NTRK Inhibitors, Exon 20 and Other Agents

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EDITORIAL

Tumor Type-Agnostic Treatment and the Future of Cancer Therapy

Luis E. Raez[1] · Edgardo S. Santos[2]

Published online: 10 October 2018

It is fascinating to see how the science of cancer therapy has evolved. We first classified tumors as "solid" or "liquid" and created the specialties of oncology and hematology to later discover that the shape of the tumors has nothing to do with their etiology, so we ended up combining both specialties. Next, we proceeded to classify cancers according to the organ they grow in, thinking that the origin of the tumors is what causes their biological behaviors, and could guide us in understanding and fighting them properly. After so many years taking this approach, with both tremendous successes and deep disappointments, we are now beginning to appreciate that there is much more complexity to cancer biology than simply the tissue that tumors arise from.

In the current issue, Kummar and Lassen [2] present a very comprehensive review of NTRK gene aberrations as one example of success in using this tumor site-agnostic approach. The authors review the diagnostic and treatment strategies that are being implemented to deal with NTRK-fusion genes and the diseases that they cause.

NTRK genes encode for the Trk-family of tyrosine kinases: TrkA, TrkB, and TrkC (encoded by NTRK1, NTRK2, and NTRK3). Normally, these proteins are involved in the development of the nervous system [3]. However, Trks are also present in solid tumors as fusion proteins responsible for the growth of cancer cells, and these oncogenic fusions are associated with poor survival in lung cancers and other tumor

NTRK inhibitors

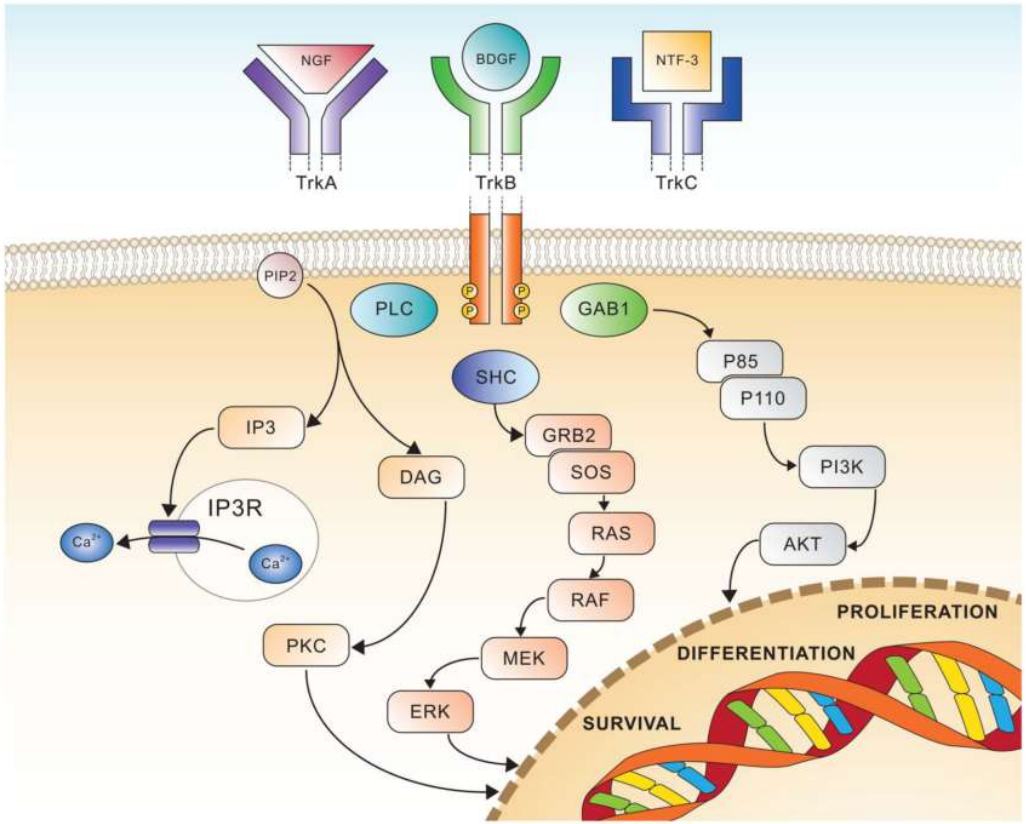
Larotrectenib

Entrectinib

LOXO 195

An Introduction to *NTRK*

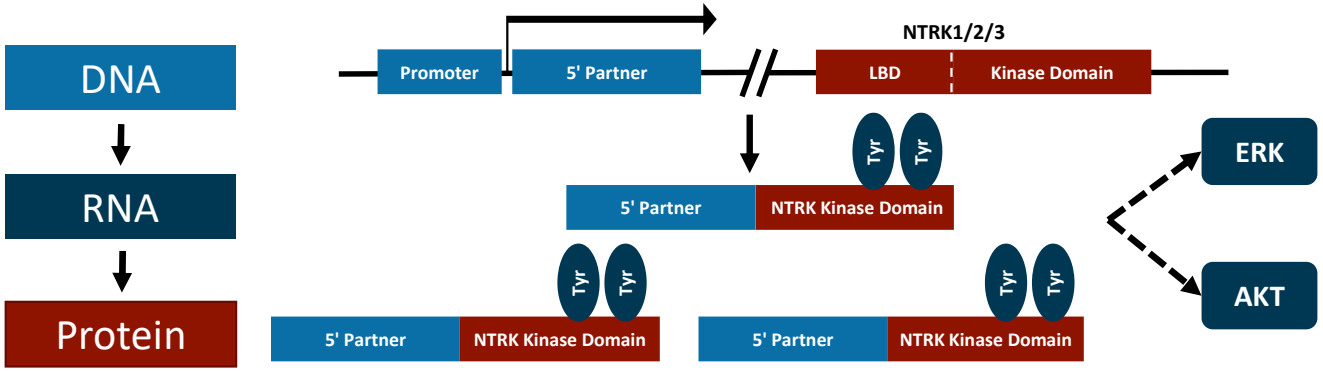
- *NTRK* genes: 1, 2, and 3 encode TRK proteins: A, B, and C
- Normally regulate neuronal development in utero and sensation of pain, proprioception, and appetite postnatally
- *NTRK* gene fusions found in large number of solid tumors and leukemias
  - Common in rare cancers:
    - Infantile fibrosarcoma/cellular CMN
  - Rare in more common cancers
    - NRSTS, gliomas, melanomas, thyroid cancer, breast cancer, other adult epithelial cancers



Amatu A, et al. *ESMO Open.* 2016;1:e000023.

NTRK Fusions

- Beyond the embryo, TRK proteins are primarily limited to the nervous system[a]
- 3 neurotrophin receptors encoded by 3 distinct genes that regulate specific normal functions[a,b]
  - NTRK1 → TRKA → Pain, thermoregulation
  - NTRK2 → TRKB → Movement, memory, mood, appetite, body weight
  - NTRK3 → TRKC → Proprioception
- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers[a,b]



a. Drilon A, et al. *N Engl J Med.* 2018;378:731-739; b. Vaishnavi A, et al. *Cancer Discov.* 2015;5:25-34.

Larotrectinib in *TRK*-fusion cancers

Diseases

Tumor type	#/ percentage
Salivary gland tumor	12 (22%)
Soft tissue sarcoma	11 (20%)
Infantile fibrosarcoma	7 (13%)
Thyroid cancer	5 (9%)
Colon cancer	4 (7%)
Lung cancer	4 (7%)
Melanoma	4 (7%)
GIST	3 (5%)
Cholangiocarcinoma	2 (4%)
Appendix	1 (2%)
Breast	1 (2%)
Pancreas	1 (2%)

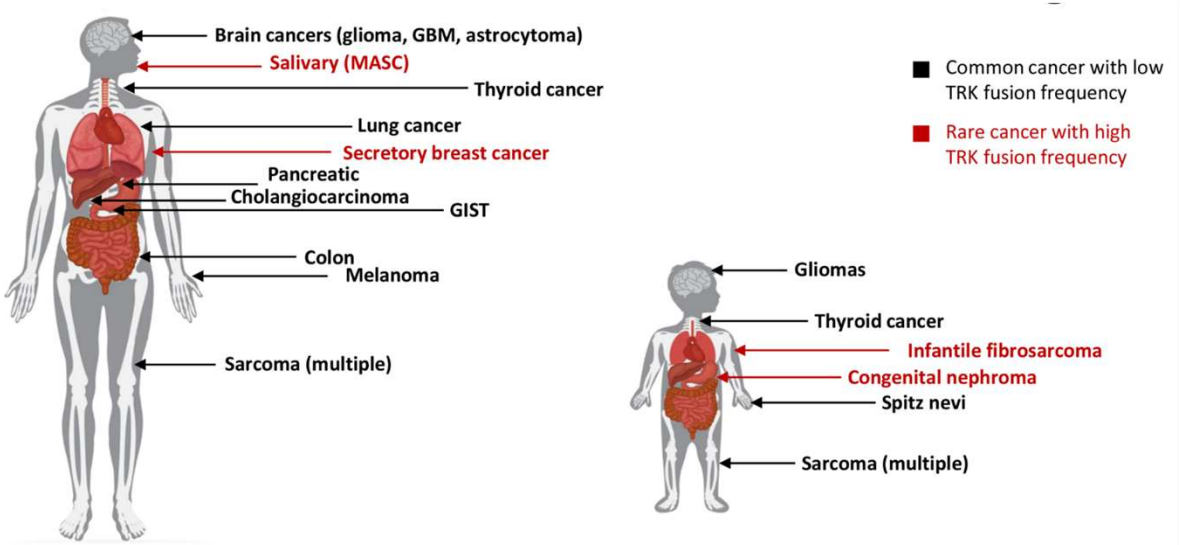
Efficacy

Parameter	Result
ORR	75% (41/55)
Median time to response	1.8 months
Median duration of response	NR
Median PFS	NR
1-year PFS	55%

Drilon et al NEJM 2018

Prevalence

- Estimated 1500 to 5000 US patients with *NTRK* fusion-positive cancers[a]



- *NTRK1* fusions are found in approximately 1% of adenocarcinomas of the lung[b]

a. Hyman DM, et al. ASCO® 2017. Abstract LBA2501; b. Tsao AS, et al. *J Thorac Oncol.* 2016;11:613-638.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

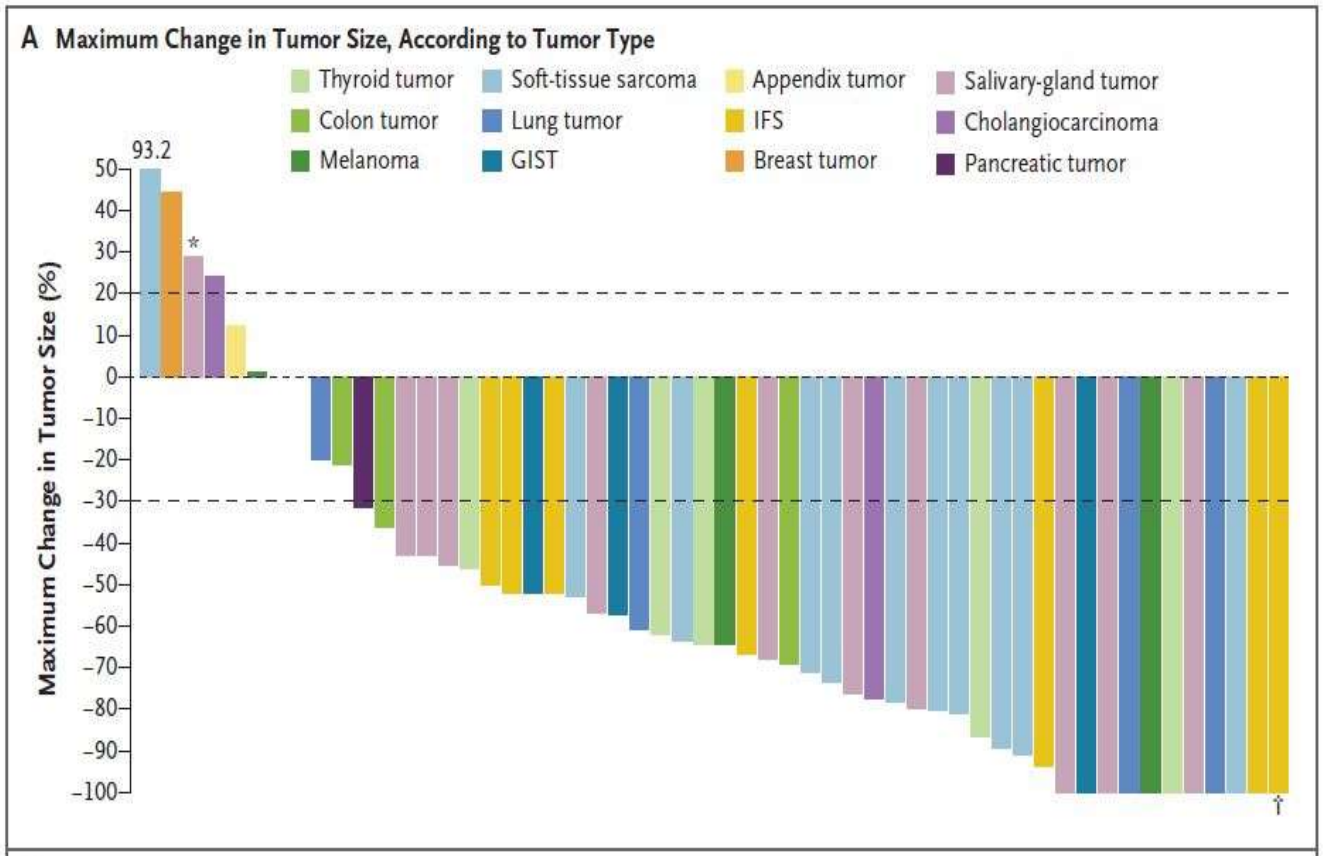
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

ABSTRACT

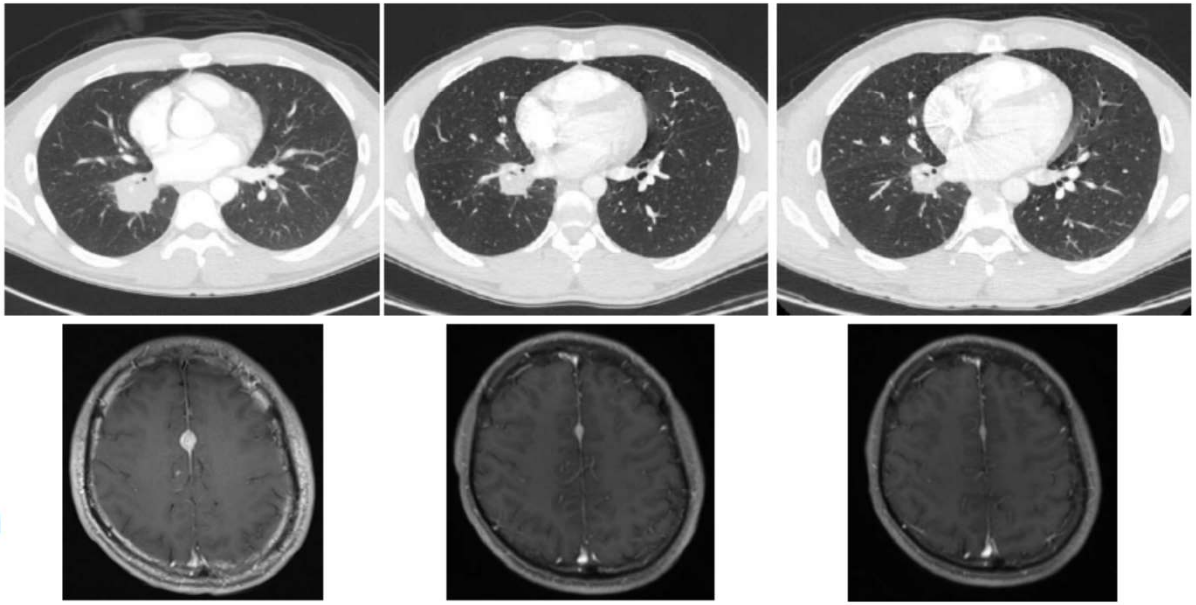
BACKGROUND

The NEW ENGLAND JOURNAL of MEDICINE



Preliminary Evidence of Brain Penetration

- 28 yo male progressed through cisplatin and etoposide
- TPR-NTRK1 non-small cell lung cancer
- 100mg BID
- Resolution of cough and pain
- Currently on study in cycle 7



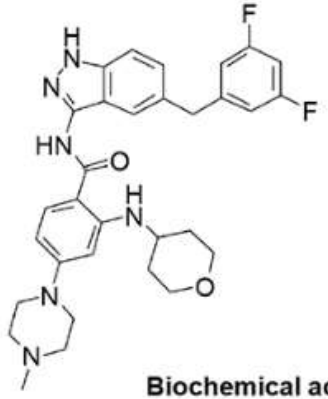
Study baseline | Study cycle 3 day 1 | Study cycle 7 day 1

Hong D et al. Proc AACR Annual Meeting 2016. Abstr CT008.

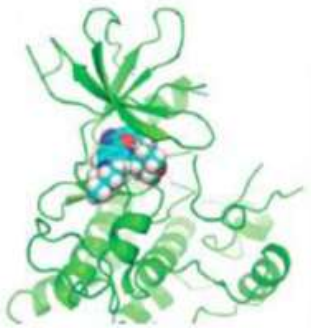
Entrectinib: Pan-TRK/ROS1/ALK Inhibitor[1]

- Orally administered inhibitor of TRKA/B/C, ROS1, and ALK

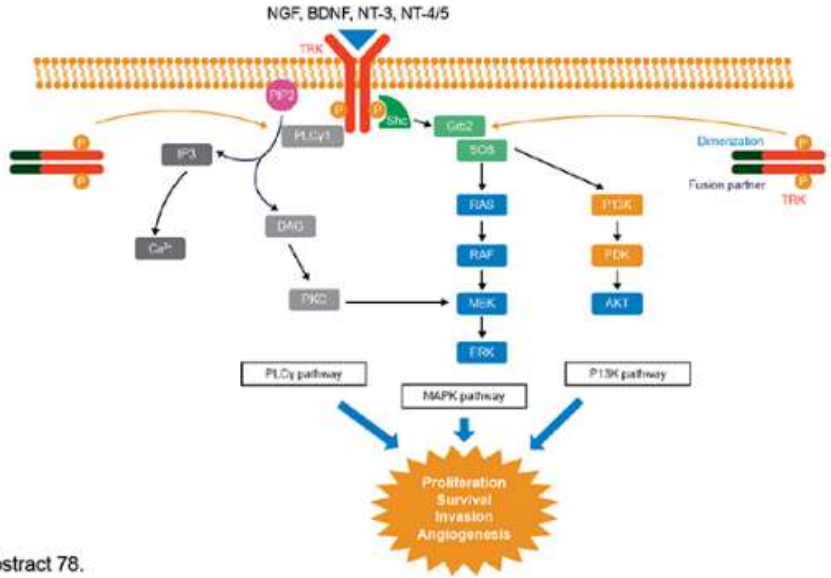
Chemical structure of entrectinib



X-ray crystallography model of entrectinib binding in the kinase pocket of TRKA



Signaling pathways of TRK and TRK fusions



Biochemical activity of entrectinib

Target	TRKA	TRKB	TRKC	ROS1	ALK
IC_{50} (nM)	1.7	0.1	0.1	0.2	1.6

1. Wei G et al. 2016 EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium. Abstract 78.

Entrectinib Development Program: Combined Phase 1 Studies[1]

ALKA-372-001 (N = 54)

- Dosing: Intermittent and continuous
- *NTRK/ROS1/ALK* alterations
- Italy
  - FIH study: Nerviano Medical Sciences in October 2012 → Ignyta assumed responsibility in November 2013

STARTRK-1 (N = 65)

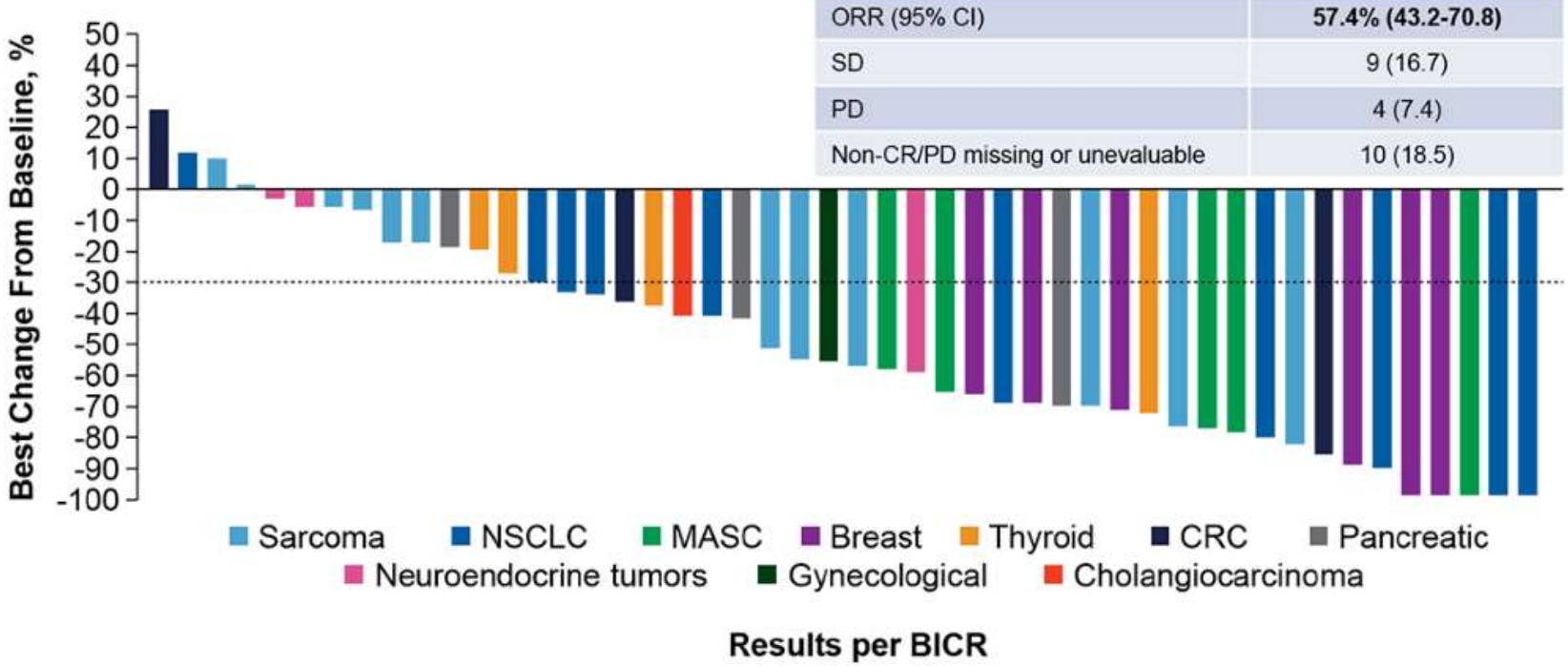
- Dosing: Continuous
- *NTRK/ROS1/ALK* alterations
- US, EU, and Asia
  - Ignyta initiated in July 2014

- RP2D: 600 mg PO once daily, continuous
- Total clinical experience (n = 119 patients)
  - Updated safety and efficacy data
  - Data cut-off: March 7, 2016

1. Drilon A et al. *Cancer Discov*. 2017;7:400-409.

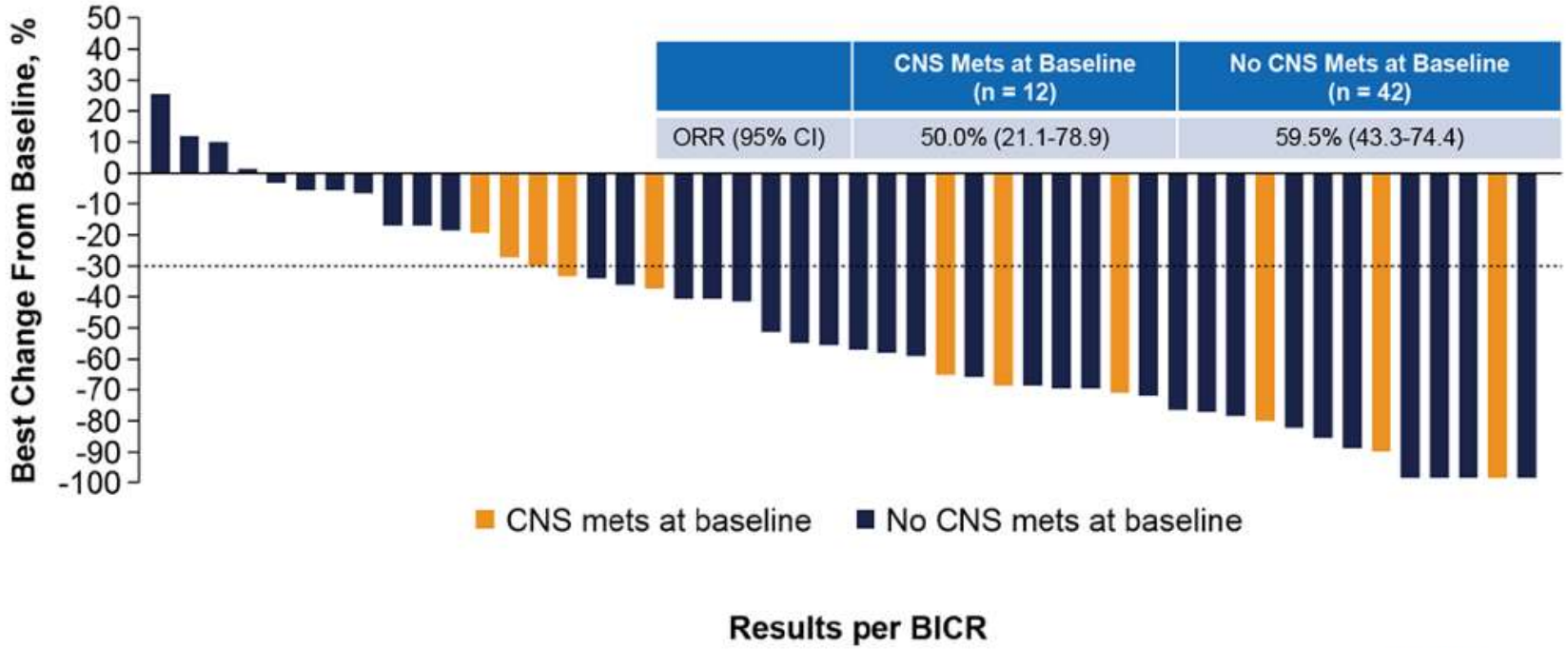
Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Patient Responses by Tumor Type[1]

	NTRK+ Patients (n = 54)
ORR (95% CI)	**57.4% (43.2-70.8)**
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD missing or unevaluable	10 (18.5)



1. Demetri GD et al. ESMO 2018. Abstract LBA17.

Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Responses by CNS Mets Status[1]



1. Demetri GD et al. ESMO 2018. Abstract LBA17.

Entrectinib: Safety Overview[1]

Treatment-Related AEs Reported in ≥10% of Patients	*NTRK* Fusion-Positive Safety Population (n = 68)		Overall safety population (N = 355)	
Patients, n (%)	Grades 1/2	Grade 3	Grades 1/2	Grade 3
Dysgeusia	32 (47.1)	0	146 (41.1)	1 (0.3)
Constipation	19 (27.9)	0	83 (23.4)	1 (0.3)
Fatigue	19 (27.9)	5 (7.4)	89 (25.1)	10 (2.8)
Diarrhoea	18 (26.5)	1 (1.5)	76 (21.4)	5 (1.4)
Oedema peripheral	16 (23.5)	1 (1.5)	49 (13.8)	1 (0.3)
Dizziness	16 (23.5)	1 (1.5)	88 (24.8)	2 (0.6)
Blood creatinine increase	12 (17.6)	1 (1.5)	52 (14.6)	2 (0.6)
Paraesthesia	11 (16.2)	0	67 (18.9)	0
Nausea	10 (14.7)	0	74 (20.8)	0
Vomiting	9 (13.2)	0	48 (13.5)	0
Arthralgia	8 (11.8)	0	42 (11.8)	2 (0.6)
Myalgia	8 (11.8)	0	52 (14.6)	2 (0.6)
Weight increased	8 (11.8)	7 (10.3)	51 (14.4)	18 (5.1)
AST increase	7 (10.3)	0	35 (9.9)	3 (0.8)
Muscular Weakness	6 (8.8)	1 (1.5)	22 (6.2)	3 (0.8)
Anaemia	5 (7.4)	8 (11.8)	27 (7.6)	16 (4.5)

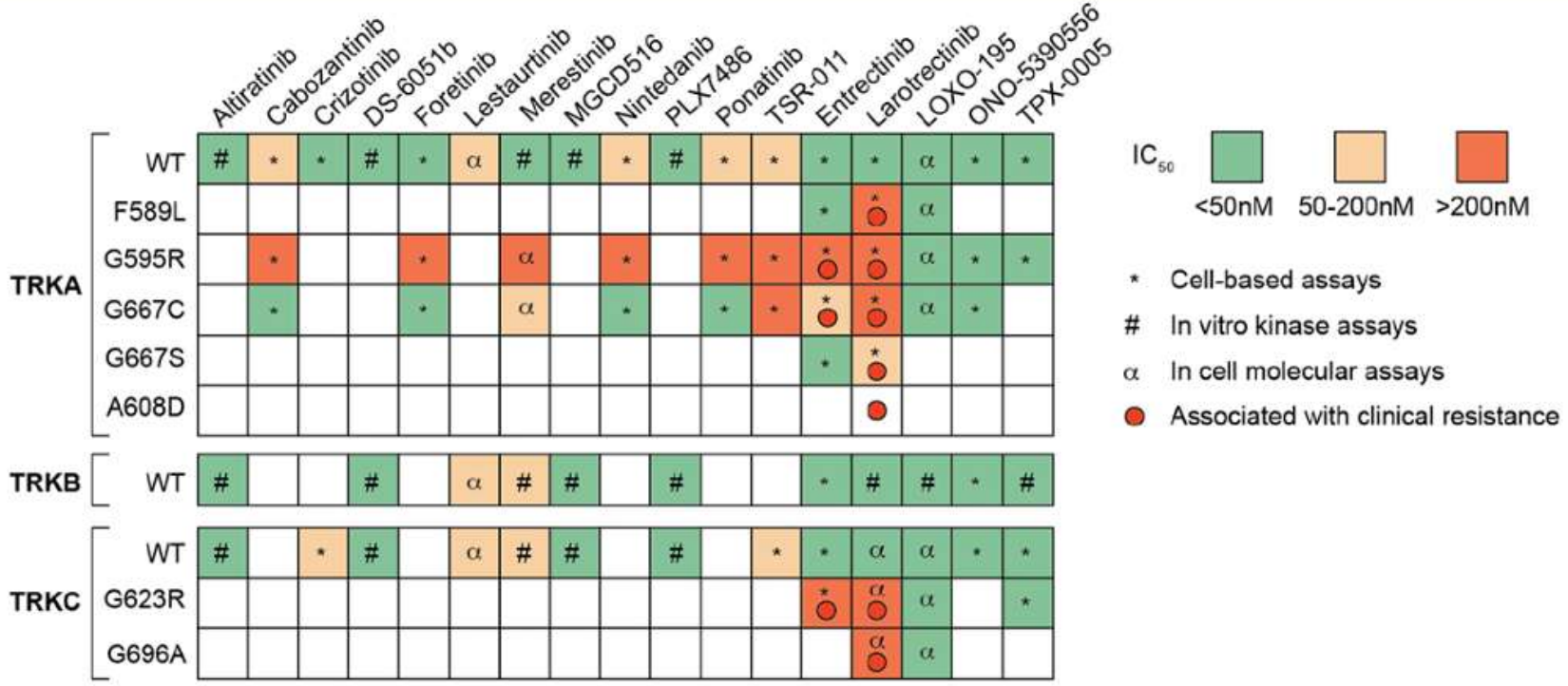
Overall safety population (N = 355)

- Most adverse events were grades 1/2 and reversible
- Treatment-related AEs leading to
  - **Dose reduction: 27.3%**
  - **Dose interruption: 25.4%**
  - **Discontinuation** from treatment: **3.9%**
- No grade 5 treatment-related events

Treatment-related AEs in the *NTRK* fusion–positive safety population are consistent with the overall safety population

1. Demetri GD et al. ESMO 2018. Abstract LBA17.

TRK Inhibitors Have Different Levels of Activity Against Emergent Mutations[1]

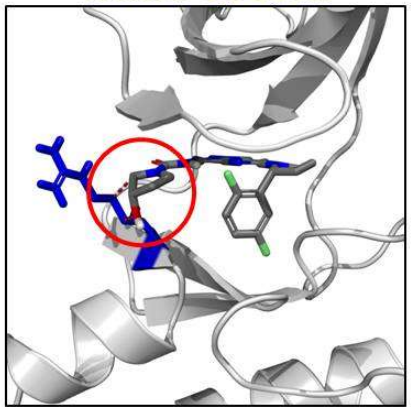


1. Cocco E et al. *Nat Rev Clin Oncol.* 2018;15:731-747.

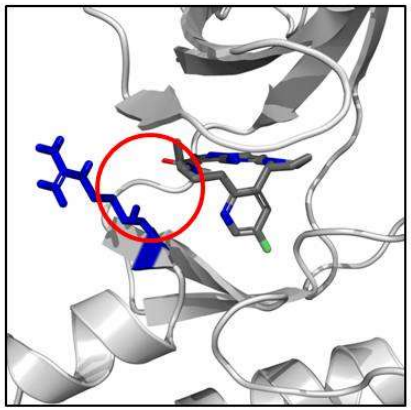
LOXO-195 to Address TRK Acquired Resistance

TRKA G595R

Larotrectinib



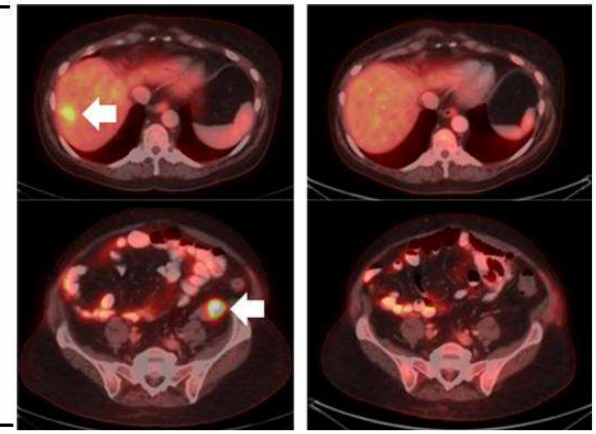
LOXO-195



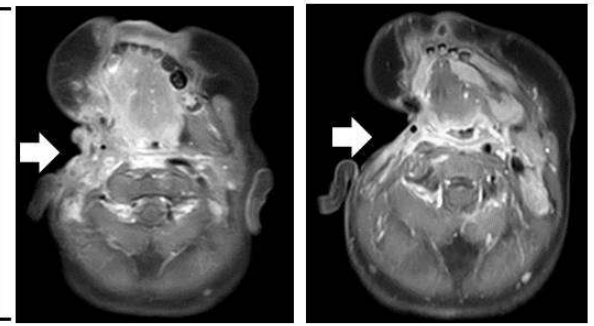
Tumor type	Fusion	Resistance mutation
Colorectal	TPM3-NTRK1	TRKA G595R
Colorectal	LMNA-NTRK1	TRKA G595R
NSCLC	TPR-NTRK1	TRKA G595R
Sarcoma[❖]	TPM3-NTRK1	TRKA G595R
IFS	ETV6-NTRK3	TRKC G623R
Cholangio[❖]	LMNA-NTRK1	TRKA F589L[*] + GNAS Q227H

TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.

LOXO-195 Treatment



Baseline | On Treatment



❖ Oligometastatic progression, continue on larotrectinib * Gatekeeper mutation
Drilon A, *Cancer Discovery*, Online First (03-JUNE-2017)

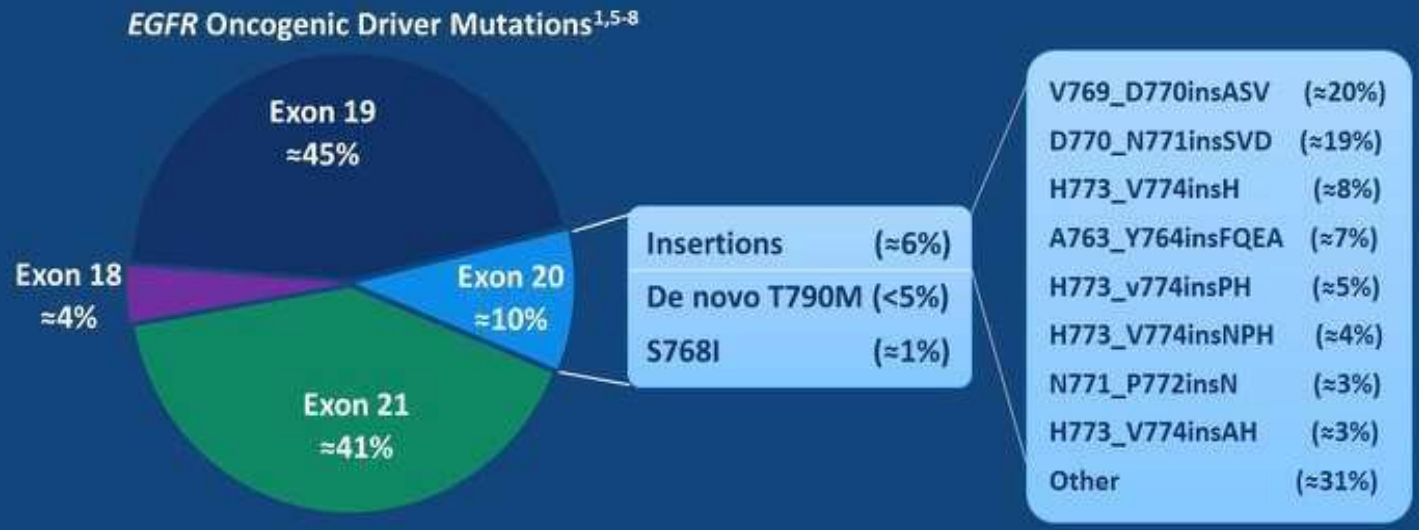
TRK inhibition

Table 1. Active clinical trials of TRK inhibitors in patients with *NTRK* fusion tumors[a]

Agent	Kinase targets	Phase	*NTRK* fusion tumor type	Start date	Status	Estimated participants
Larotrectinib	TRKA, TRKB, TRKC	I	Advanced solid tumors	May 2014	Recruiting	90
		II	Advanced solid tumors	October 2015	Recruiting	151
		I/II	Advanced solid or primary CNS tumors (pediatric)	December 2015	Recruiting	92
Entrectinib	TRKA, TRKB, TRKC, ALK, ROS1	I	Locally advanced or metastatic solid tumors[b]	June 2014	Recruiting	125
		II	Locally advanced or metastatic solid tumors[b]	October 2015	Recruiting	300
		I/Ib	Recurrent or refractory solid tumors and primary CNS tumors (pediatric)	December 2015	Recruiting	190
DS-6051b	TRKA, TRKB, TRKC, ROS1	I	Advanced solid tumors[c]	September 2014	Not recruiting	70
		I	Advanced solid tumors (Japanese patients)	February 2016	Not recruiting	15
TSR-011	TRKA, TRKB, TRKC, ALK	I/IIa	Advanced solid tumors and lymphomas[d]	October 2012	Unknown	72
TPX-0005[e]	TRKA, TRKB, TRKC, ALK, ROS1	I/II	Locally advanced or metastatic solid tumor (including non-Hodgkin lymphoma)[b]	February, 2017	Recruiting	450
LOXO-195[e]	TRKA, TRKB, TRKC	I/II	Advanced solid tumor progressing after prior TRK inhibitor treatment	July, 2017	Recruiting	93

CNS central nervous system
[a]As registered with ClinicalTrials.gov.
[b]Inclusion of patients with *ROS1*, or *ALK* gene rearrangements permitted.
[c]Inclusion of patients with *ROS1* gene rearrangements permitted.
[d]Inclusion of patients with *ALK* gene rearrangements permitted.
[e]Second generation TRK inhibitor with activity against TRK proteins with resistance mutations.

EGFR Exon 20 Insertions in NSCLC



- Approximately 6% of *EGFR*-mutated NSCLC tumors have *EGFR* exon 20 insertion mutations, and there are no approved targeted treatment options for patients with these mutations[1]
- Currently approved EGFR TKIs have shown efficacy in NSCLC patients with common activating *EGFR* mutations, but are largely ineffective in patients with *EGFR* exon 20 insertions, with poor response rates and median PFS of approximately 2 months[2,4]

EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor. 1. Kobayashi Y, Mitsudomi T. *Cancer Sci* 2016;107:1179–1186; 2. Wu J-Y et al. *Clin Cancer Res* 2008;14:4877–4882; 3. Naidoo J et al. *Cancer* 2015;121:3212-3220; 4. Yasuda H et al. *Sci Transl Med*. 2013;5:1-23; 5. Arcila ME et al. *Mol Cancer Ther* 2013;12:220–229; 6. Oxnard GR et al. *J Thorac Oncol* 2013;8:179–184; 7. Inukai M et al. *Cancer Res*. 2006;66:7854-7858; 8. Yasuda H et al. *Lancet Oncol*. 2012;13:e23-31.

TAK-788 Antitumor Activity in Patients With *EGFR* Exon 20 Insertions

Exon 20 Insertion Variant	No. of Patients	No. of Confirmed Responders, n	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Exact variant unknown	4	2	50%
Other	15	6	40%

- Median (range) best percent change: -32.5% (-100%, 26.3%)
- Three patients were excluded from the waterfall plot: 1 patient had nonmeasurable baseline target lesions, and 2 patients had no follow-up scans

IO, immuno-oncology therapy; PD, progressive disease.

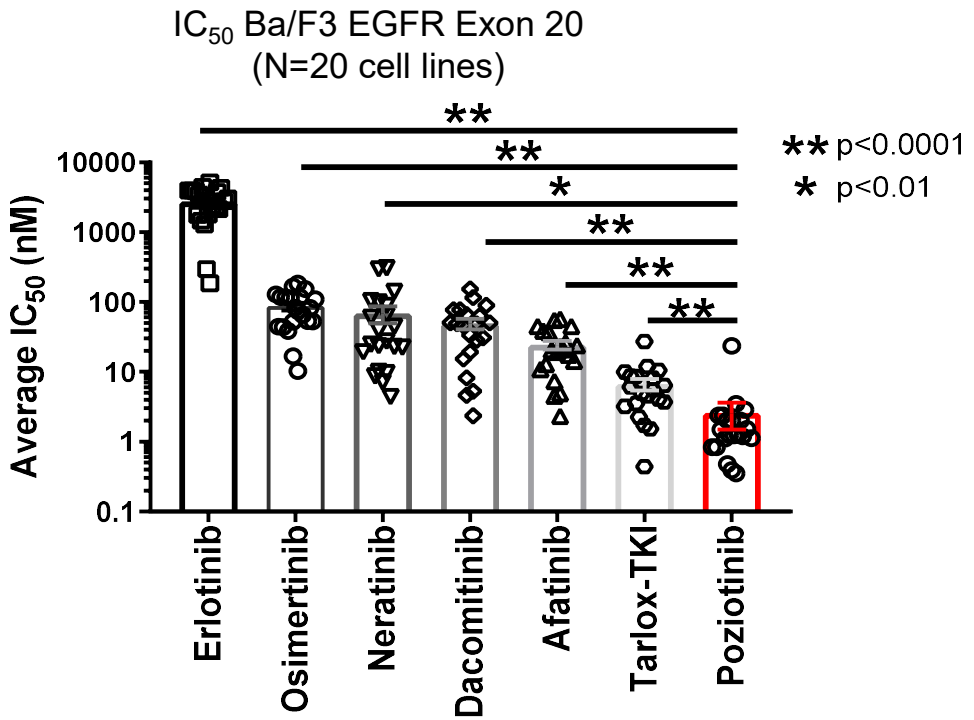
Treatment-Related AEs in Patients Treated With TAK-788

Any grade: ≥20% of all patients Grade ≥3: ≥3% of all patients	All Patients Treated at 160 mg qd[a] (n=72)		All Patients Treated at Any Dose[b] (N=137)	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Diarrhea	85	18	74	12
Nausea	43	6	33	4
Rash	36	1	26	1
Vomiting	29	3	22	2
Decreased appetite	25	1	22	1
Stomatitis	18	4	14	3
Increased lipase	10	6	8	3
Increased amylase	8	4	8	3

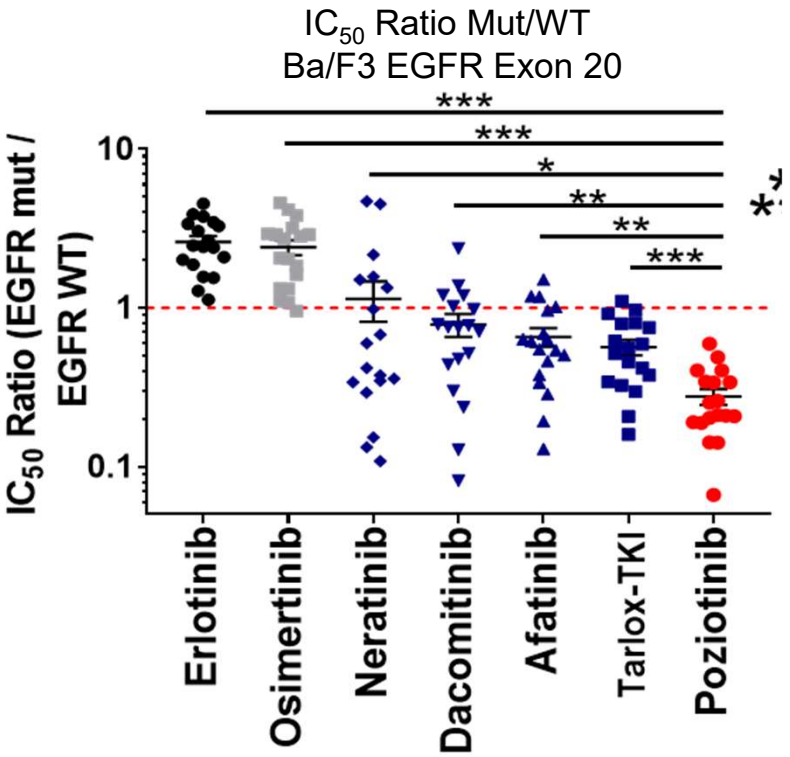
[a] Patients who received at least 1 dose of TAK-788 at 160 mg qd (initial dose) during dose escalation or expansion cohorts 1 to 7. [b] Patients who received at least 1 dose of TAK -788 (5–180 mg total daily dose) during the escalation or expansion phase. Data cutoff: 1 Mar 2019.

- Most treatment-related AEs were grade 1–2 and reversible
- Per protocol, no primary prophylaxis plan for AEs was in place
- Food instructions have been updated in this ongoing study with the potential to improve gastrointestinal tolerability based on emerging data in healthy subjects that suggest lack of low-fat meal effect on PK of TAK-788

Poziotinib is a potent selective inhibitor of EGFR exon 20 insertions *in vitro*

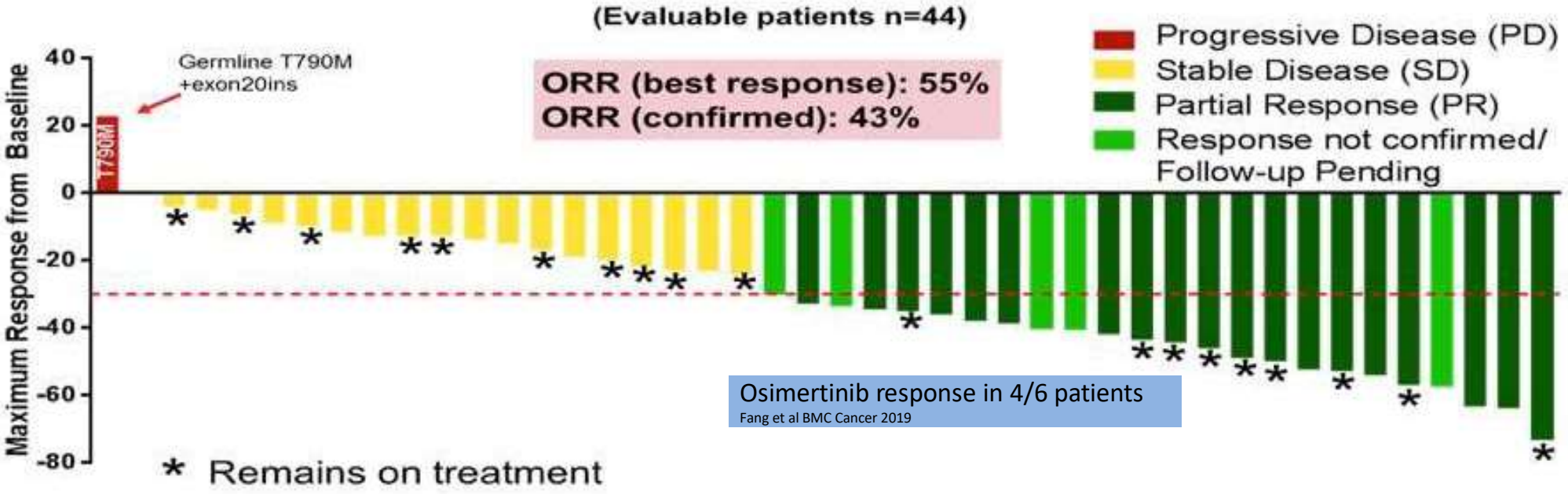


Ratio IC_{50} to Poziotinib	1075	34.8	27.3	19.7	9.7	2.7



Ratio to Poziotinib	9.4	8.7	4.1	2.8	2.4	2.0

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC



Osimertinib response in 4/6 patients
Fang et al BMC Cancer 2019

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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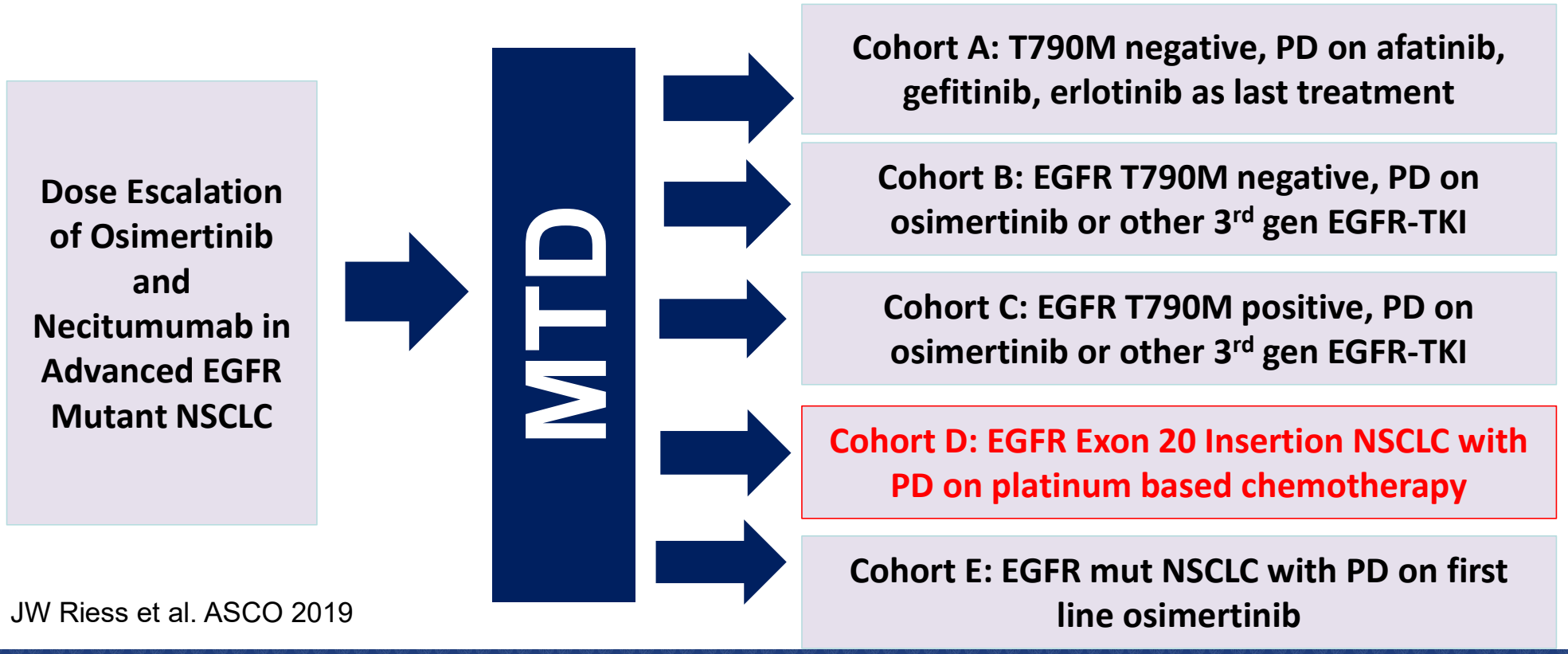
Presented By John Heymach at 2019 ASCO Annual Meeting

JV Heymach, WCLC Toronto 2018

Conclusion

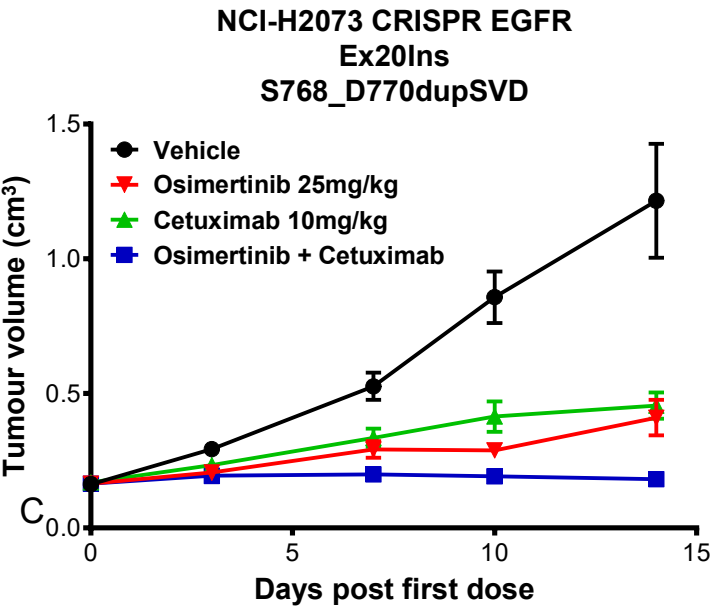
- Poziotinib is a potent selective inhibitor of EGFR exon 20 mutant *in vitro*, and is associated with PFS of 5.5 months and confirmed response rate of 43% in a phase II clinical trial
- Similar resistance mechanisms observed as other approved EGFR TKIs: EGFR-dependent mechanisms (T790M) and other EGFR tyrosine kinase domain point mutations
- EGFR-independent resistance mechanisms include activation of bypass pathways and EMT
- Pre-clinical studies to overcome/delay resistance are underway.

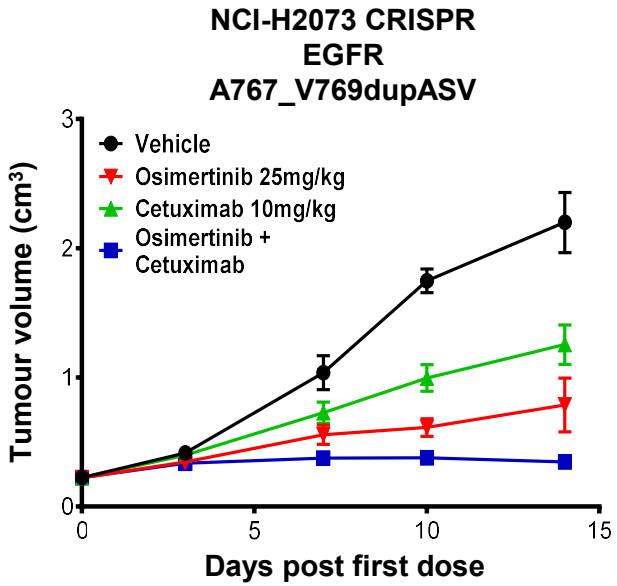
Osimertinib and Necitumumab in EGFR mutant NSCLC (NCI: 9898)

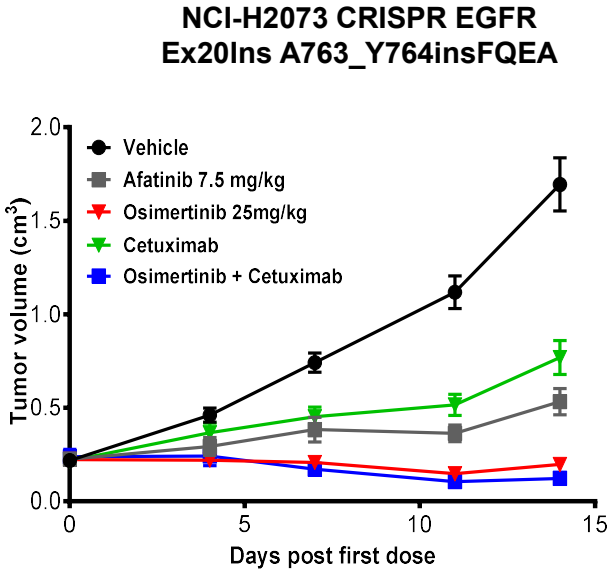


JW Riess et al. ASCO 2019

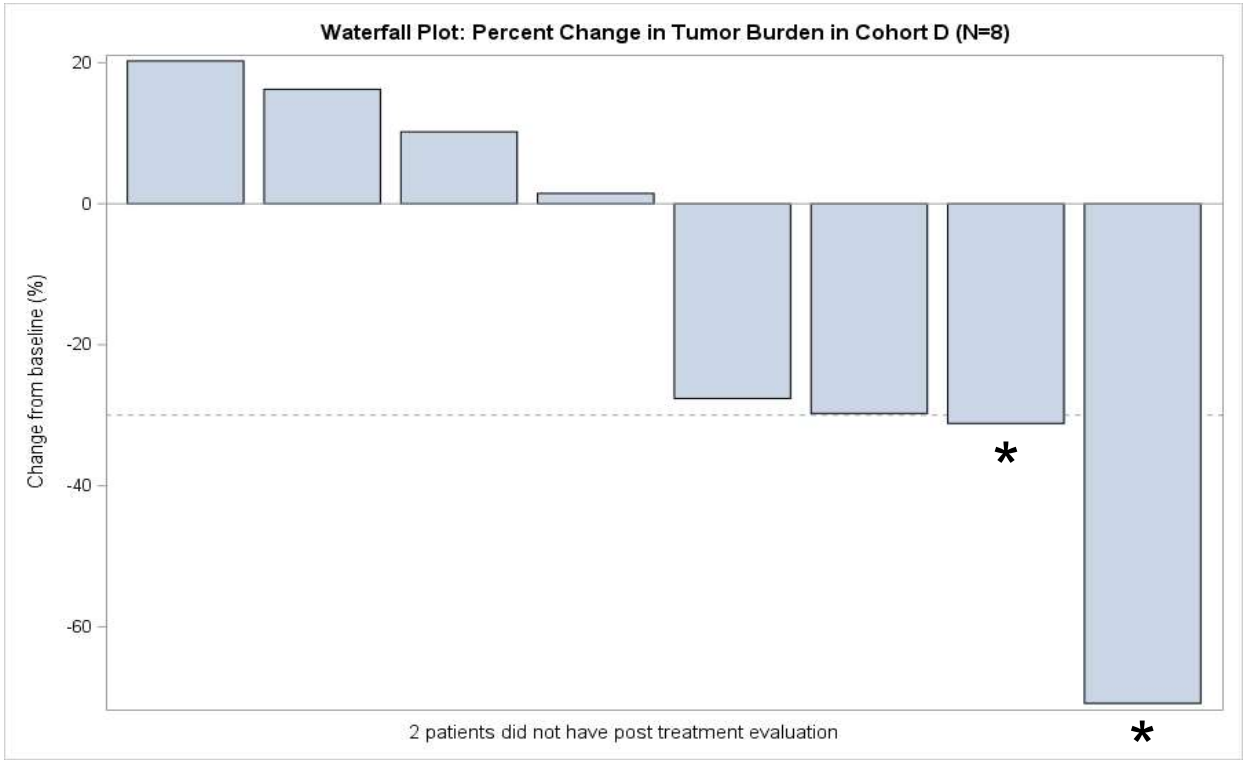
Osimertinib and EGFR-moAb Inhibits Tumor Growth in CRISPR-engineered EGFR Exon 20 ins Models







Osimertinib and Necitumumab is Clinically Active in EGFR Exon 20 ins NSCLC



2 confirmed responses
8 pts evaluable for response
Accrual until N=18 for cohort

* Confirmed Response

WCS
WINTER CANCER
SYMPOSIUM