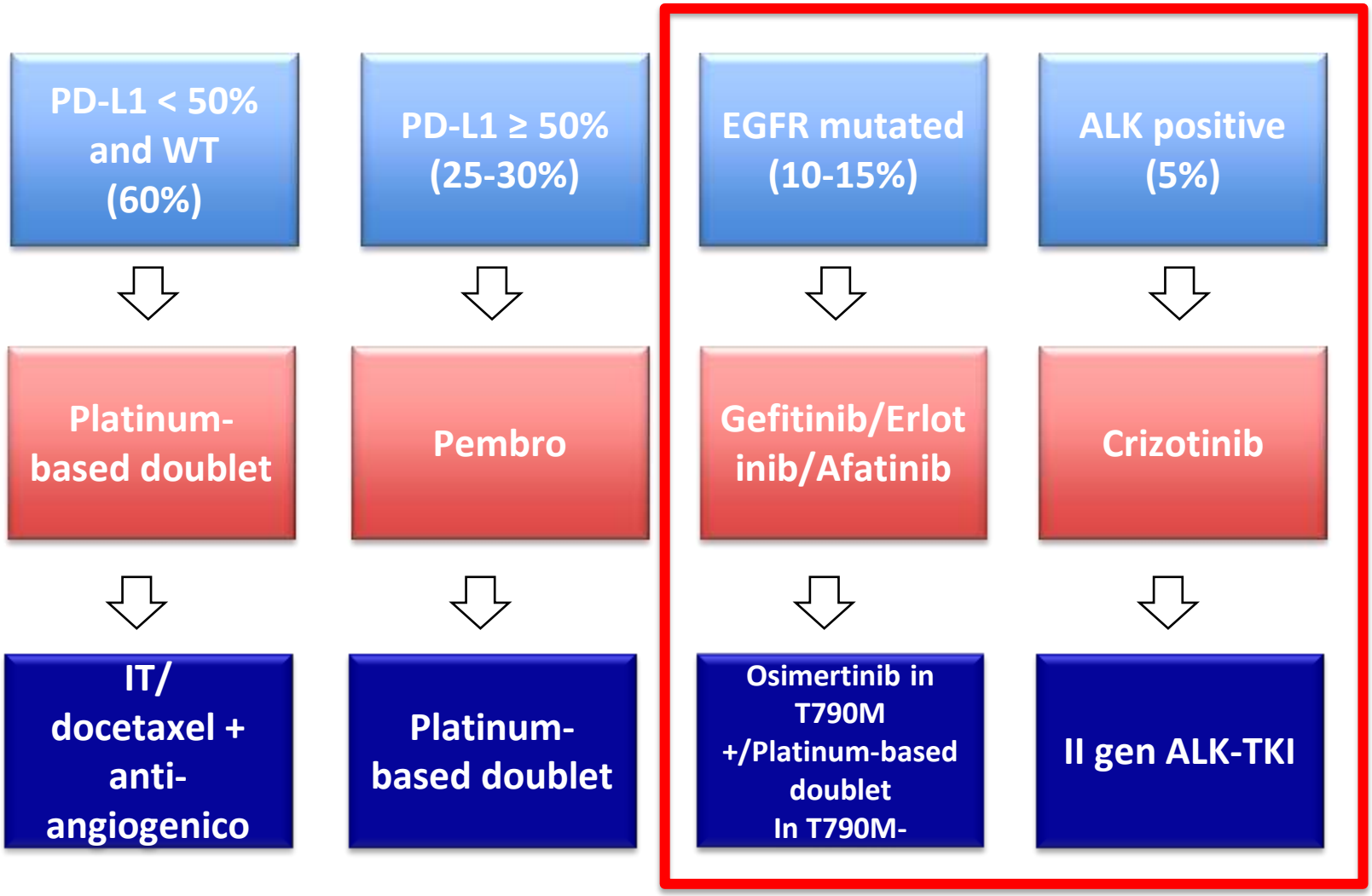
Agenda

Sequenza terapeutica o nuova generazione up-front?

- **EGFR-TKI:**
  - ARCHER 1050 trial: dati di OS con Dacomitinib
  - FLAURA trial: dati di Osimertinib in I linea
  - combo con Bevacizumab e combo con la CT
- **ALK-TKI:**
  - ALEX trial: dati aggiornati di PFS con alectinib in I linea
  - ALTA1L: brigatinib in I linea
  - Dati di Lorlatinib

Immunoterapia e oncogene addiction

Fattori da considerare nella scelta terapeutica del NSCLC avanzato



Strategia terapeutica nei pazienti oncogene-addicted: sequenza o up-front?

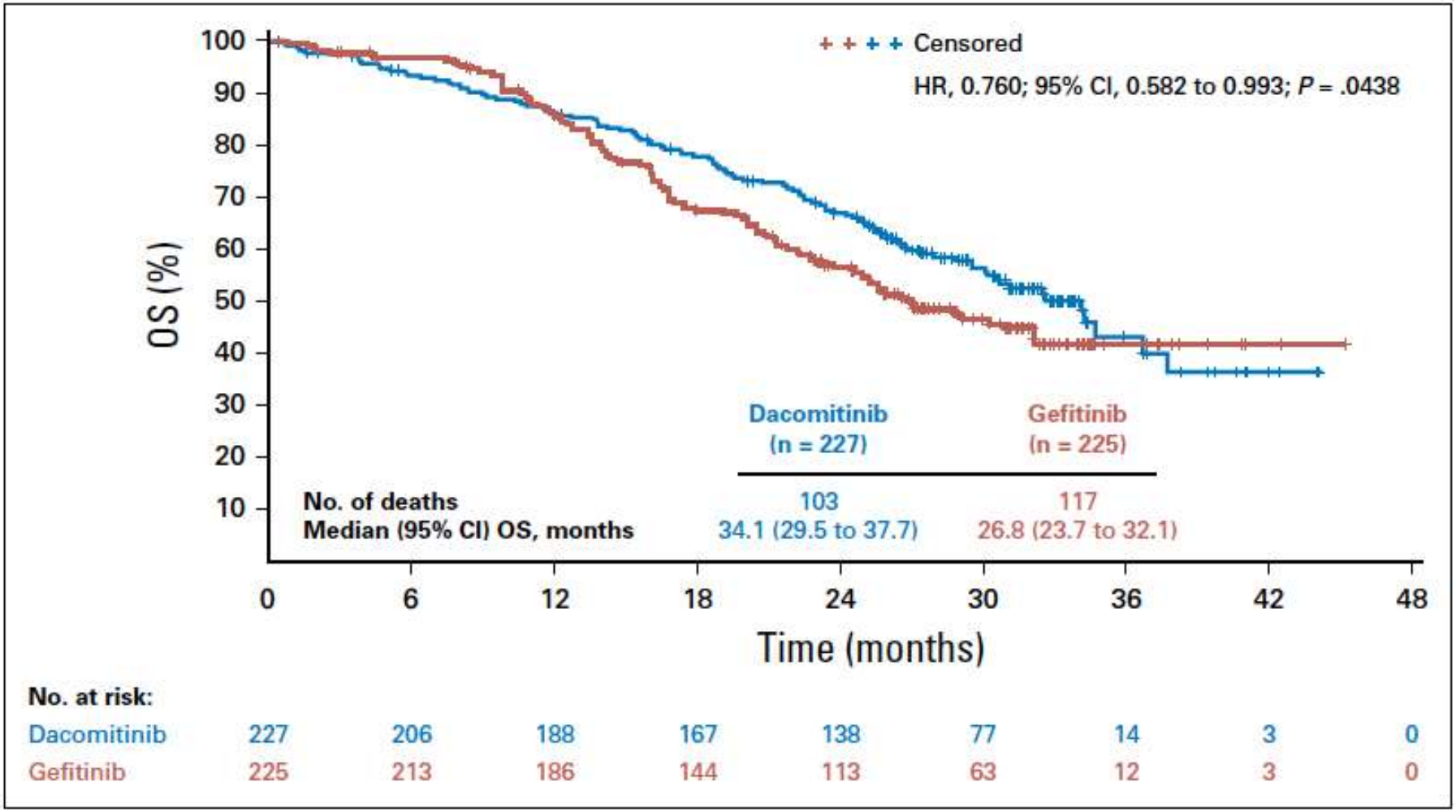
	Arguments in favor of either strategy
1st generation upfront	Reliable long follow-up
	Impressive long overall survival
	Oligoprogressive treatment prolong PFS
	Multiple subsequent available treatment options
Next generation upfront	Less toxicity
	Enhanced brain activity
	Less need for subsequent molecular diagnostic
	Potentially less persister cells

Recondo et al, Nat Rev Clin Oncol 2018

Mutazioni di EGFR e TKIs: stato dell'arte 2018

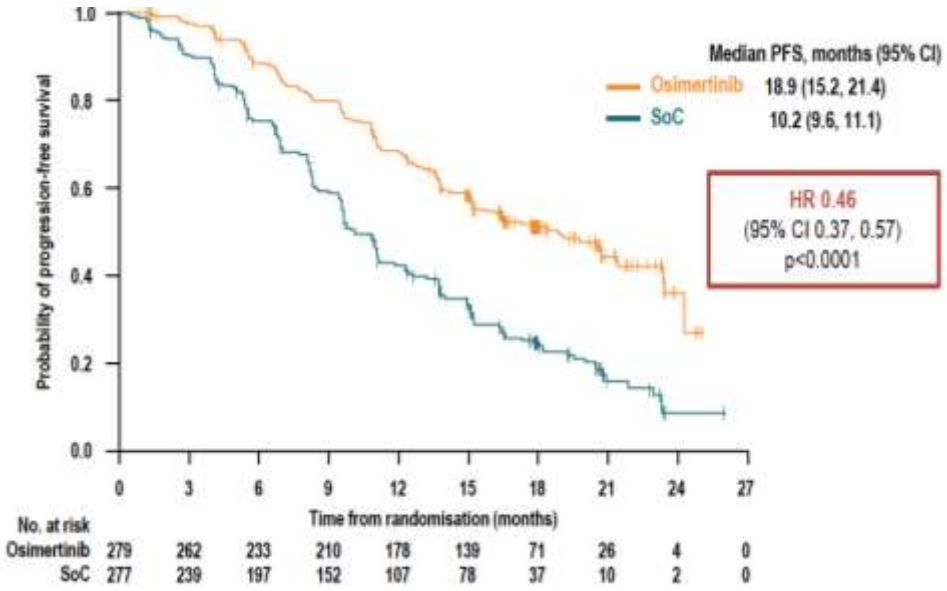
- **Netto impatto dei trattamenti in OS: 2-3 anni**
- **11 studi random di I linea vs CT**
  - TKI > CT in RR (60-70%), PFS (9-13 mesi), QoL
- **3 TKIs in I linea** (2 rev: Gefitinib e Erlotinib; 1 irr: Afatinib)
  - non confronti diretti di fase III in I linea (solo LL7, fase IIb)
- Tossicità peculiari (diarrea e tossicità cutanea)
- **Instaurarsi inevitabile di resistenza**
- **Necessità di re-biopsia** (liquida o tissutale) al fine di ottimizzare il percorso terapeutico alla PD
- **Osimertinib nuovo standard of care nei pazienti EGFR-TKI res con T790M**; CT nei T790M negativi

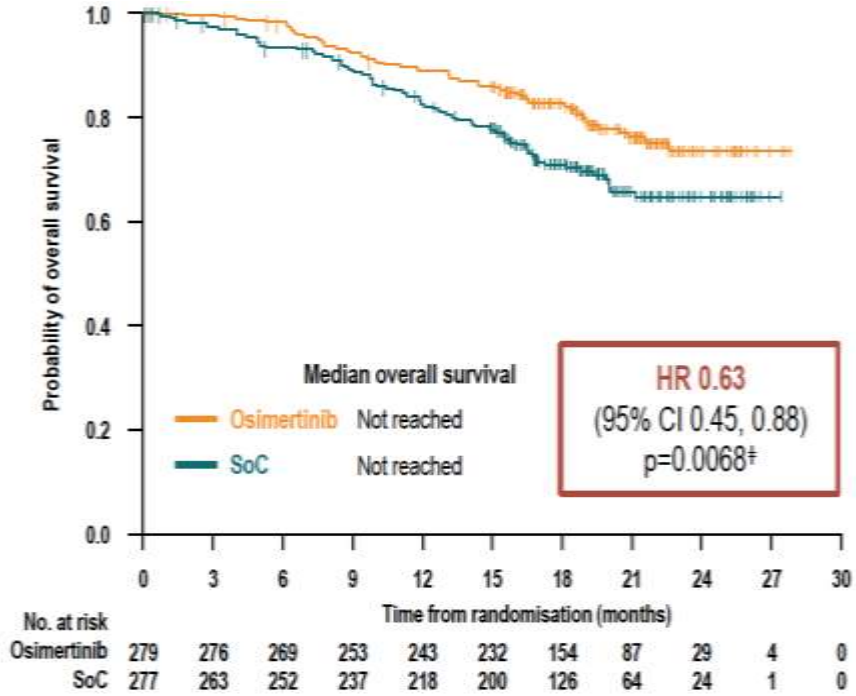
ARCHER 1050
Dacomitinib vs Gefitinib: OS



Mok et al, ASCO 2018 and J Clin Oncol 2018

FLAURA trial
PFS e OS con Osimertinib in I linea

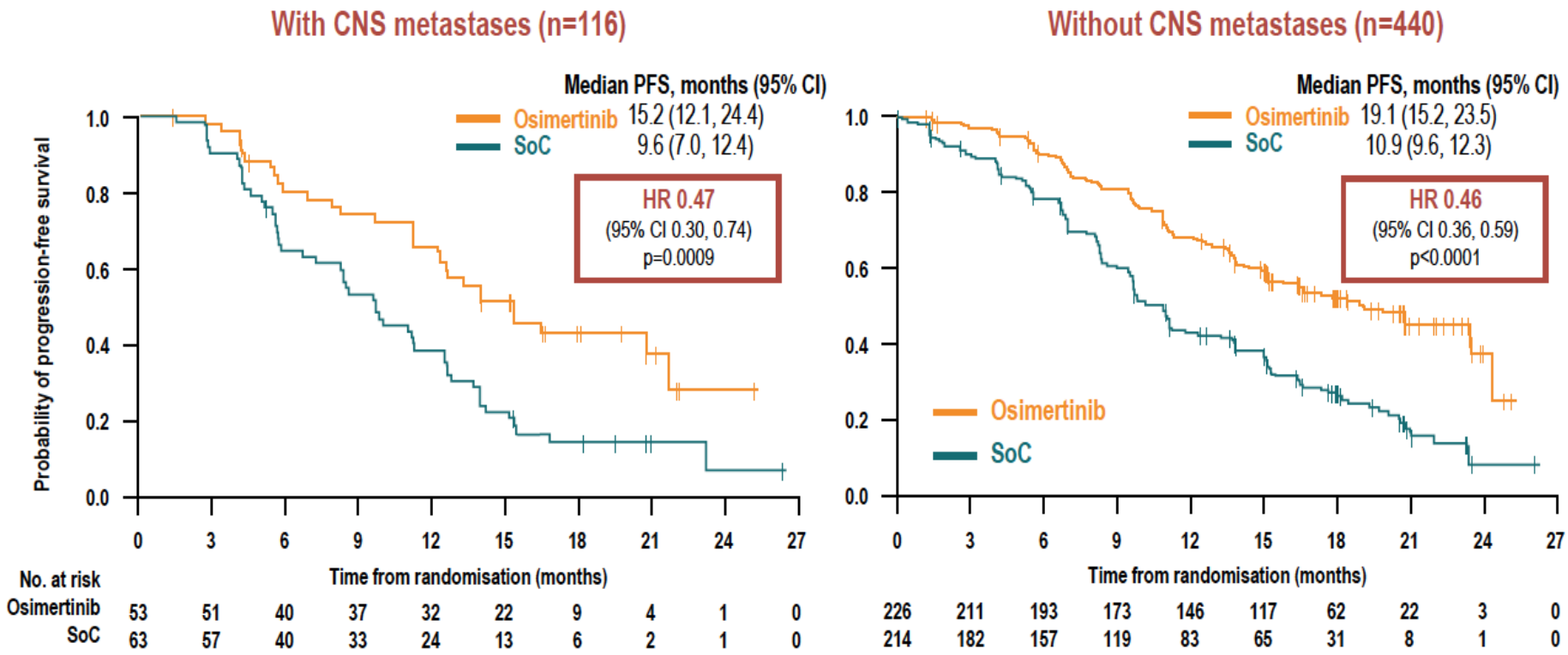




‡A p-value of <0.0015 was required for statistical significance at current maturity

Ramalingam et al, ESMO 2017 and Soria et al, NEJM 2017

FLAURA trial
effetto sulle brain mts di Osimertinib



CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data; *By Investigator assessment
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; SoC, standard-of-care

Ramalingam et al, ESMO 2017 and Soria et al, NEJM 2017

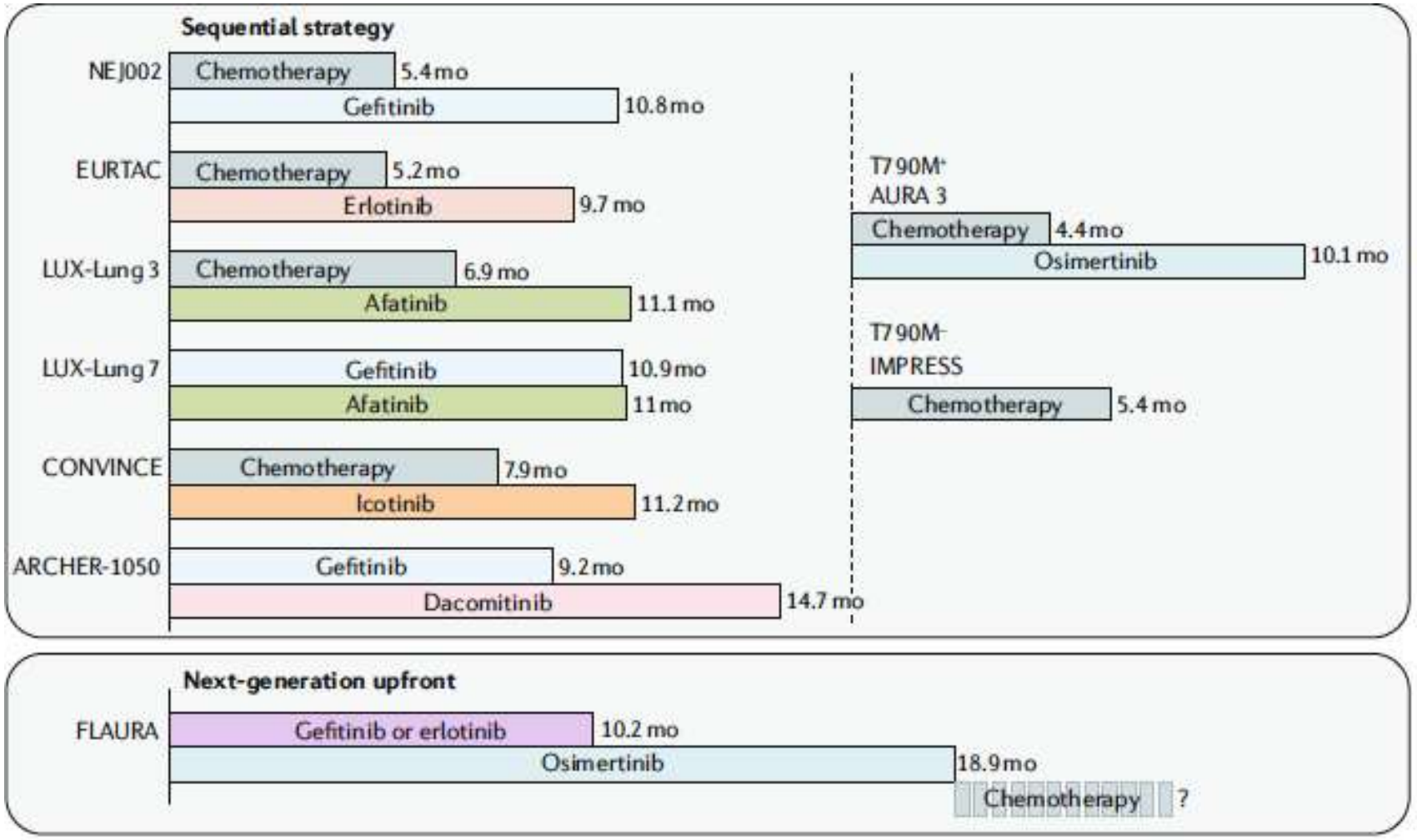
FLAURA trial
Osimertinib in I linea: safety

AE, any cause*, n (%)	Osimertinib (n=279)	SoC (n=277)
Any AE	273 (98)	271 (98)
Any AE Grade ≥3	94 (34)	124 (45)
Any AE leading to death	6 (2)	10 (4)
Any serious AE	60 (22)	70 (25)
Any AE leading to discontinuation	37 (13)	49 (18)
AE, possibly causally related#, n (%)		
Any AE	253 (91)	255 (92)
Any AE Grade ≥3	49 (18)	78 (28)
Any AE leading to death	0	1 (<1)
Any serious AE	22 (8)	23 (8)

FLAURA data cut-off: 12 June 2017
*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; #As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication
AE, adverse event; SoC, standard-of-care

Ramalingam et al, ESMO 2017 and Soria et al, NEJM 2017

Strategia terapeutica nei pazienti NSCLC EGFR +: sequenza o up-front?



Recondo et al, Nat Rev Clin Oncol 2018

Strategia terapeutica nei pazienti NSCLC EGFR +: Osimertinib subito?

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

PRO

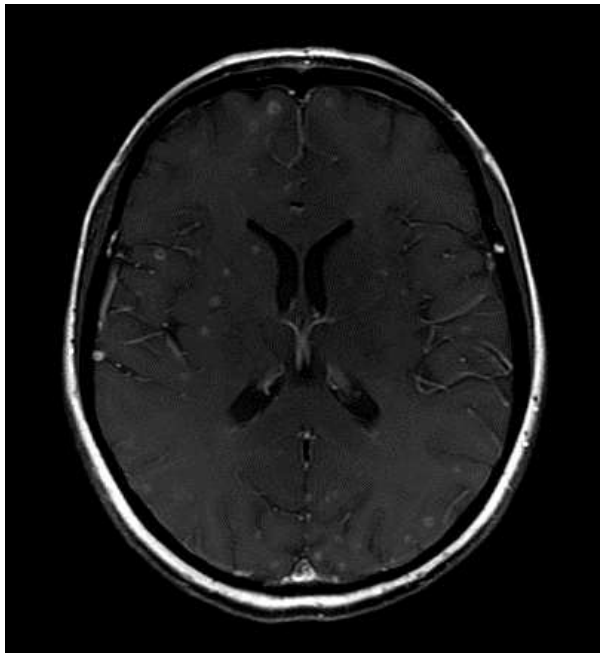
- Tutti ricevono Osimertinib, non solo i T790M positivi
- Tutti ricevono Osimertinib, non perdiamo pazienti che non sarebbero testati per T790, che non ricevono II linea (30-40% negli studi di I linea con TKI)
- Profilo di tollerabilità
- Effetto a livello del SNC
- Dato di PFS molto rilevante (consistente negli studi)
- Non necessaria re-biopsia (se non alla PD dopo 19 mesi)

CONTRA (pro sequenza)

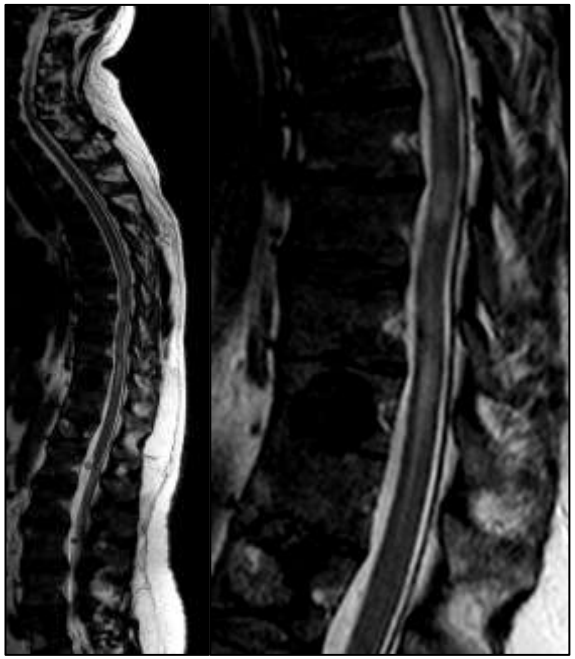
- Non disponibili dati di OS del FLAURA
- Non completamente chiari i mecc di resistenza
- Non si conoscono ancora le modalità di PD, diverse?
- Non chiare strategie successive
- Non elementi predittivi noti
- Costi

Osimertinib subito assolutamente si

miliary metastatic brain involvement



Leptomeningeal or Endomedullary involvement

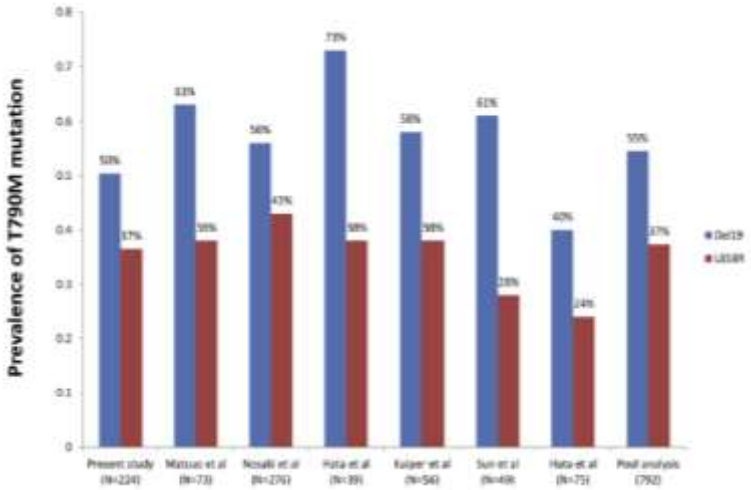


First-Line Osimertinib in Patients with Treatment-Naive Somatic or Germline *EGFR* T790M-Mutant Metastatic NSCLC

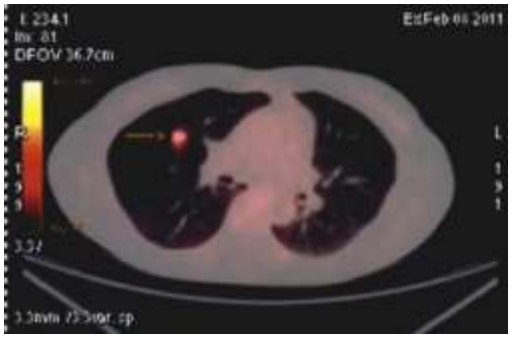
Katerina Ancevski Hunter, MD, David M. Friedland, MD, Liza C. Villaruz, MD, Timothy F. Burns, MD, PhD

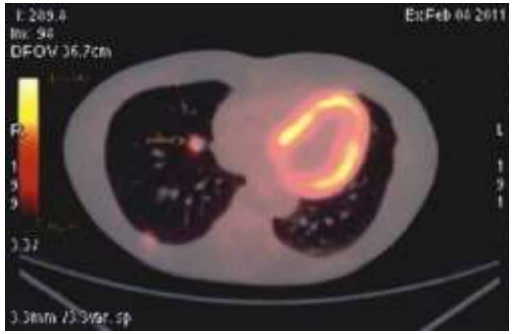
Sequenza?

Solo se Delezione 19?

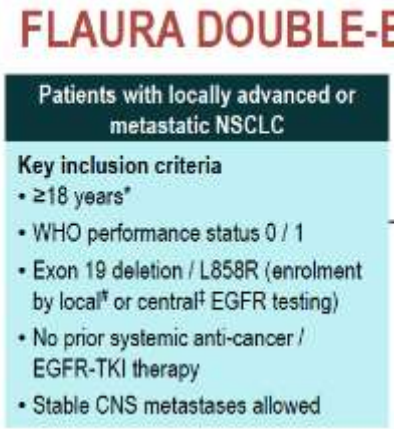


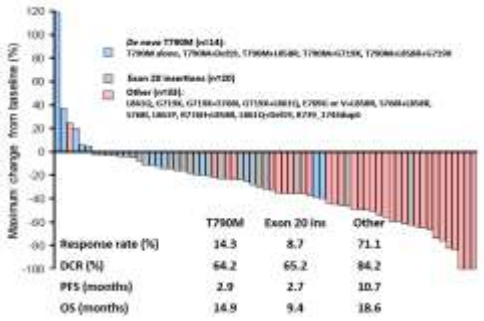
Ridotto carico di malattia?
Possibilità di re-biopsia?





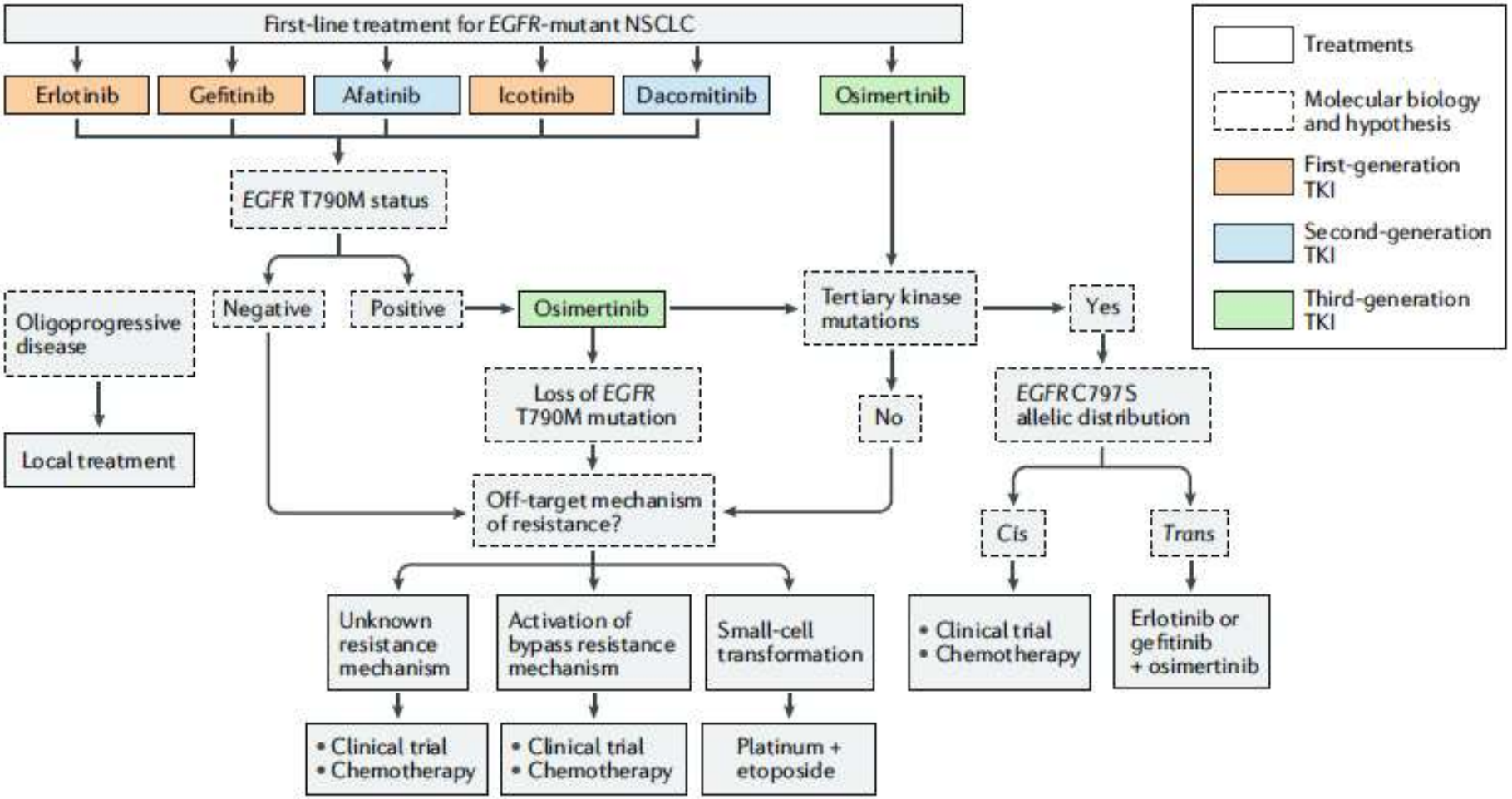
Mutazioni Uncommon?





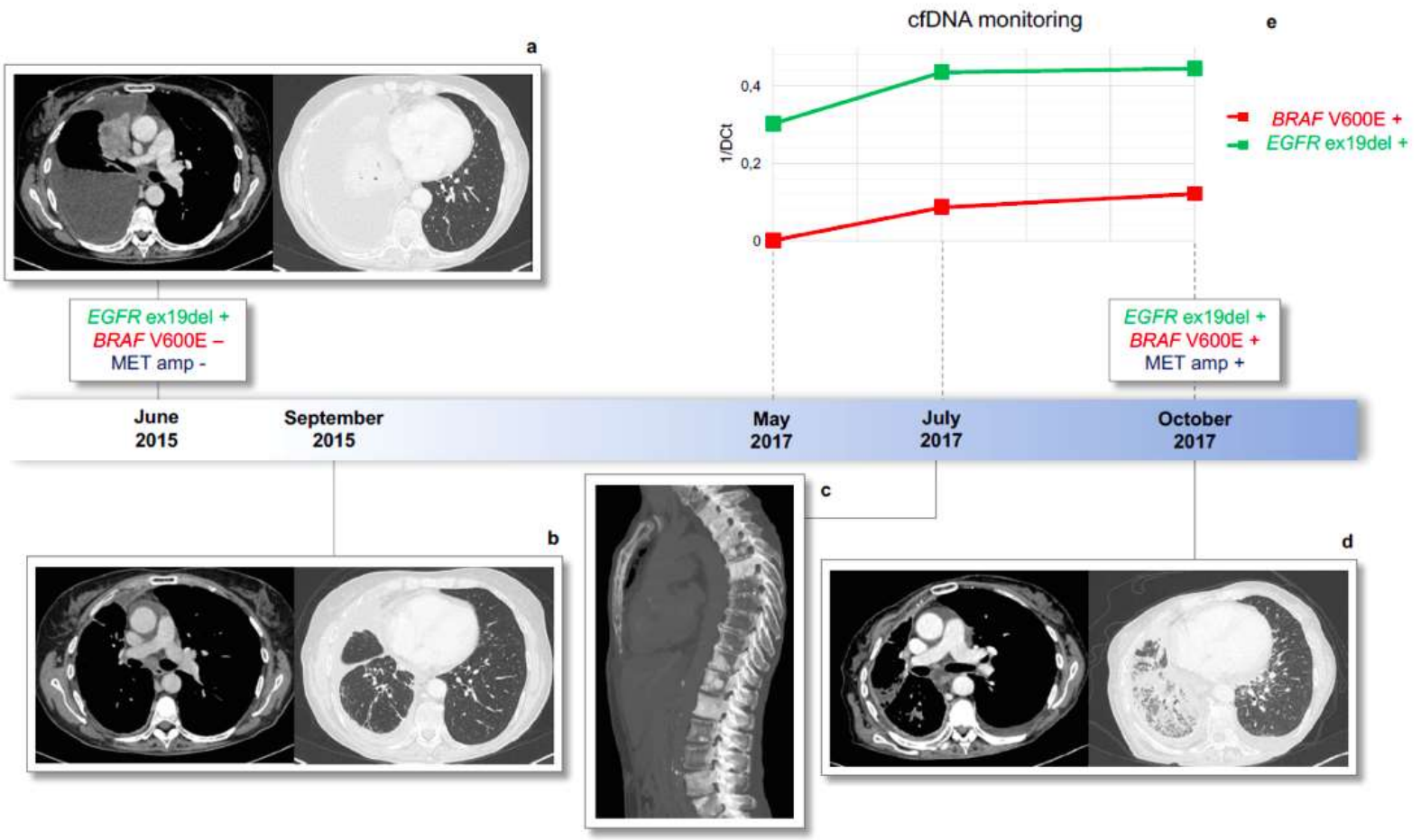
Yang et al, Lancet Oncology 2015

Strategia terapeutica nei pazienti NSCLC EGFR +: sequenza o up-front?



Recondo et al, Nat Rev Clin Oncol 2018

Osimertinib in I linea: mecc. di resistenza – BRAF e MET

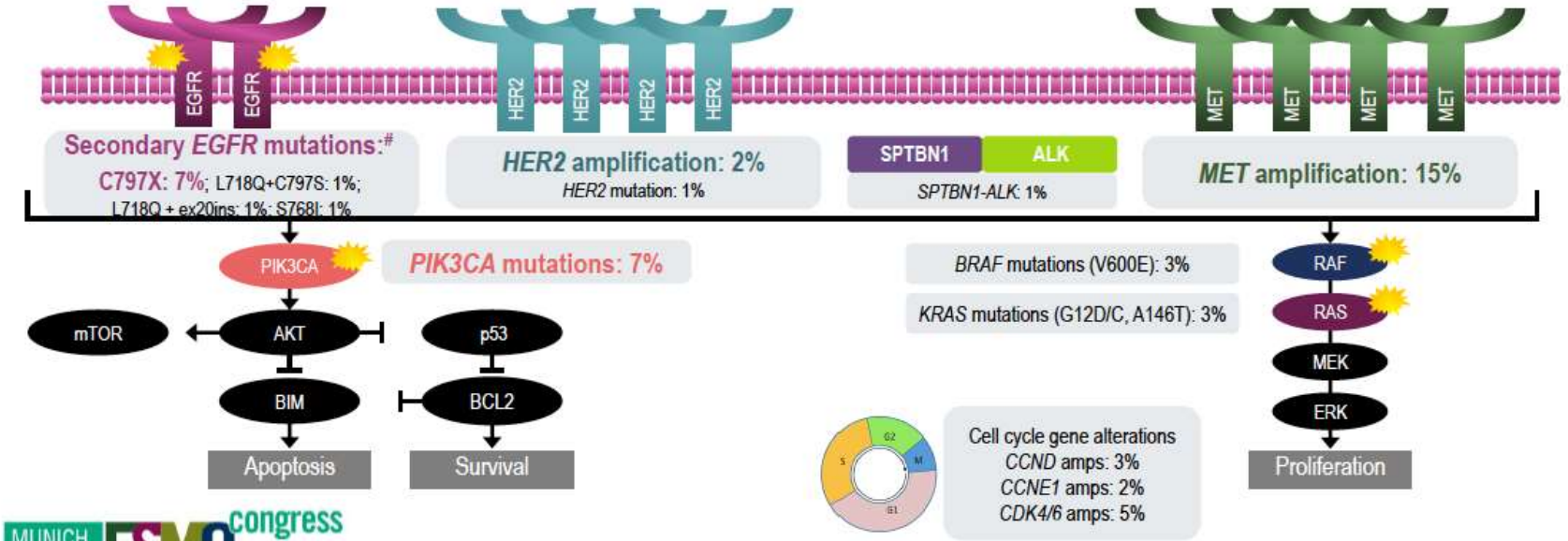


Minari et al, J Thoracic Oncol 2018

Osimertinib in I linea: mecc. di resistenza – FLAURA trial

RESULTS: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

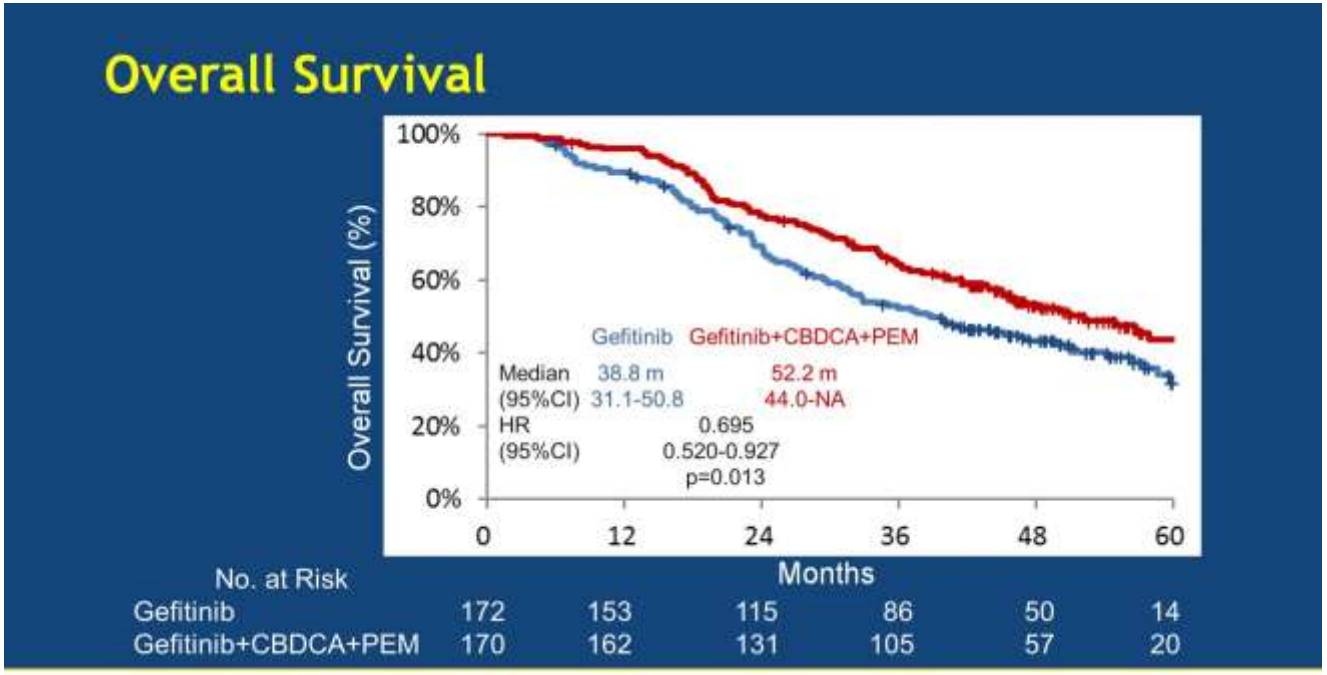
- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were ***MET*** amplification and EGFR C797S mutation
  - Other mechanisms included ***HER2*** amplification, ***PIK3CA*** and ***RAS*** mutations



MUNICH 2018 ESMO congress

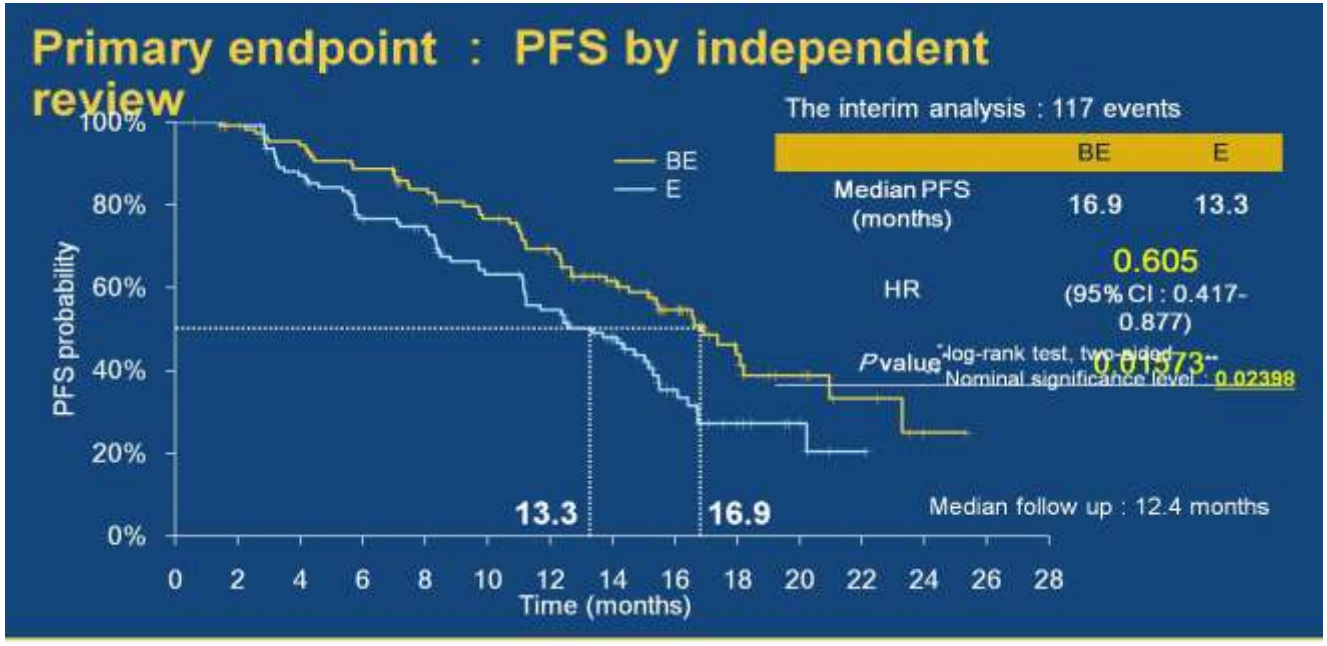
*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

Ramalingam et al, ESMO 2018



Gefitinib vs Carbo-Pem + Gefitinib

Nakamura et al, ASCO 2018



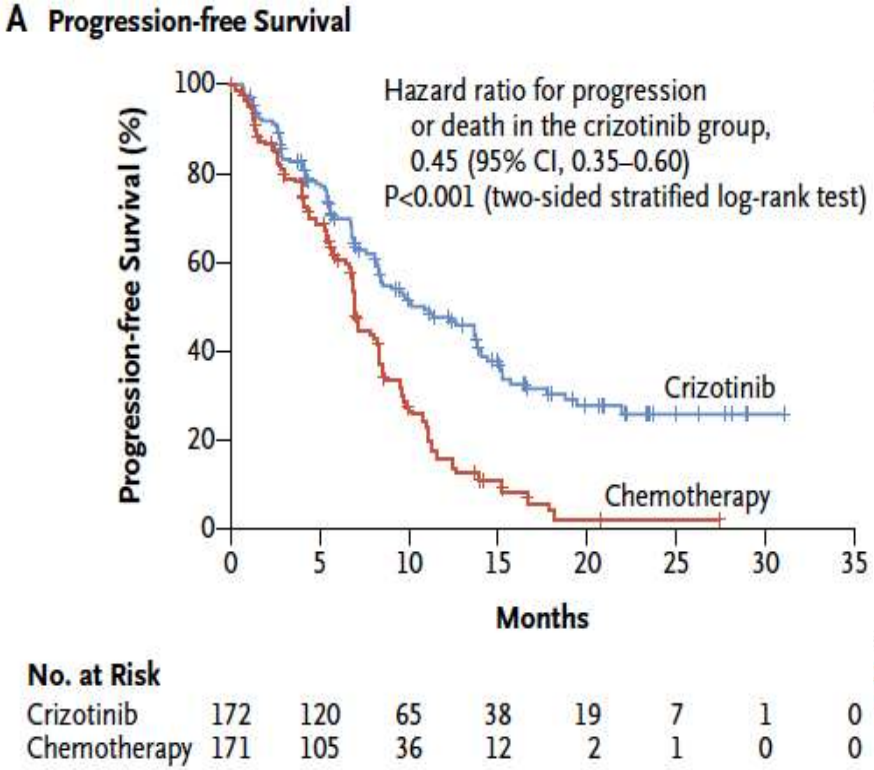
Erlotinib vs Beva + Erlotinib

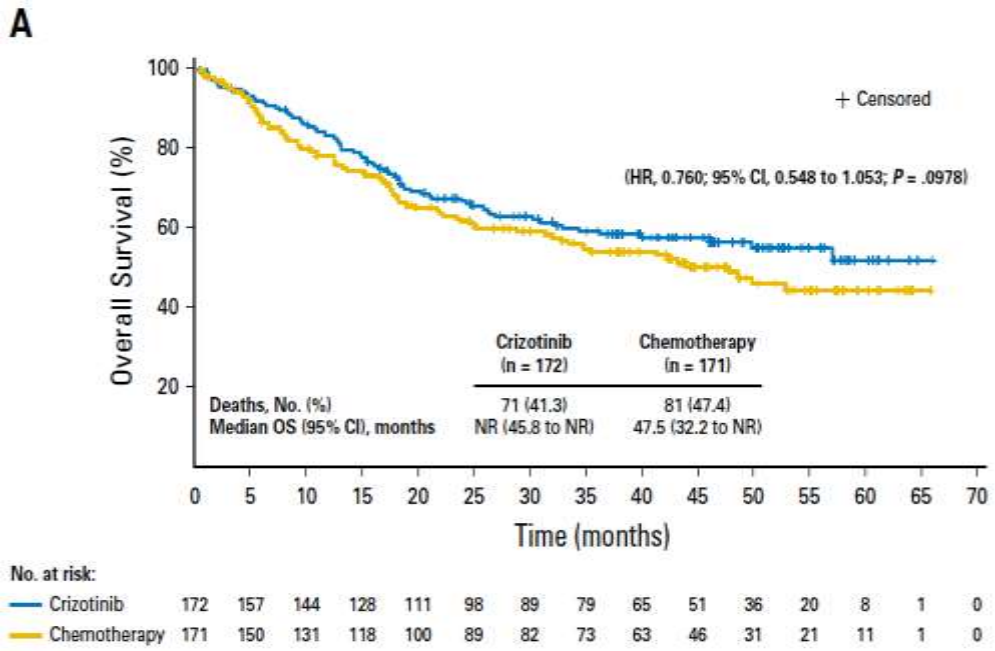
Furuja et al, ASCO 2018

NSCLC ALK positivo: stato dell'arte 2018

- **Netto impatto dei trattamenti in OS: 4-5 anni**
- Attuale standard di I linea **crizotinib**
- In caso di progressione limitata ad una singola o poche sedi (es. encefalo) può essere indicato trattamento locale, con la prosecuzione di crizotinib
- **Instaurarsi di resistenza con Crizotinib dopo circa 9-10 mesi**
- Avvento di **inibitori di II-III generazione** con maggiore potenza di inibizione di ALK ed in grado di superare BEE che rappresentano il **nuovo standard di cura a progressione dopo Crizotinib**

Crizotinib PROFILE 1014: PFS e OS

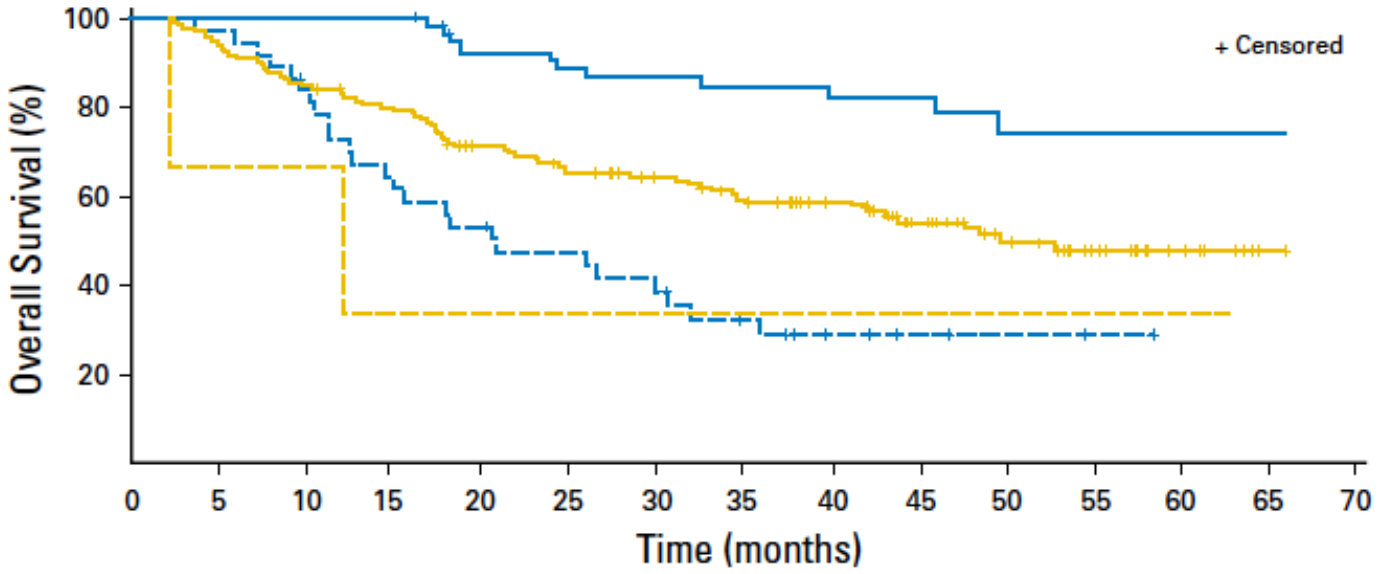




Solomon et al, NEJM 2014

Solomon et al, J Clin Oncol 2018

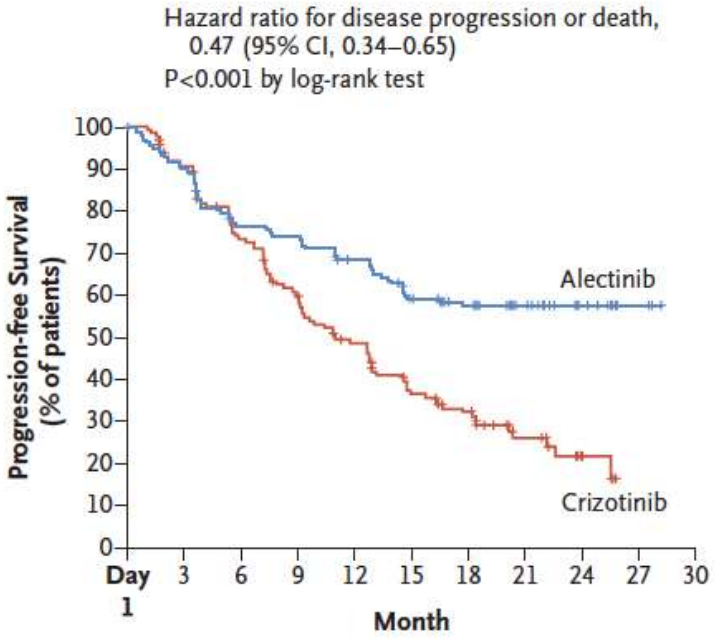
ALK positivi impatto in OS delle sequenze: PROFILE 1014

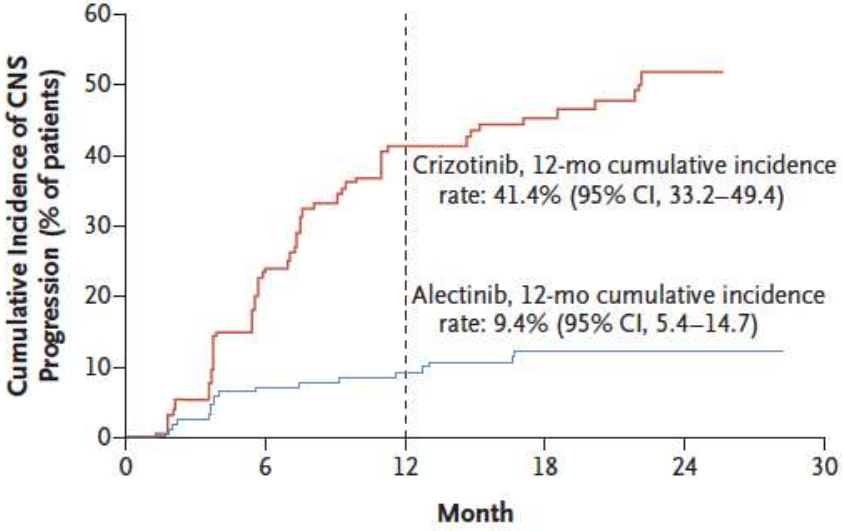


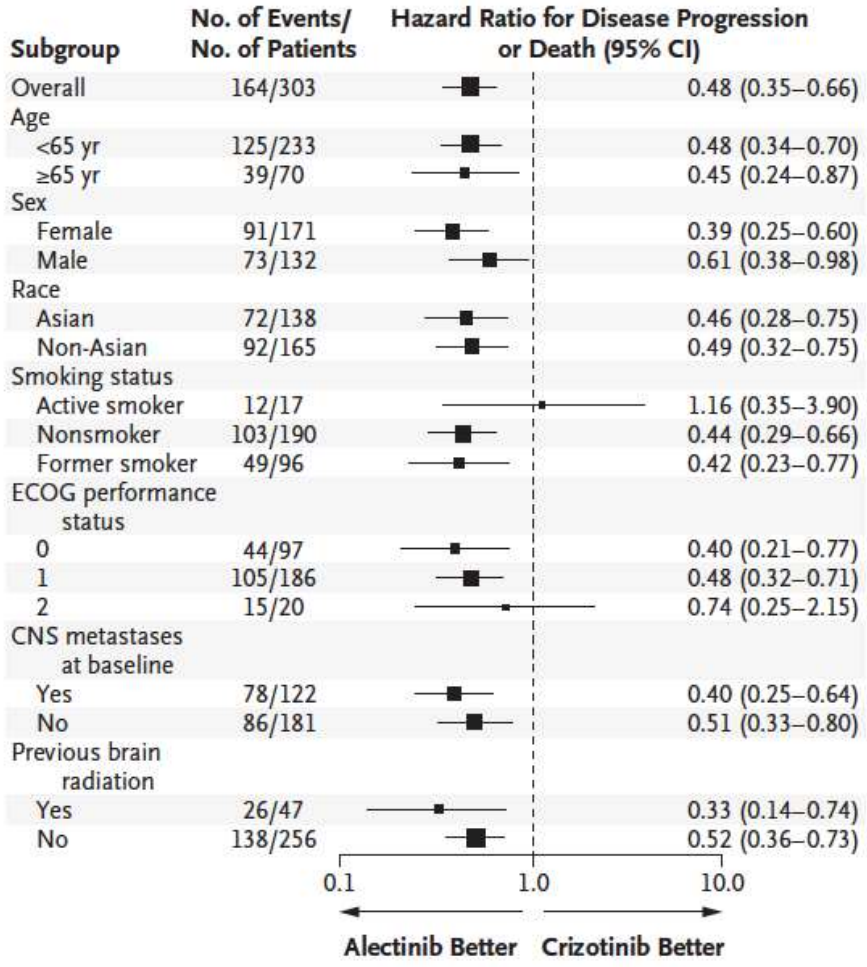
No. at risk:															
Crizotinib followed by any ALK TKI	57	57	57	57	50	45	42	40	33	25	16	8	3	1	0
Crizotinib followed by any follow-up therapy other than ALK TKI	37	36	30	22	19	16	13	9	5	3	2	1	0	0	0
Chemotherapy followed by any ALK TKI	145	136	123	113	97	86	79	70	60	43	30	20	10	1	0
Chemotherapy followed by any follow-up therapy other than ALK TKI	3	2	2	1	1	1	1	1	1	1	1	1	1	0	0

Solomon et al, J Clin Oncol 2018

ALEX trial

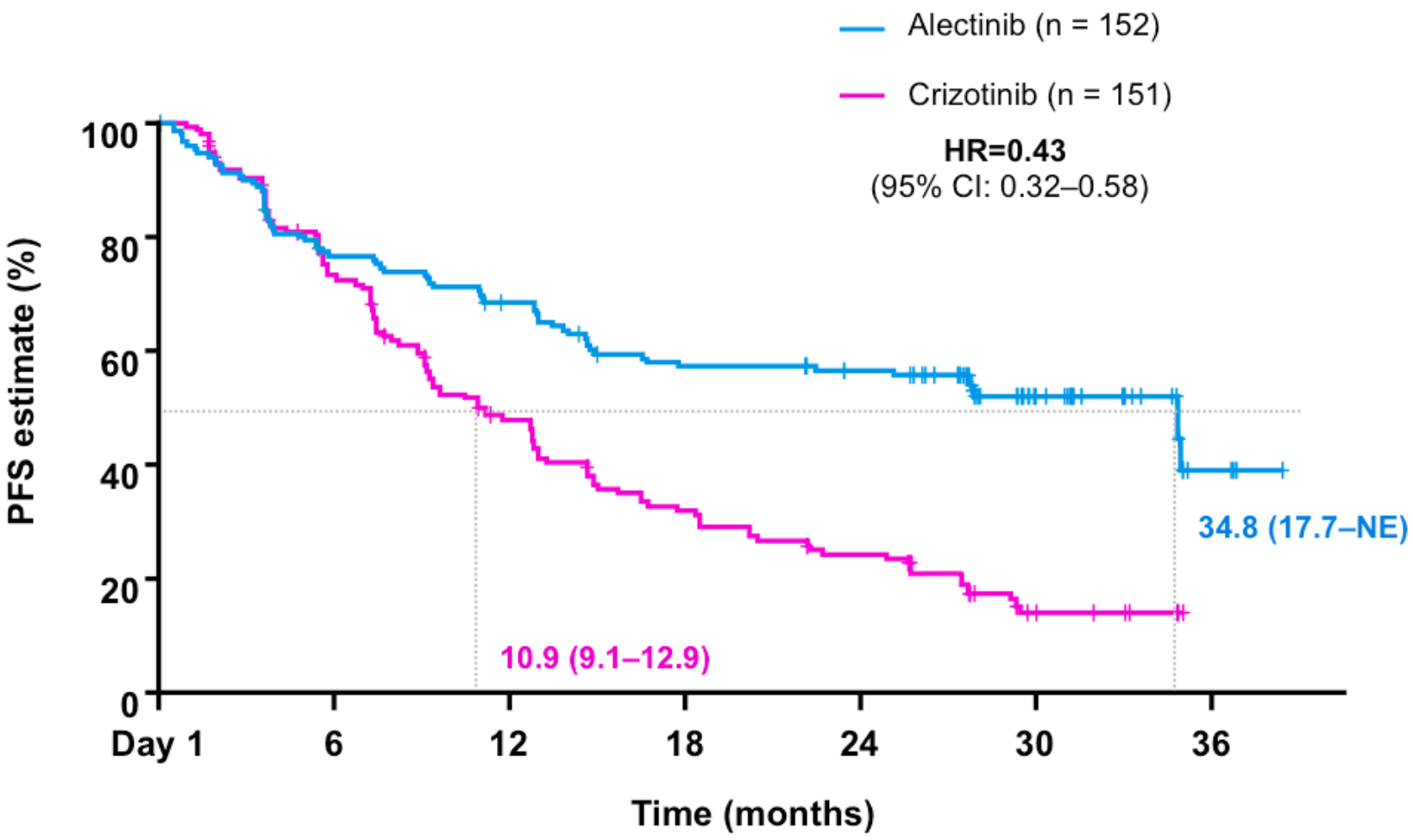






Peters S et al, NEJM 2017

ALEX trial:
PFS aggiornata ASCO 2018



Camidge et al, ASCO 2018

ALEX trial: PFS aggiornata ASCO 2018

Patients with CNS metastases at baseline

	Alectinib (n = 64)	Crizotinib (n = 58)
Median PFS	**27.7**	**7.4**
(95% CI)	(9.2–NE)	(6.6–9.6)
HR	0.35	
(95% CI)	(0.22–0.56)	

Patients without CNS metastases at baseline

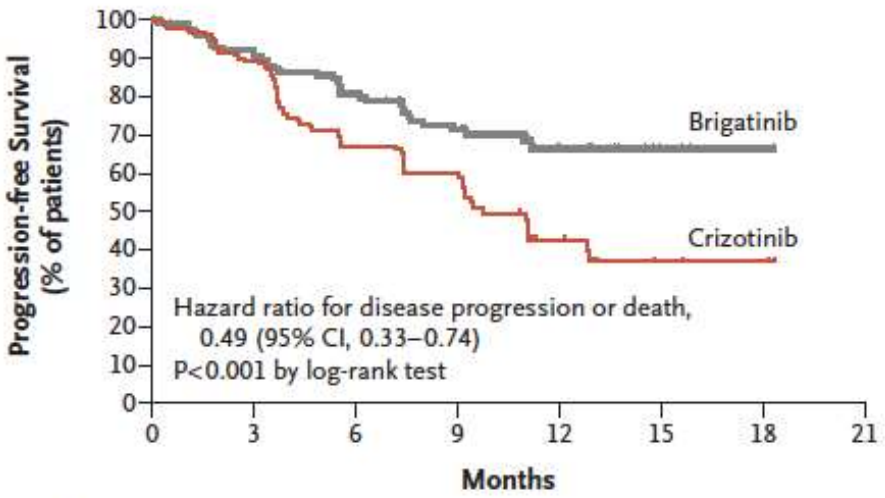
	Alectinib (n = 88)	Crizotinib (n = 93)
Median PFS	**34.8**	**14.7**
(95% CI)	(22.4–NE)	(10.8–20.3)
HR	0.47	
(95% CI)	(0.32–0.71)	

Camidge et al, ASCO 2018

ALTA1L trial: Brigatinib vs Crizotinib

A Progression-free Survival

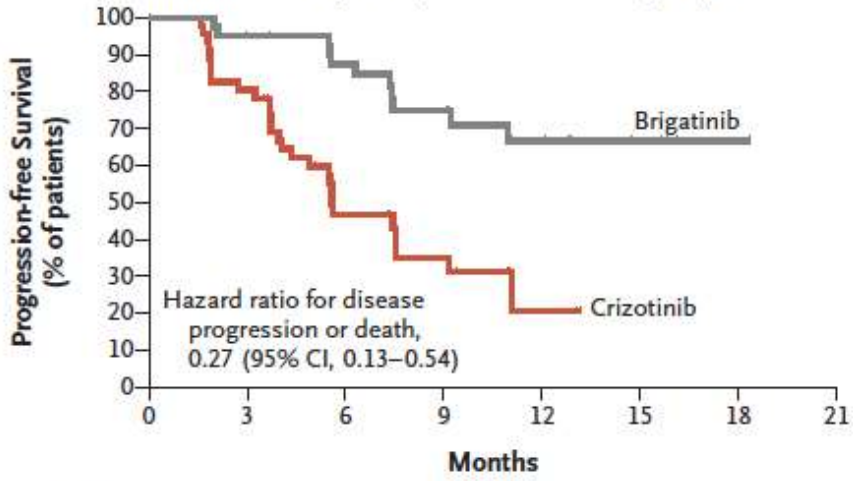
	Median (95% CI) *mo*	At 1 Yr (95% CI) %
Brigatinib	NR	67 (56–75)
Crizotinib	9.8 (9.0–12.9)	43 (32–53)



No. at Risk							
Brigatinib	137	114	90	64	26	3	1
Crizotinib	138	117	75	50	18	3	2

D Survival without Intracranial Disease Progression among Patients with Brain Metastases at Baseline

	Median (95% CI) *mo*	At 1 Yr (95% CI) %
Brigatinib	NR (11–NR)	67 (47–80)
Crizotinib	5.6 (4.1–9.2)	21 (6–42)



No. at Risk							
Brigatinib	43	39	32	22	9	5	1
Crizotinib	47	37	16	9	2	0	0

Camidge et al, WCLC 2018 and NEJM 2018

ALEX vs ALTA1L trials

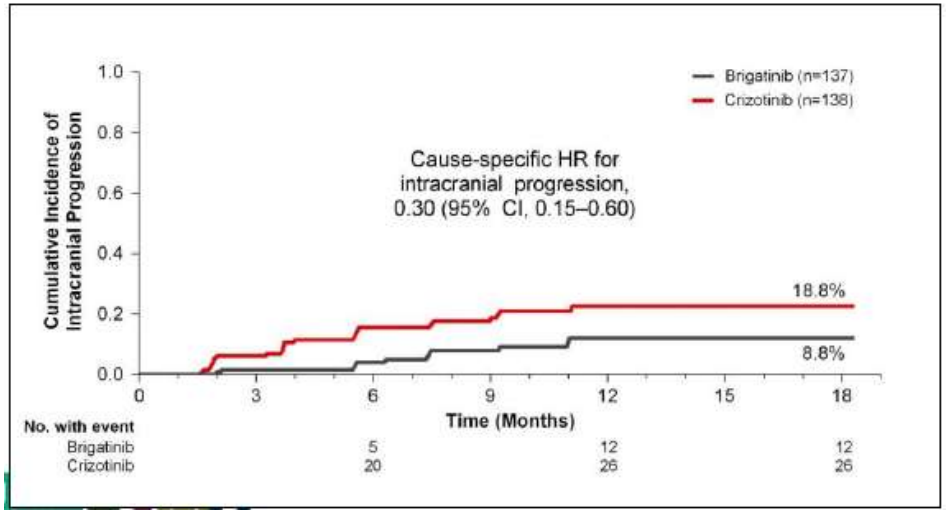
	ALTA-1L Camidge NEJM 2018		ALEX Peters NEJM 2017		ALEX : updated analysis Camidge ASCO 2018	
	Brigatinib	Crizotinib	Alectinib	Crizotinib	Alectinib	Crizotinib
Patients (N)	137	138	152	151	152	151
Median FU mths	11	9.25	18.6	17.6	27.8	22.8
ORR (%)	76	73	82.9	75.5		
Median PFS mths (95% CI)	**NR**** (NR, NR)	9.8 (9.0, 12.9)	**25.7**** (19.9, NR)	10.4 (7.7, 14.6)	**34.8*** (17.7-NR)	10.9*
HR (95%CI) Log rank p value	0.49 (0.33, 0.74) 0.0007		0.5 (0.36, 0.7) <0.001		0.43 (0.32, 0.58)	

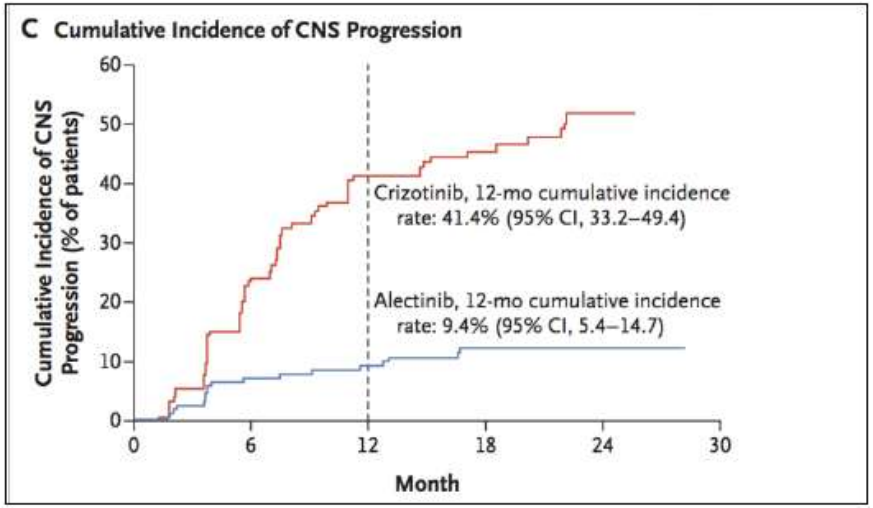
** Investigator assessed ** Independent review committee assessed*

Fiona Blackhall, ESMO 2018

ALEX vs ALTA1L trials

Intracranial Efficacy	ALTA-1L		ALEX	
	Brigatinib	Crizotinib	Alectinib	Crizotinib
Measurable Brain Metastases (N)	**18**	**21**	**21**	**22**
ORR % (95% CI)	**78** (52,94)	29 (11,52)	**81** (58,95)	50 (28,72)
Any brain metastases (N)	43	47	64	58
HR (95%CI) for PFS with BM	**0.27 (0.13-0.54) <0.0001**		**0.40 (0.25-0.64)**	





Fiona Blackhall, ESMO 2018
Popat et al, LBA58, ESMO 2018

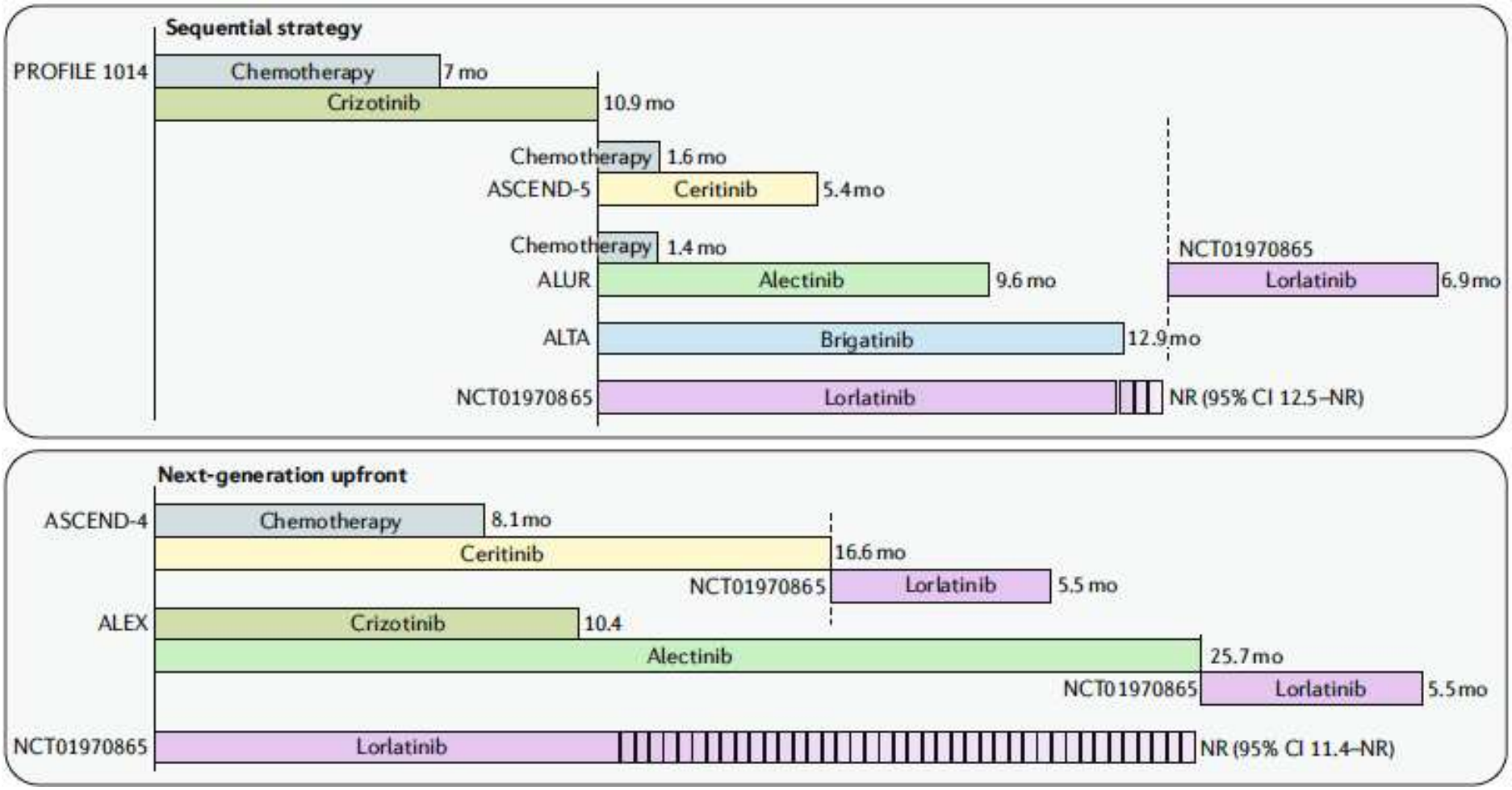
ALEX vs ALTA1L trials

	ALTA-1L Camidge WCLC 2018		ALEX Peters NEJM 2017	
	Brigatinib	Crizotinib	Alectinib	Crizotinib
Any grade AE leading to dose reduction %	29	21	16	21
Any grade AE leading to treatment discontinuation %	12	9	11	13

- ALTA-1L
- Interstitial lung disease (ILD)/pneumonitis at any time: brigatinib 4% (5/136); crizotinib 2% (3/137)
  - Early-onset ILD/pneumonitis (within 14 days of treatment initiation): brigatinib, 3% (onset: Days 3–8); crizotinib, none reported
  - For brigatinib, dose reductions were due to increased CPK (10.3%), increased lipase (5.1%); increased amylase (2.9%) and increased AST, hypertension, pneumonitis, pruritic rash (1.5% each)
- No clinical cases of pancreatitis; no difference in incidence of any grade myalgia or musculoskeletal pain; no grade ≥3 myalgia or musculoskeletal pain reported

Fiona Blackhall, ESMO 2018

Strategia terapeutica nei pazienti NSCLC ALK +: sequenza o up-front?

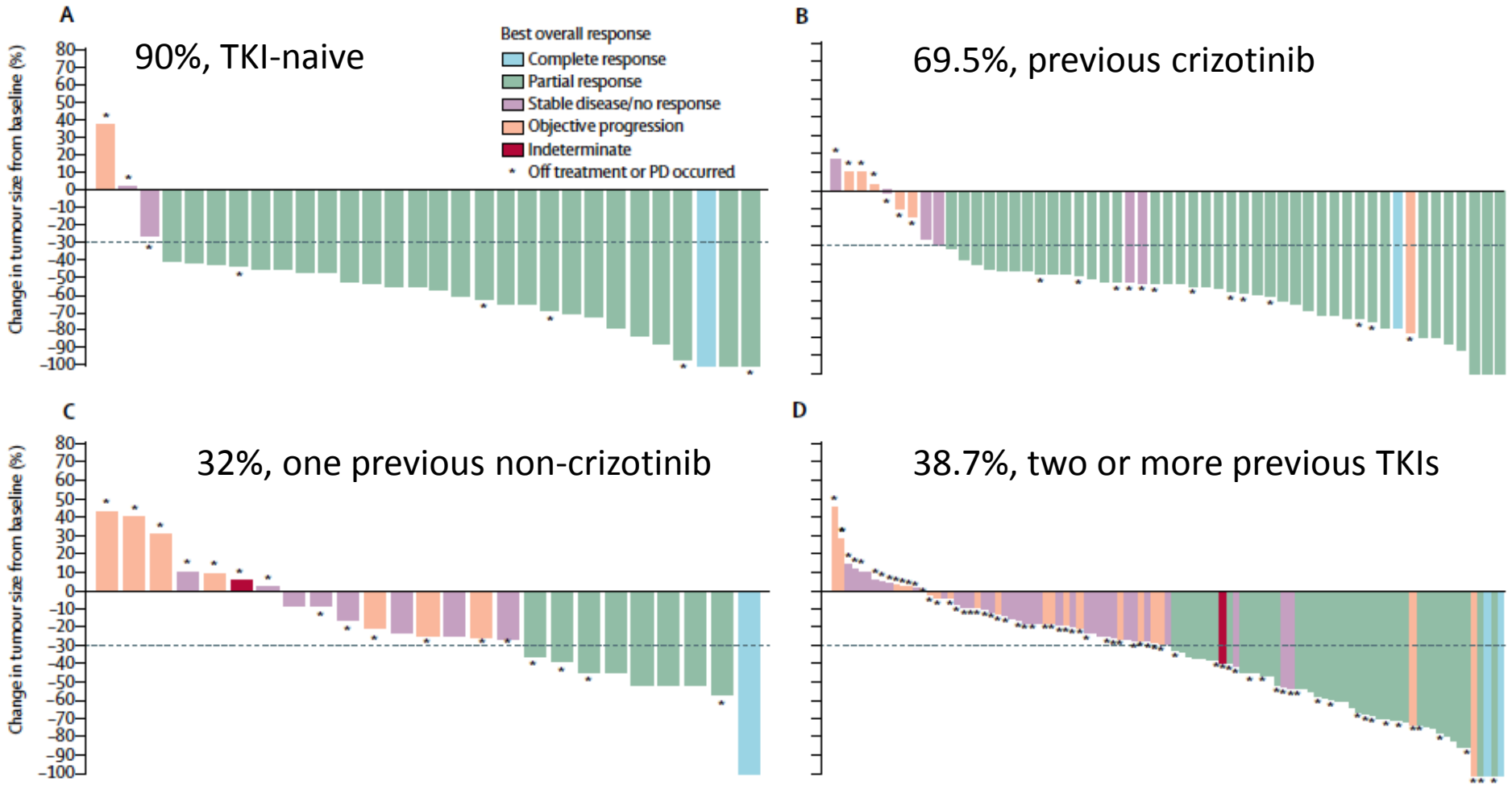


Recondo et al, Nat Rev Clin Oncol 2018

Strategia terapeutica nei pazienti NSCLC ALK +: Alectinib subito?

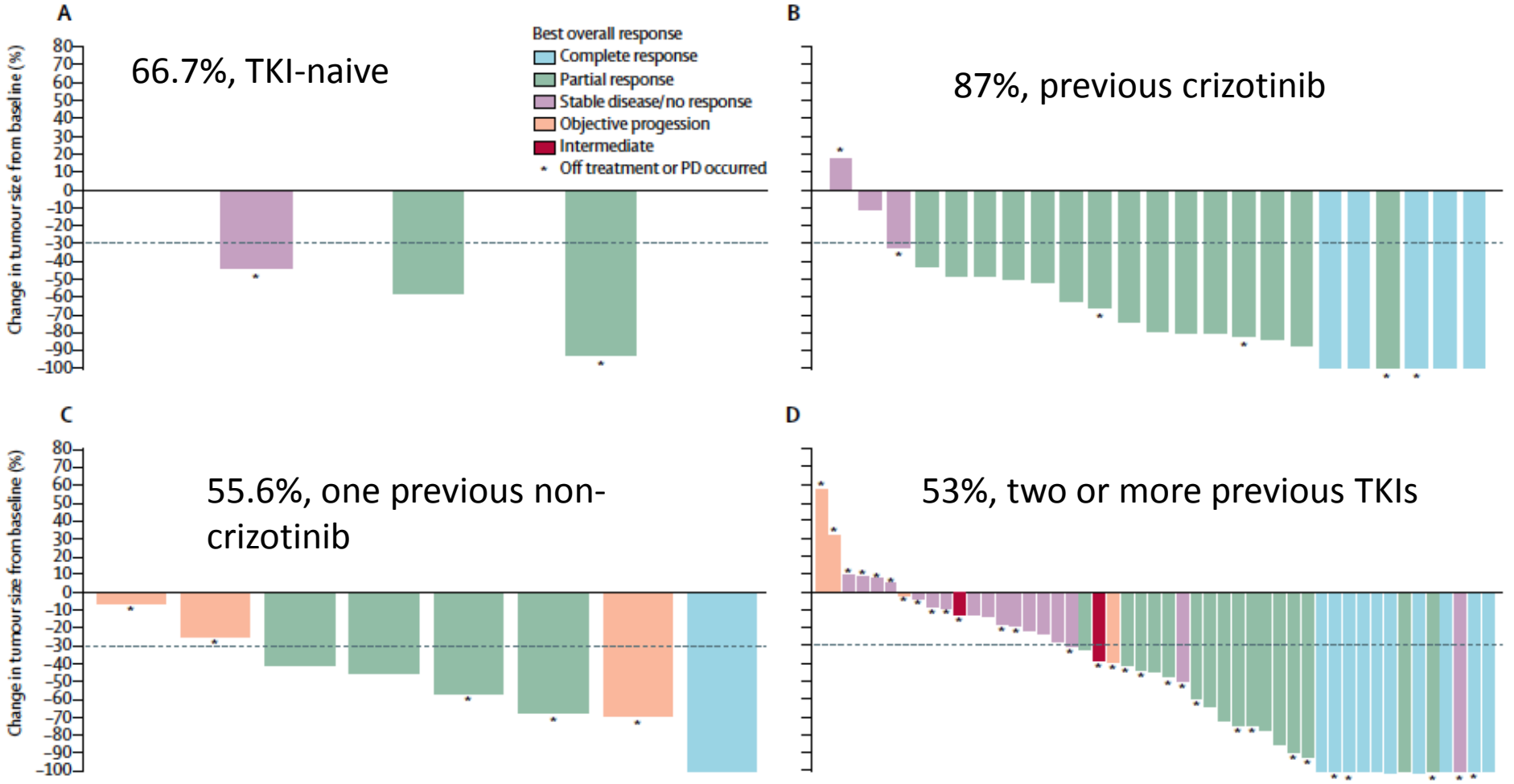
- Sequenza 10.9 Crizo + 8.9 Alectinib (circa 20 mesi) vs 35 mesi con Alectinib subito
- Profilo di tollerabilità
- Effetto a livello del SNC
- Partendo con Crizotinib, circa 20% potrebbero sviluppare mut di ALK G1202R o I1171 (res Alectinib)
- Possibile attività di Lorlatinib dopo Alectinib

Lorlatinib in NSCLC ALK+: Tumor response



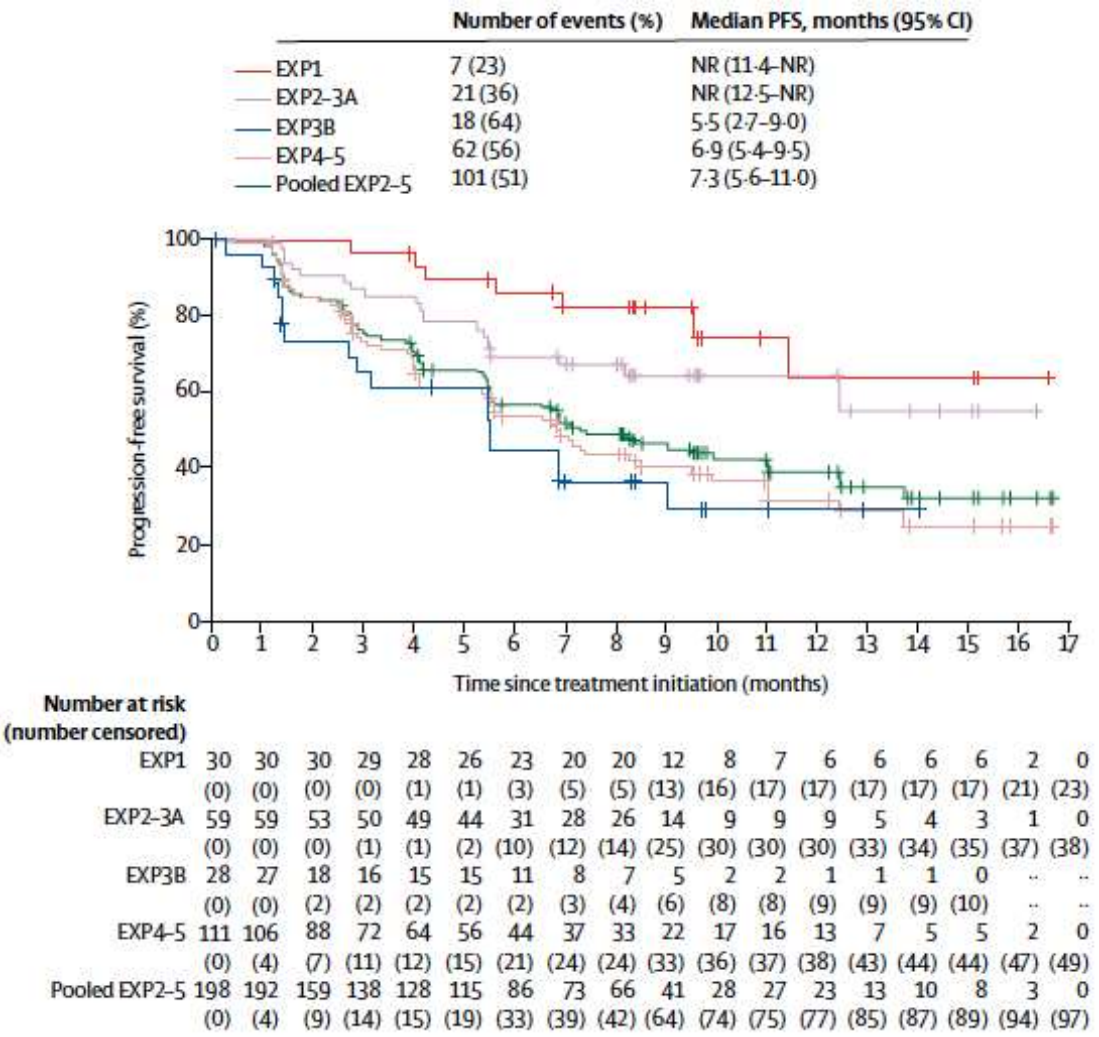
Besse et al, ASCO 2018 and Salomon et al, Lancet Oncol 2018

Lorlatinib in NSCLC ALK+: Brain mts response



Besse et al, ASCO 2018 and Salomon et al, Lancet Oncol 2018

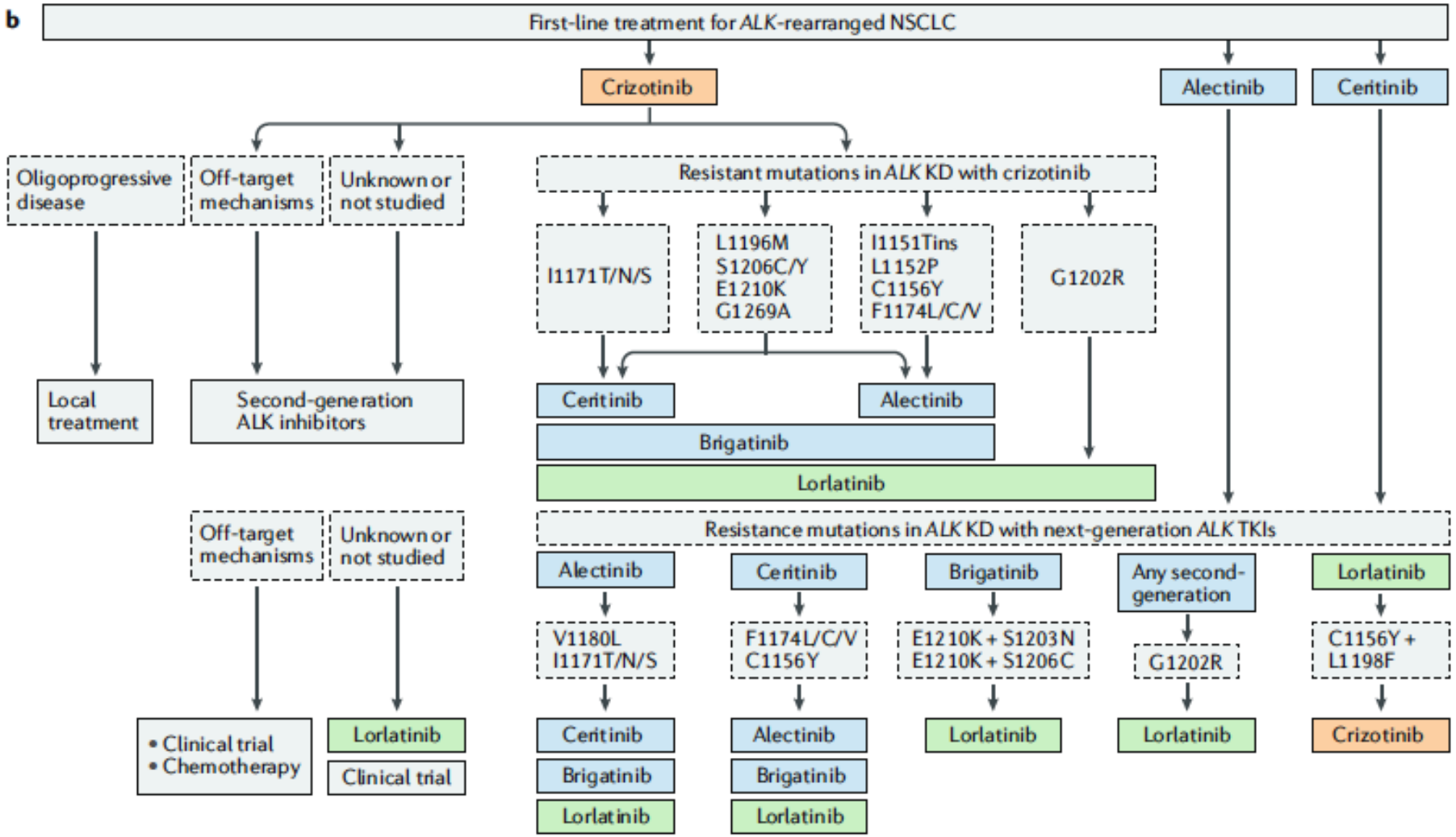
Lorlatinib in NSCLC ALK+: PFS and toxicity



The most common TRAEs:
Hypercholesterolaemia 81% and 16% grade 3–4
Hypertriglyceridaemia 60% and 16% grade 3–4
Serious TRAEs occurred 7% patients;
3% permanently discontinued treatment

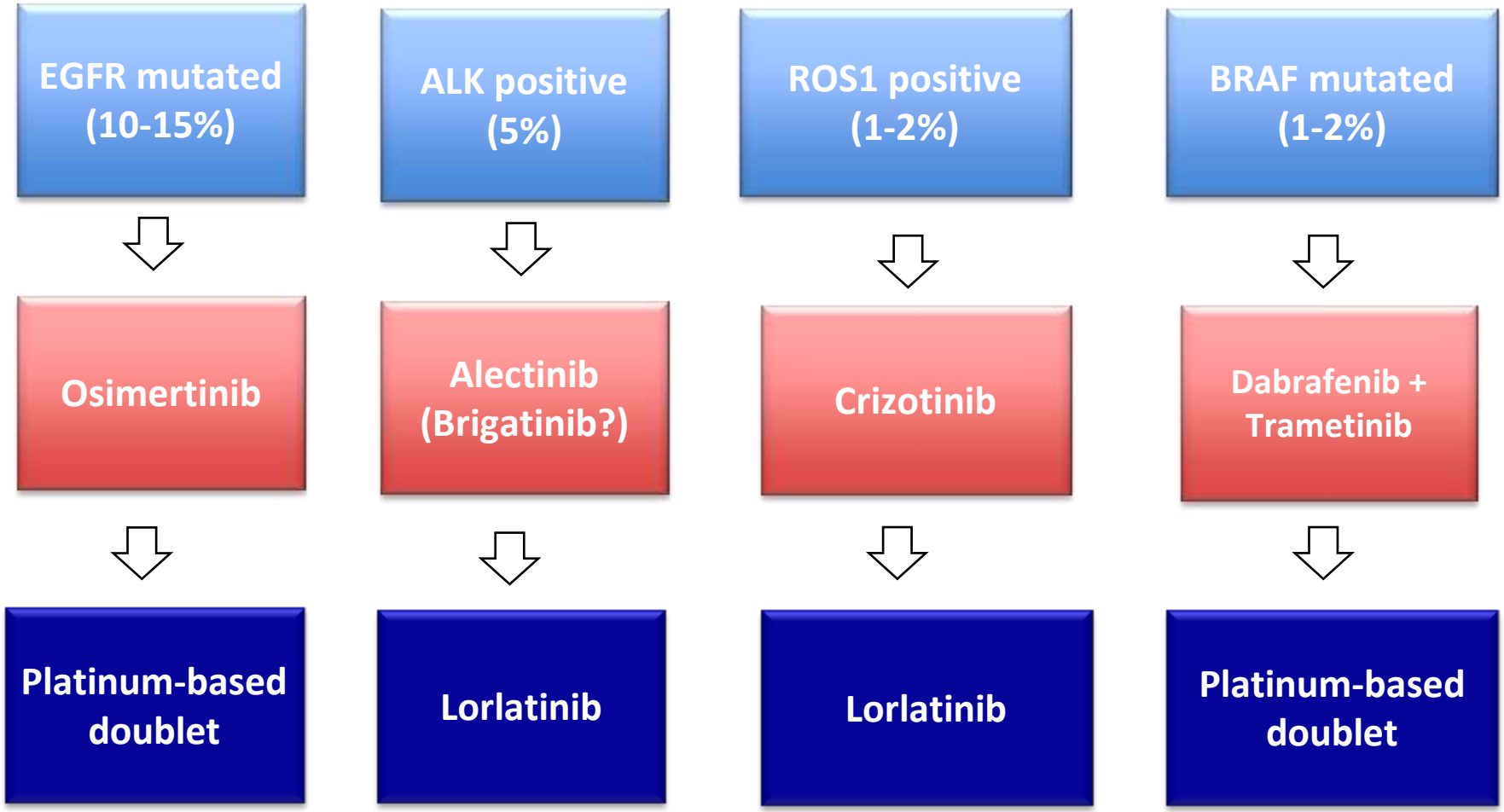
Besse et al, ASCO 2018 and Salomon et al, Lancet Oncol 2018

Strategia terapeutica nei pazienti NSCLC ALK +: sequenza o up-front?



Recondo et al, Nat Rev Clin Oncol 2018

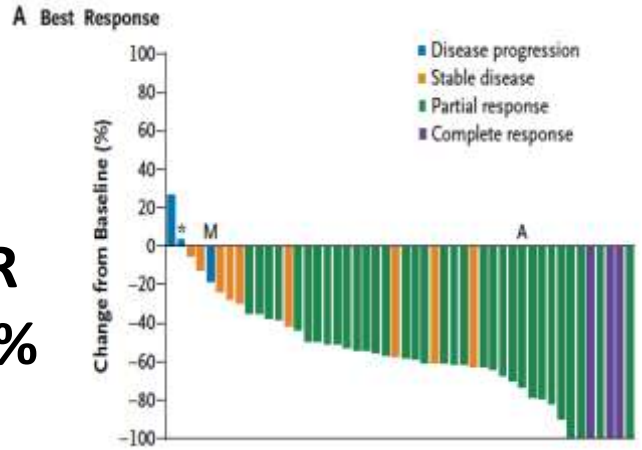
NSCLC oncogene-addicted



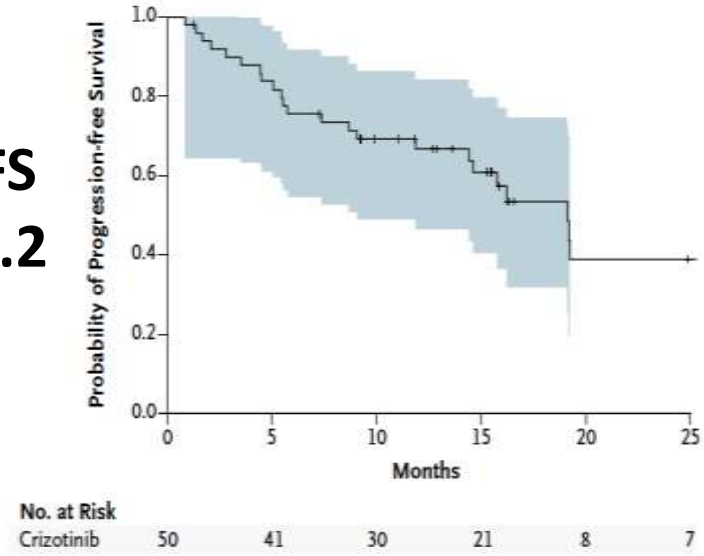
Pazienti ROS1 e BRAF V600

Crizotinib

RR 72%



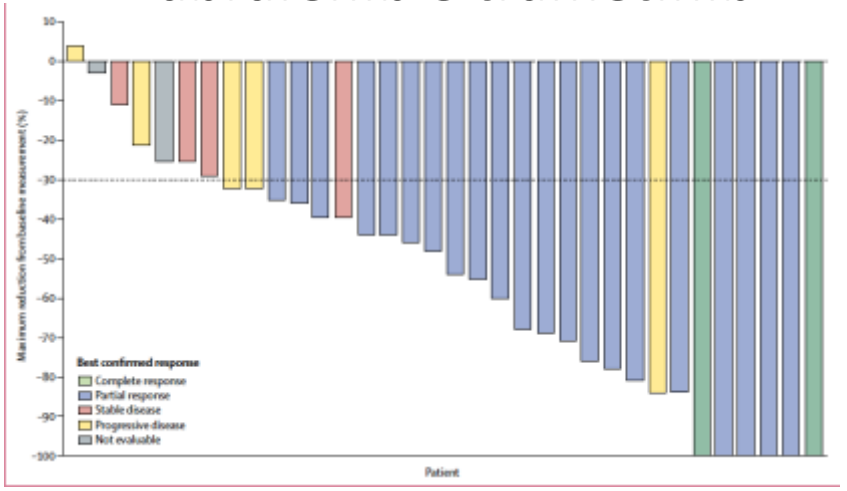
PFS 19.2



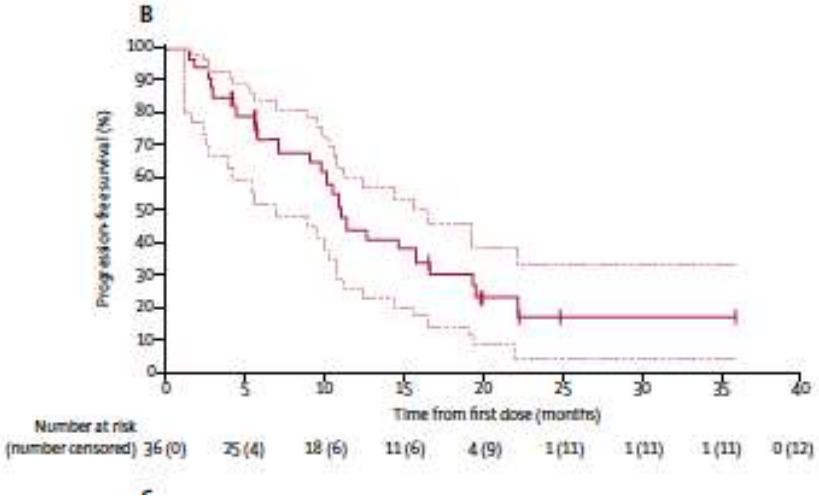
Shaw et al, N Engl J Med 2014

Dabrafenib e trametinib

RR 64%



PFS 14.6



Planchard et al, Lancet Oncology 2017

Immunoterapia e oncogene addiction

Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget).

Meeting with ICI

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Julien MAZIERES

Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	X	+	X	NA	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	X	X	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

Conclusioni

- Dacomitinib difficilmente entrerà nella pratica clinica, come anche le combinazioni con Beva e CT
- Osimertinib e Alectinib hanno mostrato netto vantaggio in PFS rispetto agli inibitori di generazione precedente e rappresentato il nuovo standard in I linea in EGFR/ALK+
- Possibilità di sequenze terapuetiche nei pazienti ALK e ROS1 positivi (vedi Lorlatinib)
- Testare anche mutazioni di BRAF V600E
- Necessarie ulteriori conoscenze sui meccanismi di resistenza
- Scarso impatto dell'immunoterapia in questi pazienti

Grazie per l'attenzione

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