Update 2019 no manejo de outras mutacoes alvo (BRAF, MET, ROS1, RET, HER2, NTRK)

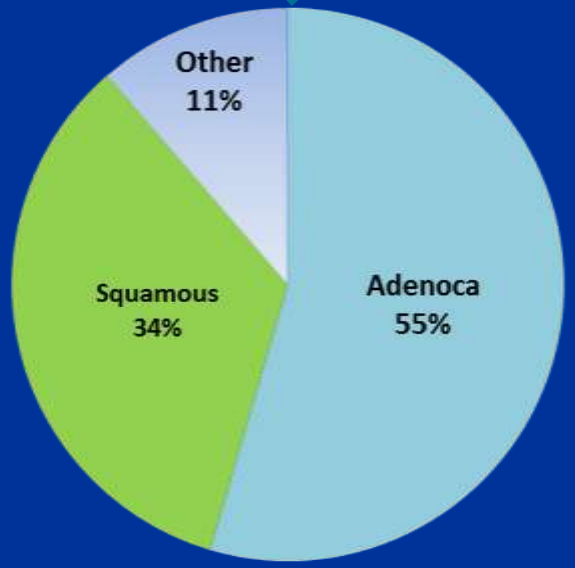
VII Simposio Internacional de Cancer de Pulmao

Sao Paulo, Brasil

Bruno Bastos, M.D.
Hematology-Oncology
Cleveland Clinic

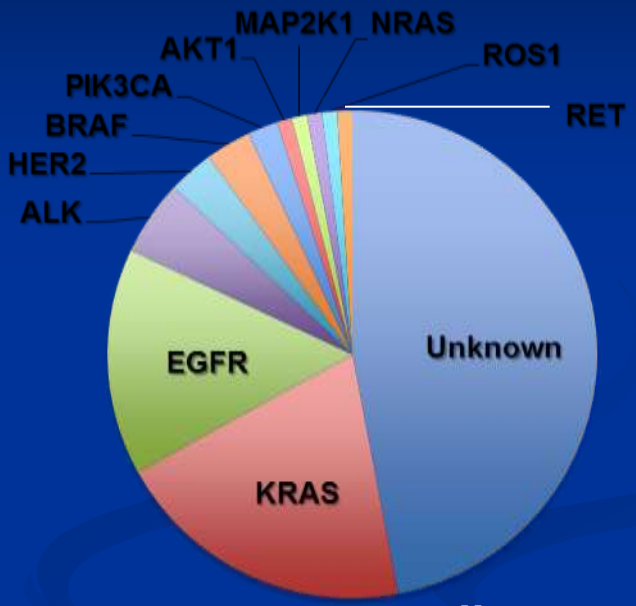
Molecular heterogeneity of NSCLC
(Li, Gandara et al: JCO 2012, in press)

NSCLC as one disease

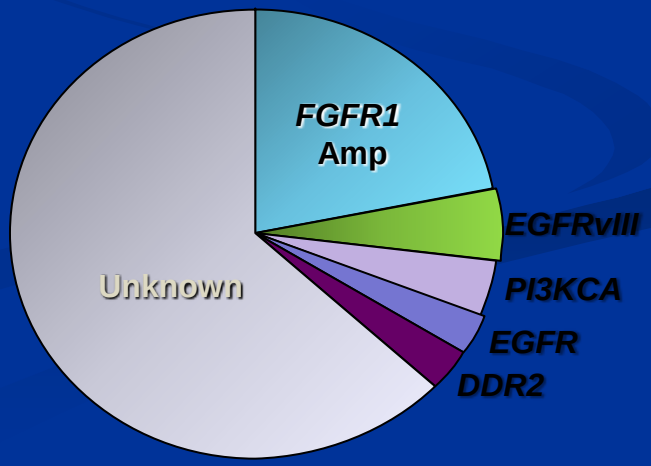


Histology-based Subtyping

Adenocarcinoma



Squamous Cell Cancer



Beyond EGFR and ALK

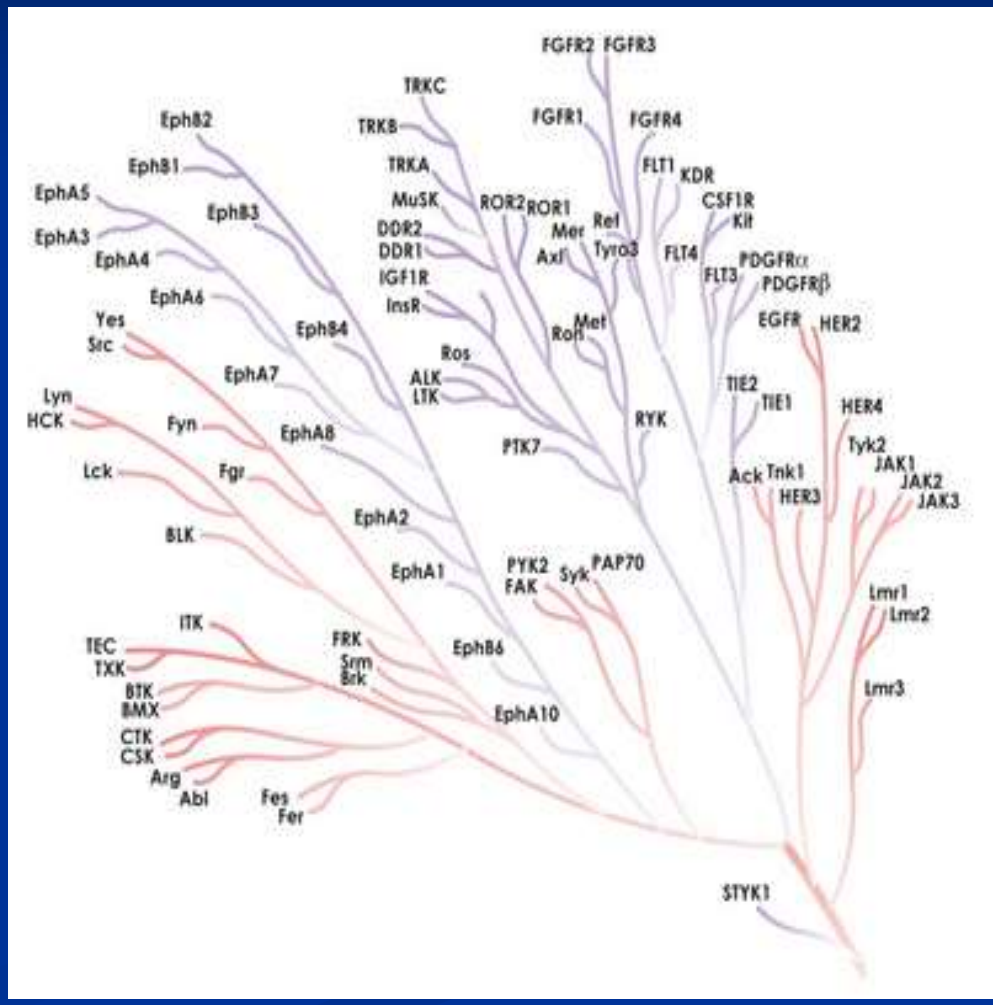
- ROS-1
  - FDA-approval: Crizotinib
- BRAF V600E
  - FDA-approval: Dabrafenib-Trametinib
- NTRK rearrangement
  - FDA-approved Larotrectinib
- MET, RET, HER-2
  - No FDA-approval yet
  - Listed nccn compendium

ROS1-positive NSCLC
1-2% cases

Crizotinib

Background on ROS1

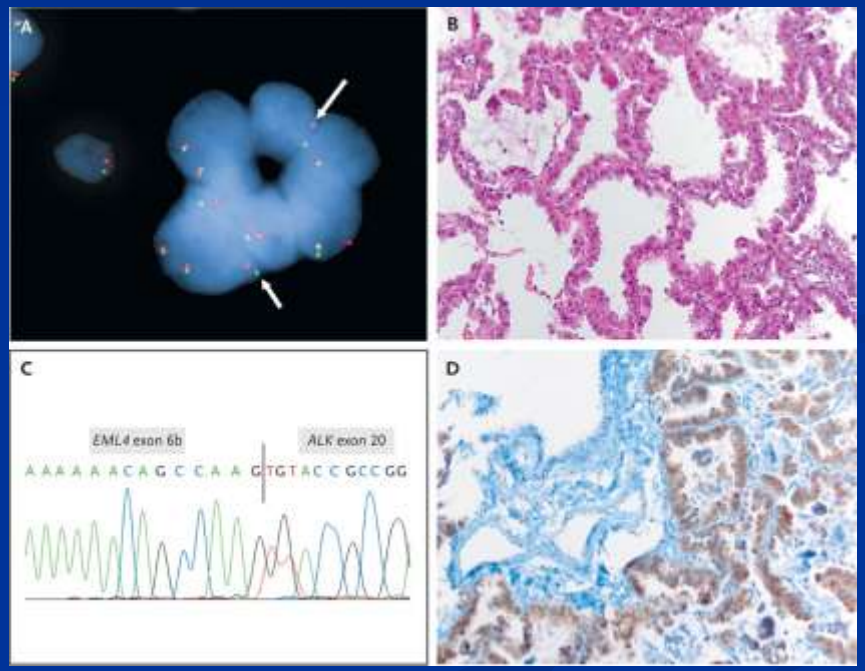
- *ROS1* fusions were identified as potential driver mutations in:
  - NSCLC cell line (**HCC78**; *SLC34A2-ROS1*)
  - NSCLC patient sample (*CD74-ROS1*).
- Pre-clinical studies have shown activity of an ALK inhibitor in HCC78 cell line.
- Crizotinib binds almost identically to ALK and ROS1 due to similar TK domains.



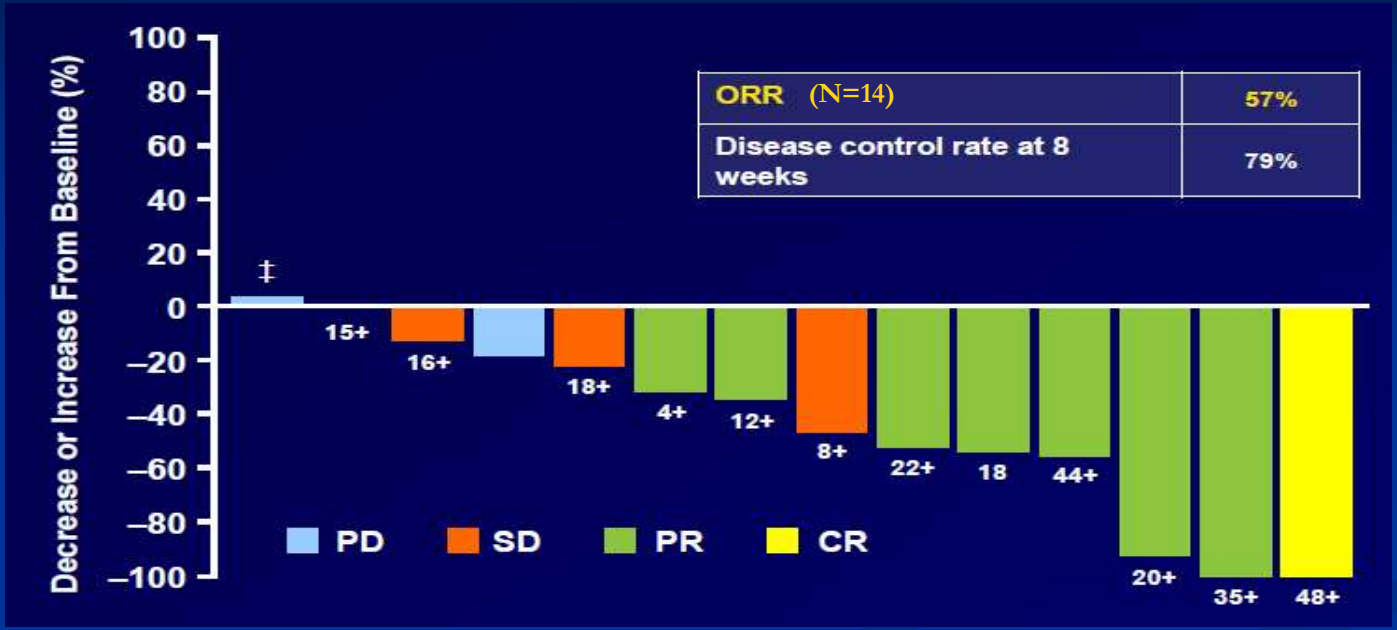
Bergethon et al. JCO March 10, 2012
Vol. 30 no. 8 863-870

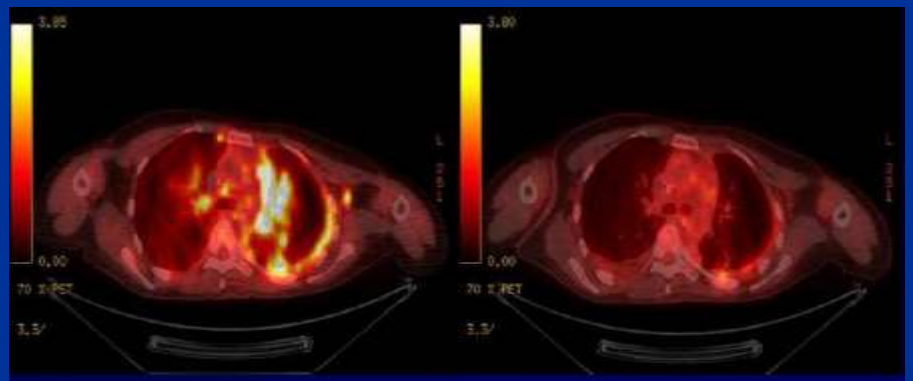
ROS-1 Lung Cancer

- More frequent in younger
- Never/light smokers
- Adenocarcinoma

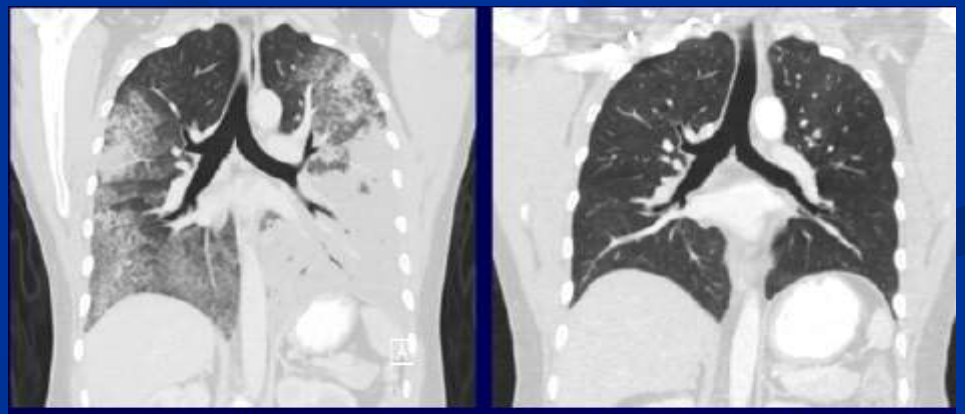


Clinical activity of crizotinib in ROS1-positive NSCLC (Shaw A *et al*)





Baseline After 4 weeks of crizotinib



Baseline After 3 months of crizotinib

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

Abstract: 7508

Crizotinib in ROS-1-Rearranged Non-Small-Cell Lung Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Raw Saigia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileia Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Darvel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

ABSTRACT

BACKGROUND

Chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (ROS1) define a distinct molecular subgroup of non–small-cell lung cancers (NSCLCs) that may be susceptible to therapeutic ROS1 kinase inhibition. Crizotinib is a small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and another proto-oncogene receptor tyrosine kinase, MET.

METHODS

We enrolled 50 patients with advanced NSCLC who tested positive for ROS1 rearrangement in an expansion cohort of the phase 1 study of crizotinib. Patients were treated with crizotinib at the standard oral dose of 250 mg twice daily and assessed for safety, pharmacokinetics, and response to therapy. ROS1 fusion partners were identified with the use of next-generation sequencing or reverse-transcriptase–polymerase-chain-reaction assays.

RESULTS

The objective response rate was 72% (95% confidence interval [CI], 58 to 84), with 3 complete responses and 33 partial responses. The median duration of response was 17.6 months (95% CI, 14.5 to not reached). Median progression-free survival was 19.2 months (95% CI, 14.4 to not reached), with 25 patients (50%) still in follow-up for progression. Among 30 tumors that were tested, we identified 7 ROS1 fusion partners: 5 known and 2 novel partner genes. No correlation was observed between the type of ROS1 rearrangement and the clinical response to crizotinib. The safety profile of crizotinib was similar to that seen in patients with ALK-rearranged NSCLC.

CONCLUSIONS

In this study, crizotinib showed marked antitumor activity in patients with advanced ROS1-rearranged NSCLC. ROS1 rearrangement defines a second molecular subgroup of NSCLC for which crizotinib is highly active. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.)

From the Massachusetts General Hospital Cancer Center (A.T.S., L.P.L., Z.Z., J.W.C., A.J.I.), Dana-Farber Cancer Institute (G.I.S.), and Beth Israel Deaconess Medical Center (D.B.C.) — all in Boston; University of California at Irvine, Irvine (S.-H.I.O.), and Pfizer Oncology, La Jolla (W.T., S.M.S., L.M.T., J.G.C., K.D.W.) — both in California; Seoul National University Hospital, Seoul, South Korea (Y.-J.B.); University of Colorado, Aurora (D.R.C., M.V.-G., R.C.D.); Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); University of Chicago, Chicago (R.S.); Memorial Sloan Kettering Cancer Center, New York (G.J.R.); Karolinska Institutet, Stockholm (Z.Z.), and Rho, Chapel Hill, NC (P.S.). Address reprint requests to Dr. Shaw at the Massachusetts General Hospital Cancer Center, Yankey 76, 32 Fruit St., Boston, MA 02110, or at ashaw1@mgh.harvard.edu.

Drs. Shaw and Ou contributed equally to this article.

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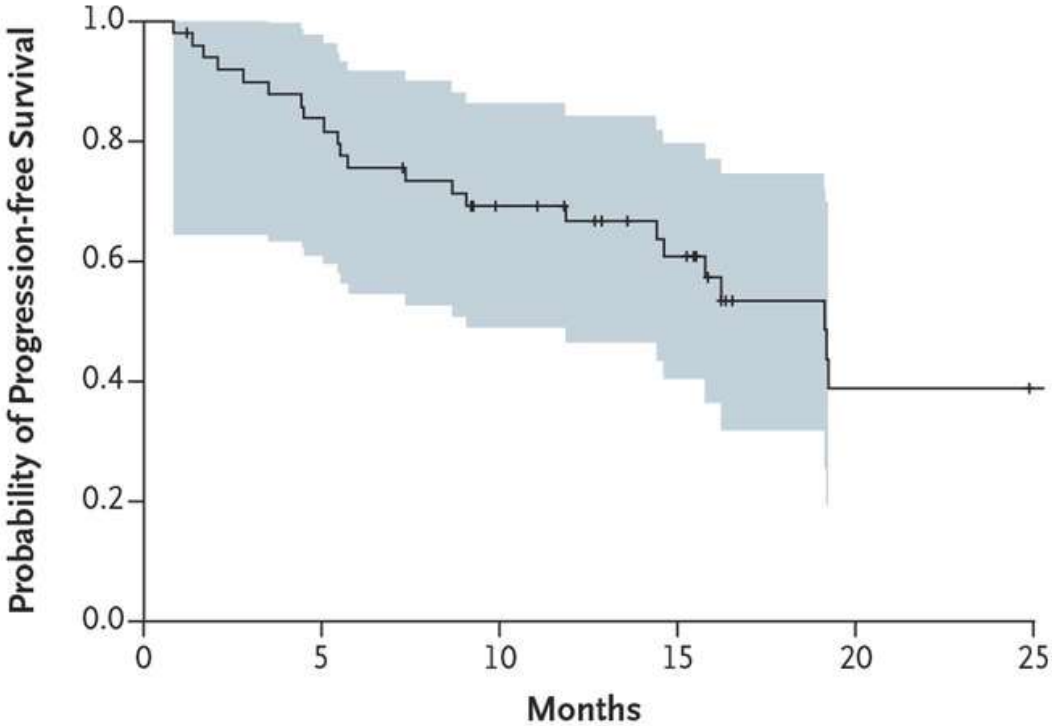
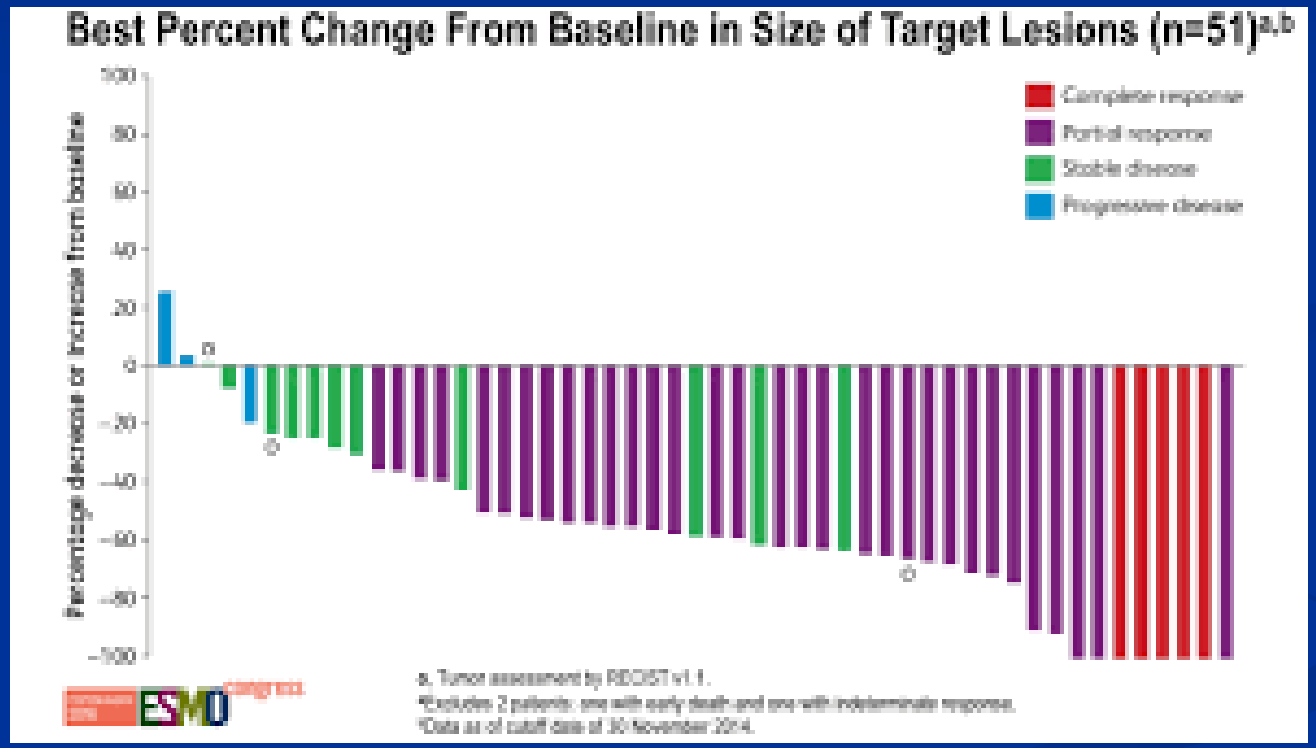
PROFILE 1001
PFS



No. at Risk						
Crizotinib	50	41	30	21	8	7

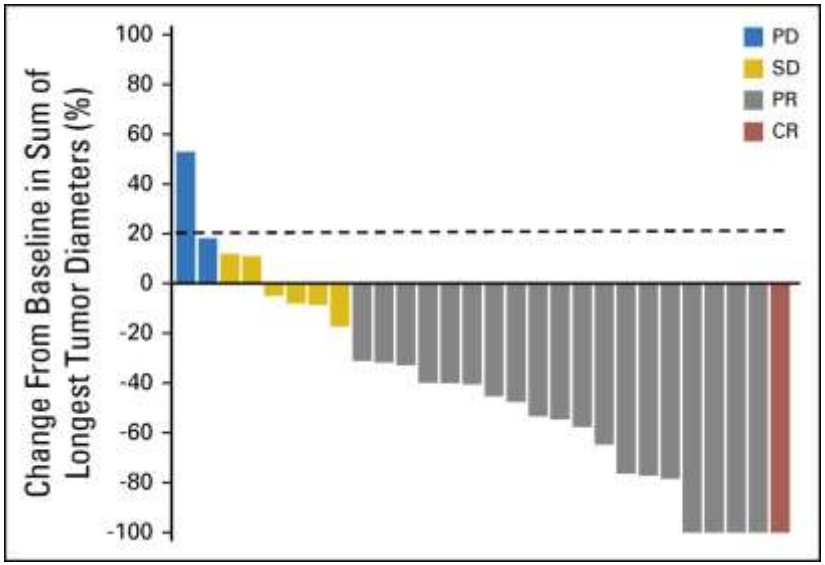
PROFILE 1001

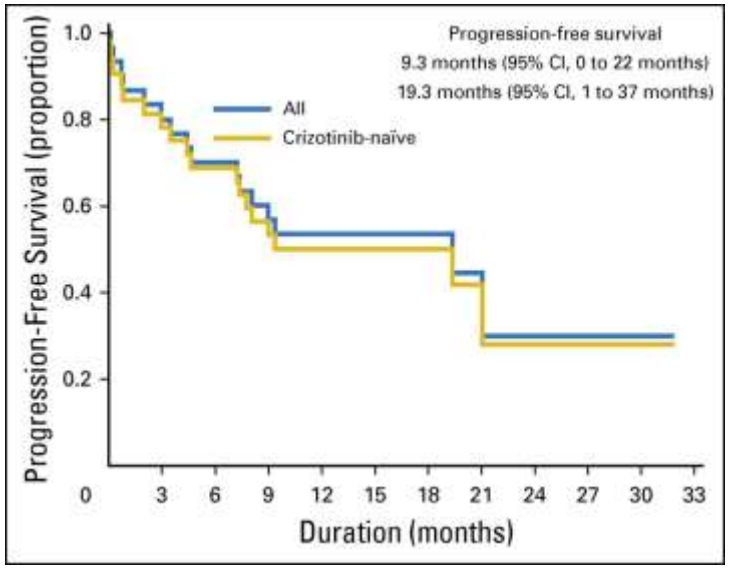


March 11, 2016 FDA approves crizotinib for ROS-1 NSCLC

Ceritinib Phase II

Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non–Small-Cell Lung Cancer Harboring ROS1 Rearrangement





32 patients:
ORR 62%
DCR 81%
(CR 3%, PR 59%, SD 19%)

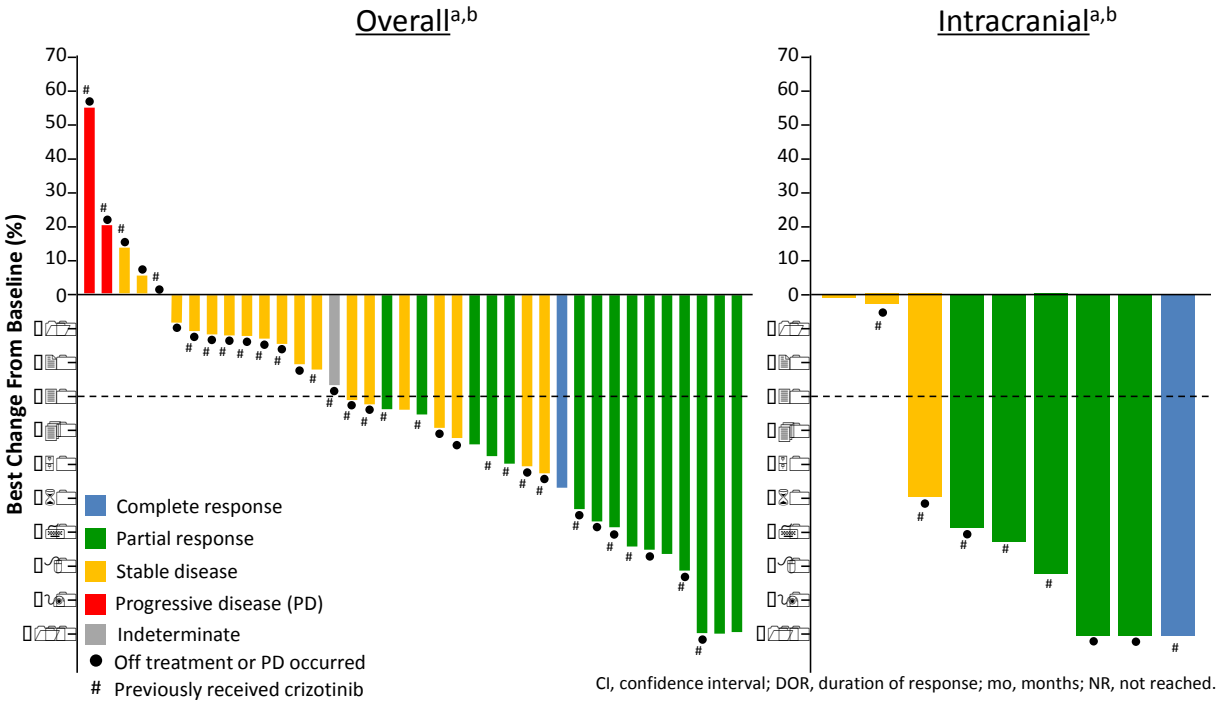
Lim et al. Journal of Clinical Oncology 35, no. 23 (August 2017) 2613-2618.

Phase II Lorlatinib
Saw et al. IASLC 2017

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)
[illegible]	12/17 (71)
Median PFS, mo (95% CI)	9.6 (4.7, NR)

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



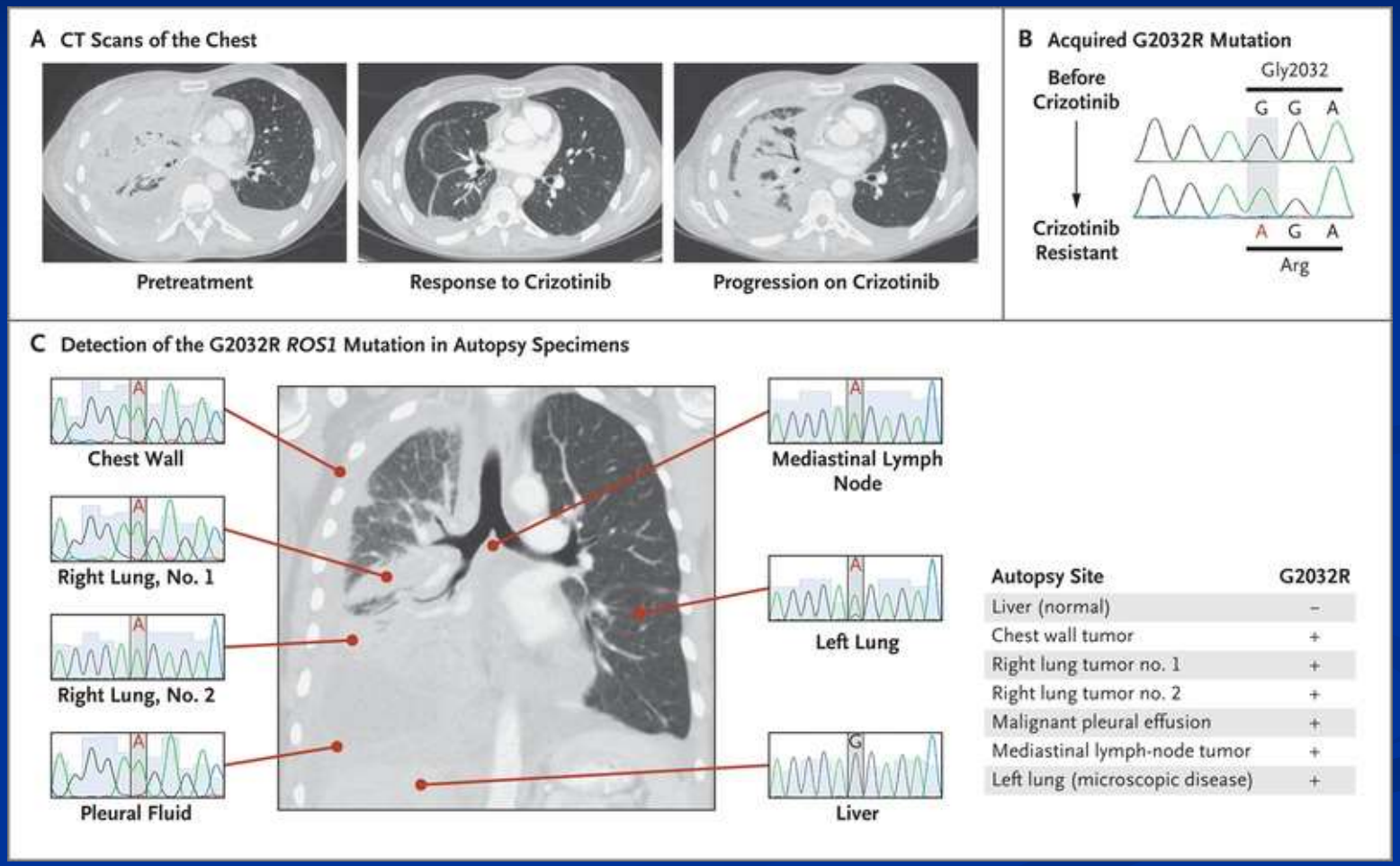
CI, confidence interval; DOR, duration of response; mo, months; NR, not reached.

[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.
[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching ≤100%. Some patients with a total change from baseline of ≤100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

Entrectinib

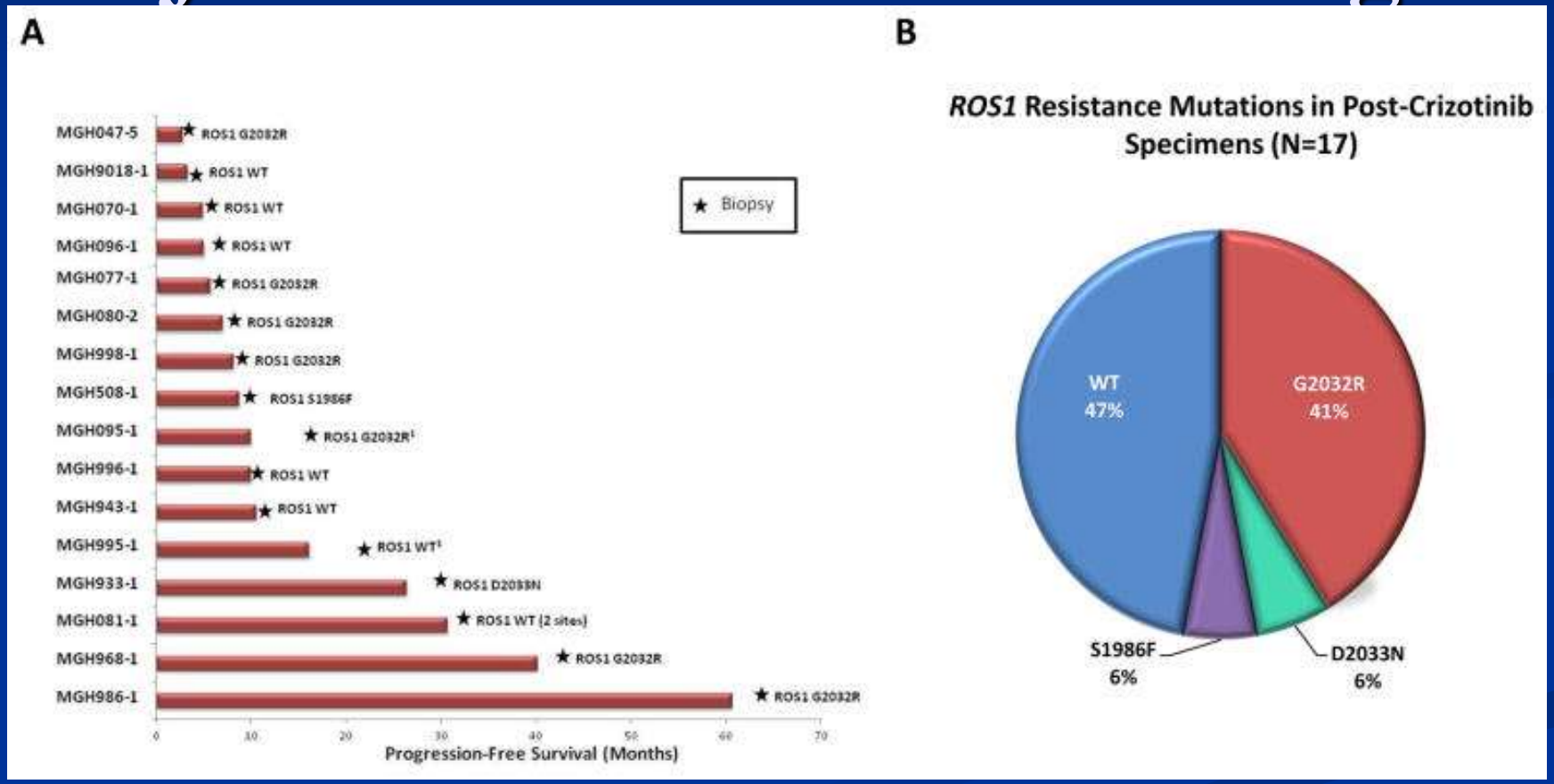
- Granted Priority Review by FDA for NTRK+ tumors and ROS1+ NSCLC
- Based on an pool analysis of the ph2 STARTRK-2, Ph1 STARTRK-1 and the Ph1 ALKA-372-001
- 53 pts with ROS-1activating gene fusion, ORR 77.4%, DOR 24.6 months and in 23 pts with cns disease, intracranial RR was 55%
- PFS 26.3 mo no CNS and 23.6 mo with brain mets.
- ORR 57.4 in NTRK fusion-positive solid tumors with DOR 10.4 months(n=54)

Awad et al. NEJM
Acquired resistance to Crizotinib



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)	+

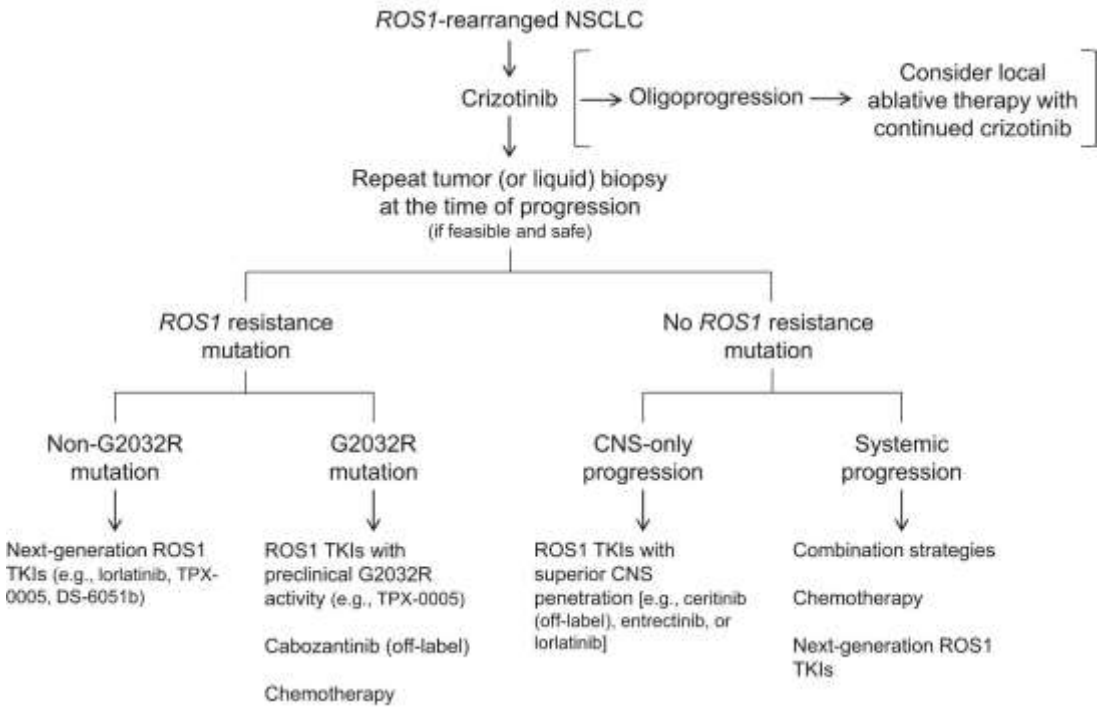
Recent retrospective analysis ROS-1 progression by Gainor et al. JCO Precis Oncol. 2017 Aug 16



Second-line

- Alectinib, Brigatinib, Ceritinib NO activity against G2032R
- TPX-0005 (repotrectinib); Cabozantinib - ?activity against G2032R
- Entrectinib, DS-6051b and Lorlatinib are now being evaluated.

ROS-1 treatment pathway



Lin and Shaw, Journal of Thoracic Oncology 2017 12, 1611-1625

BRAF Mutation

V600E mutations

FDA Approved regimen:

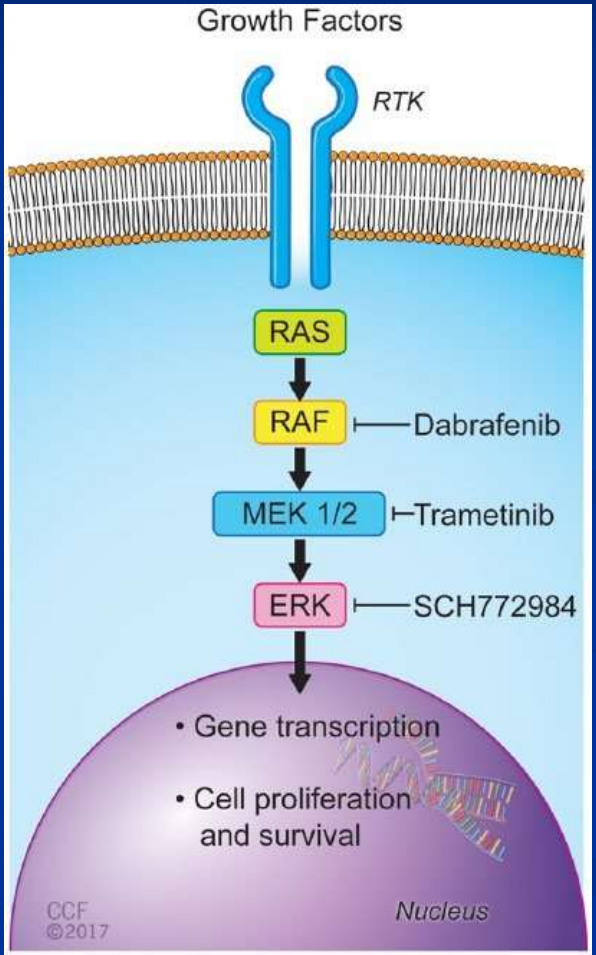
Dabrafenib/Tremetinib

BRAF Mutations in NSCLC

- Found in approximately 3% of NSCLC
  - 50% are BRAF V600E mutants
  - 35% G469A
  - 10% D595G
- 3,500/year in US and 35,000 worldwide.
- Occur more commonly in current and former smokers

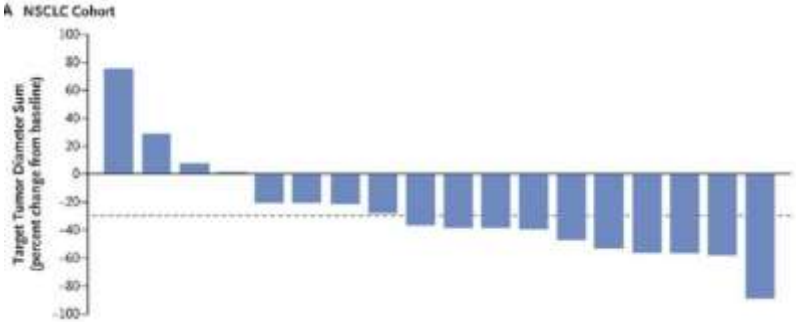
Palik P K et al. JCO 2011; 29:2046-2051

RAS/Raf/Mek/Erk signaling pathway

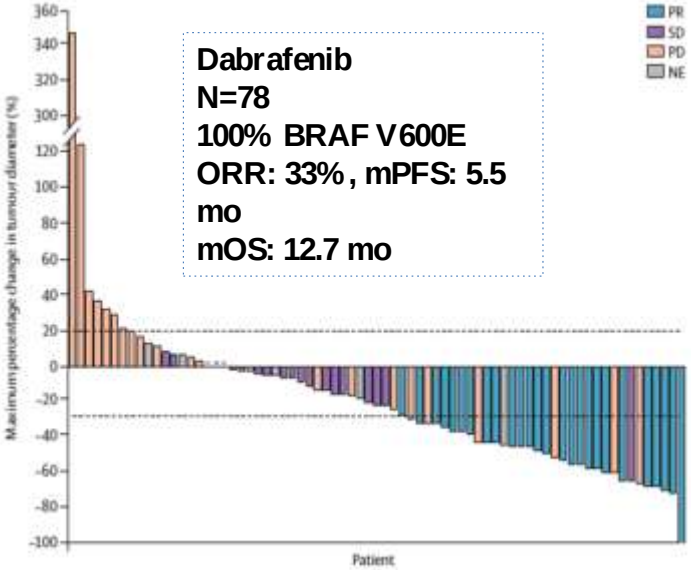


BRAF inhibitor
Single Agent Activity

Braf Inhibition in NSCLC: Single Agent Activity



Vemurafenib
N=20
90% BRAF V600E
ORR: 42%
mPFS: 7.3 mo
mOS NR
(Hyman et al. N Engl J Med. 2015 Aug 20; 373(8): 726–736.)



Dabrafenib
N=78
100% BRAF V600E
ORR: 33%, mPFS: 5.5 mo
mOS: 12.7 mo

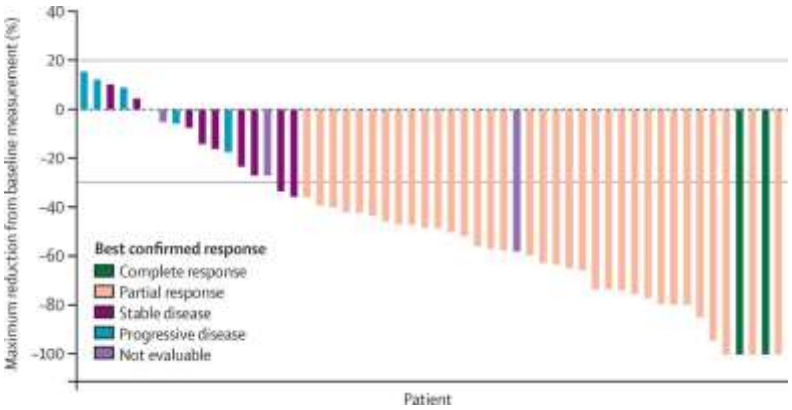
Planchard, J Clin Oncol 33(Suppl.): abstract 8006.

- **EURAF Study BRAFi: ORR 53%, DCR 85%, mPFS 5.0 mo, mOS 10.8 mo**

Gautschi et al. J Thorac Oncol. 2015 Oct;10(10):1451-7.

BRAF/MEK dual inhibition with Dabrafenib/Trametinib

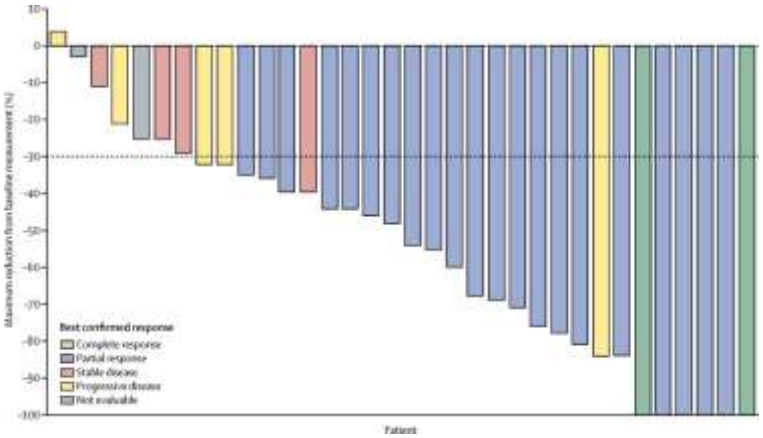
Dabrafenib/trametinib in previously treated BRAF V600E patients



ORR 63%
DCR 75.4%
mPFS 8.6 mo
(independent assessment, n=57)

Planchard et al. Lancet Oncol. 2016 Jul;17(7):984-993

Dabrafenib/trametinib in previously untreated BRAF V600E patients



ORR 64%
DCR 72%
mPFS 14.6 mo
(independent review, n=36)

Planchard et al. Lancet Oncol. 2017 Oct;18(10):1307-1316.

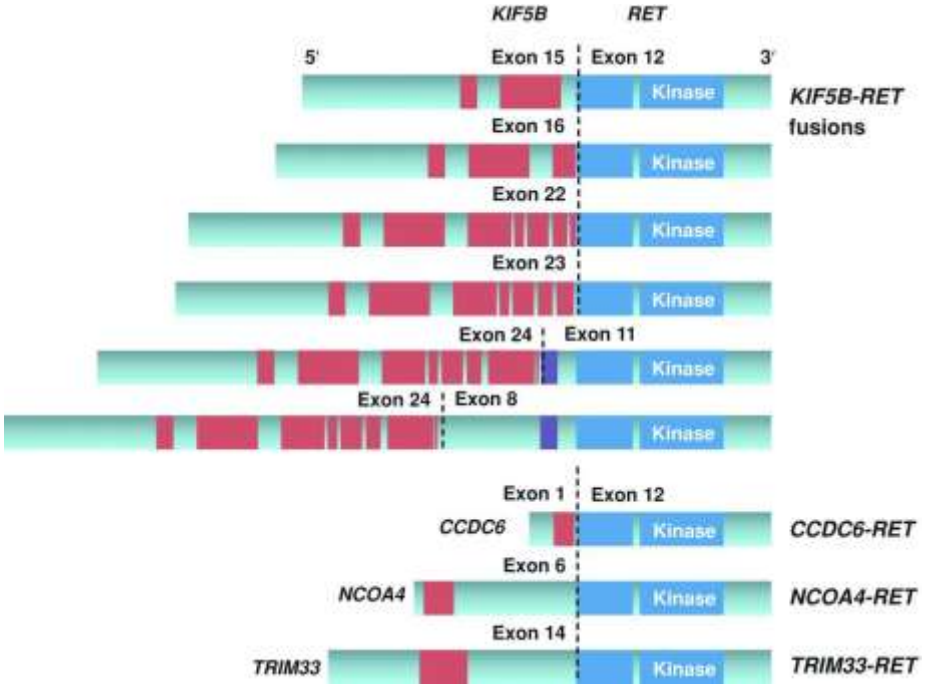
BRAF/MEK inhibitor toxicity

- Pyrexia
- Cardiomyopathy, rare
- Uveitis
- Hyperglycemia
- Skin changes
- G6PD deficiency
  - Watch for hemolytic anemia

RET

RET – Rearranged during Transfection – in 1-2% of NSCLC

RET fusions reported in the literature are depicted including major recurrent KIF5B–RET fusions, CCDC6–RET, NCOA4–RET (14–16, 20), and the novel TRIM33–RET.



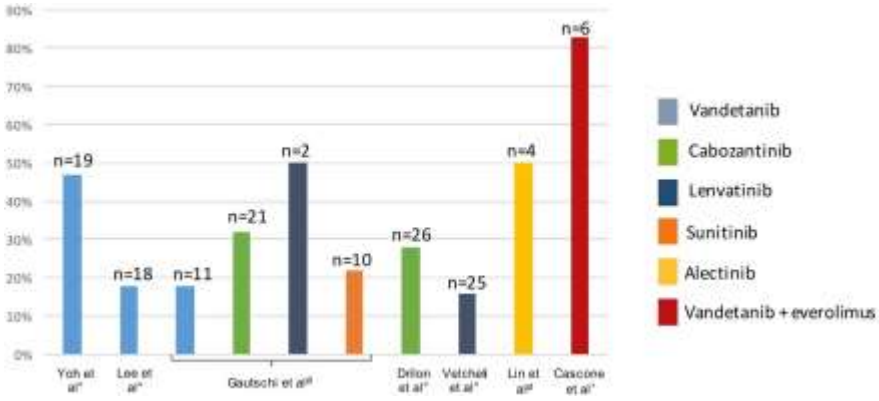
Drilon A et al. Cancer Discovery 2013;3:630-635

©2013 by American Association for Cancer Research

American Association for Cancer Research

RET inhibitor comparison

RET Inhibition in NSCLC



Overall response rates of multikinase inhibitors in patients with rearranged during transfection proto-oncogene gene (*RET*)-rearranged NSCLC, by study. ∗, Phase I; °, phase II, and φ, retrospective.

Summary of Response and Survival Outcomes according to RET Inhibitor Drug

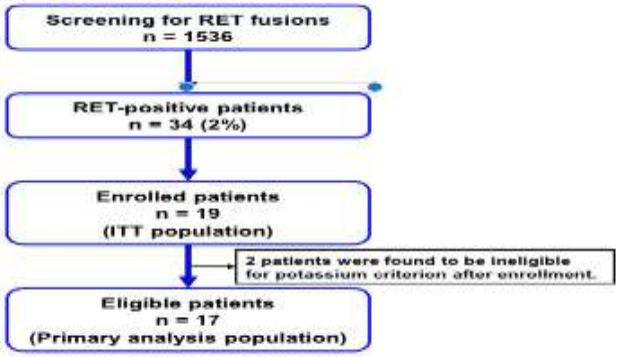
Type of RET Inhibitor	Study	No. of Patients	ORR	mPFS (mo)	mOS (mo)
Vandetanib	Yoh et al. (2016) LURET[65]	19	47%	4.7	11.1
	Lee et al. (2017)[50]	18	18%	4.5	11.6
	Gautschi et al. (2017) GLORY[49]	11	18%	2.9	10.2
	Platt et al. (2015)[9]	3	0%	NA	NA
Cabozantinib	Drilon et al. (2016)[51]	26	28%	5.5	9.9
	Gautschi 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 Thorac Oncol. 2018 Jan;13(1):27-45.

Vandetanib

LURET STUDY: PHASE 2 STUDY OF VANDETANIB IN PTS WITH ADVANCED RET-REARRANGED NSCLC

Figure 2. Study profile



(The data-cutoff date was August 31, 2015)

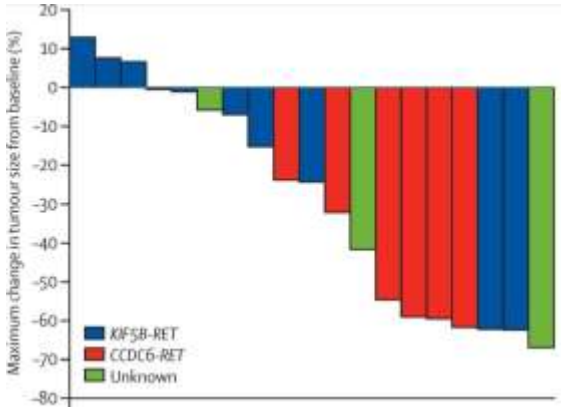
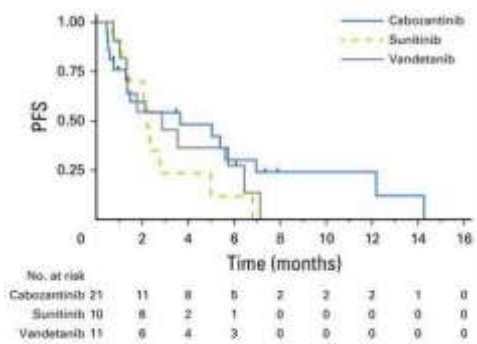


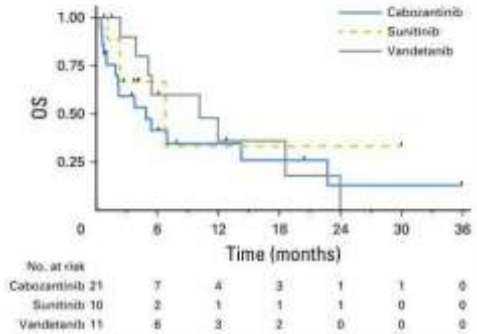
Table 2. Efficacy according to the type of RET fusion

Outcome	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-yr OS, % (95% CI)	47 (21, 69)	42 (11, 71)	67 (5, 95)	33 (1, 77)

Yoh Lancet Respir Med 17

RET registry





Global RET registry

RET Inhibitor	Best response (%, 95% CI)	Median PFS (95% CI)	Median OS (95% CI)
Cabozantinib (21)	37% (95% CI : 16.3; 61.6)	3.6 months (1.3-7.0 months)	4.9 months (1.9-14.3 months)
Vandetanib (11)	18% (95% CI : 2.3; 51.8)	2.9 months (1.0-6.4 months)	10.2 months (2.4-NR months)
Sunitinib (10)	22% (95% CI : 2.8; 60.0)	2.2 months (0.7-5.0 months)	6.8 months (1.1-NR months)

Largest database (n=165 pts, 53 pts treated with RET inhibitors)

Gautschi JCO 17

Summary and future directions of RET

TARGETING RET

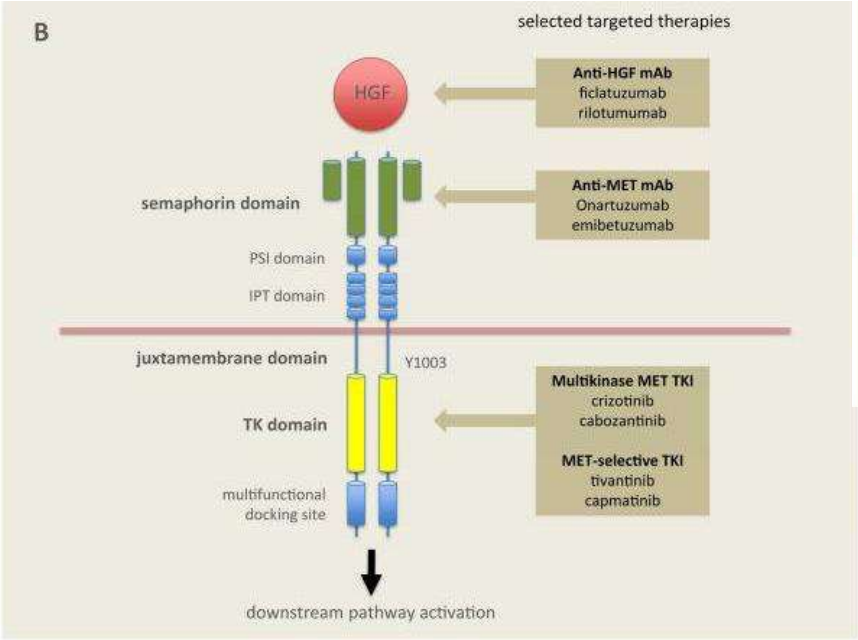
- Several RET inhibitor compounds, initially designed to target other tyrosine kinases
- At present phase II vandetanib, cabozantinib, lenvatinib, with moderate activity and substantial toxicity (activity against VEGFR kinases)
- New studies with RET inhibitors:

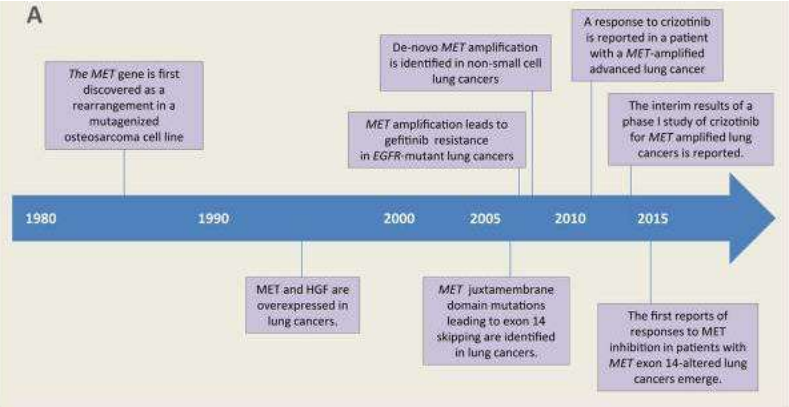
- WCLC 17**:** "LOXO-292, a potent, highly selective RET inhibitor, in MKI-resistant RET fusion-positive lung cancer patients with and without brain metastases" ***(Velcheti et al, November 2017 Volume 12, Issue 11, Supplement 2, Page S1778)***

- ETOP trial: alectinib for RET-rearranged NSCLC (ALERT lung trial)

MET

MET - Mesenchymal Epithelial Transition factor receptor in NSCLC





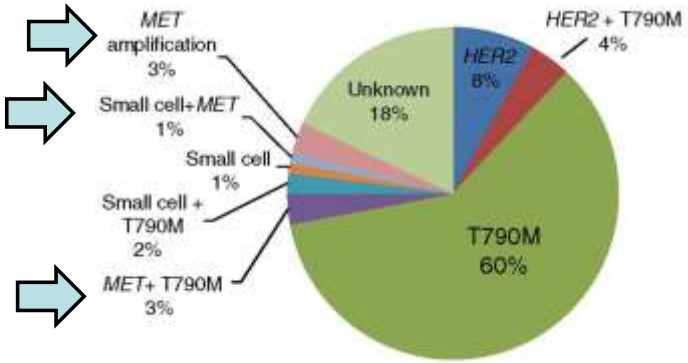
- **History of MET spans > 3 decades**
  - MET proto-oncogene first discovered in the mid-1980s
  - MET found to be dysregulated in lung cancers in the mid-1990s
- **More than 20 targeted therapies targeting MET or its ligand have been developed.**
- **No targeted therapy approved to date for patients with cancers driven by MET.**

Drilon et al. J Thorac Oncol . 2017 January ; 12(1): 15–26

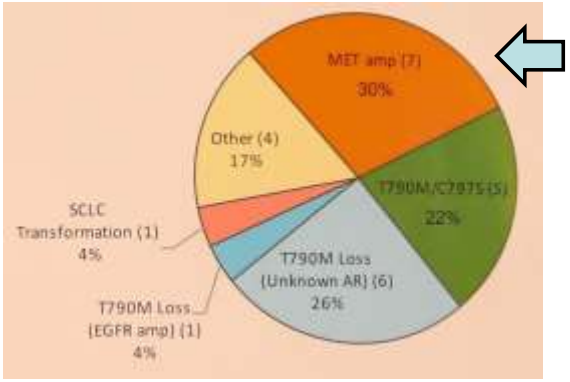
EGFR resistance: Met amplification

MET in resistance to EGFR TKIs

acquired resistance to 1st generation EGFR TKI therapy in *EGFR*-mutant lung cancers



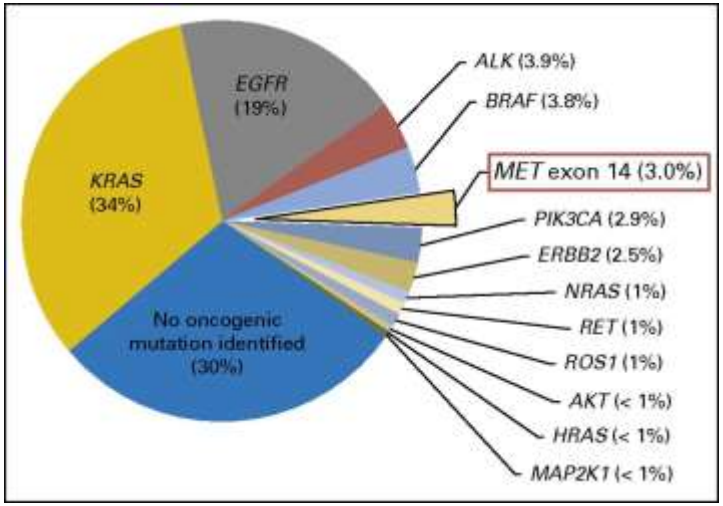
acquired resistance to 3rd generation EGFR TKI therapy in *EGFR*-mutant lung cancers

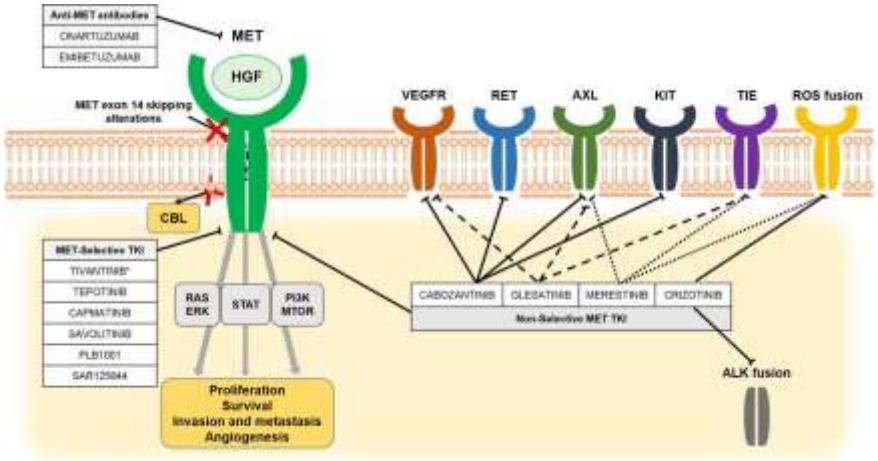


MET amplification also found in TKI-naïve metastatic *EGFR*-mutant lung cancers

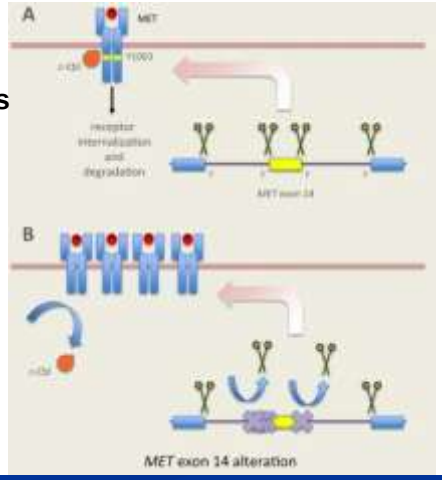
Yu H et al, Clin Cancer Res, 2013; Piotrowska Z et al, ASCO 2017; Lai et al, WCLC 2017

MET incidence





MET mutation no concurrence with known driver mutations but tended to coexist with MET amplification or copy number gain (P < 0.001)
(Awad et al. J Clin Oncol. 2016 Mar 1;34(7):721-30)



- **Incidence**
  - 3-4% of nonsquamous NSCLCs
  - 8-30% of sarcomatoid lung carcinomas
- **Clinicopathologic features**
  - older patients
  - [illegible]
  - mutually exclusive with other drivers
  - 15-20% with concurrent *MET* amplification

MET trials

Randomized Trials with Anti-MET Agents in Lung Cancer

Randomized trials with anti-MET agents in lung cancer.

Agent	Trial	Population	MET abnormalities	Setting	Arms	N	Primary endpoint	Medians (mo)	HR (p-value)
Onartuzumab	GO27820 [37] Phase II	Squamous	Unselected	1st line	Plat/Pac + Onartuzumab	55	PFS	4.9	0.95
					Plat/Pac + Placebo	54		4.9	(p = 0.80)
		Squamous	IHC MET-positive (2+ or 3+ in ≥50% of TC)	1st line	Plat/Pac + Onartuzumab	27	PFS	5.0	1.27
					Plat/Pac + Placebo	27		5.2	(p = 0.44)
	GO27821 [38] Phase II	Non-squamous	Unselected	1st line	Beva/Plat/Pac + Placebo	69	PFS	6.8	1.25
					Beva/Plat/Pac + Onartuzumab	70		5.0	(p = 0.33)
					Plat/Pem + Placebo	59		5.1	1.23
					Plat/Pem + Onartuzumab	61		4.9	(p = 0.33)
		Non-squamous	IHC MET-positive (2+ or 3+ in ≥50% of TC)	1st line	Beva/Plat/Pac + Placebo	50	PFS	6.9	1.71
					Beva/Plat/Pac + Onartuzumab	45		4.8	(n.r.)
					Plat/Pem + Placebo	32		5.0	1.25
					Plat/Pem + Onartuzumab	29		5.0	(n.r.)
	OAM4558 g [34] Phase II	NSCLC	Unselected	2nd-3rd line	Erlotinib + Onartuzumab	69	PFS	2.2	1.09
					Erlotinib + Placebo	68		2.6	(p = 0.69)
		NSCLC	IHC MET-positive (2 + or 3+)	2nd-3rd line	Erlotinib + Onartuzumab	35	PFS	2.9	0.53
					Erlotinib + Placebo	31		1.5	(p = 0.04)
	METLung [36] Phase III	NSCLC	IHC MET-positive (2 + or 3+)	2nd-3rd line	Erlotinib + Onartuzumab	250	OS	6.8	1.27
					Erlotinib + Placebo	249		9.1	(p = 0.067)
		NSCLC	FISH positive	2nd-3rd line	Erlotinib + Onartuzumab	71	OS	6.4	1.28
					Erlotinib + Placebo	85		9.4	(n.r.)
Tivantinib	NCT00777309 [39] Phase II	NSCLC	Unselected	Pretreated	Erlotinib + Tivantinib	84	PFS	3.8	0.81
					Erlotinib + Placebo	83		2.3	(p = 0.24)
		NSCLC	MET GCN ≥ 4	Pretreated	Erlotinib + Tivantinib	19	PFS	3.6	0.71
					Erlotinib + Placebo	18		3.6	(p = 0.51)
	MARQUEE [40] Phase III	Non-squamous	Unselected	Pretreated	Erlotinib + Tivantinib	526	OS	8.5	0.98
					Erlotinib + Placebo	522		7.8	(p = 0.81)
		Non-squamous	IHC MET- positive (2+ or 3+ in ≥50% of TC)	Pretreated	Erlotinib + Tivantinib	104	OS	9.3	0.70
					Erlotinib + Placebo	107		5.9	(p = 0.03)
	ATTENTION [41] Phase III	Non-squamous WT-EGFR [Asian]	Unselected	Pretreated	Erlotinib + Tivantinib	154	OS	12.7	0.89
					Erlotinib + Placebo	153		11.1	(p = 0.427)
		Non-squamous WT-EGFR [Asian]	IHC MET- positive (2+ or 3+ in ≥50% of TC)	Pretreated	Erlotinib + Tivantinib	83	OS	n.r.	0.83
					Erlotinib + Placebo	77		n.r.	(n.r.)
Cabozantinib	E1512 [42] Phase II	Non-squamous WT-EGFR	Unselected	2nd-3rd line	Erlotinib + Cabozantinib	43	PFS	4.7	0.37 *
					Cabozantinib	40		4.3	(p = 0.003)
					Erlotinib	42		1.8	0.39#
									(p = 0.003)
		Non-squamous WT-EGFR	IHC MET- positive (1+ or 2+ or 3+)	2nd-3rd line	Cabozantinib arms	50	PFS	5.0	n.r.
					Erlotinib	24		1.8	
	NCT00940225 [117] Phase II RDT	NSCLC SD after 12 weeks of cabozantinib	Unselected	Pretreated	Cabozantinib	8	PFS	2.3	n.r.
					Placebo	7		2.4	
Emibetuzumab	NCT01900652 [56] Phase II RDT	NSCLC EGFR mutant	IHC MET- positive (2+ or 3+ in ≥10% of TC)	Pretreated	Emibetuzumab	28	ORR	4.3%	n.r.
					Erlotinib + Emibetuzumab	83		3.0%	
			High IHC MET- positive (2+ or 3+ in ≥60% of TC)	Pretreated	Emibetuzumab	21	ORR	4.8%	n.r.
					Erlotinib + Emibetuzumab	53		3.8%	

MET amplification in EGFR mutant

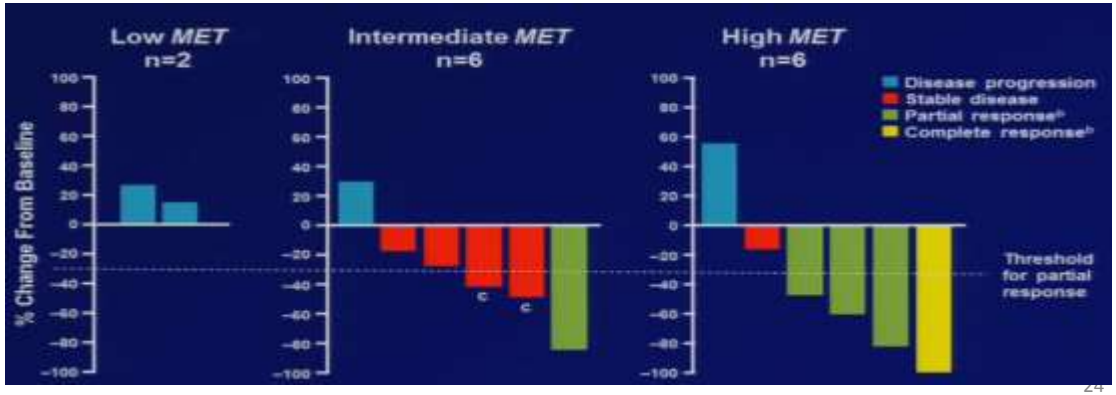
Targeting *MET* amplification

	Low *MET* Amp, n=2	Intermediate *MET* Amp, n=6	High *MET* Amp,n=6
Overall response	0% (95%CI 0-84)	17% (95%CI 0-64)	67% (95%CI 22-96)
Medan DoR	N/A	16 weeks	73.6 weeks

Multicenter phase 1 expansion cohort, crizotinib 250 mg twice daily

Primary endpoint: overall response

Camidge DR et al, ASCO 2014

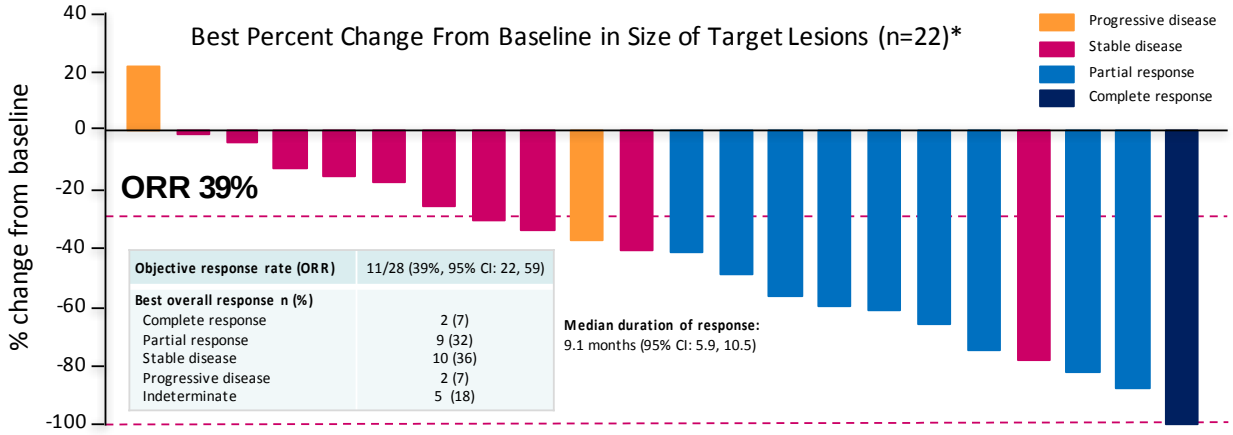


- **Moro-Sibilot, WCLC 15**: 25 MET-amplified pts treated with crizotinib - PR 32%, mPFS 3.2 m
- **Noonan, JTO 16:** The most appropriate method for defining MET amplification - uncertain FISH MET/CEP7 ratio of 5 or higher?

Crizotinib in MET exon 14 altered

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Response to Crizotinib in *MET* Exon 14-Altered Lung Cancers



*Includes patients with measurable disease at baseline and 1 response assessment scan; excludes 1 patient with early death, 4 patients with indeterminate response and 1 patient (CR responder) with no measurable target lesions at baseline

Drilon A et al, WCLC 2016; Paik et al, Cancer Discov 2015; Schuler et al, ASCO 2016; Kollmansberger et al, ASCO 2015

Osimertinib plus Savolitinib with progression EGFR TKI

OA 09.03: TATTON Ph Ib Expansion Cohort: Osimertinib plus Savolitinib for Pts with EGFR-Mutant MET-Amplified NSCLC after Progression on Prior EGFR-TKI – Ahn M-J, et al

Key results

- AEs of any grade and causality occurred in 92% of patients, with nausea (44%) and vomiting (35%) the most common
- [illegible]
- Preliminary anti-tumour activity was promising across all groups among patients with centrally confirmed MET-positive status

Response, n (%)	Prior 3rd gen T790M-directed EGFR-TKI (n=25)	No prior 3rd gen T790M-directed EGFR-TKI		Total (n=47)
		T790M+ (n=7)	T790M- (n=15)	
CR	0	0	0	0
PR	7 (28)	4 (57)	8 (53)	19 (40)
SD [illegible]	13 (52)	3 (43)	6 (40)	22 (47)

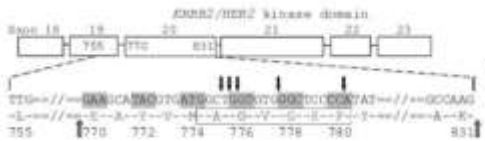
Conclusions

- This phase 1b expansion cohort showed a safety profile consistent with the first phase of this study
- Osimertinib + savolitinib showed anti-tumour activity in all the MET-positive groups, regardless of EGFR T790M mutation status or prior T790M-directed EGFR-TKI therapy

Ahn M-J et al. J Thorac Oncol 2017;12(suppl):Abstr OA 09.03

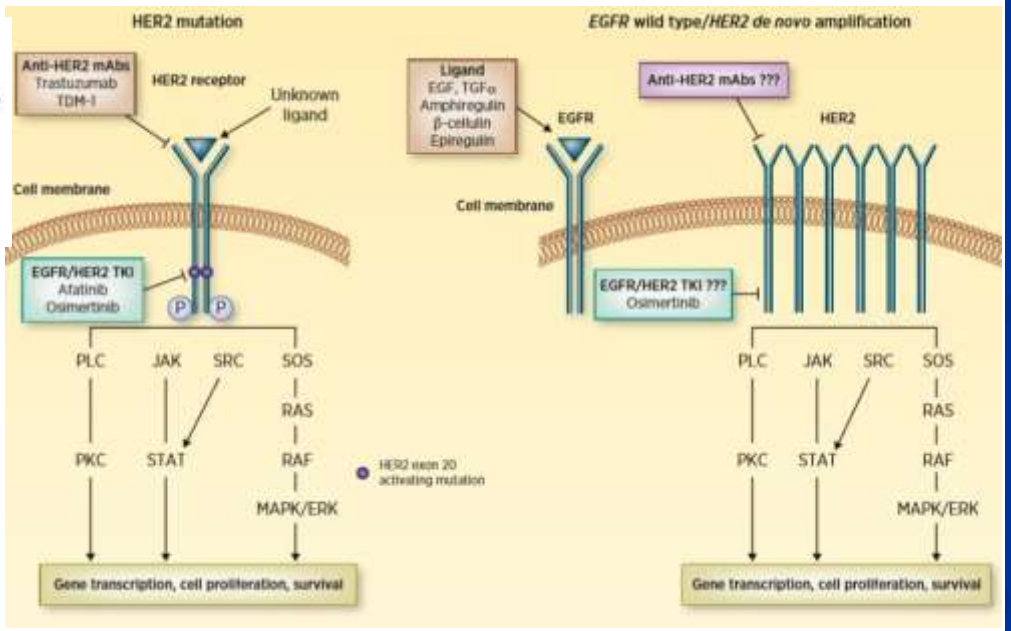
HER-2

Targeting HER2 in Lung Cancer



Wild-type sequence, exon 20

12bp insertion, exon 20



- HER2 mutations 2% of lung cancer
- Most common exon 20 insertion
  (12 bp [illegible]
- HER2 amplification
  ~3% of lung cancer EGFR TKI naive
  ~10% EGFR TKI resistance

Chemo plus HER-2 therapy

Lung cancer patients with *HER2* mutations treated with chemotherapy and *HER2*-targeted drugs: results from the European EUHER2 cohort (101 patients)

Overall response rate (ORR), disease control (DC), progression-free survival (PFS, weeks), and overall survival (OS, weeks) according to drug type

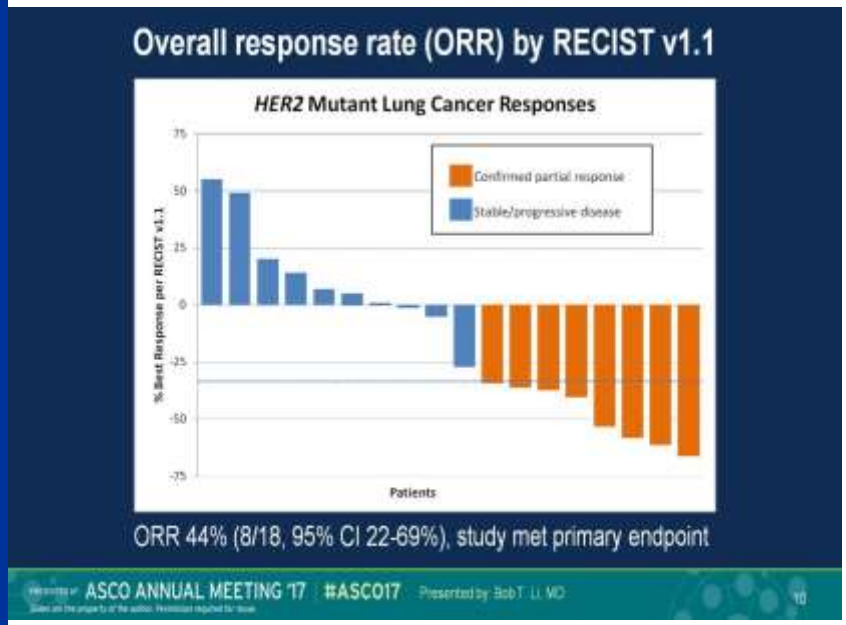
Treatment	*n*	ORR	DC	PFS median (95% CI)	OS median (95% CI)
First-line: without HER2-targeting treatment	93	43.5%	70.7%	6 (5; 7.1)	24 (19.1; 36.4)
Second-line: without HER2-targeting treatment	52	10%	36%	4.3 (3.1; 5)	19.4 (9.6; 24.7)
EGFR-TKI [a]	26	7.6%	26.8%	2.99 (1.87; 4.47)	20.14 (7.14; 32.95)
Trastuzumab combination, T-DM1 [a]	58	50.9%	75.5%	4.8 (3.4; 6.5)	13.3 (8.1; 15)
Neratinib, lapatinib, and afatinib [a]	29	7.4%	55.5%	3.4 (2.4; 4)	6.5 (4.7; 30.6)

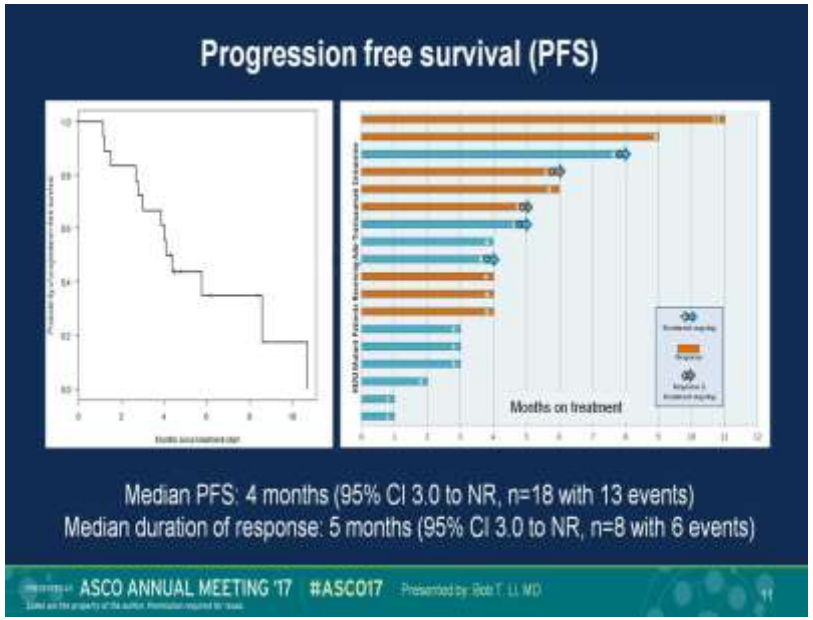
[a] If the same drug has been given more than one time, the results presented here are from their first administration.

Mazieres et al. Ann Oncol. 2016 Feb;27(2):281-6

T-DM1 in HER-2 mutation

T-DM1 in lung ADC with HER2 mutations





Li et al. J Clin Oncol 35, 2017 (suppl; abstr 8510)

HER-2 current status

HER2 in NSCLC – Other Studies

- HER2-mut and response to **trastuzumab** ***(Cappuzzo NEJM 06)***

- **Dacomitinib** ***(Kris Ann Oncol 15)***
  - 26 p with HER2-mut, 3 PR (12%) / mOS 9 mo
  - 4 p with HER2 amplification, no responses

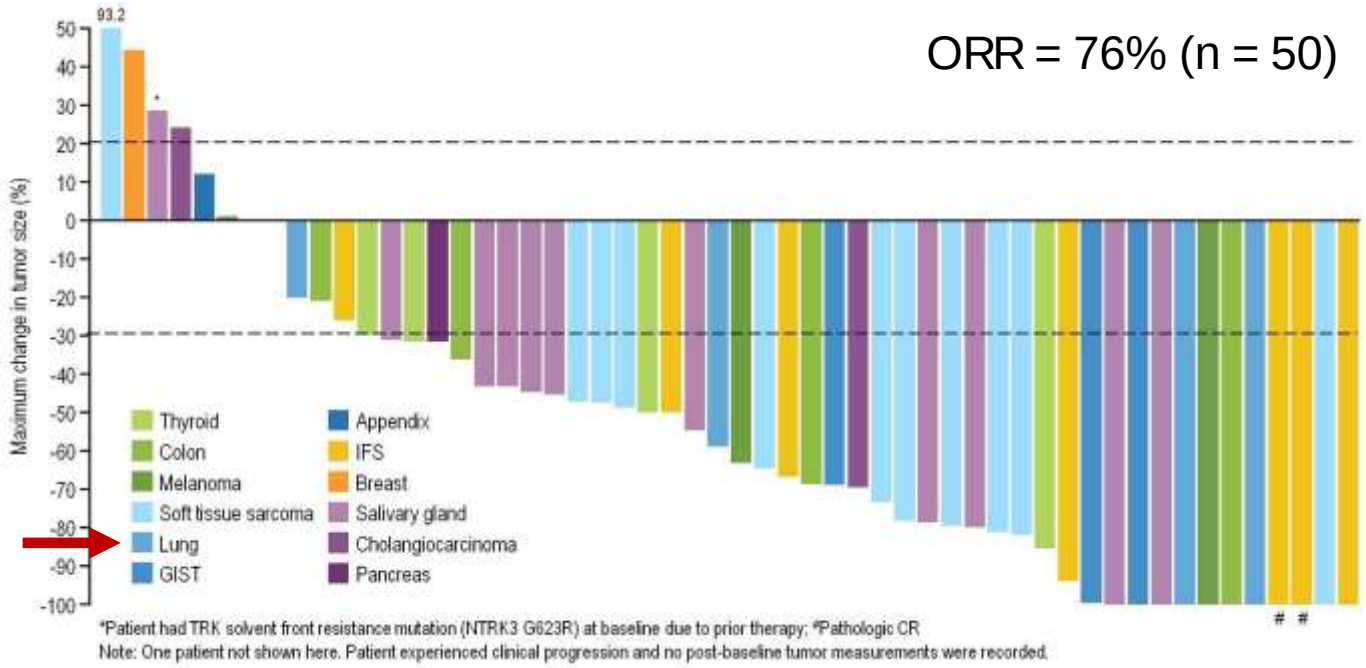
- Stage I of a 2-stage phase II comparing **neratinib with/without temsirolimus** in NSCLC pts with HER2-mut ***(Besse ESMO 14)***
  - 13 pts received neratinib, 14 pts neratinib/temsirolimus
  - Neratinib arm: 54% SD / 46% PD; PFS 2.9 mo
  - Neratinib/temsirolimus: 21% PR / 79% SD; PFS 4.0 mo

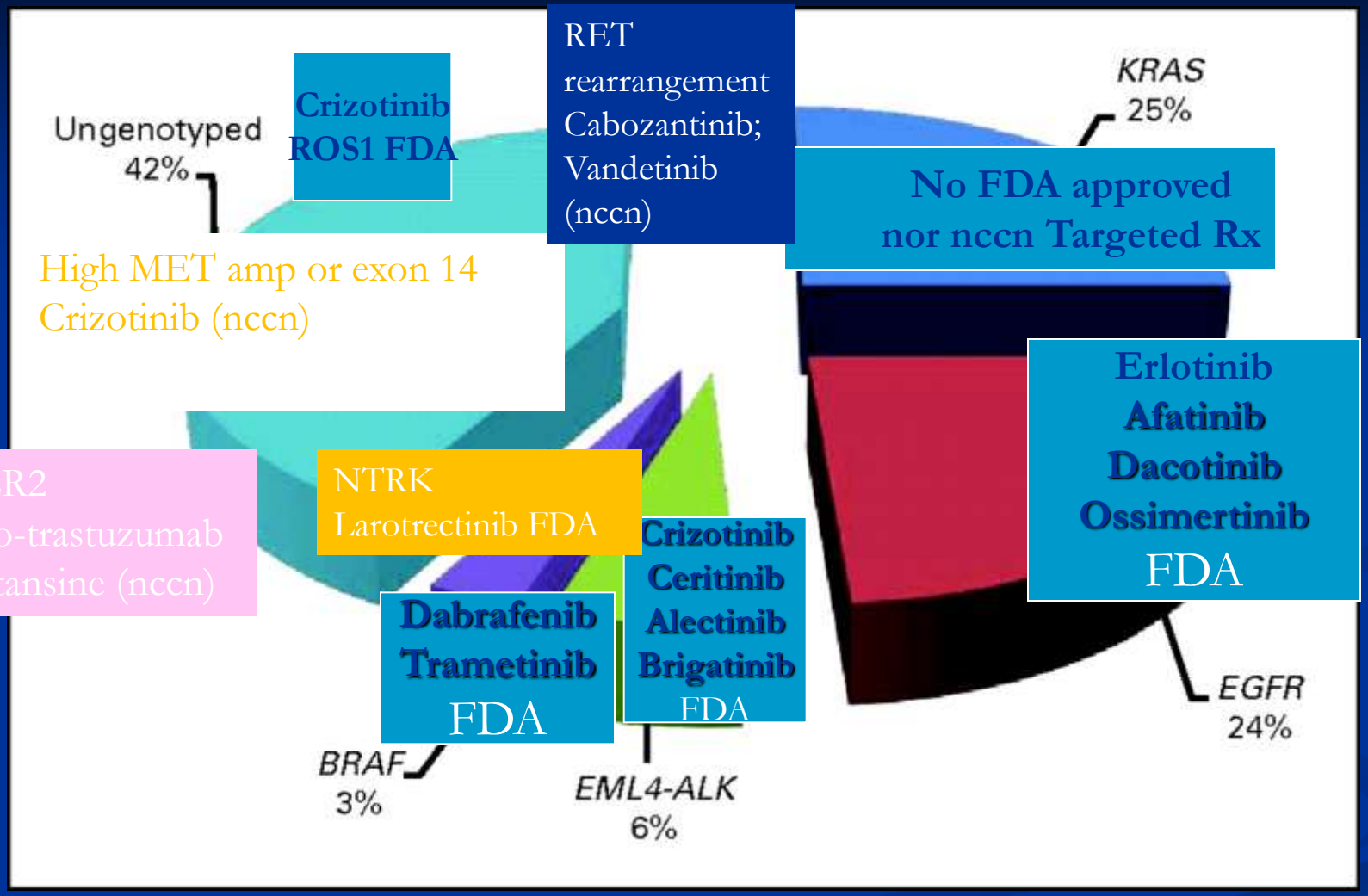
- Phase II study of **T-DM1** monotherapy in relapsed NSCLC with documented HER2 positivity (***Hotta JTO 2018***) (IHC 3+, IHC 2+ and FISH+ or exon 20 mut)
  - 15 patients
  - PR 6.7% (1/15), SD 46.7%, PD 46.7%
  - mPFS 2.0 mo, mOS 10.9 mo

- **Future aspects**: 3rd gen EGFR TKI **Osimertinib** for HER2 aberrations (mouse models) (***Liu CCR 2018***), **neratinib/trastuzumab** in HER2 mutant lung cancer (patient derived tumor organoids) (***Paweletz WCLC 2017***)

NTRK fusion - Larotrectinib

Efficacy of larotrectinib in *NTRK1/2/3* fusion cancers



Hyman et al., ASCO 2017

Summary of targeted agents for driver mutations