Targeted Therapy for NSCLC

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Disclosures

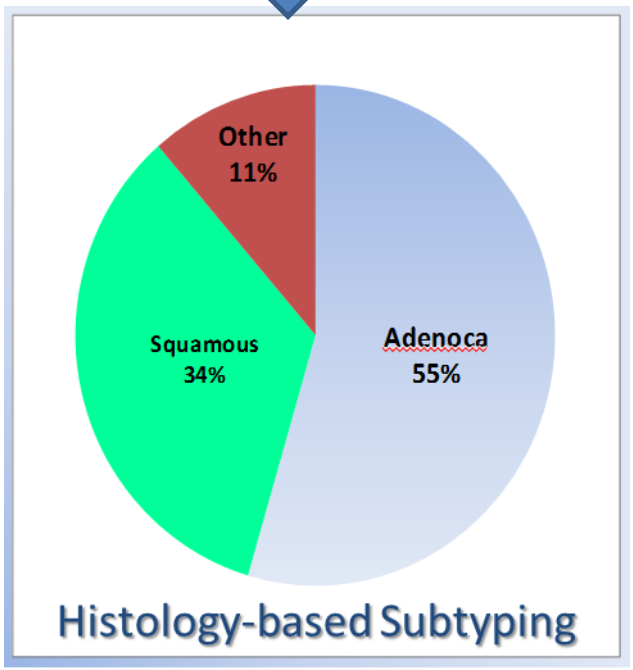
- Relevant financial relationships in the past 12 months.

- Consultant: Abbvie, Celgene, Takeda/Ariad, Biodesix

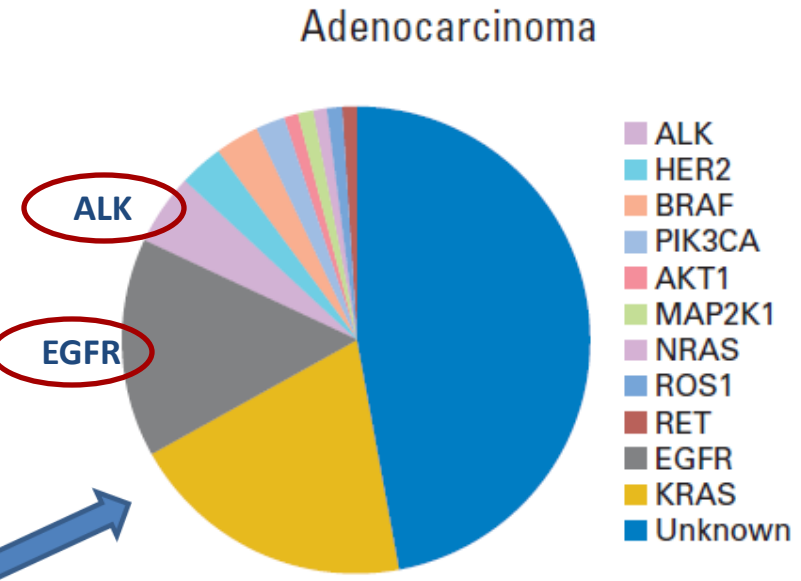
- The speaker will directly disclose the use of products for which are not labeled.

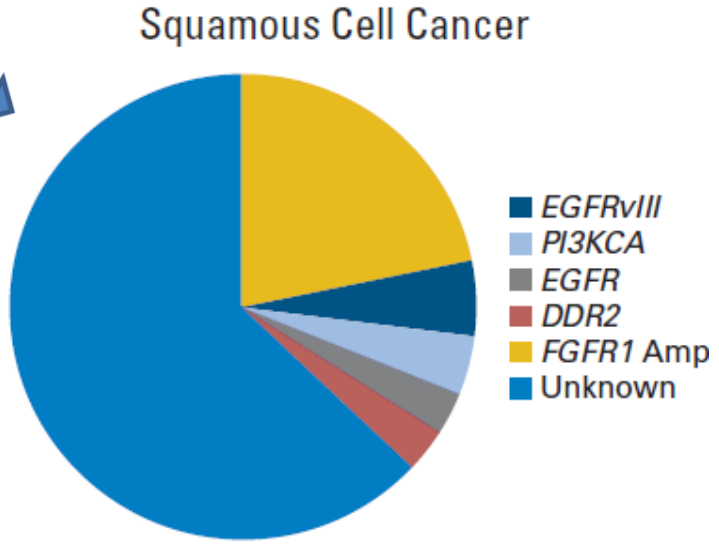
Evolution of NSCLC Subtyping from Histologic to Molecular-Based

NSCLC as one disease



First Targeted Therapies In NSCLC





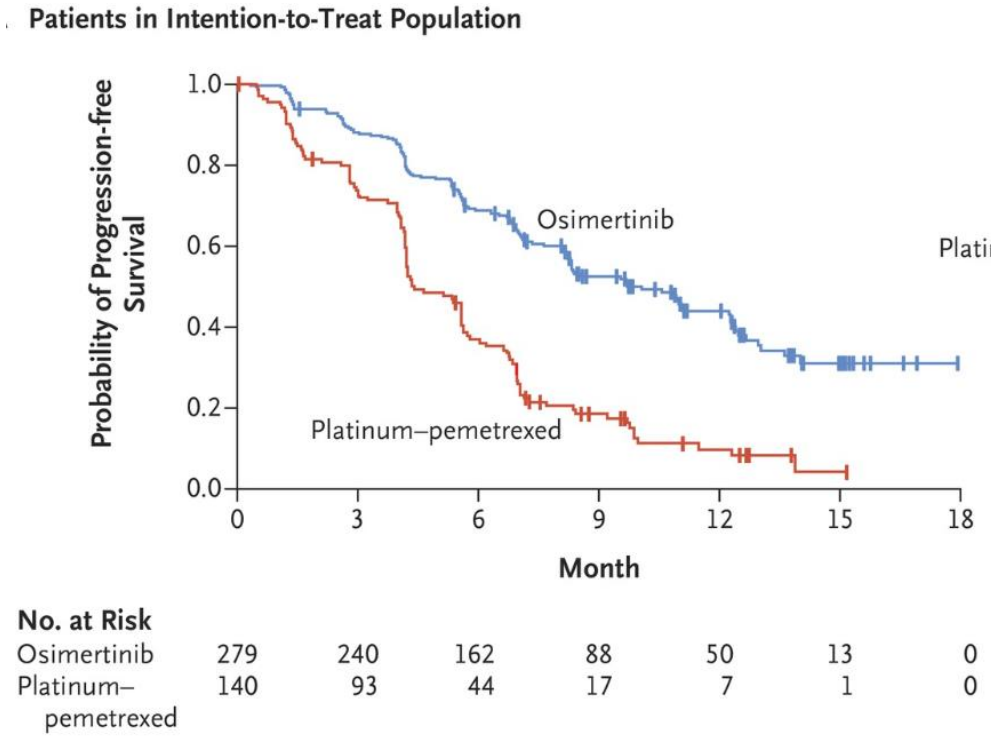
Randomized Studies of First-Line EGFR TKIs in Patients With *EGFR* Mutations

Author	Study	Agent	N (*EGFR* mut+)	RR	Median PFS (mo)	OS (mo)
Mok et al	IPASS	Gefitinib	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
Han et al	First-SIGNAL	Gefitinib	42	84.6% vs 37.5%	8.0 vs 6.3	27.2 vs 25.6
Mitsudomi et al	WJTOG 3405	Gefitinib	172	62.1% vs 32.2%	9.2 vs 6.3	30.9 vs NR
Maemondo et al	NEJGSG002	Gefitinib	230	73.7% vs 30.7%	10.8 vs 5.4	30.5 vs 23.6
Zhou et al	OPTIMAL	Erlotinib	154	83% vs 36%	13.7 vs 4.6	22.7 vs 28.9
Rosell et al	EURTAC	Erlotinib	174	58% vs 15%	9.7 vs 5.2	19.3 vs 19.5
Wu et al	ENSURE	Erlotinib	217	62.7% vs 33.6%	11.0 vs 5.5	26.3 vs 25.5
Sequist et al	LUX-Lung 3	Afatinib	345	56% vs 23%	13.6 vs 6.9	30.3 vs 26.2
Wu et al	LUX-Lung 6	Afatinib	364	67% vs 23%	11.0 vs 5.6	22.1 vs 22.2

EGFR, epidermal growth factor receptor; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.

Mok TS, et al. *N Engl J Med*. 2009;361(10):947-957. Han JY, et al. *J Clin Oncol*. 2012;30(10):1122-1128. Mitsudomi T, et al. *Lancet Oncol*. 2010;11(2):121-128. Maemondo M, et al. *N Engl J Med*. 2010;362(25):2380-2388. Zhou C, et al. *Lancet Oncol*. 2011;12(8):735-742. Zhou C, et al. *J Clin Oncol*. 2012;30(Suppl): Abstract 7520. Rosell R, et al. *Lancet Oncol*. 2012;13(3):239-246. Wu YL, et al. *Ann Oncol*. 2015;26:1883-1889. Sequist LV, et al. *J Clin Oncol*. 2013;31(27):3327-3334. Wu YL, et al. *Lancet Oncol*. 2014;15(2):213-222.

Osimertinib in T790M Acquired Resistance

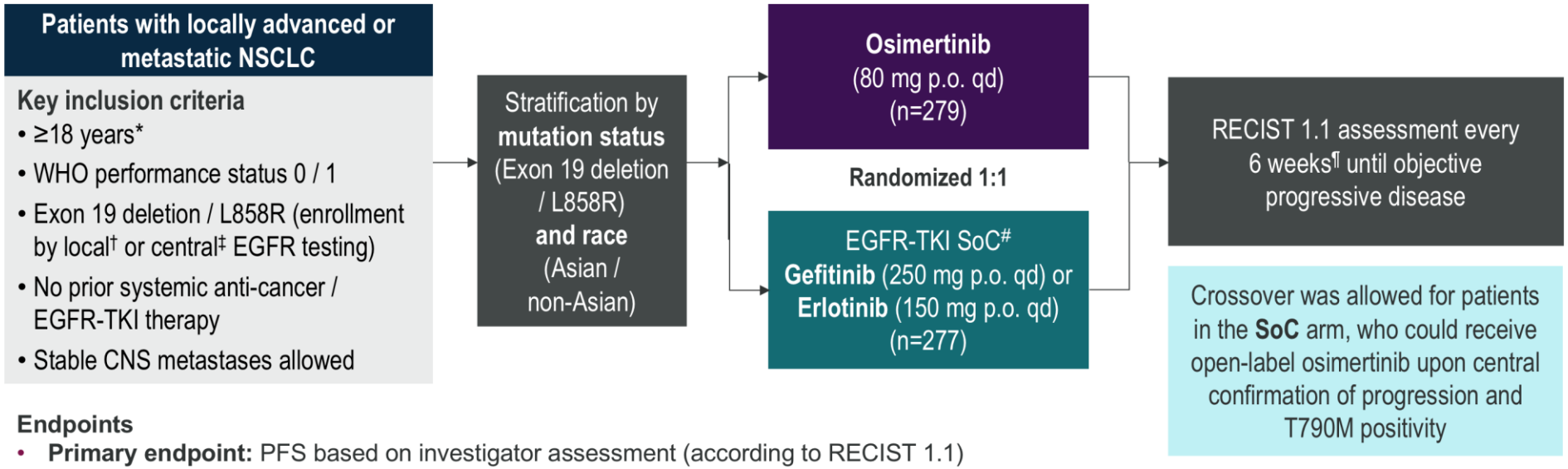


	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

Mok et al, N Engl J Med, 2017

FLAURA Study Design



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

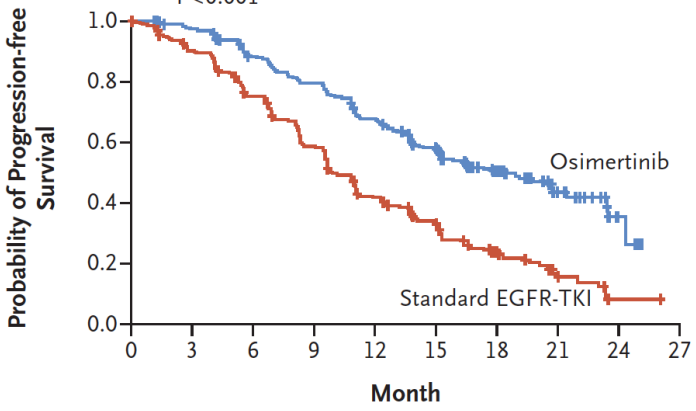
Soria et al, N Engl J Med, 2018

FLAURA: Efficacy

Progression-free Survival in Full Analysis Set

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

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



No. at Risk

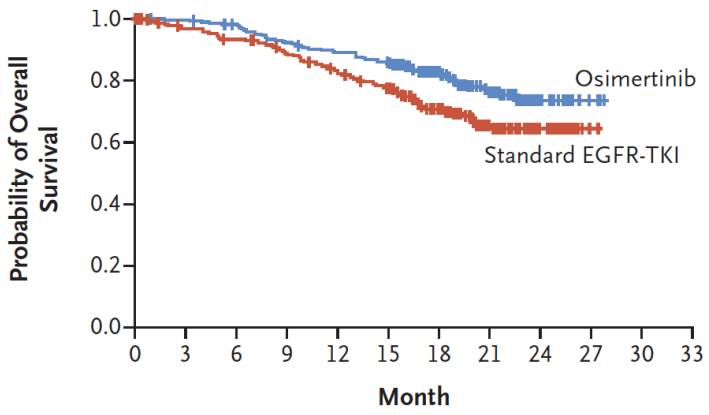
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

Soria et al, N Engl J Med, 2018

Overall Survival

	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

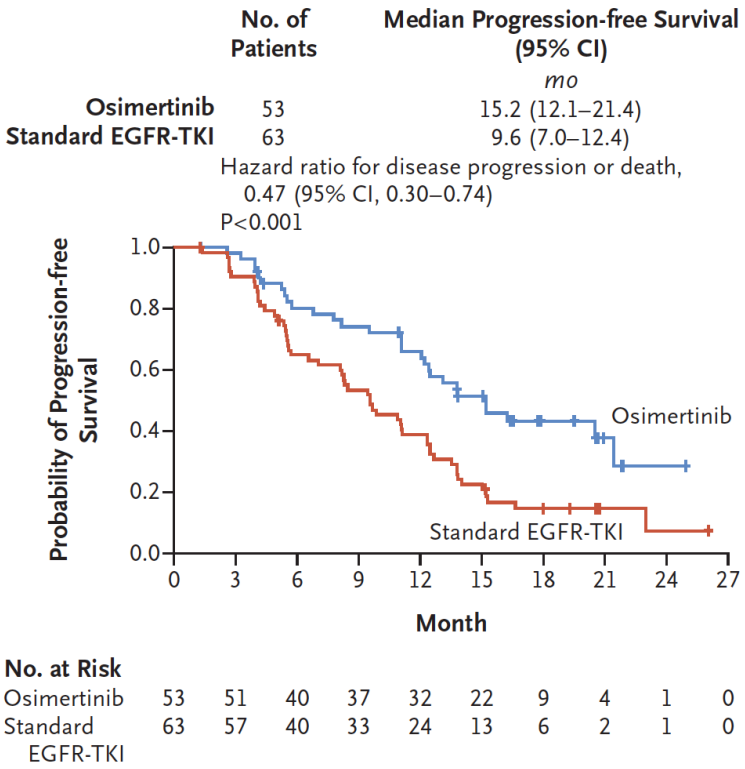
Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



No. at Risk

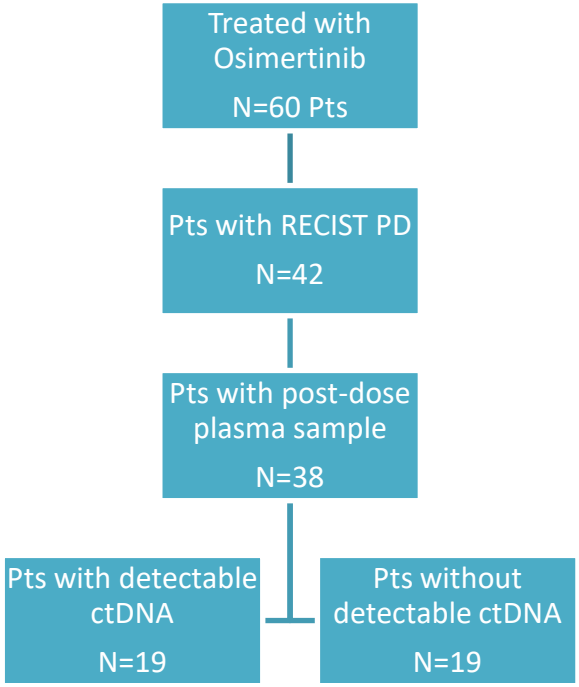
Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

PFS in Patients with Brain Metastasis



Soria et al, N Engl J Med, 2018

Resistance to 1st Line Osimertinib



Resistance mechanisms	N
EGFR C797S	2
JAK2 V617F	1
PIK3CA E545K	1
HER2 ex20 Ins	1
MEK1 G128V	1
KRAS G12D	1
MET CNV	1
KRAS CNV	1
Other mutations identified post-dose: P53 (N=7); RB1 (N=4).	

Mean TTP

No detectable ctDNA: 19.6m

Detectable ctDNA: 13.1m

Ramalingam et al, J Clin Oncol, 2017

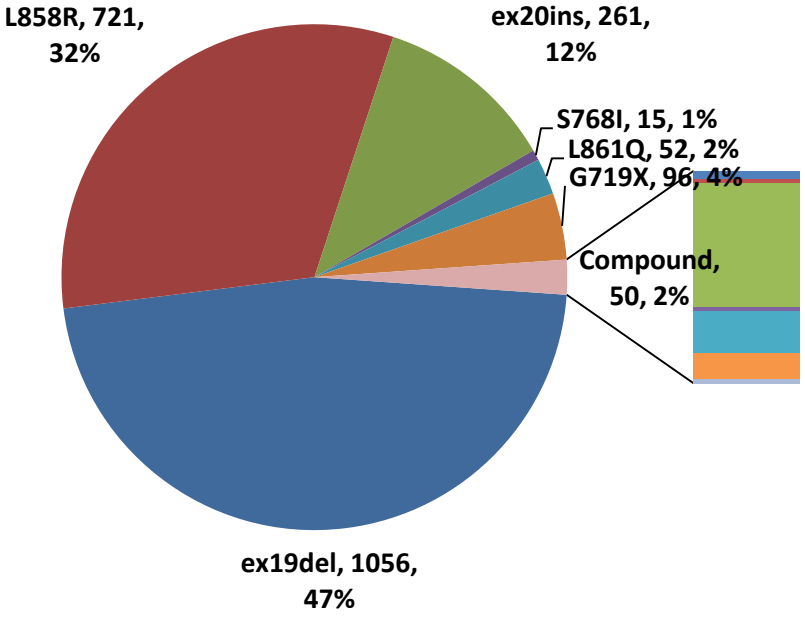
ARTICLES
https://doi.org/10.1038/s41591-018-0007-9
nature medicine

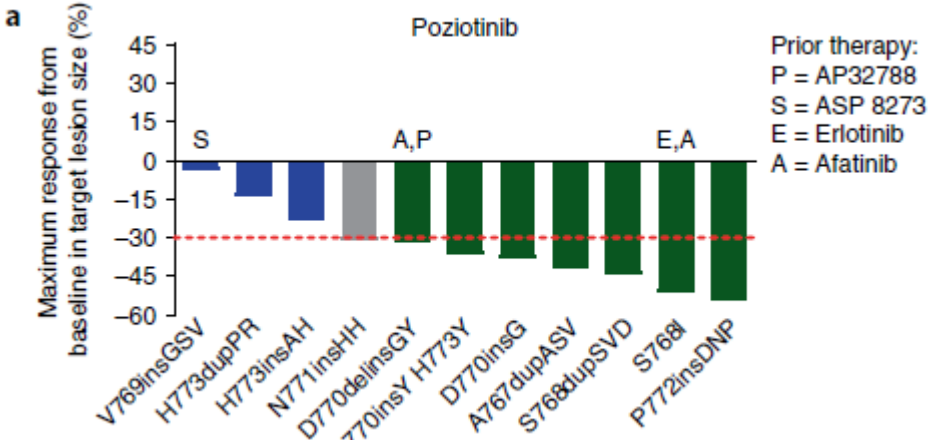
Mechanisms and clinical activity of an EGFR and HER2 exon 20–selective kinase inhibitor in non–small cell lung cancer

Jacqulyne P. Robichaux[1], Yasir Y. Elamin[1], Zhi Tan[2], Brett W. Carter[3], Shuxing Zhang[2], Shengwu Liu[4], Shuai Li[4], Ting Chen[4], Alissa Poteete[1], Adriana Estrada-Bernal[5], Anh T. Le[5], Anna Truini[6], Monique B. Nilsson[1], Huiying Sun[1], Emily Roarty[1], Sarah B. Goldberg[6,7], Julie R. Brahmer[8], Mehmet Altan[1], Charles Lu[1], Vassiliki Papadimitrakopoulou[1], Katerina Politi[6,7,9], Robert C. Doebele[5], Kwok-Kin Wong[10] and John V. Heymach[1]*

Although most activating mutations of epidermal growth factor receptor (EGFR)-mutant non–small cell lung cancers (NSCLCs) are sensitive to available EGFR tyrosine kinase inhibitors (TKIs), a subset with alterations in exon 20 of *EGFR* and *HER2* are intrinsically resistant and lack an effective therapy. We used in silico, in vitro, and in vivo testing to model structural alterations induced by exon 20 mutations and to identify effective inhibitors. 3D modeling indicated alterations restricted the size of the drug-binding pocket, limiting the binding of large, rigid inhibitors. We found that poziotinib, owing to its small size and flexibility, can circumvent these steric changes and is a potent inhibitor of the most common EGFR and HER2 exon 20 mutants. Poziotinib demonstrated greater activity than approved EGFR TKIs in vitro and in patient-derived xenograft models of EGFR or HER2 exon 20 mutant NSCLC and in genetically engineered mouse models of NSCLC. In a phase 2 trial, the first 11 patients with NSCLC with *EGFR* exon 20 mutations receiving poziotinib had a confirmed objective response rate of 64%. These data identify poziotinib as a potent, clinically active inhibitor of *EGFR* and *HER2* exon 20 mutations and illuminate the molecular features of TKIs that may circumvent steric changes induced by these mutations.

EGFR Exon 20 Ins NSCLC





Other drugs in development

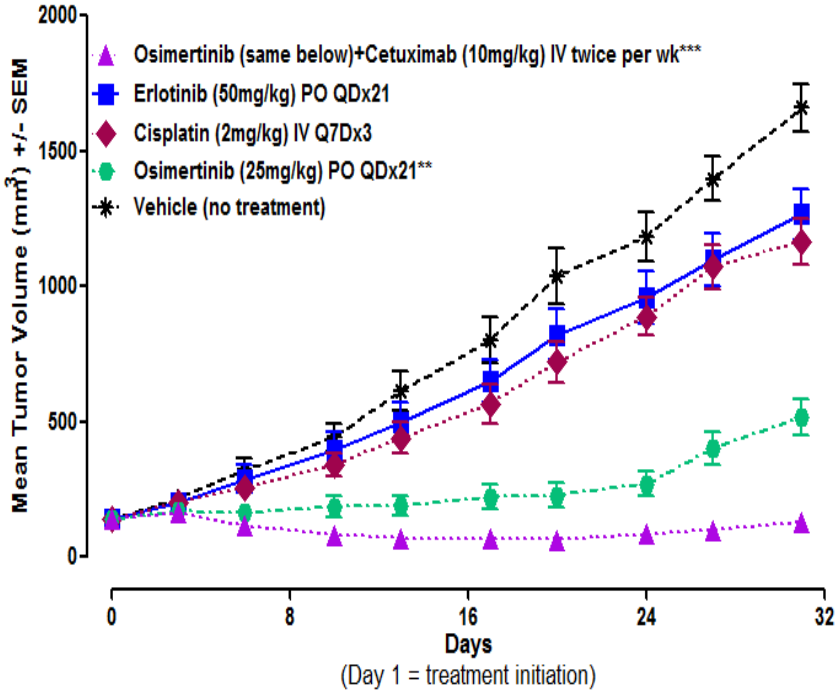
TAK788

Osimertinib

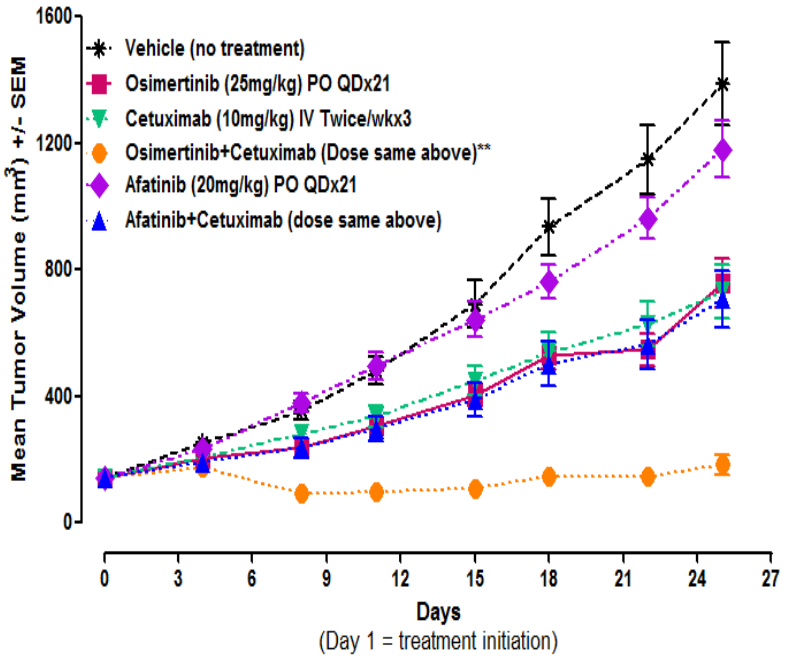
EGF816

Osimertinib and Necitumumab (PHI-77)

EGFR Exon 20 Insertion PDX (S768_D770dupSVD)/*EGFR* amplification with Tumor Growth Inhibition to Osimertinib and Cetuximab

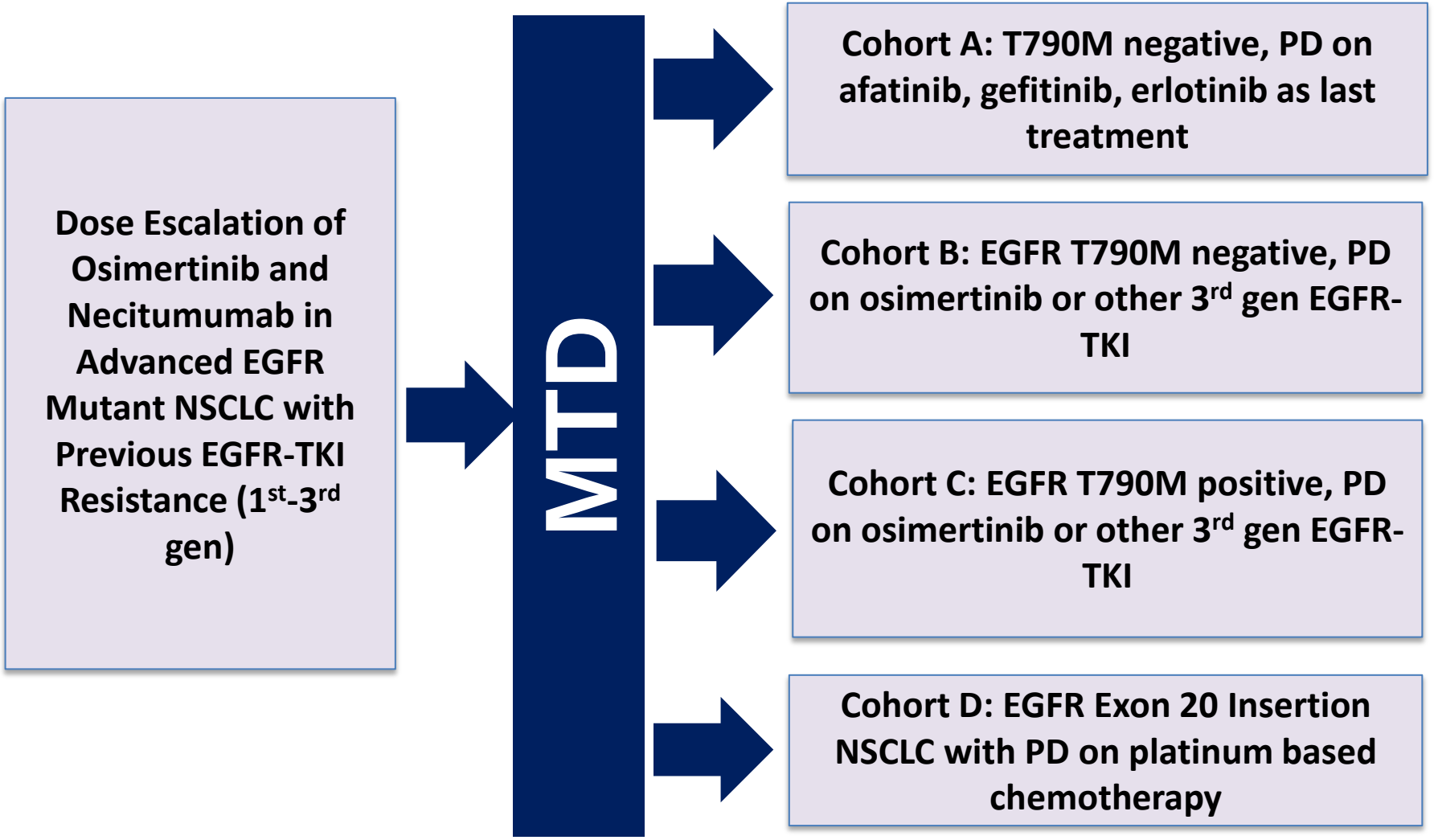


** & *** P<0.05; Compared to Vehicle group. One-way ANOVA followed Dunnett's Multiple Comparison test.

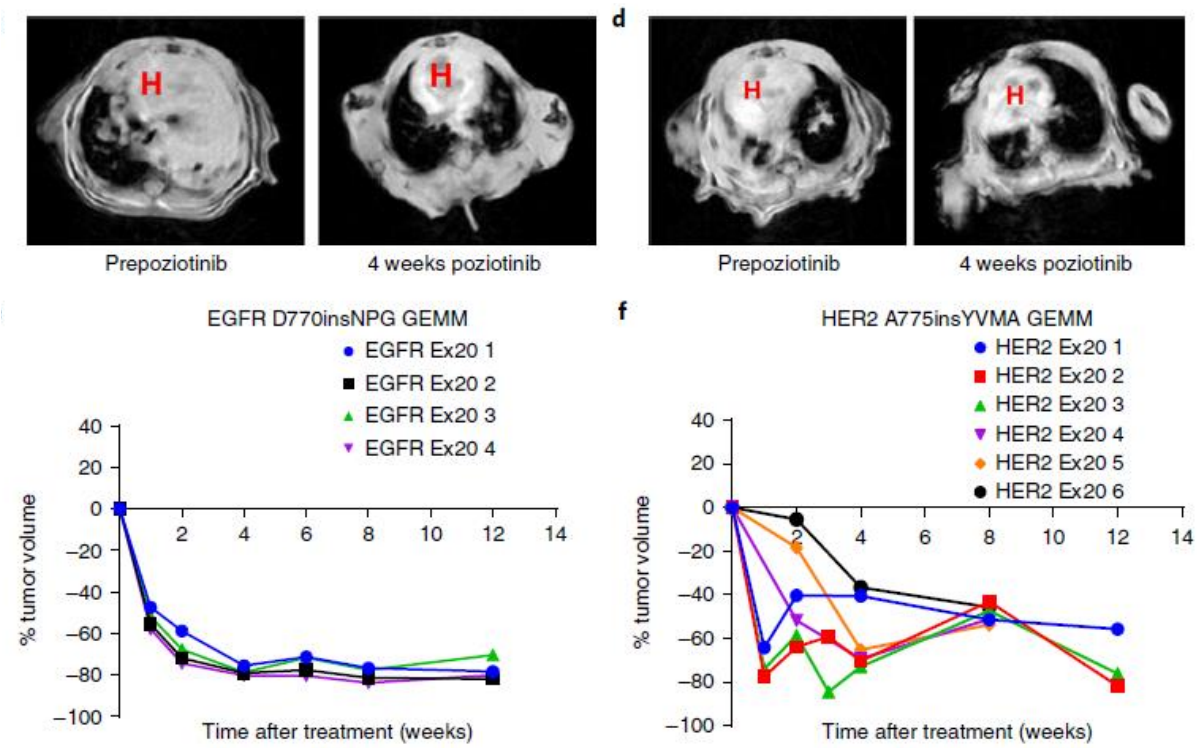


** P<0.05; Compared to Vehicle group. One-way ANOVA followed Dunnett's Multiple Comparison test.

A Phase I Trial of Osimertinib and Necitumumab in EGFR Mutant NSCLC with Previous EGFR-TKI Resistance

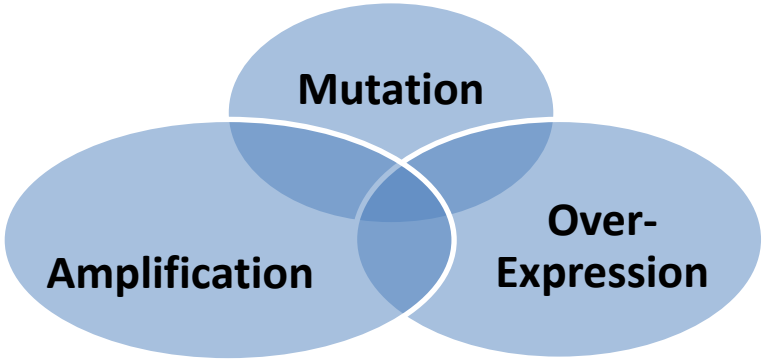


Poziotinib is effective in pre-clinical models of both EGFR Exon 20 & HER2 Exon 20 insertion mutations



Robichaux, Heymach et al: NatureMed 2018

Relative Non-Overlap of HER2 Alterations in NSCLC



Author (N of cases)		Amplification (FISH)	Mutation	Amp /Mut Overlap
		Prevalence	Prevalence	
Hosokawa (N=1,126)	Asia (Japan)	5.3%	1.9%	1 / 227
Mazieres (N=3,800)	Europe	9%	1.7%	3 / 34
Arcila (N=1,478)	USA	2%	1.7%	No
Goss (N=245; SQ)	Global	NA	4.9%	NA

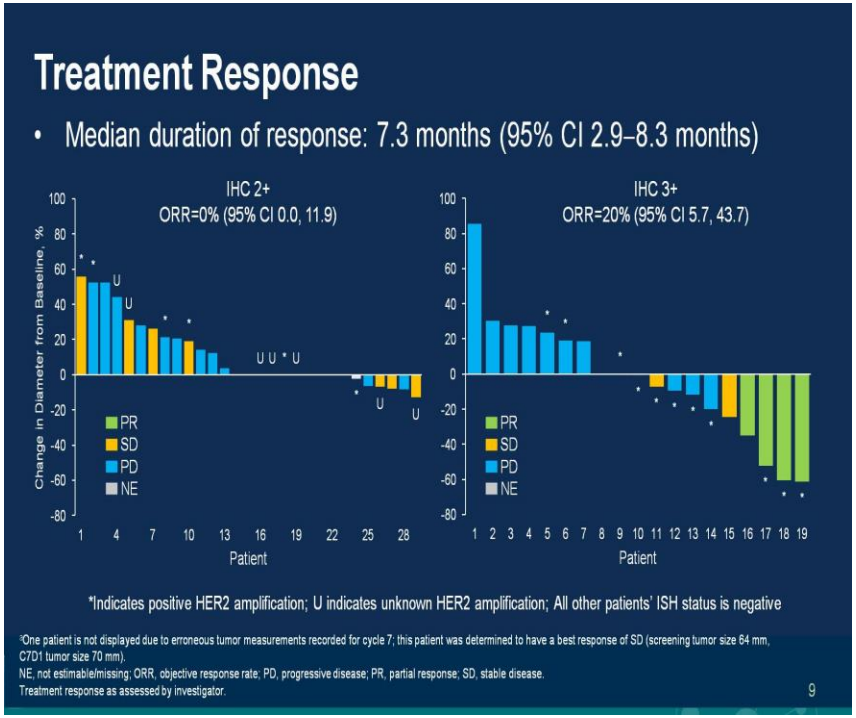
Targeted TKIs for HER2 mutant Cancers

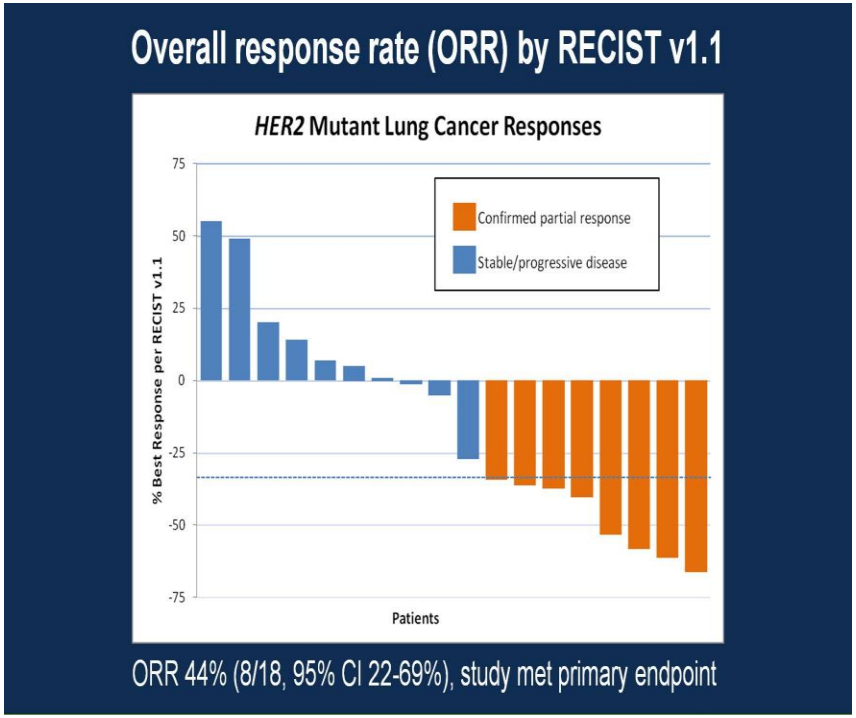
Targeted Agent	Author	Response Rate
Neratinib	Gandhi	0/17 (0%)
Neratinib+Temsirolimus	Gandhi	8/43 (19%)
Afatinib	Lai	3/22 (14%)
Dacomitinib	Kris	3/26 (12%)

What's New?
Ado-Trastuzumab Emtansine
Afatinib in SQ-HER2-mutated
Poziotinib (pre-clinical)

Kris et al. *Ann Oncol* 2015
Gandhi et al. *WCLC* 2016
Lai et al. *ASCO* 2017

Ado-Trastuzumab Emtansine in Lung Cancer HER2 Overexpression vs. *HER2* mutation

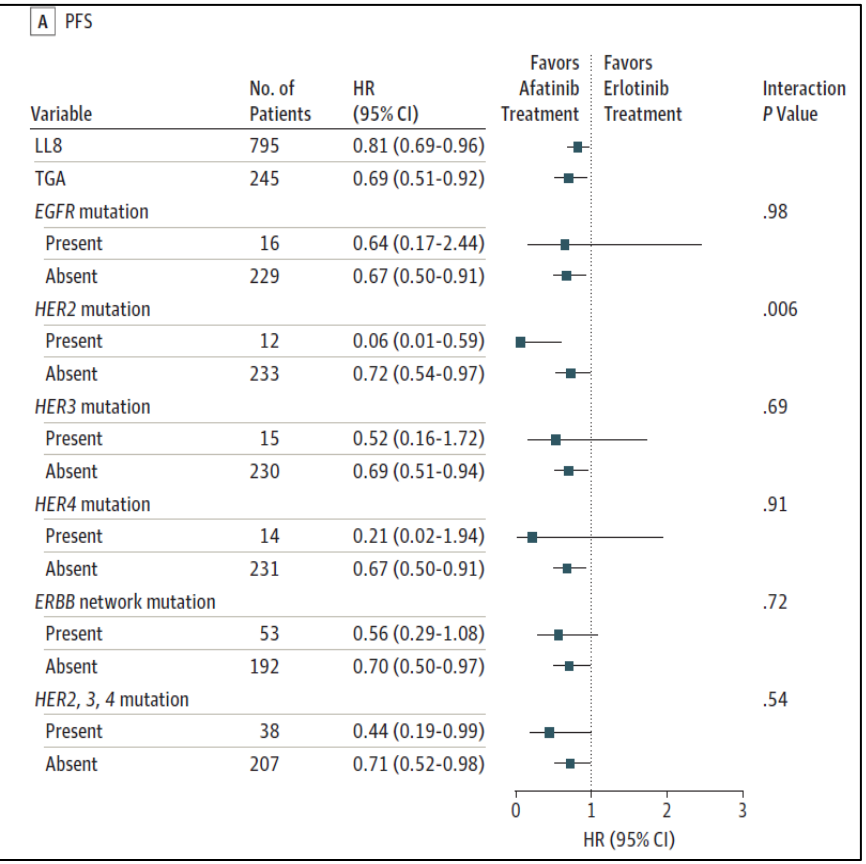


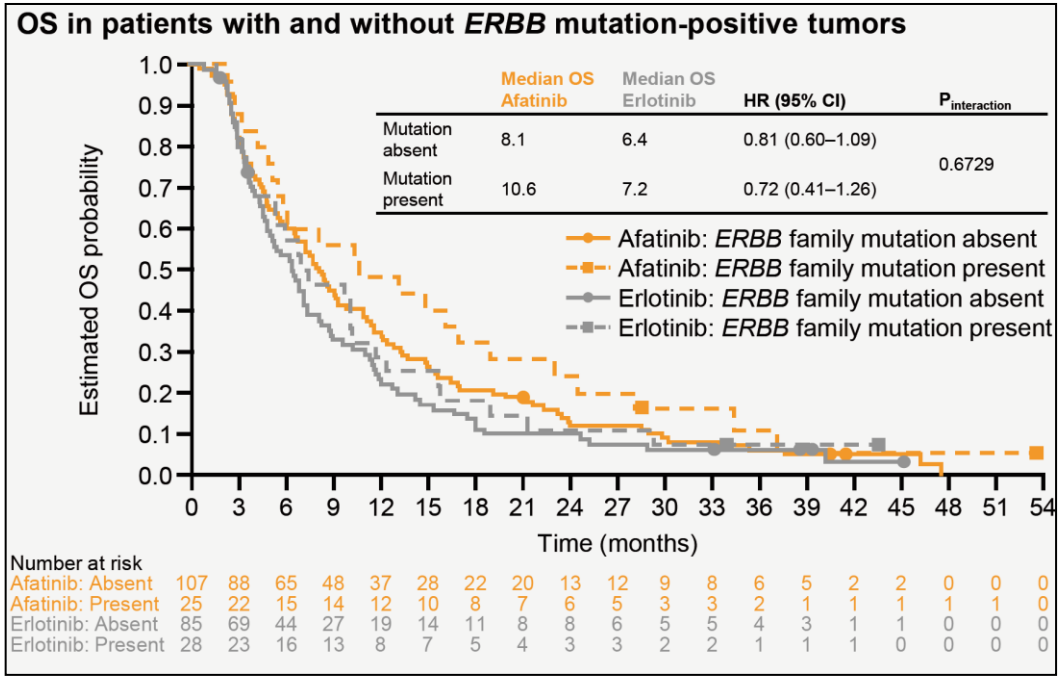


Stinchcombe T, et al. ASCO 2017 (abstr 8509)

Li et al. ASCO 2017 & JCO 2018

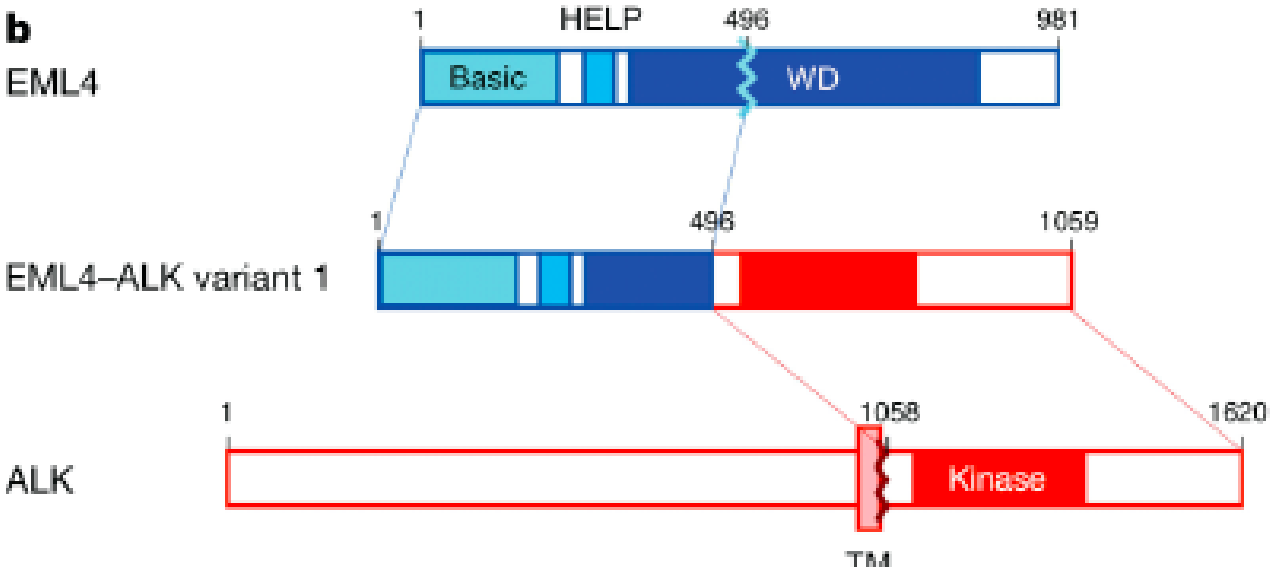
ERBB Family Mutation-Positive vs Negative Cancers in LUX-Lung 8





Goss et al. *JAMA Oncol*. 2018

ALK is a fusion oncogene

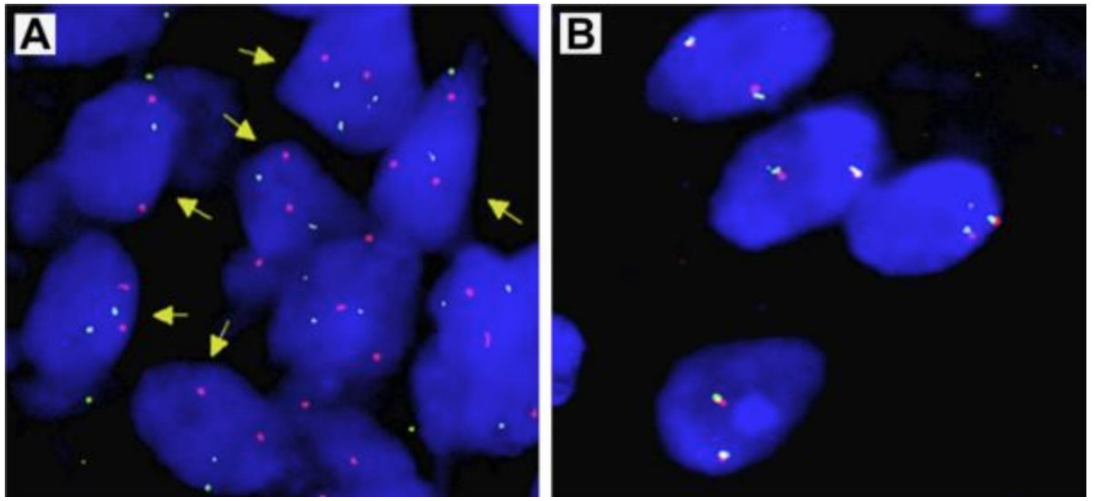


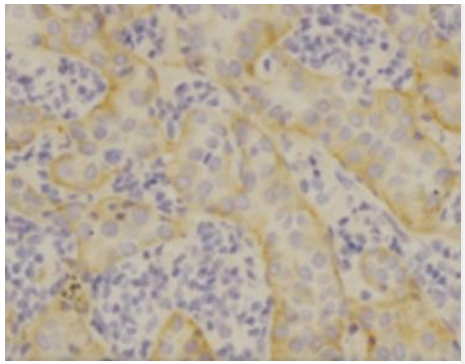
- ligand-independent constitutive activation of ALK tyrosine kinase
- detection methods: FISH, IHC, NGS
- 3-7% frequency NSCLC
- **See slides from Lung Cancer Case Presentation**

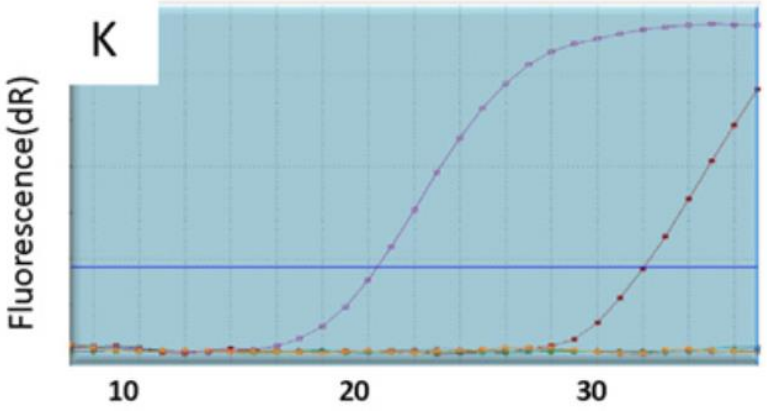
Soda M et al. Nature. 2007 Aug 2;448(7153):561-6.

ROS1

- 1-2% of NSCLC-adenocarcinoma.
- ~2500 patients/annually
- ROS1 fusions (Chromosome 6) share sequence homology to ALK
- Transforming in preclinical models
- Detection by FISH and Sequencing methods (RT-PCR, NGS)

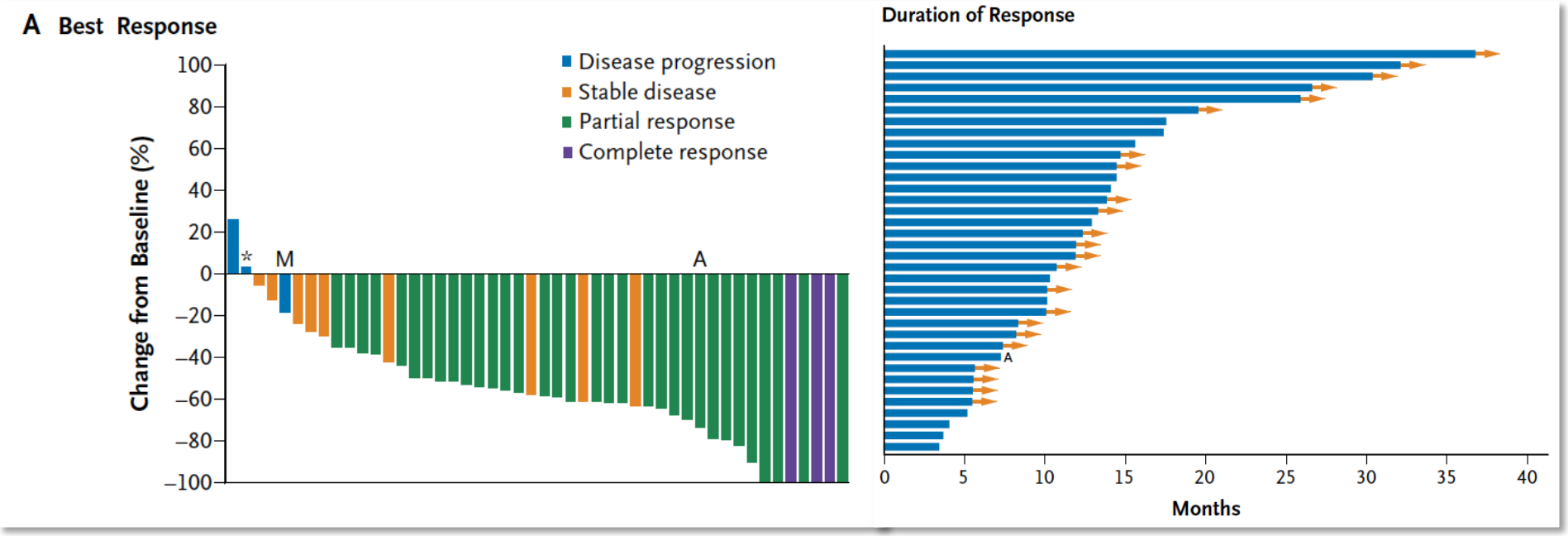






Bergenthon et al JCO 2012. Riess et al CLC 2013. Shan et al PLOS One 2015.

ROS1 Inhibition With Crizotinib

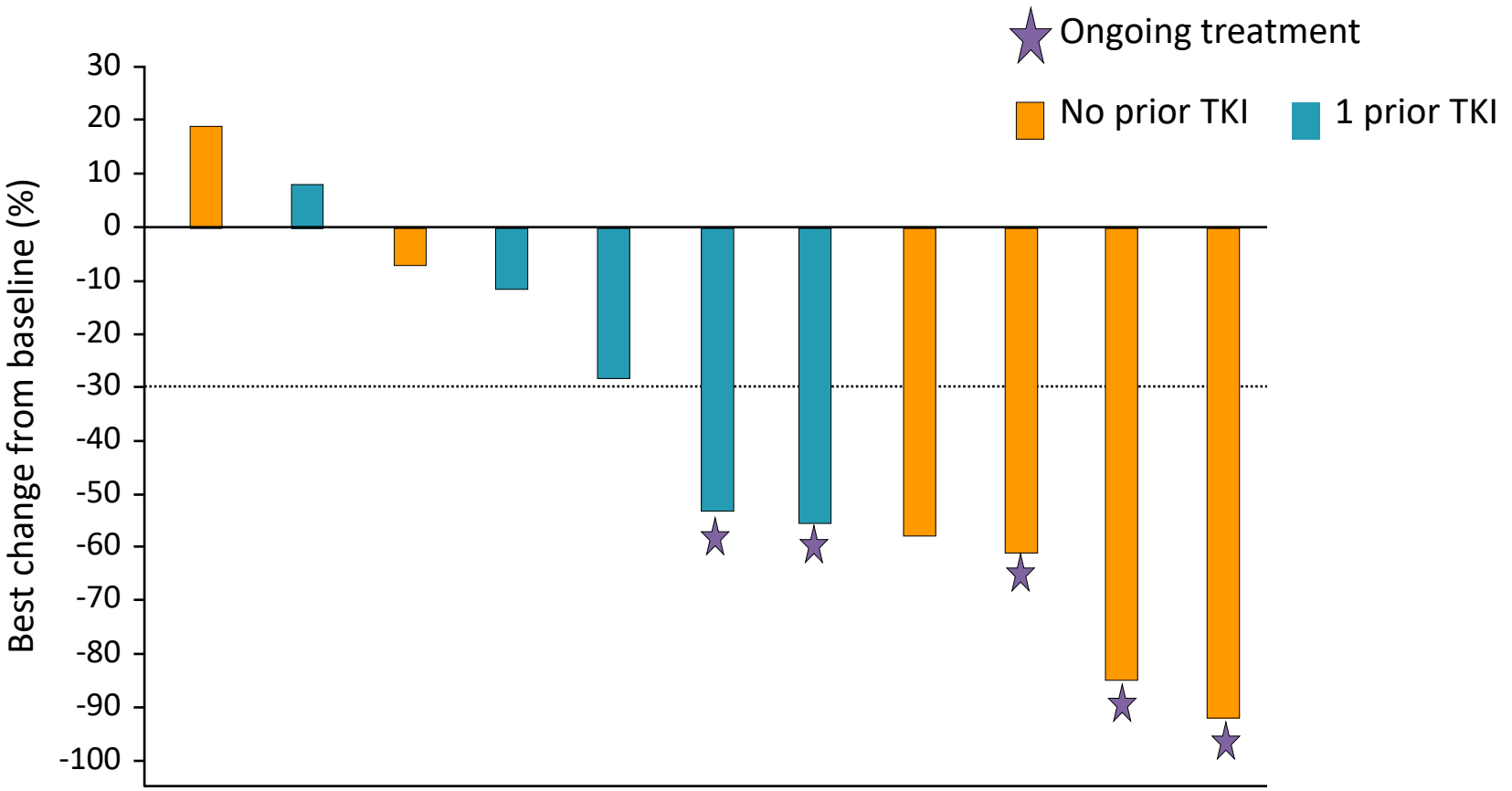


ORR = 72%

Median PFS = 19.2 mos.

AT Shaw et al NEJM 2014

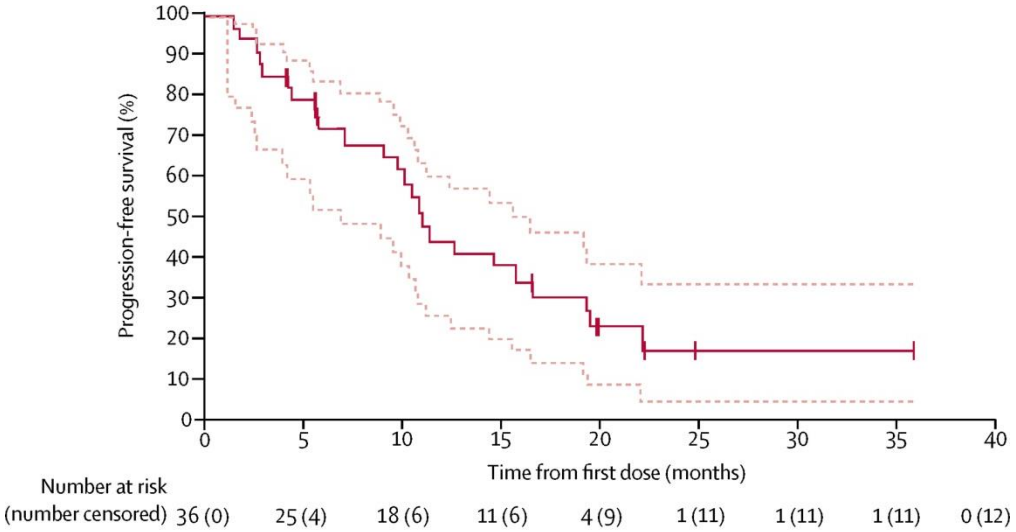
On Lorlatinib Majority of ROS1 patients had a Decrease in Target Lesion Size*

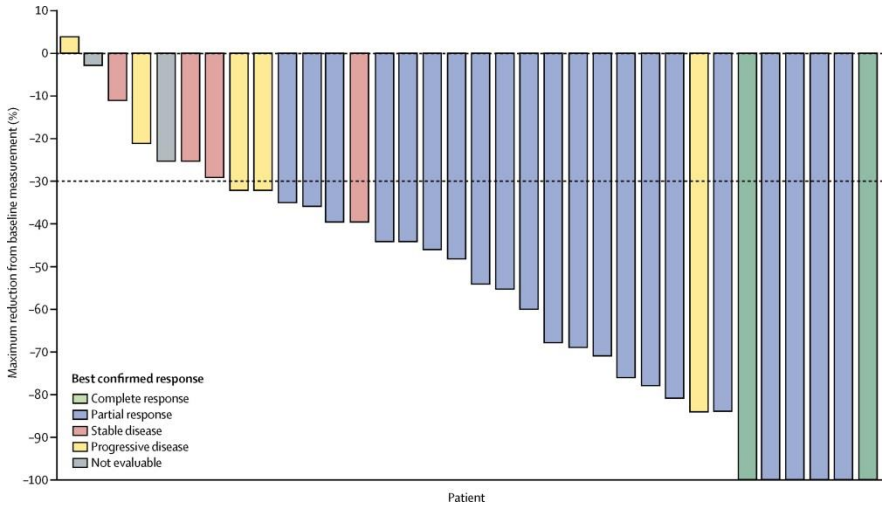


*Number of prior TKIs counted by line

Adapted from Solomon et al ASCO 2016

Dabrafenib and Trametinib in BRAF V600E/K NSCLC (~2%)

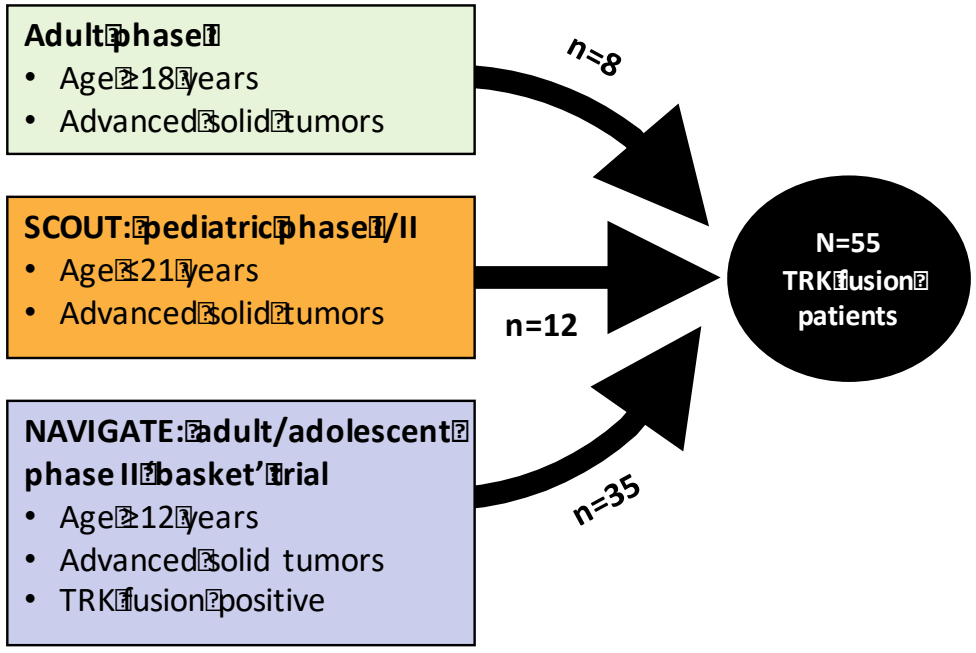




Drug	ORR	PFS
Dabrafenib+Trametinib	64%	10.9 months
Dabrafenib	33%	5.5 months
Vemurafenib	37%	6.5 months

D. Planchard et al. Lancet Oncol. 2017; V. Subbiah et al JCO 2017

Larotrectinib development program for *NTRK* fusion-positive cancers

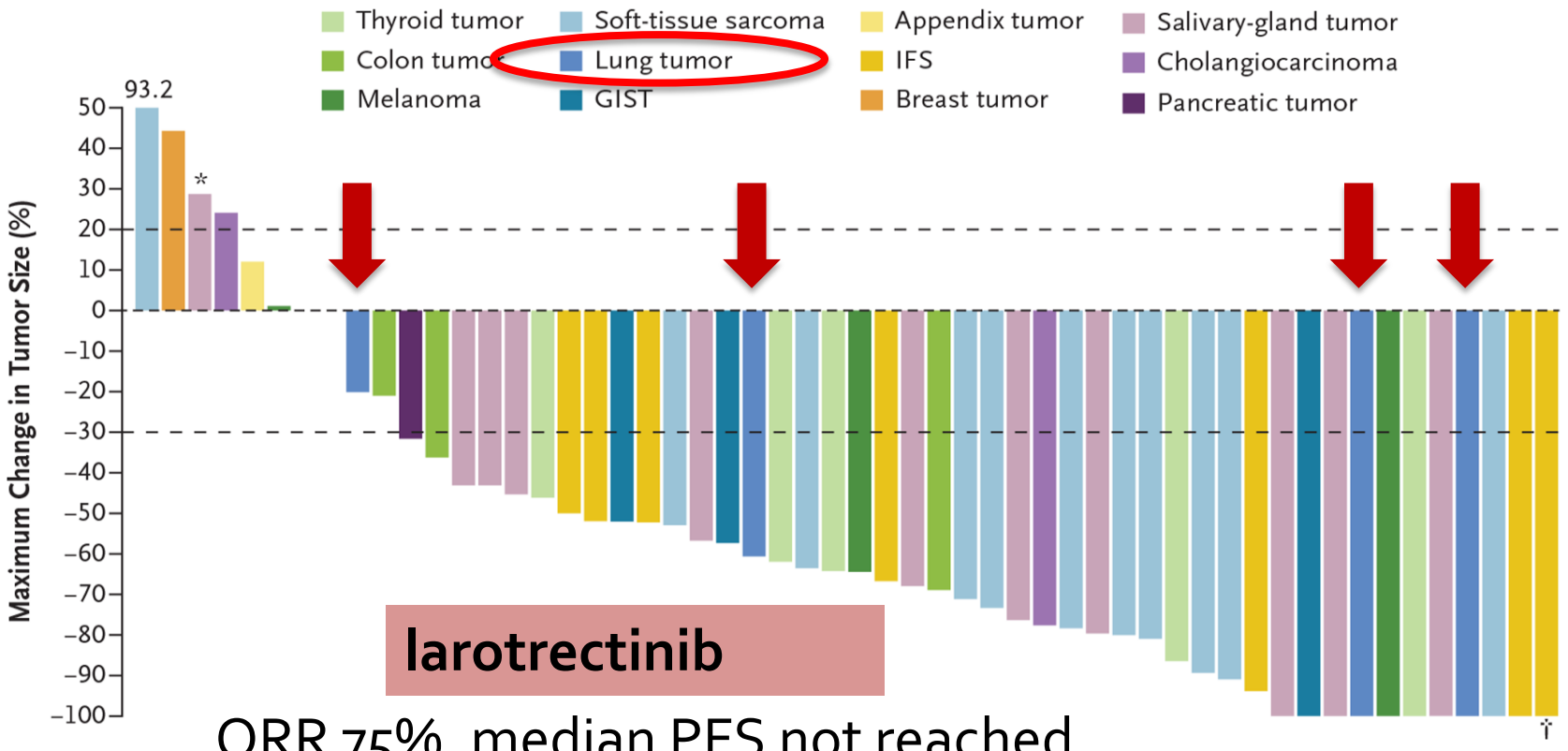


Data cut-off: April 14, 2017

- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (ORR)
  - RECIST v1.1 per investigator assessment
- **Secondary endpoints**
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Drilon et al, N Engl J Med 2017

NTRK fusion-positive cancers are sensitive to TRK TKI therapy in a tissue-agnostic manner



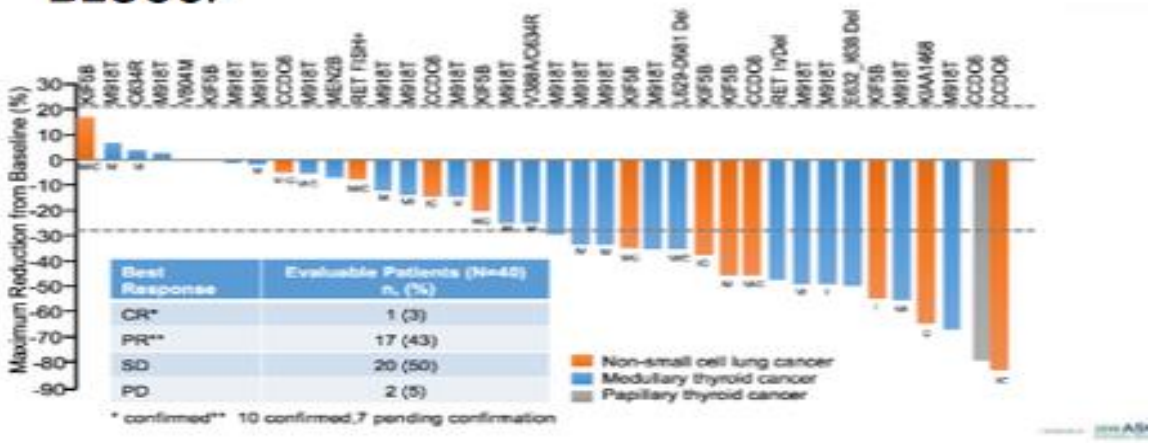
ORR 75%, median PFS not reached

Drilon et al, New Engl J Med 2017

RET Fusions in NSCLC

- ~2% NSCLC
- KIF5B most common fusion partner
- Previous RET inhibitors (cabozantinib about 33% ORR)

BLU667



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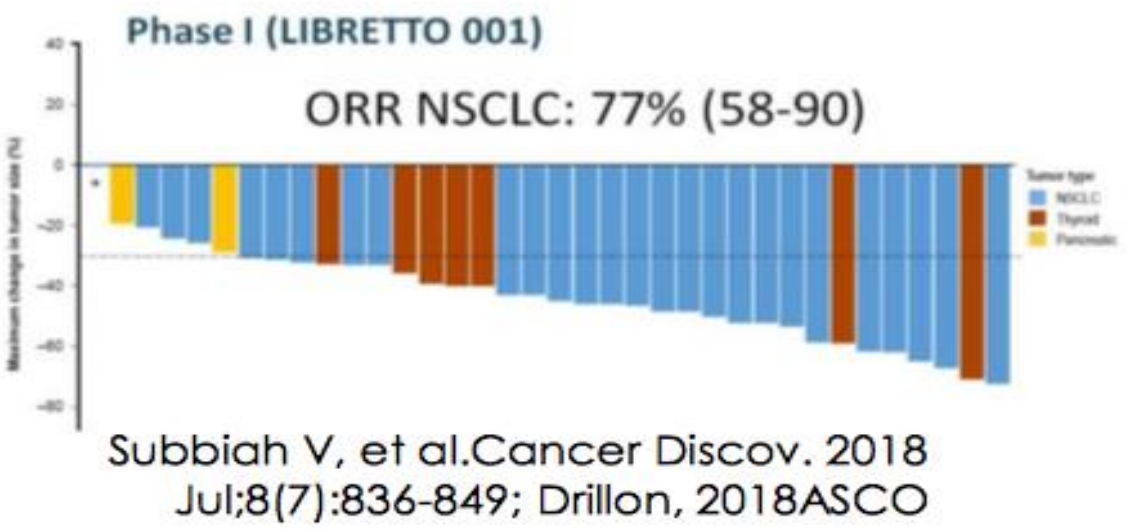
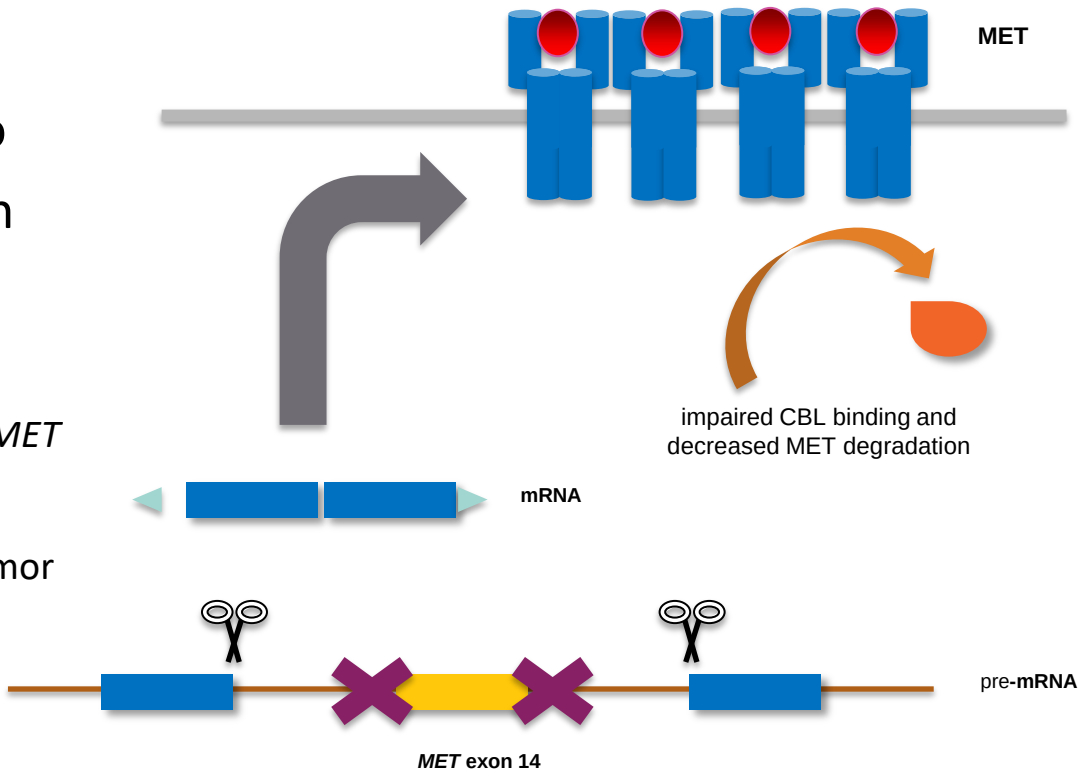


MET Exon 14 Alterations

- *MET* mutations that lead to decreased MET degradation
  - deletions, insertions, or base substitutions
  - many disrupt splice sites flanking *MET* exon 14 → exon 14 skipping
  - increased MET receptor on the tumor cell surface

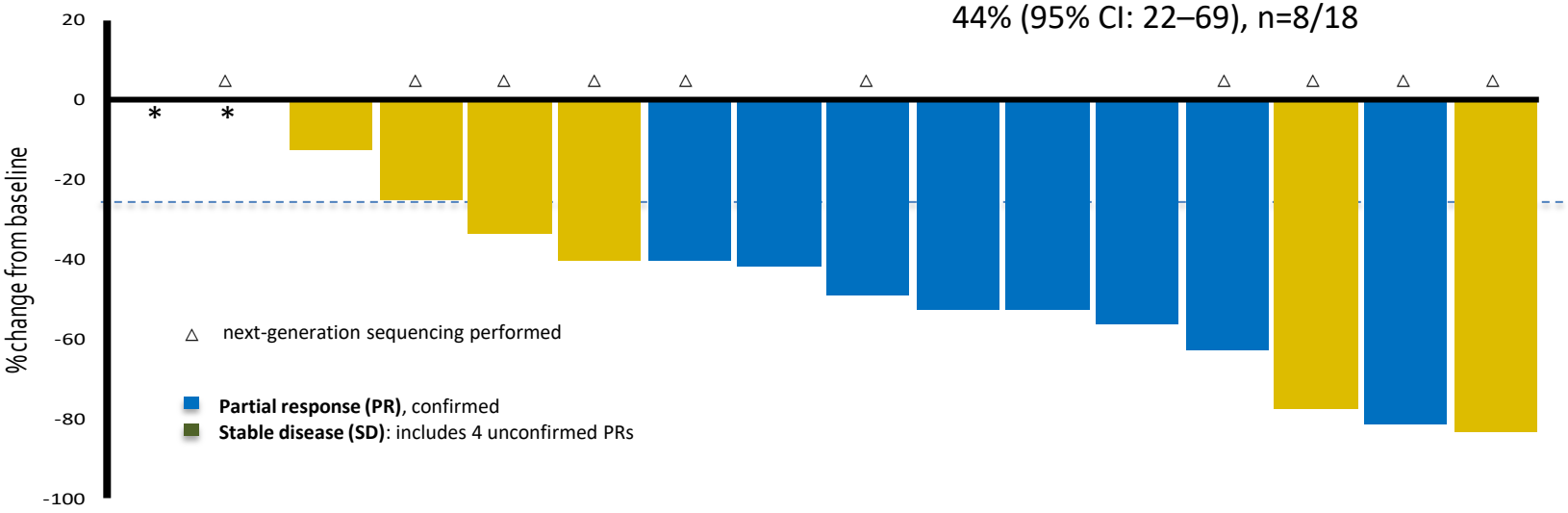


Drilon et al Clin Cancer Res 2016; Kong-Beltran M et al. Cancer Res 2006;66. Ma et al. Cancer Res 2003;63. Frampton GM et al. Cancer Discov 2015;5. Drilon A. Clin Cancer Res 2016.

Crizotinib in *MET*ex14-altered lung cancers

Multicenter phase 1 expansion cohort
Crizotinib 250 mg twice daily
Primary endpoint: overall response

Overall response rate (ORR)
44% (95% CI: 22–69), n=8/18



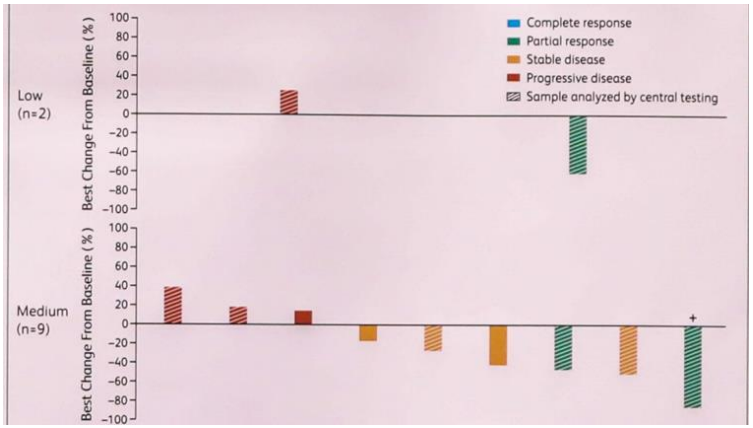
Drilon et al, ASCO Annual Meeting 2016

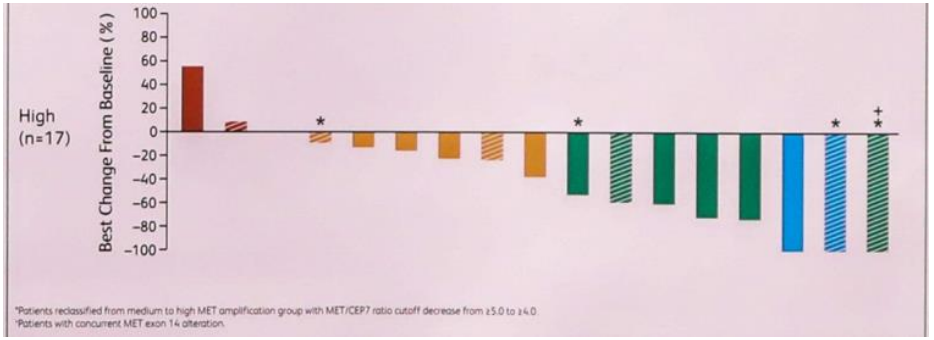
Crizotinib in *MET*-amplified lung cancers

Multicenter phase 1 expansion cohort
Crizotinib 250 mg twice daily
Primary endpoint: overall response

MET amplification determined by FISH

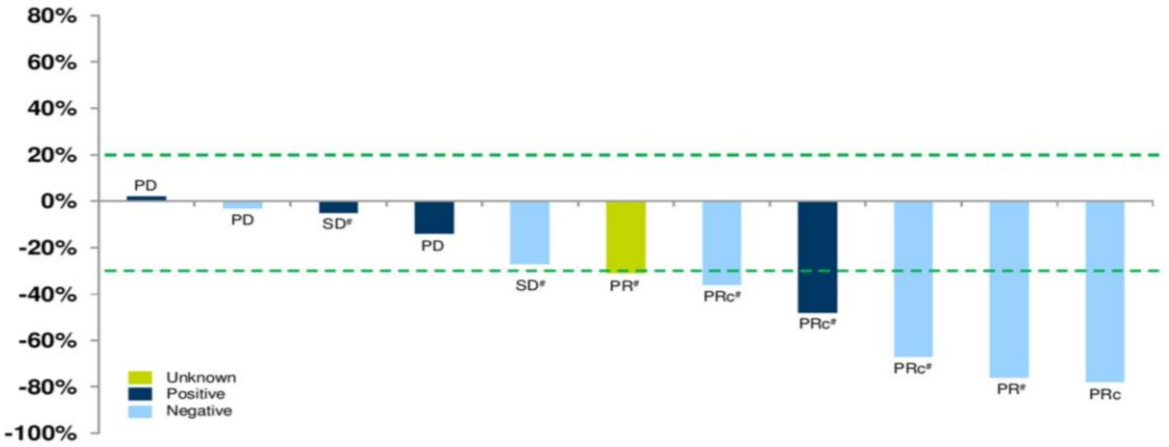
	Low *MET* (*MET/CEP7* 1.8-2.2) n=3	Intermediate *MET* (*MET/CEP7* >2.2-<5.0) n=14	High *MET* (*MET/CEP7* ≥5.0) n=20
Overall response, n (%)	1 (33%) (95%CI 0.8-90.6)	2 (14.3%) (95%CI 1.8-42.8)	8 (40%) (95%CI 19.1-63.9)
Medan DoR (mo)	12.1	3.7	5.5
PFS (mo)	1.8 (0.8, 14.0)	1.9 (1.3, 5.5)	6.7 (3.4, 7.4)



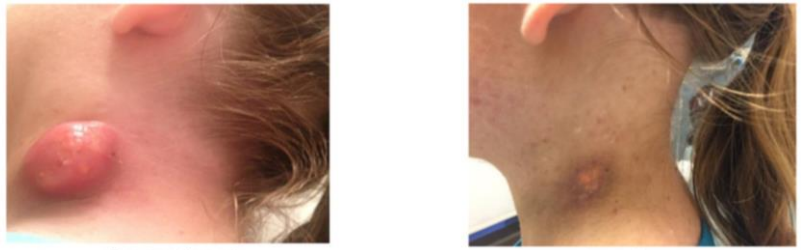


Camidge et al, ASCO Annual Meeting 2018; abstract 9062

Osimertinib and Savolitinib in *EGFR*+ NSCLC



*Population: all patients dosed who had a baseline and 6-week RECIST assessment
#Patients ongoing treatment at data cut-off
PD, progressive disease; PR, partial response; PRc, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease



Pre-treatment **4 weeks**

32-year-old female with a tumor harboring exon 19 deletion and high MET amplification responds to AZD9291/savolitinib 800 mg.

Oxnard et al J Clin Oncol 2015; abstract 2509

Multitargeted TKIs

Multitarget tyrosine kinase inhibitors (small molecules)				
PF02341066 (crizotinib)	38 (I), 5 (I/II), 37 (II), 13 (III), 3 (IV) and case reports	Breast cancer, renal clear cell cancer, glioblastoma, inflammatory myofibroblastic tumours, lymphoma, papillary renal cancers, MET$^+$ gastric adenocarcinoma, MET$^+$ or RON$^+$ metastatic urothelial cancer and NSCLC	Substantial antitumour activity in patients with oesophagogastric, lung and glioblastoma tumours and *MET* amplification and/or exon 14 deletion[52,154,169,216–219]	• Targets: ALK, ROS1 and MET • Approved for the treatment of NSCLC with EML4–ALK in 2011 and NSCLC with CD74–ROS1 in 2016
XL184 (cabozantinib)	19 (I), 3 (I/II), 37 (II), 6 (III), 2 (IV) and case reports	Breast cancer, glioblastoma, HCC, kidney cancer, medullary thyroid cancer, melanoma, NSCLC, ovarian cancer and prostate cancer	Complete response was reported for a patient with *MET* exon 14 deletion[52]. However, the majority of trials failed to show any benefit, likely because patients were not selected for *MET* alterations	• Targets: MET, RET and others. • Approved for treatment of medullary thyroid cancer
GSK1363089 (foretinib)	4 (I), 2 (I/II) and 5 (II)	Mixed cancer, breast cancer, gastric cancer, head and neck cancer, liver cancer, NSCLC and papillary renal cancer	Foretinib showed no activity in unselected patients with previously treated metastatic gastric can	• Targets: MET, RON, AXL, TIE2 and VEGFR2 • In 2014, product development was terminated, and no other clinical trials have been started
MGCD265 (glesatinib)	5 (I) and 2 (II)	Mixed cancer and NSCLC	Results pend g: hase II trial NCT02544633 the only one that includes *MET* netic alterations as a biomarker	Targets: MET and AXL
MP470 (amuvatinib)	2 (1) and 1 (II)	Mixed cancer, gastric cancer, glioblastoma, pancreatic cancer and SCLC	Results pending: patients are not selected for *MET* alterations	Targets: MET, RET, FLT3 and PDGFRA
E7050 (golvatinib)	4 (I) and 4 (I/II)	Mixed cancer, gastric cancer, head and neck cancer and HCC	Results pending: patients are not selected for *MET* alterations	Targets: MET and VEGFR2

Comoglio, Trusolino & Boccaccio Nat Rev Cancer 2018; 341-358

MET-specific TKIs

Specific MET tyrosine kinase inhibitors (small molecules)				
ARQ197 (tivantinib)	21 (I), 4 (I/II), 17 (II) and 4 (III)	Mixed cancer, colorectal cancer, HCC, liver cancer, mesothelioma, NSCLC, stomach cancer and SCLC	Phase II and III trials failed despite reported weak overall survival benefit in patients with high MET expression[156,221,222]. One phase III tri… recruiting patients with MET+ HCC… (NCT02029157), has remained op… since 2013	Tivantinib is a questionable MET inhibitor; the effects observed are likely explained … by the taxane-like cytotoxic …tivity[157,158]
INCB28060 (also known as INC280 and capmatinib)	9 (I), 5 (I/II), 11 (II) and 1 (IV)	Mixed cancer, colorectal cancer, glioblastoma, head and neck cancer, HCC, NSCLC and papillary renal cancer	In phase I and II trials, significant responses were reported in patient… with high *MET* amplification and… *MET* exon 14 deletion[44,223,224]	One phase IV rollover trial (NCT03040973) to assess long-term follow-up of MET-dependent tumours started in May 2017
AZD6094 (also known as HMPL-504, HMP-504, savolitinib or volitinib)	6 (I), 2 (I/II), 3 (II) and 1 (III)	Mixed cancer, colorectal cancer, gastric cancer, kidney cancer, NSCLC and papillary renal cancer	Results pending	NA
AMG337	1 (I), 2 (I/II) and 2 (II)	Mixed cancer, renal clear cell cancer, oesophageal cancer and stomach cancer	Results pending: one phase II trial (NCT0314797… selecting patients with tumours ov… expressing MET has been starte… The phase II trial NCT02016534 including *MET*-amplified tumours was terminated owing to safety concerns	NA
MSC2156119J (tepotinib)	2 (I) and 2 (I/II)	Mixed cancer, lung cancer and NSCLC	Results pending: latest phase II trial (NCT02864992) will study tumours with *MET* exon 14 deletion that did not respond to chemotherapy	NA
OMO-1 (also known as JNJ-38877618)	1(I)	Mixed cancer, lung cancer and NSCLC	Results pending	Placebo-like adverse event profile observed up to the highest dose tested; favourable pharmacokinetic profile after oral dosing

Comoglio, Trusolino & Boccaccio Nat Rev Cancer 2018; 341-358

Summary

- Active, approved therapies for EGFR-mut, ALK, ROS1 rearranged NSCLC, BRAF V600E/K NSCLC
- Promising activity for RET fusion, NTRK fusion, MET fusion, HER2 mutation, EGFR Exon 20 ins.
- More pieces of the pie!!!