MIAMI CANCER MEETING

16th ANNUAL MIAMI CANCER MEETING (MCM)

Immunotherapy and Targeted Therapy in 2019: Moving Forward with Personalized Cancer Therapy

"Other Driver Mutations: ROS-1, RET, HER-2, MET & Exon 20 Insertions"

Edgardo S. Santos, M.D., FACP
Medical Director of Cancer Research
Thoracic and Head and Neck Cancer Programs
Eugene M. & Christine E. Lynn Cancer Institute
Associate Professor of Clinical Biomedical Science
Charles E. Schmidt College of Medicine
Florida Atlantic University
Boca Raton, FL, USA

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Oncology Latin American Association
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Speaker's Disclosure

Speaker Bureau: Genentech, Merck, Pfizer, Novartis, Takeda, Celgene, Astrazeneca, Boehringer-Ingelheim, Amgen

Consultancy: None

Royalties: None

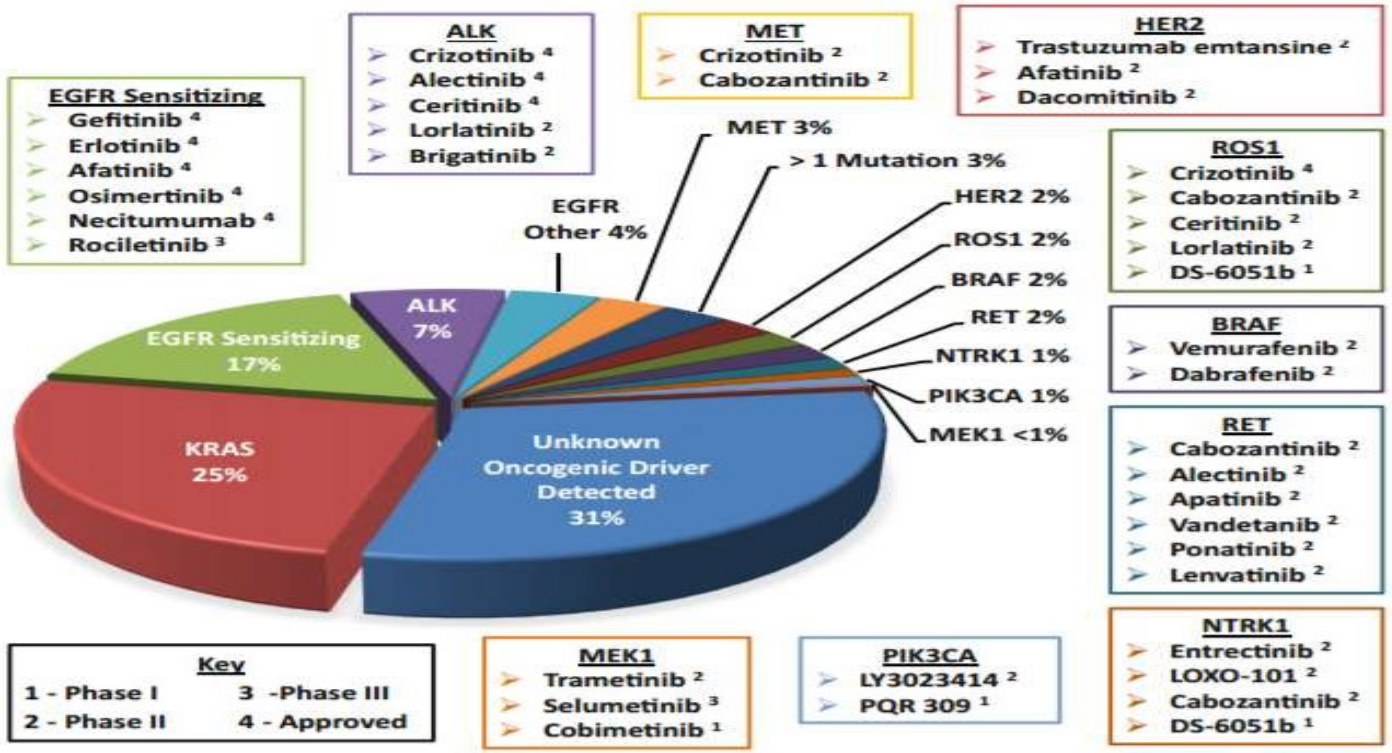
Research: None

Employment: None

Stocks: None

Other: None

Emerging Targets and Targeted therapies

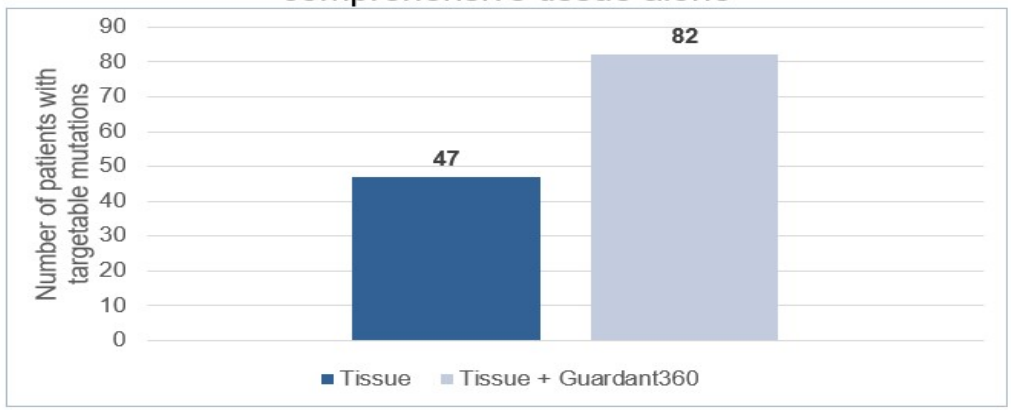


Tsao et al Journal of Thoracic Oncology 2015

Comprehensive Genomic Profiling— Is Key!!
Liquid & Tissue MP

Since tissue can fail, adding Guardant360 nearly doubled the number of patients identified with targetable mutations

Patients with targetable mutations detected with comprehensive tissue testing + Guardant360 **vs** comprehensive tissue alone



- **86%** of patients treated with targeted therapy based on Guardant360 results reached a complete response, partial response, or stable disease

~90% concordance with tissue at diagnosis

Aggarwal et al. 2018 *JAMA Oncology*

ROS-1

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WCLC2018.IASLC.ORG http://bit.ly/2xw1EA7 #WCLC2018

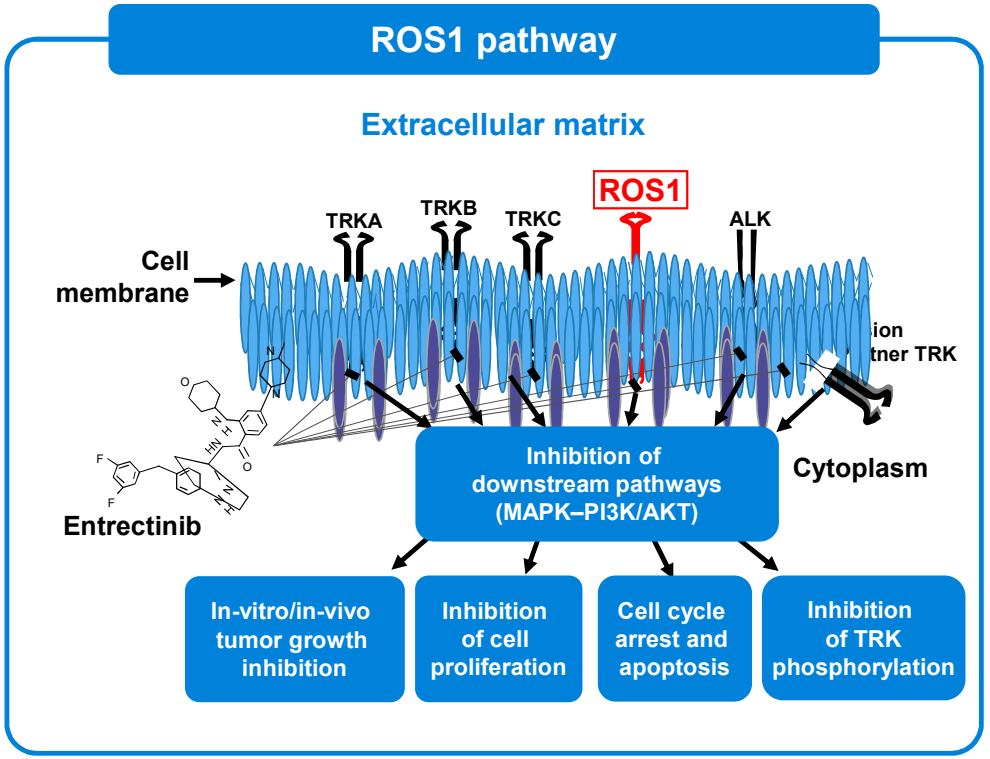
Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic *ROS1*-Positive Non-Small Cell Lung Cancer (NSCLC)

Robert C. Doebele,[1] Myung-Ju Ahn,[2] Salvatore Siena,[3,4] Alexander Drilon,[5] Matthew G. Krebs,[6,7] Chia-Chi Lin,[8,9] Filippo G. De Braud,[10] Thomas John,[11] Daniel S.W. Tan,[12] Takashi Seto,[13] Rafal Dziadziuszko,[14] Hendrick-Tobias Arkenau,[15] Fabrice Barlesi,[16] Christian Rolfo,[17] Jürgen Wolf,[18] Edna Chow-Maneval,[19] Pratik S. Multani,[19] Na Cui,[20] Todd Riehl,[20] Byoung Chul Cho[11]

[1]University of Colorado, Aurora, CO, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, and Università degli Studi di Milano, Milan, Italy; [4]Università degli Studi di Milano, Milan, Italy; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]The University of Manchester, Manchester, UK; [7]The Christie NHS Foundation Trust, Manchester, UK; [8]National Taiwan University Hospital, Taipei, Taiwan; [9]National Taiwan University College of Medicine, Taipei, Taiwan; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [11]Olivia Newton-John Cancer Centre, Austin Health, Melbourne, Australia; [12]National Cancer Centre Singapore, Singapore; [13]National Kyushu Cancer Center, Fukuoka, Japan; [14]Medical University of Gdansk, Gdansk, Poland; [15]Sarah Cannon Research Institute, London, UK; [16]Aix Marseille University, Assistance Publique-Hôpitaux de Marseille, Marseille, France; [17]Antwerp University Hospital, Antwerp, Belgium; [18]Center for Integrated Oncology Köln-Bonn, University Hospital of Cologne, Cologne, Germany; [19]Ignyta, Inc., San Diego, CA, USA; [20]Genentech, South San Francisco, CA, USA

WCLC 2018

Entrectinib Biology and Pharmacology



Entrectinib is an oral, potent and selective ROS1/NTRK/ALK tyrosine kinase inhibitor that is CNS active[1,2]

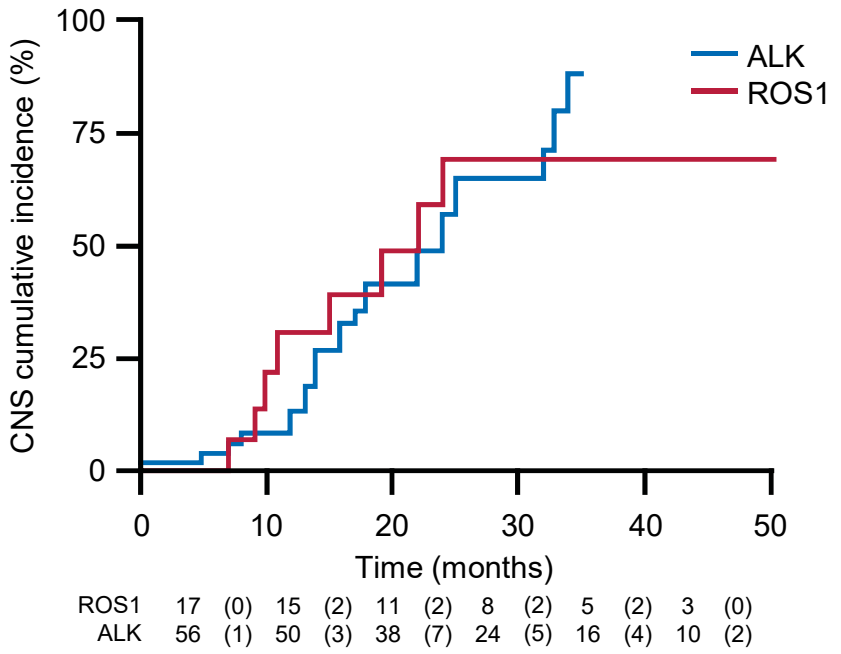
- **More potent ROS1 inhibitor** than crizotinib in preclinical studies[1]
- Potent pan-TRK inhibitor in clinical development; demonstrated clinical activity in multiple tumor histologies
- **Designed to cross the blood–brain barrier and remain within CNS**, with demonstrated clinical activity in primary brain tumors and secondary CNS metastases

1. Rolfo, et al. Expert Opin Investig Drugs 2015; 2. Ahn, et al. WCLC 2017

Brain metastases as an unmet need in patients with *ROS1*+ NSCLC

- ***ROS1 fusions are oncogenic driver mutations occurring in 1–2% of NSCLC patients[1,2]***
- Brain metastases are common in treatment-naïve stage IV *ROS1*+ NSCLC (36%), however, the incidence does not differ from other oncogene cohorts
- Current standard of care is crizotinib*; pivotal data from PROFILE 1001[3] (n=50):
  - ORR=72%; median PFS=19.2 months; median DOR=17.6 months[3]
- The CNS is a common first site of progression in patients with *ROS1*+ NSCLC receiving crizotinib (47%)
- Patients with *ROS1*+ tumors may also benefit from the use of a CNS-penetrant ROS1 inhibitor in the first-line setting

Cumulative development of brain metastases in NSCLC patients treated with crizotinib[4]

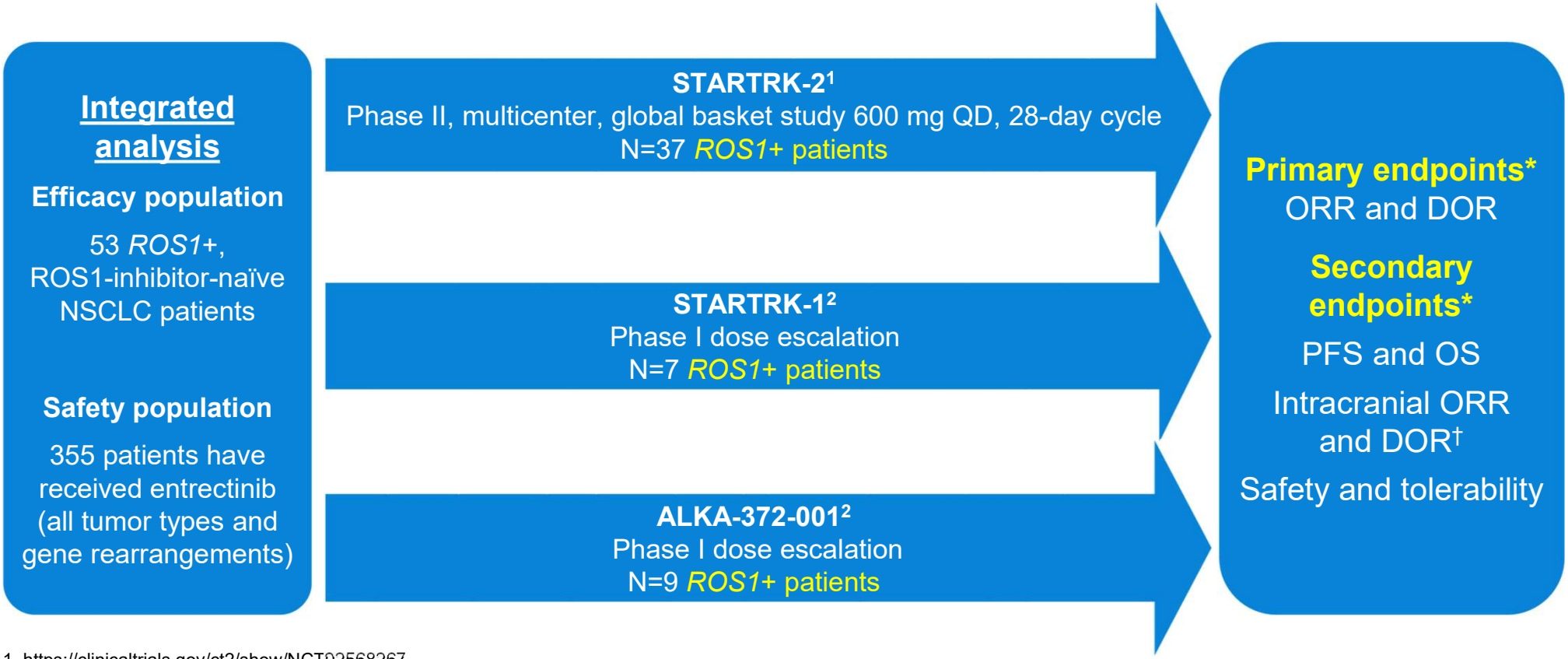


Risk table values = number at risk of CNS/death (number of CNS events)

1. Bergethon, et al. J Clin Oncol 2012; 2. Dugay, et al. Oncotarget 2017; 3. Shaw, et al. NEJM 2014; 4. Adapted from Patil, et al. J Thorac Oncol 2018; 5. Wu, et al. J Clin Oncol 2018

*Studies investigating crizotinib show variable outcomes/heterogeneity in patients, depending on the presence/absence of CNS disease and baseline ECOG PS[3,5]

Integrated Analysis of Three Studies: Entrectinib in *ROS1*+ NSCLC



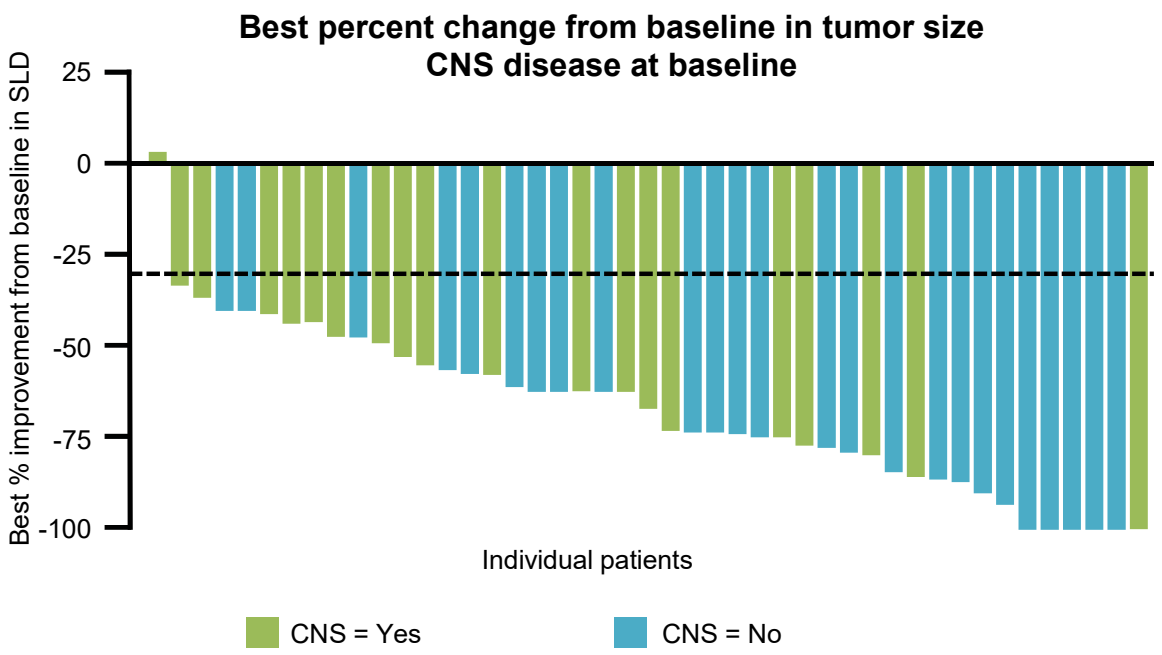
1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017

Data cut-off 31 May 2018

*BICR, blinded independent central review (RECIST v1.1)
†Patients with measurable and non-measurable CNS lesions at baseline

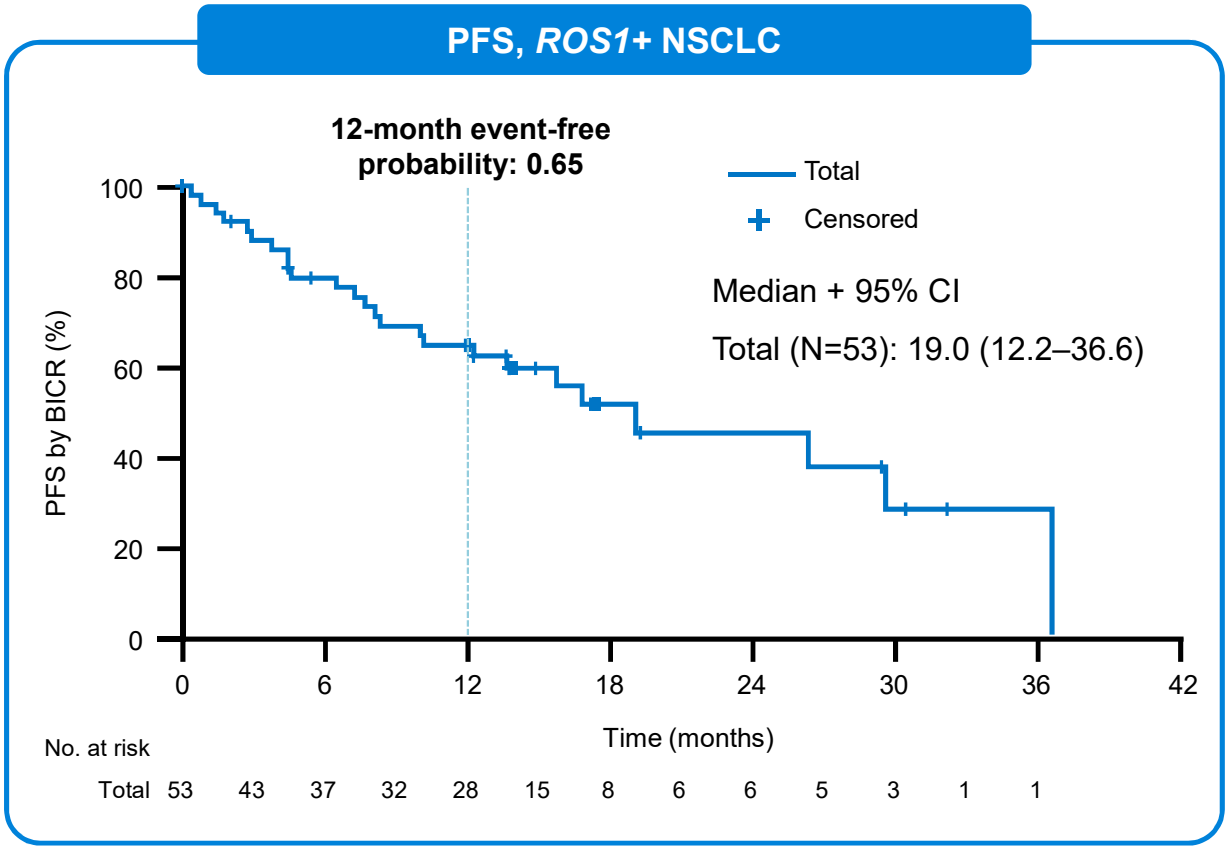
Objective Response Rate (BICR assessment)

Change in tumor size: *ROS1*+ NSCLC population



n (%)	Total (N=53)	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
ORR (95% CI)	**41 (77.4)** (63.8, 87.7)	**17 (73.9)** (51.6, 89.8)	**24 (80.0)** (61.4, 92.3)
CR	3 (5.7)	0	3 (10.0)
PR	38 (71.7)	17 (73.9)	21 (70.0)
SD	1 (1.9)	0	1 (3.3)
PD	4 (7.5)	4 (17.4)	0
Non-CR/PD	3 (5.7)	0	3 (10.0)
Missing or unevaluable	4 (7.5)	2 (8.7)	2 (6.7)
Clinical benefit rate* (95% CI)	41 (77.4) (63.8, 87.7)		

Progression-Free Survival (BICR assessment)



	Total N=53	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts with event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
PD, n Death, n	20 5	8 3	12 2
Time to event (months) **Median** (95% CI)	**19.0** (12.2, 36.6)	**13.6** (4.5, NE)	**26.3** (15.7, 36.6)

Median PFS 19.0 months (95% CI 12.2, 36.6)

Median follow up: 15.5 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Entrectinib → Safety Summary

- 355 patients have been treated with entrectinib across 3 clinical studies
- Most AEs were Grade 1–2 and reversible
- Treatment-related AEs
  - **leading to discontinuation from study treatment: 3.9%**
  - leading to dose reduction: 27.3%
  - leading to dose interruption: 25.4%
  - serious AEs: 8.5%
  - no Grade 5 events

Most common (≥10%) treatment-related AEs, n (%)	Safety evaluable population (N=355)	
	All grades	Grade ≥3
Dysgeusia	147 (41.4)	1 (0.3)
Fatigue	99 (27.9)	10 (2.8)
Dizziness	90 (25.4)	2 (0.6)
Constipation	84 (23.7)	1 (0.3)
Nausea	74 (20.8)	0
Diarrhea	81 (22.8)	5 (1.4)
Weight increased	69 (19.4)	18 (5.1)
Paresthesia	67 (18.9)	0
Blood creatinine increased	54 (15.2)	2 (0.6)
Myalgia	54 (15.2)	2 (0.6)
Edema peripheral	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	44 (12.4)	2 (0.6)
Aspartate aminotransferase increased	39 (11.0)	4 (1.1)*

*One Grade 4 event (increased aspartate aminotransferase) and **no Grade 5 events** were evaluated by investigators to be related to study treatment
Data cut-off date: May 31 2018 (median duration of entrectinib treatment: 9.17 months (Q1, Q3: 4.60, 14.65), integrated analysis population

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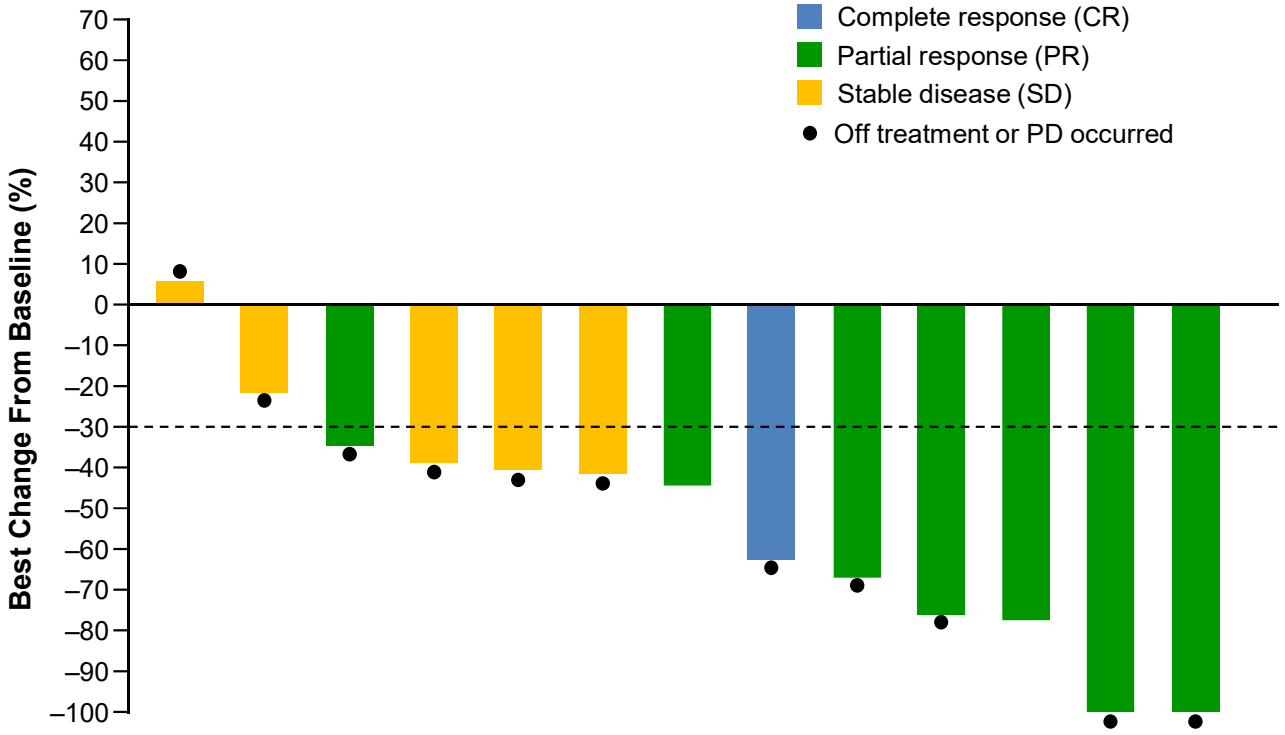
Clinical Activity of Lorlatinib in Patients With ROS1+ Advanced Non-Small Cell Lung Cancer: Phase 2 Study Cohort EXP-6

Sai-Hong Ignatius Ou,[1] Alice T. Shaw,[2] Gregory J. Riely,[3] Rita Chiari,[4] Jessica R. Bauman,[5] Jill S. Clancy,[6] Holger Thurm,[7] Gerson Peltz,[8] Antonello Abbattista,[9] Benjamin J. Solomon[10]

[1]University of California Irvine, Irvine, CA, USA; [2]Massachusetts General Hospital, Boston, MA, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy; [5]Fox Chase Cancer Center, Philadelphia, PA, USA; [6] Pfizer Oncology, Cambridge, MA, USA; [7]Pfizer Oncology, La Jolla, CA, USA; [8]Pfizer Oncology, Groton, CT, USA; [9]Pfizer Oncology, Milan, Italy; [10]Peter MacCallum Cancer Center, Melbourne, Victoria, Australia

Overall Efficacy in Crizotinib-naïve ROS1+ Patients

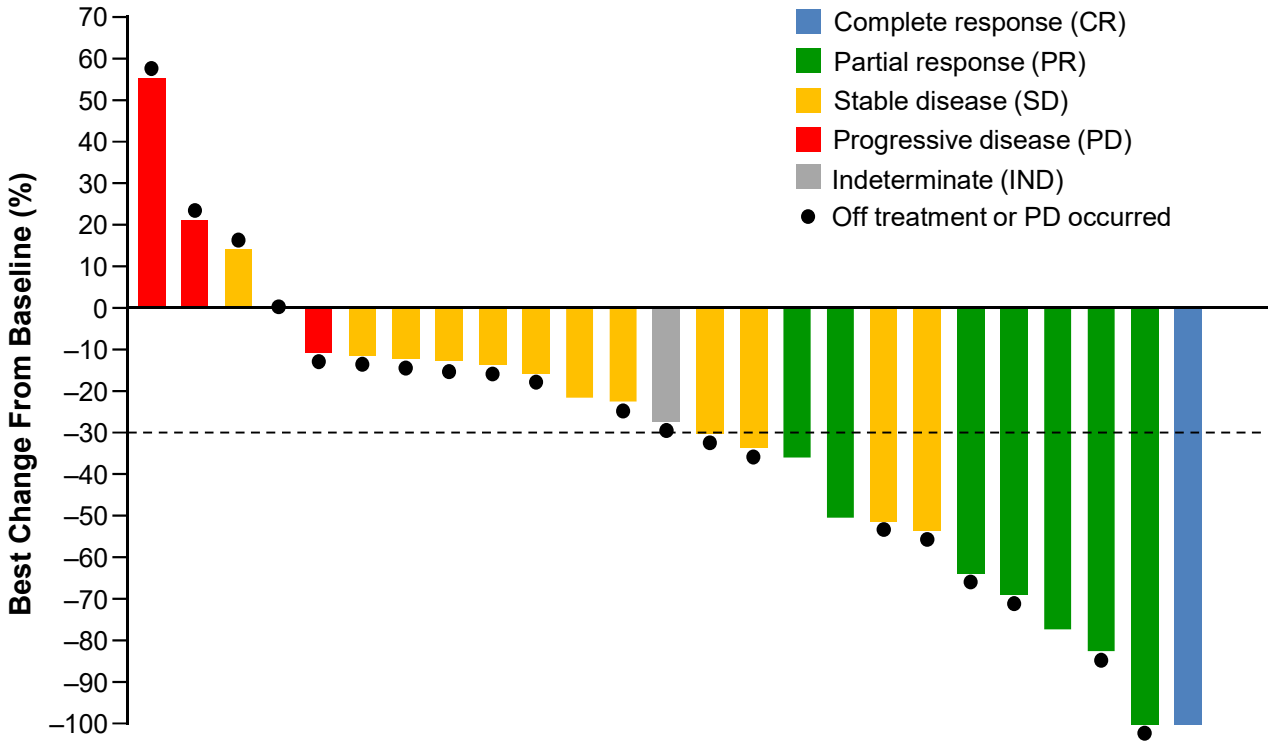


Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

	Crizotinib-naïve (n=13)
BOR, n (%)	
CR	1 (7.7)
PR	7 (53.8)
SD	5 (38.5)
PD	0
IND	0
ORR, n (%)	8 (61.5)
95% CI	31.6, 86.1
Median TTR, mo	1.4
Range	1.3–8.3
Median DOR, mo	19.6
95% CI	4.0, 25.3
DOR ≥12 mo, n^{o}/n (%)	5/8 (62.5)
Median PFS, mo	21.0
95% CI	4.2, 26.7

BOR, best overall response; CI, confidence interval; DOR, duration of response; IND, indeterminate; mo, months; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; TTR, time-to-first tumor response.

Overall Efficacy in Crizotinib-pretreated ROS1+ Patients



	Crizotinib-pretreated (n=34)
BOR, n (%)	
CR	2 (5.9)
PR	7 (20.6)
SD	16 (47.1)
PD	3 (8.8)
IND	6 (17.6)
ORR, n (%)	9 (26.5)
95% CI	12.9, 44.4
Median TTR, mo	2.5
Range	1.4–4.2
Median DOR, mo	NR
95% CI	7.1, NR
DOR ≥12 mo, n[a]/n (%)	5/9 (55.6)
Median PFS, mo	8.5
95% CI	4.4, 18.0

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.

BOR, best overall response; CI, confidence interval; DOR, duration of response; mo, months; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TTR, Time-to-first tumor response.

Lorlatinib → Safety Summary
ROS1+ NSCLC

TRAEs in ≥10% of Patients, n (%)	Total (N=47)	Grade 3	Grade 4
Hypercholesterolemia*	39 (83.0)	4 (8.5)	0
Hypertriglyceridemia*	28 (59.6)	9 (19.1)	0
Edema*	21 (44.7)	1 (2.1)	0
Peripheral neuropathy*	16 (34.0)	1 (2.1)	0
Cognitive effects*	11 (23.4)	0	0
Weight increased	10 (21.3)	3 (6.4)	0
Dizziness	7 (14.9)	2 (4.3)	0
Mood effects*	6 (12.8)	0	0
Lipase increased	6 (12.8)	3 (6.4)	0
Fatigue*	5 (10.6)	1 (2.1)	0
ALT increased	5 (10.6)	0	0
Arthralgia	5 (10.6)	0	0
Thrombocytopenia	5 (10.6)	0	1 (2.1)

Ou et al WCLC 2018

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Safety and Preliminary Clinical Activity of Repotrectinib (TPX-0005), a ROS1/TRK/ALK Inhibitor, in Advanced *ROS1* Fusion-Positive Non-Small Cell Lung Cancer

NCT03093116

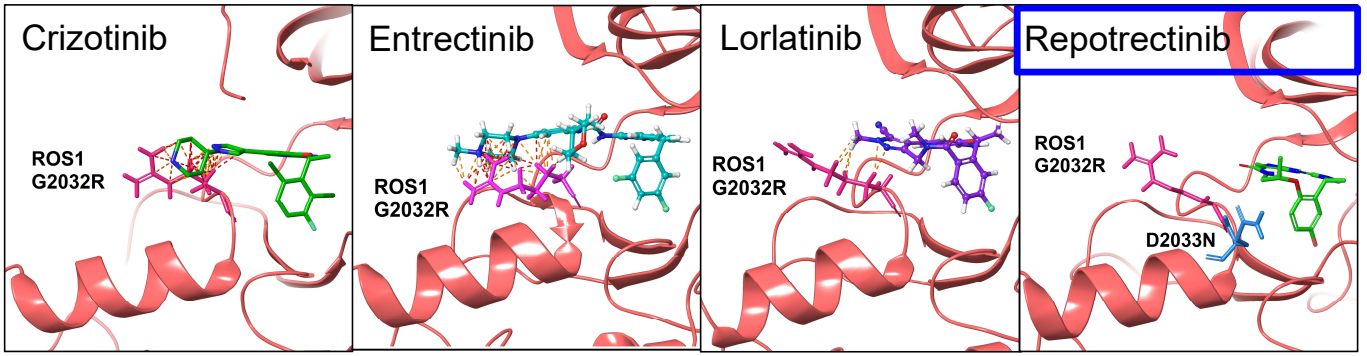
Jessica J. Lin,[1] Dong-Wan Kim,[2] Alexander Drilon,[3] Robert C. Doebele,[4] Jeeyun Lee,[5] Viola W. Zhu,[6] Myung-Ju Ahn,[5] John K. Lim,[7] Shanna Stopatschinskaja,[7] J. Jean Cui,[7] David M. Hyman,[3] D. Ross Camidge,[4] Sai-Hong Ignatius Ou,[6] Alice T. Shaw,[1] Byoung Chul Cho[8]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Seoul National University Hospital, Seoul, Republic of Korea; [3]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; [7]TP Therapeutics Inc., San Diego, CA, USA; [8]Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction: Repotrectinib, a Next-Generation ROS1/TRK/ALK TKI

- *ROS1* rearrangement is an oncogenic driver in 1-2% of NSCLC
- Crizotinib is the only approved targeted therapy for patients with advanced *ROS1*+ NSCLC
- ***G2032R is the most common ROS1 resistance mutation after crizotinib treatment[1]***
- **Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor, designed to overcome TKI resistance mutations, especially solvent front *ROS1* G2032R[2]**

[1]Gainor JF et al., JCO Precis Oncol 2017
[2]Drilon A et al., Cancer Discov 2018



CD74-ROS1 Ba/F3 Cell Proliferation IC_{50} (nM)*

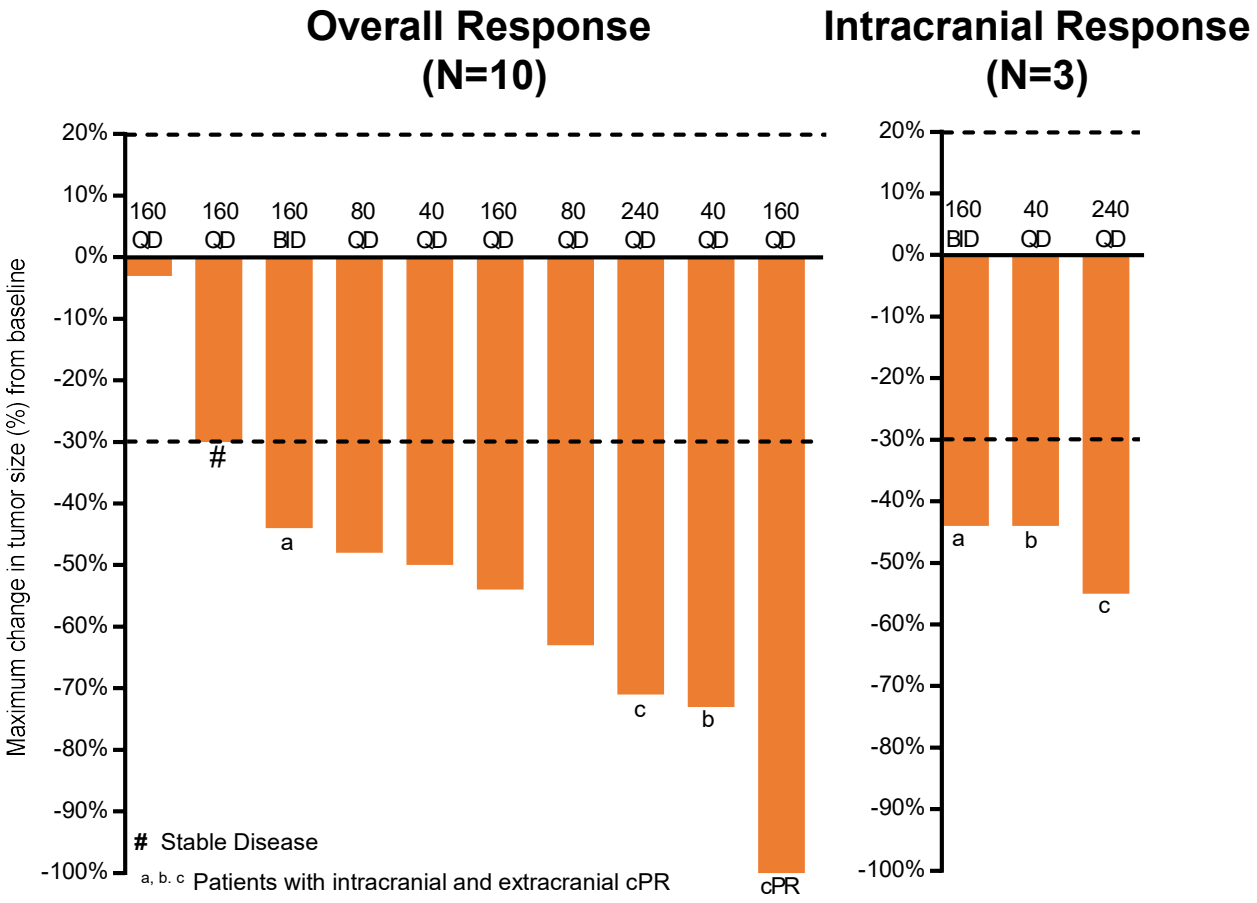
ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	**266.2**	**1391**	**11.3**	**1813**	**160.7**	**3.3**
D2033N	200.9	535.4	0.2	169.2	3.3	1.3
L2026M	606.4	ND	29.1	2026	930.6	10
S1986F	63.7	68	5.5	3.4	0.4	<0.2
L1951R	157.6	785.5	91.8	35.4	2.8	<0.2

Preliminary Efficacy of Repotrectinib in TKI-naïve *ROS1*+ NSCLC by BICR

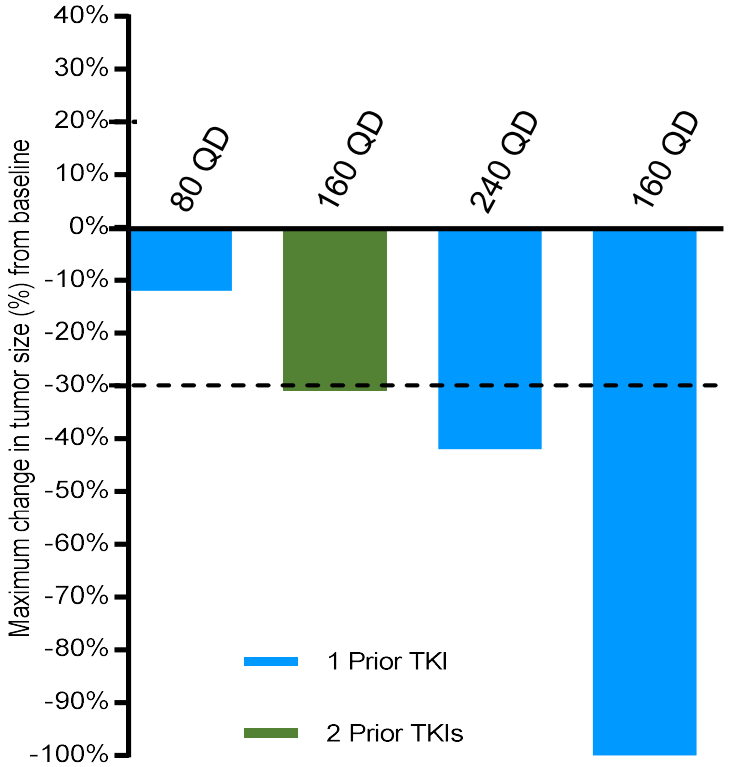
	TKI-naïve (N=10)
Confirmed ORR, n/N (%)	**8/10 (80%)**
95% CI (%)	(44 – 97)
Time to response (TTR), mo	
Median	1.6
Range	1.4 – 3.3
Intracranial ORR, n/N (%) (measurable disease)	3/3 (100%)
95% CI (%)	(29 – 100)
CBR*, n/N (%)	10/10 (100%)
95% CI (%)	(69 – 100)

**Clinical benefit rate (CBR) = CR + PR + SD ≥ 2 cycles*

5 of 8 patients remain in cPR (3.7+ – 11.1+mo)



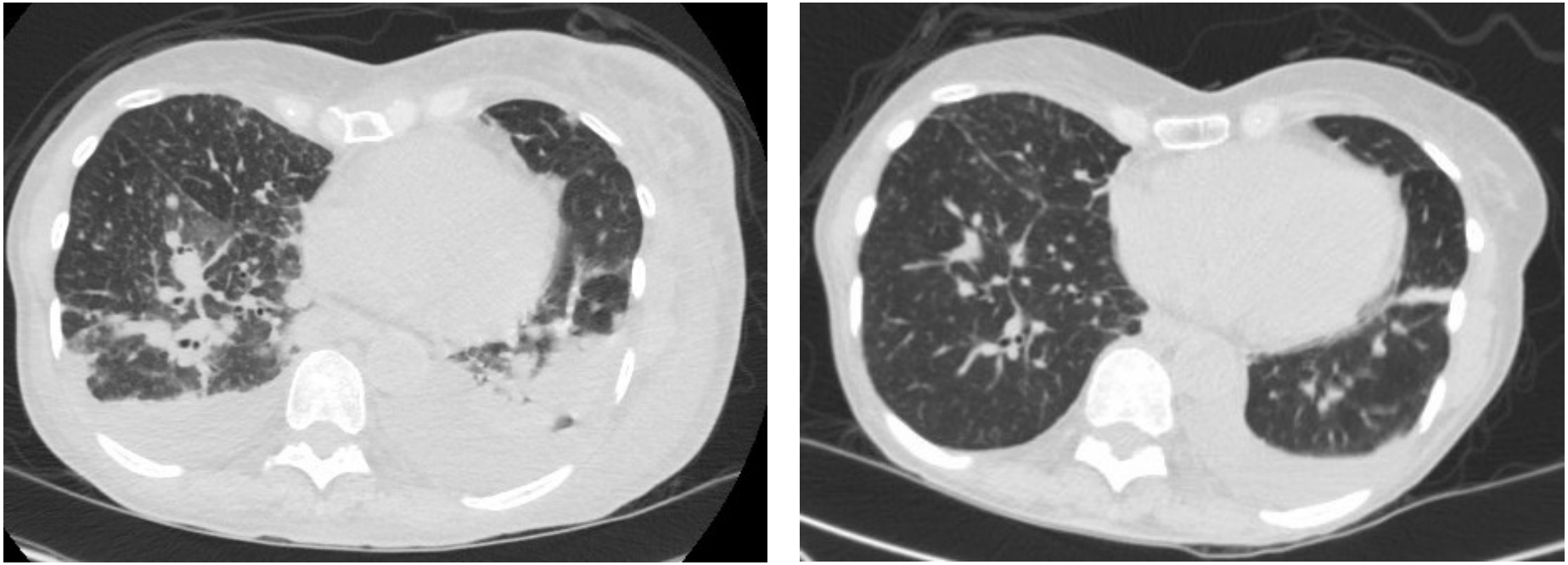
Preliminary Clinical Activity of Repotrectinib Against ROS1 G2032R



- 16 of 17 TKI-pretreated subjects had baseline plasma cfDNA tested by NGS (Guardant360)
- *ROS1* G2032R detected in 4 subjects (25%) who had been crizotinib-pretreated
- ***All 4 subjects experienced tumor regressions on Repotrectinib***
- 1 cPR at 160 mg QD (DOR 7.4 mos and remains on treatment at 11+ mos)

Case Example of the Clinical Activity of Repotrectinib Against *ROS1* G2032R

Baseline ***After 7 weeks of Repotrectinib***



Tumor regression on Repotrectinib in a patient with *ROS1*+ NSCLC, resistant to crizotinib and chemotherapy and found to have *ROS1* G2032R on liquid biopsy

Presented by: Jessica J. Lin, Massachusetts General Hospital, USA

RET

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RET Rearranged NSCLC

- *RET* rearrangements are detected in 1-2% of adenocarcinomas, 8% among patients who are *EGFR* and *ALK* negative.
- *RET* proto-oncogene is rearranged with partner gene: *KIF5B* most common but others are *CCDC6*, *NCOA4, or TRIM33*
- Multi-targeted TKI's investigated in prospective phase 2 studies
- Frequent dose reductions for "off target" toxicities were observed, often related to VEGF and/or EGFR activity

Gautschi et al JCO 2017, Yoh et al Lancet Respiratory 2017, Drilon et al Lancet Oncology 2016, Lee et al Annals of Oncology 2017

Phase 2 Trials of RET inhibitors

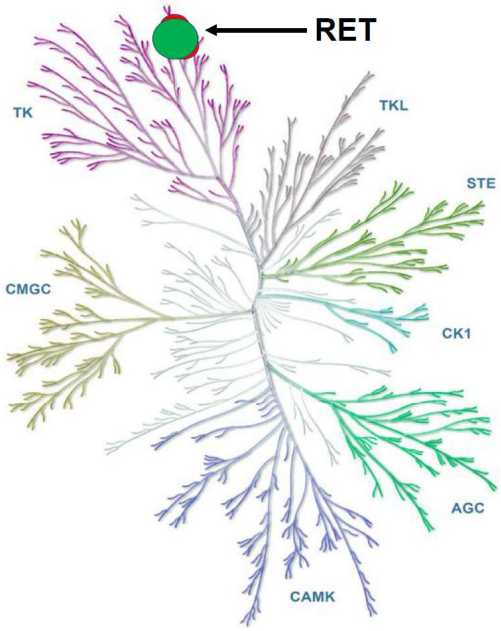
Agent	# of patients	ORR	PFS	Dose reduction
Vandetanib	17	47% (n=9) 95% CI: 24-71%	4.7 months 95% CI: 2.8-8.5	53% of patients
Vandetanib	18	18% (n=3)	4.5 months	22% of patients
Cabozantinib	26	28% (n=7) 95% CI: 12-49%	5.5 months 95% CI: 3.8-8.4	73% of patients
Platinum-based chemotherapy*	84	51% (n=33) 95% CI: 38-63	7.8 months 95% CI: 5.3-10.2	

- Of 84 patients 66 received platinum-pemetrexed
- Median OS 24.8 months

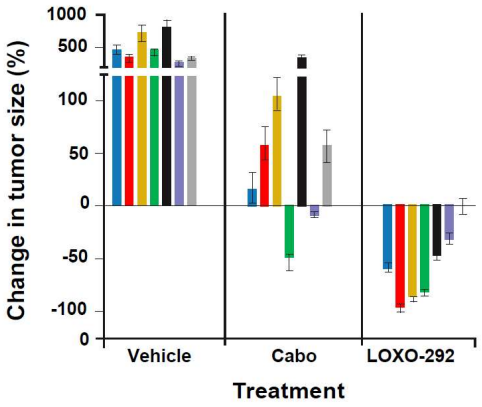
Yoh et al Lancet Respiratory 2017, Drilon et al Lancet Oncology 2016, Lee et al Annals of Oncology 2017

LOXO-292 is a Potent and Selective RET Inhibitor

Kinome selectivity
Highly selective for RET

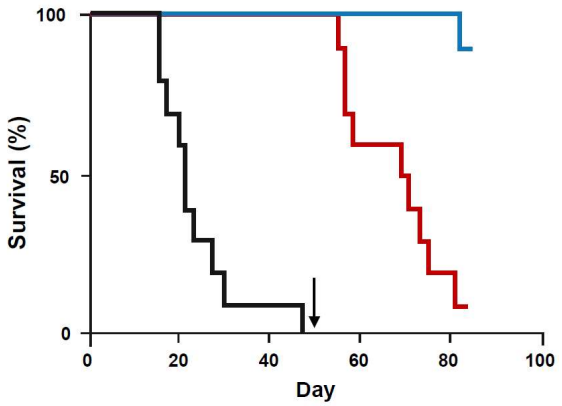


Xenograft models
Multiple fusions/mutations/histologies



Tumor models
- KIF5B-*RET* (PDX-NSCLC)
- CCDC6-*RET* (PDX-CRCA)
- CCDC6-*RET*-V804M (PDX-CRCA)
- KIF5B-*RET* (NIH-3T3)
- KIF5B-*RET*-V804M (NIH-3T3)
- RET C634W (TT cell line-MTC)
- CCDC6-*RET* (LC-2/ad cell line-NSCLC)

Orthotopic brain model
CCDC6-RET orthotopic brain PDX



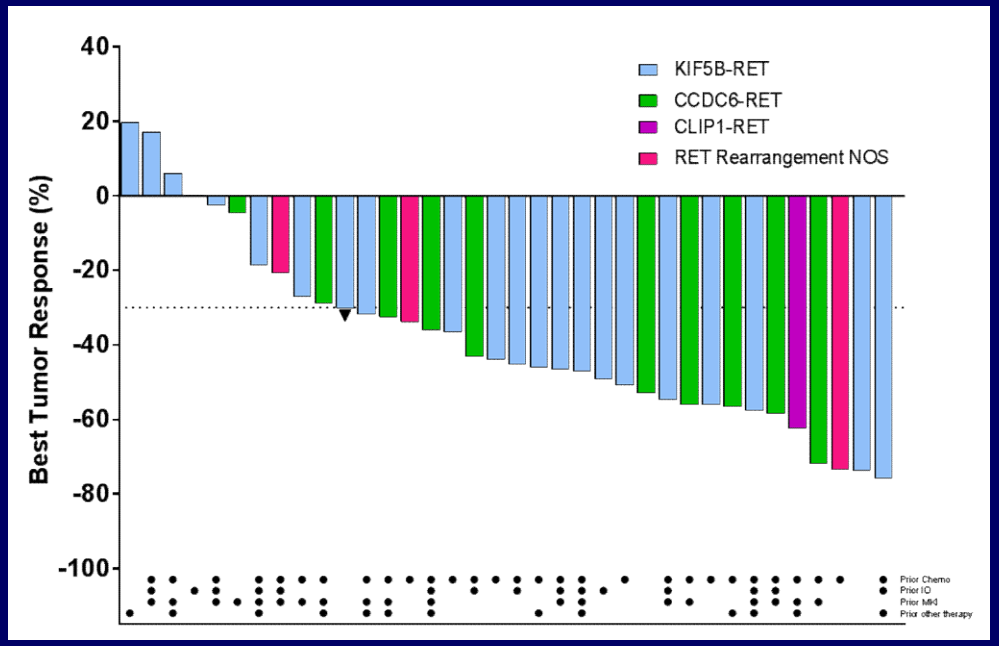
Treatments
- Vehicle
- LOXO-292 30 mg/kg BID → Day 52 → 3 mg/kg BID
- Ponatinib 20 mg/kg QD → Day 52 → 2 mg/kg QD

Oxnard et al WCLC 2018

Subbiah et al. Ann Oncol 2018; Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily

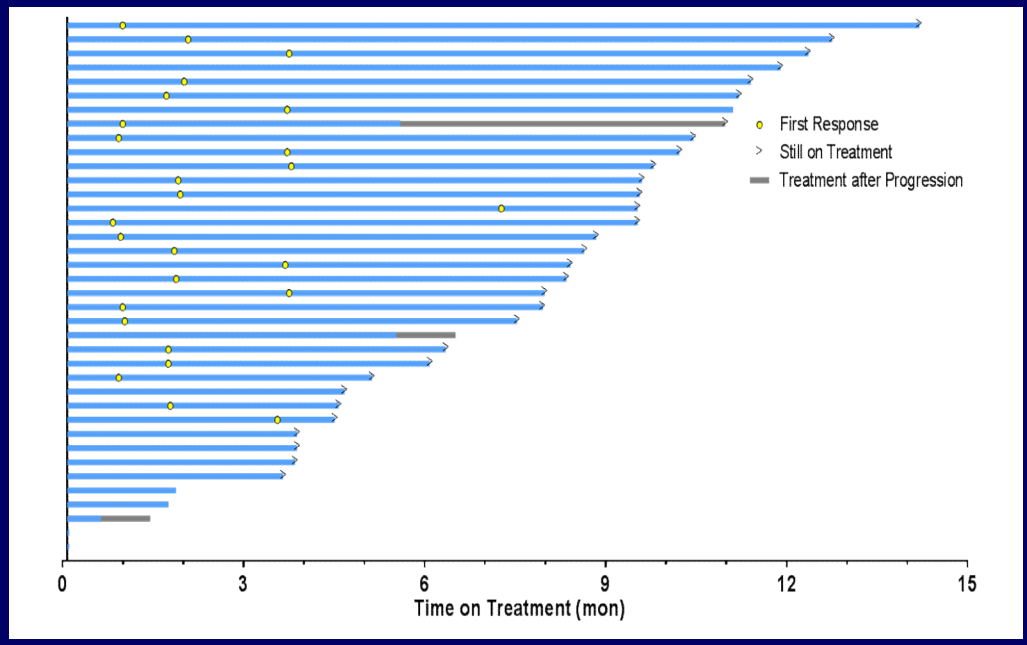
Efficacy of LOXO-292 in RET Fusion NSCLC

Responses



ORR: 68% (26/38)

Swimmers plot



24/26 responses on going at time of analysis

Oxnard et al WCLC 2018

LOXO-292 Safety Profile

	All doses and patients, n=82								
	Treatment-emergent AEs (≥10% overall)						Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total		Grade 3	Grade 4	Total
Diarrhea	15%	7%	1%	-	23%		1%	-	11%
Fatigue	9%	13%	-	-	22%		-	-	17%
Dry Mouth	21%	-	-	-	21%		-	-	13%
Constipation	17%	2%	-	-	20%		-	-	4%
Hypomagnesemia	12%	1%	-	-	13%		-	-	2%
Cough	11%	1%	-	-	12%		-	-	1%
Headache	10%	1%	1%	-	12%		-	-	1%
Nausea	9%	4%	-	-	12%		-	-	5%

- Most treatment-emergent AEs were Grade 1 in severity and judged not related to LOXO-292
- Four patients experienced treatment-related AEs ≥ grade 3: diarrhea, increased ALT/AST, thrombocytopenia (DLT @ 240mg BID), tumor lysis syndrome (DLT @ 240mg BID)
- Dose exploration ongoing at 200 mg BID

AE = adverse event; DLT = dose limiting toxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding. Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.

Oxnard et al WCLC 2018

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Phase 1 Trial of BLU-667 in Patients with Advanced RET-altered Solid Tumors

- 53 patients enrolled: 29 medullary thyroid cancer and 19 NSCLC.
- MTD 400 daily with dose-limiting toxicities of hyponatremia and hypertension.
- Grade ≥ 3 AE's: increased liver tests, hypertension, diarrhea, fatigue, neutropenia
- Response evaluable patients (n=40): CR 1 (3%), PR 17 (43%), SD 20 (50%), PD 2 (5%)
- ORR in RET-fusion NSCLC: 50%
- 41 of 51 RET altered patients remain on treatment

Subbiah et al AACR 2018, Subbiah et al Cancer Discovery 2018

HER-2

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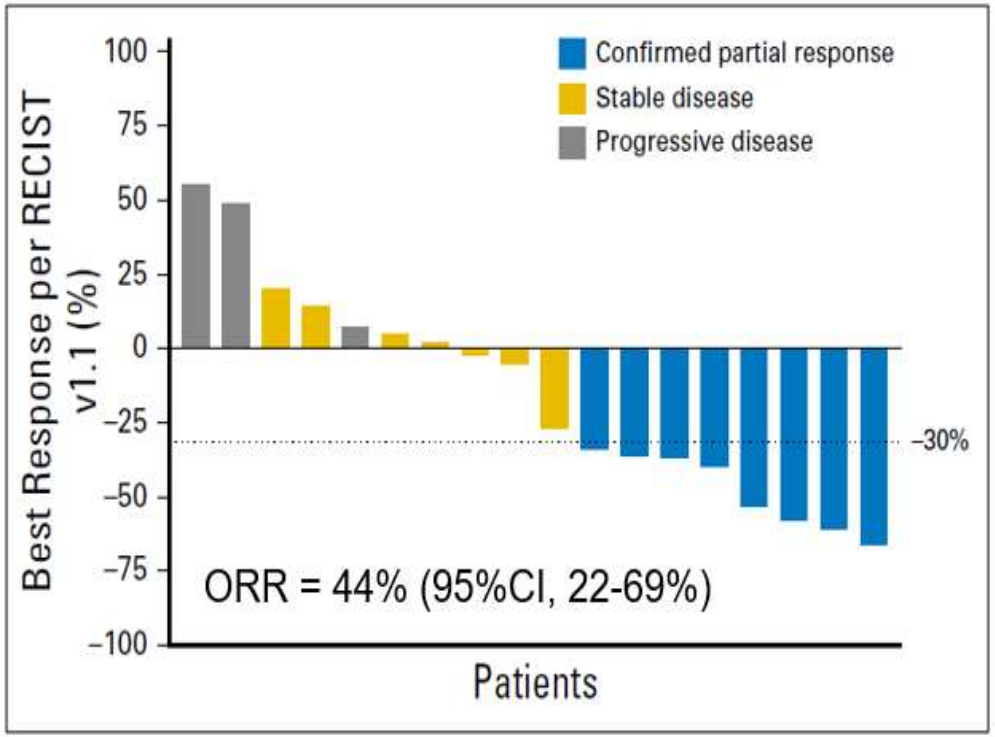
JOURNAL OF CLINICAL ONCOLOGY

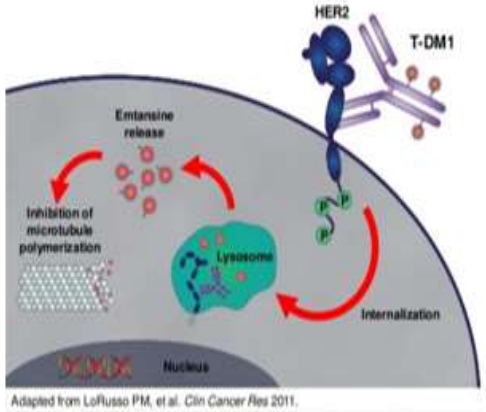
ORIGINAL REPORT

Ado-Trastuzumab Emtansine for Patients With *HER2*-Mutant Lung Cancers: Results From a Phase II Basket Trial

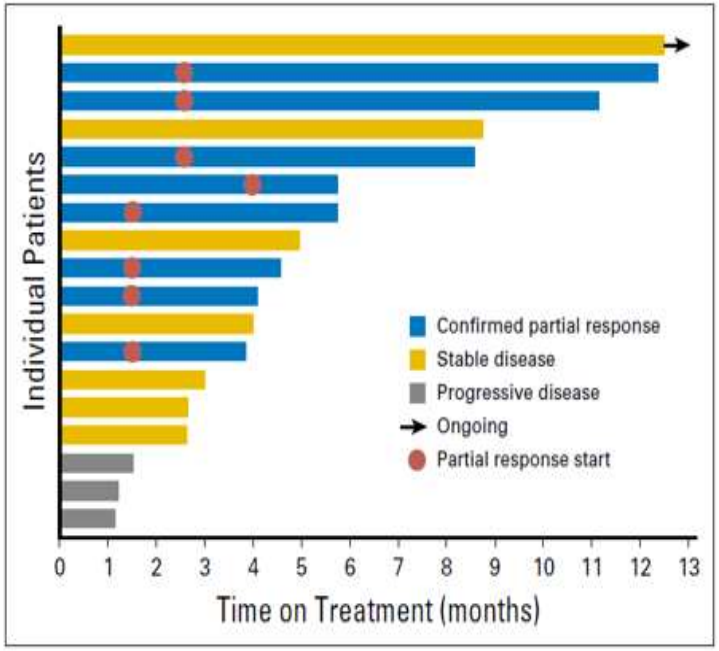
Bob T. Li, Ronglai Shen, Darren Buonocore, Zachary T. Olah, Ai Ni, Michelle S. Ginsberg, Gary A. Ulaner, Michael Offin, Daniel Feldman, Todd Hembrough, Fabiola Cecchi, Sarit Schwartz, Nick Pavlakis, Stephen Clarke, Helen H. Won, Edyta B. Brzostowski, Gregory J. Riely, David B. Solit, David M. Hyman, Alexander Drilon, Charles M. Rudin, Michael F. Berger, Jose Baselga, Maurizio Scaltriti, Maria E. Arcila, and Mark G. Kris



T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.



Who Where These Patients? What Kind of Mutations?

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)
Total patients treated	18 (100)
Median age, years (range)	64 (47-74)
Female	13 (72)
Smoking status	
Former smoker	11 (61)
Never-smoker	7 (39)
Karnofsky performance status	
90%	7 (39)
80%	8 (44)
70%	3 (17)
Histology, adenocarcinoma	18 (100)
Median No. of lines of prior systemic therapy (range)	2 (0-4)
0 prior line	3
1 prior line	5
2 prior lines	4
3 prior lines	3
4 prior lines	3
Prior HER2-targeted therapy	9 (50)
Neratinib	7 (39)
Afatinib	2 (11)
Trastuzumab	2 (11)

Table 3. HER2 Biomarker Analysis

NGS Result	FISH Result (HER2/CEP17 ratio)	IHC Result	Mass spectrometry (amol/μg)	Partial Response
Exon 20 p.A775_G776insYVMA	1.1 (2.7/2.5)	0	NA	Yes
Exon 20 p.A775_G776insYVMA	1.8 (8.1/4.5)	2+	642	No
Exon 20 p.A775_G776insYVMA	NA	NA	NA	No
Exon 20 p.A775_G776insYVMA	1.4 (4.5/3.3)	1+	586	Yes
Exon 20 p.A775_G776insYVMA	1.9 (5.6/2.9)	1+	548	Yes
Exon 20 p.G778_P780dup	1.6 (7.6/4.8)	1+	0	No
Exon 20 p.G778_P780dup	1.8 (4.6/2.5)	2+	507	Yes
Exon 20 p.G778_P780dup	1.4 (5.8/4.2)	2+	NA	No
Exon 20 p.G778-779 insCPG	1.6 (4.3/2.7)	0	NA	No
Exon 20 p.G776_V777>VCV	NA	NA	NA	Yes
Exon 20 p.G776delinsVC	1.6 (5.7/3.6)	0	205	Yes
Exon 19 p.L755P	1.5 (3.2/2.1)	2+	434	No
Exon 19 p.L755P	NA	0	NA	No
Exon 17 p.V659E	1.2 (2.4/2.0)	2+	NA	No
Exon 17 p.V659E	1.1 (2.3/2.0)	2+	688	Yes
Exon 8 p.S310F, amplification fold change 2.8	4.1 (8.4/2.5)	2+	1,495	Yes
Exon 8 p.S310F	1.8 (3.2/1.8)	0	0	No
Exon 8 p.S335C	2.4 (4.8/2.0)	2+	902	No

Abbreviations: FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not available; NGS, next-generation sequencing.

Li BT et al. J Clin Oncol. 36(24), 2532-7, 2018.

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IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Updated results of a phase 1 study of DS-8201a in HER2-expressing or -mutated advanced non-small cell lung cancer (NSCLC)

Junji Tsurutani[1,2], Haeseong Park[3], Toshihiko Doi[4], Shanu Modi[5], Shunji Takahashi[6], Kazuhiko Nakagawa[1], Ian E. Krop[7], Saiama Waqar[3], Kiyotaka Yoh[4], Bob Li[5], Shinichiro Taira[6], Takahiro Jikoh[8], Jasmeet Singh[8], Masahiro Sugihara[9], and Pasi A. Jänne[7]

[1]Kindai University Faculty of Medicine, Osaka, Japan; [2]Advanced Cancer Translational Research Institute, Department of Medical Oncology, Showa University, Tokyo, Japan, [3]Washington University School of Medicine, St Louis, MO, USA; [4]National Cancer Center Hospital East, Chiba, Japan; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [6]The Cancer Institute Hospital of Japanese Foundation For Cancer Research, Tokyo, Japan; [7]Dana-Farber Cancer Institute and the Belfer Center for Applied Cancer Science, Boston, MA, USA; [8]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [9]Daiichi Sankyo Co., Ltd, Tokyo, Japan

Presenter: Junji Tsurutani, MD, PhD. Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan

WCLC 2018

Background

- ***Approximately 10% to 30% of NSCLC tumors are HER2-overexpressing (IHC 2+ or 3+) and approximately 2% to 3% have HER2-activating mutations[1-4]***

- In preclinical studies, DS-8201a—a novel HER2 surface receptor targeting ADC—demonstrated activity across a broad range of tumors with HER2 cell surface expression[5]

- An ongoing phase 1 trial (NCT02564900) was initiated in 2015 to assess the efficacy and safety of DS-8201a in subjects with HER2-positive advanced breast cancer and gastric cancers, as well as other HER2-expressing/-mutated solid tumors including NSCLC[6]

- In preliminary results of this trial, DS-8201a had promising antitumor activity (confirmed ORR of 49.3%) and a manageable safety profile in subjects receiving either the 5.4 or 6.4 mg/kg dose across multiple tumor types[7]

ADC, antibody drug conjugate; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate.

1. Heinmoller P, et al. *Clin Cancer Res*. 2003; 9:5238-43. 2. Scheurle D, et al. *Anticancer Res*. 2000; 20:2091-6. 3. Mazieres J, et al. J Clin Oncol. 2013; 31:1997-2003. 4. Shigematsu H, et al. *Cancer Res*. 2005; 65:1642-6. 5. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097-108. 6. Doi T, et al. *Lancet Oncol* 2017;18:1512-22. 7. Iwata H, et al. *J Clin Oncol.* 2018; 36:(suppl; abstr 2501).

Efficacy Outcomes (Efficacy Evaluable Subjects)

	Confirmed ORR*, % (n/N)	DCR, % (n/N)	DOR, median (range), months	TTR, median (range), months	PFS, median (range), months
HER2-expressing or HER2-mutated NSCLC N = 18	58.8% (10/17)	83.3% (15/18)	9.9 (0.0+, 11.5)	1.4 (1.0, 4.2)	14.1 (0.9, 14.1)
HER2-mutated NSCLC n = 11	**72.7% (8/11)**	**100% (11/11)**	**11.5 (0.03+, 11.5)**	**1.4 (1.0, 4.2)**	**14.1 (4.0+, 14.1)**

Data cutoff, August 24, 2018.
*Confirmed response includes subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.
+ after value indicates censoring.
DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TTR, time to response.

Adverse Events of Special Interest

	Overall 5.4 or 6.4 mg/kg (N = 247)		NSCLC (N = 18)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AST increased	51 (20.6)	4 (1.6)	1 (5.6)	0
ALT increased	38 (15.4)	2 (0.8)	0	0
Blood bilirubin increased	5 (2.0)	0	0	0
Ejection fraction decreased	2 (0.8)	0	0	0
Electrocardiogram QT prolonged	12 (4.9)	1 (0.4)	0	0
Interstitial lung disease	10 (4.0)	2 (0.8)	1 (5.6)	0
Pneumonitis	21 (8.5)	6 (2.4)	1 (5.6)	1 (5.6)
Infusion-related reactions	3 (1.2)	0	0	0

- Observed laboratory abnormalities (eg, LFT, QTc, and LVEF) were generally low grade and asymptomatic
  - DS-8201a treatment was continued in these subjects with laboratory abnormalities
- The frequency of infusion reactions was low and no serious reactions have been reported to date
- There were 5 fatal cases of ILD/pneumonitis observed in the overall population (1 in the NSCLC subgroup)
- The grade 5 ILD case in NSCLC was adjudicated as unrelated to the study drug by an independent adjudication committee

Data cutoff, August 24, 2018.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; LFT, liver function tests; LVEF, left ventricular ejection fraction; NSCLC, non-small cell lung cancer; QTc, QT interval corrected for heart rate.

MET

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MET Exon 14 Skipping Mutation

- Introns flanking *MET* exon 14 in pre-mRNA are spliced out resulting MET mRNA which is translated into functional MET receptor.
- *MET* exon 14 encodes the ubiquitin ligase binding site which is used in receptor degradation.
- *Mutations that disrupt splice sites result in MET exon 14 skipping producing a MET receptor that lacks ubiquitin binding site* → *reduced degradation of MET protein* → *sustained MET activation.*
- Next generation sequencing the preferred testing method.
- *MET* exon 14 skipping mutations in 20-30% of *pulmonary sarcomatoid carcinoma*, and can be seen in squamous histology.

Drilon et al JTO 2017, Liu et al JCO 2016

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Crizotinib in *MET* Amplified NSCLC: Context Matters

MET/CEP7 ratio	N	ORR	PFS
≥1.8 to ≤ 2.2	3	33%	1.8
> 2.2 to < 4.0	14	14.3%	1.9
≥ 4.0	20	40%	6.8

- MET amplified defined by copy number as well. Copy number cut-off vary depending on testing
- MET amplification present in 15-20% of samples of MET exon 14 alteration
- 2/19 patients of *MET* amplified patients had *MET* exon 14 alterations (10.5%)

Camidge et al ASCO 2018

Frequency of *MET* alterations

Molecular alteration	Screening	# of positive cases	Pts included
***MET* amplification**	**4191**	**252 (6.0%)**	**25 patients**
***MET* mutation**	**1192**	**86 (7.2%)**	**29 patients**

Moro-Sibilot et al WCLC 2018

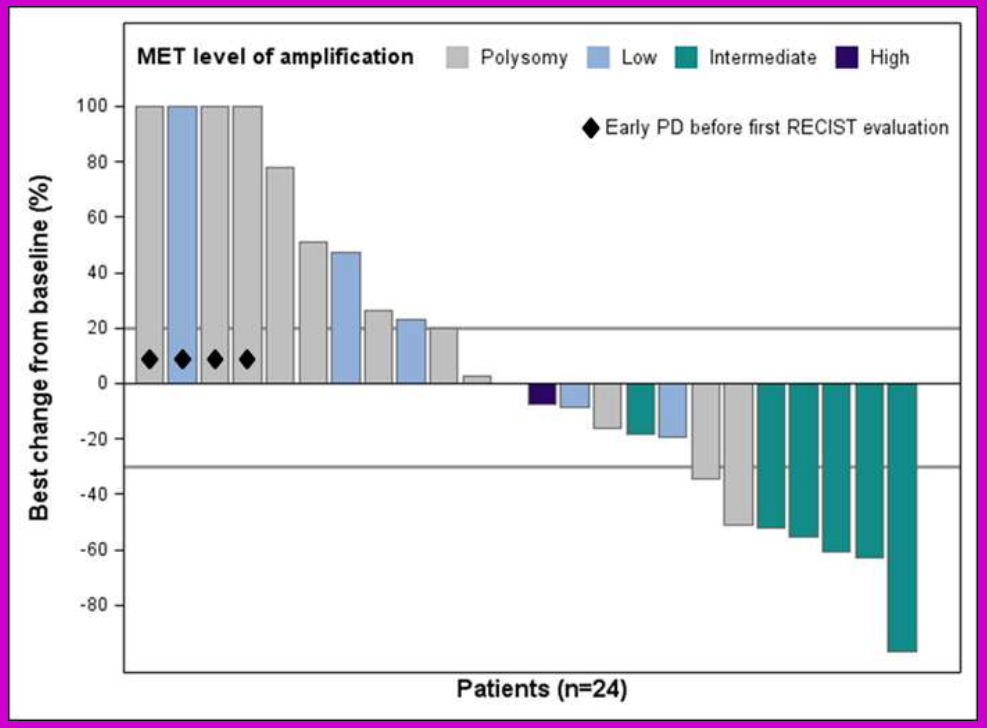
Selected Patient Characteristics

Patient and disease characteristics	*MET* amplification	*MET* mutation
Number	25 Median copy #: 8 (6-12)	28 (Exon 14: n=25)
Male	56%	32%
Median age (range)	59 (30-92)	72 (35-85)
Adenocarcinoma	21 (84%)	26 (92%)
Smokers (current and former)	18 (76%)	11 (52%)
Brain metastases	5 (20%)	7 (25%)

Moro-Sibilot et al WCLC 2018

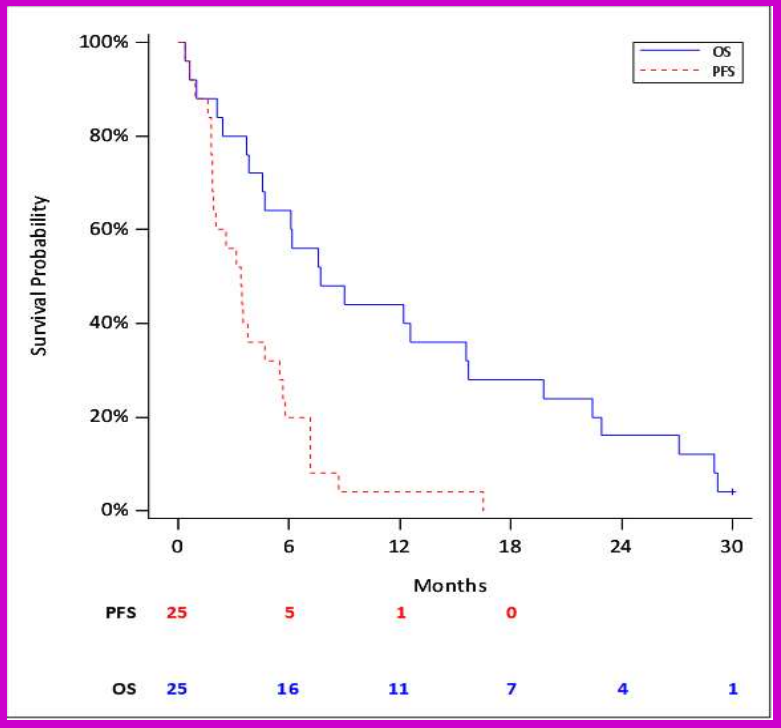
MET Amplification

Response



ORR: 32% (8/25)

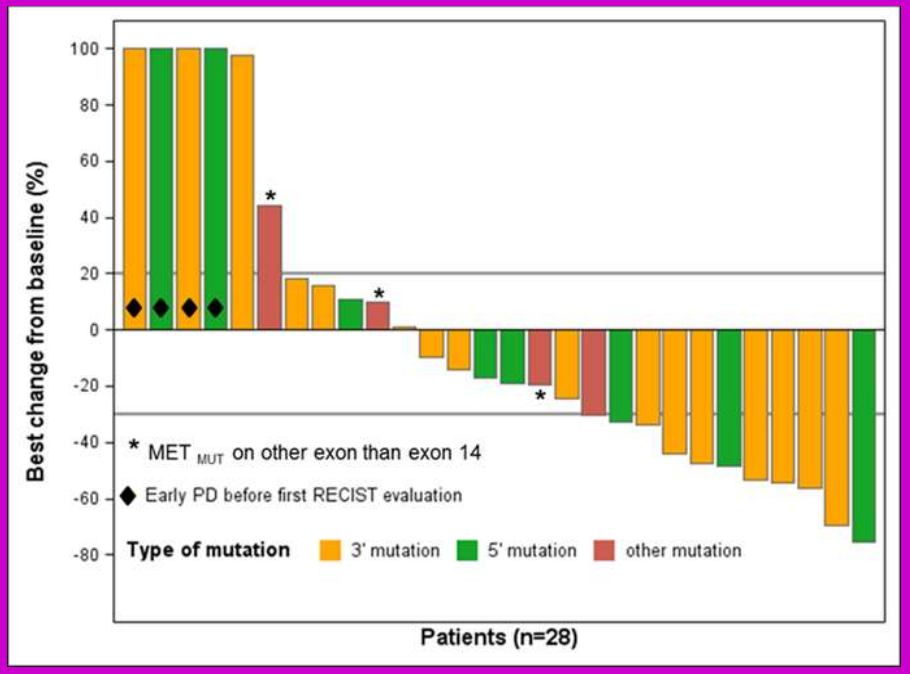
PFS and OS

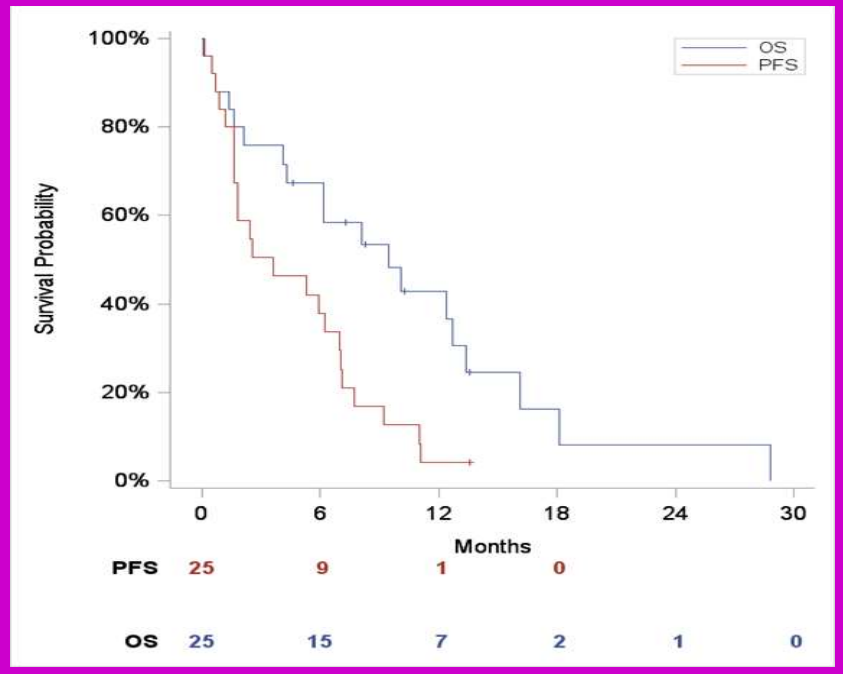


Median PFS: 3.4 months
Median OS: 7.7 months

Moro-Sibilot et al WCLC 2018

MET exon 14 Skipping Mutation





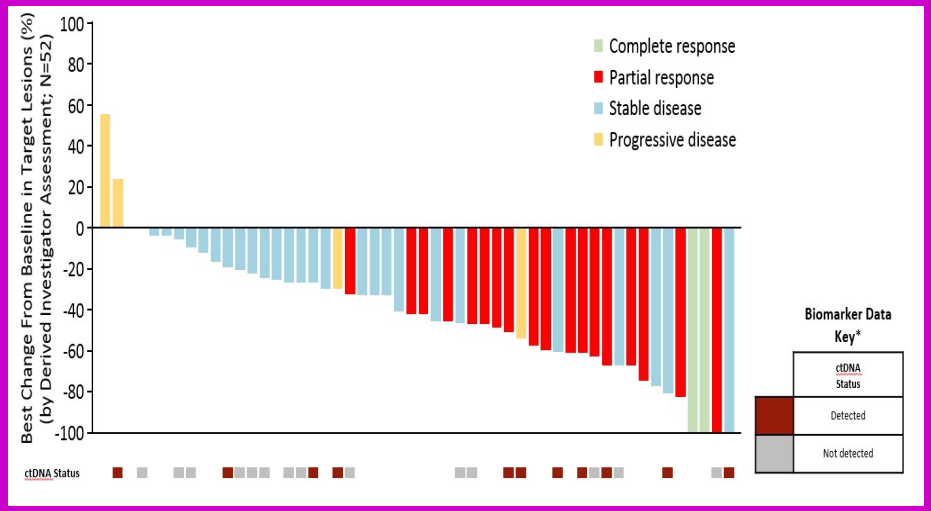
ORR 40% (10/25)

Median PFS 3.6 months
Median OS: 9.5 months

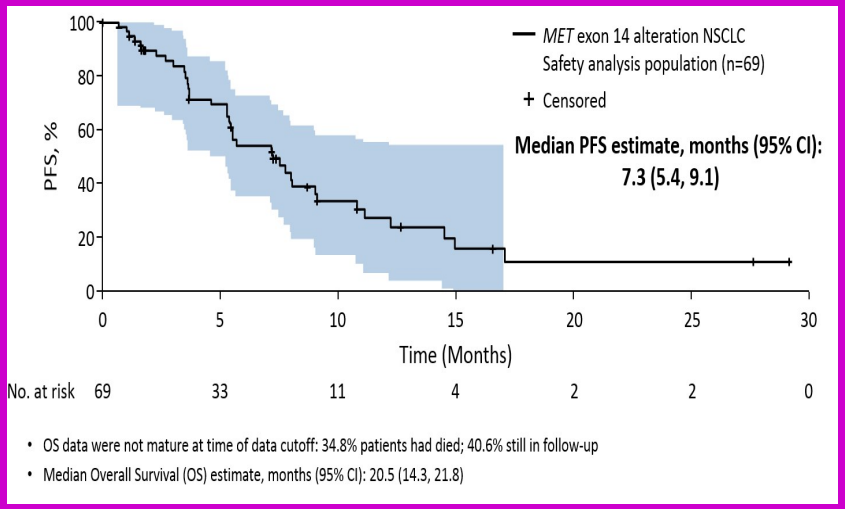
Moro-Sibilot et al WCLC 2018

Crizotinib in *MET* Exon 14 alterations

Responses



Progression-Free Survival



ORR: 32% (28/65)
DOR: 9.1 months

Median OS estimate: 20.5 months

Drilon et al WCLC 2018

Novel Agents for MET exon 14

Agent	Patient population	ORR	PFS
Capmatinib (INC280)	MET exon 14 Pre-treated	39% 27/69	Not available
Capmatinib (INC280)	MET exon 14 Treatment naïve	72% (18/25)	Not available
Tepotinib	MET exon 14 Pre-treated	35% (14/40)	Not available

Wolf et al ESMO 2018, Felip et al WCLC 2018

EXON 20 INSERTION

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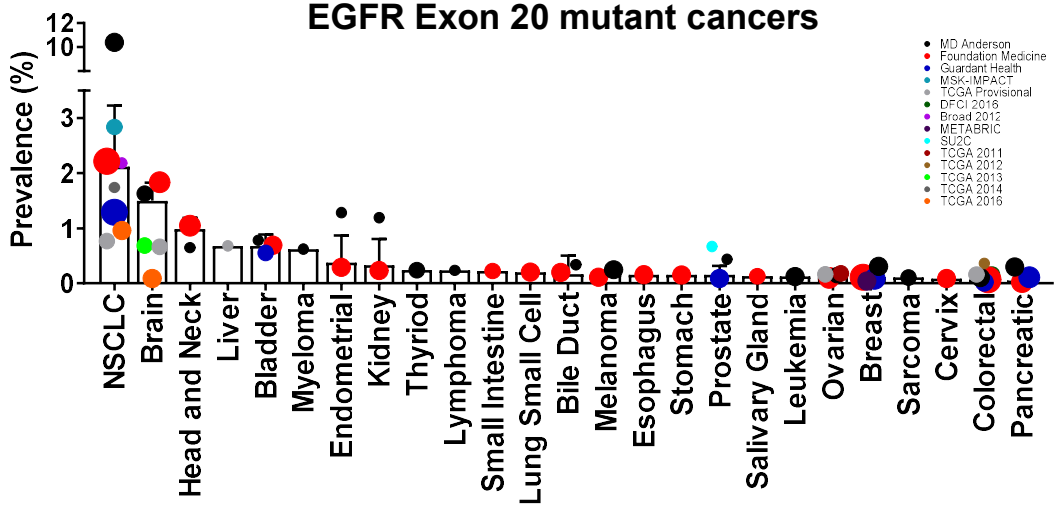
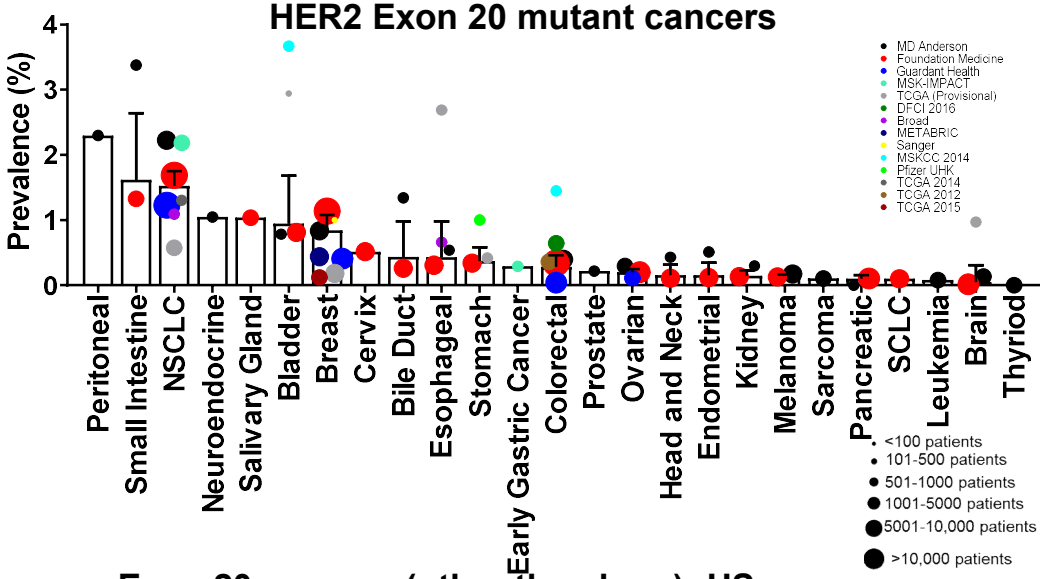
Phase II trial of poziotinib for EGFR and HER2 exon 20 mutant NSCLC

John V. Heymach, MV Negrao, JP Robichaux, BW Carter, A Patel, M Altan, DL Gibbons, F Fossella, G Simon, V Lam, G Blumenschein, AS Tsao, JM Kurie, F Mott, DM Jenkins, D Mack, L Feng, B Roeck, Z Yang, V Papadimitrakopoulou, YY Elamin

University of Texas MD Anderson Cancer Center
Houston, Tx, USA

EGFR and HER2 exon 20 insertions occur in NSCLC and many other cancer types (N=390,000 pts)





Exon 20 NSCLC: US and China

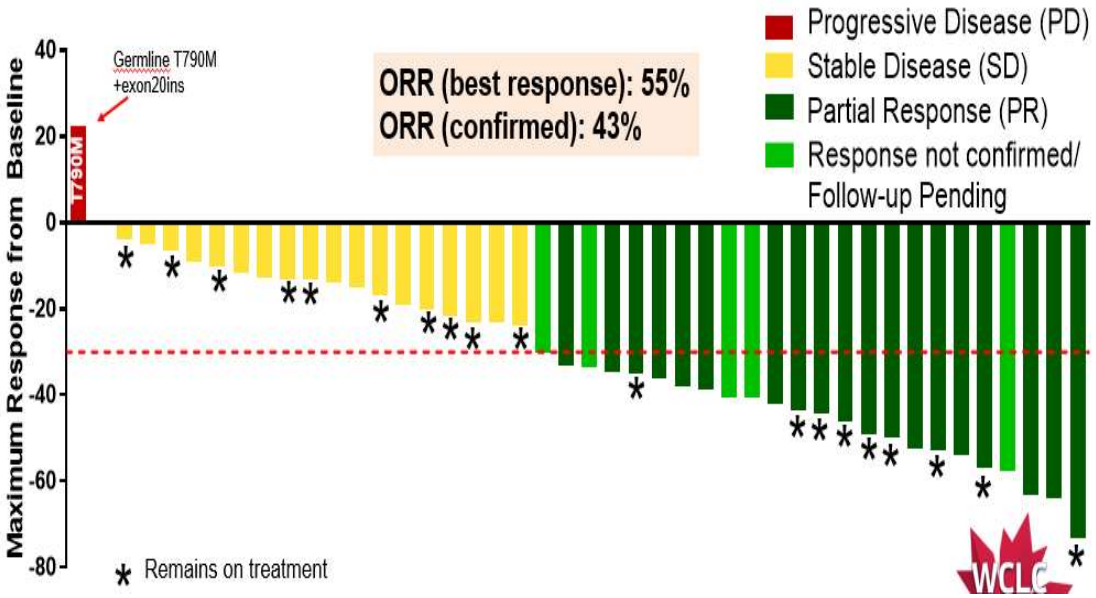
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR	2.1%	3.6%	7700
	HER2	1.5%		
China	EGFR	2.4%	6.3%	41100
	HER2	3.9%		

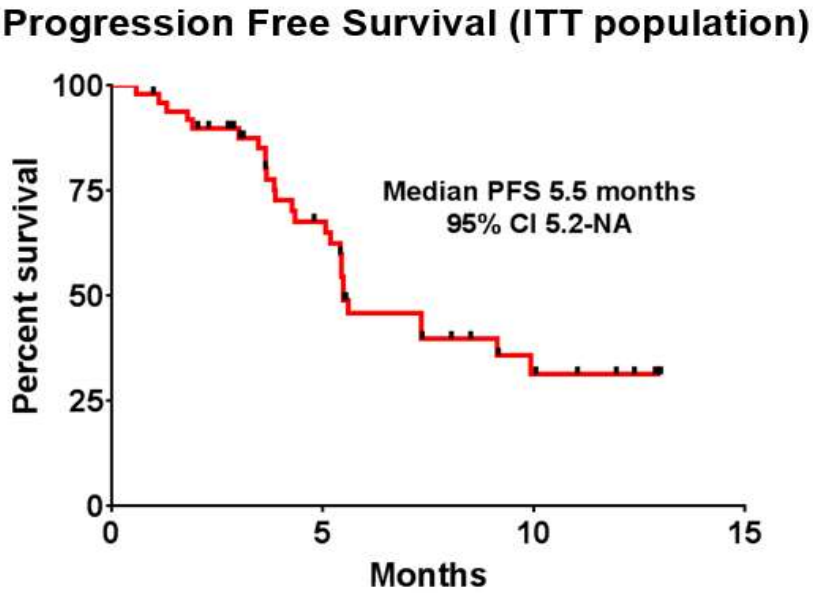
Exon 20 cancers (other than lung): US

	Exon 20 frequency (%)	Total Exon 20 patients/year	
EGFR	3710 (0.2%)	0.6%	8400
HER2	4691 (0.4%)		

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC

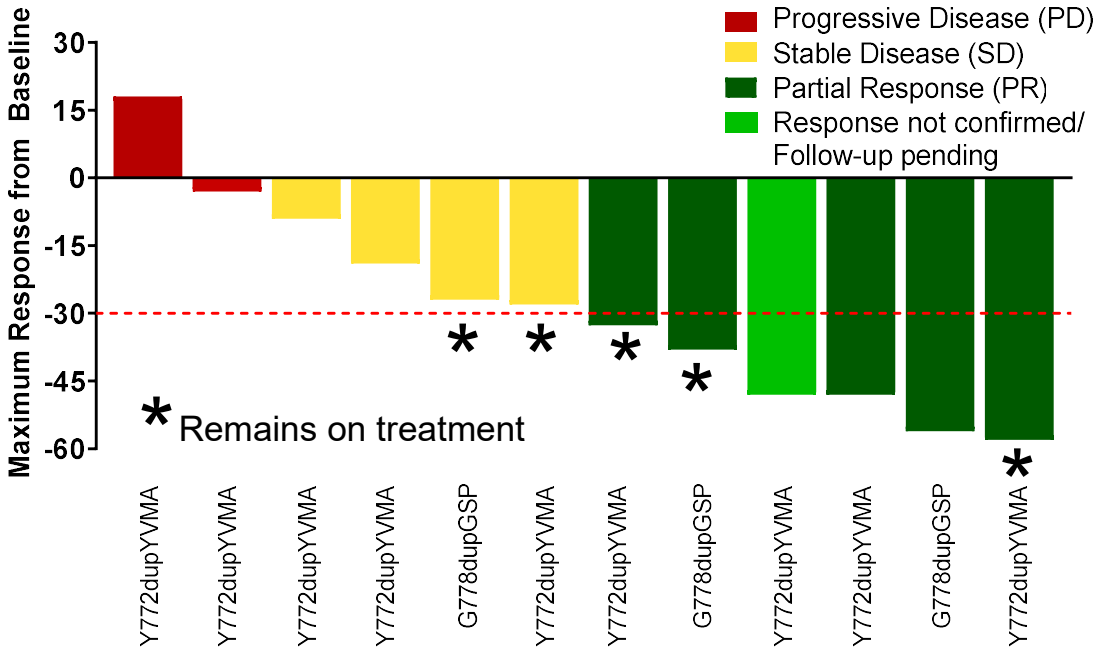
(Evaluable patients n=44)



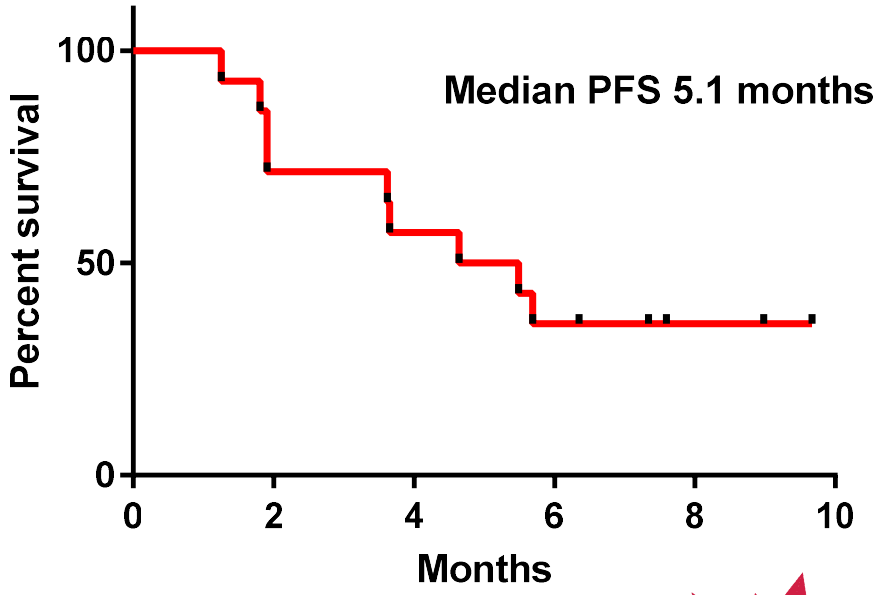


Poziotinib efficacy in HER2 Exon 20 insertion mutant NSCLC

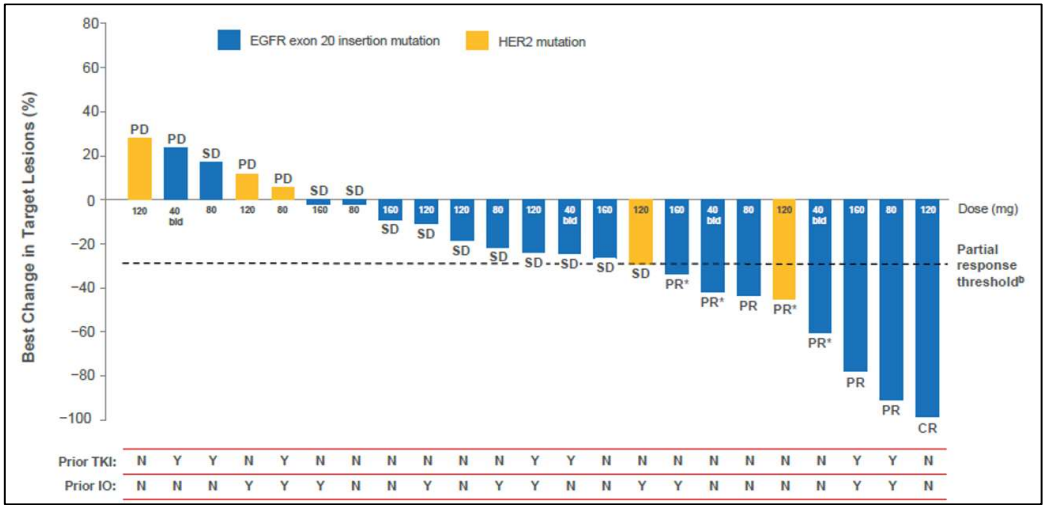
Best response HER2 (Evaluable patients n=12)

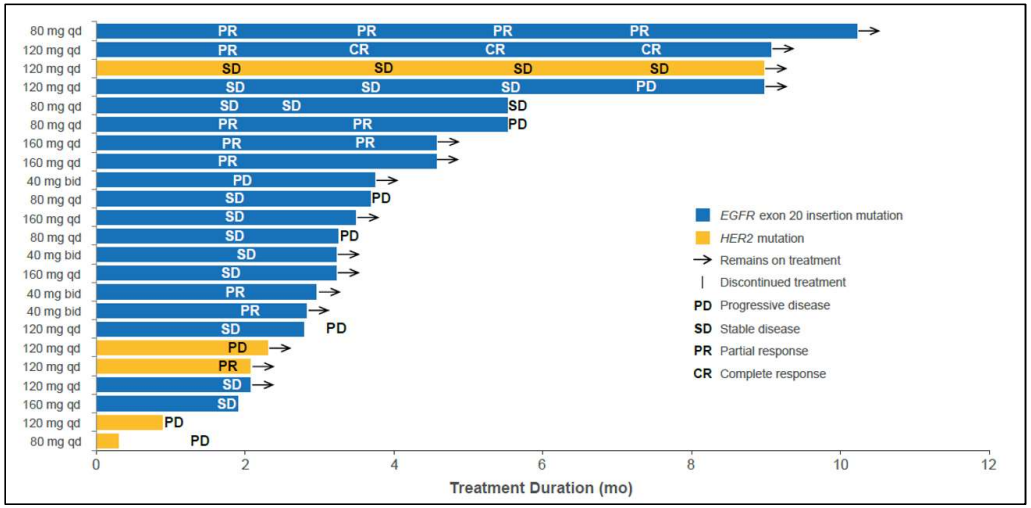


Progression-free Survival HER2 (All patients n=13)



TAK-788





	5–40 mg qd (n=12)	80 mg qd; 40 mg bid (n=9)	120 mg qd; 60 mg bid (n=9)	160 mg qd (n=6)	80–160 mg Total Daily Dose (n=24)
Patients with ≥1 post-baseline scan	n=10	n=9	n=4	n=5	n=18
ORR, n (%)	0	4 (44)[a]	1 (25)	2 (40)[b]	7 (39)
CR	0	0	1 (25)	0	1 (6)
PR	0	4 (44)[a]	0	2 (40)[b]	6 (33)[c]
DCR, n (%)	3 (30)	8 (89)	4 (100)	5 (100)	17 (94)

Neal et al. WCLC 2018

Conclusions

- ROS1+ NSCLC patients may have novel therapeutic options in the near future including entrectinib, repotrectinib and lorlatinib; these agents induces high ORR and have IC penetration.
- LOXO-292 and BLU-667 represent potent and selective RET inhibitors with good ORR and safety profile.
- DS-8201a was designed with the goal of improving critical attributes of an antibody-drug conjugate; it shown promising results in patients with HER2 alterations either overexpression and/or mutations.
- Crizotinib works in both MET amplification and exon 14 skipping mutation.
- Poziotinib and TAK788 have shown activity in exon 20 insertions in both EGFR and HER2.

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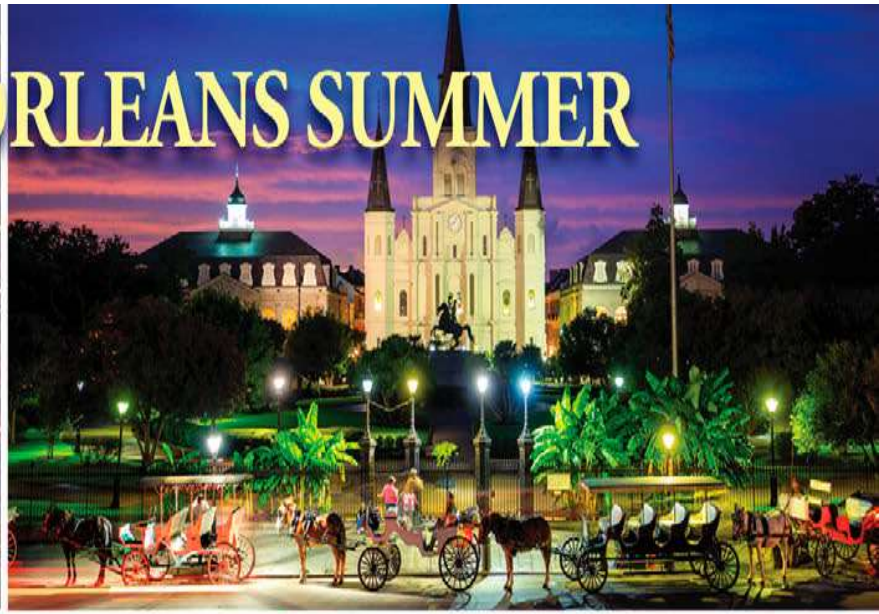
July 19-21, 2019

14th ANNUAL NEW ORLEANS SUMMER CANCER MEETING



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