Altri target molecolari: che novità ci sono?

Marcello Tiseo

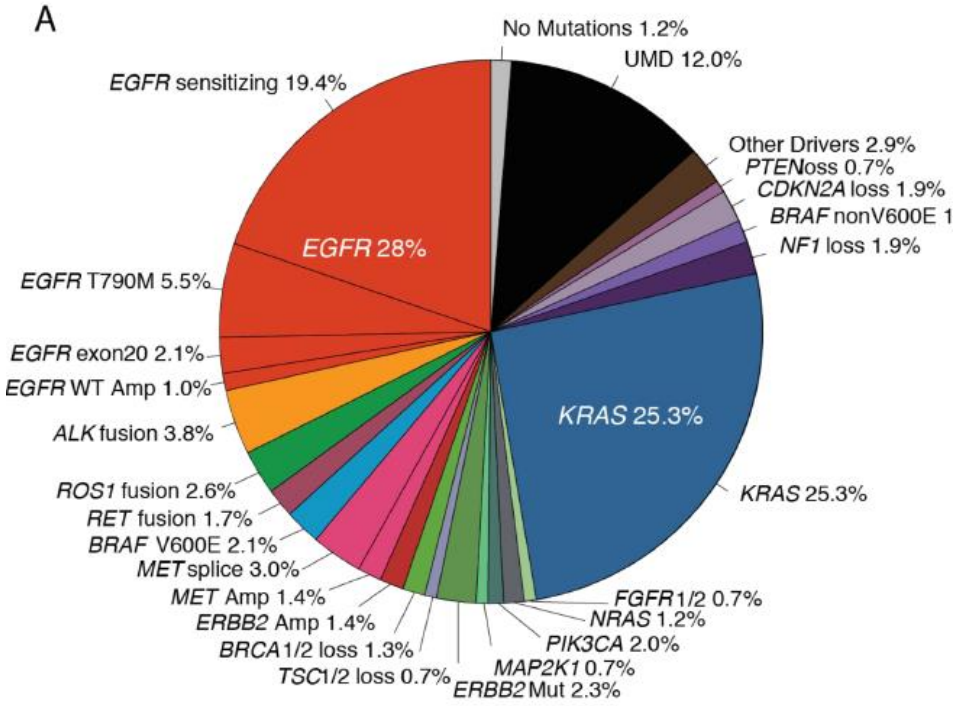
Oncologia Medica

Coordinatore PDTA Oncologia Toracica

Azienda Ospedaliero-Universitaria Parma

Altri target molecolari oltre EGFR e ALK: agenda

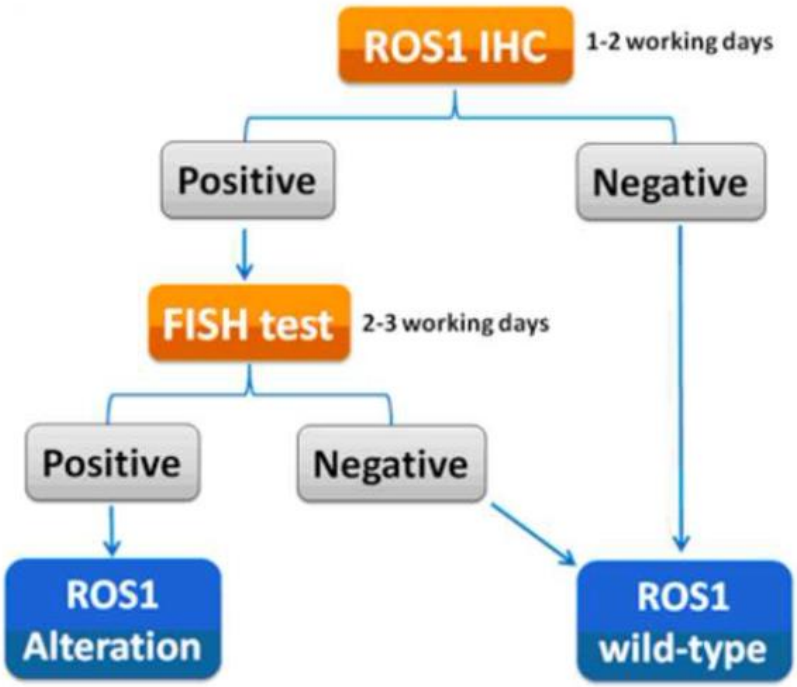
- ROS1 riarrangiamenti
- Mutazioni di BRAF
- RET riarrangiamenti



Jordan et al, Cancer Discovery 2017

Altri target molecolari oltre EGFR e ALK: agenda

- ROS1 riarrangiamenti
- Mutazioni di BRAF
- RET riarrangiamenti



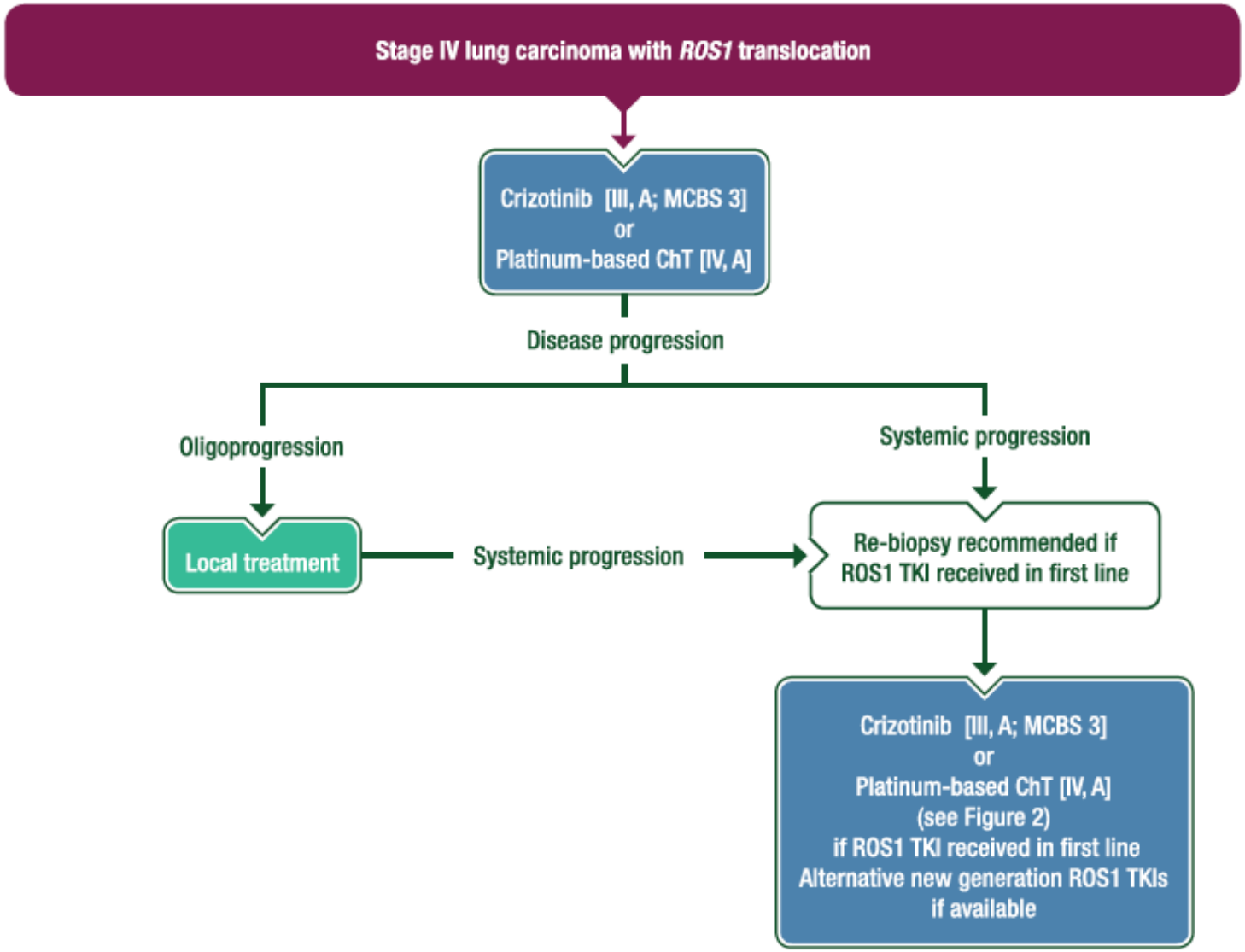
Chiari et al, Clin Lung Cancer 2014

ALK vs ROS1

	Homologies	Disparities
Biology	Phylogenic origin	EML4 (with its variants) largerly the most frequent ALK partner gene; more variability for ROS1 fusion partners
	> 80% sequence identity in ATP-binding sites	
Clinics	Molecular-driven cancers arising preferentially in young and non-smokers patients	Better prognosis in advanced disease for ROS1+
		Brain progression under crizotinib more fequent in ALK+
Drugs	Pemetrexed sensitivity	Longer disease control with crizotinib in ROS1+
	Specific TKI shared	Against ROS1, ceritinib only slighly better than crizotinib, while alectinib inactive
Resistance	Corresponding mutational hostspots for resistance	Differential frequence of emergence of specific mutations
	Bypass mechanisms for resistance shared	Lorlatinib: IC50 values lower for ALK translating in activity in ALK G1202R, while lack of activity in the corresponding ROS1 G2032R

Facchinetti et al, Cancer Treat Rew 2017

NSCLC ROS1 +: ESMO 2018

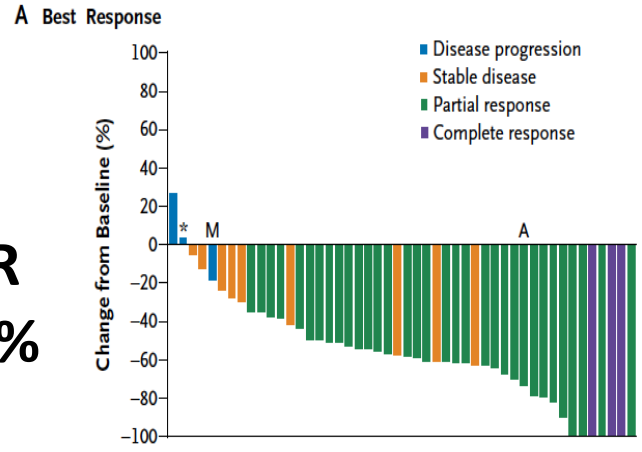


Planchard et al, ESMO guidelines 2018, Ann Oncol 2018

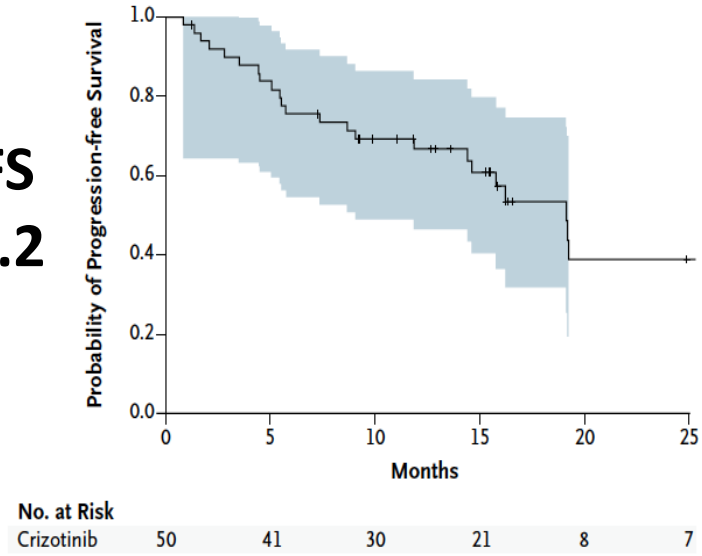
Pazienti ROS1

Crizotinib

RR 72%



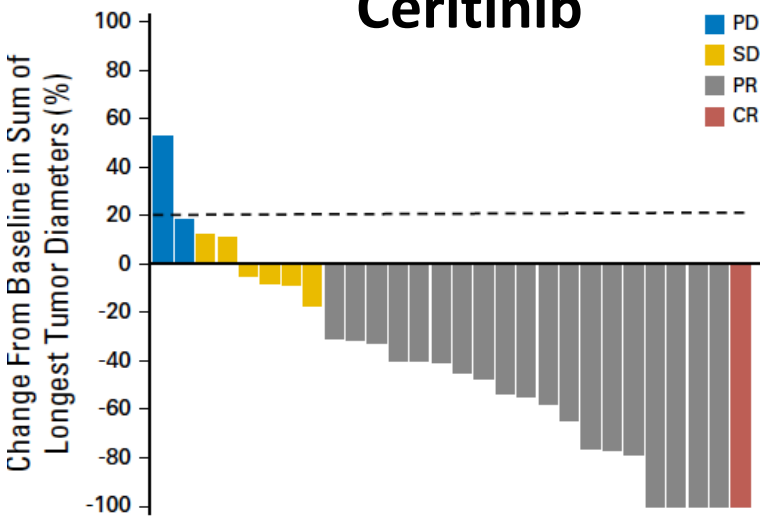
PFS 19.2



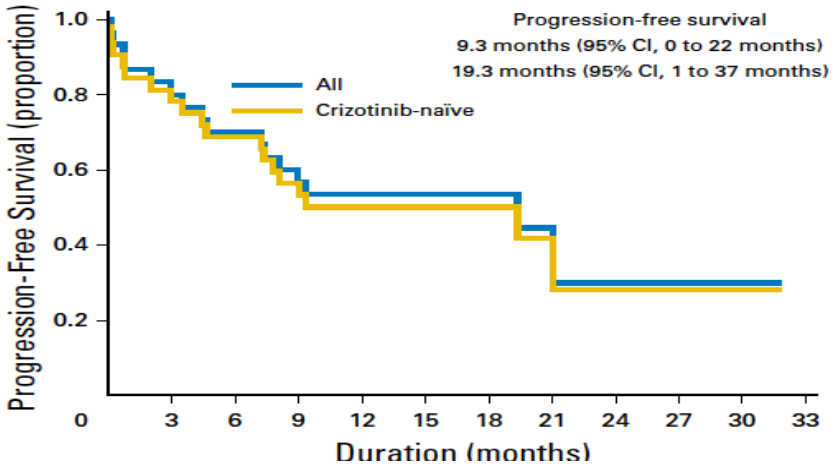
Shaw et al, N Engl J Med 2014

Ceritinib

RR 67%



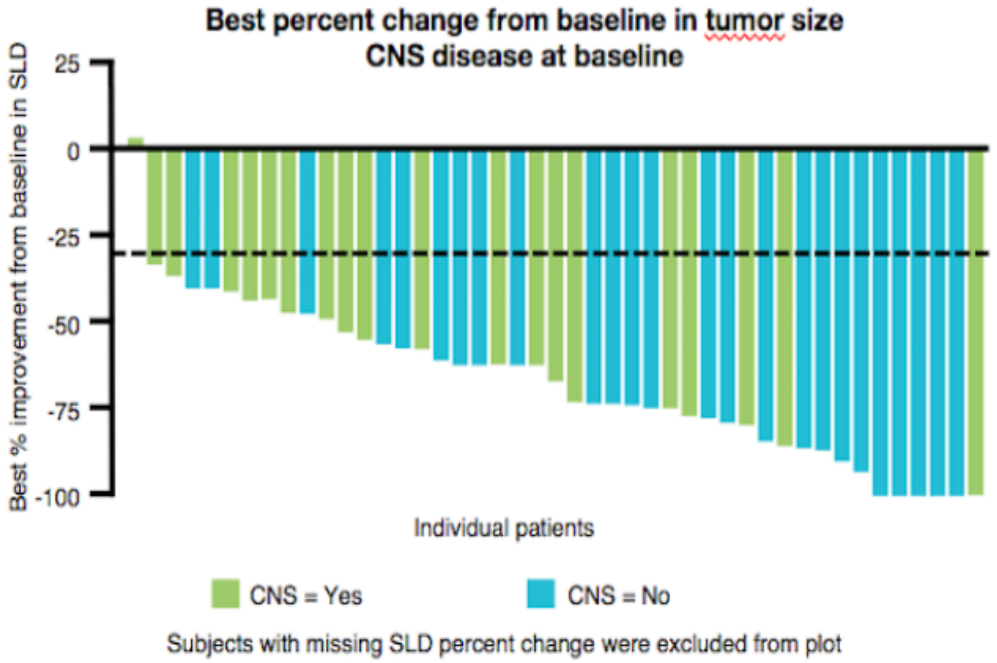
PFS 19.3



Lim et al, J Clin Oncol 2017

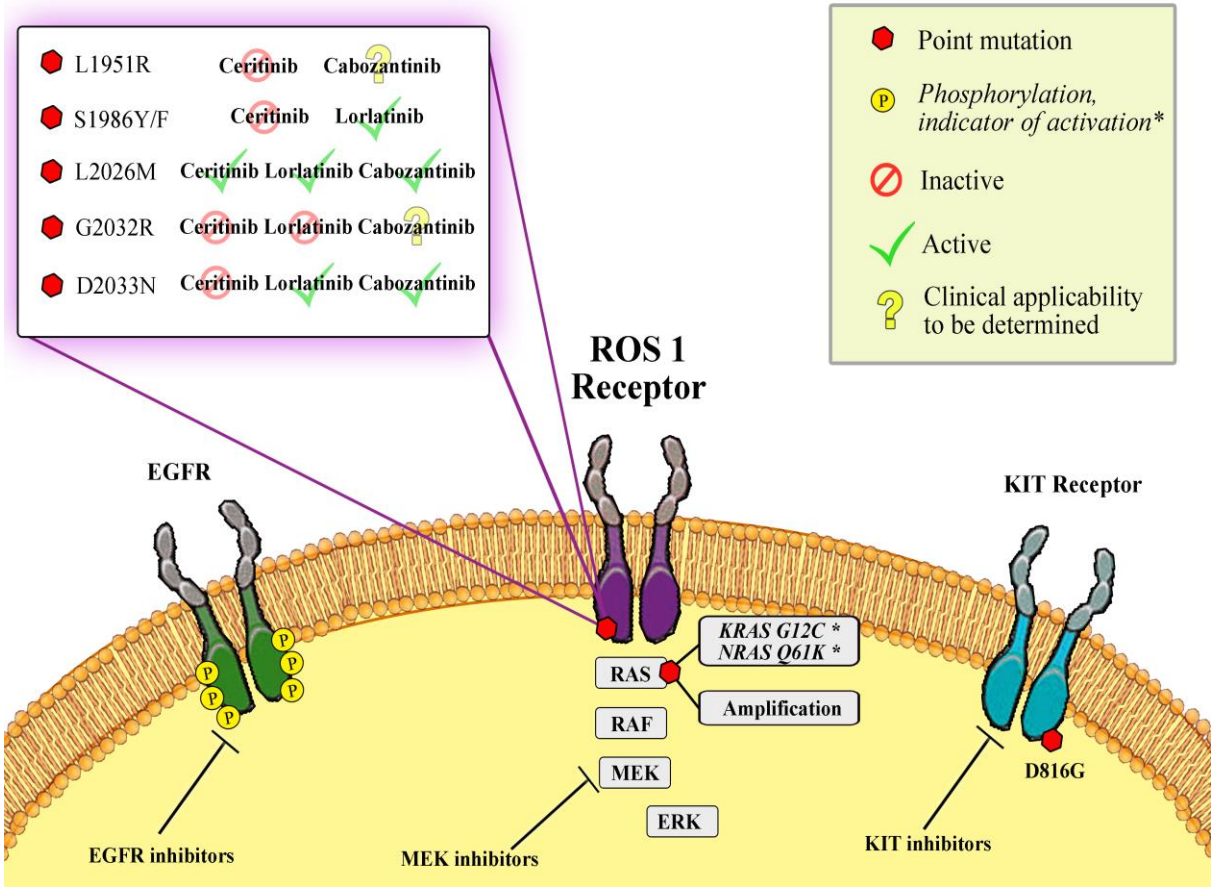
Pazienti ROS1, Entrectinib

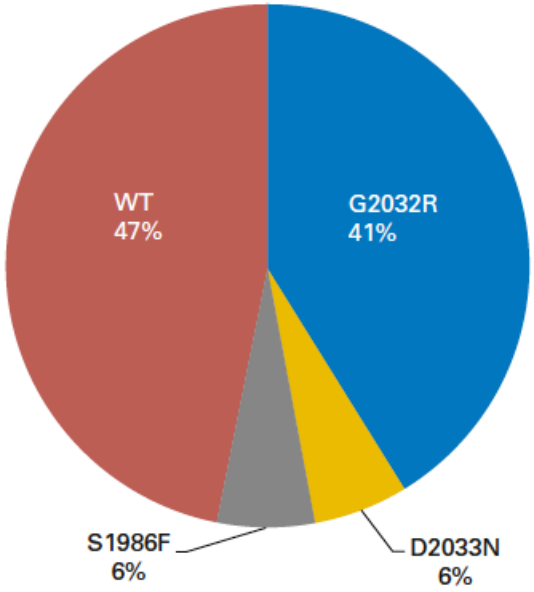
N=53 TKI naïve,
43% brain metastases at baseline
ORR = 77%
Intracranial RR = 55%
Median PFS = 19 months
26.3 months (without CNS metastases)
13.6 months (with CNS metastases)



Doebele et al, WCLC 2018

ROS1+:
Meccanismi di resistenza a Crizotinib





Facchinetti et al, Cancer Treat Rew 2017

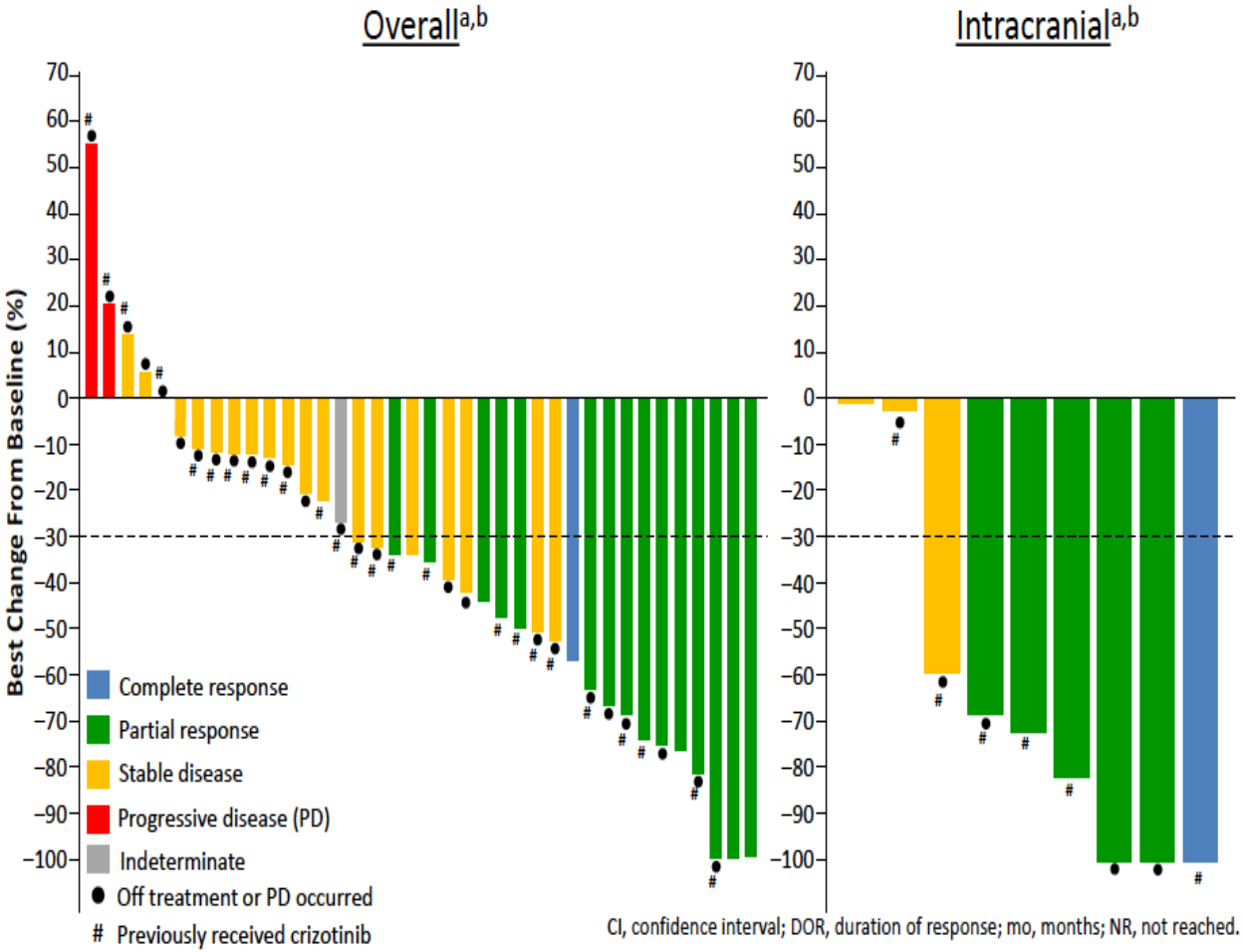
Gainor et al, JCO Precision Medicine 2017

Lorlatinib in ROS1+

Efficacy in EXP6 (ROS1+ With Any Prior Treatment)

	EXP6 (n=47)
ORR, n/N (%) (95% CI)	17/47 (**36**) (23, 52)
IC ORR, n/N (%) (95% CI)	14/25 (**56**) (35, 76)
Median DOR, mo (95% CI)	13.8 (11.1, NR)
DOR ≥6 mo, n%n (%)	12/17 (71)
Median PFS, mo (95% CI)	9.6 (4.7, NR)

- 25 patients (53%) had brain metastases at baseline.

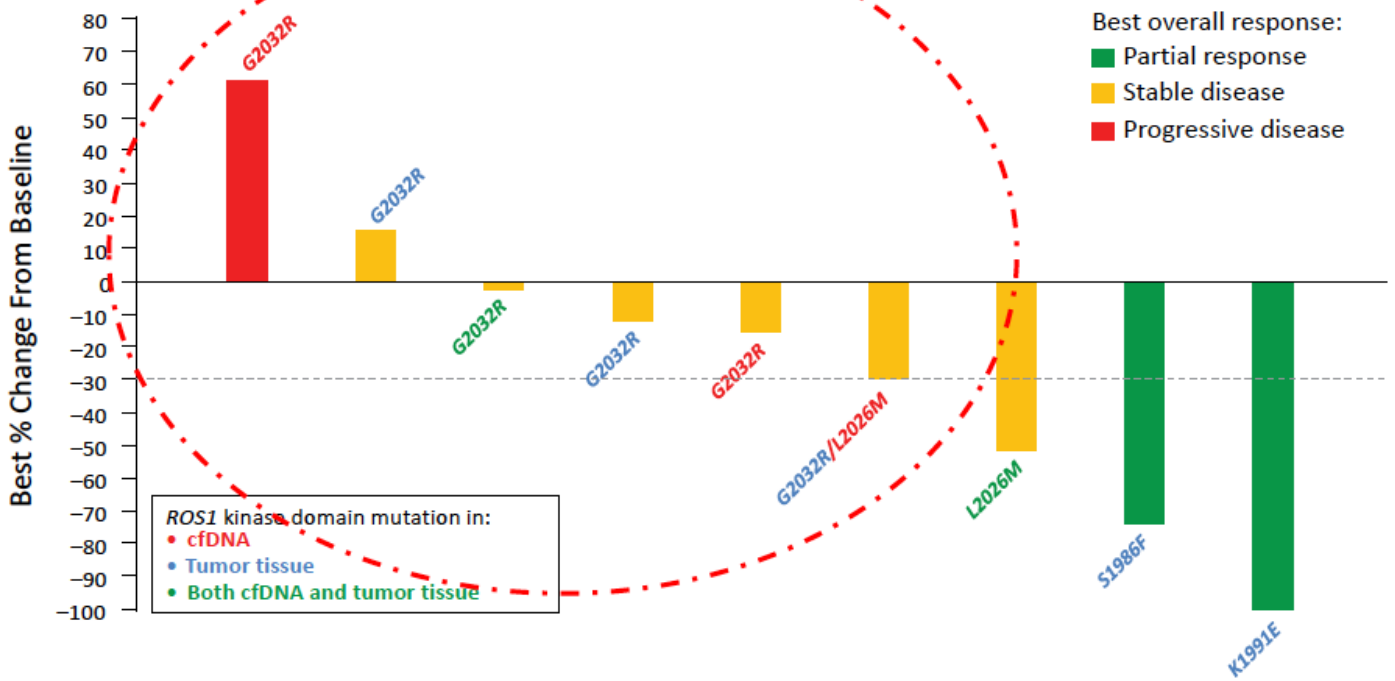


CI, confidence interval; DOR, duration of response; mo, months; NR, not reached.

Solomon et al. WCLC 2017

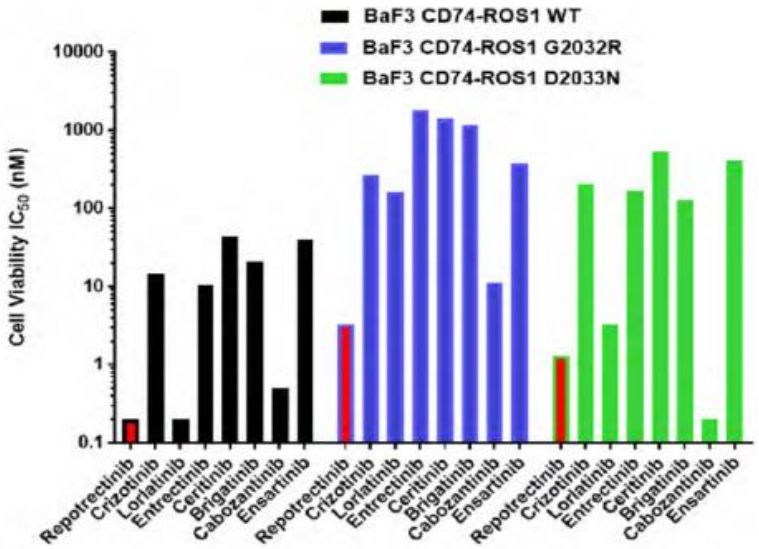
Lorlatinib in ROS1+

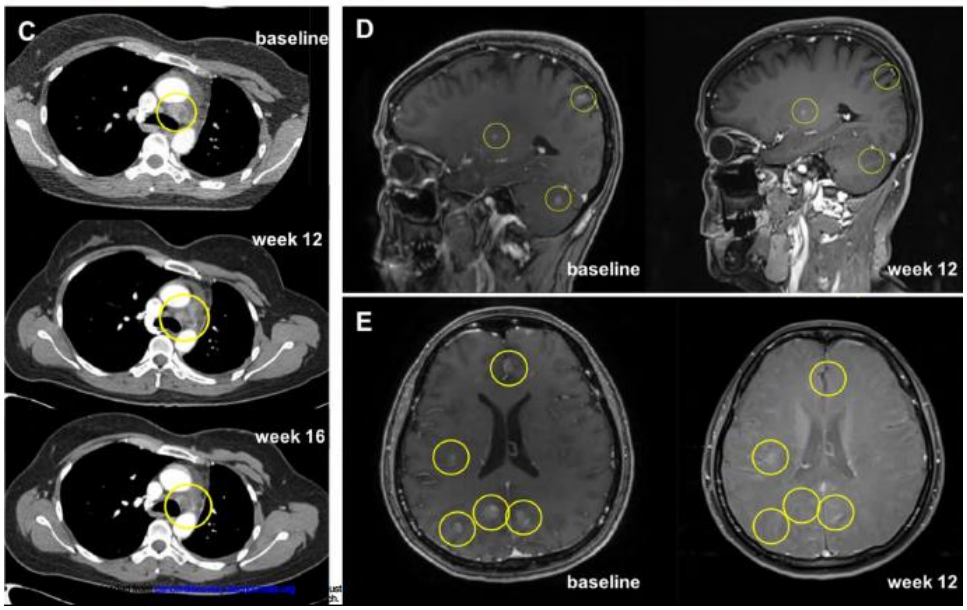
BEST PERCENT CHANGE IN TUMOR SIZE FROM BASELINE IN PATIENTS WITH ≥1 *ROS1* KINASE DOMAIN MUTATION IN cfDNA AND/OR TUMOR TISSUE (ARCHIVAL OR DE NOVO)



Solomon et al. ESMO 2018

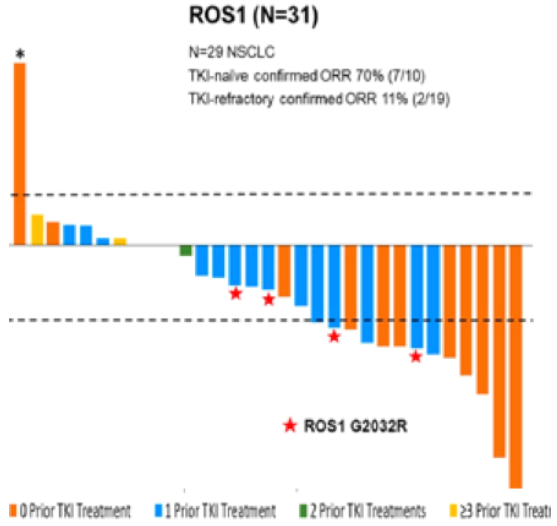
Repotrectinib: anti-ALK,-ROS1,-NTRK

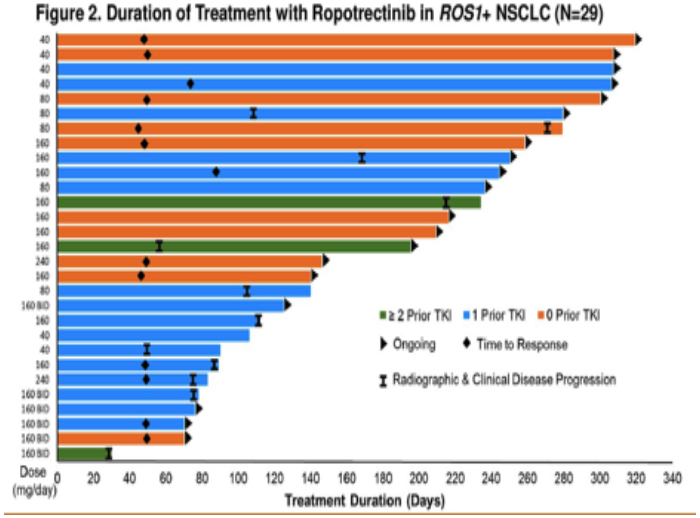




CD74-ROS1-rearranged NSCLC with ROS1 G2032R-mediated resistance to crizotinib

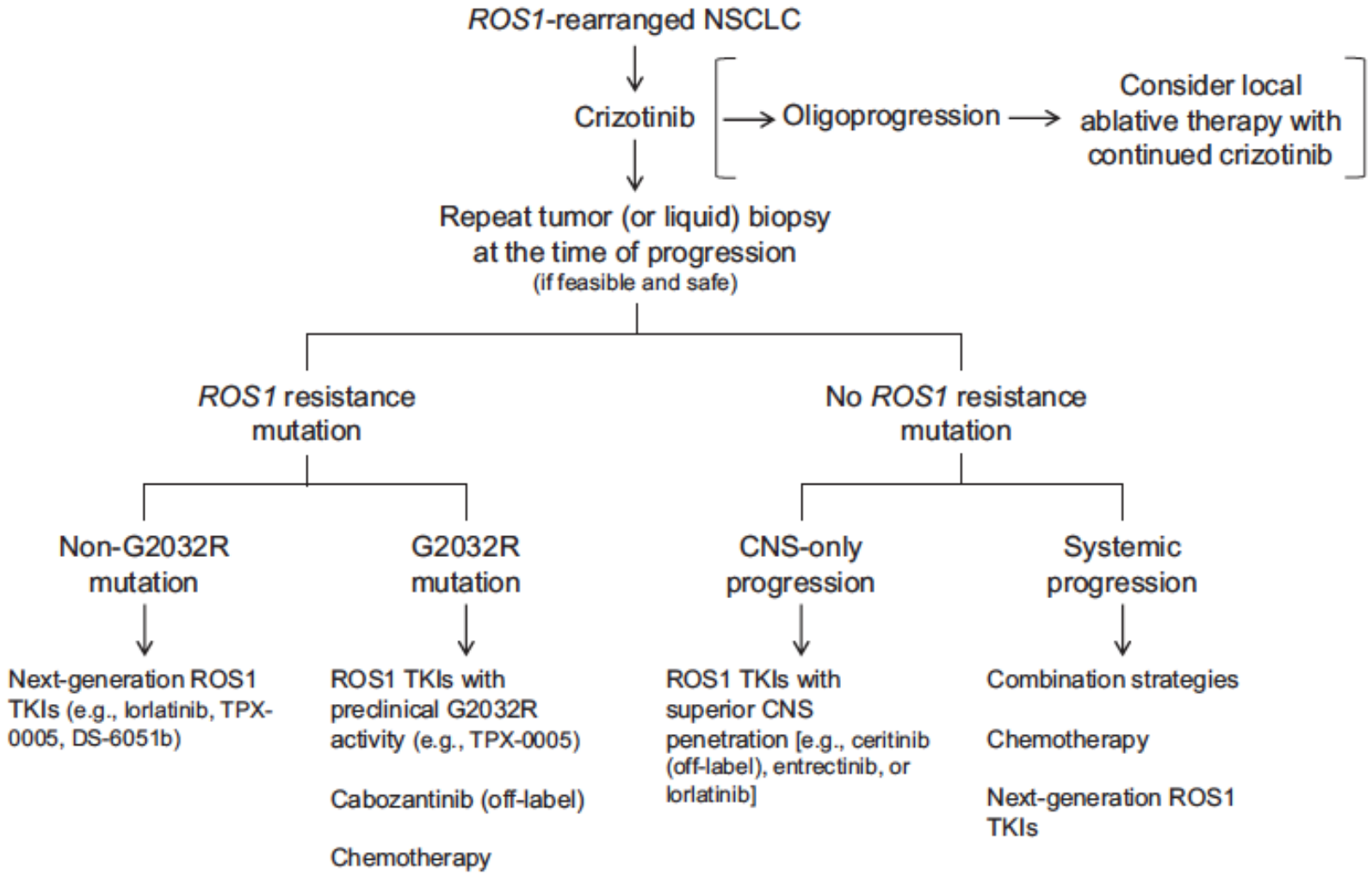
Drilon et al, Cancer Discovery 2018





Drilon et al, ASCO 2018

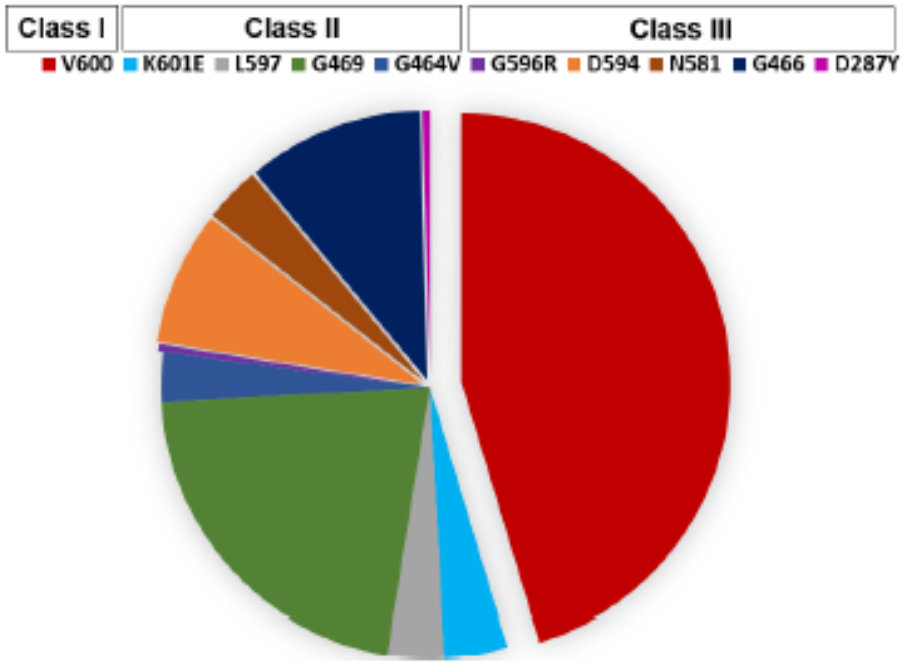
ROS1+: meccanismi di resistenza e algoritmo



Lin and Shaw, J Thoracic Oncol 2017

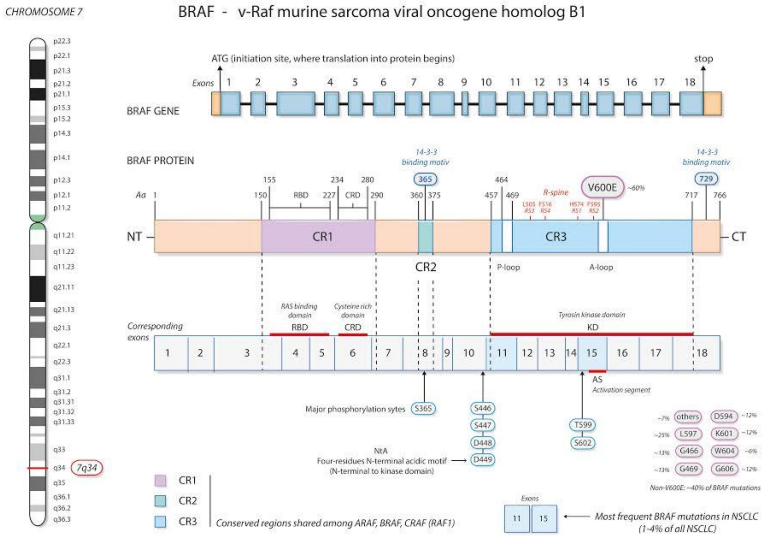
Altri target molecolari oltre EGFR e ALK: agenda

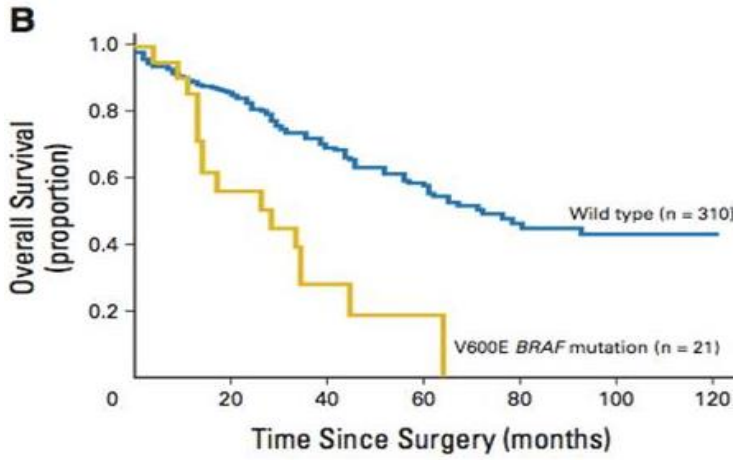
- ROS1 riarrangiamenti
- Mutazioni di BRAF
- RET riarrangiamenti



Dagogo-Jack et al, Clin Cancer Res 2018

BRAF mutations



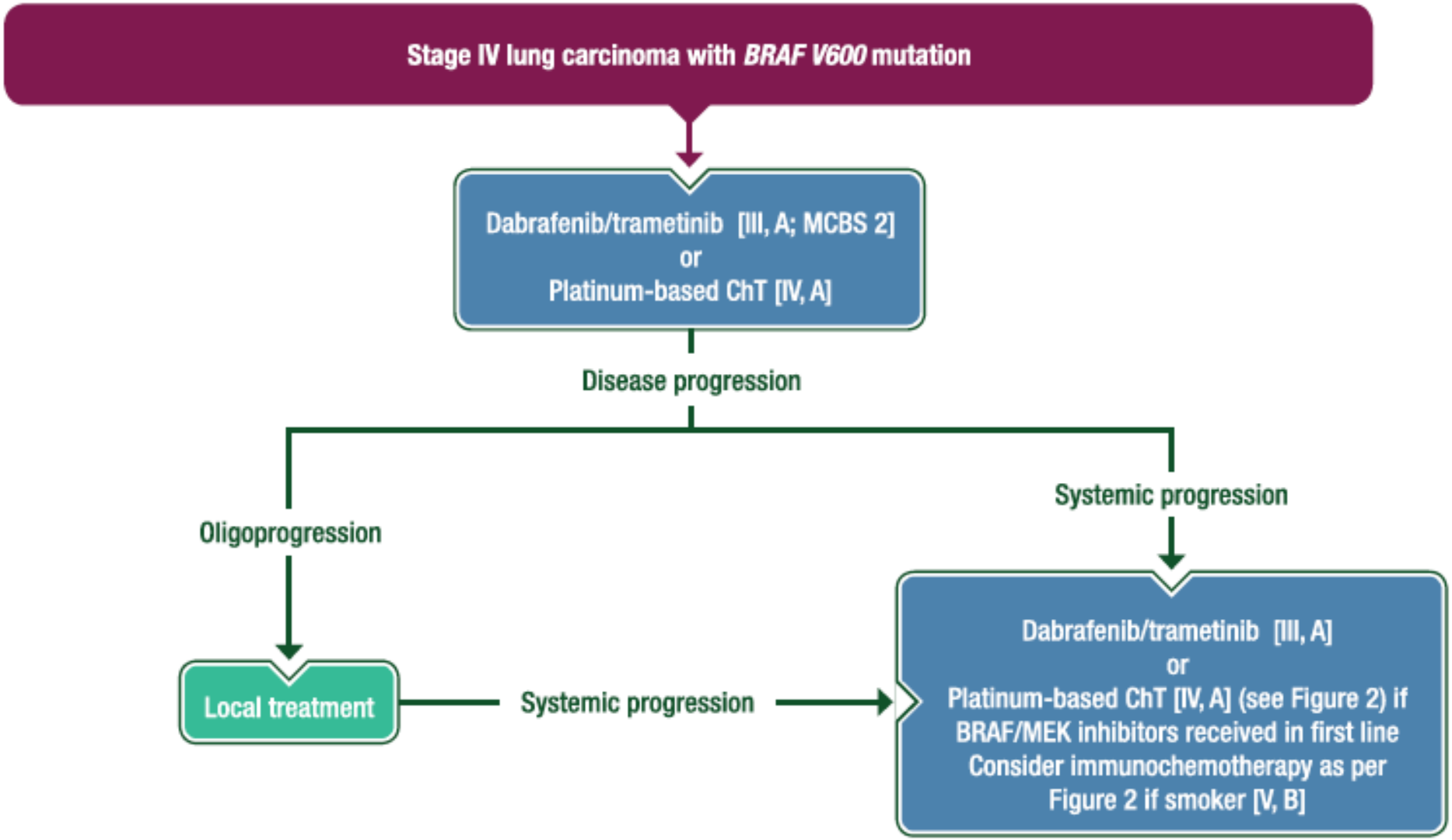


- Found in 1-3% of NSCLC, ADK; about 50% V600E
- Patients with V600 mutations were more likely to be light/never-smokers compared with non-V600
- Associated with more aggressive disease
- Represent an emerging mechanism of resistance to EGFR-TKIs

Marchetti et al, J Clin Oncol 2012

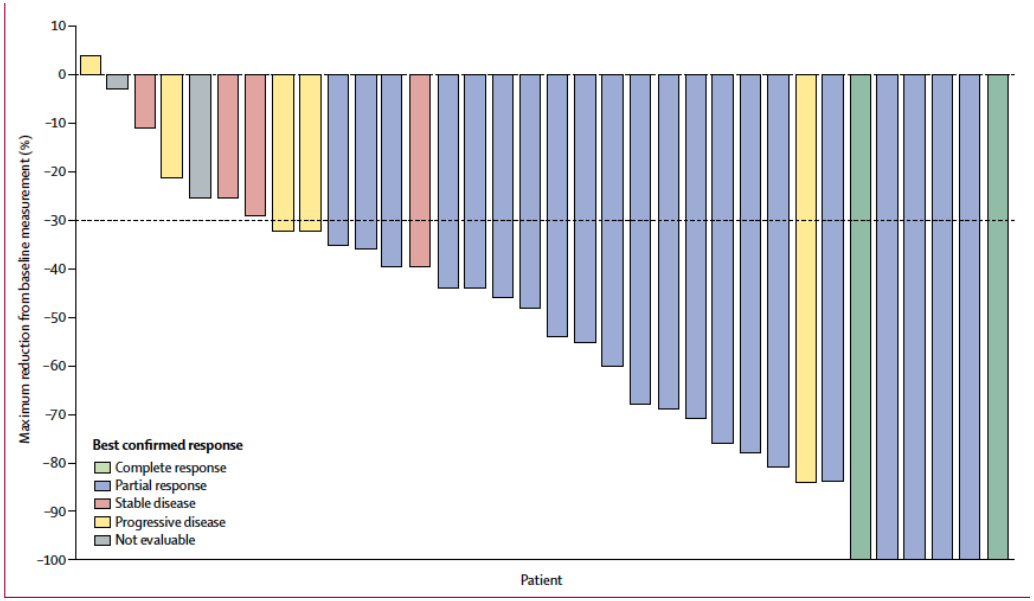
Leonetti et al, Cancer Treat Rew 2018

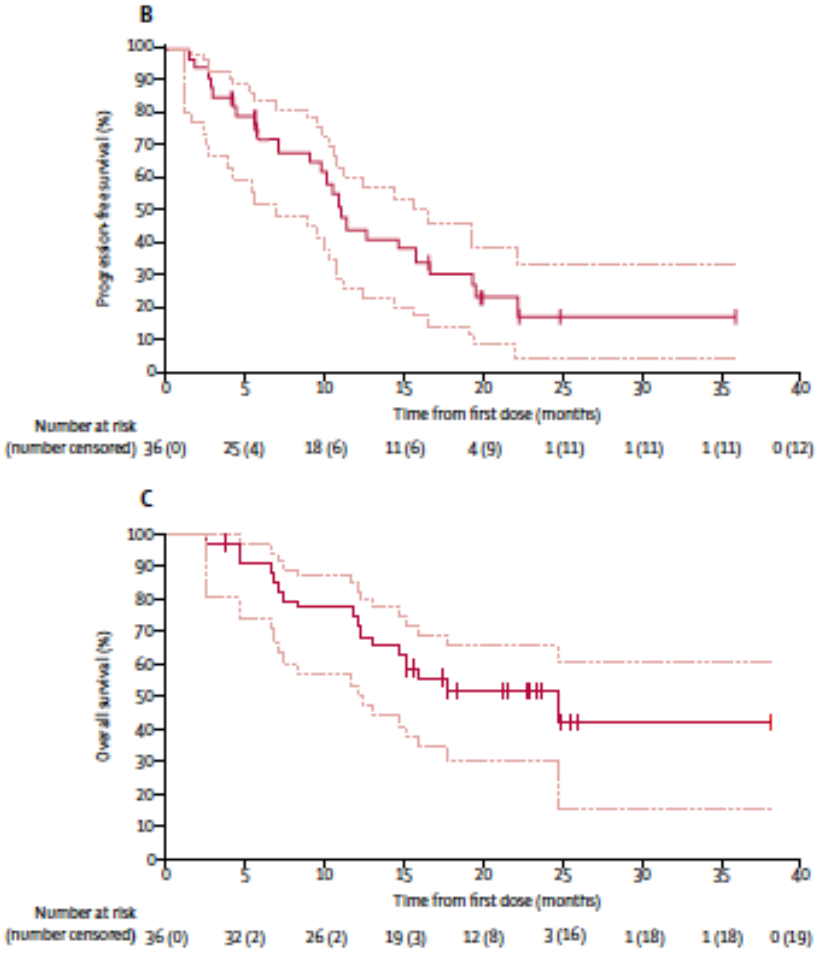
NSCLC BRAF +: ESMO 2018



Planchard et al, ESMO guidelines 2018, Ann Oncol 2018

Dabrafenib e trametinib in NSCLC BRAF mutati I linea





RR: 64%

PFS 14.6 mesi

OS 24.6 mesi

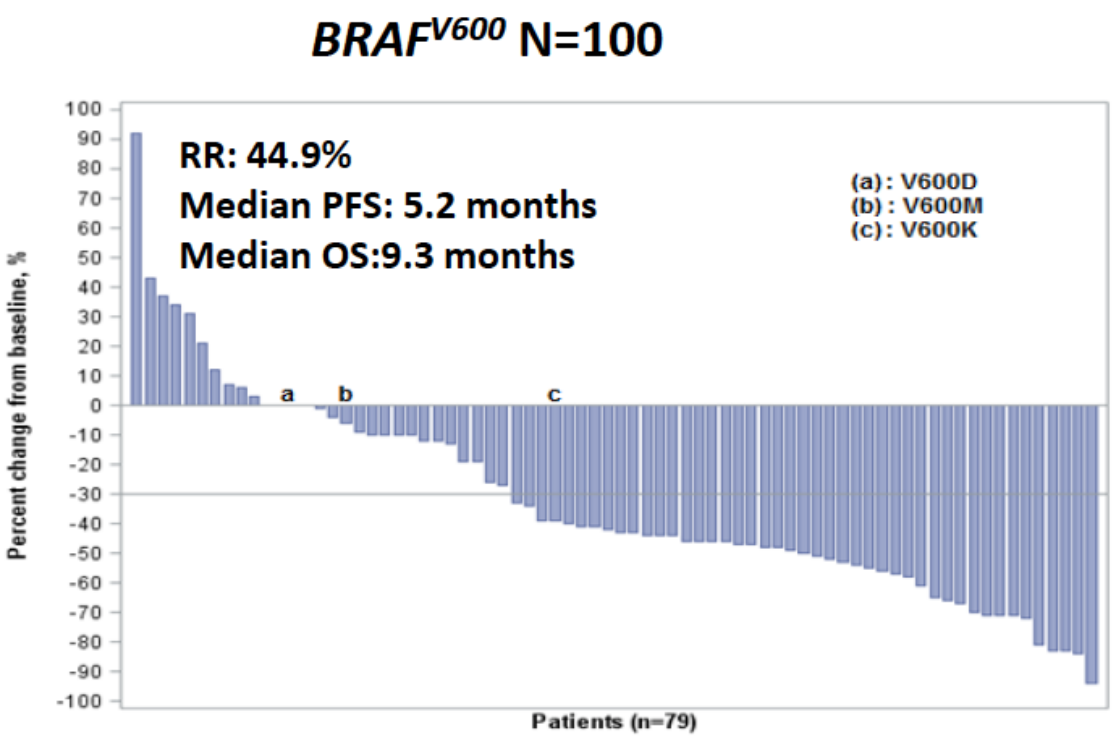
Planchard et al, Lancet Oncology 2017

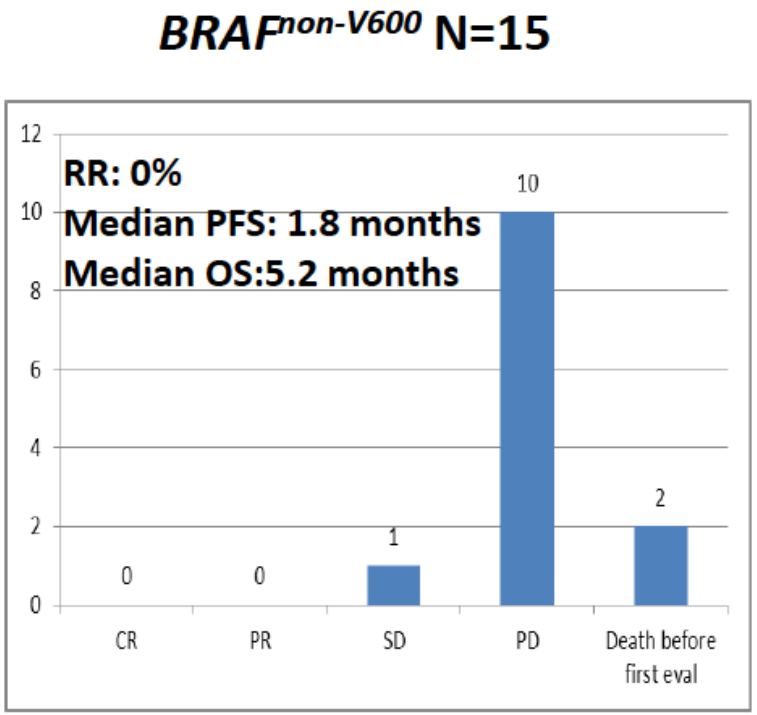
BRAF mutations and TKIs

Reference	Study	Drugs	*BRAF* mutations	Line of treatment	Patients (n)	CR + PR (%)*	DC (%)*	mPFS* (months)	mDoR (months)	mOS (months)
Hyman 2015 New Engl J Med [118]	Phase II	Vemurafenib	V600 (>> V600E)	≥ second	19	8 (42)	16 (84)	7.3	NR	NR
Mazières 2016 J Thor Oncol [120]	Phase II	Vemurafenib	V600	≥ second (>>)	56	20 (36)[#]	34 (61)[#]	4.2	NR	8.7
			Non-V600		9	0[#]	0[#]	1.9	NR	4.7
Subbiah 2017 J Clin Oncol [123]	Phase II	Vemurafenib	V600	First	8	3 (38)	8 (100)	12.9	NE	NE
				≥ second	54	20 (37)	41 (76)	6.1	6.1	15.4
Gautschi 2015 J Thor Oncol [119]	Retrospective	Vemurafenib/ Dabrafenib	V600E[§] Non-V600E	5 first line (vemurafenib) 29 ≥ second	33	17 (50)	28 (85)	5[§]	NR	10.8[§]
Among which Non-V600E				≥ second	6	1 (17)	NR	NR	NR	NR
Planchard 2016 Lancet Oncol [46, 128]	Phase II	Dabrafenib	V600E	First	6	4 (67)	6 (100)	8.3	NR	NR
				Second	40	16 (40)	26 (65)	6.8	NR	13.3
				> second	38	11 (29)	18 (47)	3.4	NR	10.6
Planchard 2016 Lancet Oncol [45, 128]	Phase II	Dabrafenib Trametinib	V600E	≥ second	57	38 (67)	46 (81)	10.2	9.8	18.2
Planchard 2017 Lancet Oncol [44]	Phase II	Dabrafenib Trametinib	V600E	First	36	23 (64)	27 (75)	10.9	10.4	24.6

Leonetti et al, Cancer Treat Rew 2018

BRAF mutations and TKIs: Vemurafenib

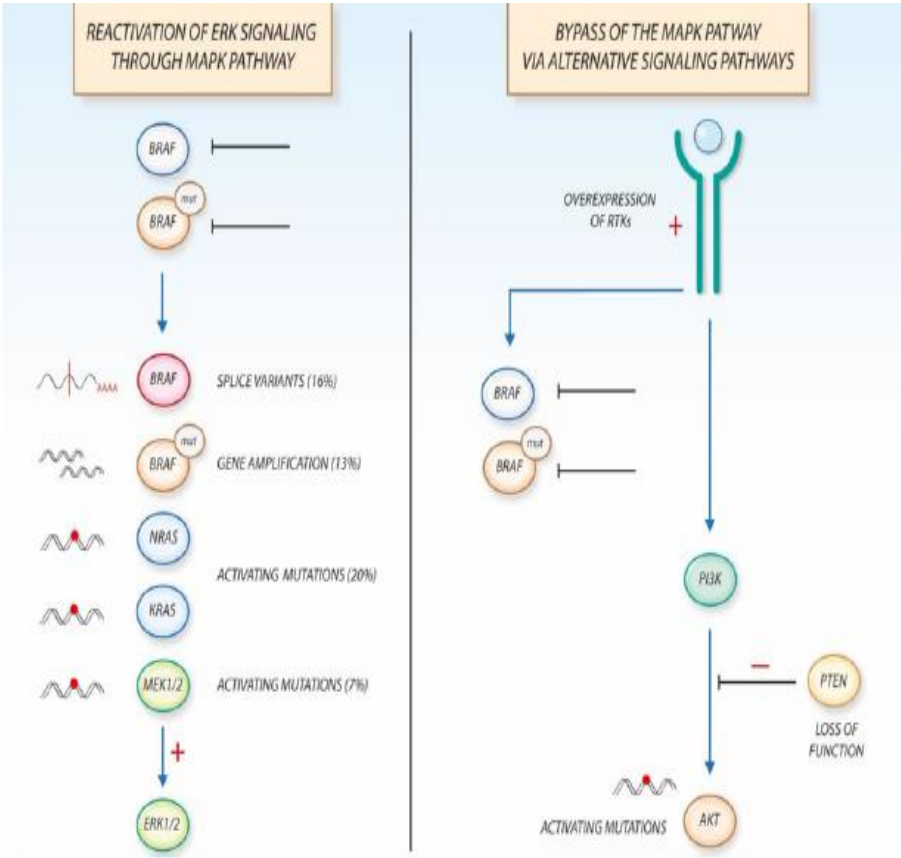




Mazieres et al, WCLC 2018

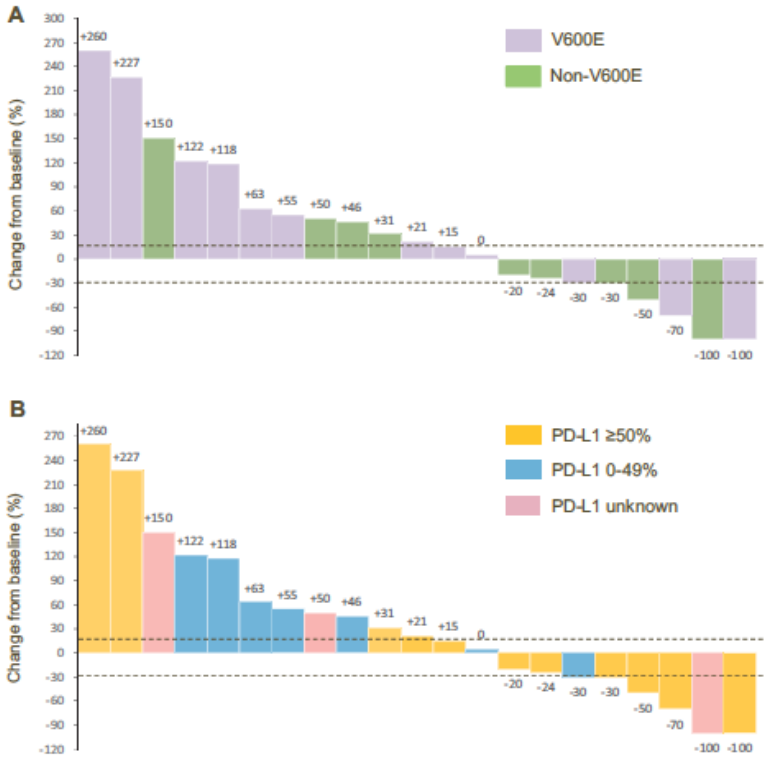
BRAF mutations and TKIs: Non-V600 and resistence

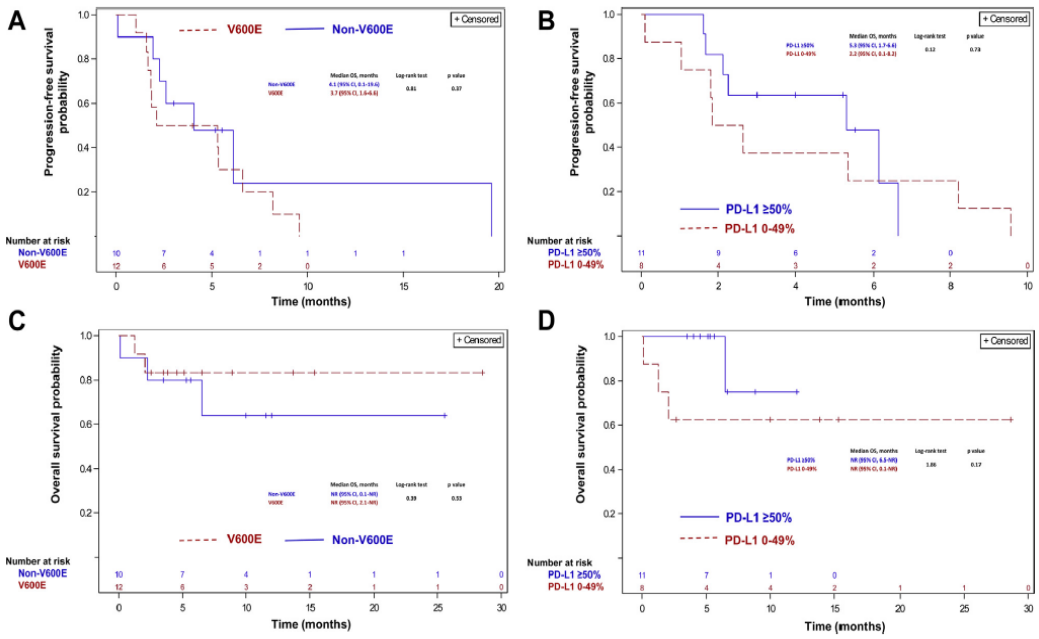
BRAF mutation	Responses to vemurafenib/ dabrafenib	Responses to other agents
G466V	Two NO response (one PD) [121,122]	
G469A	Three NO response (one PD) [121,122]	
G469L	Two NO response (one PD) [122,123]	
G469R	One PR* [43]	One PR to sorafenib [136]
G469V	One PD [122]	One PR to sorafenib [135]
Y472C		One CR to dasatinib [137]
N581S	One PD [122]	
G596R	One PD [122]	
G596V	One PR [122]	
V600D	One PR [122]	
V600G	One SD [120]	
V600K	One SD One NO response [121,122]	
V600M	One PR [122]	
K601E	Two NO response (one PD) [121,122]	
K601N	Two PD [122]	
V600_K601delinsE	One PD [124]	



Leonetti et al, Cancer Treat Rew 2018

BRAF mutations and IT





V600 (n = 21): RR 25%, PFS 3.7 m

Non-V600 (n = 18): RR 33%, PFS 4.1 m

Dudnik et al, J Thoracic Oncol 2018

Immunoterapia e oncogene addiction

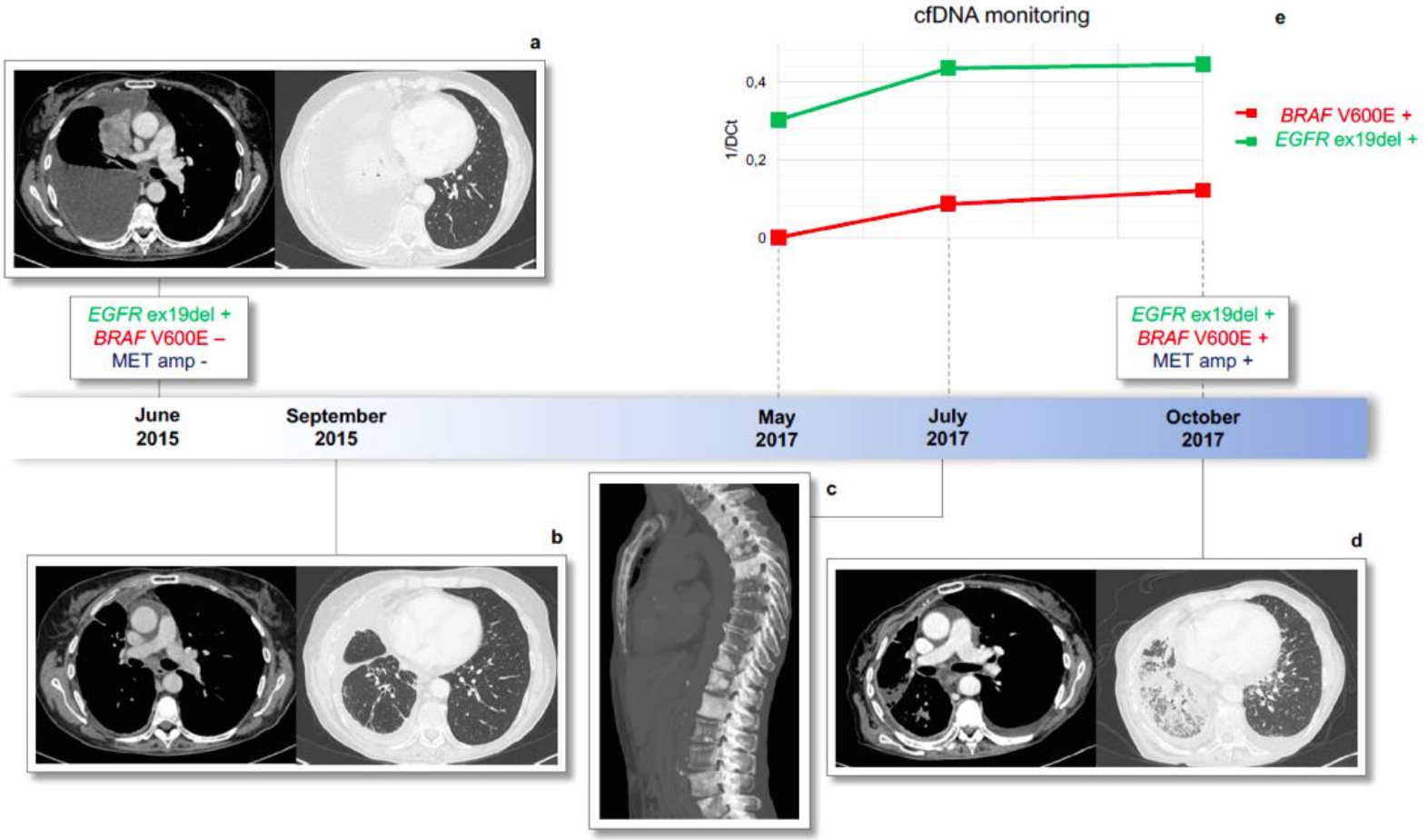
Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget).

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%	-	-					

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



Minari et al, J Thoracic Oncol 2018

ESMO 2018: Other drivers…

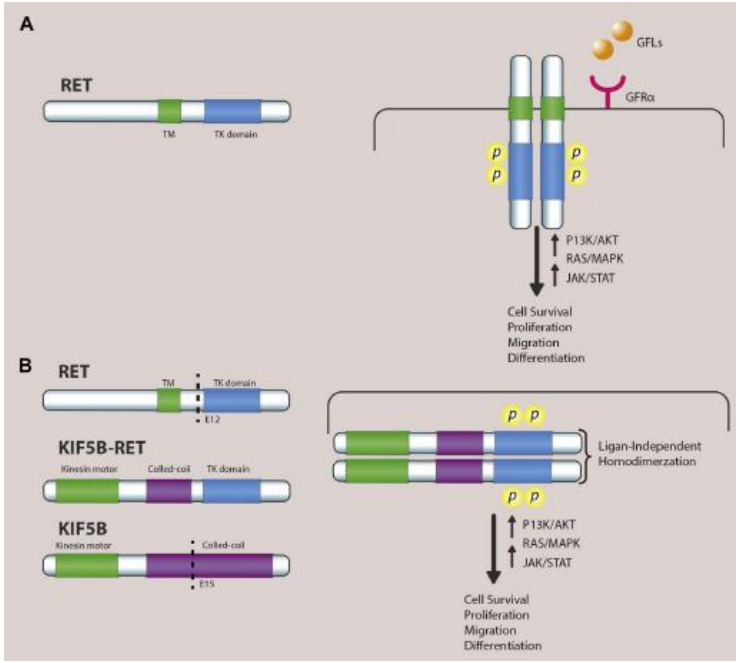
Patients with NSCLC with other actionable oncogenic driver

- Targeting RET is not currently routinely recommended and recruitment into open trials is encouraged [III, C]
- Targeting *MET* amplification is not currently routinely recommended and recruitment into open trials is encouraged [III, C]
- Targeting *METex14* variants (while evidence of benefit is stronger) is not currently routinely recommended and recruitment into open trials is encouraged [III, C]
- Crizotinib has demonstrated potential clinical efficacy for *METex14* variant NSCLC that needs to be confirmed [III, C]
- Given the paucity of robust data, targeting *HER2* dysregulation is not currently recommended and recruitment into open trials is encouraged [III, C]
- Targeting *NRTK* fusions is not currently recommended and recruitment into open trials is encouraged [III, C]

Planchard et al, ESMO guidelines 2018, Ann Oncol 2018

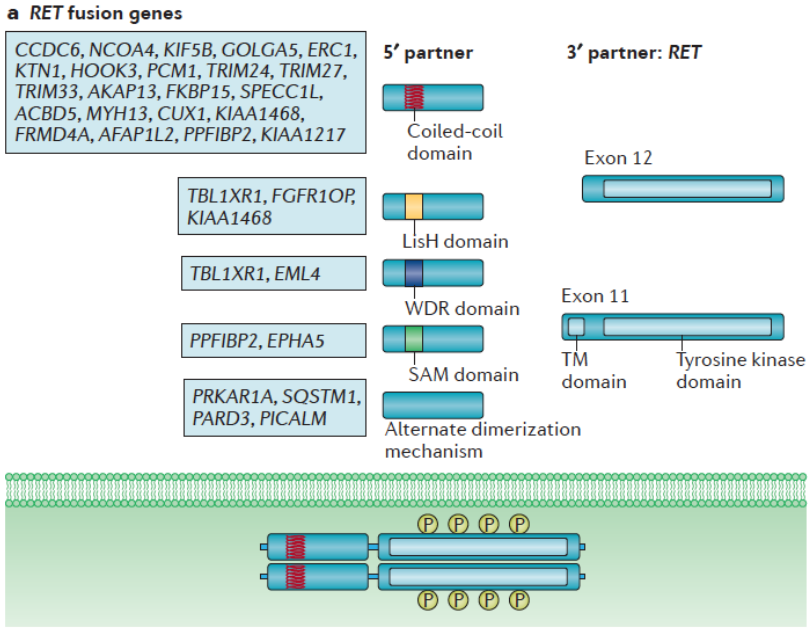
Altri target molecolari oltre EGFR e ALK: agenda

- ROS1 riarrangiamenti
- Mutazioni di BRAF
- RET riarrangiamenti

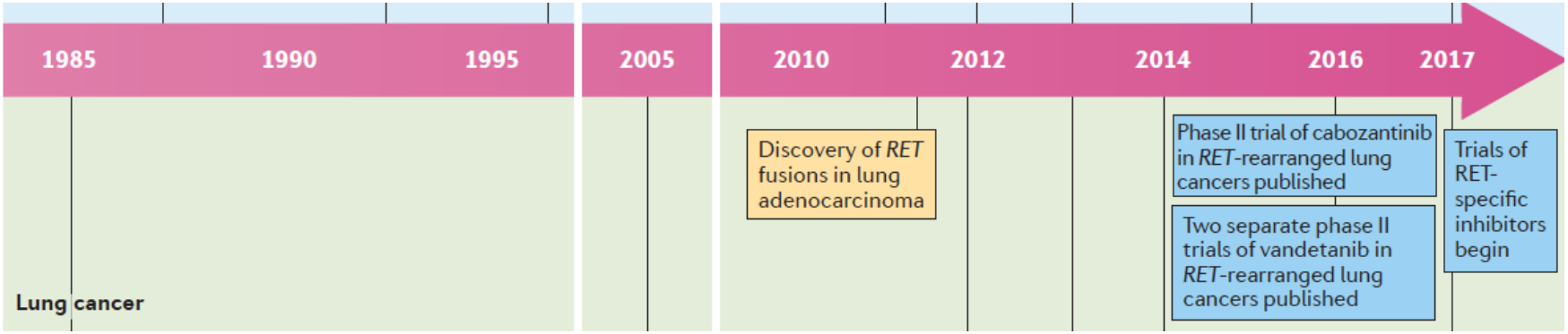


Ferrara et al, J Thoracic Oncol 2017

RET Rearrangements



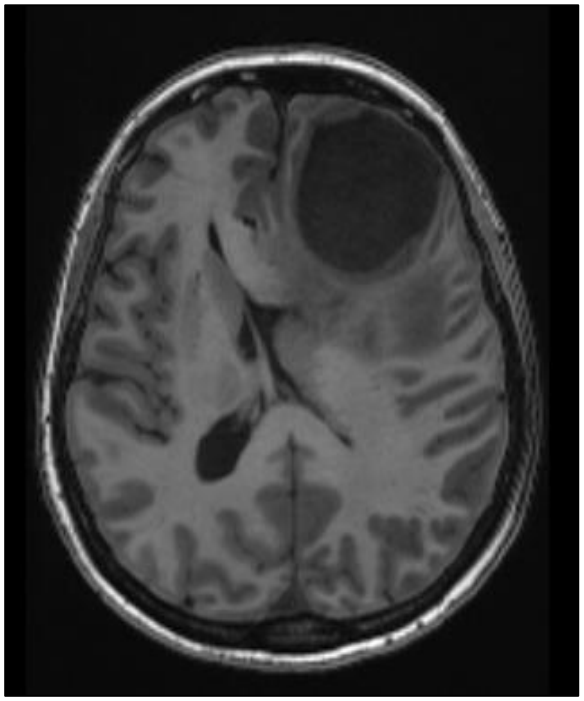
- RET rearrangements 1-2% of NSCLC (ADK)
- Found in ADK, younger, more commonly in never smokers and mutually exclusive with other mutations

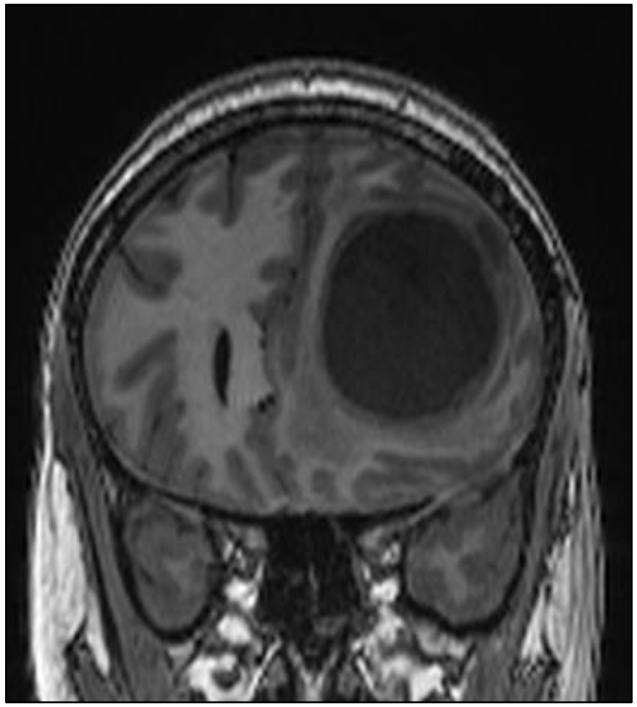


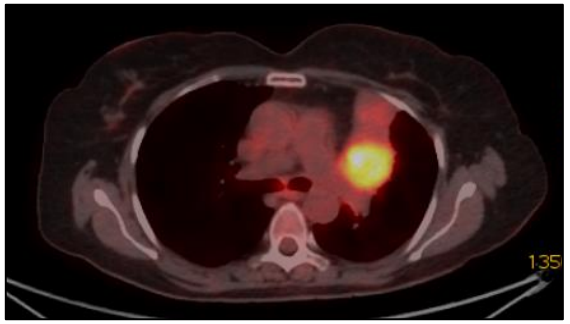
Drilon et al, Nat Rev Clin Oncol 2018

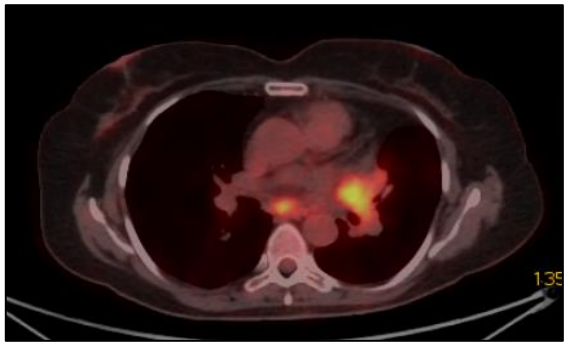
62 anni, donna, non fumatrice
ADK, EGFR, K-ras wt, ALK e ROS1-

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



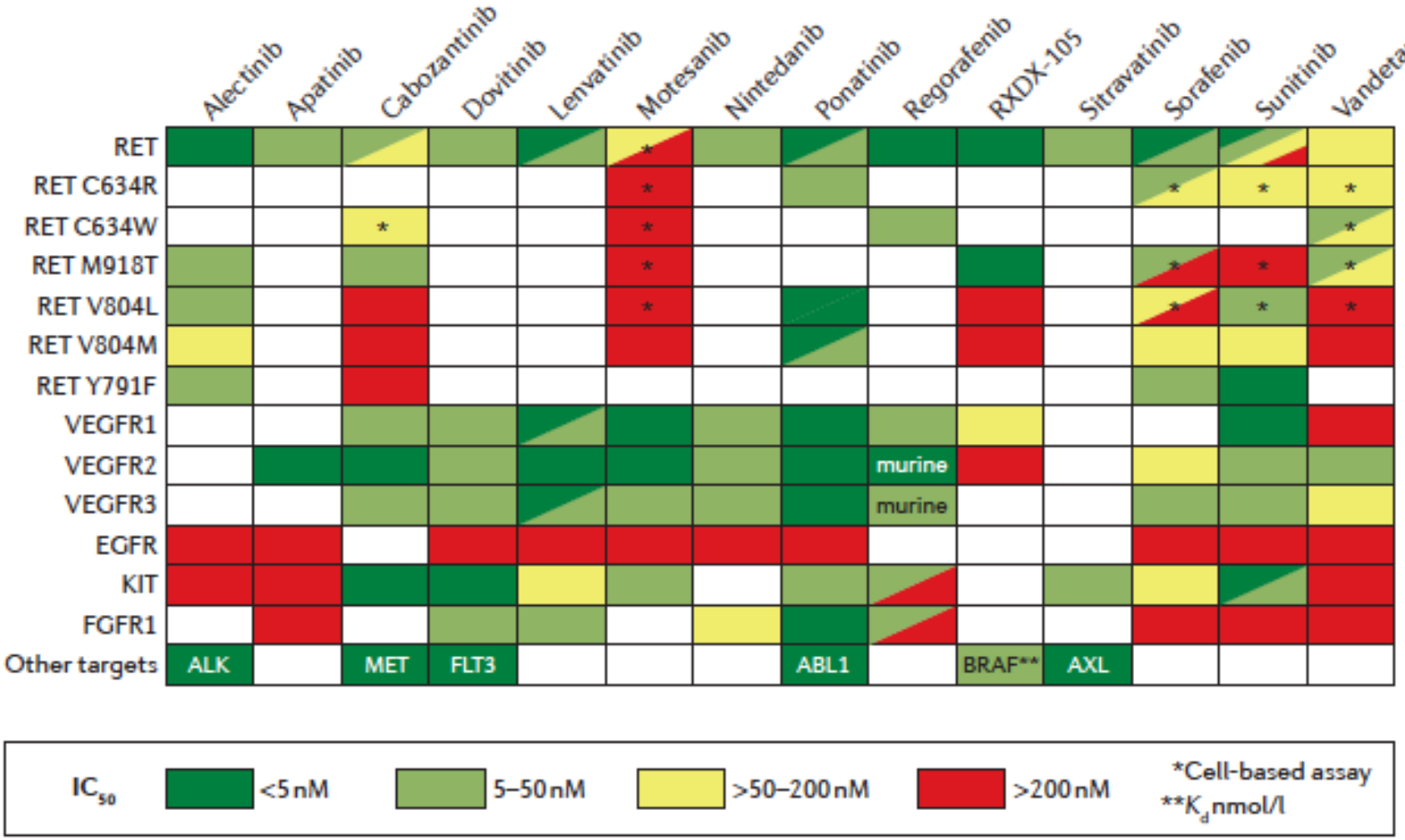






Facchinetti et al, in press

RET Rearrangements and TKIs

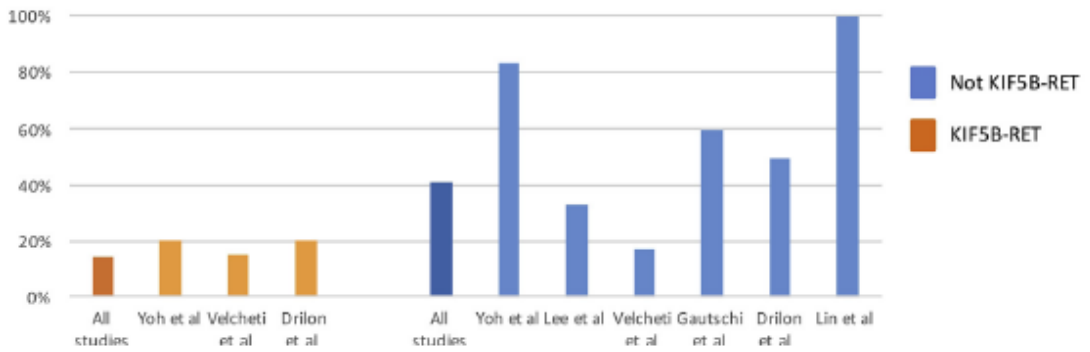


Drilon et al, Nat Rev Clin Oncol 2018

RET Rearrangements and TKIs

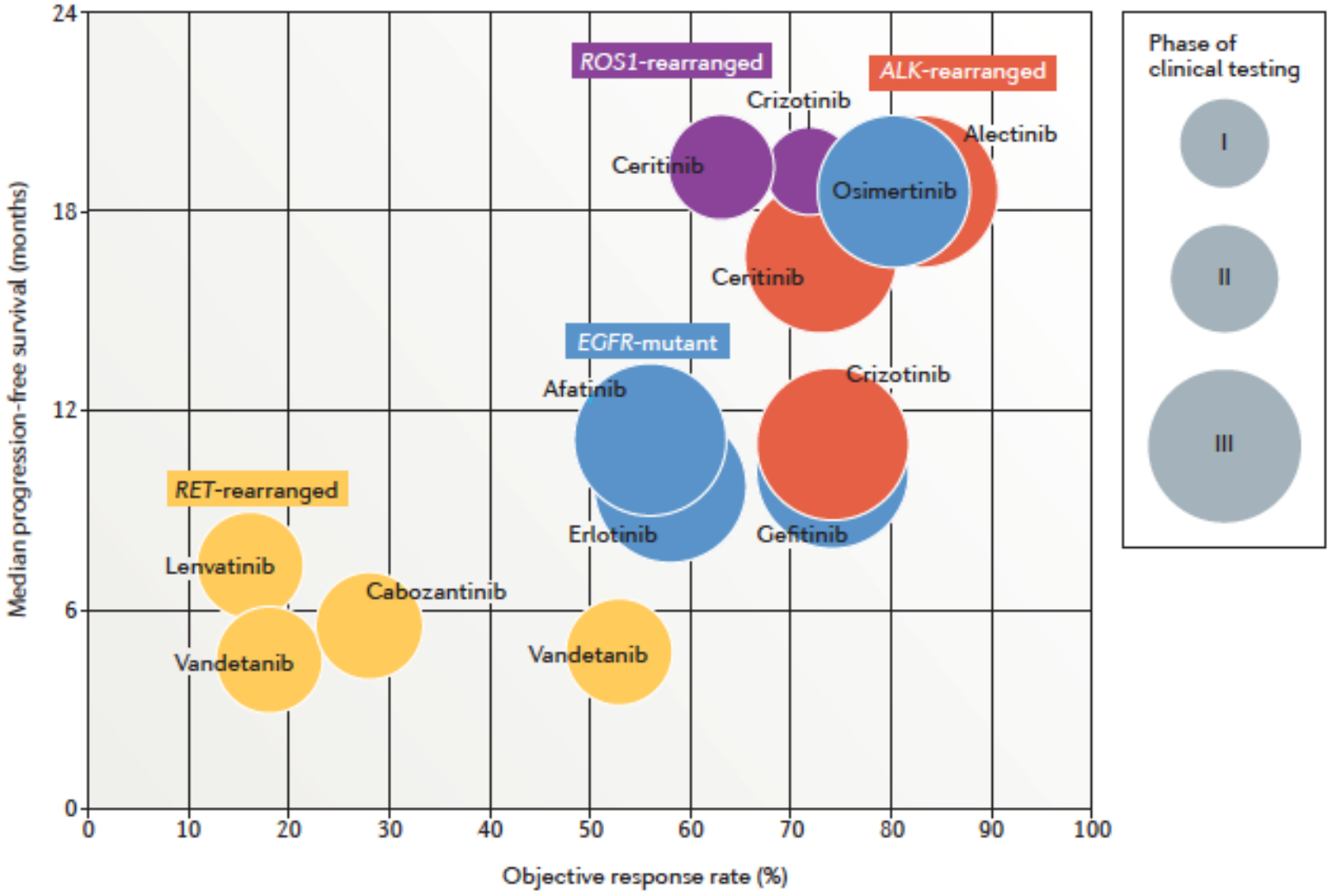
Table 4. Summary of Response and Survival Outcomes according to RET Inhibitor Drug

Type of RET Inhibitor	Study	No. of Patients	ORR	mPFS (mo)	mOS (mo)
Vandetanib	Yoh et al. (2016) LURET[65]	19	47%	4.7	11.1
	Lee et al. (2017)[50]	18	18%	4.5	11.6
	Gautschi et al. (2017) GLORY[49]	11	18%	2.9	10.2
	Platt et al. (2015)[9]	3	0%	NA	NA
Cabozantinib	Drilon et al. (2016)[51]	26	28%	5.5	9.9
	Gautschi et al. (2017) GLORY[49]	21	32%	3.6	4.9
Lenvatinib	Velcheti et al. (2016)[75]	25	16%	7.3	NA
	Gautschi et al. (2017) GLORY[49]	2	50%	NA	NA
Sunitinib	Gautschi et al. (2017) GLORY[49]	10	22%	2.2	6.8
Alectinib	Lin et al. (2016)[77]	4	50%	NA	NA
	Gautschi et al. (2017) GLORY[49]	2	0%	NA	NA
Sorafenib	Gautschi et al. (2017) GLORY[49]	2	0%	NA	NA
	Horiike et al. (2016)[78]	3	0%	NA	NA
Ponatinib	Gautschi et al. (2017) GLORY[49]	2	0%	NA	NA
Vandetanib + everolimus	Cascone et al. (2016)[76]	6	83%	NA	NA



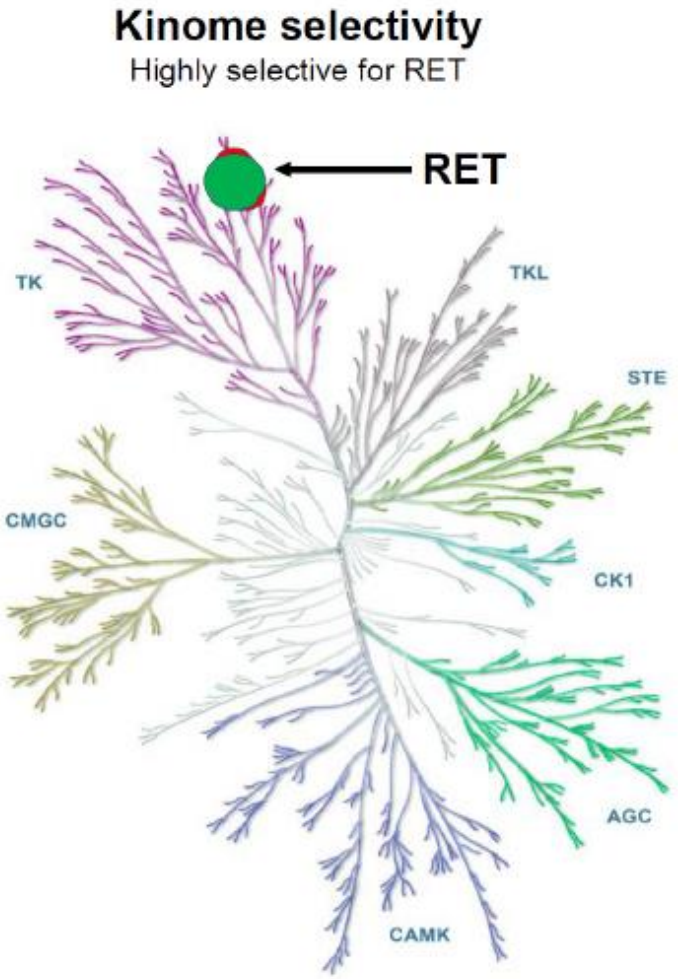
Ferrara et al, J Thoracic Oncol 2017

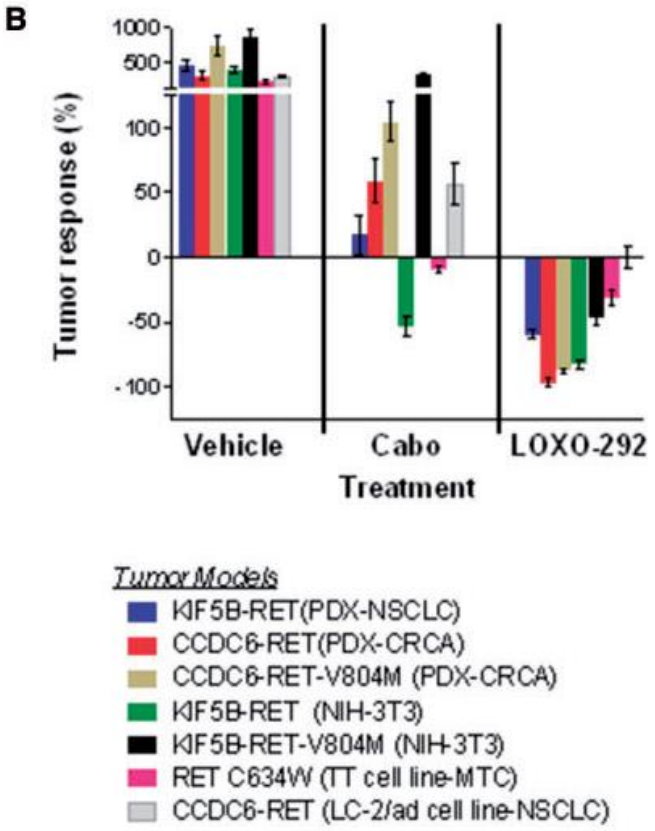
RET Rearrangements and TKIs



Drilon et al, Nat Rev Clin Oncol 2018

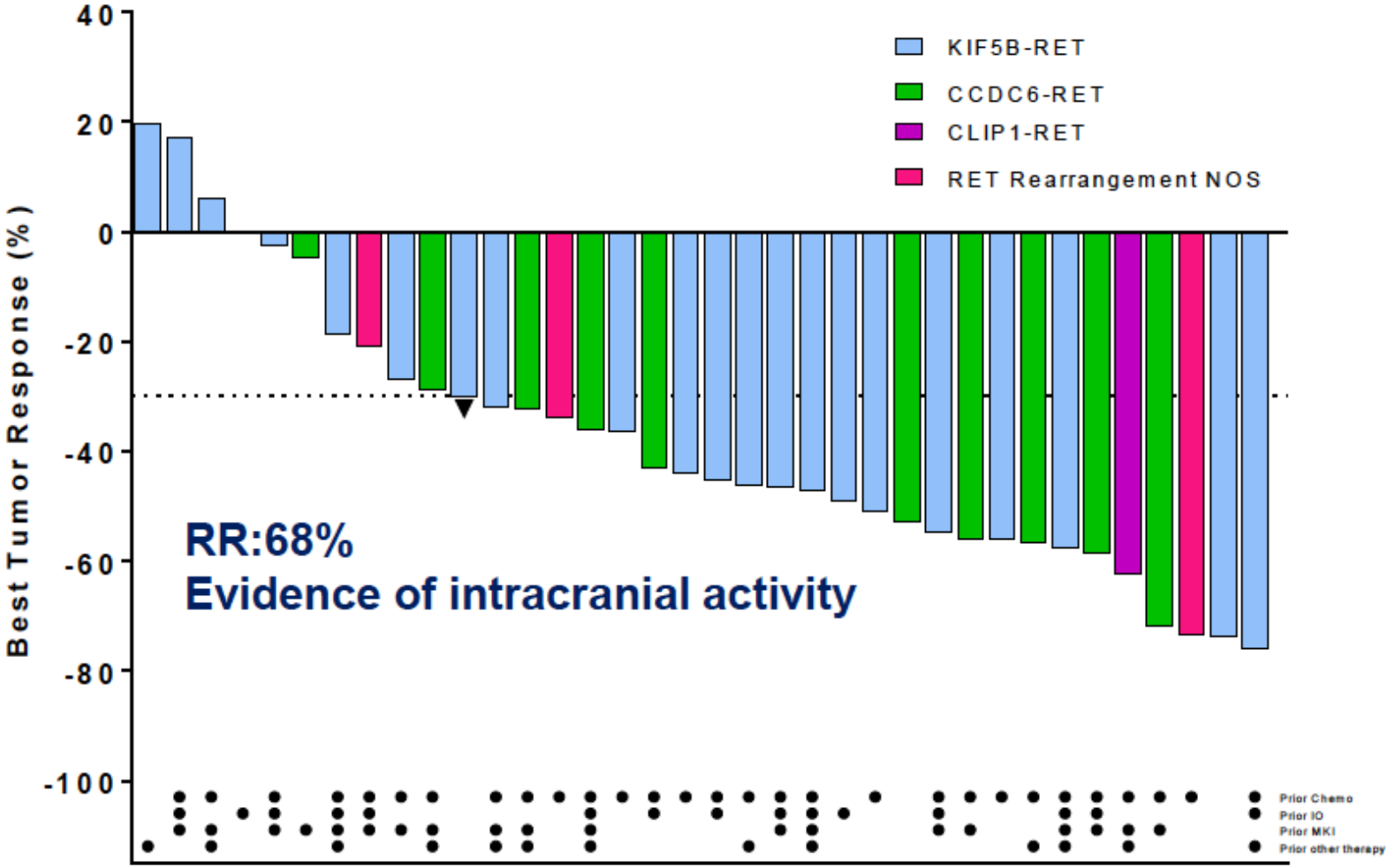
LOXO-292:
potent and selective anti-RET





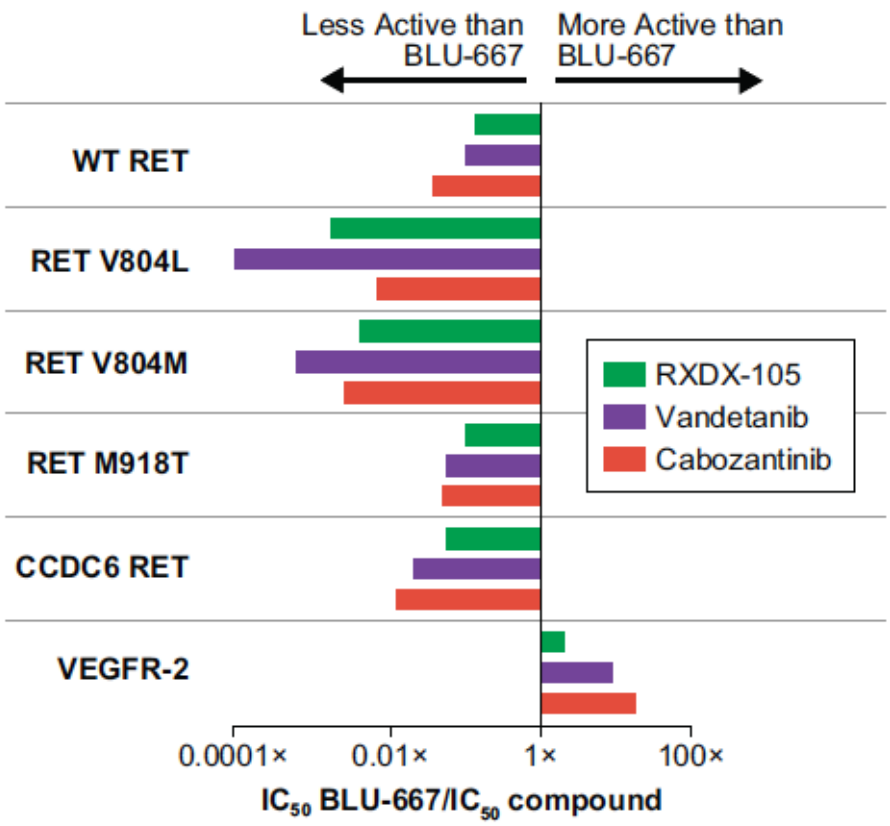
Subbiah et al, Ann Ancol 2018

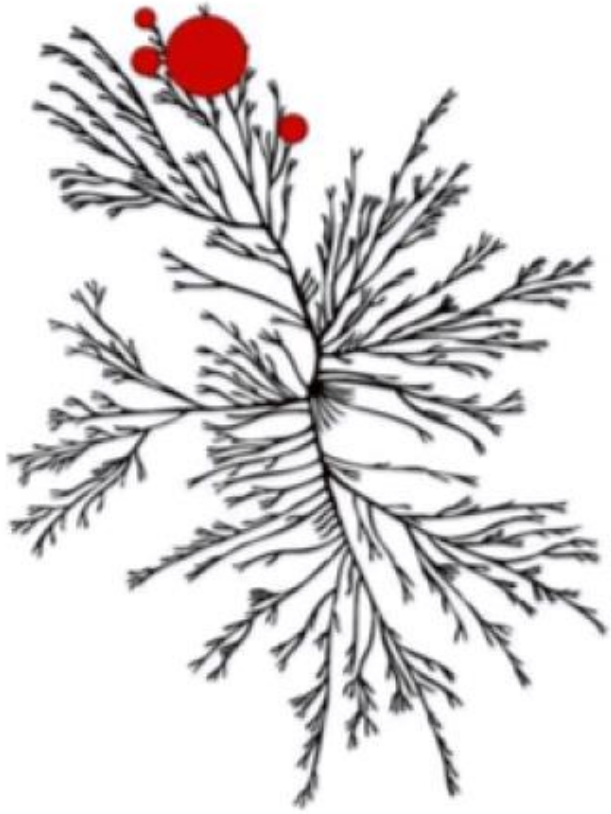
LOXO-292:
LIBRETTO 001 phase 1 trial



Oxanard et al, WCLC 2018

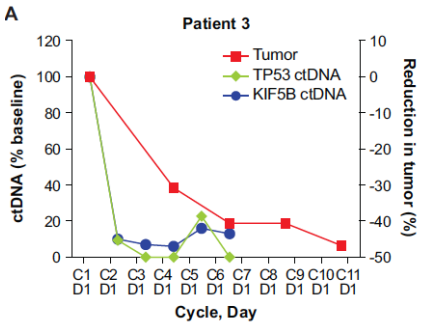
BLU-667:
potent and selective anti-RET

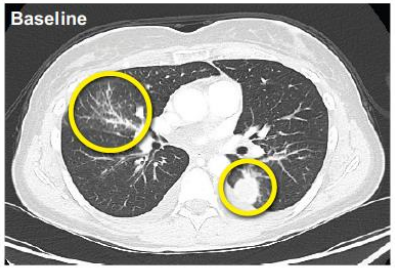


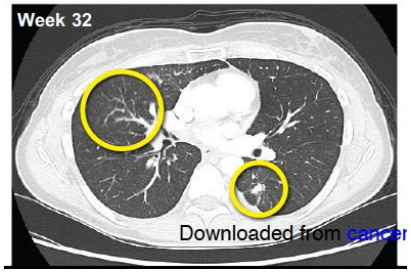


Subbiah et al, Cancer Discovery 2018

BLU-667:
ARROW phase 1 trial





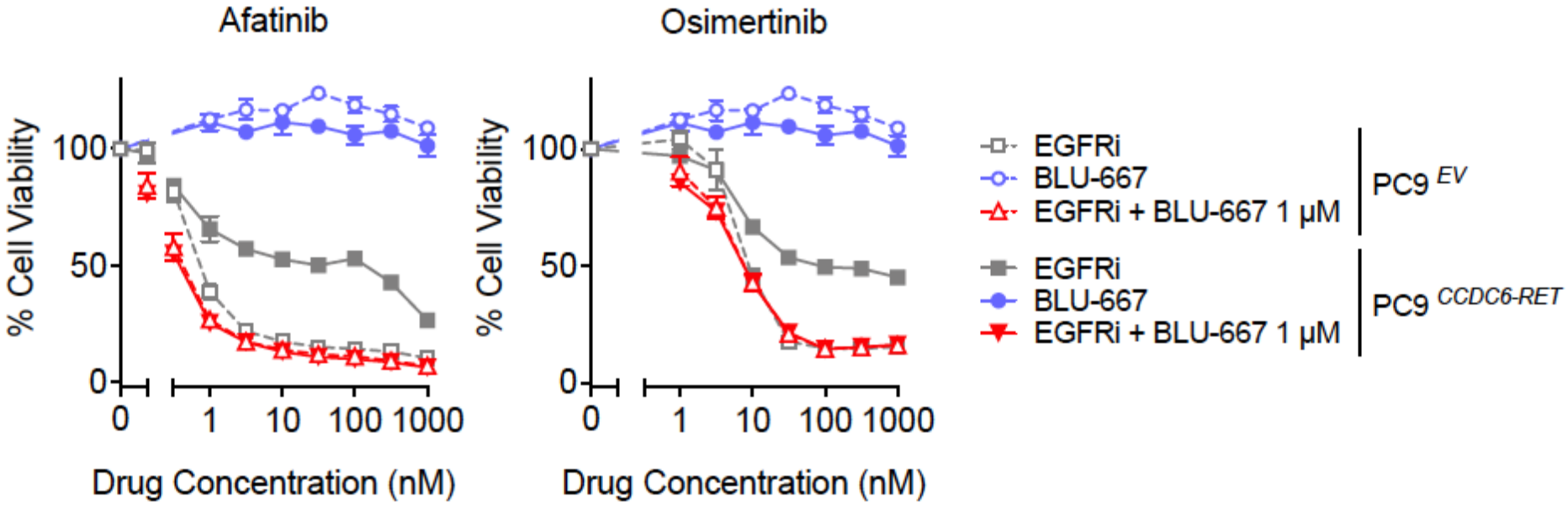


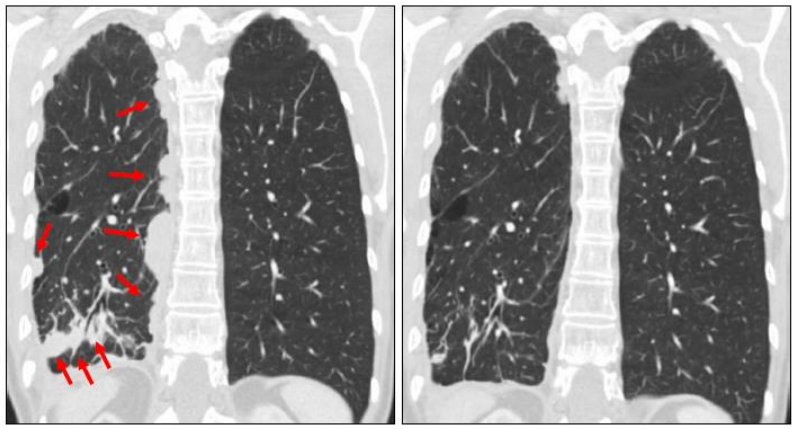
Subbiah et al, Cancer Discovery 2018

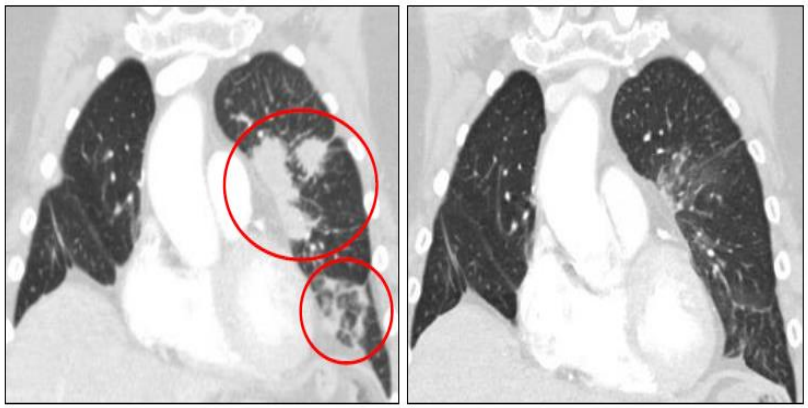
Best response	RET fusion (N=15*) n, (%)	MKI-naive (N=8) n , (%)
PR	8 (53)†	5 (63)
SD	5 (33)	6 (37)
PD	2 (13)	0

Subbiah et al, AACR 2018

RET fusions and Osimertinib resistence







Piotrowska et al, Cancer Discovery 2018

Conclusioni

- Rapida evoluzione delle conoscenze e disponibilità di nuova farmaci per vari target (oltre a EGFR/ALK, testare ROS1 e BRAF)
- Nella malattia ROS1 positiva standard crizotinib; I linea con next-generation TKI? Quale migliore TKI a fallimento della I linea (Lorlatinib)?
- Dabrafenib e Trametinib standard in caso di V600E; non dati al momento per non-V600; immunoterapia potenzialmente efficace
- Nuovi agenti selettivi anti-RET; dati preliminari e necessità di trials clinici

Grazie per l'attenzione

mtiseo@ao.pr.it