Les autres addictions

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IOT
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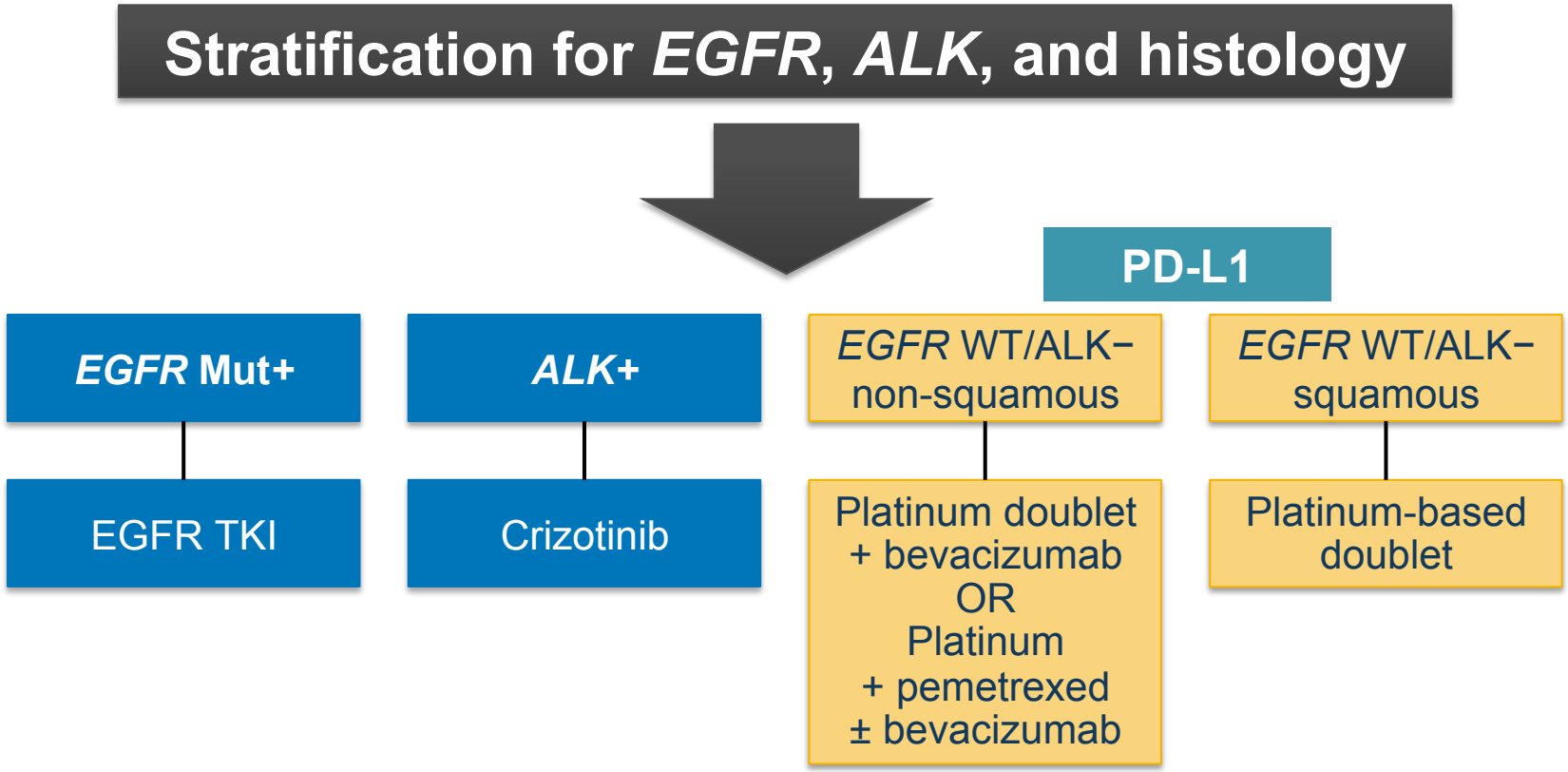
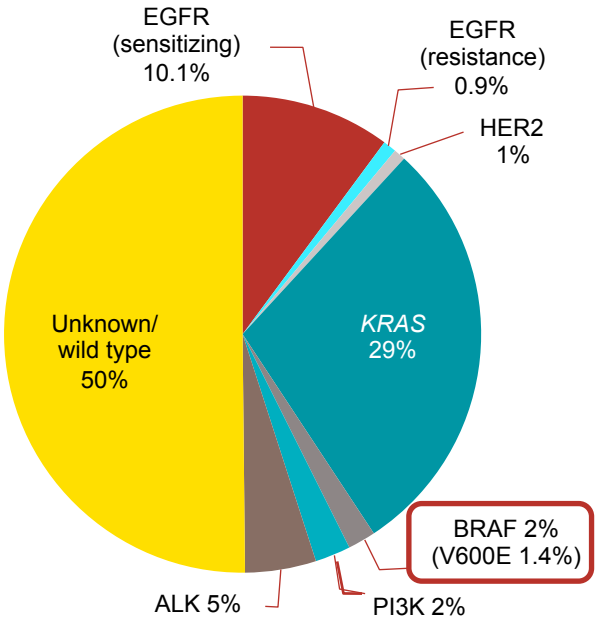
Great advances have been made in lung cancer therapy

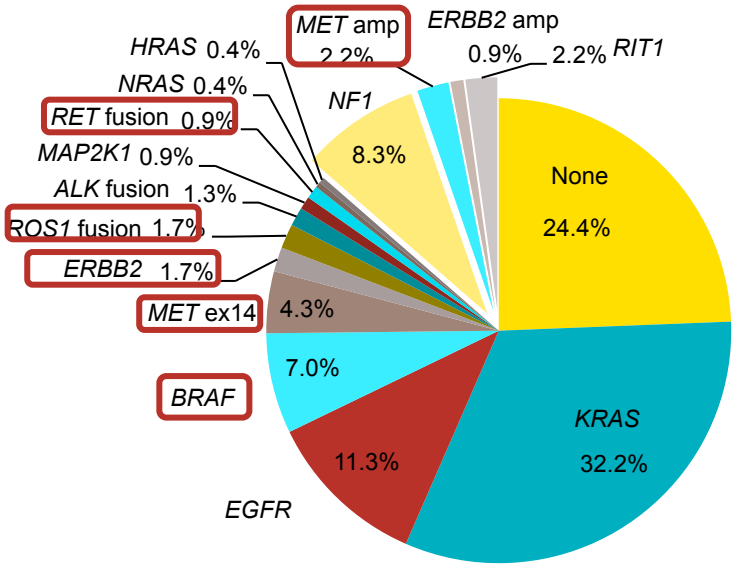


Out of EGFR and ALK there are many other potential driver mutations in lung adenocarcinoma

Biomarker France (IFCT)



Cancer Genome Atlas Research Network

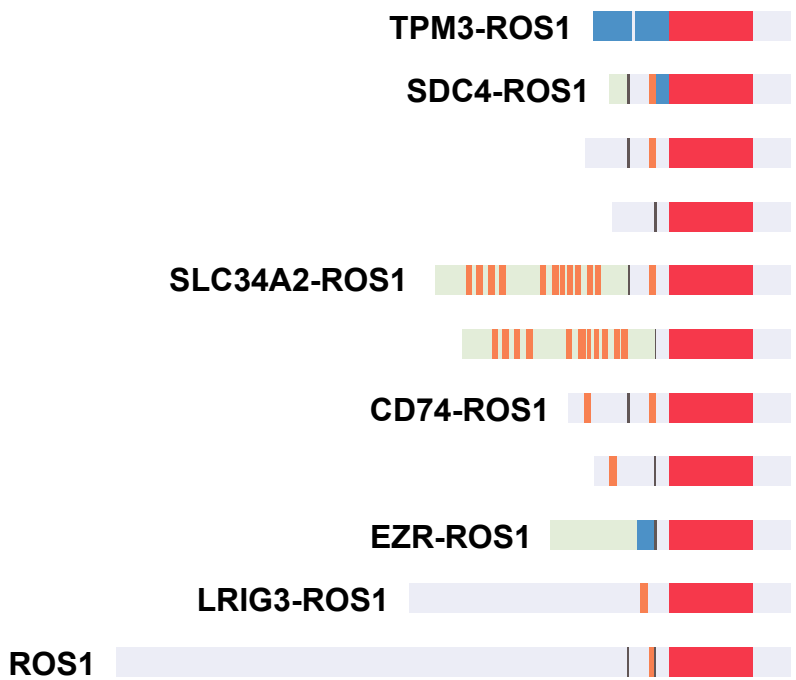


By including amplification of MET and ERBB2, MET exon 14 splicing mutations, RIT1 mutations, and NF1 loss-of-function mutations, the driver-positive group increases to ~75% of cases

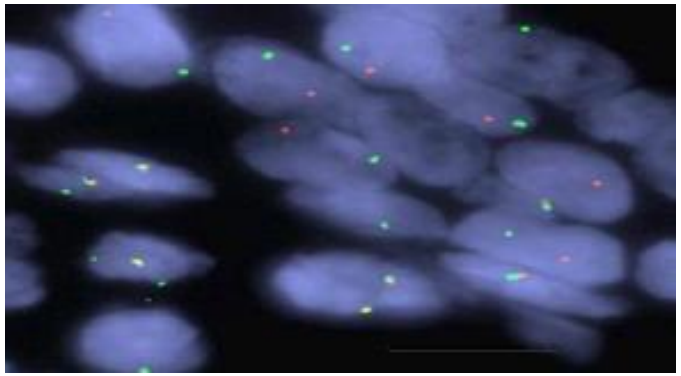
IFCT, French Cooperative Thoracic Intergroup.

Barlesi F, et al. Lancet. 2016;387:1415-26.
Cancer Genome Atlas Research Network. Nature. 2014;511:543-50.

ROS1 rearrangements in NSCLC



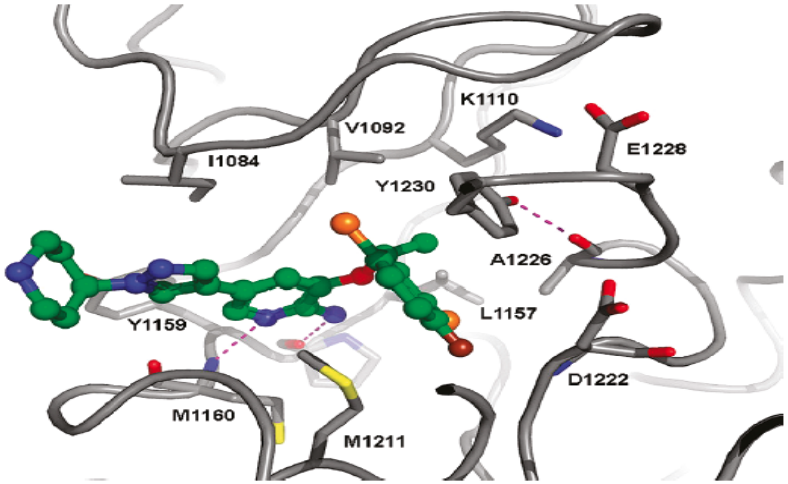
- **Present in ca. 1% of NSCLC cases** (also found in some GBMs and cholangiocarcinomas)
- Enriched in younger, never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers



GBM, glioblastoma.

Bergethon K, et al. J Clin Oncol. 2012;30:863-70.
Takeuchi K, et al. Nat Med. 2012;18:378-81.

Crizotinib:
Inhibitor of c-MET, ALK and ROS1



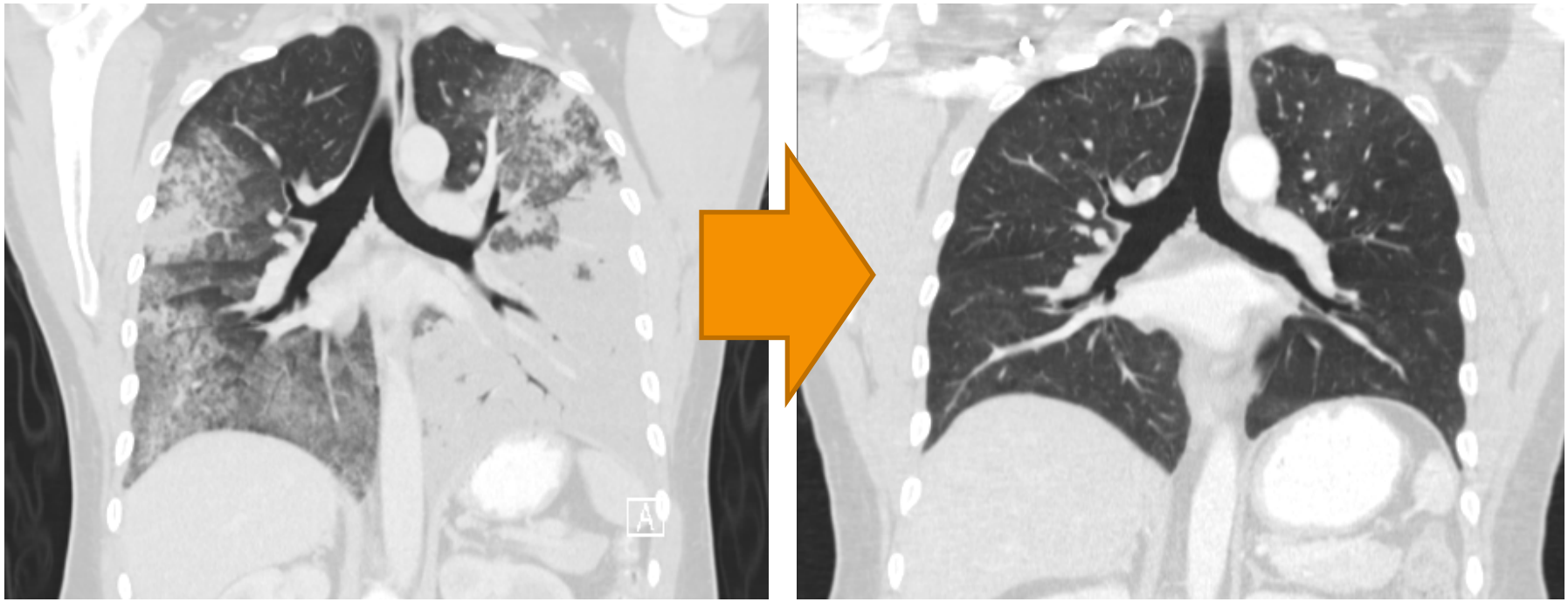
Co-crystal structure of crizotinib (PF-02341066) bound to c-MET

Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	40-60	5-8X
ROS1	60	7X
RON	80	10X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

Camidge et al, ASCO 2014

Cui et al. J Med Chem 54: 6342-63, 2011 and Pfizer data on file

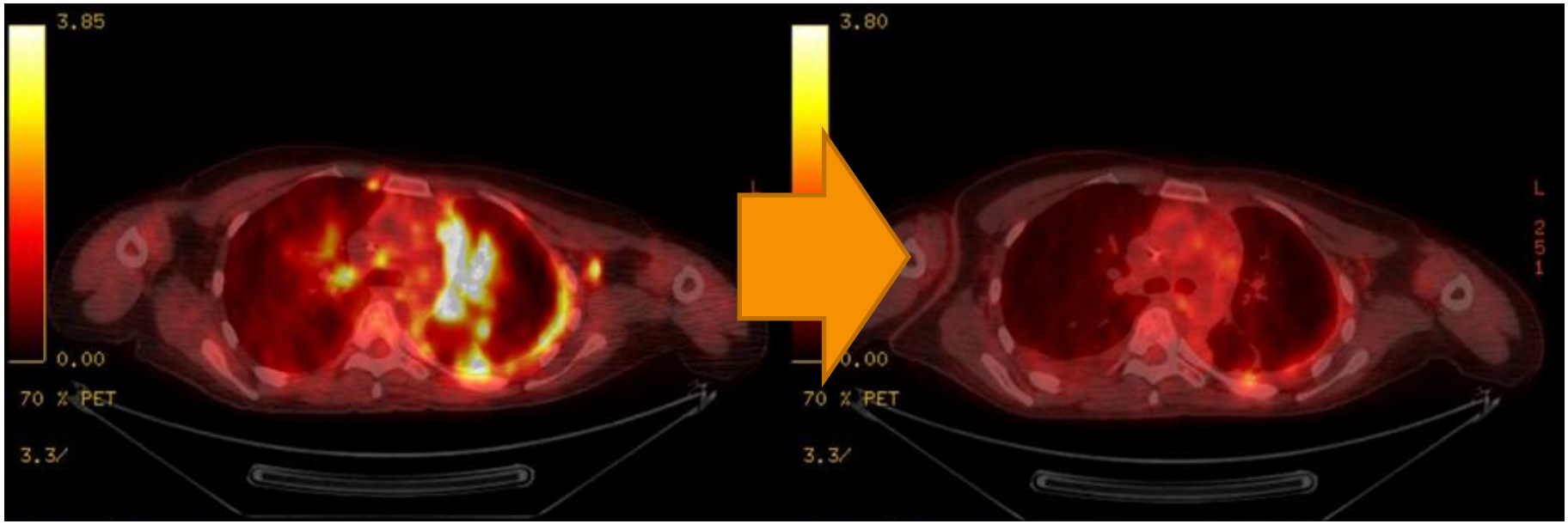
Significant Responses to Crizotinib in Patients with ROS1-Positive NSCLC



Baseline **After 3 months of crizotinib**

Bergethon et al., JCO 30(8): 863-70, 2012

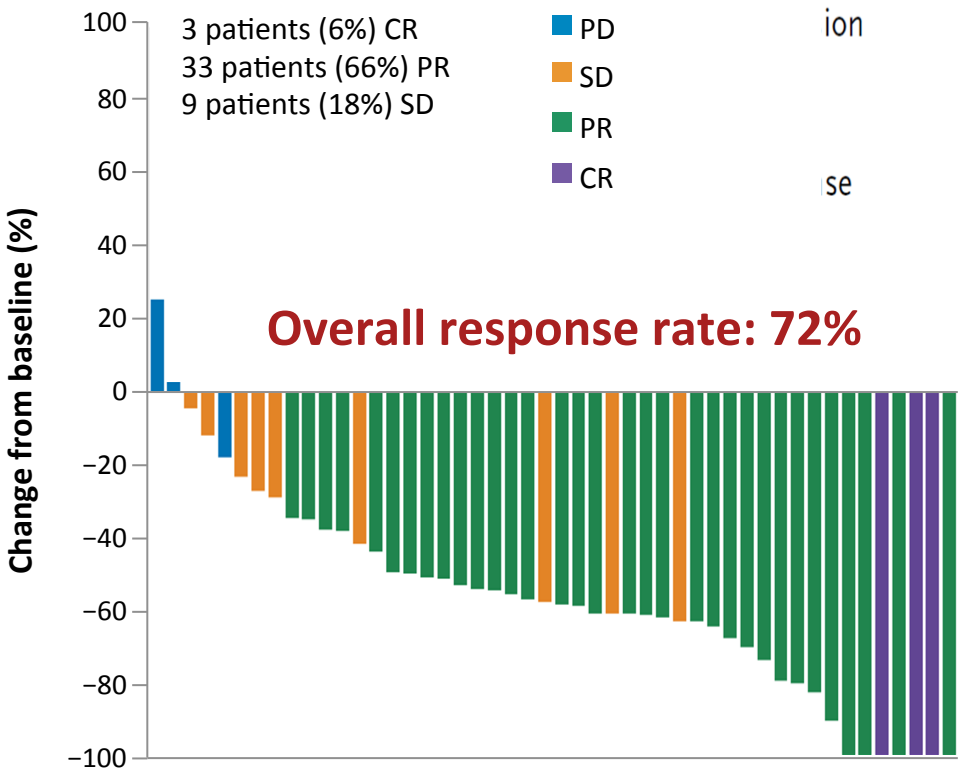
Rapid Responses to Crizotinib in Patients with ROS1-Positive NSCLC



Baseline **After 4 weeks of crizotinib**

Image courtesy of Ignatius Ou

Crizotinib and *ROS1+* patients



Best response	N = 50
ORR, n (%)	36 (**72**)
CR, n (%)	3 (6)
PR, n (%)	33 (66)
SD, n (%)	9 (18)
DOR, median (95% CI), mo	**17.6** (14.5–NR)
PFS, median (95% CI), mo	**19.2** (14.4–NR)
OS, median (95% CI), mo	12.7 (7.3–16.9)

NR, not reached.

Shaw AT, et al. N Engl J Med. 2014;371:1963-71.

AcSé Crizotinib : objectives

- To identify patients with an advanced malignancy presenting a crizotinib-target alteration and to generate epidemiological data

- Single biomarker tests in the 15 malignancies

ROS1 or ALK translocation/amplification

- IHC signal (≥1+) ➔ **FISH (100 nuclei)**
- translocation threshold **> 15 % positive cells**
- amplificiation threshold **> 6 copies**

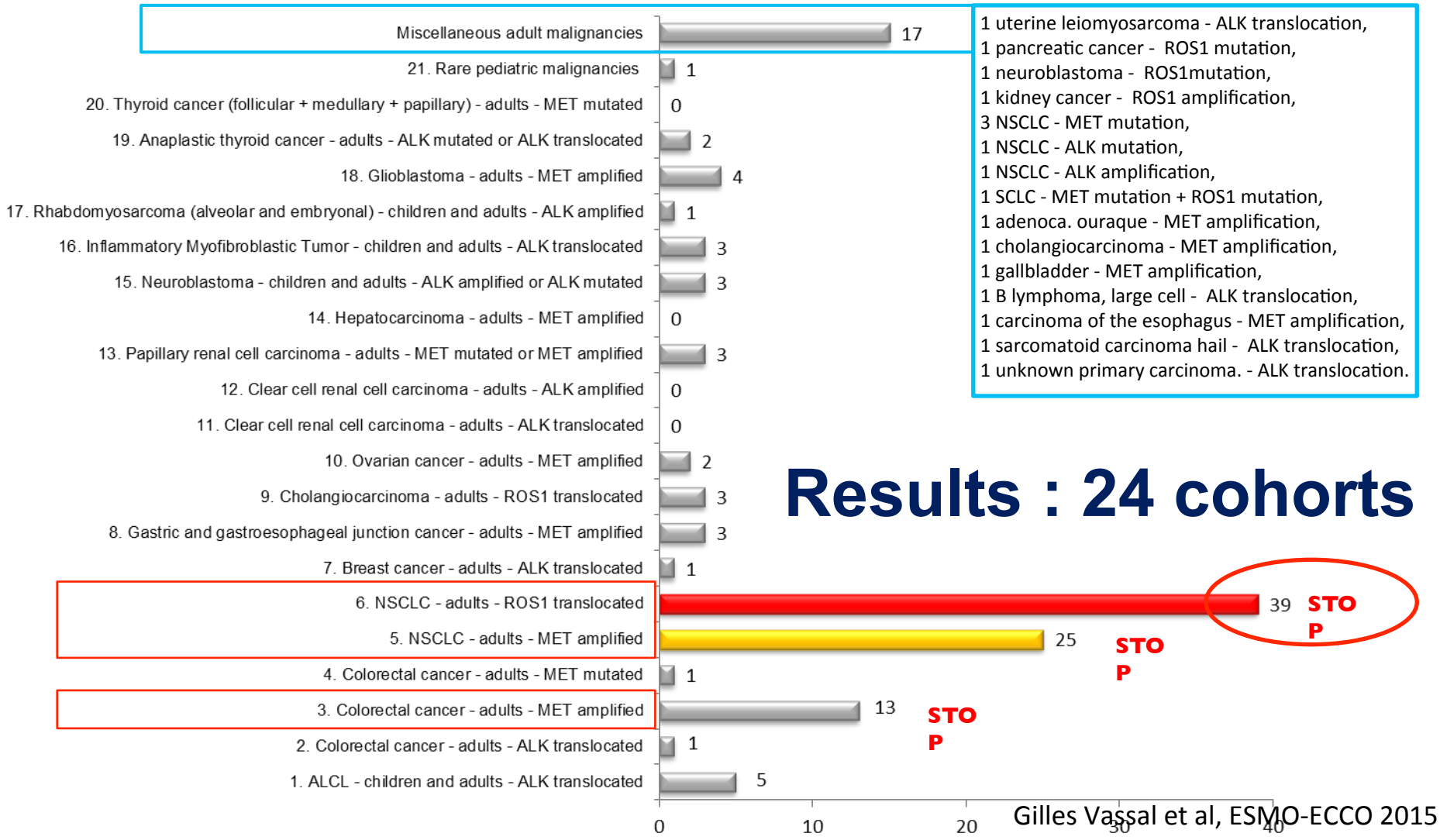
ALK and MET Mutation

- ALK : exons 23 to 25.
- MET: exon 14 and exons 16 to 19

MET amplification

- IHC signal (≥2+) ➔ **FISH (100 nuclei)**
- Amplification threshold: **> 6 copies**
- GBM two cohorts high polysomy and true amplification (MET/CEP7 ratio)

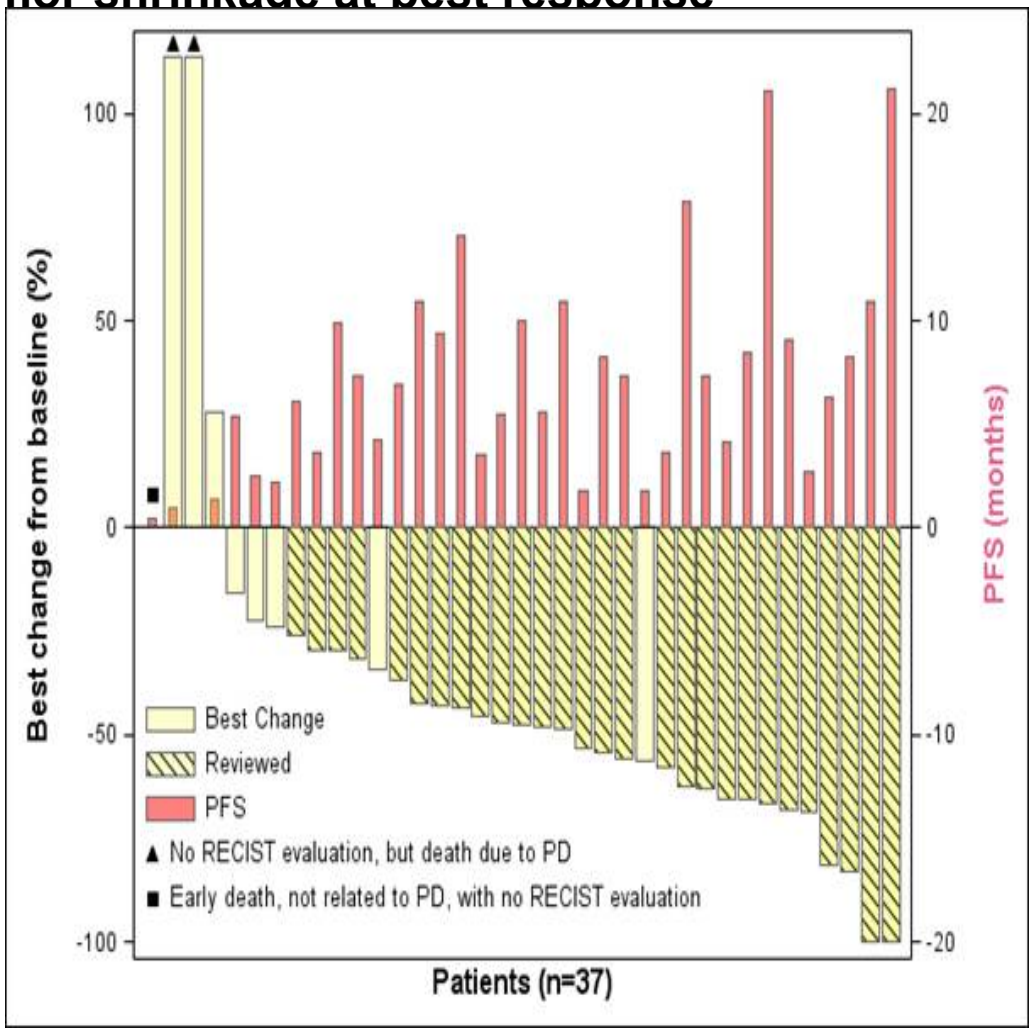
Gilles Vassal et al, ESMO-ECCO 2015



Results : 24 cohorts

Gilles Vassal et al, ESMO-ECCO 2015

Tumor shrinkage at best response



Best response

ORR = 26/36
72 % [55% ; 86%]

DCR = 32/36
89 % [74% ; 97%]

44% PFS
at 12 months

Results: ROS1+ NSCLC

Gilles Vassal et al, ESMO-ECCO 2015

Comparison of crizotinib efficacy across studies *on ROS1+* NSCLC

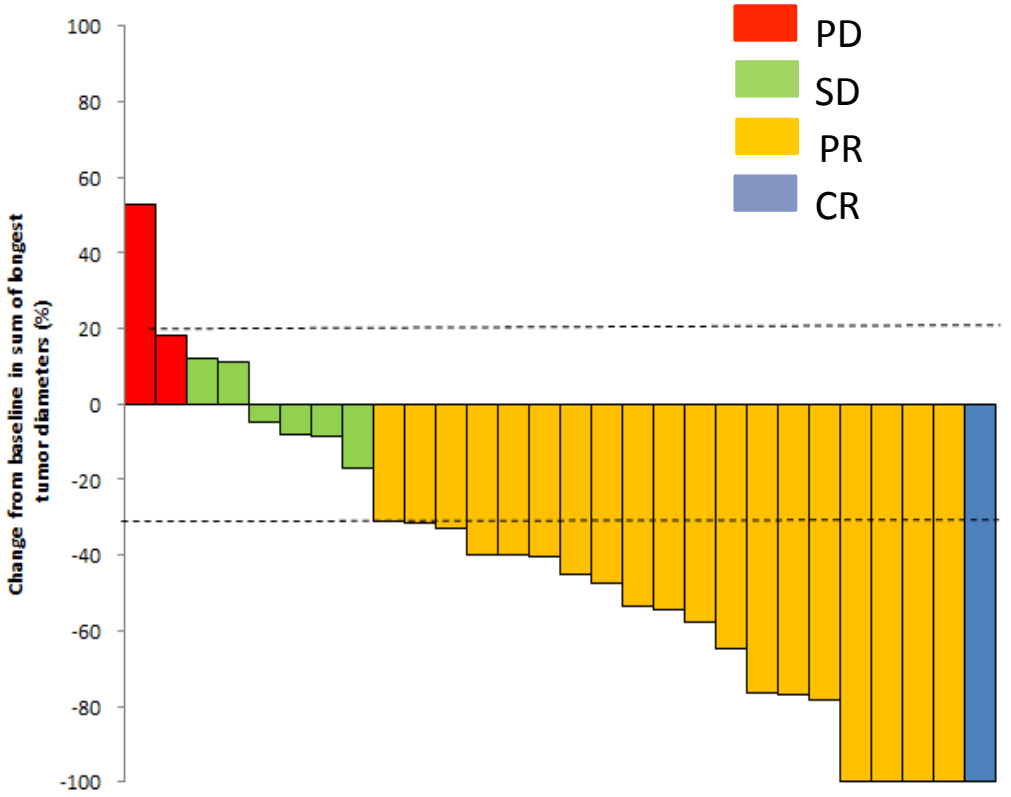
	Profile 1001[1] (N = 50)	EUROS1[2] (N = 31)	AcSé[3] (N = 36)
Trial	Phase 1 expansion	Retrospective	Phase 2
Ethnicity	Global (42% Asian)	Europe	France
Diagnostic	Local FISH	Local FISH	FISH
Response rate	72%	80%	72%
Median PFS, months	19.2	9.1	44% at 12 months

The FDA and EMA approved crizotinib for the treatment of *ROS1*+ NSCLC (March and August 2016, respectively)

1. Shaw AT, et al. N Engl J Med. 2014;371:1963-71. 2. Mazières J, et al. J Clin Oncol. 2015;33:992-9. 3. Vassal G, et al. ECCO 2015; abstract 12LBA.

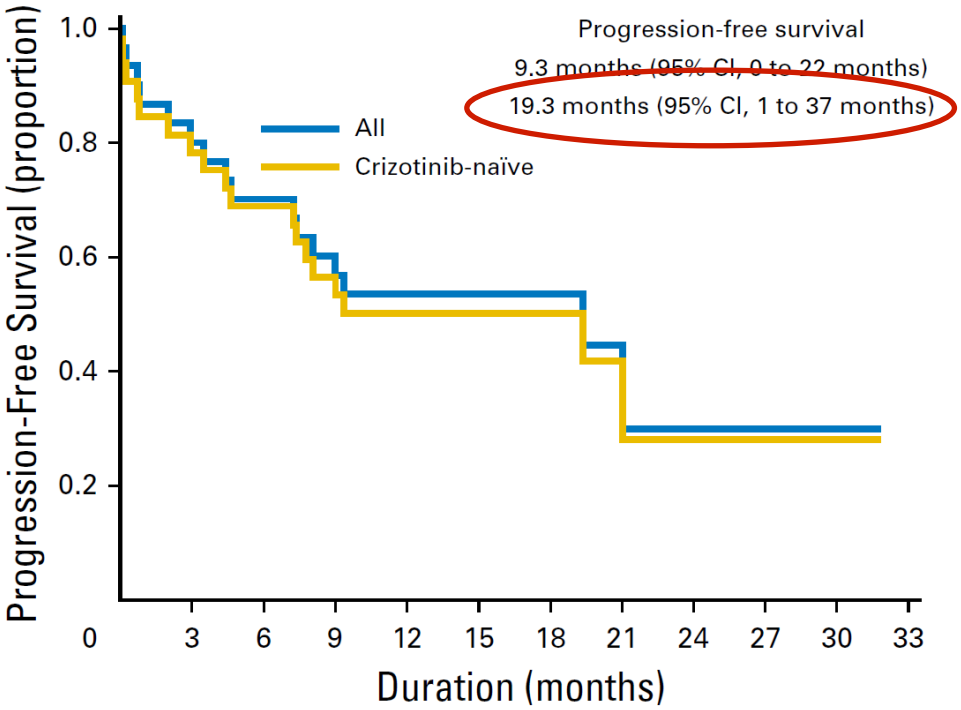
Ceritinib in ROS1-rearranged (Korean Nationwide P hase II Study)

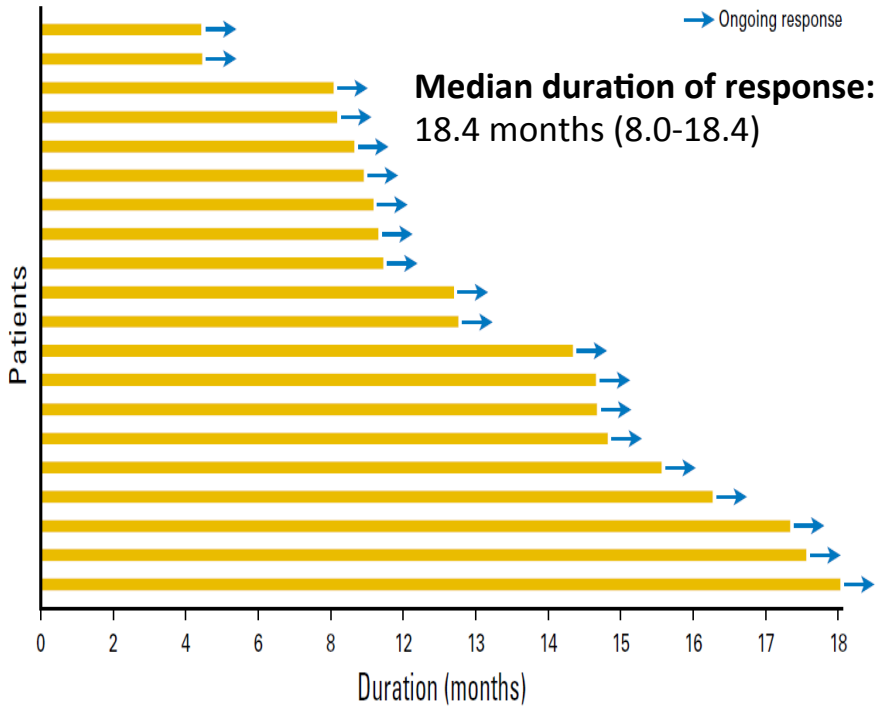
Best response*, n (%)	All (N= 32)	Crizotinib-naïve (N= 30)
CR	1 (3)	1 (3)
PR	19 (59)	19 (59)
SD	6 (19)	6 (19)
PD	2 (6)	2 (6)
Not evaluable**	4 (6)	2 (7)
Overall response rate , n (%)	**20 (62%)**	**20 (67%)**
Disease control rate (CR+PR+SD), n (%)	26 (81)	26 (87)
Duration of response, months Median (95% CI)	18.4 (8.0-18.4)	



Sun Min Lim et al, JCO 2017 B.C.Cho et al, IASLC 2016

Progression-free Survival



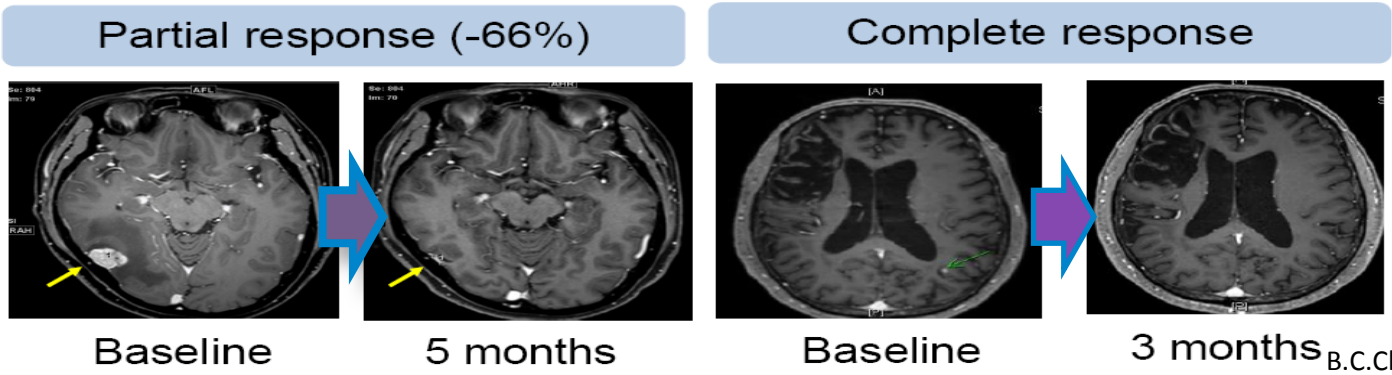


Sun Min Lim et al, JCO 2017

Intracranial Response to Ceritinib

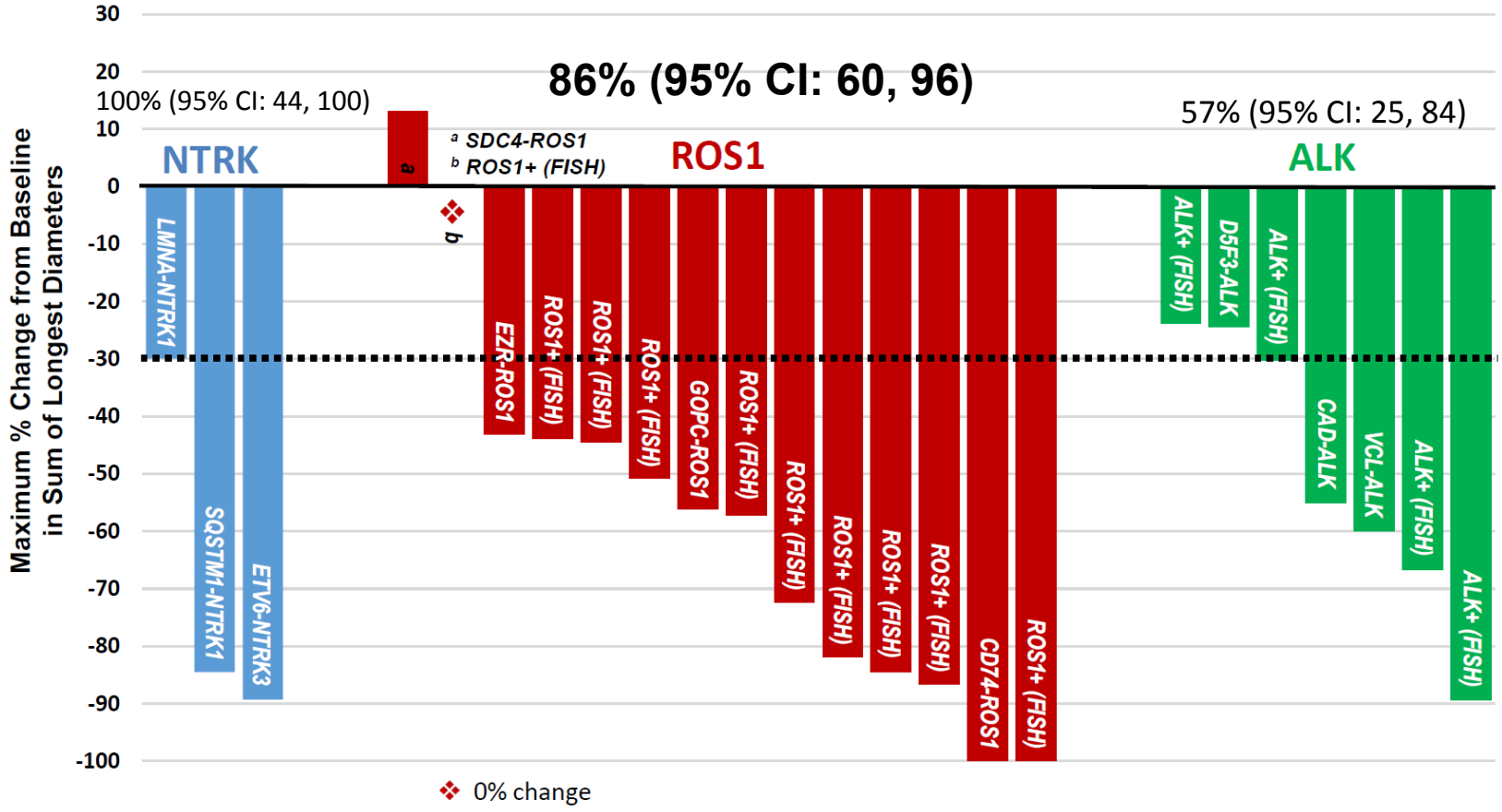
Best response, n (%)	Patients with brain metastases at baseline (N=8)
CR	1 (13)
PR	1 (13)
SD*/Non-CR/Non-PD#	3 (37)
PD	0
Not evaluable	3 (37)
Overall intracranial response rate, n(%)	**2 (25)**
Intracranial disease control rate (CR + PR + SD*/Non-CR/Non-PD#), n (%)	5 (63)

*SD for measurable brain metastases; #Non-CR/Non-PD for non-measurable brain metastases



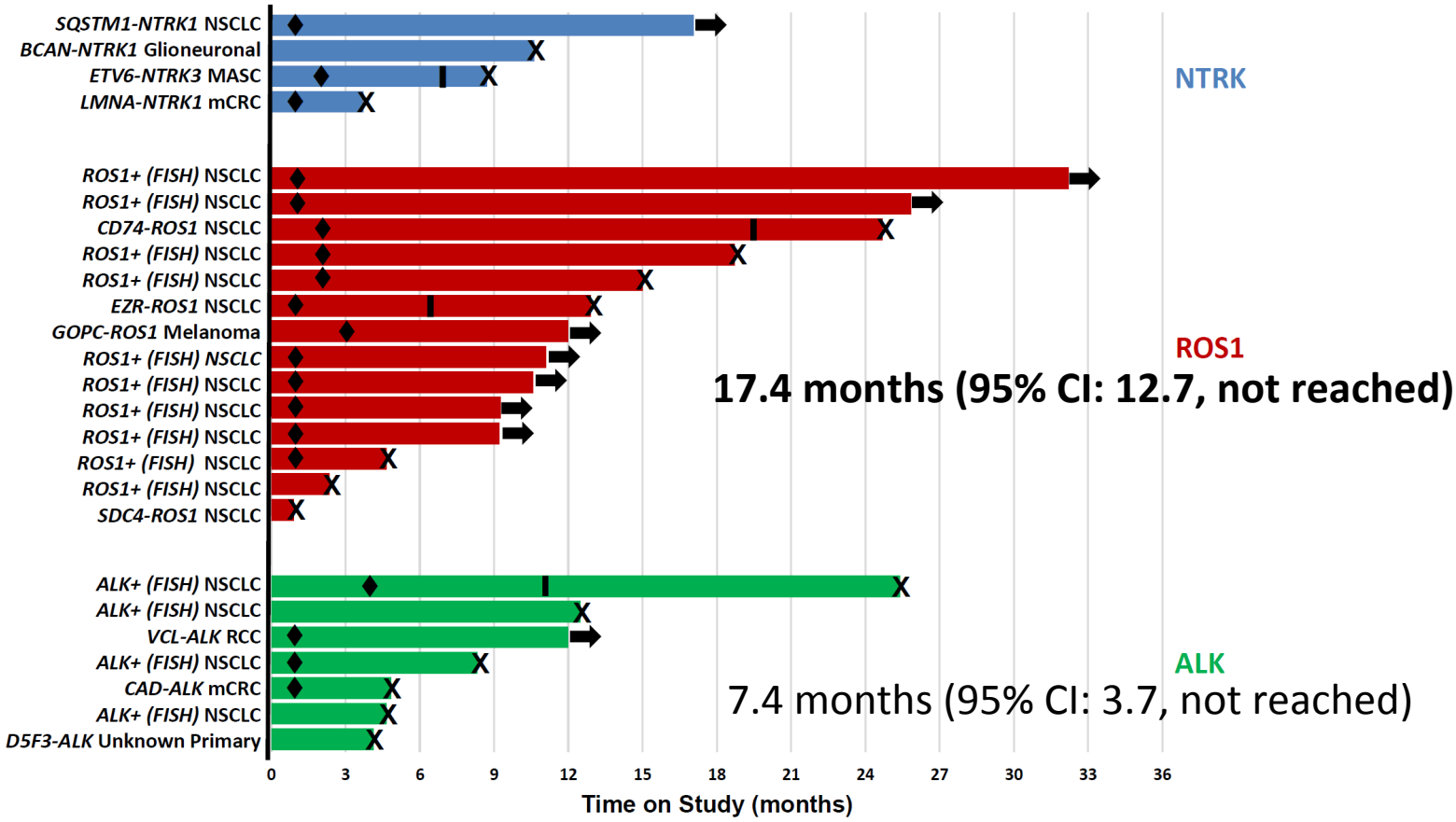
B.C.Cho et al, IASLC 2016

Safety and Antitumor Activity of the Multi-Targeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib (RXDX-101): Combined Results from Two Phase 1 Trials (ALKA-372-001 and STARTRK-1)



Alexander Drilon et al, cancer discovery 2017

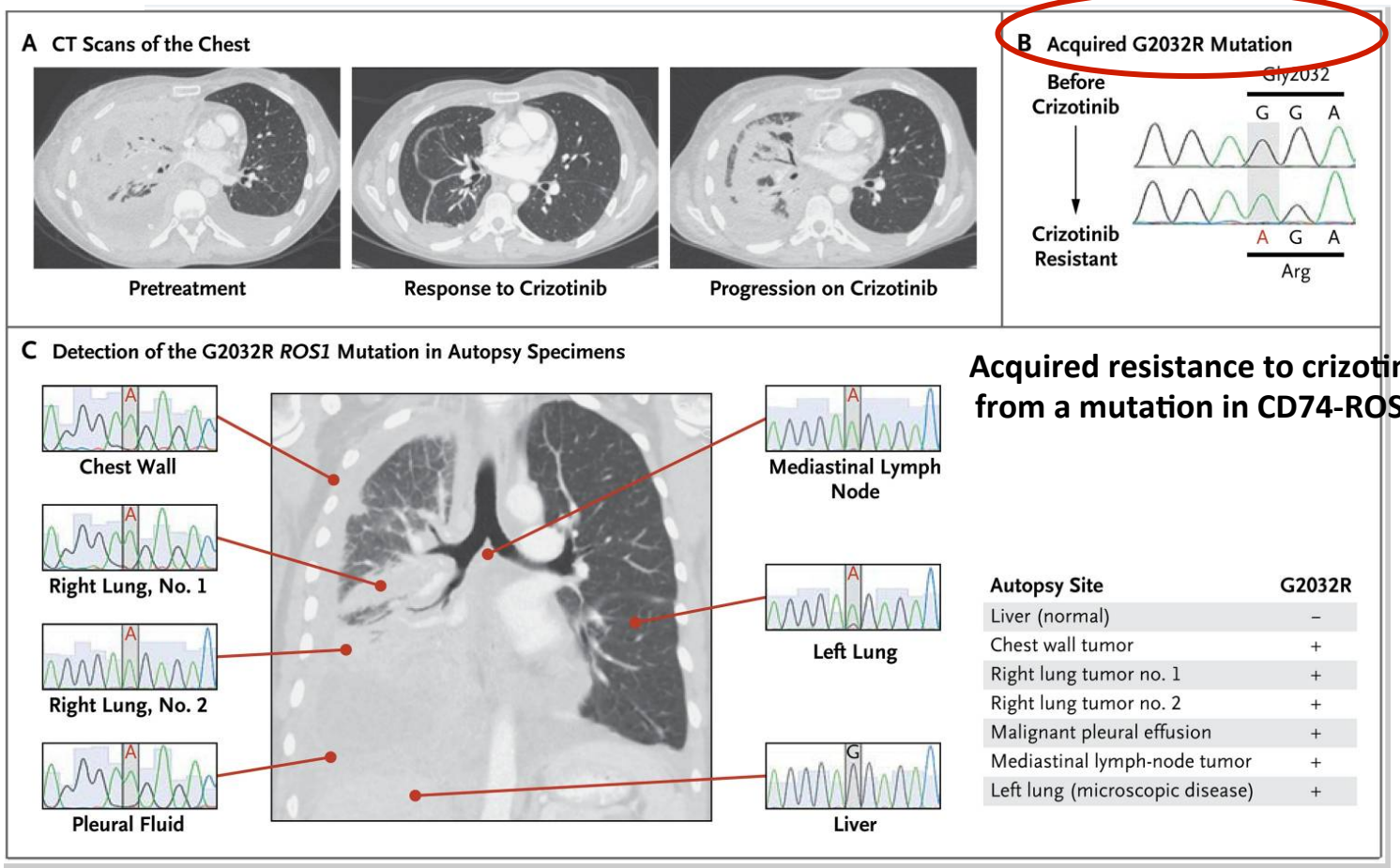
Duration of Treatment



Alexander Drilon et al, cancer discovery 2017

The NEW ENGLAND JOURNAL of MEDICINE

Acquired Resistance to Crizotinib from a Mutation in CD74–ROS1



Acquired resistance to crizotinib from a mutation in CD74-ROS1.

Autopsy Site	G2032R
Liver (normal)	–
Chest wall tumor	+
Right lung tumor no. 1	+
Right lung tumor no. 2	+
Malignant pleural effusion	+
Mediastinal lymph-node tumor	+
Left lung (microscopic disease)	+

N Engl J Med. 2013

Lorlatinib Is Active Against Mutations that Confer Resistance to Existing ALK and ROS1 TKIs*

Mutation Status	Cell Line	Cellular ALK Phosphorylation Mean IC_{50} (nM)			
		PF-06463922	Crizotinib	Ceritinib (LDK-378)	Alectinib (CH-5424802)
EML4-ALK v1	NIH3T3	1.3	80	NA	62
	BaF3	3.6	90	41	24
EML4-ALK L1196M	NIH3T3	21	843	NA	250
	BaF3	43	1154	70	113
EML4-ALK G1269A	NIH3T3	15	605	NA	NA
	BaF3	80	689	134	112
EML4-ALK G1202R	NIH3T3	77	1003	>1000	>10,000
	BaF3	113	562	549	362
EML4-ALK I1151Tins	NIH3T3	38	1268	1066	1770
	BaF3	50	902	296	126
EML4-ALK S1206Y	NIH3T3	4.2	626	NA	NA
	BaF3	3.2	152	60	29
EML4-ALK C1156Y	NIH3T3	1.6	478	NA	NA
	BaF3	15	406	177	21
EML4-ALK F1174L	NIH3T3	0.2	165	NA	NA
	BaF3	4.0	150	161	26

Target/ Cell Line (engineered)	Cellular ROS1 Phosphorylation Mean IC_{50} (nM)		
	PF-06463922	Crizotinib	Ceritinib (LDK-378)
CD74-ROS1(s) NIH3T3	0.23	11	51*
CD74-ROS1(s) BaF3	0.11	3.9	
CD74-ROS1(s) G2032R BaF3	186	2033	2666

IC_{50} < 100 nM
IC_{50} ≥ 100 < 200 nM
IC_{50} ≥ 200 nM

*Based on results in BaF3 cell line
‡ Alectinib does not inhibit ROS1

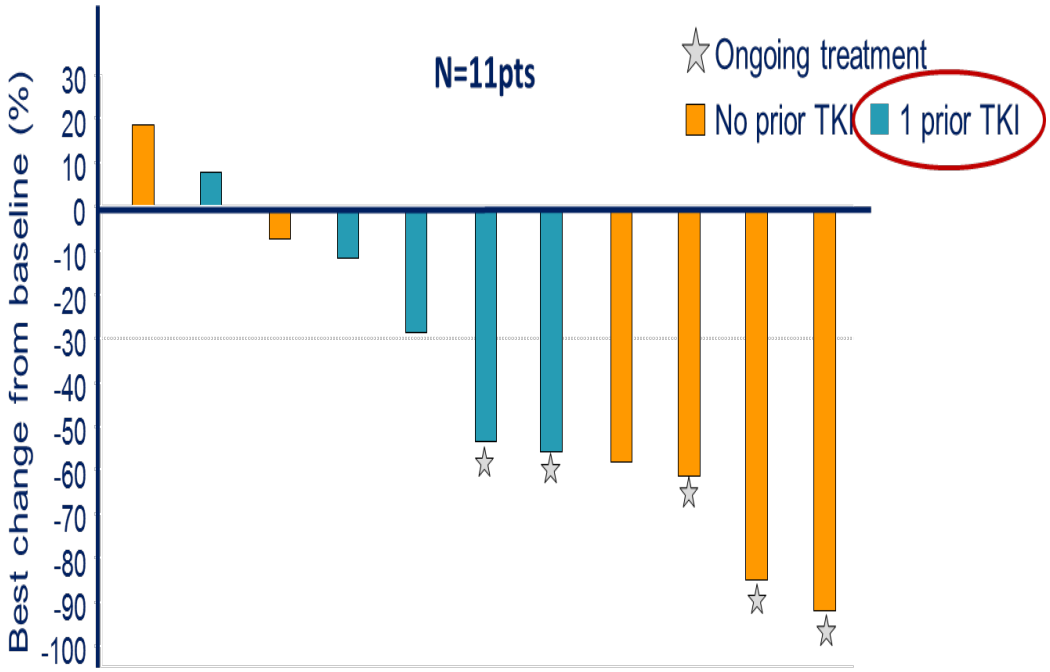
ALK, anaplastic lymphoma kinase; IC_{50}, half-maximal inhibitory concentration; NA, not available; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor

Zou HY, et al. AACR-NCI 2013, poster A277

B. Solomon et al, ASCO 2016

Lorlatinib (PF-06463922) phase I: Majority of ROS1 Patients Had a Decrease in Target Lesion Size*

		No prior TKI (n=6)	1 prior TKI (n=6)	Total ROS1 (n=12)
Best overall response, n (%)	Complete response	0	0	0
	Partial response	4 (67)	2 (33)	6 (50)
	Stable disease	1 (17)	1 (17)	2 (17)
	Progressive disease	1 (17)	2 (33)	3 (25)
	Indeterminate	0	1 (17)	1 (8)
ORR, n (%)		4 (67)	2 (33)	6 (50)
95% CI‡		22–96	4–78	21–79



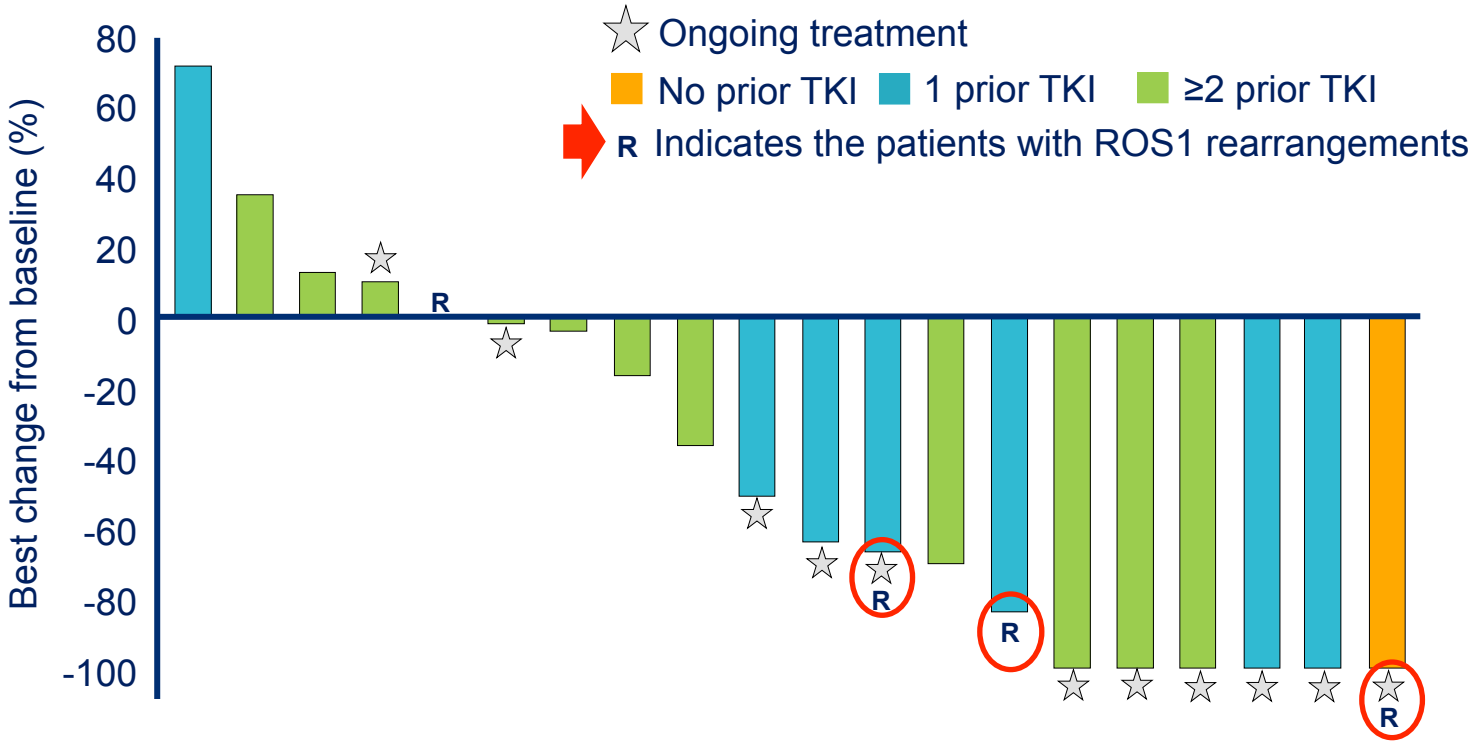
All patients who received 1 prior TKI received crizotinib

*Number of prior TKIs counted by line

B. Solomon et al, ASCO 2016

CNS Responses in ALK/ROS1+

Patients with Measurable Disease

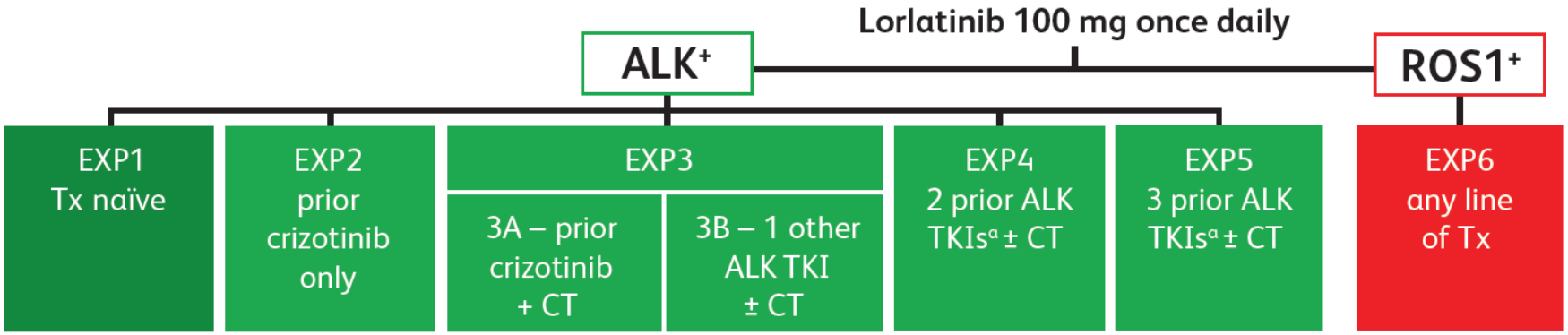


ALK, anaplastic lymphoma kinase; PD, progressive disease; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor

B. Solomon et al, ASCO 2016

Preliminary Efficacy and Safety of Lorlatinib in Patients With ROS1+ NSCLC

Figure 1. Study Design



[a]Lines of therapy (if the same TKI is given twice, this is counted as two prior lines of treatment).
CT, chemotherapy; Tx, treatment.

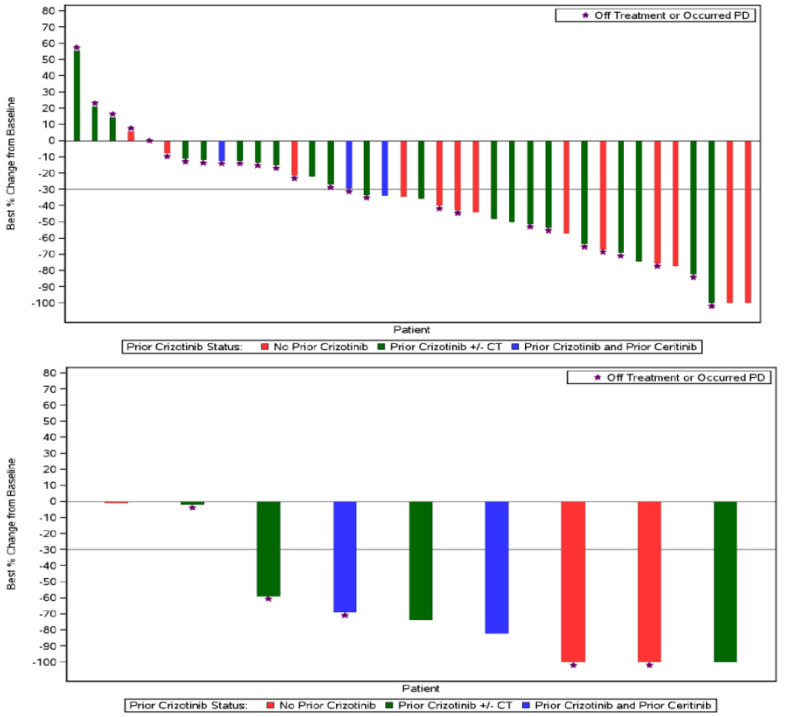
PRELIMINARY EFFICACY AND SAFETY OF LORLATINIB IN PATIENTS WITH ROS1-POSITIVE NON-SMALL CELL LUNG CANCER

- 47 patients with ROS1+ NSCLCtreated;
  - 25 **(53%) had CNS** involvement at baseline
  - and **72%** of patients had received prior crizotinib

- The overall response rate (ORR) and intracranial (IC) ORR was
  - 17/47 (**36.2%;** 95% CI: 22.7, 51.5)
  - and 14/25 (**56.0%;** 95% CI: 34.9, 75.6)

- As of the date of data cutoff, 12/17 (71%) patients with confirmed responses had a response durations ≥6 months.

Best Change in Tumor Size From Baseline by Prior TKI Therapy in (A) Overall and (B) Intracranial Tumors



Adverse Events

- The majority of TRAEs were Grade 1 and Grade 2 in severity; there were no Grade 4-5 TRAEs.
- TRAEs leading to dose interruptions and dose reductions occurred in 15 (32%) and 11 (23%) patients, respectively.
- There were no treatment-related discontinuations or deaths.

Treatment-Related Adverse Events Occurring in ≥10% of Patients With ROS1-positive NSCLC (N=47)

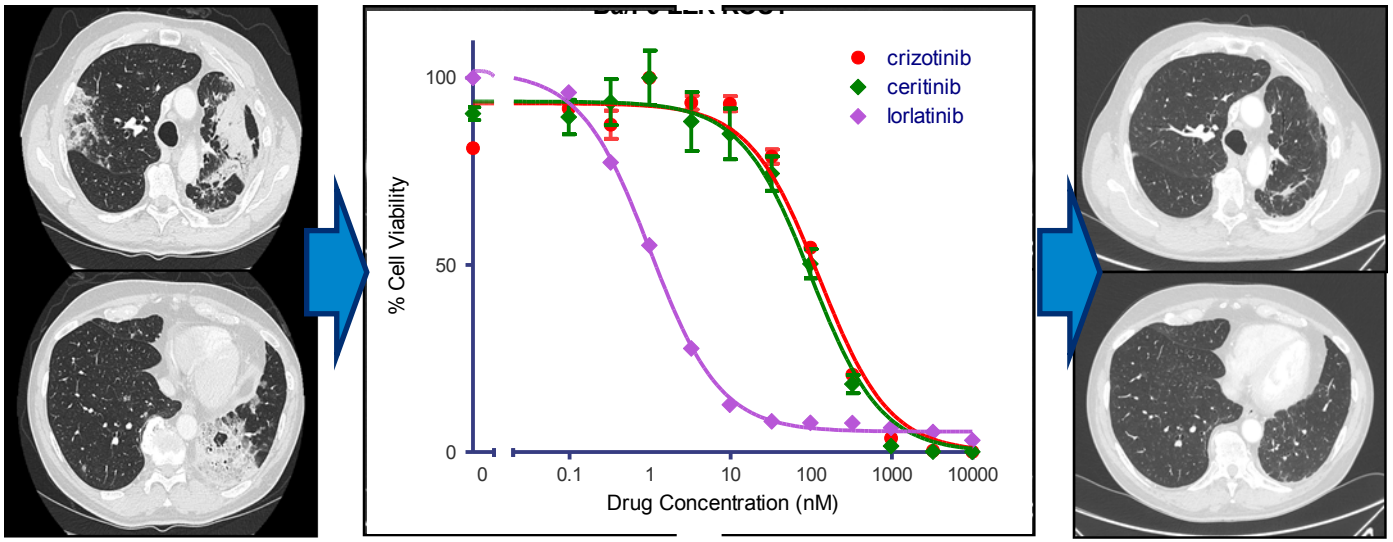
Adverse Event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
Hypercholesterolemia[a]	12 (26)	23 (49)	4 (9)	39 (83)
Hypertriglyceridemia[a]	8 (17)	9 (19)	9 (19)	26 (55)
Edema[a]	16 (34)	4 (9)	1 (2)	21 (45)
Peripheral neuropathy[a]	9 (19)	3 (6)	1 (2)	13 (28)
Weight increased	4 (9)	3 (6)	2 (4)	9 (19)
Cognitive effects[a]	5 (11)	3 (6)	0	8 (17)
Dizziness	5 (11)	0	2 (4)	7 (15)
Mood effects[a]	5 (11)	1 (2)	0	6 (13)
Lipase increased	3 (6)	0	3 (6)	6 (13)
ALT increased	5 (11)	0	0	5 (11)
Arthralgia	3 (6)	2 (4)	0	5 (11)

[a]Refers to AE cluster terms

ROS1 - Acquired Resistance to Crizotinib

Crizotinib, 26 months

Lorlatinib, ongoing

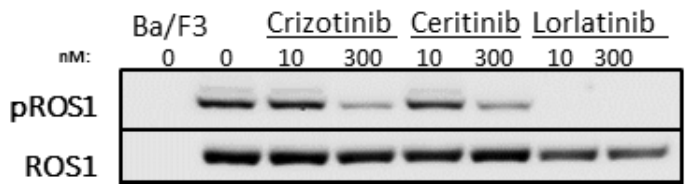


Baseline

Best Response

Progression

Response



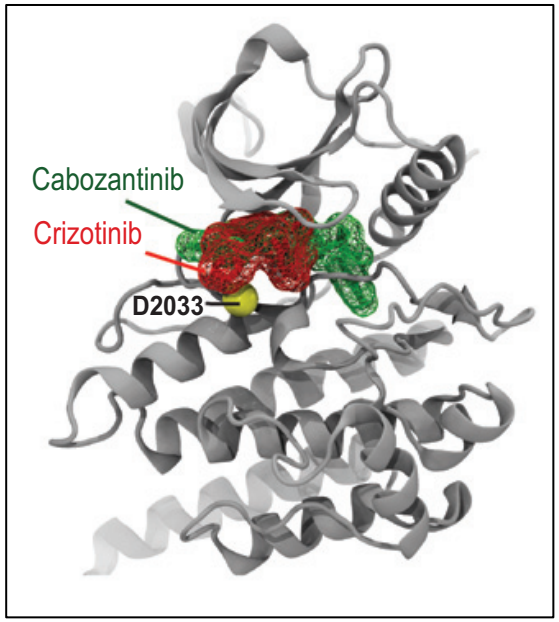
Biopsy

S1986

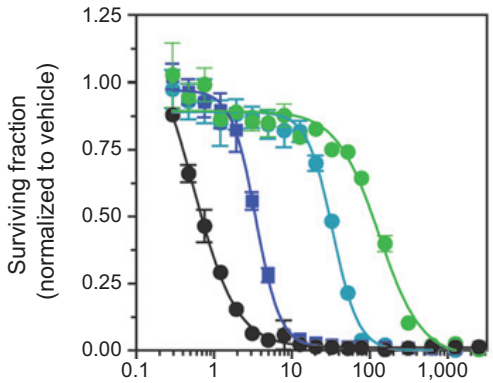
MTB

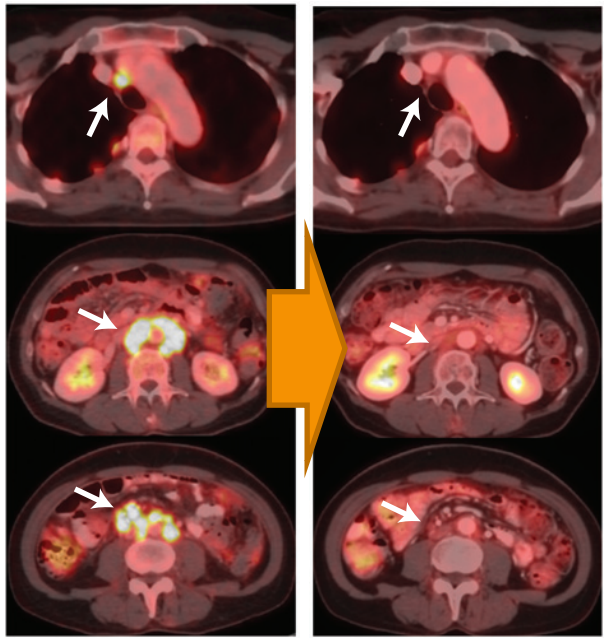
Francesco Facchinetti et al, CCR 2015

ROS1 D2033N mutation: resistance to crizotinib can be overcome by cabozantinib



Ba/F3 CD74-ROS1	IC_{50} (nmol/L)	IC_{90} (nmol/L)
Native + Crizotinib	21	72
D2033N + Crizotinib	132	410
Native + Cabozantinib	2.8	7.6
D2033N + Cabozantinib	0.8	2.7





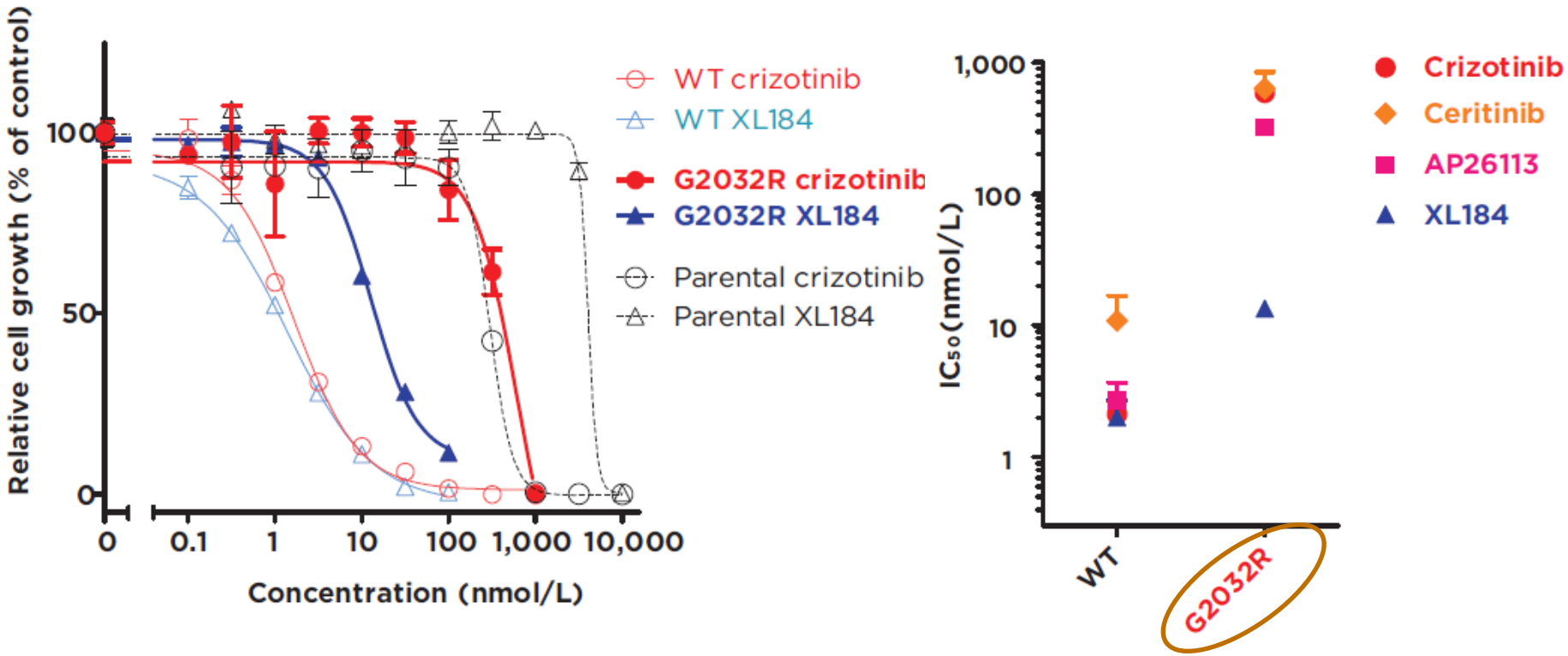
Progression on crizotinib

Cabozantinib response at 4 weeks

cMET/RET/vascular endothelial growth factor (VEGFR) inhibitor cabozantinib

Drilon et al, CCR 2016

Cabozantinib (XL184) overcomes crizotinib resistance caused by the mutations in CD74–ROS1 (G2032R)



cMET/RET/vascular endothelial growth factor (VEGFR) inhibitor cabozantinib

Ryohei Katayama et al, CCR 2015

Mutations in the ROS1 kinase domain conferring crizotinib resistance

Mutation	Location	ROS1 fusion	Active next generation inhibitor
G2032R[1]	solvent front	CD74-ROS1	- cabozantinib, lorlatinib, foretinib, brigatinib (in vitro)[4] - cabozantinib, lorlatinib (patient)
D2033N[2]	solvent front	CD74-ROS1	cabozantinib (in vitro, patient)[2]
L2155S (cell line)3	n.r.	SLC34A2-ROS1	n.r.
L2026M[4]	gate-keeper	CD74-ROS1	cabozantinib, brigatinib, certinib, foretinib, lorlatinib[4]
S1986Y/F[5]	double mutation	EZR-ROS1	lorlatinib (patient)[5]
L1951[6]	solvent front		cabozantinib (in vitro, pat.-derived cells)[6]

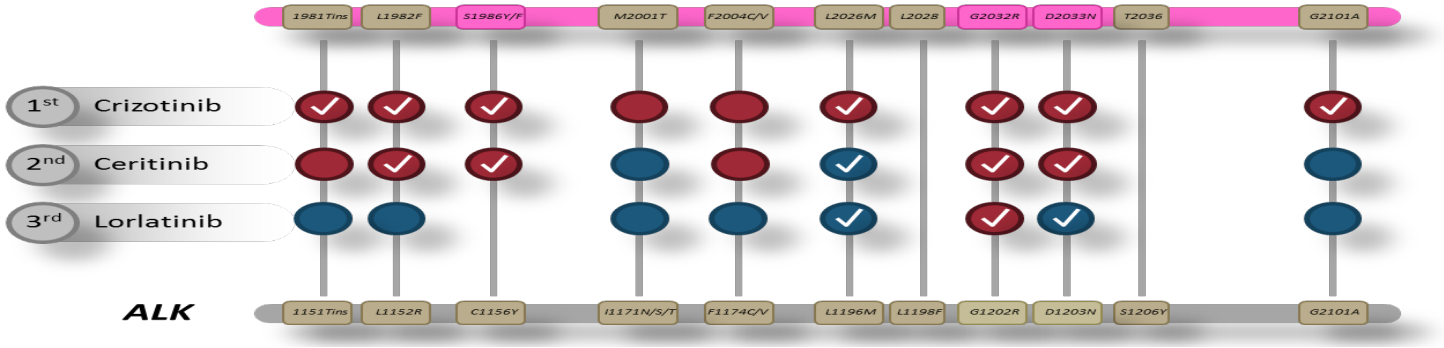
[1]Awad et al, NEJM 2013; [2]Drilon et al, 2015; [3]Song et al, 2015; [4]Chong et al, CCR 2016; [5]Facinetti et al., CCR 2016 [6]Katayama et al, CCR 2015

So ROS1 and NSCLC…

- **ROS1 rearrangement** is a therapeutically tractable oncogenic driver that occurs in 1% to 2% of patients
- Given the high homology in the kinase domains of ROS1 and ALK, ALK inhibitors have been shown to be efficacious in ROS1-positive cell lines and tumors

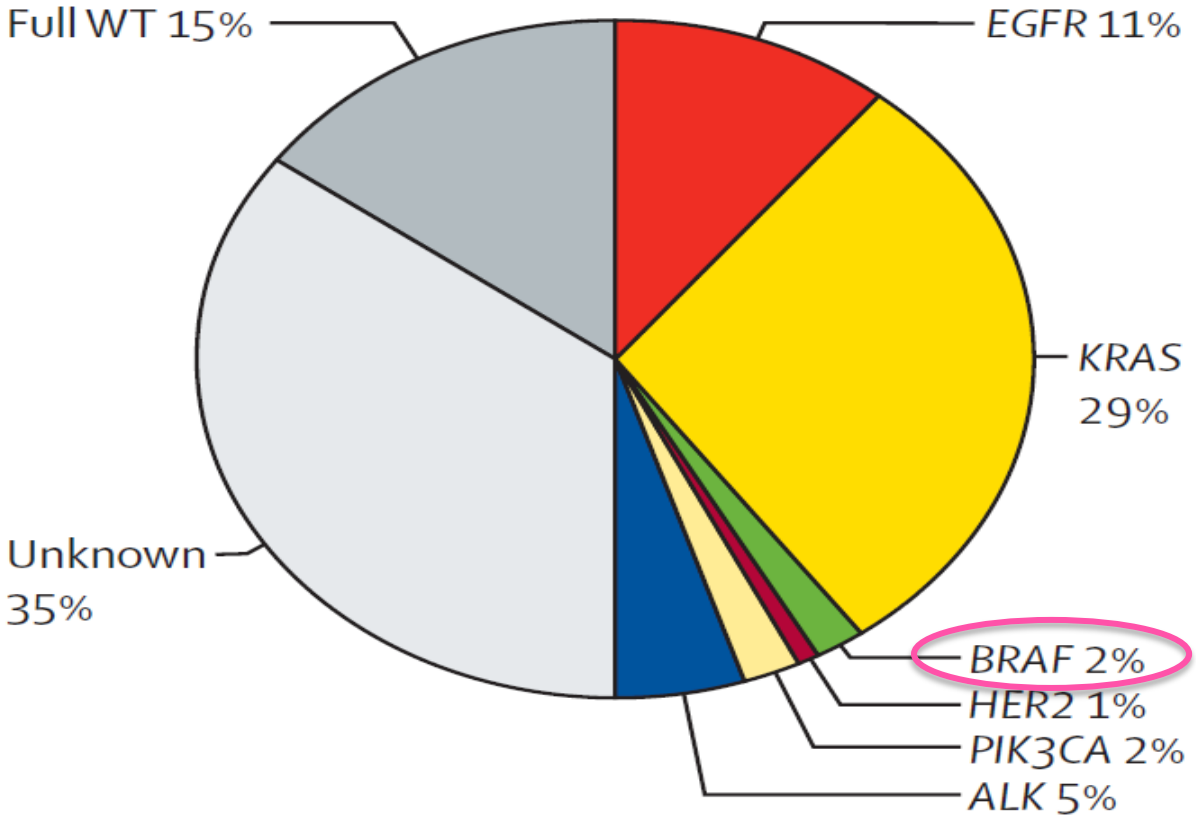
Crizotinib EMA and FDA approved

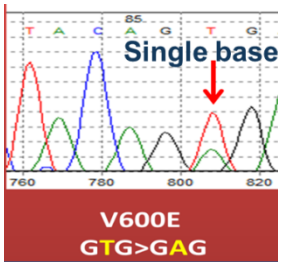
- **Acquired ROS1 mutations** after crizotinib treatment could be overcome by next generation inhibitors like cabozantinib and lorlatinib



Frequency of genetic alterations

1-year nationwide programme in France



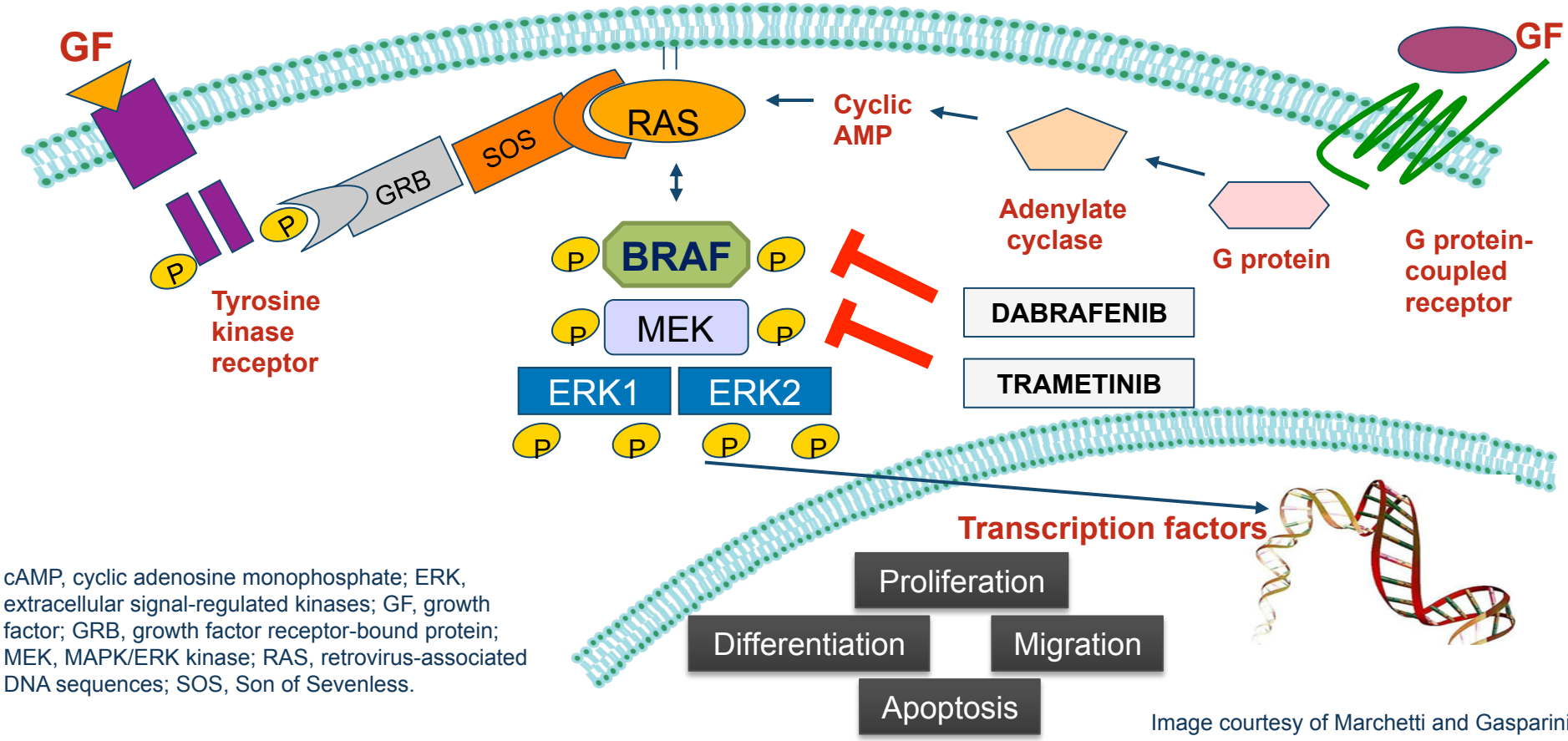


V600E : 80%

from 18 679 analysed samples

F.Barlesi et al, lancet 2016

BRAF and its signal transduction pathway



cAMP, cyclic adenosine monophosphate; ERK, extracellular signal-regulated kinases; GF, growth factor; GRB, growth factor receptor-bound protein; MEK, MAPK/ERK kinase; RAS, retrovirus-associated DNA sequences; SOS, Son of Sevenless.

Image courtesy of Marchetti and Gasparini.

Preliminary evidence suggests that BRAF V600E mutation may be associated with poor prognosis

NSCLC who received radical resection of a primary NSCLC

Multivariate Overall Survival Analysis 331 Patients With Lung ADC

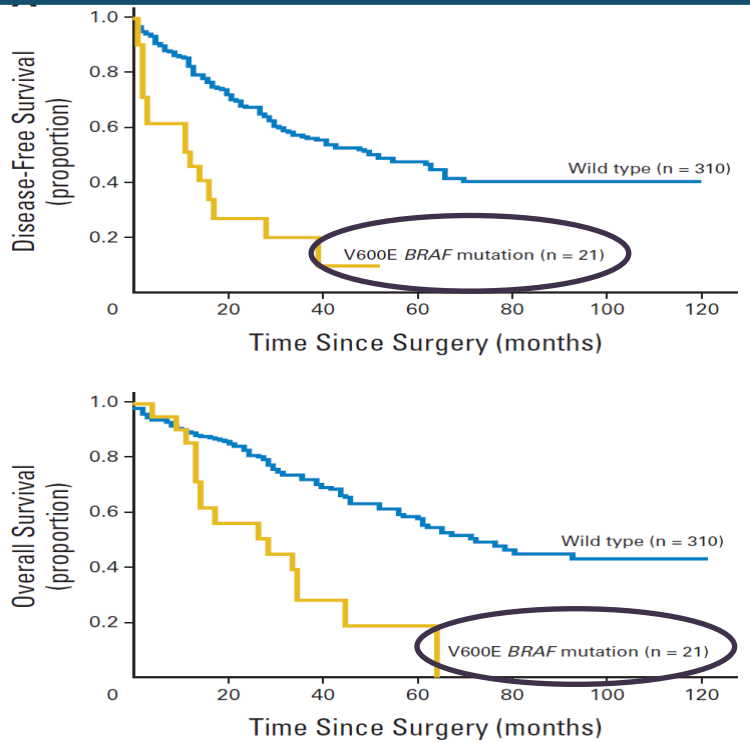
Stage I-IV BRAF+ NSCLC Adenocarcinoma[1]

- Disease stage and BRAF V600E mutation were found to be the **only independent and significant factors to predict both DFS and OS***

**results remained consistent across univariate and additional subgroup analysis of study population*

Variable	Category	HR	95% CI	P-value
Smoking	Never smoker/Smoker	1.09	.56-2.09	NS
Sex	Female/Male	1.2	0.63-2.27	NS
Non-V600E	Mutated/wild type	1.46	.46-4.64	NS
V600E	**Mutated/wild type**	**2.18**	**1.17-4.04**	**0.014**
Stage	III + IV/I + II	2.92	1.95-4.37	< .001

NS = not significant



Sources: 1. Antonio Marchetti et al. JCO 2011;29:3574-3579; 2. Stephanie Cardarella et al. Clin Cancer Res 2013;19:4532-4540

Outcomes stratified by line of therapy and molecular alteration: second line

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

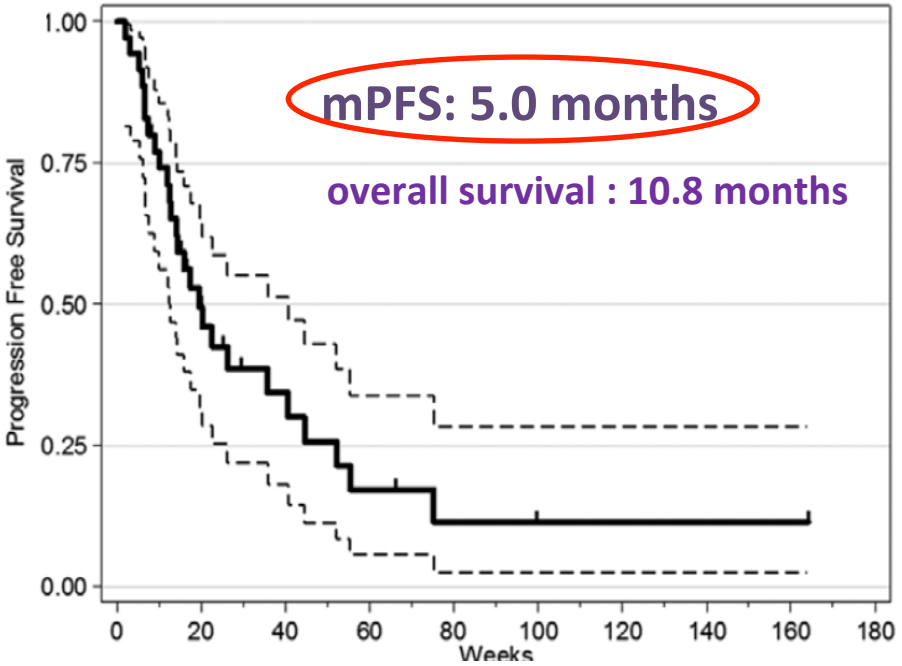
Second-line

	Overall population	*EGFR* mutation	*KRAS* mutation	***BRAF* mutation**
Overall response (available data)	3,325	441	762	59
Overall response, % (ORR)	13	31	8	9
95% CI	11.6–13.8	26.5–35.1	5.8–9.6	1.4–15.6
PFS (available data)	4,029	518	1,017	71
PFS, median, months (PFS)	3.1	5.6	2.5	3.1
95% CI	3.0–3.3	4.3–6.6	2.3–2.9	1.4–6.1
6-month PFS, %	36	48	33	41
95% CI	34.7–38.0	43.5–53.1	29.5–36.0	28.7–53.9
12-month PFS, %	24	33	25	18
95% CI	22.1–25.5	27.4–37.8	21.3–27.9	6.2–30.1
Overall survival (available data)	7,821	1,017	1,966	132
OS, median, months	13.8	NR	11.7	13.8
95% CI	13.3–14.4	NR	10.6–13.1	8.5–21.9

Barlesi F, et al. Lancet. 2016;387:1415-26.

Targeted therapy for patients with *BRAF*-mutant lung cancer results from the European EURAF cohort

Sample size	35
BRAF inhibitor therapy	35 (100%)
BRAF inhibitors and lines (total)	39
Vemurafenib	29
Dabrafenib	9
Sorafenib	1
Sequential *BRAF* inhibitors	
No	31 (89%)
Yes	4 (11%): 3x vemurafenib → dabrafenib and 1x sorafenib → vemurafenib
BRAF inhibitor used in	
1st line	5 (14%)
Further lines	30 (86%)



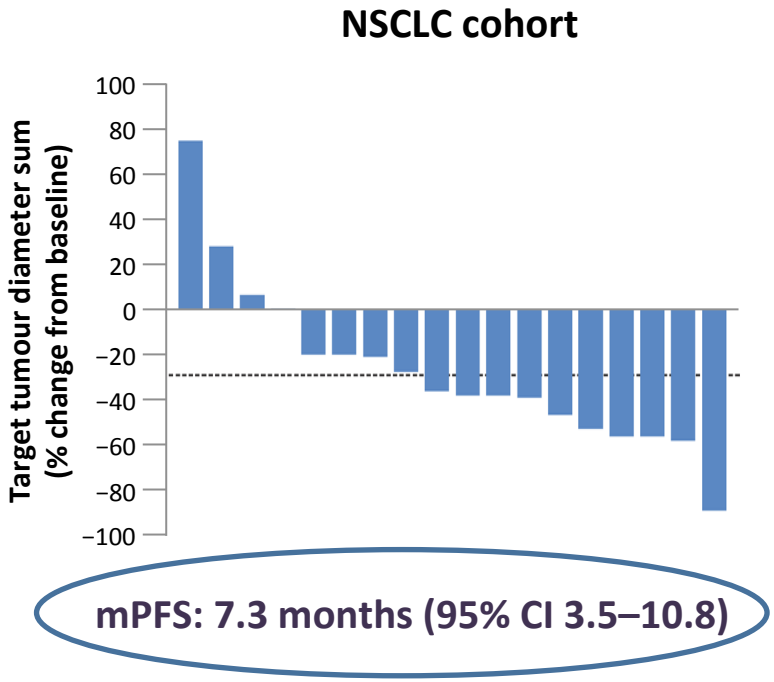
-**All tumors with non-V600E mutations** located outside of the activation segment of the BRAF kinase domain were refractory to BRAF therapy (17%: G466V, G469A, G469L,G596V, V600K, K601E).
-**One patient with G596V** achieved PR with vemurafenib

Oliver Gautschi et al, JTO 2014

Vemurafenib in BRAF V600 nonmelanoma cancers (BASKET trial): Preliminary best response

Basket trial (multiple non-melanoma cancers)

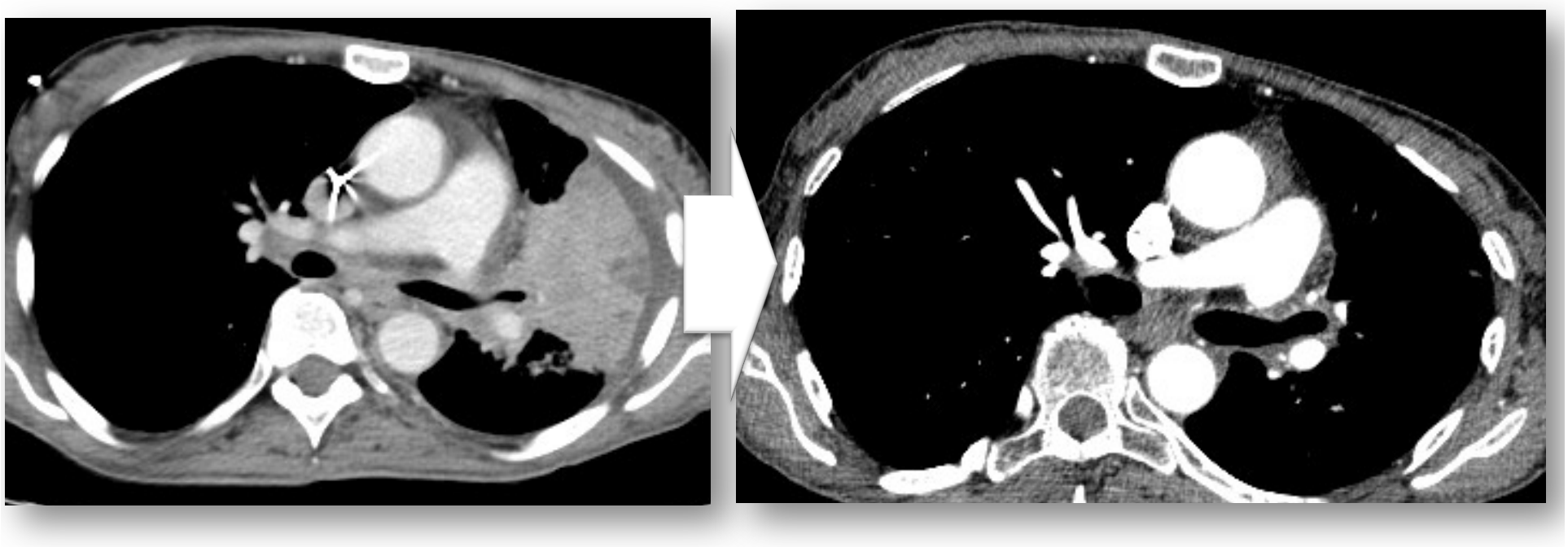
Variable	NSCLC[a] (N = 20)	Colorectal cancer[a]	
		Vemurafenib (N = 10)	Vemurafenib + cetuximab (N = 27)
Patients with ≥ 1 post-baseline assessment, n	19	10	26
CR, n (%)	0	0	0
PR, n (%)	8 (42%)	0	1 (4)
SD, n (%)	8 (42)	5 (50)	18 (69)
PD, n (%)	2 (11)	5 (50)	7 (27)
Missing data, n (%)	1 (5)	0	0
OR, n (%) [95% CI]	8 (42) [20–67]	0	1 (4) [< 1–20]



[a]Patients with several pre-specified cancers were enrolled into the study, including NSCLC and colorectal cancer.
CI, confidence interval; CR, complete response; mPFS, median PFS; OR, overall response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Hyman DM, et al. N Engl J Med. 2015.

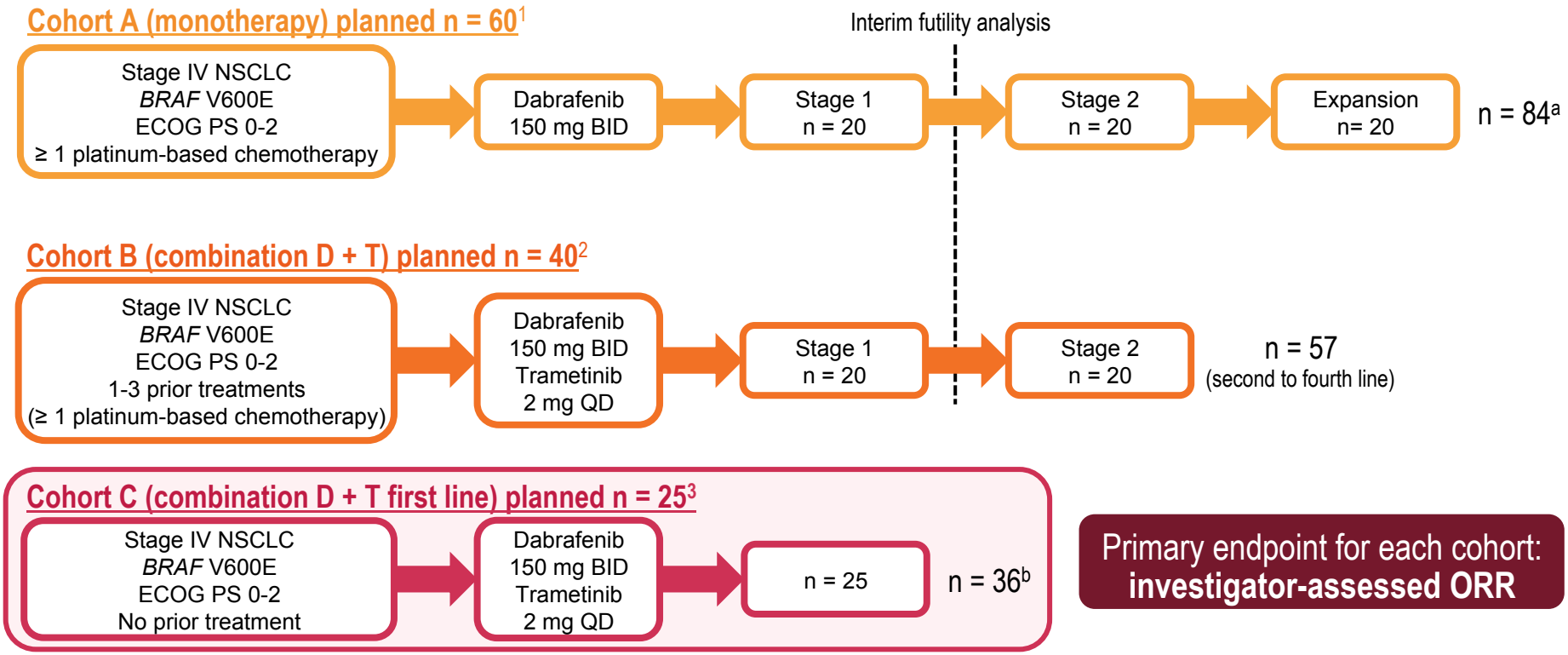
BRAF V600E and Vemurafenib



B.Besse, Gustave Roussy

BRF113928 study design

Multicohort, nonrandomized, open-label phase 2 study



BID, twice daily; D, dabrafenib; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; QD, once daily; T, trametinib. [a] Includes n = 6 patients who were treatment naive. [b] Includes 2 patients with no prior treatment originally enrolled in cohort B due to protocol deviation. 1. Planchard D, et al. *Lancet Oncol*. 2016;17:642-650; 2. Planchard D, et al. *Lancet Oncol*. 2016;17:984-993; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01336634. Accessed May 9, 2017.

Treatment of *BRAF* V600E-mutant NSCLC with dabrafenib ± trametinib in phase 2 trials

Patients with advanced NSCLC who received dabrafenib as second-line or later treatment (n = 78)[1]	
Age (range), years	66 (28–85)
Sex, n (%)	
Male	39 (50)
Female	39 (50)
Ethnic origin, n (%)	
White	59 (76)
Asian	17 (22)
African American	2 (3)
ECOG performance status, n (%)	
0	16 (21)
1	50 (64)
2	12 (15)
Smoking history, n (%)	
Never smoked	29 (37)
≤ 30 pack-years	25 (32)
> 30 pack-years	24 (31)
Histology at diagnosis, n (%)	
Adenocarcinoma	75 (96)
Other	3 (4)

Patients with metastatic NSCLC who received dabrafenib plus trametinib as second-line or later treatment (n = 57)[2]	
Age (range), years	64 (58–71)
Sex, n (%)	
Male	29 (51)
Female	28 (49)
Ethnic origin, n (%)	
White	49 (86)
Black	2 (4)
Asian	4 (7)
Mixed	1 (2)
Missing	1 (2)
ECOG performance status, n (%)	
0	17 (30)
1	35 (61)
2	5 (9)
Histology at initial diagnosis, n (%)	
Adenocarcinoma	56 (98)
Large cell	1 (2)
History of tobacco use, n (%)	
Never smoked	16 (28)
Current smoker	6 (11)
Former smoker	35 (61)

1. Planchard D, et al. Lancet Oncol. 2016
2. Planchard D, et al. Lancet Oncol. 2016

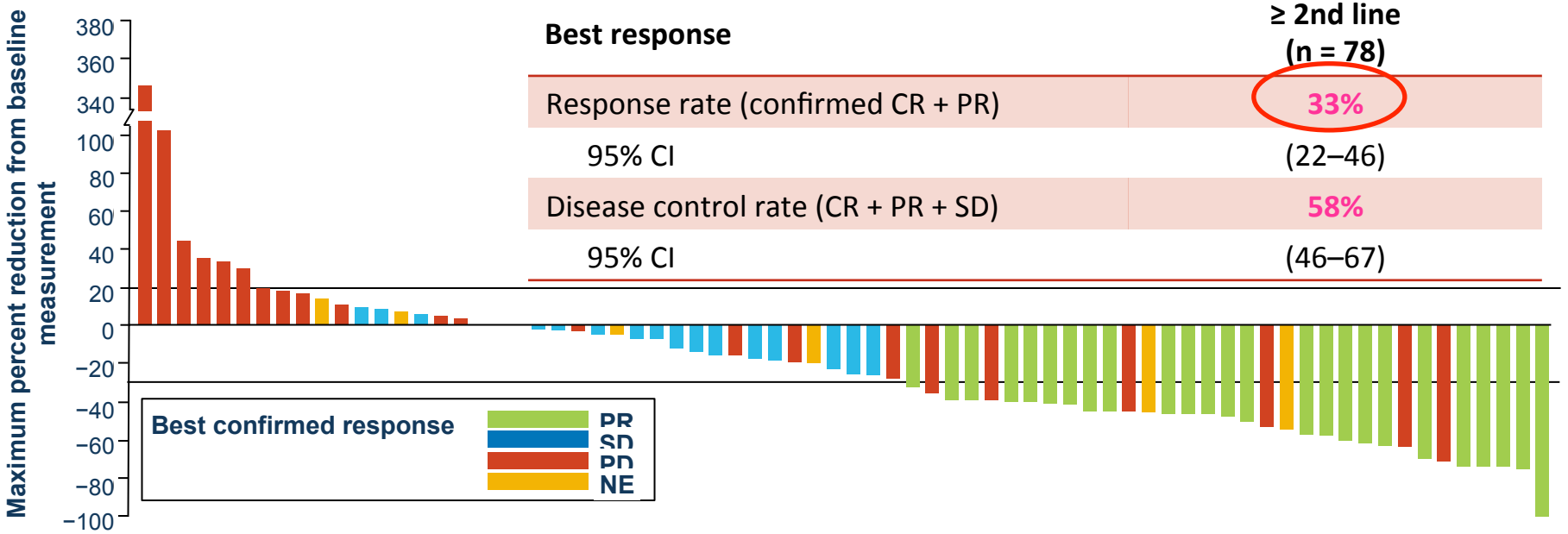
Dabrafenib monotherapy (cohorte A): Maximum reduction

Stage IV NSCLC
BRAF V600E
ECOG PS 0–2
≥ 1 platinum-based chemotherapy

→ Dabrafenib 150 mg b.i.d. → Stage 1 n = 20 → Stage 2 n = 20 → Expansion n = 20

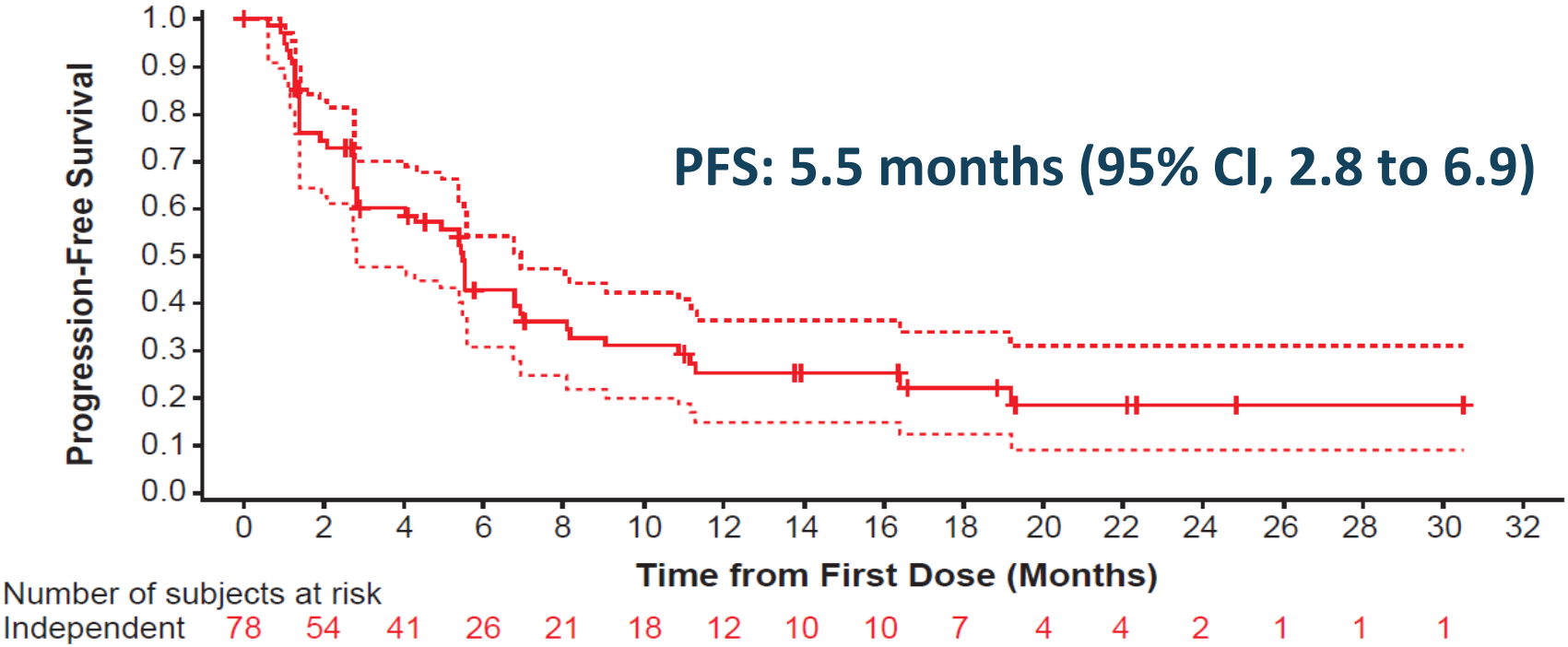
n = 78 (≥ 2nd line)

Best response	≥ 2nd line (n = 78)
Response rate (confirmed CR + PR)	33%
95% CI	(22–46)
Disease control rate (CR + PR + SD)	58%
95% CI	(46–67)



Planchard D, et al. Lancet Oncol. 2016;17:642-50.

Progression-Free Survival (independent review)



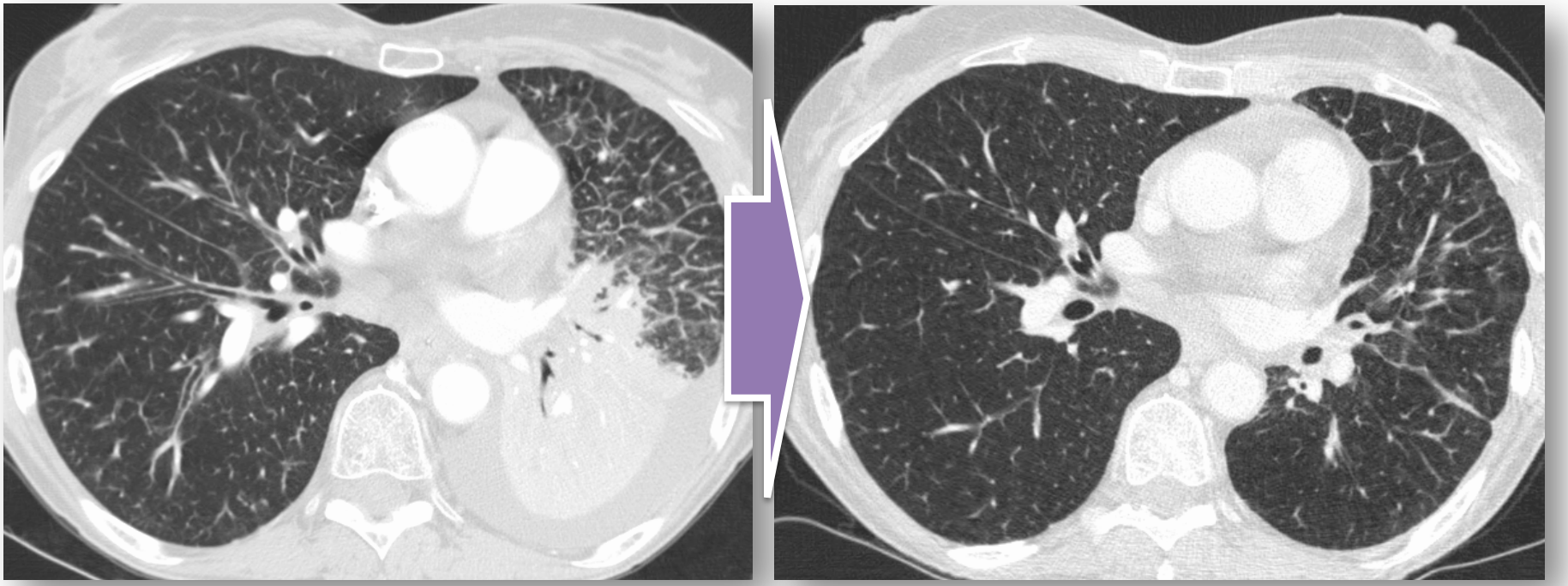
PFS: 5.5 months (95% CI, 2.8 to 6.9)

D.Planchard et al, lancet onco 2016

Dabrafenib Activity in BRAF V600E NSCLC

- 72 year old white female, 2nd line, former smoker, 10 pack years (stop in1985)
- ECOG PS2
- Adenocarcinoma, BRAFV600E, T3N3M1b (pleural, pulmonary, lymph nodes)
- Progression after one line of platinum-pemetrexed

October 2012 → **+ 6 weeks of Dabrafenib**



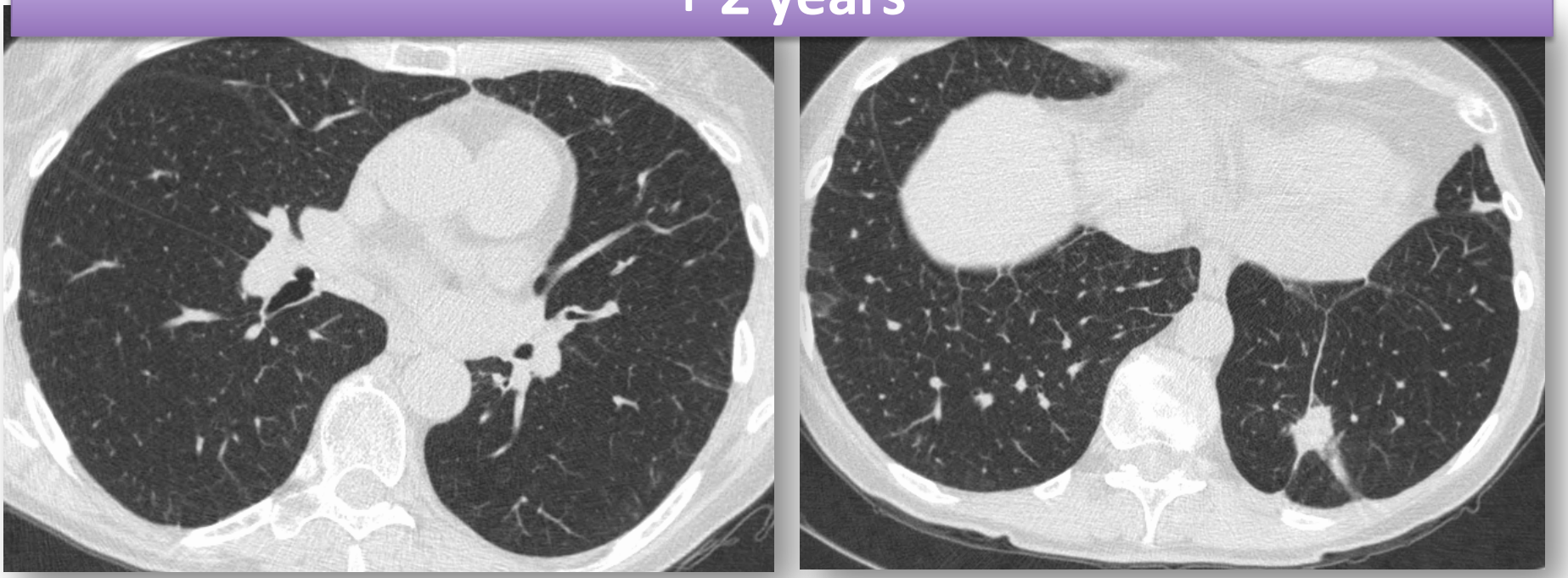
Baseline CT-Scan → **ECOG PS0**

J. Mazieres et al, Hôpital Larrey CHU Toulouse

D.Planchard et al, ESMO 2014

- ECOG PS:0
- Asymptomatic
- Very good safety profile (rare episodes of fever)

+ 2 years

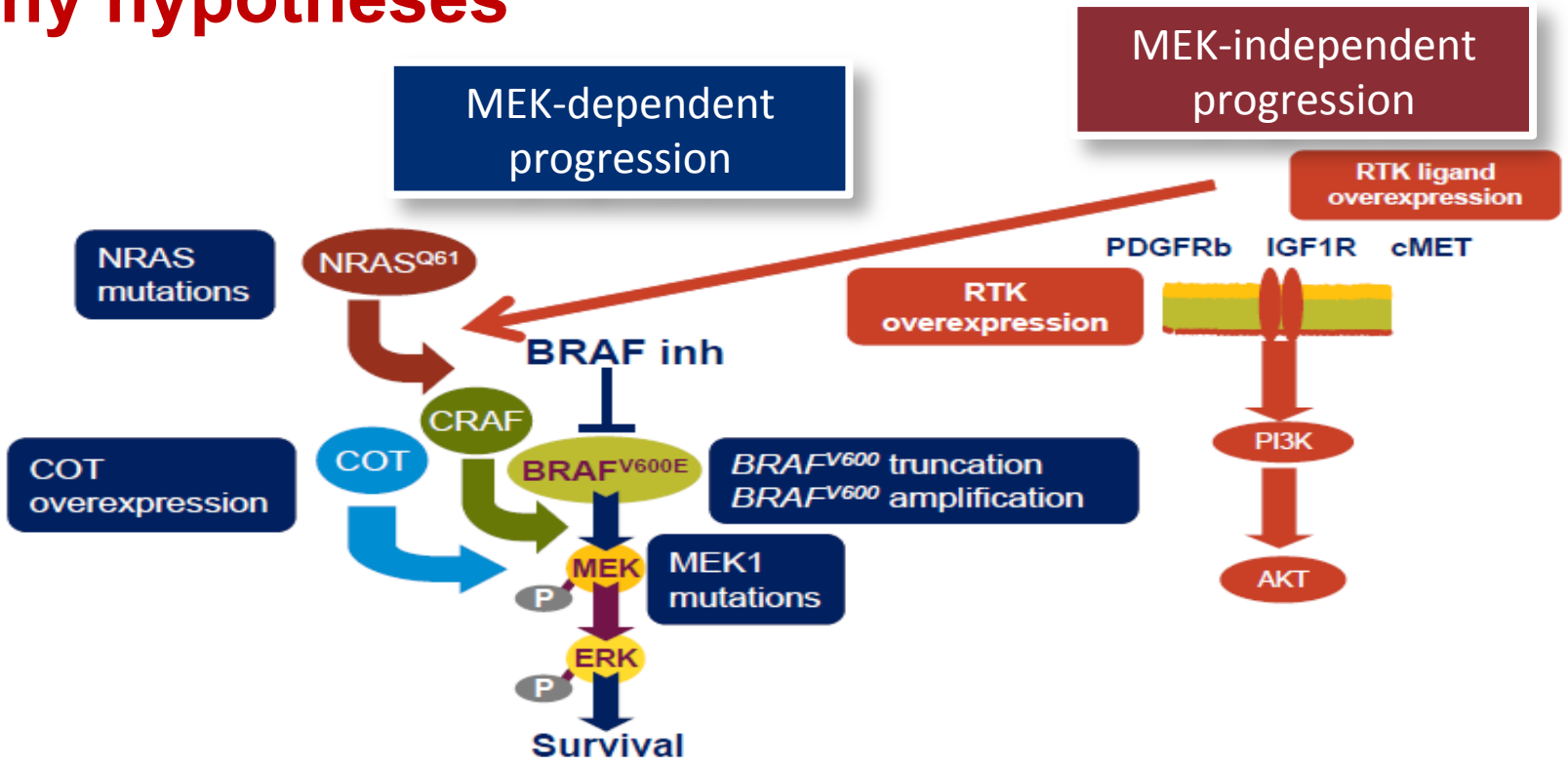


- Unique residual disease in the lower left lung
- Discussion for a local treatment 2 years after the start of dabrafenib

J. Mazieres et al, Hôpital Larrey CHU Toulouse

D.Planchard et al, ESMO 2014

Acquired resistance to BRAF inhibition: many hypotheses



Johannessen CM, et al. Nature. 2010;468:968-72. Nazarian R, et al. Nature. 2010;468:973-7. Poulikakos PI, et al. Nature. 2011;480:387-90. Shi H, et al. Nature Commun. 2012;3:724. Straussman R,et al. AACR. 2012;abstract 4837. Villanueva J, et al. Cancer Cell. 2010;18:683-95. Wagle N, et al. J Clin Oncol. 2011;29:3085-96.

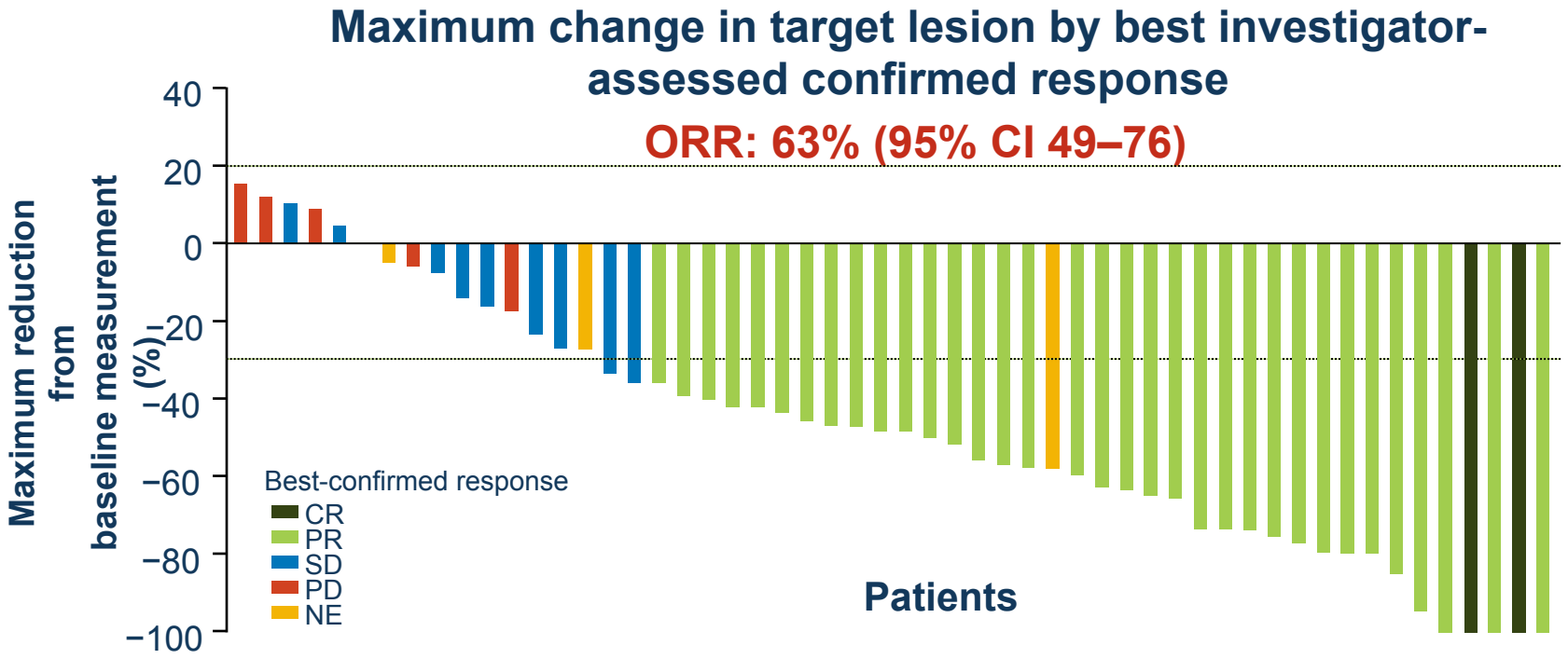
Cohorte B: Dabrafenib + trametinib: Best-confirmed response

	Investigator assessment (n = 57)	Independent assessment (n = 57)
Best response, n (%)		
CR	2 (4)	0
PR	34 (60)	36 (63)
SD[a]	9 (16)	4 (7)
PD	7 (12)	8 (14)
Non-CR/non-PD[b]	0	3 (5)
Not evaluable	5 (9)	6 (11)
ORR (CR + PR), n (%) [95% CI]	**36 (63) [49–76]**	**36 (63) [49–76]**
Disease control rate (CR + PR + SD), n (%) [95% CI]	45 (79) [66–89]	43 (75) [62–86]

[a] SD is defined as meeting SD criteria for ≥ 12 weeks.
[b] Patients were nonmeasurable by independent review committee.

Planchard D, et al. Lancet Oncol. 2016;17:984-93.

Dabrafenib + trametinib: Maximum change in target lesion



NE patients either had no post-baseline CT scan or discontinued before 12 weeks without documented progression

NE, not evaluable.

Planchard D, et al. Lancet Oncol. 2016;17:984-93.

Dabrafenib + trametinib vs dabrafenib: AEs

		Dabrafenib + Trametinib		Dabrafenib	
Category	**AEs, n (%)**	**All Grades**	**Grade 3**	**All Grades**	**Grade 3**
General	Pyrexia	26 (46)	1 (2)	30 (36)	2 (2)
	Asthenia	18 (32)	2 (4)	25 (30)	3 (4)
	Decreased appetite	17 (30)	0	24 (29)	1 (1)
	Chills	13 (23)	1 (2)	13 (15)	1 (1)
	Peripheral oedema	13 (23)	0	-	-
Skin	Arthralgia	11 (19)	0	14 (17)	1 (1)
	Dry skin	15 (26)	1 (2)	19 (23)	0
	Rash	12 (21)	1 (2)	17 (20)	1 (1)
	Hyperkeratosis	6 (10)	1 (2)	25 (30)	1 (1)
	Basal-cell carcinoma	2 (2)	1 (2)	4 (5)	4 (5)
	Squamous-cell carcinoma	2 (4)	2 (4)	10 (12)	10 (12)
	Skin papilloma	-	-	22 (26)	0
Digestive	Nausea	23 (40)	0	23 (27)	1 (1)
	Vomiting	20 (35)	0	17 (20)	1 (1)
	Diarrhoea	19 (33)	1 (2)	14 (17)	1 (1)

Planchard D, et al. Lancet Oncol. 2016;17:984-93.
Planchard D, et al. Lancet Oncol. 2016;17:642-50.

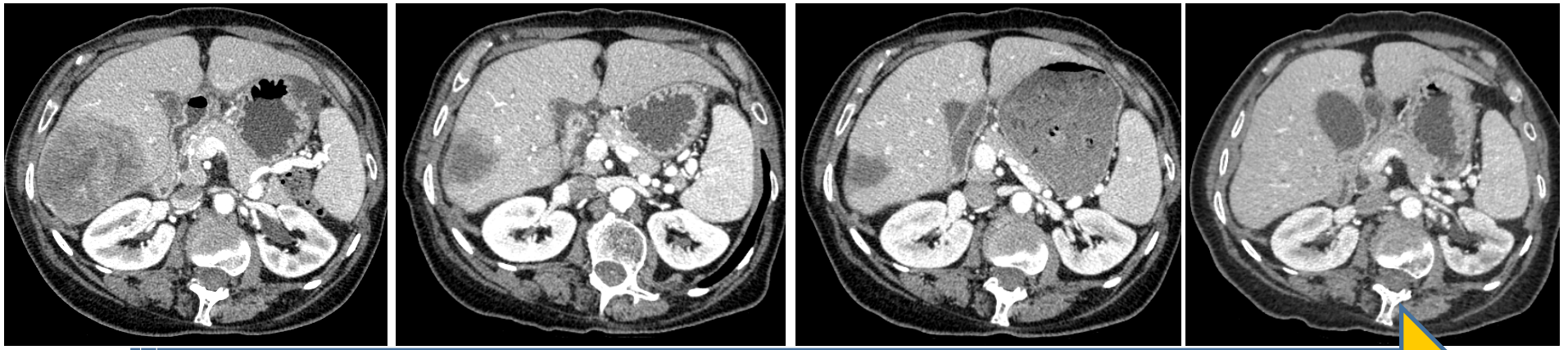
The patient received the association: Dabrafenib (150mg/d) + Trametinib (2mg twice a day)

61-year-old woman, never smoked

Adenocarcinoma with pleural effusion, liver metastases, 4th line (CDDP-pemetrexed, docetaxel, gemcitabine)

July 2014

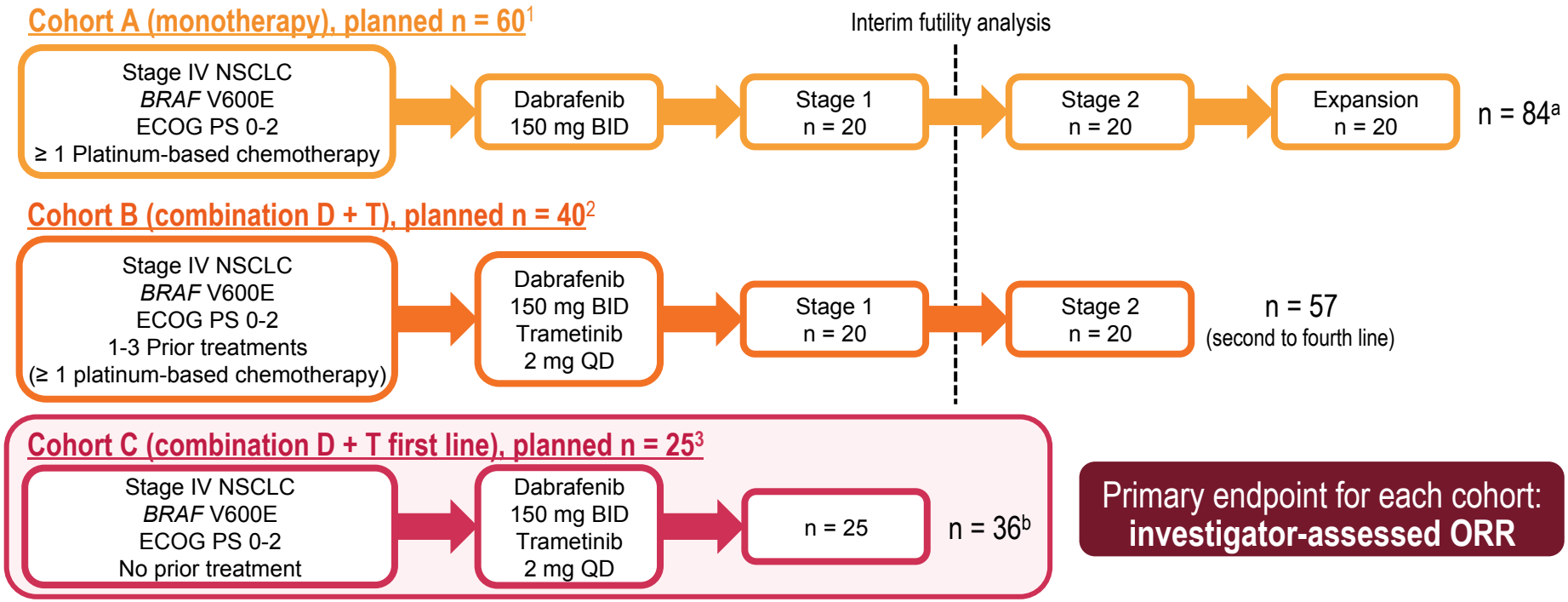
March 2017



+ 32 months

D.Planchard et al, Gustave Roussy

BRF113928: STUDY DESIGN



BID, twice daily; D, dabrafenib; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; QD, once daily; T, trametinib. [a] Includes 6 patients who were treatment naive. [b] Includes 2 patients with no prior treatment originally enrolled in cohort B due to protocol deviation. 1. Planchard D, et al. *Lancet Oncol*. 2016;17:642-650; 2. Planchard D, et al. *Lancet Oncol*. 2016;17:984-993; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01336634. Accessed May 9, 2017.

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BEST CONFIRMED RESPONSE

	Investigator Assessed (n = 36)	IRC Assessed (n = 36)
Best response, n (%)		
CR	2 (6)	2 (6)
PR	21 (58)	21 (58)
SD	4 (11)	3 (8)
PD	5 (14)	7 (19)
NE	4 (11)	3 (8)
Overall response rate (CR + PR), n (%) [95% CI]	23 (**64**) [46-79]	23 (**64**) [46-79]
Disease control rate (CR + PR + SD), n (%) [95% CI]	27 (**75**) [58-88]	26 (**72**) [55-86]

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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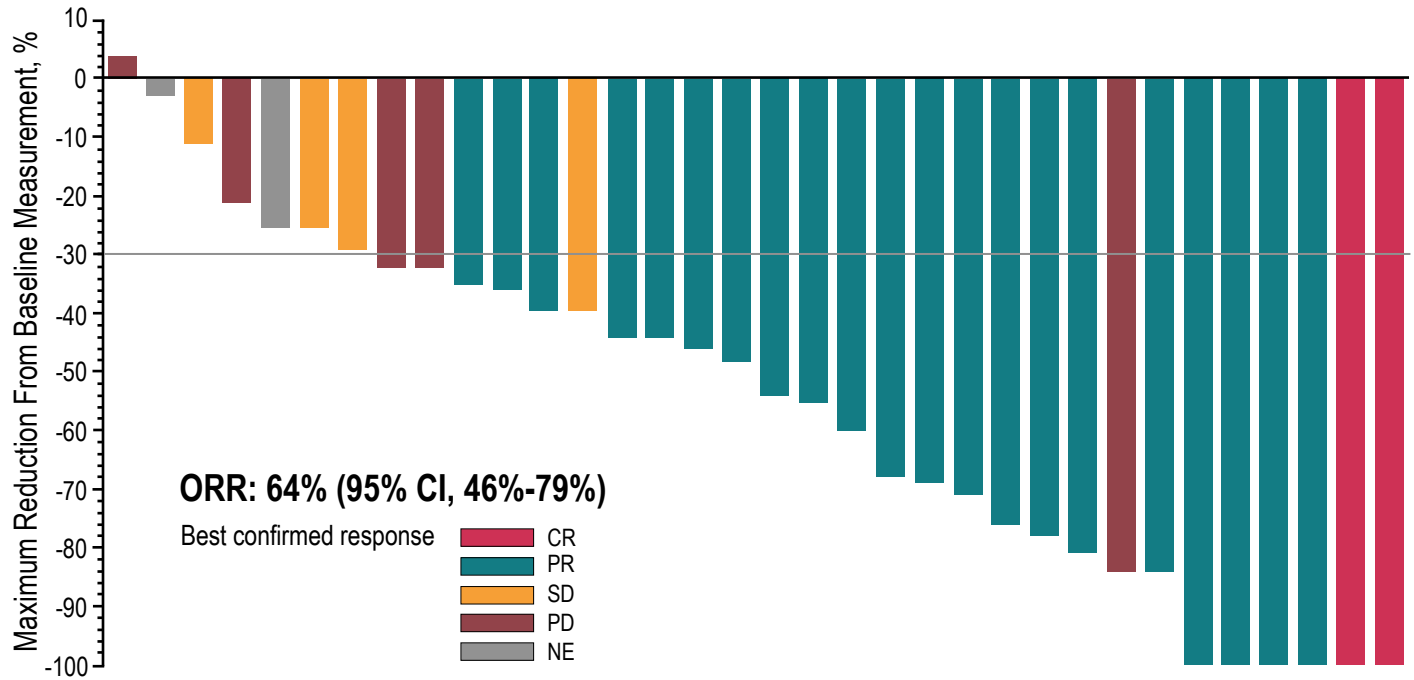
INVESTIGATOR-ASSESSED MAXIMUM CHANGE IN TARGET LESION BY BEST RESPONSE

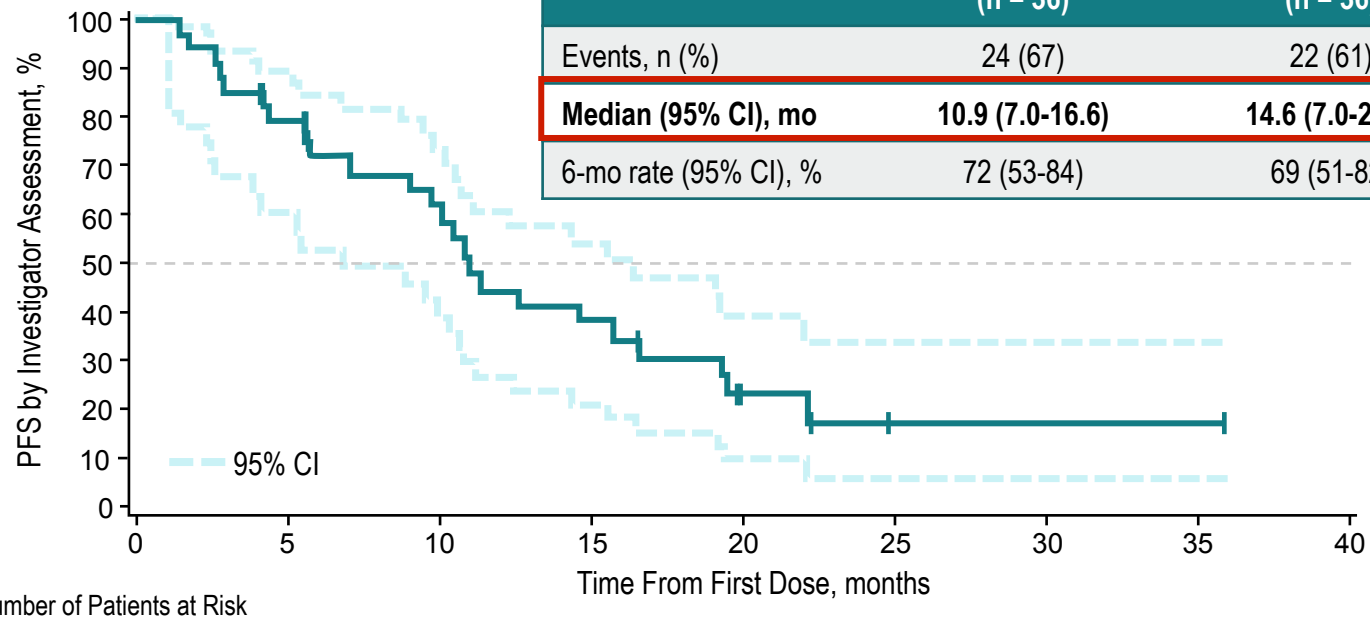


Grey line at −30 represents the threshold for partial response per RECIST v1.1 criteria.

MADRID 2017 ESMO congress

PROGRESSION-FREE SURVIVAL

	Investigator Assessed (n = 36)	IRC Assessed (n = 36)
Events, n (%)	24 (67)	22 (61)
Median (95% CI), mo	**10.9 (7.0-16.6)**	**14.6 (7.0-22.1)**
6-mo rate (95% CI), %	72 (53-84)	69 (51-82)



Number of Patients at Risk

36	25	18	11	4	1	1	1	0

Numerical differences in median PFS between investigator and IRC assessments were primarily driven by censored observations for IRC (5 patients who were assessed by the investigators as having PD had values for PFS close to the medians). Because no further tumour assessment scans were collected for these patients, and because the IRC did not assess these last scans as PD, these patients were censored.

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CONCLUSIONS (CONT)

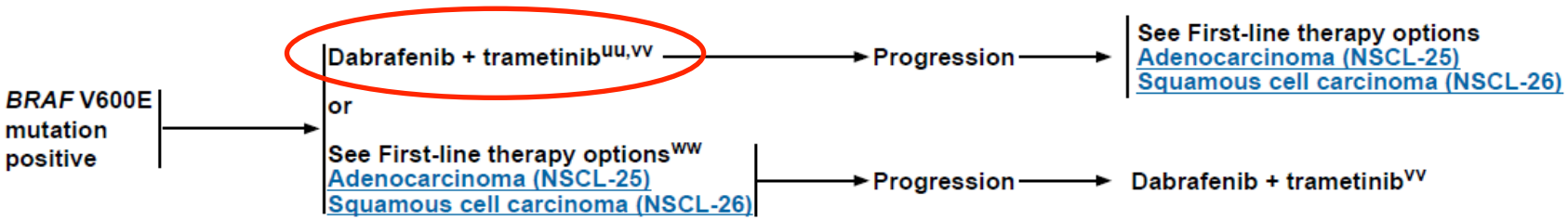
- The ORR, DOR, and PFS observed in treatment naive patients were similar to those reported for the previously-treated cohort receiving combination treatment

	Previously Treated		Treatment Naive
	Dabrafenib Monotherapy[1,2] (n = 78)	Dabrafenib Plus Trametinib[2] (n = 57)	Dabrafenib Plus Trametinib (n = 36)
ORR (95% CI), %	33 (23–45)	67 (53–79)	**64 (46–79)**
DOR, median (95% CI), months	9.6 (5.4–15.2)	9.8 (6.9–16.0)	**10.4 (8.3–17.9)**
PFS, median (95% CI), months	5.5 (3.4–7.3)	10.2 (6.9–16.7)	**10.9 (7.0–16.6)**
OS, median (95% CI), months	12.7 (7.3–16.3)	18.2 (14.3–NE)	**24.6 (12.3–NE)**

- Based on these results, dabrafenib plus trametinib was recently approved by the European Commission and US FDA for use in patients with metastatic NSCLC harboring this mutation regardless of prior treatment history

1. Planchard D, et al. *Lancet Oncol*. 2016; 17:642-650; 2. Planchard D, et al. *J Clin Oncol*. 2017; 35 (suppl) [abstract 9075].

BRAF V600E MUTATION POSITIVE



So BRAF and NSCLC…

- BRAF should testing in pts EGFR and ALK wild type

- Dabrafenib + Trametinib (for Tafinlar® and Mekinist®) demonstrated clinically meaningful anti-tumor activity with higher ORR when compared indirectly with dabrafenib or Vemurafenib in BRAF V600E NSCLC

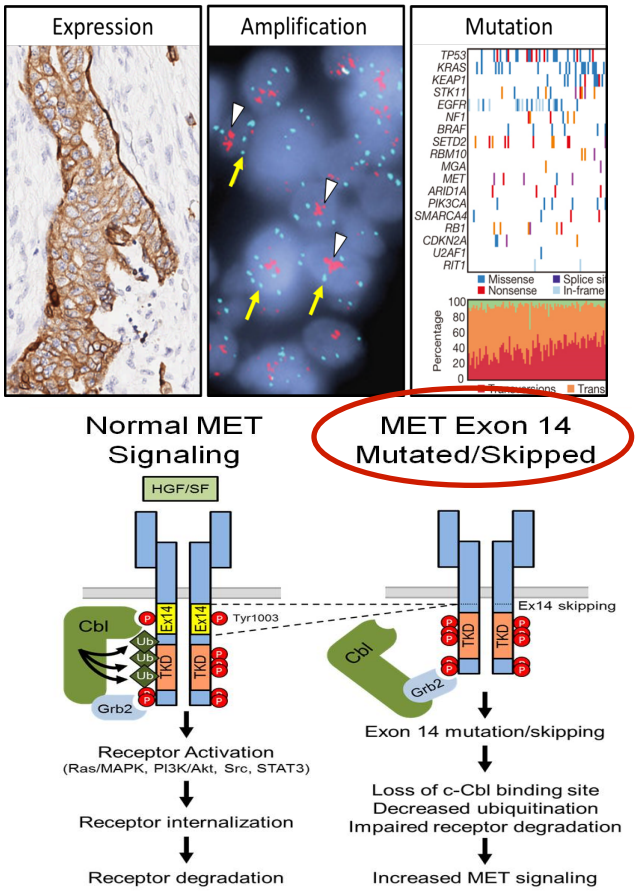
EMA and FDA approved

-**Next step**: immunotherapy is tempting, and clinical trials testing these combinations are ongoing in melanoma

-**Strong need** to better characterize resistance mechanisms in NSCLC

MET activation: amplification and/or exon 14 mutation/skipping

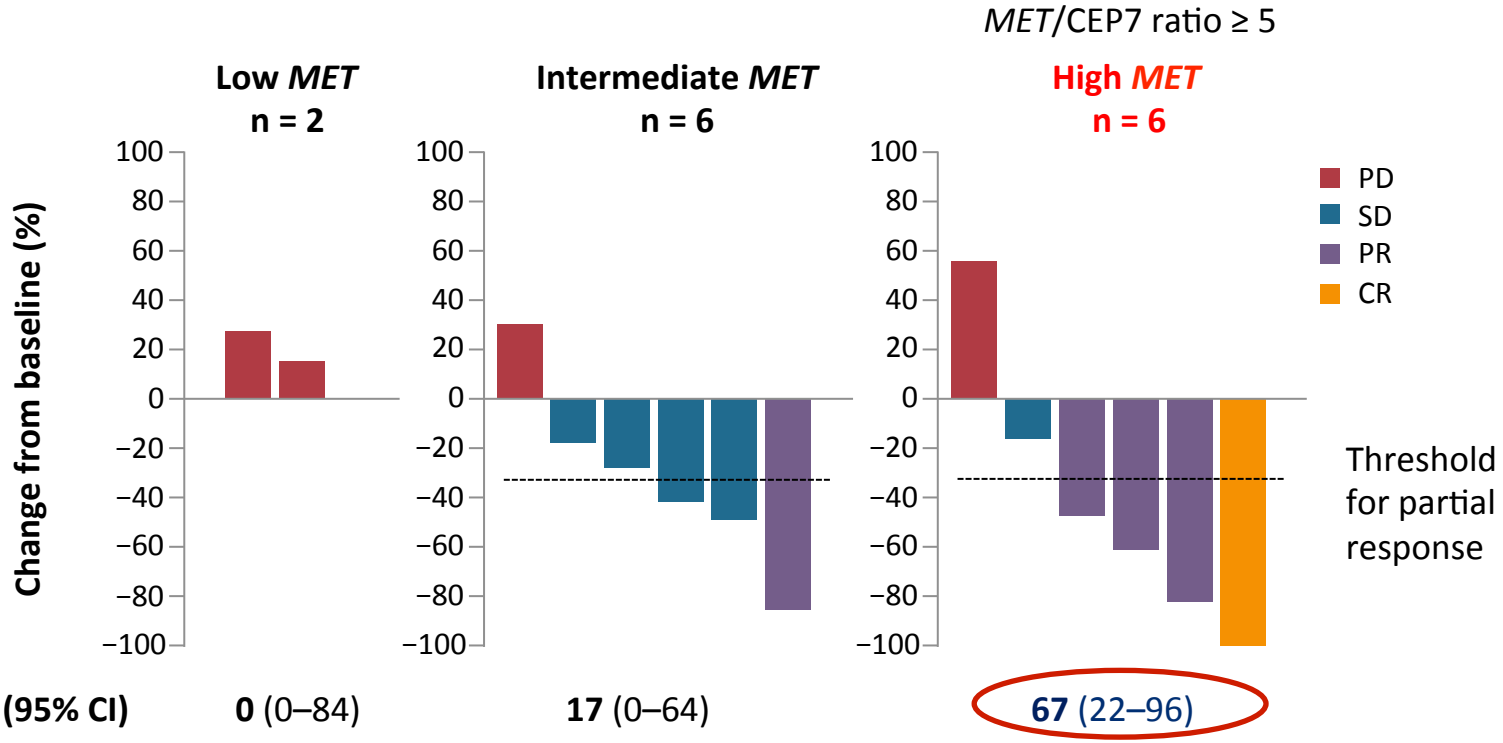
- Implicated in tumour cell migration, invasion, proliferation, and angiogenesis
- Mechanisms of MET activation
  - Amplification, point mutations, deletions
- **MET amplification**
  - poor prognosis in NSCLC
  - resistance to EGFR TKI
  - 1–4% of lung NSCLC
- **MET exon 14 mutation**
  - 3–4% of nonsquamous NSCLCs
  - 20–30% of sarcomatoid lung carcinomas



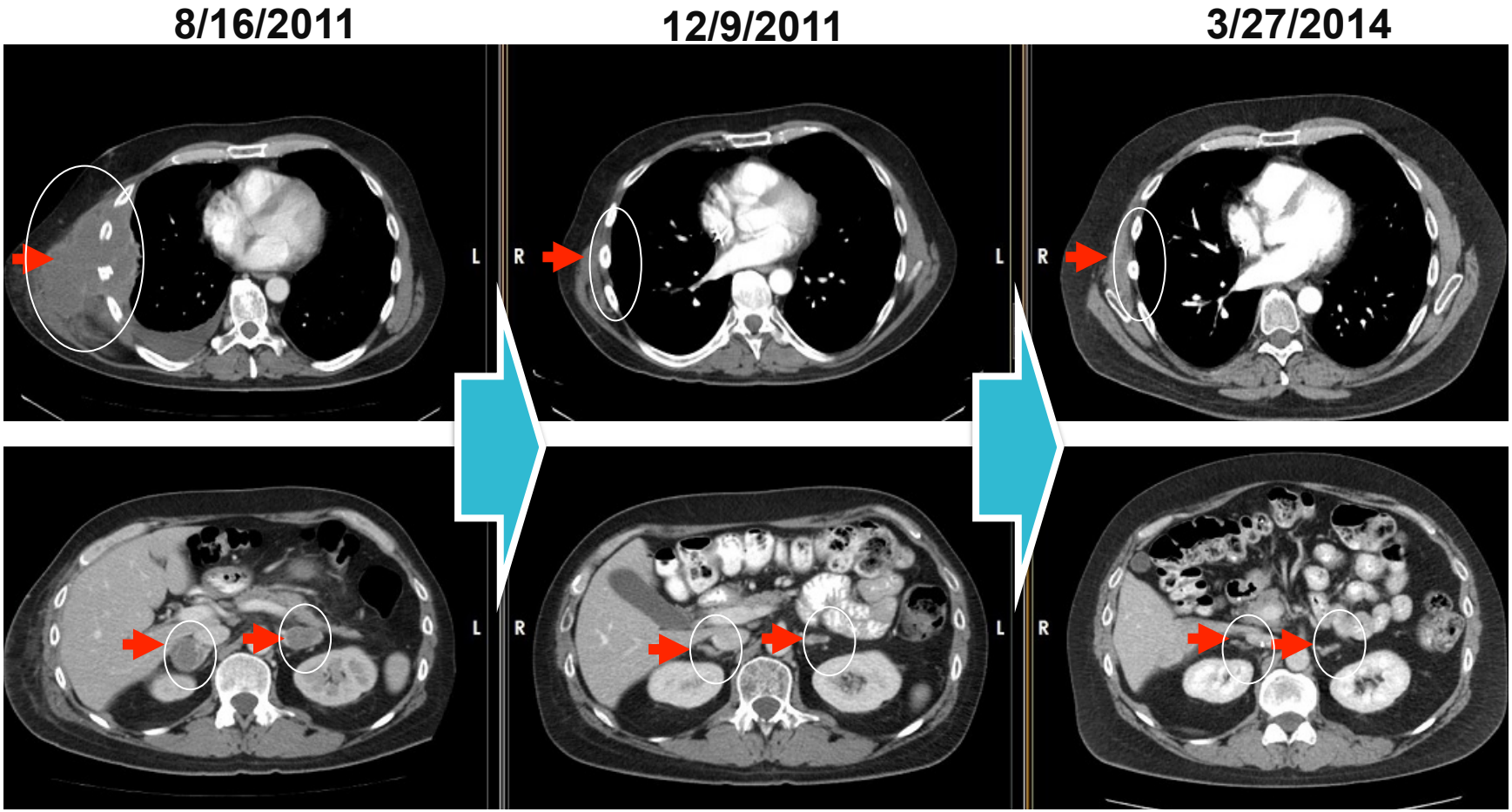
Ou SH, et al. J Thorac Oncol. 2011;6:942-6. Cancer Genome Atlas Research Network. Nature. 2014;511:543-50.

Tumour shrinkage seen with crizotinib treatment in intermediate and high *MET* cohorts

Best percent change from baseline in target tumour lesions by patient



Camidge DR, et al. ASCO 2014.
J Clin Oncol. 2014;32:5s (suppl; abstract 8001).



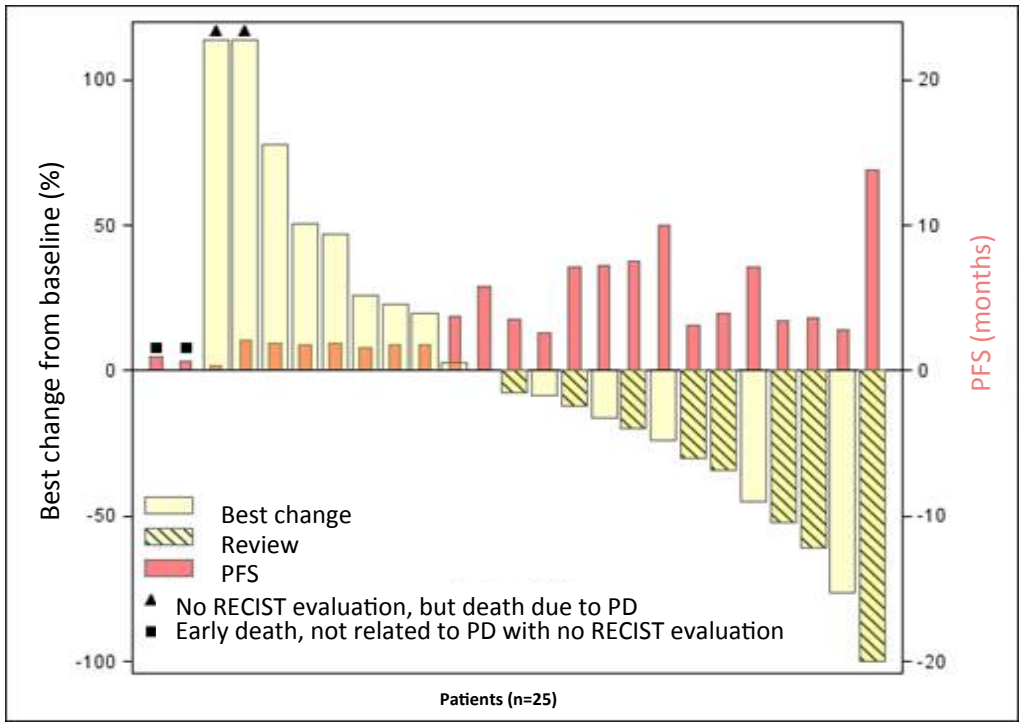
[a]MET/CEP7 ratio: >5

Duration of response: 31+ months

Images: G. Shapiro DFCI

The French national AcSé Program Results: MET_{AMP} NSCLC

Tumor shrinkage at best response



MET amplification

- IHC signal (≥ 2+) ➔ FISH (100 nuclei)
- Amplification threshold: > 6 copies
- GBM two cohorts high polysomy and true amplification (MET/CEP7 ratio)

Best response

ORR = 7/25

28 % [12% ; 49%]

DCR = 15/25

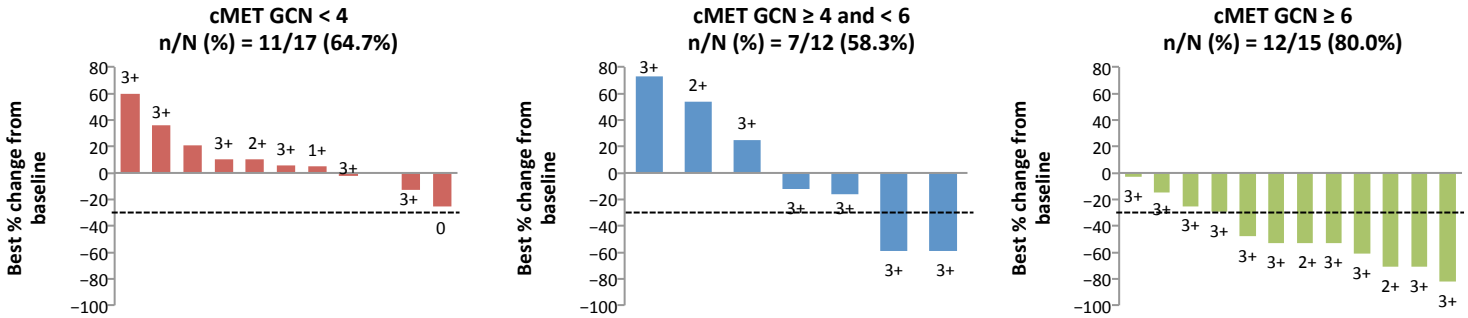
60 % [41%;79%]

No correlation observed between the number of MET copies and best response (p=0,10).

G.Vassal et al 2015

Tumour shrinkage observed with capmatinib treatment in intermediate and high *MET* cohorts

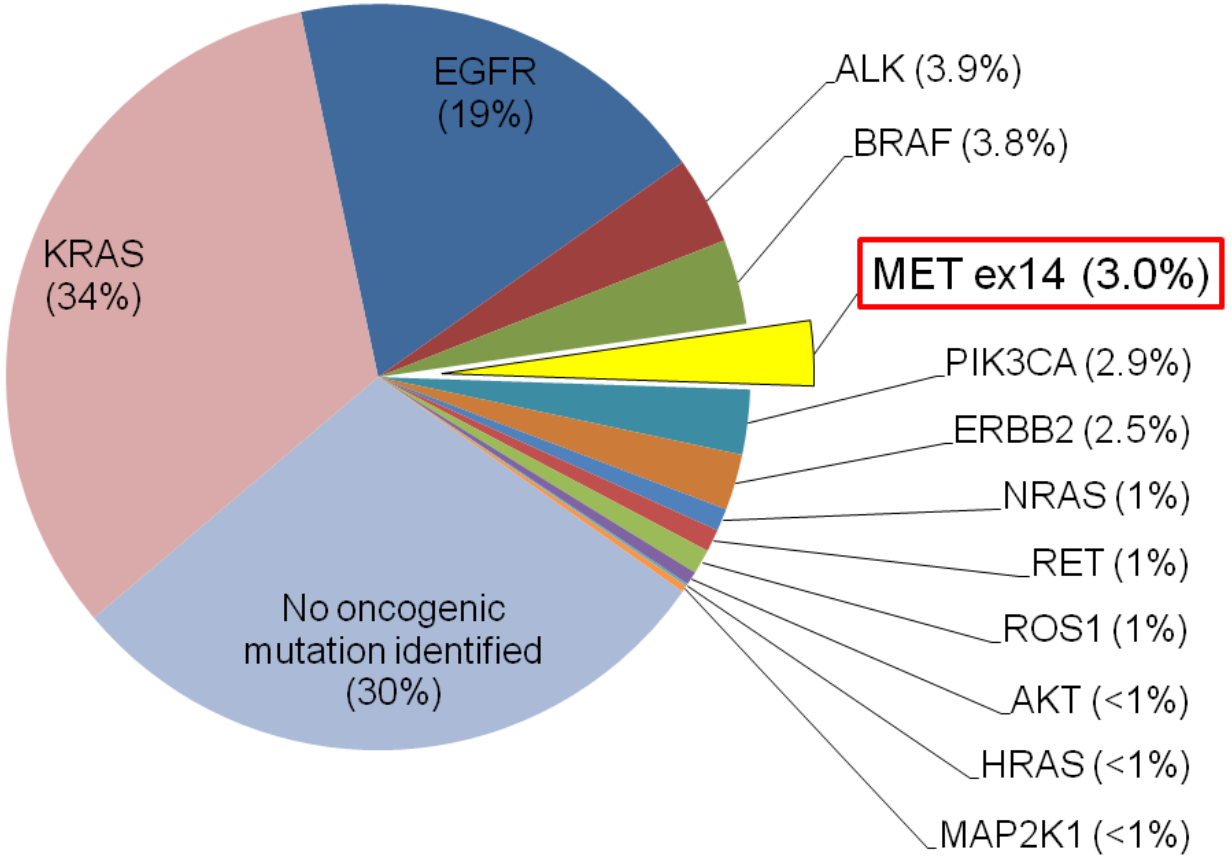
Best response n (%)	GCN < 4 (n = 17)	GCN ≥ 4 and < 6 (n = 12)	GCN ≥ 6 (n = 15)
CR	0	0	0
PR	**0**	**2 (17)**	**7 (47)**
SD	8 (47)	3 (25)	5 (33)
PD	5 (29)	3 (25)	2 (13)
Unknown	4 (24)	4 (33)	1 (7)
ORR 95% CI	**0**	**2 (17)** **2.1–48.4**	**7 (47)** **21.3–73.4**
DCR 95% CI	8 (47) 23.0–72.2	5 (42) 15.2–72.3	12 (80) 51.9–95.7



GCN, gene copy number.

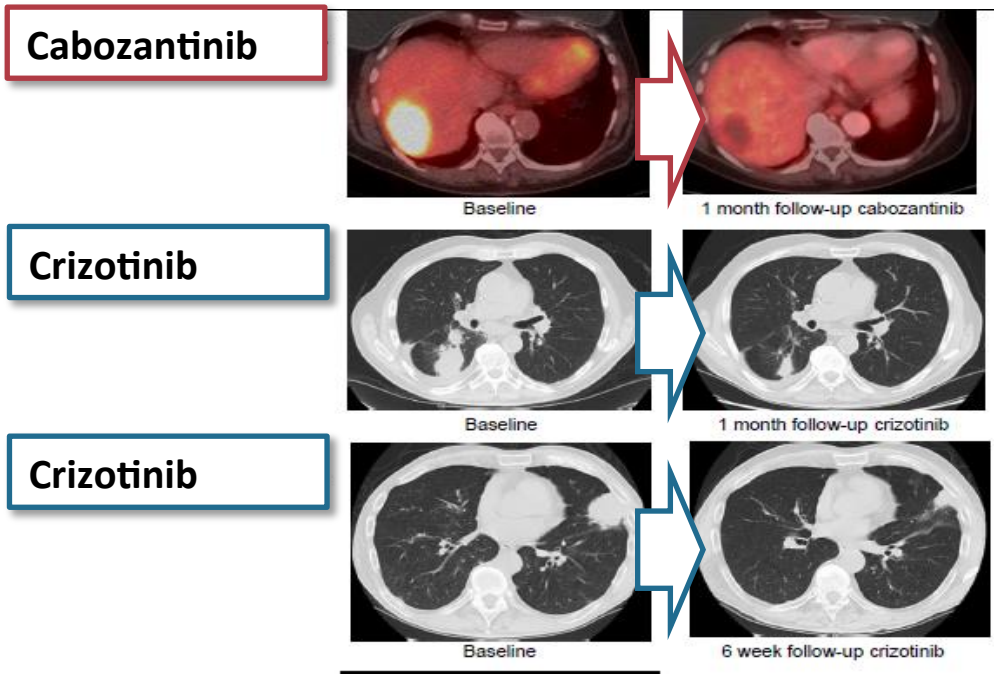
Schuler M, et al. ASCO 2016. J Clin Oncol. 2016;34 Suppl:abstract 9067.

Prevalence of *MET* Exon 14 Mutations in NSCLC



Awad MM, et al, *J Clin Oncol*. 2016 Jan 4.

MET exon 14-mutant NSCLC (3-4% nonsquamous)



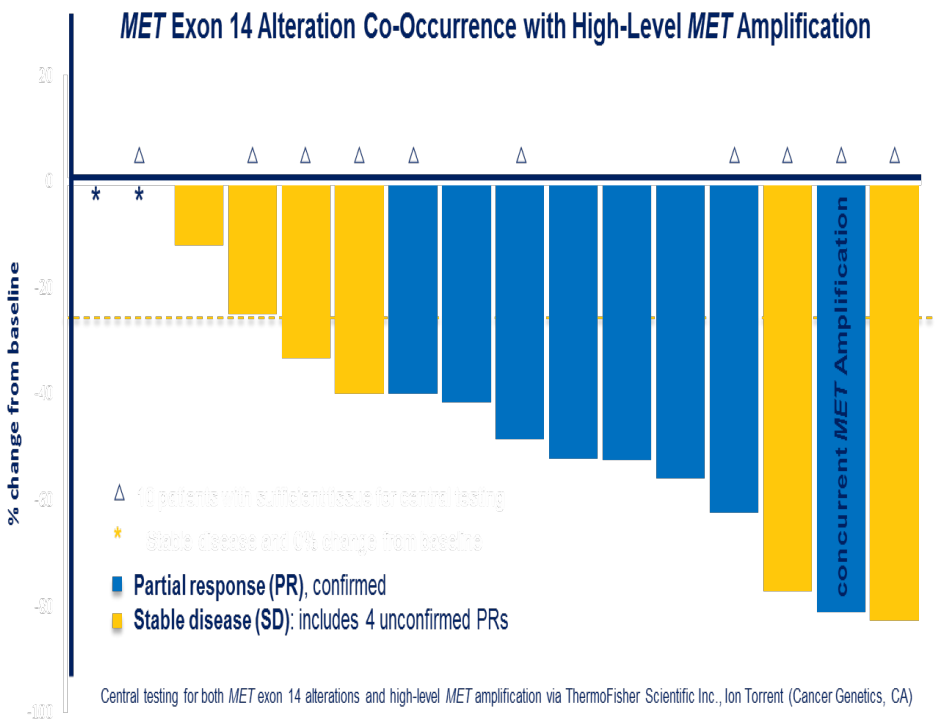
Antitumour activity of crizotinib (PROFILE 1001 study)

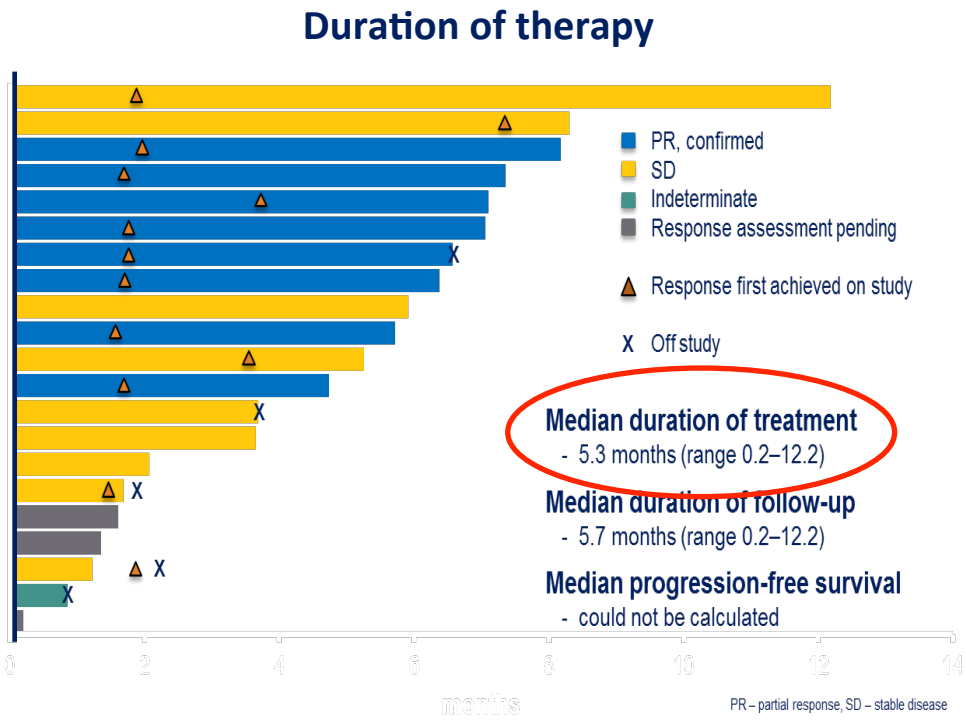
Response-evaluable population (n = 18)	
Best OR, n (%)	
CR	0
PR	8 (44%)
SD	9 (50%)
Unconfirmed CR/PR[a]	5 (28%)
PD	0
Indeterminate[b]	1 (6%)
ORR	**8 (44%) 95% CI 22–69**

a Of the 5 patients, 2 await confirmation, 3 cannot be confirmed. b This patient discontinued therapy in cycle 1; response imaging could not be performed but response-evaluable per protocol.

Drilon AE, et al. ASCO 2016. J Clin Oncol. 2016;34 Suppl:abstract 108. Frampton GM, et al. Cancer Discov. 2015;5:850-9. Paik PK, et al. Cancer Discov. 2015;5:842-9. Waqar SN, et al. J Thorac Oncol. 2015;10:e29-31.

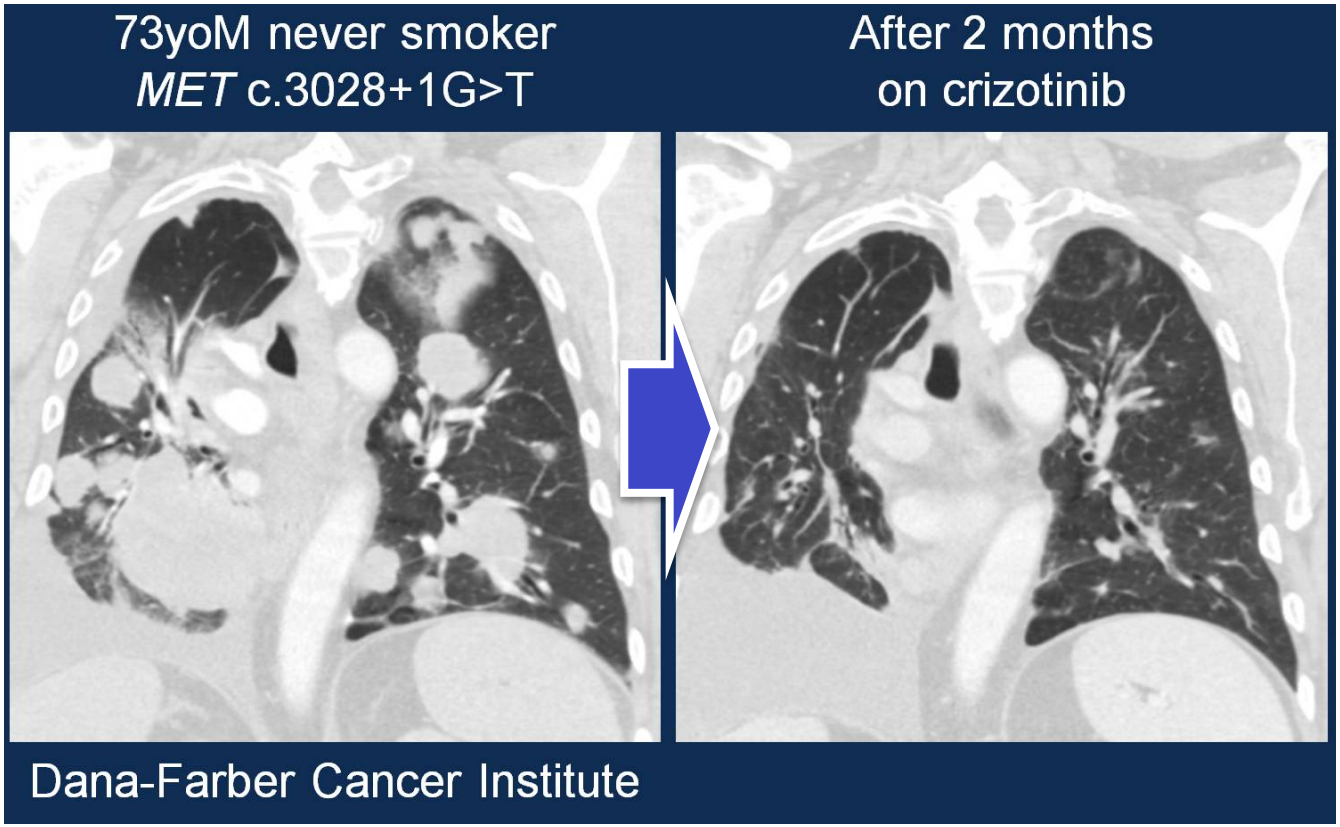
Antitumor Activity (PROFILE 1001 study)





A.Drilon et al, ASCO 2016

Impact of MET inhibitors on survival among pts with MET exon 14 mutant



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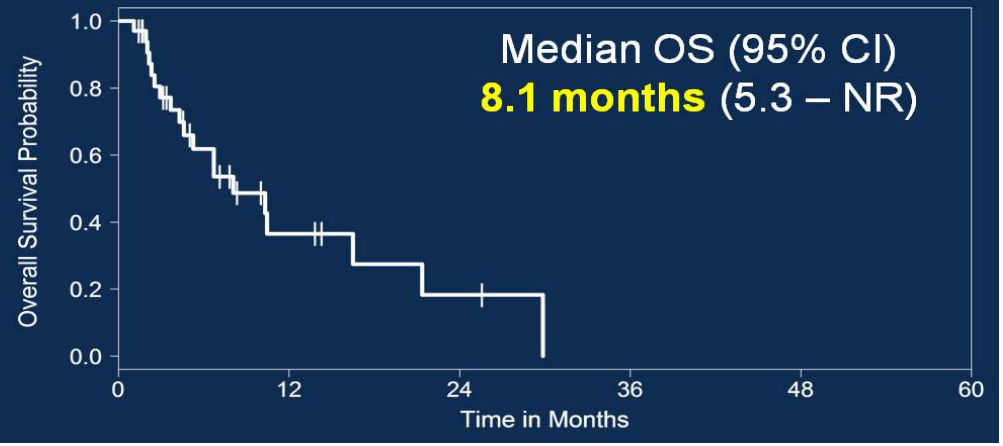
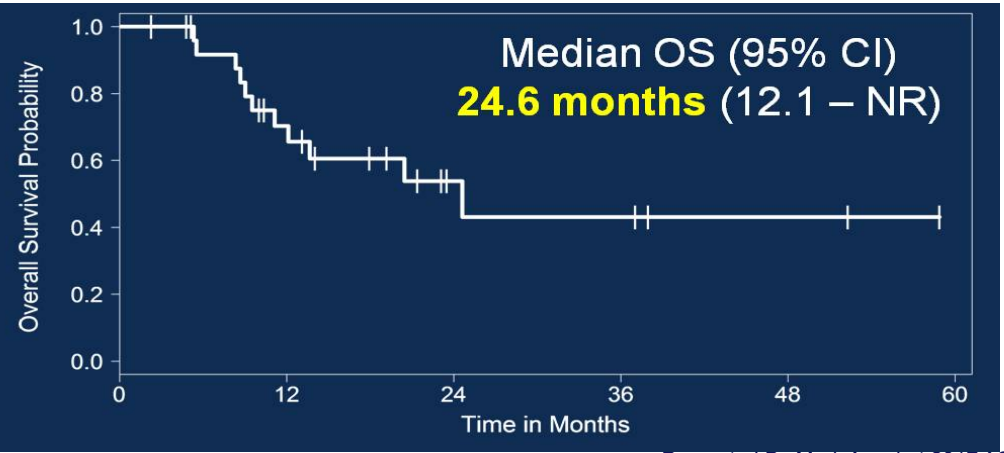
Overall survival date of stage IV (MET exon 14 mutant)

Never received
a MET TKI
N = 34



Received
a MET TKI
N = 27



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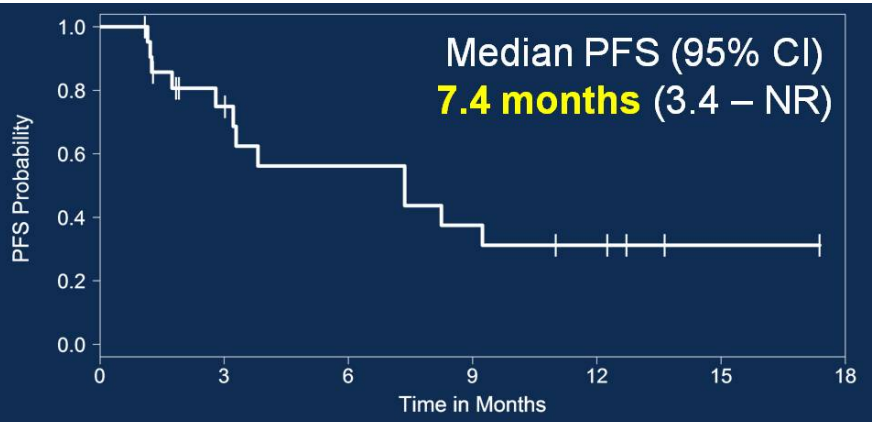
Outcomes on crizotinib (MET exon 14 mutant)

Progression-free survival
on crizotinib
(and no prior MET TKI)
N = 22



Overall survival
on crizotinib
(and no other MET TKI)

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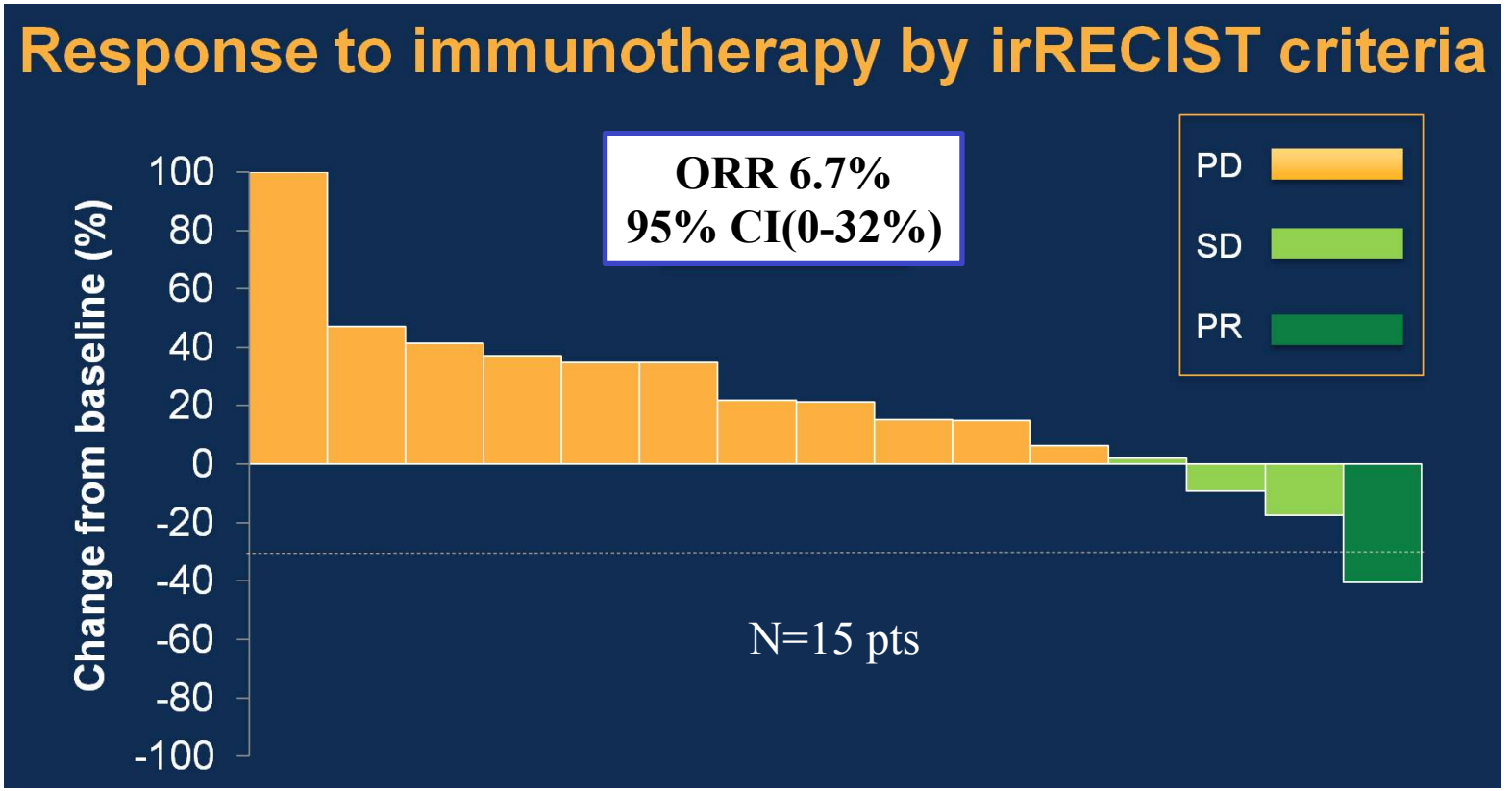
PD-L1 expression and response to immunotherapy in pts with MET exon 14 mutant (retrospective review)



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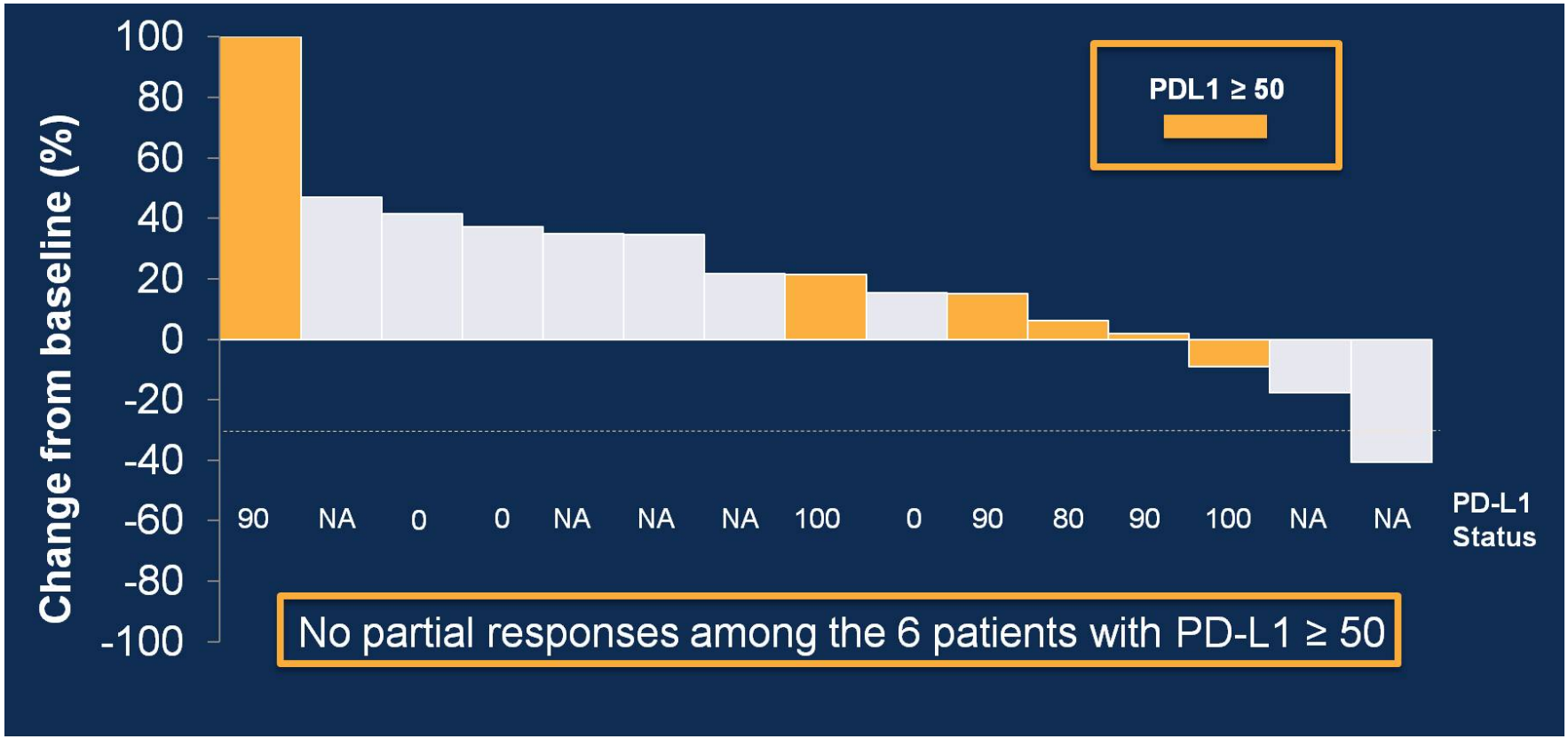
PD-L1 and response to IO (Cell signaling, clone E1L3N)



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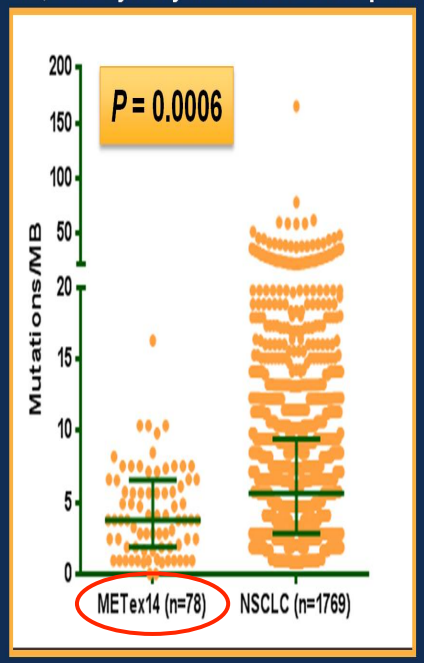
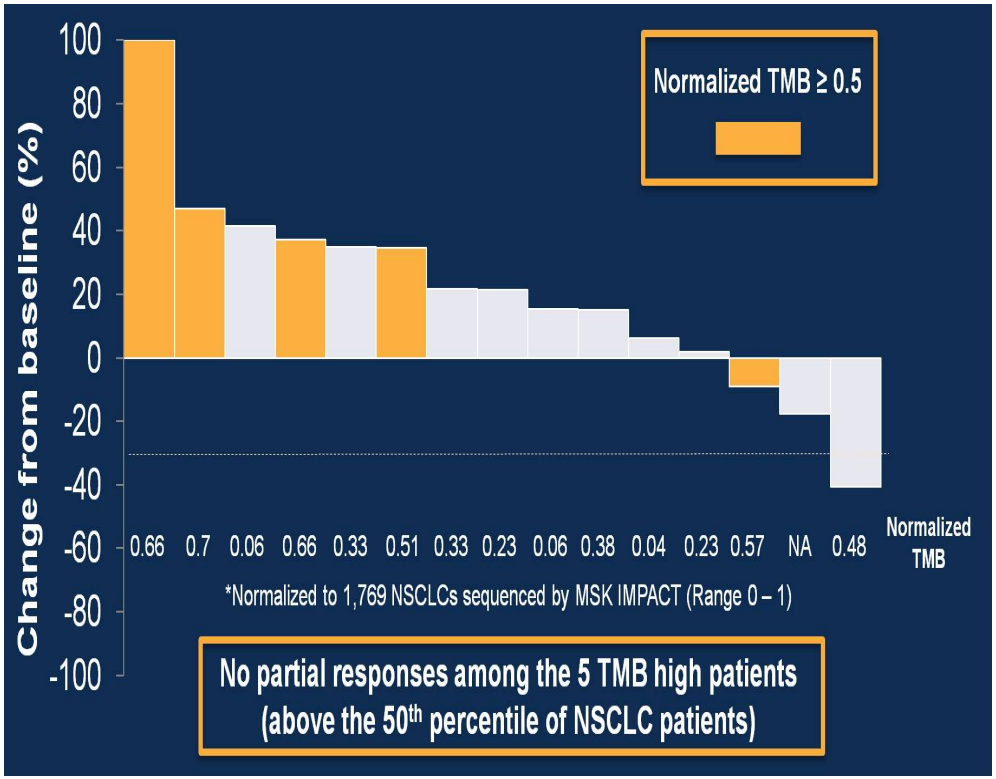
Tumor mutational burden (TMB)

- Number of somatic, non-synonymous mutations per megabase (MB)



	*MET*e14	NSCLC
n	78	1769
Median	3.8	5.7
Range	0 – 16	0 - 165

TMB is lower in patients with *MET* exon 14 altered NSCLCs



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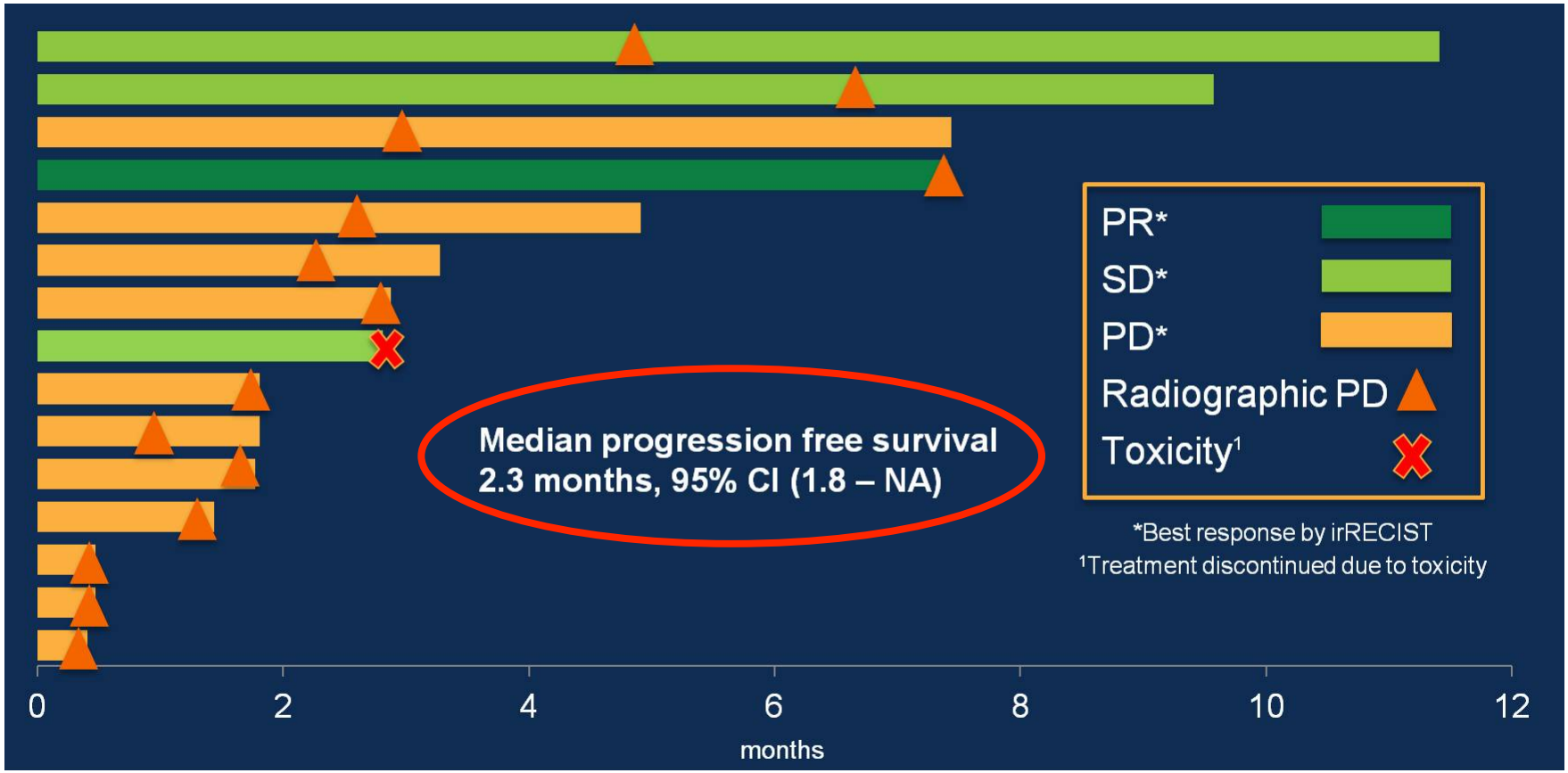
Duration on IO



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MET inhibition

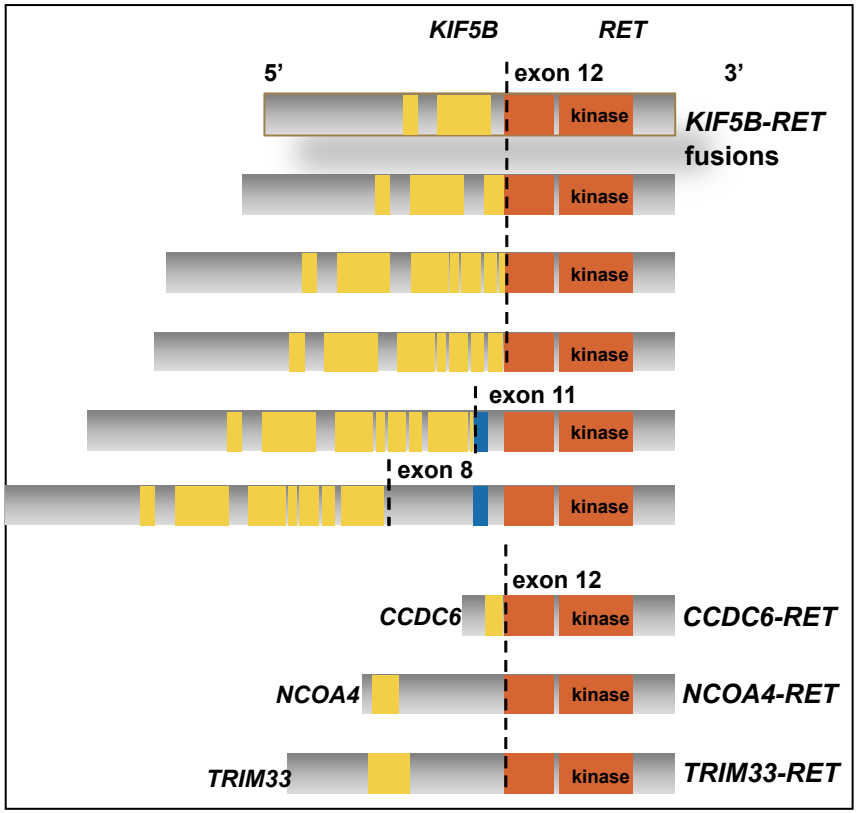
MET inhibitors	Pts nb	ORR (%)	Survival (months)
Crizotinib			
PROFILE 1001 amp Camidge ASCO 2014	12	33 (67% high Met)	-
PROFILE 1001 ex14 Drillon WCLC 2016, ASCO 2016	28	44	PFS=8
AcSé MET amp Moro-Sibilot WCLC 2015, Vassal ESMO 2015	25	28	PFS=3 ; SG=7
METROS amp/ex14 Landi WCLC 2016	10	20	-
Other MET/HGF inhibitors			
Onartuzumab Spigel JCO 2017	250	10	PFS=3 ; SG=9
Capmatinib Wu ASCO 2014	43	19	-
Capmatinib Schuler ASCO 2016	16	47 (GCN ≥ 6)	
Tivantinib+Erlotinib Scagliotti JCO 2015	211 MET+	10v7	PFS=4v2 ; SG=9v6
Cabozantinib+Erlotinib Neal Lancet Oncol 2016	72	14	PFS=5
Emibetuzumab+Erlotinib Rosen Clin Cancer Res 2016	23 (tumeurs solides)	(3 patients)	

Adapted from O.Gautschi

RET rearrangements

- **1–2% of unselected NSCLCs**
- Clinical features: young, never or former light cigarette smokers

- **Intact tyrosine kinase domain fused to an upstream gene partner**
  - most common: KIF5B
  - others: CCDC6, NCOA4, TRIM33, KIAA1468
- Result in ligand-independent dimerization and downstream growth pathway activation
- Oncogenic in vitro and in vivo
- **diagnosis**
  - FISH, DNA-based NGS, RNAseq (IHC not helpful)

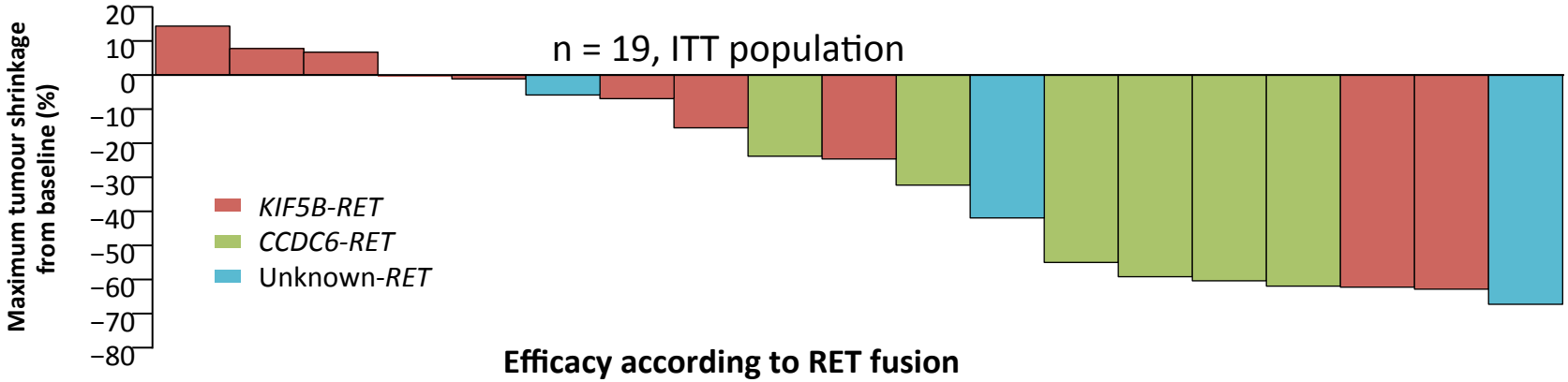


Drilon A, et al. Cancer Discov. 2013;3:630-5. Kohno T, et al. Nat Med. 2012;18:375-7. Lipson D, et al. Nat Med. 2012;18:382-4. Saito M, et al. Carcinogenesis. 2014;35:2452-6. Suehara Y, et al. Clin Cancer Res. 2012;18:6599-608. Takeuchi K, et al. Nat Med. 2012;18:378-81.

Multi-kinase inhibitors targeting RET activity

Compound	Tradename	Manufacturer	IC_{50} (nM) In vitro kinase	IC_{50} (nM) Cellular kinase	IC50 (nM) In vitro kinase RET V804M	Other targets
Regorafenib	Stivarga	Bayer	1.5	~10	NR	VEGFR1-3, BRAF, c-kit, PDGF-b
Levantinib	Lenvima	Eisai	1.5	48	NR	VEGFR1-3, FGFR1-3, c-kit, PDGFR
Alectinib	Alecensa	Roche/Chugai	4.8	?	53 V804L (32)	ALK (1.9 nM)
Cabozantinib	Cometriq	Exelixis	5.2	27-85	4094	VEGFR2, MET
Ponatinib	Iclusig	ARIAD	7	0.7-11	12	Bcr-abl, FGFR1-4
Sunitinib	Sutent	Pfizer	30	40-164	55	VEGFR, PDGFR, c-kit, Flt-3
Sorafenib	Nexaavar	Bayer	47	~20-50	12	RAF, VEGFR2-3, PDGFR, c-kit, Flt-3
Vandetanib	Capresia	AstraZeneca	100	NR	> 10,000	VEGFR, EGFR

Phase 2 study to evaluate efficacy and safety of vandetanib in *RET*-rearranged NSCLC



Efficacy according to RET fusion

	All (n = 19)	*KIF5B-RET* (n = 10)	*CCDC6-RET* (n = 6)	Unknown (n = 3)
ORR, % (95% CI)	**47** (24–71)	**20** (3–56)	**83** (36–99.6)	**67** (9–99)
DCR, % (95% CI)	90 (67–99)	90 (56–99.7)	100 (54–100)	67 (9–99)
Median PFS, mo (95% CI)	**4.7** (2.8–8.5)	**2.9** (1.1–15.7)	**8.3** (4.7–8.5)	**4.7** (1.0–10.9)
1-year OS, % (95% CI)	47 (21–69)	42(11–71)	67 (5–95)	33 (1–77)

ITT, intention-to-treat.

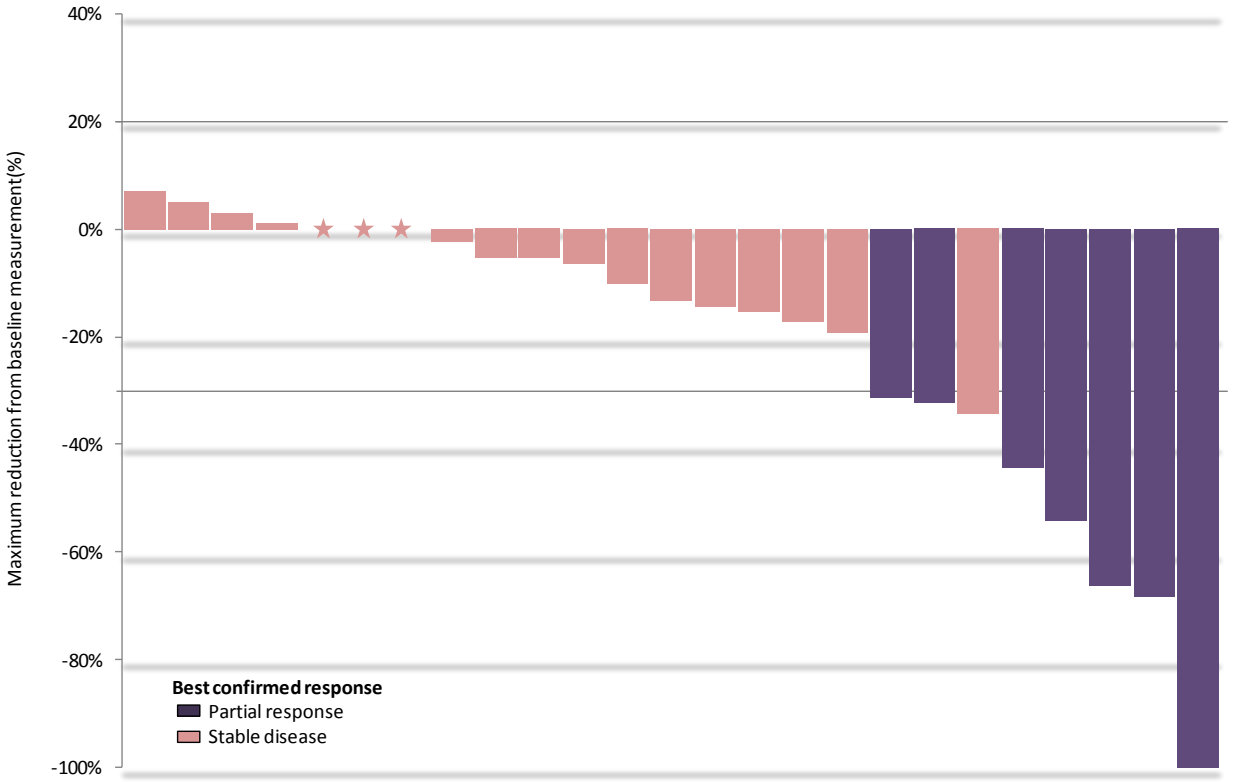
Seto T, et al. ASCO 2016. J Clin Oncol. 2016;34 Suppl:abstract 9012.

A Phase 2 Study of Cabozantinib for Patients with Advanced *RET*-Rearranged Lung Cancers

Primary endpoint met:
5 responses required to meet endpoint
7 responses observed

Best Response	% (n)
PR	28% (7/25)
SD	72% (18/25)
ORR 28%, 95% CI 12–49	

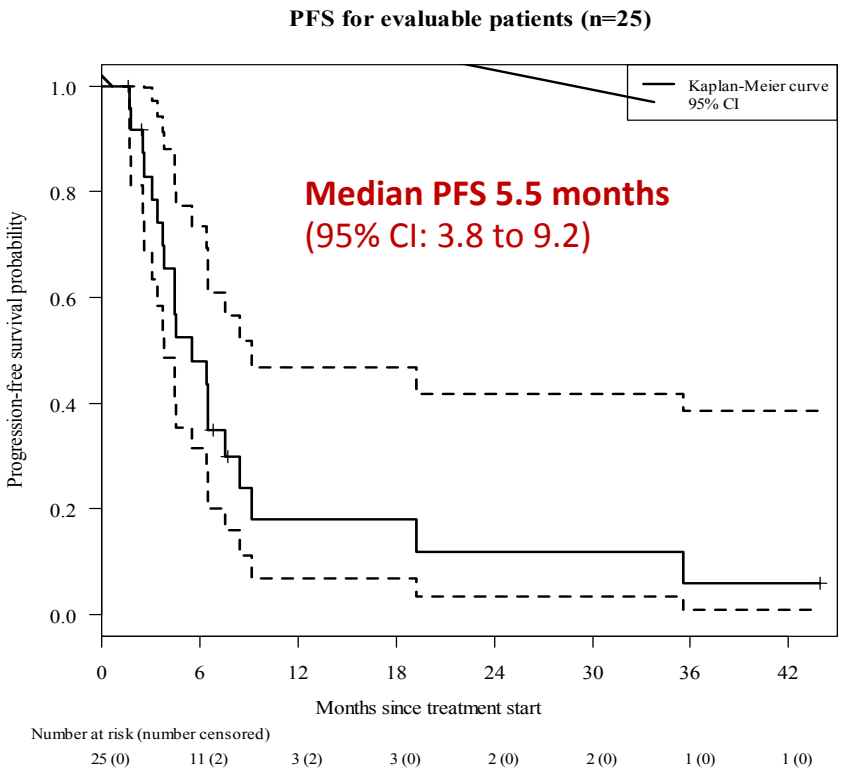
*no complete responses or primary progressive disease observed, RECIST v1.1

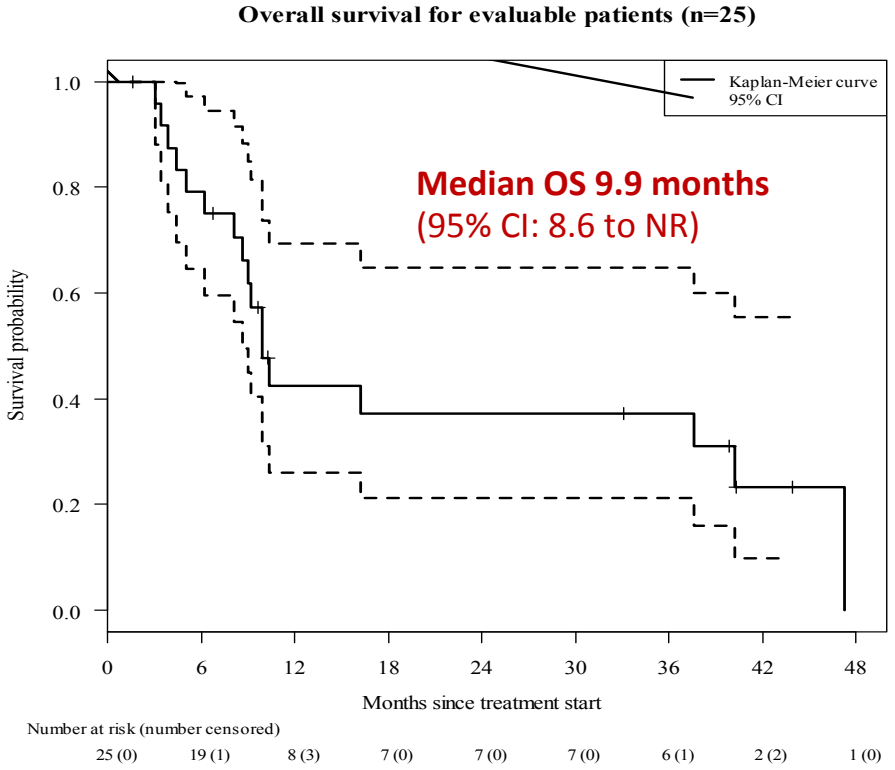


A.Drilon et al, IASLC 2016

Results: PFS and OS

Median duration of treatment
6.4 months (IQR: 2.5 to 8.3)

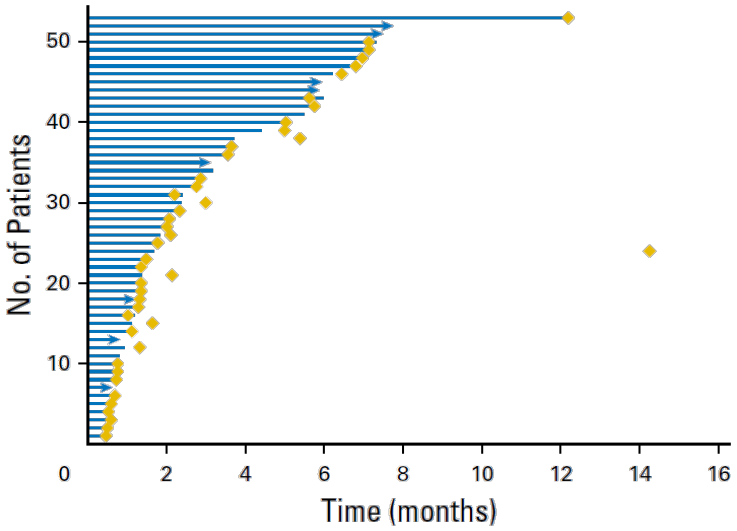


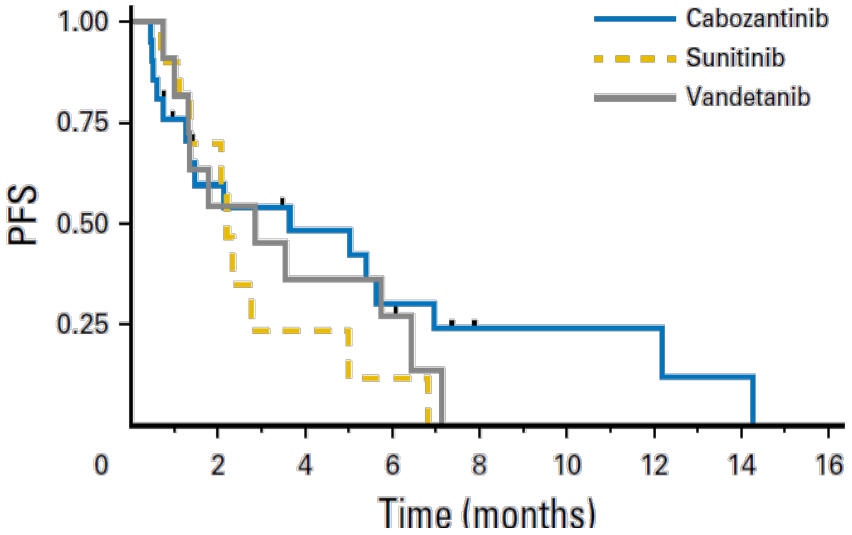


Median follow up time: 9.5 months (IQR: 5.0 to 27.5), updated data cutoff October 2016

A.Drilon et al, IASLC 2016

Global RET Registry





RET inhibitor	Best response (% ; 95 % CI)	Median DoT (range	Median PFS (95% CI)	Median OS (95% CI)
Cabozantinib	7 of 19 evaluable (37%; 16.3 to 61.6)	1.6 months (0.5 to 12.2 months)	3.6 months (1.3 to 7.0 months)	4.9 months (1.9 to 14.3 months)
Vandetanib	2 of 11 evaluable (18%; 2.3 to 51.8)	2.9 months (0.8 to 7.1 months)	2.9 months (1.0 to 6.4 months)	10.2 months (2.4 to NR)
Sunitinib	2 of 9 evaluable (22%; 2.8 to 60.0)	2.2 months (0.7 to 6.6 months)	2.2 months (0.7 to 5.0 months)	6.8 months (1.1 to NR)

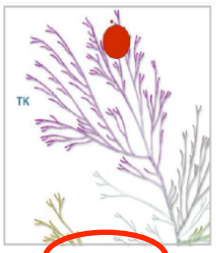
Gautschi et al, JCO 2017

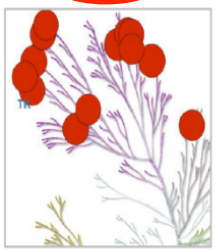
RET inhibition

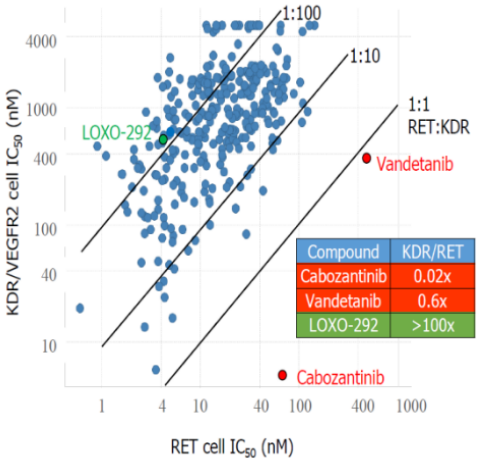
Inhibiteur du RET	Nb pts	ORR (%)	PFS (months)
Vandetanib Platt BMC Cancer 2015	3	0%	-
Vandetanib Yoh Lancet Respir Med 2017	19	47%	PFS=5
Vandetanib Lee Ann Oncol 2016	18	18%	PFS=5
Vandetanib Gautschi JCO 2017	11	18%	PFS=3
Lenvatinib Velcheti ESMO 2016	25	16%	PFS=7
Sunitinib Gautschi ICO 2017	9	22%	PFS=2
Cabozantinib Drillon Lancet Oncol 2016	26	18%	PFS=6
Cabozantinib Gautschi ICO 2017	19	37%	PFS=4
Alectinib Lim JTO 2016	4	50%	-
RX**DX-105** Li Clin Cancer Res 2016	(1 responder reported from an ongoing phase I trial)		

Adapted from O.Gautschi

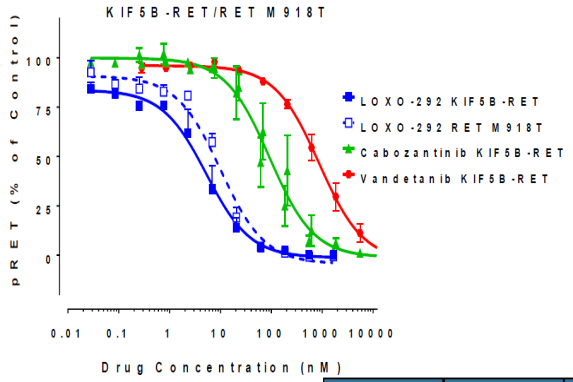
Novel agents more specific to target RET…

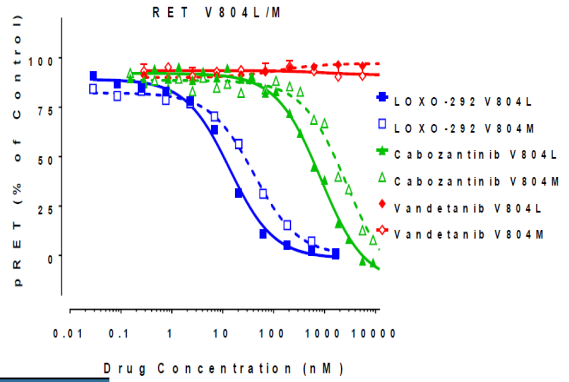






LOXO-292





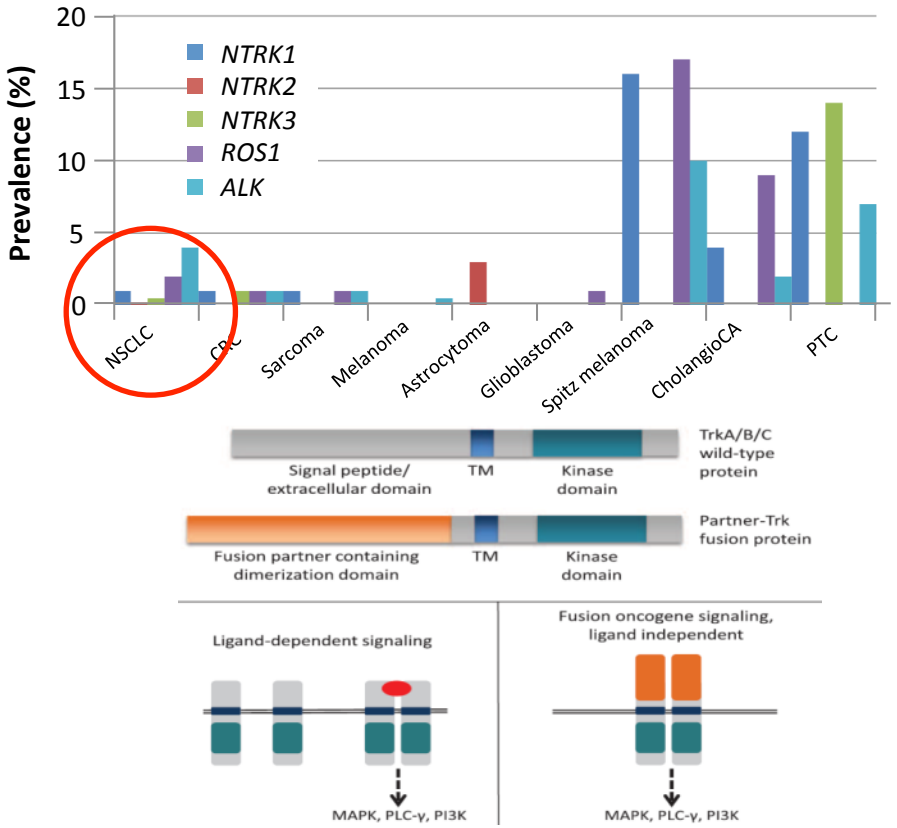
RET Mutation	Enzyme Fold vs. WT RET	Cellular Fold vs. WT RET
WT	1	1
V804M	2	8
V804L	2	3
A883F	4	ND
M918T	2	2
S891A	2	ND

LOXO-292 is currently being evaluated in a global, multi-center Phase 1 trial in patients with advanced solid tumors

Brandhuber et al, EORTC-NCI-AACR 2016

Trk prone to fusion proteins, similar to *ALK*, that induce constitutive activation of cell signalling

- **Oncogenic drivers across a variety of cancers**
  - upstream partner can provide dimerization domains and ligand-independent signalling
  - activation of downstream pathways
- **Detectable in the clinic**
  - FISH
  - RNAseq
  - DNA-based NGS
- **Select fusions are clinically actionable**
  - responses to targeted therapy can be dramatic and durable



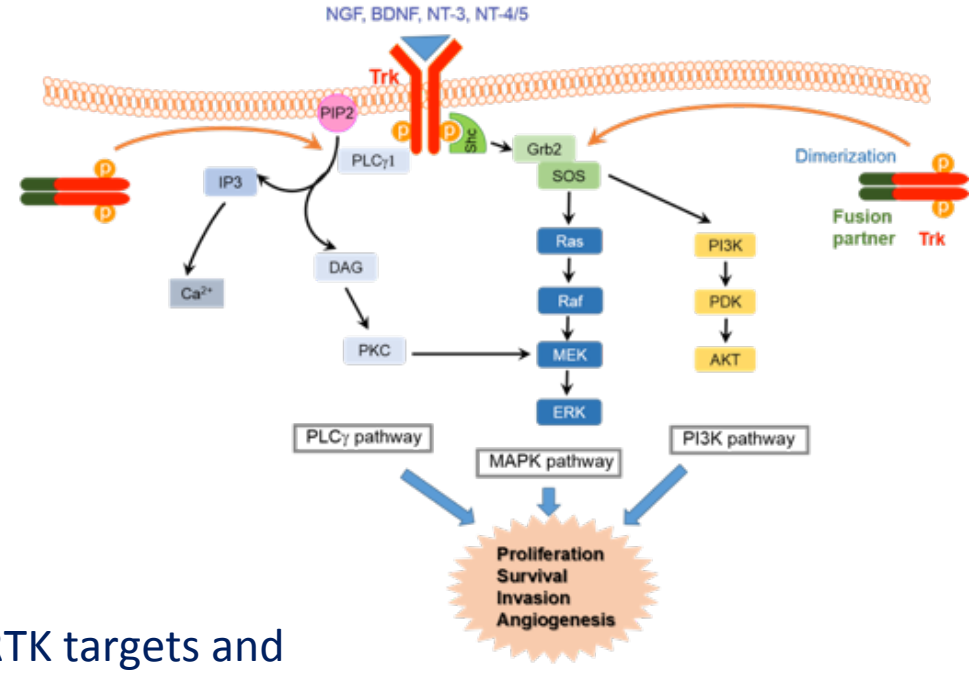
PTC, papillary thyroid cancer; CRC, colorectal cancer.

Drilon A, et al. AACR 2016:abstract CT007. Farago AF, et al. J Thorac Oncol. 2015;10:1670-4.

Entrectinib: a First-in-Class Trk Inhibitor

Target	TrkA	TrkB	TrkC	ROS1	ALK
IC50* (nM)	1.7	0.1	0.1	0.2	1.6

- Initially discovered by Nerviano Medical Sciences (NMS) as next-generation ALK inhibitor
- **Later discovered to have potent TrkA/B/C and ROS1 activity**
- Trk and ROS1 prone to fusion proteins, similar to ALK, that induce constitutive activation of cell signaling

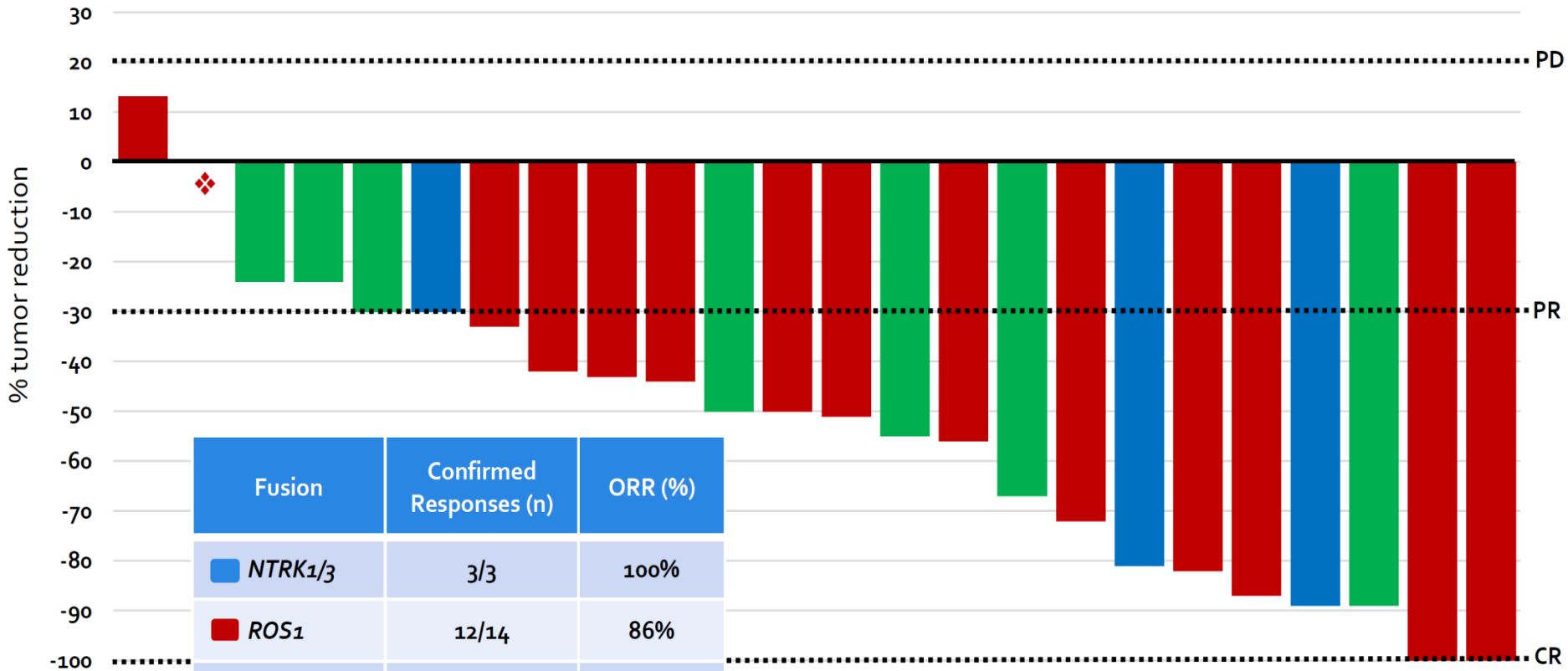


- Entrectinib demonstrates inhibition of its RTK targets and downstream effectors in the PLCγ, MAPK and PI3K/AKT pathways

* Biochemical kinase assay

Antitumor Activity (phase I studies)

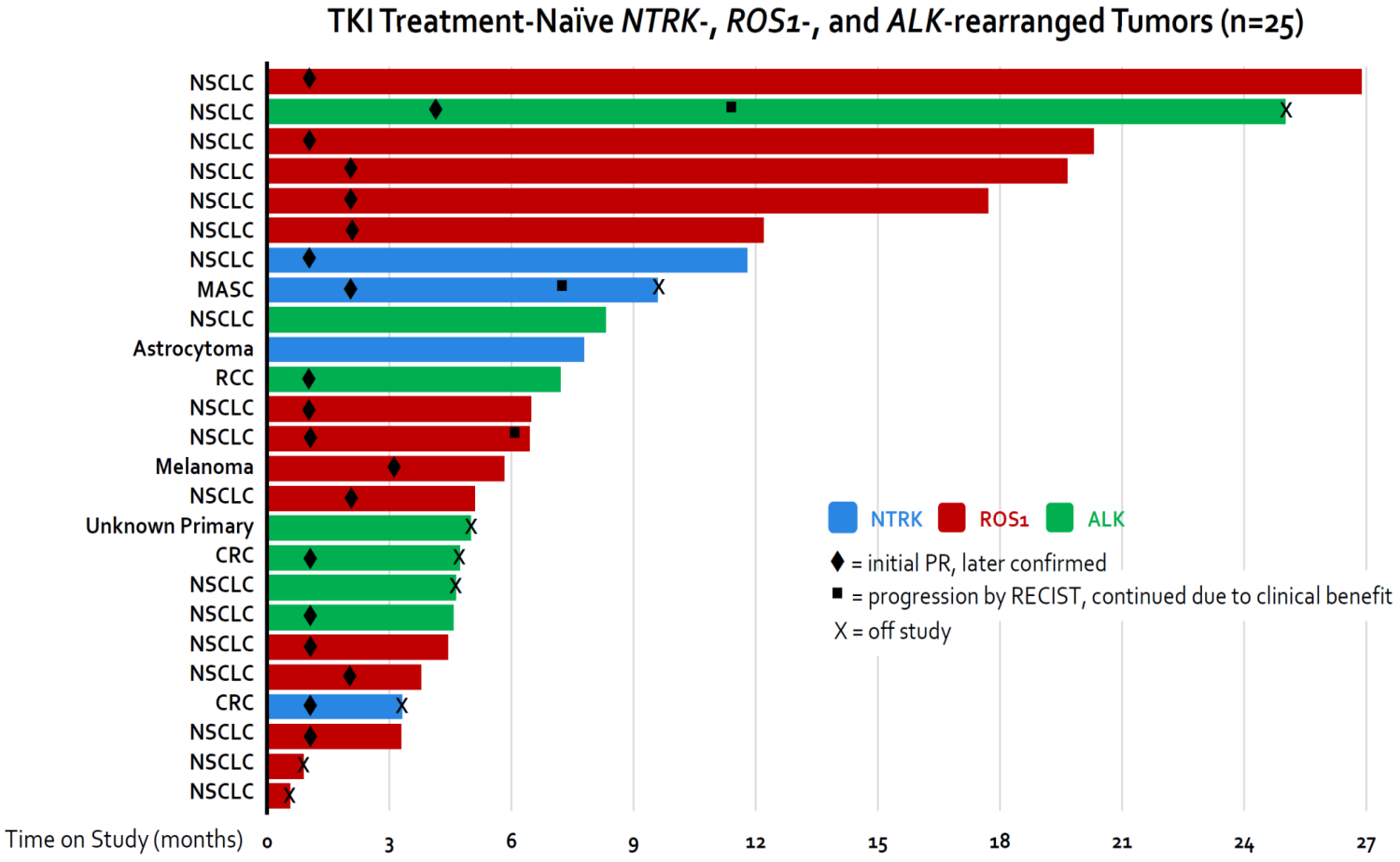
Best Response in TKI Treatment-Naïve *NTRK*-, *ROS1*-, and *ALK*-rearranged Tumors (n=24)



Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%
ALK	4/7	57%

Alexander Drilon et al, AACR 2016

Duration of Clinical Benefit



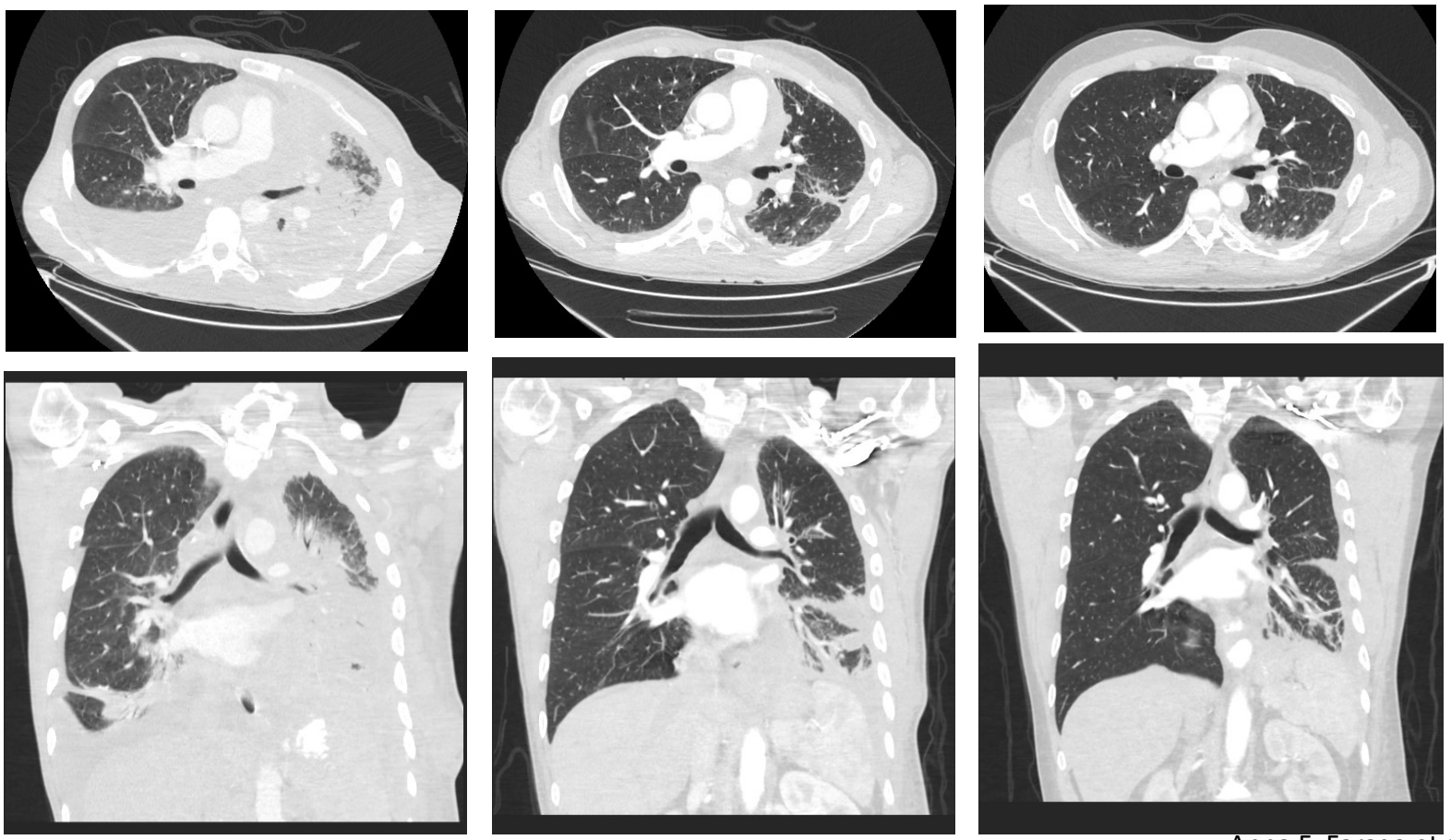
PTC: Papillar y thyroid cancer, CRC: colorectal cancer

Alexander Drilon et al, AACR 2016

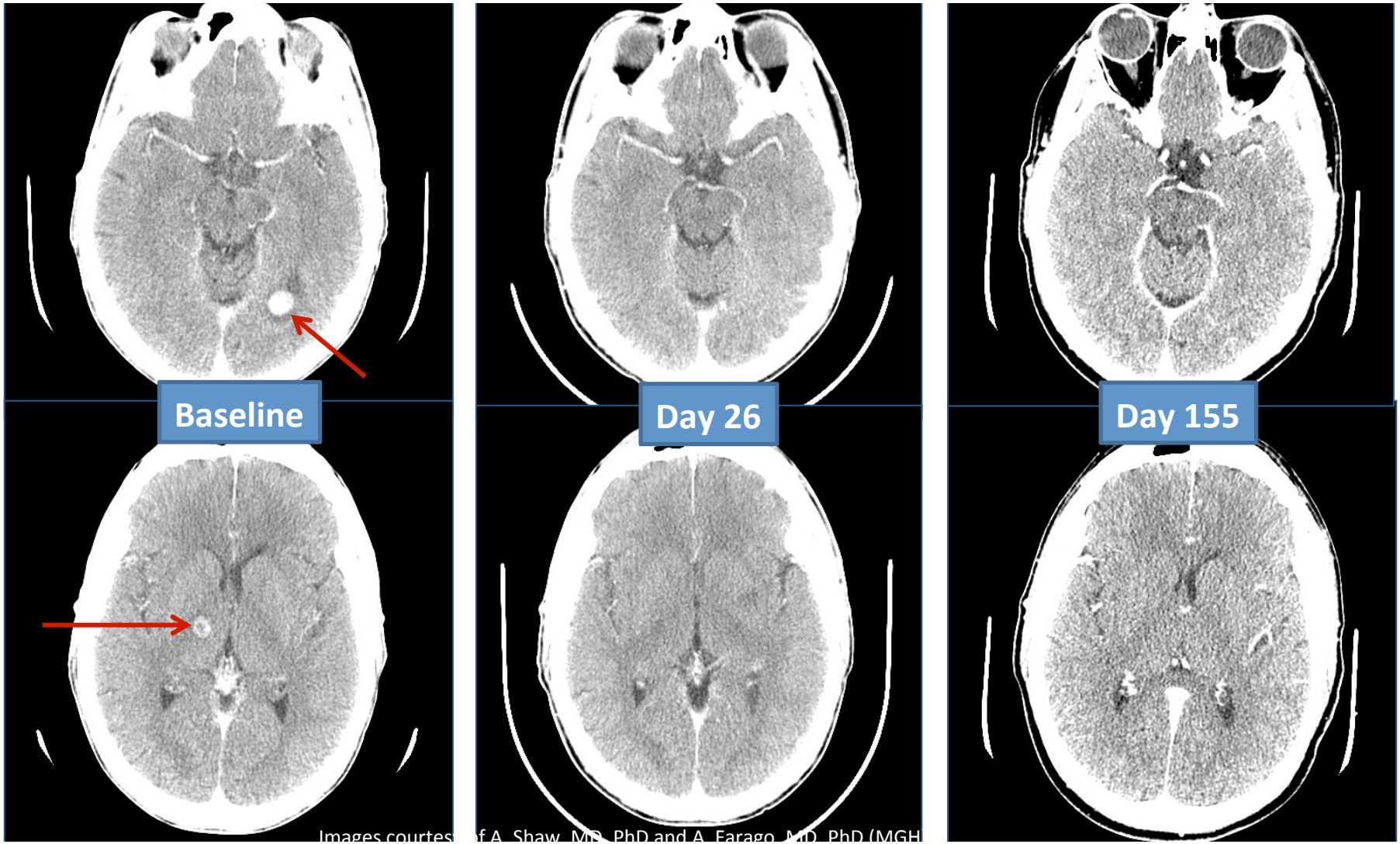
Baseline

Day 26: **- 47% response**

Day 155: **- 77% response**



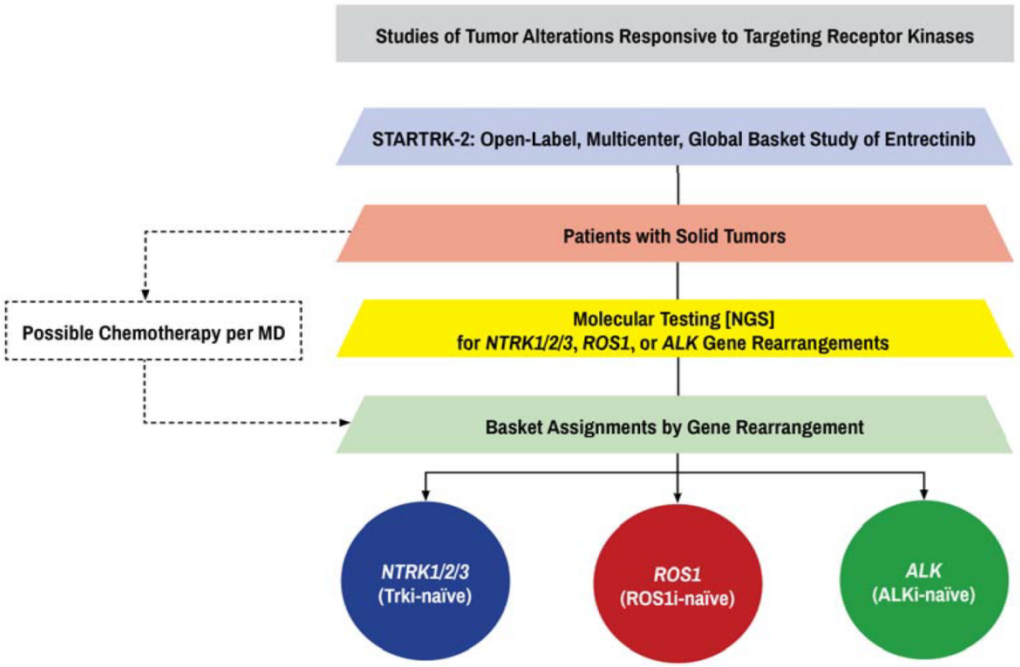
Anna F. Farago et al, JTO 2015


Baseline
Day 26
Day 155
Images courtes f A. Shaw, MD, PhD and A. Farago, MD, PhD (MGH

Current Directions

STARTRK-2

An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene



HER2 and NSCLC

- HER2 overexpression assessed by IHC associated with poor prognosis in NSCLC (adenocarcinoma)[1,2]
- In contrast to breast and gastric cancer, in NSCLC HER2 overexpression does not always co-occur with HER2 amplification[3-5]
- HER2 amplifications and HER2 mutations are generally mutually exclusive in NSCLC[6]

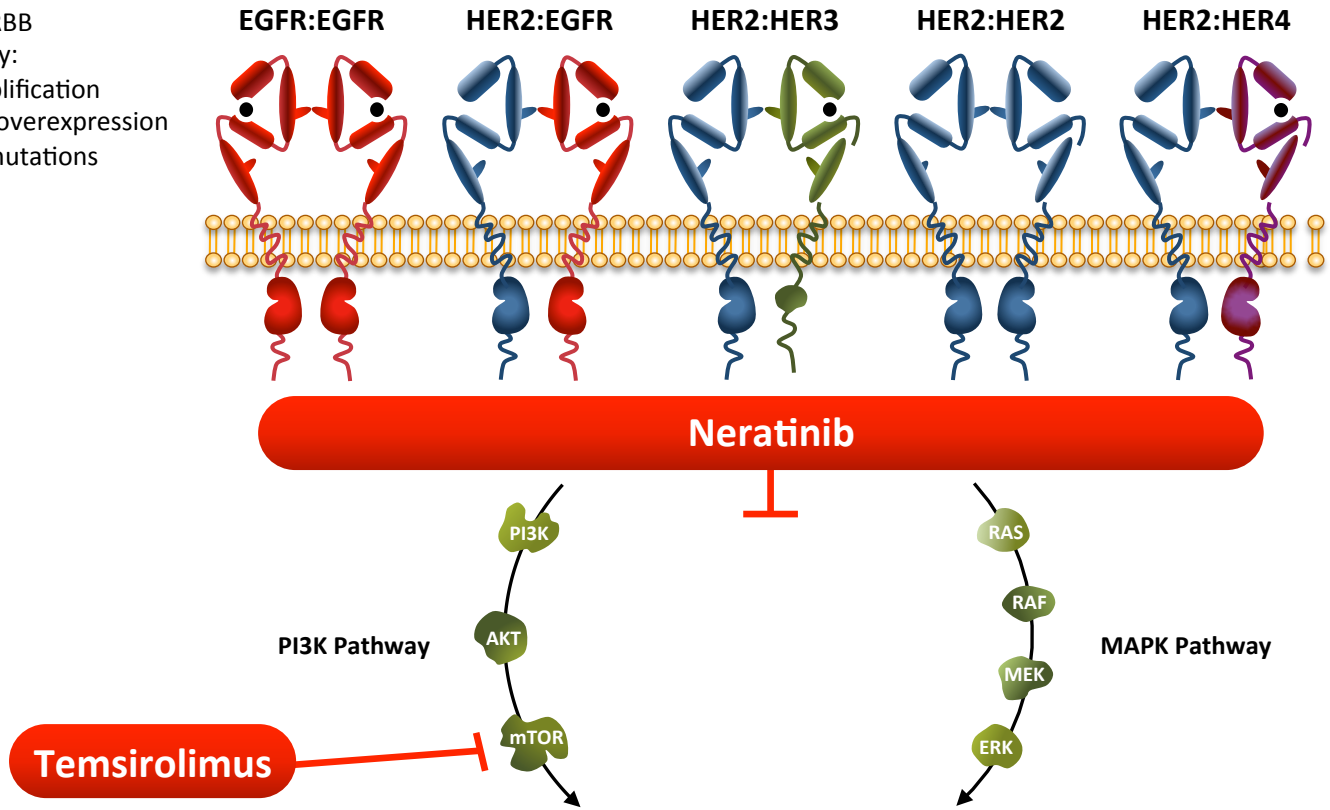
HER2 in NSCLC	Frequency
Overexpression (IHC 2+ and 3+)[1,2,7-9]	15–30%
Overexpression (IHC 3+ only)[2,8,9]	2–6%
Amplification (ISH)[1,8,10]	2–6%
Mutations[1,8,11-13]	1–5%

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small cell lung carcinoma.

1. Liu L, et al. *J Thorac Oncol* 2010. 2. Nakamura H, et al. *Cancer* 2005. 3. Bunn PA, et al. *Clin Cancer Res*. 2001. 4. Kern JA, et al. *Am J Respir Cell Mol Biol.* 1992. 5. Roche internal data on file. 6. Li BT, et al. *J Thorac Oncol.* 2016. 7. Bansal P, et al. *Front Oncol* 2016. 8. Heinmoller P, et al. *Clin Cancer Res* 2003. 9. Menard S, et al. *Ann Oncol* 2001. 10. Peters S, et al. *Transl Lung Cancer Res* 2014. 11. Rothschild SI. *Cancers* 2015. 12. Pellegrini C, et al. *Clin Cancer Res* 2003. 13. Buttitta F, et al. *Int J Cancer* 2006.

Aberrant ERBB activation by:

- Gene amplification
- Receptor overexpression
- Somatic mutations



- Cell cycle control and proliferation
- Cell survival and decreased apoptosis
- Cellular migration and metastasis
- Angiogenesis

ERBB receptor dimerization

Kinase activation

Downstream signal transduction

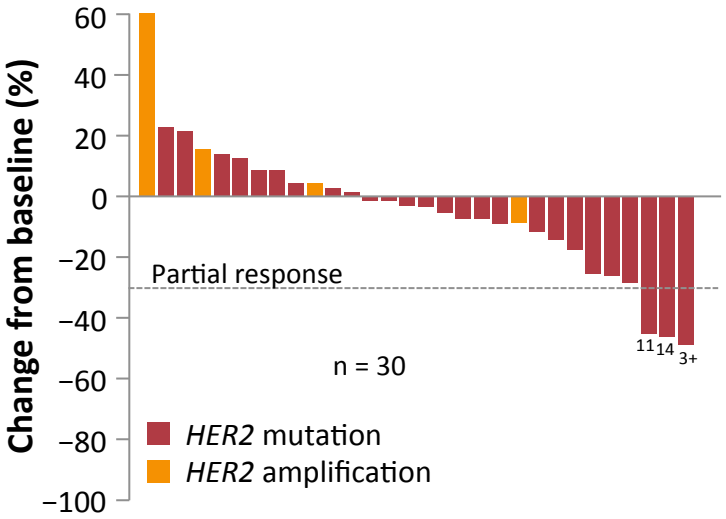
Tumor growth, survival and spread

B.Besse et al, ESMO 2014

Targeting *HER2* aberrations

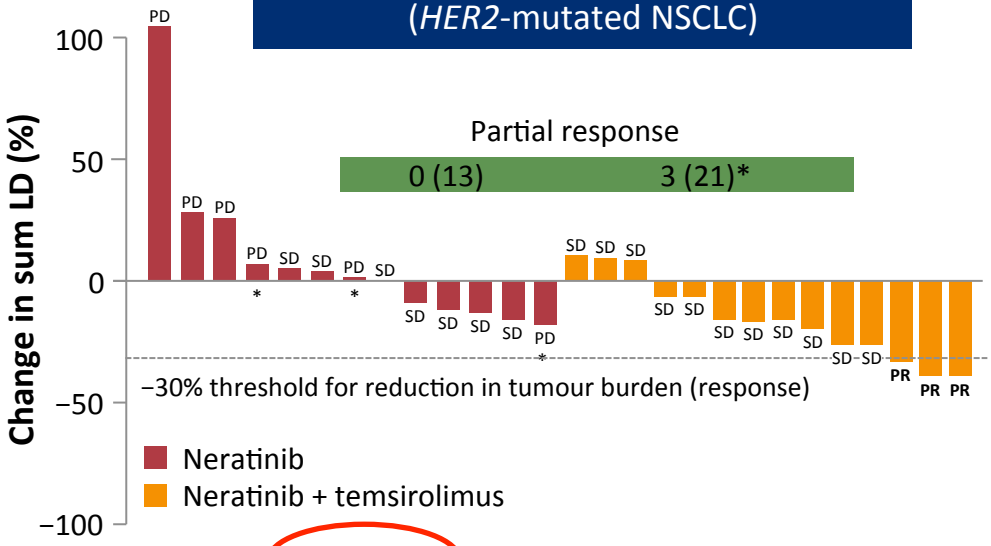
HER2 mutations in ~1–4% and *HER2* amplifications in 2–5%

Dacomitinib (pan-HER inhibitor)
(*HER2*-mutated or amplified NSCLC)



Only 3/26 of *HER2*-mutant patients had a response **(ORR 12%)**

Neratinib (pan-HER inhibitor)
± temsirolimus (mTOR inhibitor)
(*HER2*-mutated NSCLC)



21% ORR and mPFS of 4 months

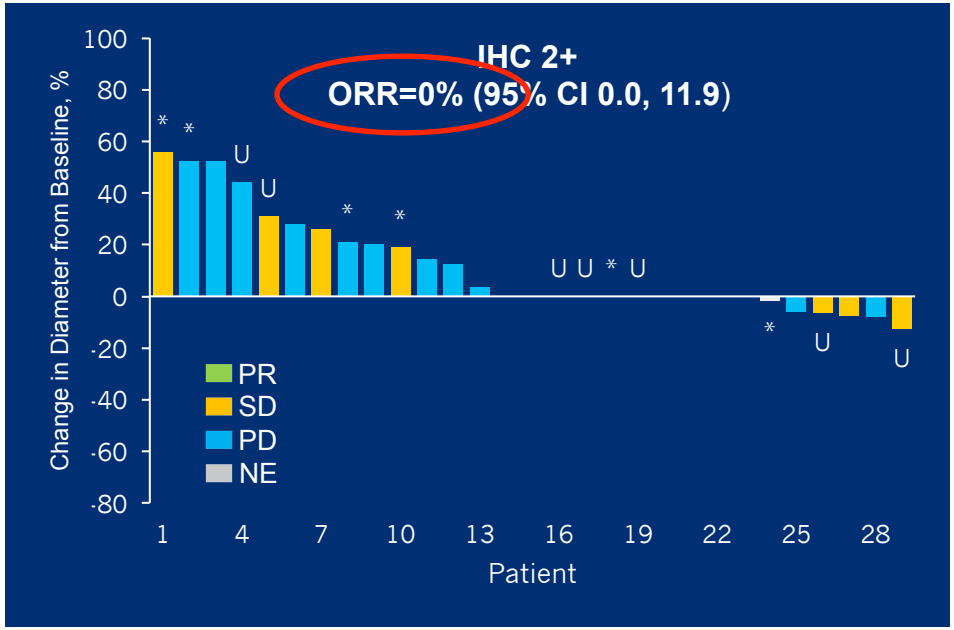
* Patients had < 20% increase in tumour burden, but were considered PD due to the appearance of new lesions

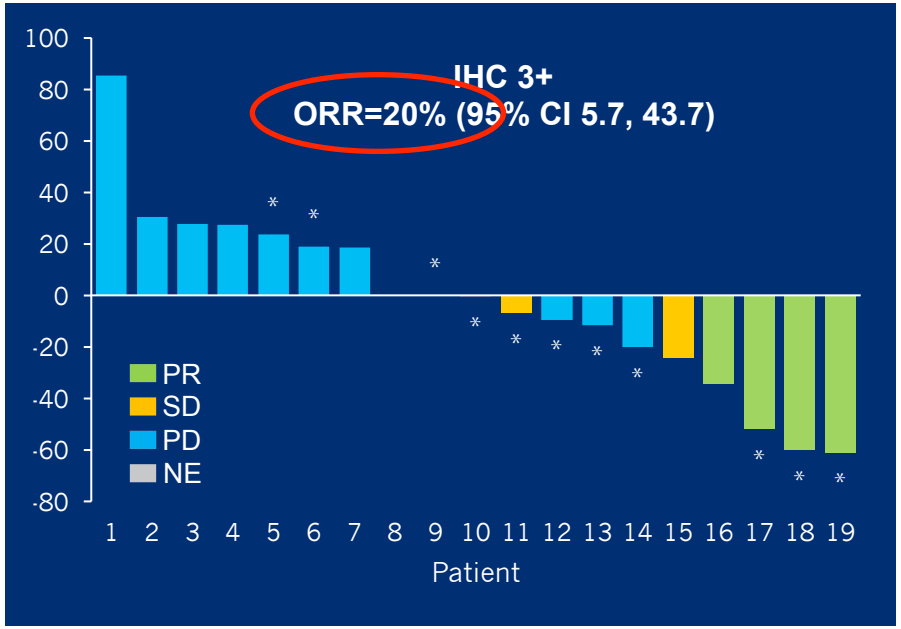
Kris MG, et al. Ann Oncol. 2015; 26:1421-7. Besse B, et al. Presented at ESMO 2014. Abstract LBA 39.

Trastuzumab Emtansine (T-DM1) in Patients with Previously Treated HER2-Overexpressing

Treatment Response

- Median duration of response: 7.3 months (95% CI 2.9–8.3 months)





*Indicates positive HER2 amplification; U indicates unknown HER2 amplification; All other patients' ISH status is negative

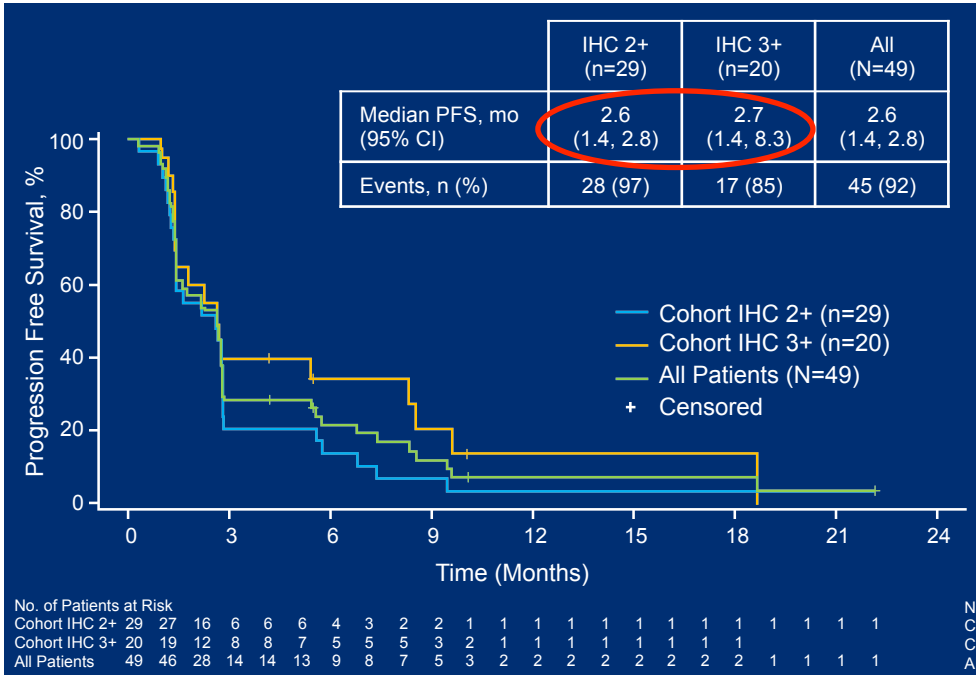
[a]One patient is not displayed due to erroneous tumor measurements recorded for cycle 7; this patient was determined to have a best response of SD (screening tumor size 64 mm, C7D1 tumor size 70 mm).
NE, not estimable/missing; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Treatment response as assessed by investigator.

Thomas Stinchcombe et al, ASCO 2017

Progression-Free Survival and Overall Survival

Progression-Free Survival[a]

	IHC 2+ (n=29)	IHC 3+ (n=20)	All (N=49)
Median PFS, mo (95% CI)	2.6 (1.4, 2.8)	2.7 (1.4, 8.3)	2.6 (1.4, 2.8)
Events, n (%)	28 (97)	17 (85)	45 (92)

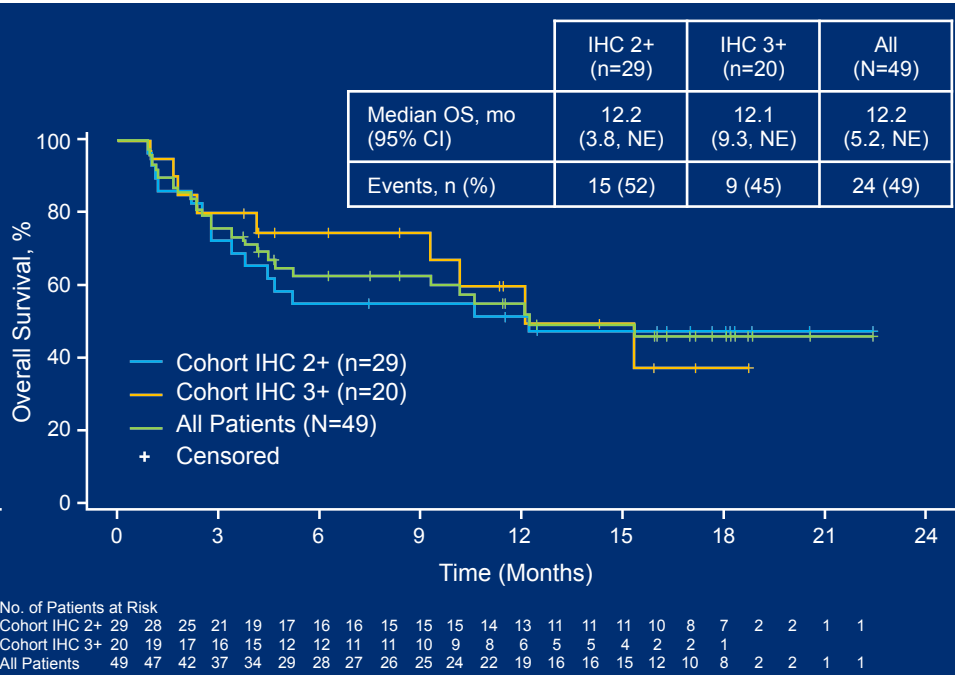


No. of Patients at Risk

Cohort IHC 2+	29	27	16	6	6	6	4	3	2	2	1	1	1	1	1	1	1	1	1	1	1	1
Cohort IHC 3+	20	19	12	8	8	7	5	5	5	3	2	1	1	1	1	1	1	1				
All Patients	49	46	28	14	14	13	9	8	7	5	3	2	2	2	2	2	2	2	1	1	1	1

Overall Survival

	IHC 2+ (n=29)	IHC 3+ (n=20)	All (N=49)
Median OS, mo (95% CI)	12.2 (3.8, NE)	12.1 (9.3, NE)	12.2 (5.2, NE)
Events, n (%)	15 (52)	9 (45)	24 (49)



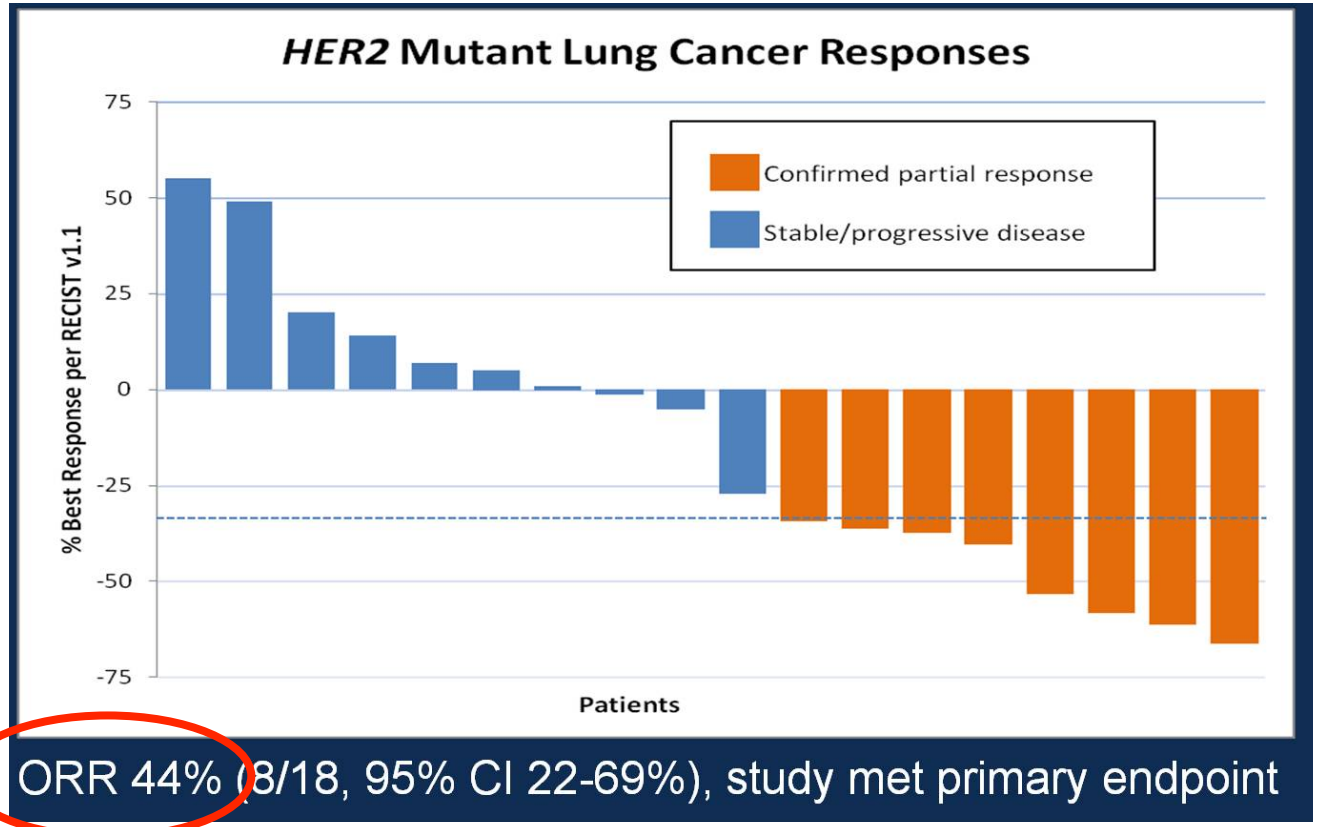
No. of Patients at Risk

Cohort IHC 2+	29	28	25	21	19	17	16	16	15	15	15	14	13	11	11	11	10	8	7	2	2	1	1
Cohort IHC 3+	20	19	17	16	15	12	12	11	11	10	9	8	6	5	5	4	2	2	1				
All Patients	49	47	42	37	34	29	28	27	26	25	24	22	19	16	16	15	12	10	8	2	2	1	1

[a]Progression-free survival as assessed by investigator.

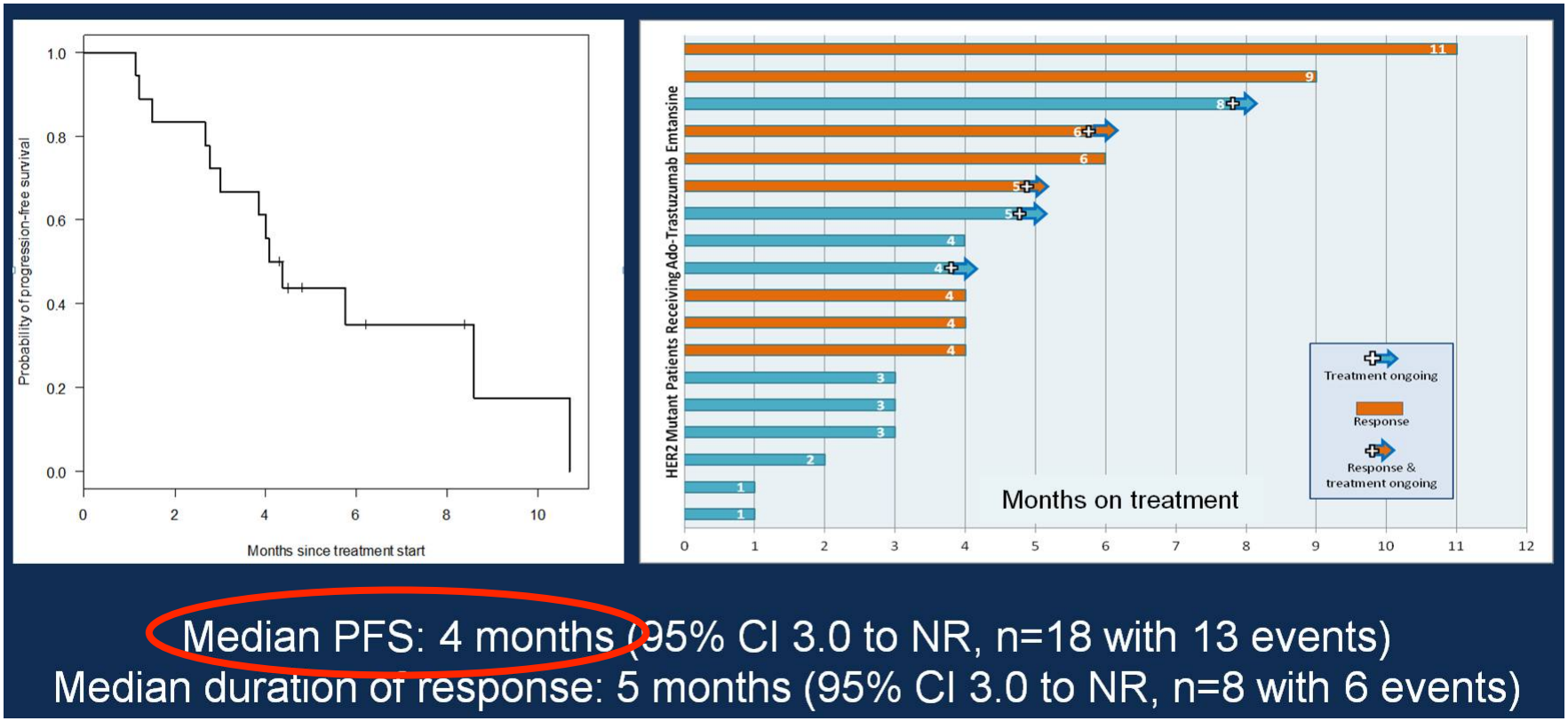
Thomas Stinchcombe et al, ASCO 2017

Ado-trastuzumab emtansine in pts with HER2 mutant lung cancer
(phase II basket trial)
Overall response rate (ORR)



Presented By Bob Li at 2017 ASCO Annual Meeting

Progression free survival



Median PFS: 4 months (95% CI 3.0 to NR, n=18 with 13 events)
Median duration of response: 5 months (95% CI 3.0 to NR, n=8 with 6 events)

Presented By Bob Li at 2017 ASCO Annual Meeting

HER2 mutant responders had low HER2 expression and no HER2 amplification

HER2 mutation NGS	FISH	IHC	Mass spectrometry HER2 expression (amol/ug)	Mass spectrometry HER3 expression (amol/ug)
Exon 20 A775_G776insYVMA	1.1 (2.7/2.5)	0	NA	NA
Exon 20 A775_G776insYVMA	1.4 (4.5/3.3)	1+	586 (Low)	279 (High)
Exon 20 A775_G776insYVMA	1.9 (5.6/2.9)	1+	548 (Low)	214 (High)
Exon 20 p.G778_P780dup	1.8(4.6/2.5)	2+	507 (Low)	0 (Negative)
Exon 20 G776_V777>VCV	NA	NA	NA	NA
Exon 20 p.G776delinsVC	1.6	0	NA	NA
Exon 17 p.V659E	1.1 (2.3/2.0)	2+	688 (Low)	199 (High)
Exon 8 p.S310F	4.1 (8.4/2.5)	2+	1495 (High)	0 (Negative)

Among responders tested by NantOmics mass spectrometry assay:

- HER2 proteins were not high in quantity
- HER3 overexpression possibly suggest active receptor dimerization

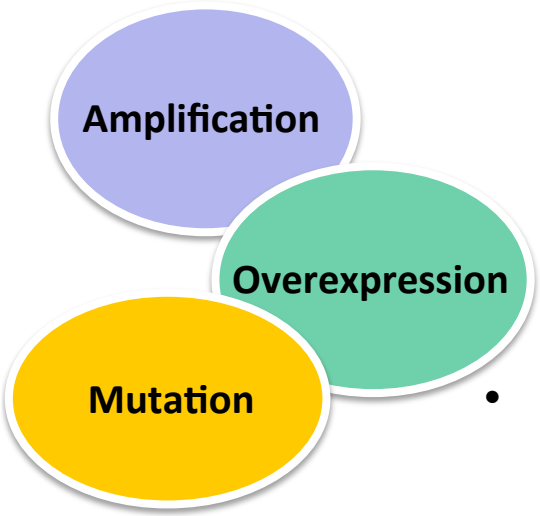
Presented By Bob Li at 2017 ASCO Annual Meeting

HER2 inhibition

Inhibiteur d'HER2	Nb pts	ORR (%)	PFS (months)
Trastuzumab + Chimiothérapie			
+ Taxane Krug cancer 2005	30/34	23/32%	SG=16/14
+ Variés (EUHER2) Mazières Ann Oncol 2016	58	51%	PFS=5 ; SG=13
TKIs			
+ Variés (EUHER2) Mazières Ann Oncol 2016	29	7%	PFS=3 ; SG=6
Afatinib De Grève Lung Cancer 2015	7	14%	-
Dacomitinib Kris Ann Oncol 2015	30	12%	SG=9
Neratinib±Temsirolimus Gandhi WCLC 2016	17/43	0/8%	PFS=3/4 ; SG=10/16
Pyrotinib Ren WCLC 2016	11	55%	PFS=6
Neratinib (SUMMIT) Hyman AACR 2017	26 (poumon)	4%	PFS=6
Afatinib (ETOP) Peters, personal communication 2017	8	Stop study at interim analysis	

Adapted from O.Gautschi

Do we have identified the right target ?



- **HER2 mutation** remains the most predictive factor for response to HER2-targeted therapy, including response to TDM-1

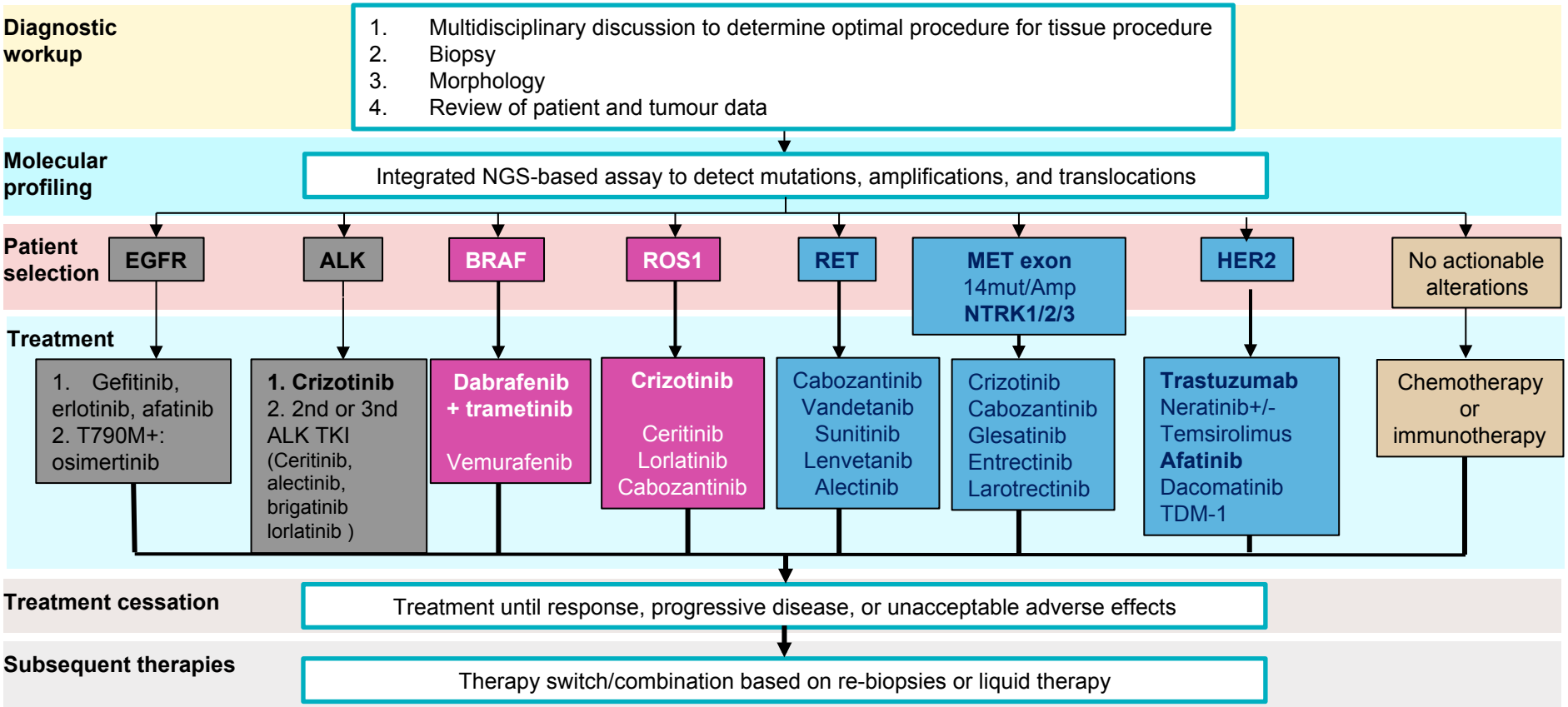
Overlap between amplification and mutation ??

- Amplification and mutation remain imperfect predictors of response to any HER2-targetd therapy

And other targetable mutations…

Gene	Alteration	Histology	Frequency (%)	Inhibitor (Phase 1 and 2)
BRAF	Mutation, fusion	ADC	1–3	Vemurafenib, dabrafenib, dabrafenib + trametinib
ROS1	Chromosomal rearrangement	ADC	1–2	Crizotinib (approved), ceritinib, cabozantinib, entrectinib, lorlatinib, DS-6051b
MET	Amplification, exon14 splicing	ADC	1–4 (amplifications) 2–4 (mutations)	Crizotinib, cabozantinib, tivantinib, capmatinib, volitinib, onartuzumab, glesatinib
RET	Fusion	ADC	1–2	Carbozantinib, sunitinib, sorafenib, lenvatinib, vandetanib, ponatinib, alectinib, apatinib
NTRK	Fusion	ADC	< 1	Entrectinib, LOXO-101, cabozantinib, DS-6051b, merestinib
HER2	Mutation (exon 20), amplification	ADC	1–4	Trastuzumab, neratinib + temsirolimus, afatinib, lapatinib, dacomitinib
KRAS	Mutation	ADC	15–25	Selumetinib, trametinib
PIK3CA	Mutation, amplification	SCC	15 (amplifications) 30–40 (mutations)	LY3023414, PQR309, AZD2014, GDC-0032, AZD8186, IPI-549, BYL719
FGFR1	Amplification	SCC	20	Lucitanib, nintedanib, dovitinib, AZD4547
FGFR2-3	Mutation	SCC	3	
FGFR1-3	Fusion	SCC	3.5	
DDR2	Mutation	SCC	4	Dasatinib

In summary….



Adapted from Thomas A, et al. Nat Rev Clin Oncol. 2015;12:511-26.

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

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THANK YOU

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Molecular Characteristics of Responding Patients

Histology	Adenocarcinoma	Adenocarcinoma	Non-squamous	Adenocarcinoma
IHC staining	IHC 3+ (15%)	IHC 3+ (75%)	IHC 3+ (100%)	IHC 3+ (60%)
ISH (gene ratio ≥2)	Negative	Positive	Positive	Positive
Amplification by NGS copy number ≥5	Negative	Equivocal[a]	Positive	Positive
HER2 mutation	Negative	HER2 Mutation G776>VC[a]	HER2 gene rearrangement	Negative
ALK rearrangement	Negative	Negative[a]	Negative	Negative
EGFR mutation	Negative	Negative[a]	Negative	Exon 19

[a]Local FMI NGS results reported by site (no study FMI results available). Amplification by NGS positive for copy number ≥7. All other results are reported by FMI NGS as part of retrospective biomarker analyses in HER2Lung.

Thomas Stinchcombe et al, ASCO 2017