MEMORIAL HEALTHCARE SYSTEM

NTRK, RET and MET in NSCLC

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Disclosures

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Syndax
Heat Biologics
Exosomes DX
Loxo Oncology

Speakers Bureau/Stocks: *None*

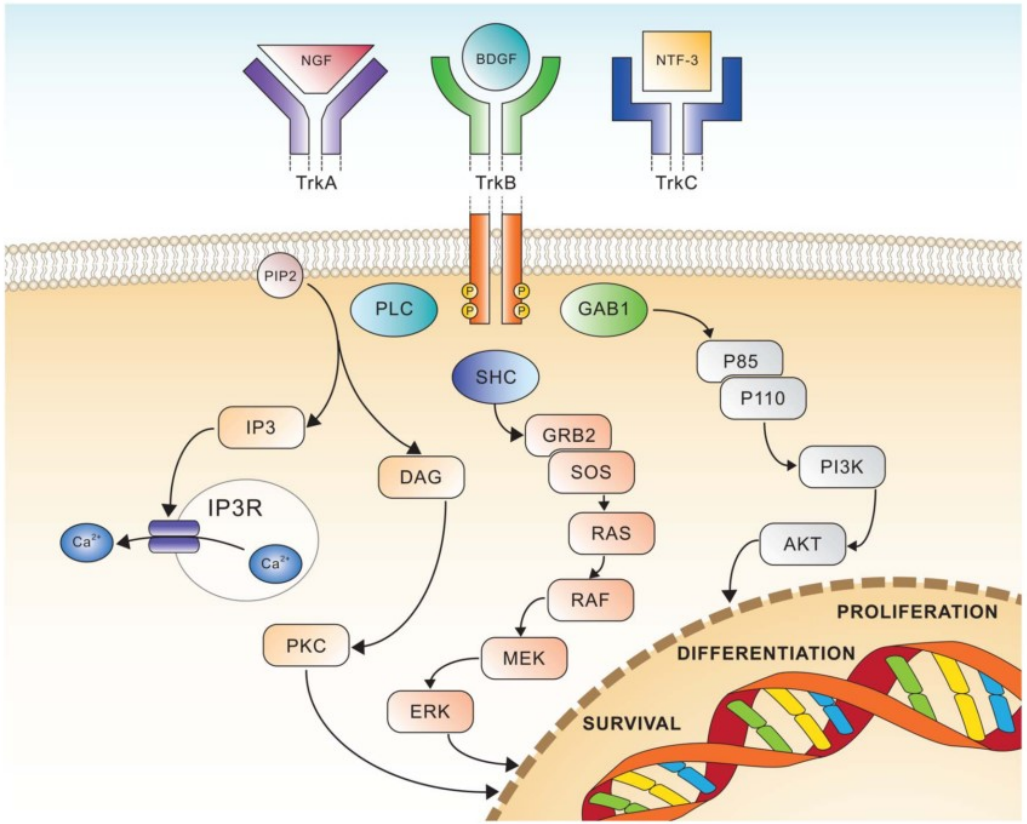
NTRK inhibitors

Larotrectenib

Entrectinib

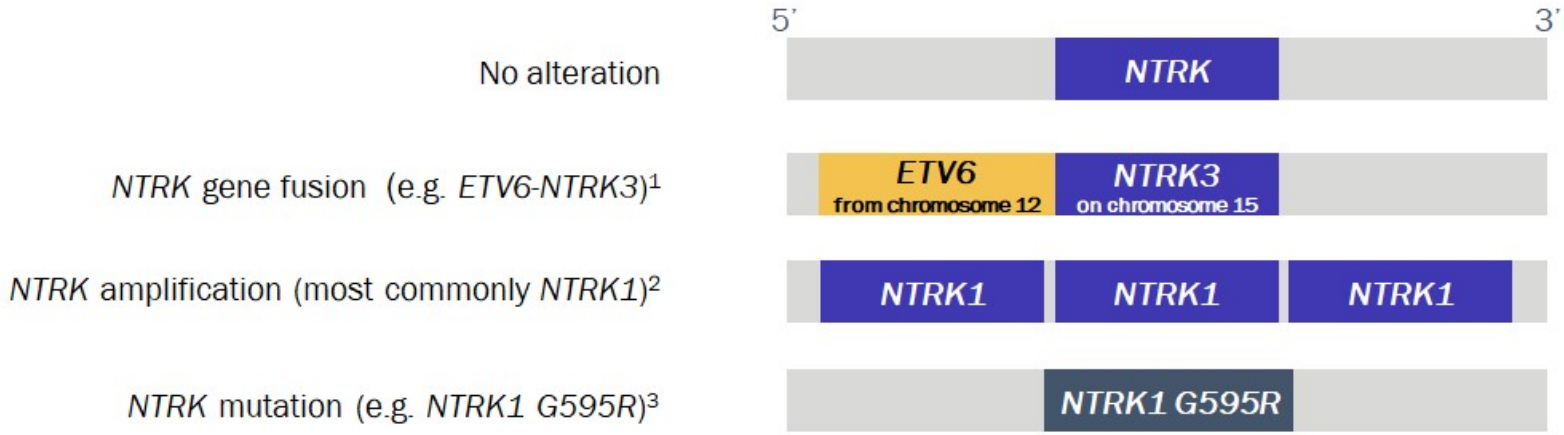
LOXO 195

- *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.

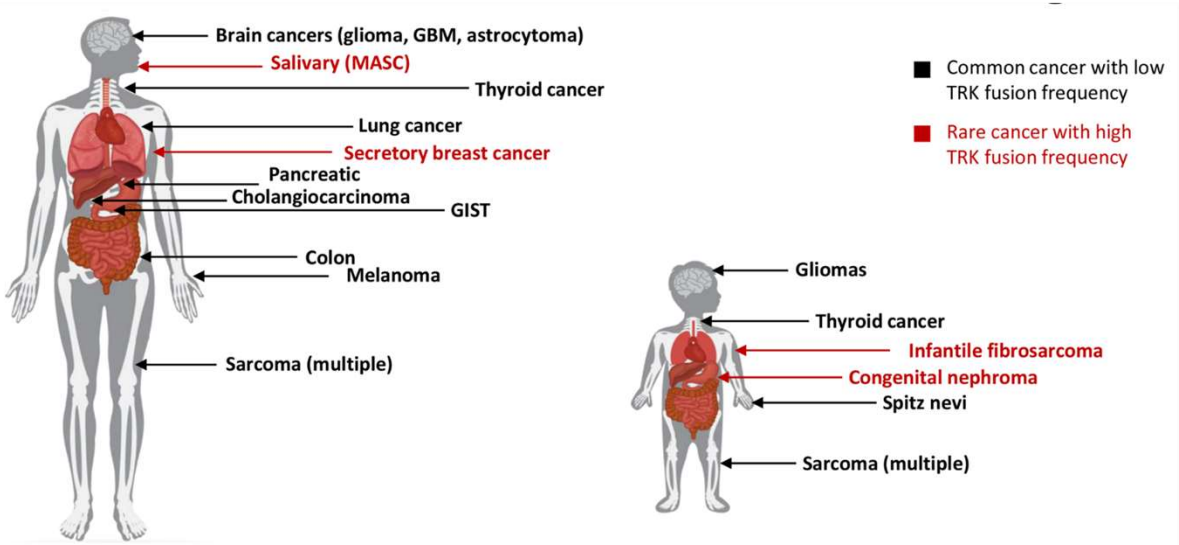
There can be several types of alteration in the *NTRK* gene



NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase. 1. Khotskaya YB, et al. *Pharm Ther*. 2017;173:58–66; 2. Lee SJ, et al. *Precis Future Med*. 2017;1:129–137; 3. Okamura R, et al. *JCO Precis Oncol*. 2018; doi: 10.1200/PO.18.00183.

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

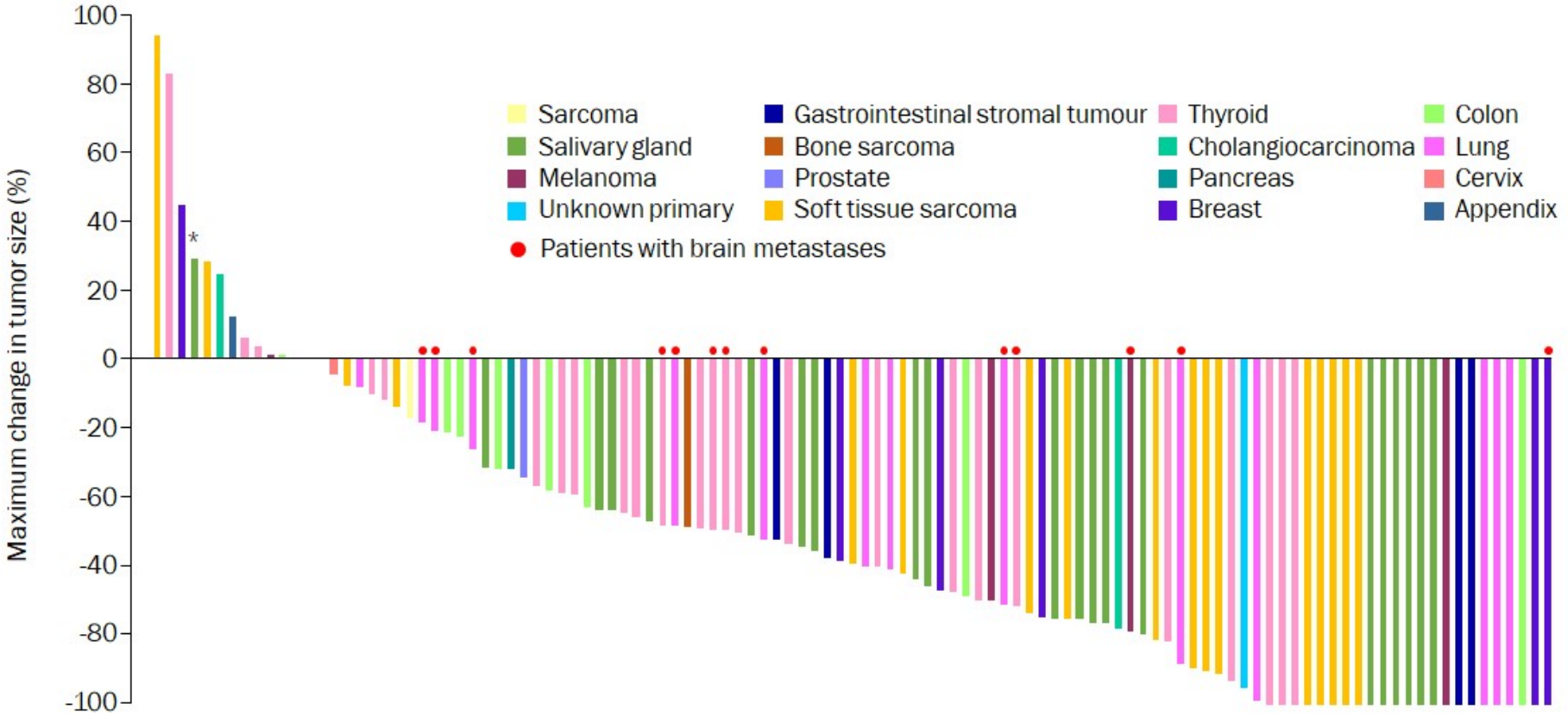
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

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

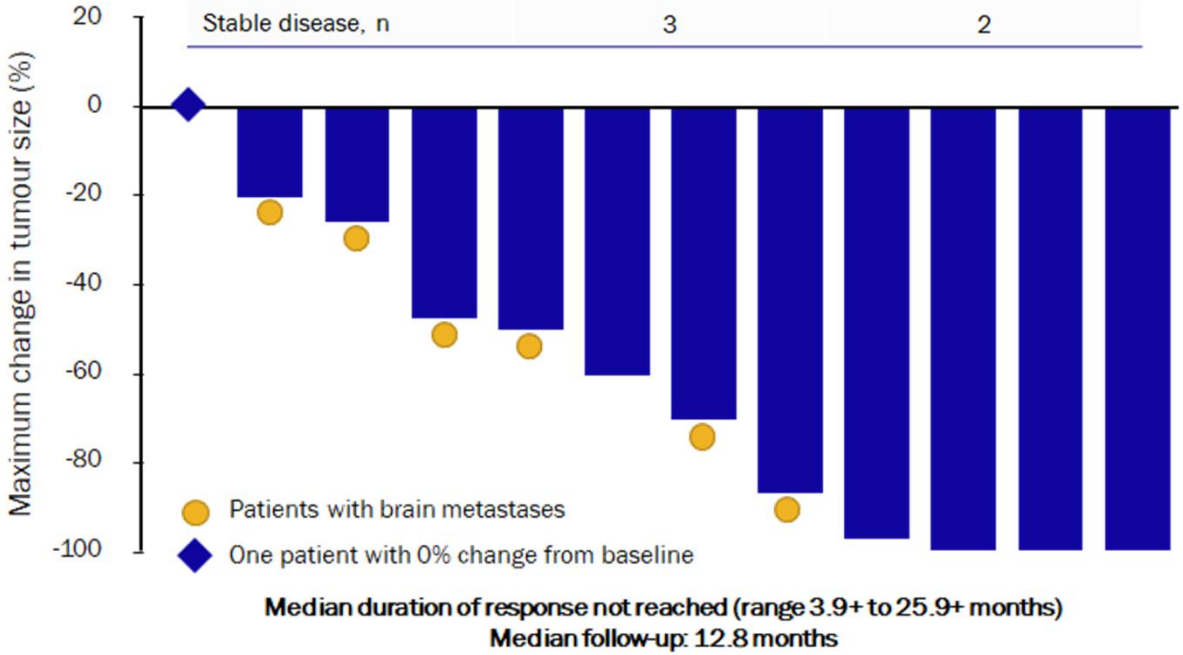
Updated adult dataset Efficacy



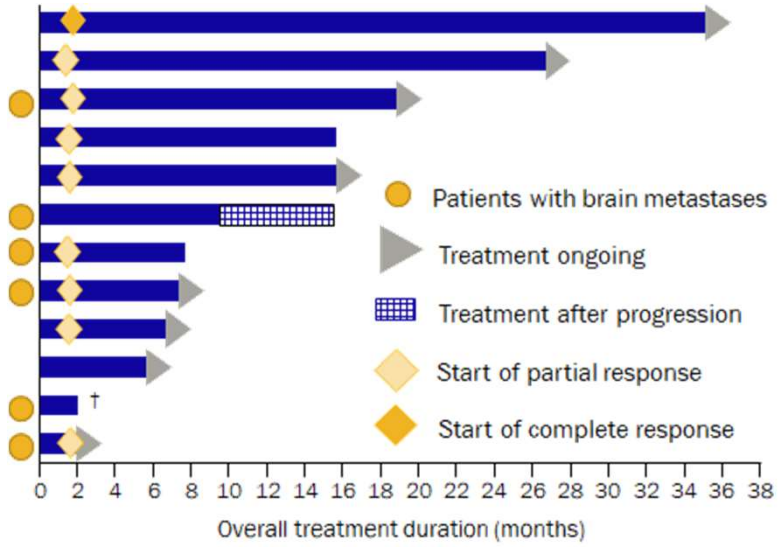
Data cut-off: 15 July 2019. *Patient had an acquired TRK solvent front resistance mutation (*NTRK3* G623R) at baseline owing to prior TRK inhibitor therapy. *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase Drilon A, et al. *J Clin Oncol*. 2020;38(suppl):Abstract 3610. Presented at ASCO 2020. May 2020. Chicago, USA. Abstract 3610.

Larotrectinib is active in TRK fusion lung cancer

	All lung cancer patients (n=12)	Patients with brain metastases (n=6)
Objective response rate (%)	**75%**	**67%**
Complete response, n	1	0
Partial response, n	8*	4*
Stable disease, n	3	2



Median duration of response not reached (range 3.9+ to 25.9+ months)
Median follow-up: 12.8 months

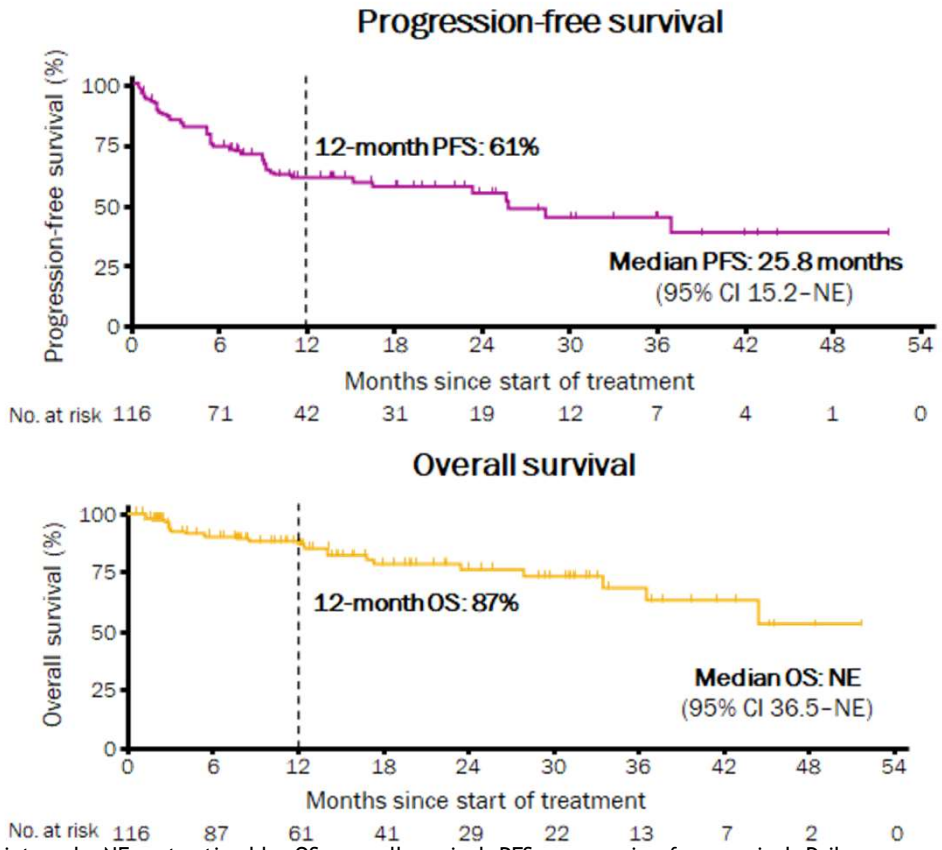


Duration of response: 1.8+ to 35.2+ months

Data cut-off: 19 February 2019. *Partial response pending confirmation in one patient. †Nontarget progressive disease in asymptomatic leptomeningeal focus. Investigator assessments as of data cut-off date. TRK, tropomyosin receptor kinase. Farago AF, et al. Presented at the World Conference on Lung Cancer. September 2019. Barcelona, Spain. Abstract MA09.07.2.

Updated adult dataset
Progression-free survival and overall survival

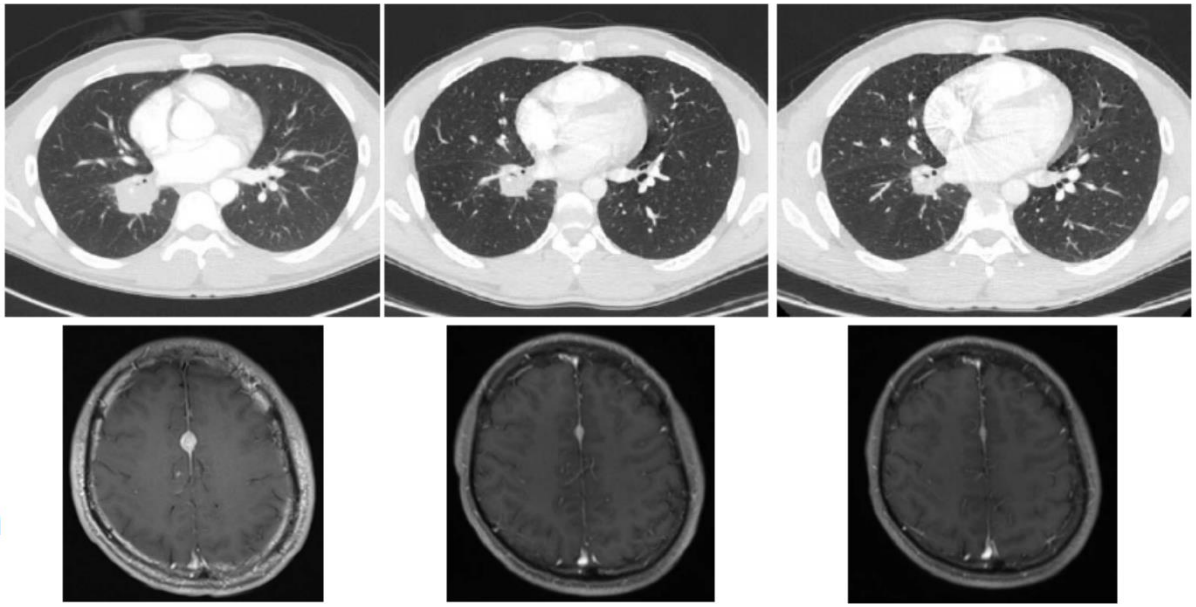
- **Median progression-free survival was 25.8 months** (95% CI 15.2–NE) at a median follow-up of 14.6 months
  - The rate of progression-free survival at ≥12 months was 61%
- Median **overall survival** was not reached (95% CI 36.5–NE) at a median follow-up of 15.8 months
  - The rate of overall survival at ≥12 months was 87%



Data cut-off: 15 July 2019. Note: vertical tickmarks represent censored patients. CI, confidence intervals; NE, not estimable; OS, overall survival; PFS, progression-free survival. Drilon A, et al.
J Clin Oncol. 2020;38(suppl):Abstract 3610. Presented at ASCO 2020. May 2020. Chicago, USA. Abstract 3610.

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



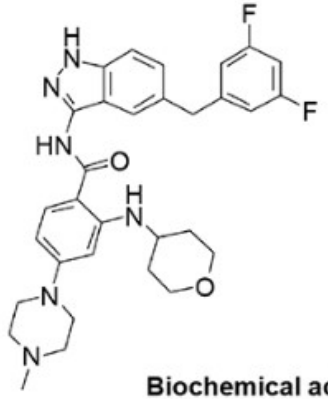
Study baseline | Study cycle 3 day 1 | Study cycle 7 day 1

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

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

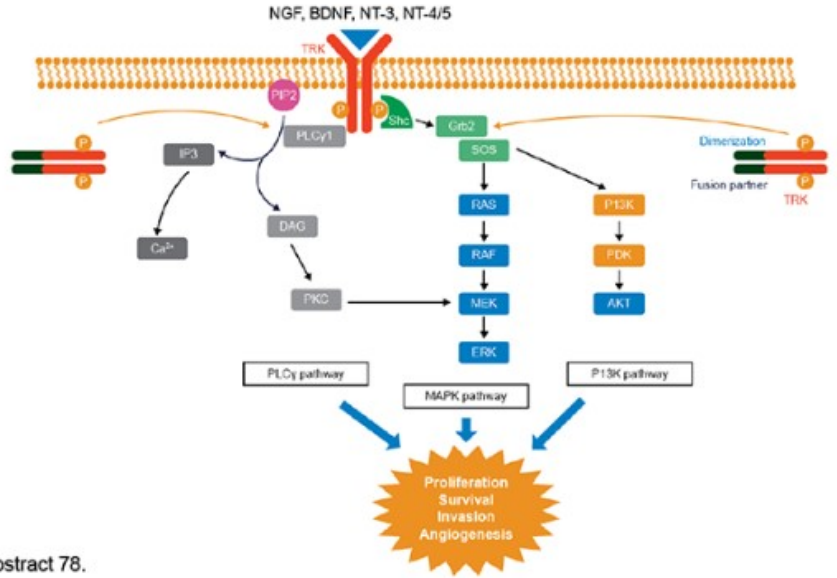
- Orally administered inhibitor of TRKA/B/C, ROS1, and ALK

Chemical structure of entrectinib



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

Signaling pathways of TRK and TRK fusions

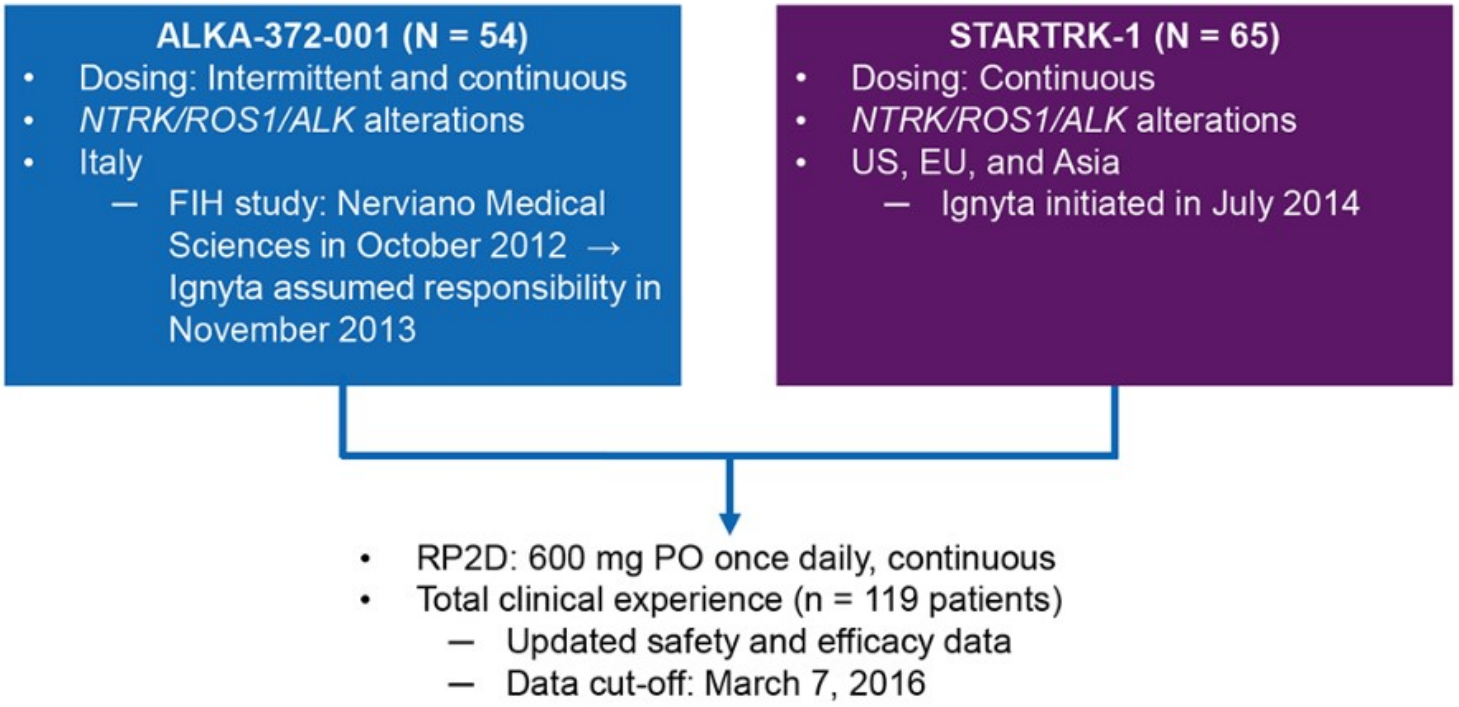


Biochemical activity of entrectinib

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.

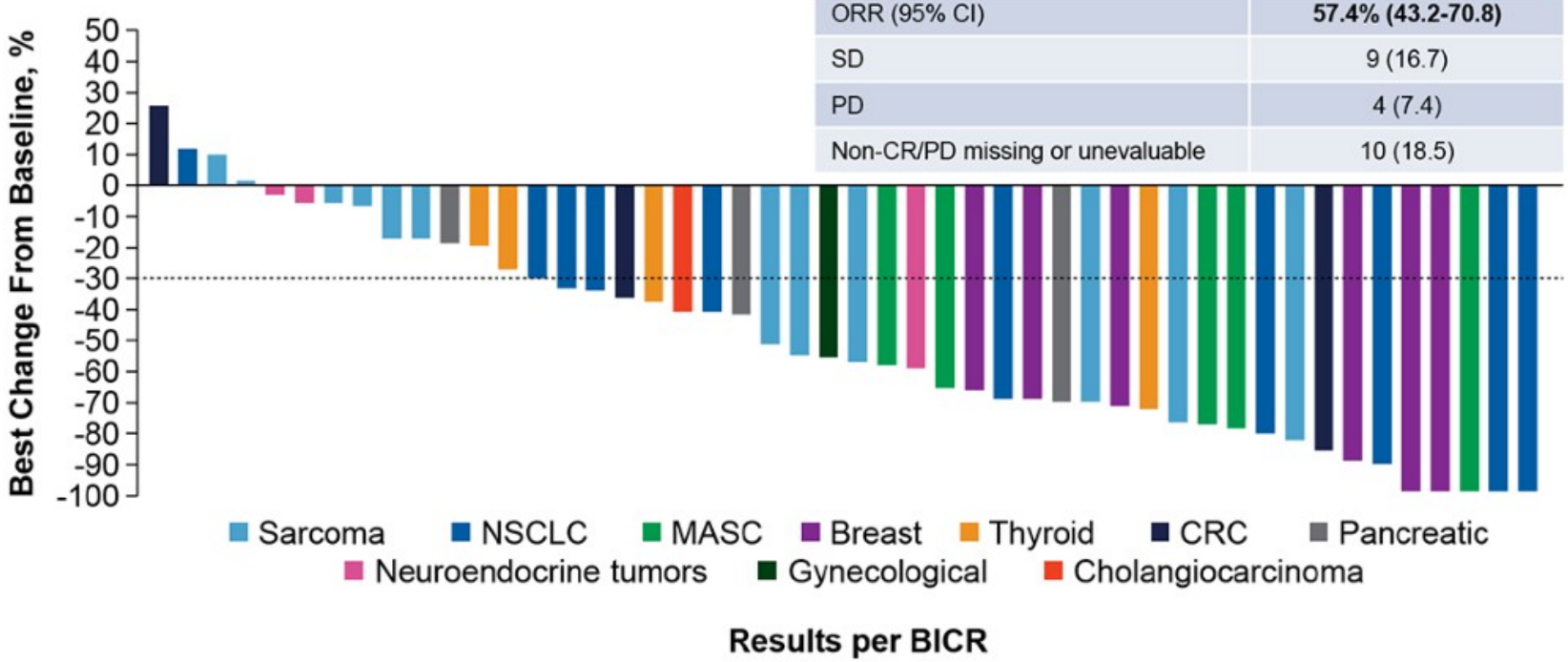
Entrectinib Development Program: Combined Phase 1 Studies[1]



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

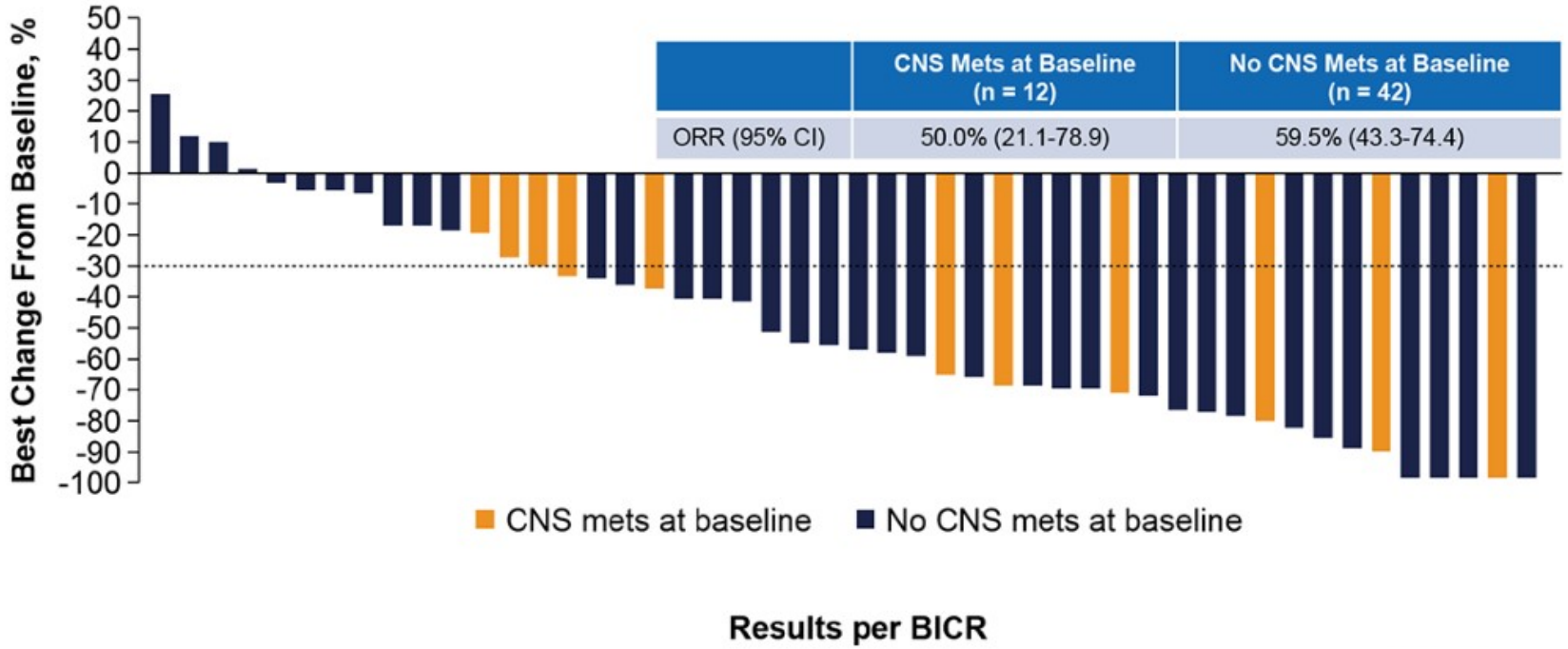
Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Patient Responses by Tumor Type[1]

	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)

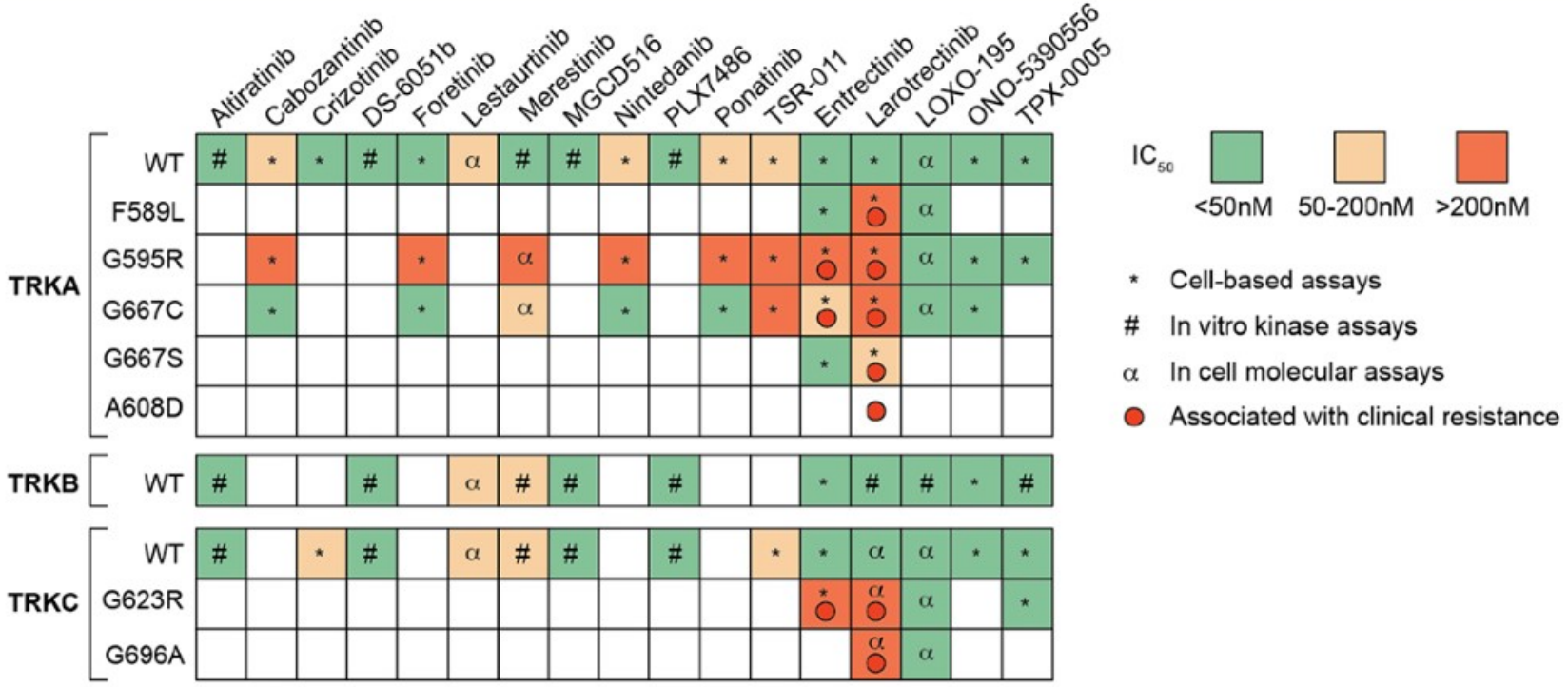
Overall safety population (N = 355)

- 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]

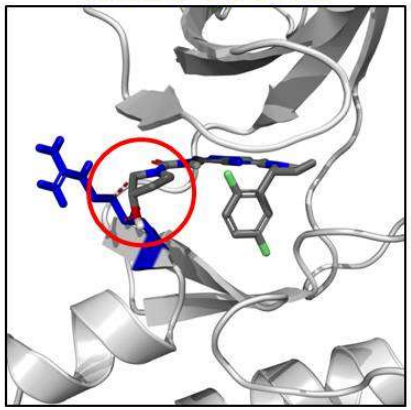


1. Cocco E et al. *Nat Rev Clin Oncol.* 2018;15:731-747.

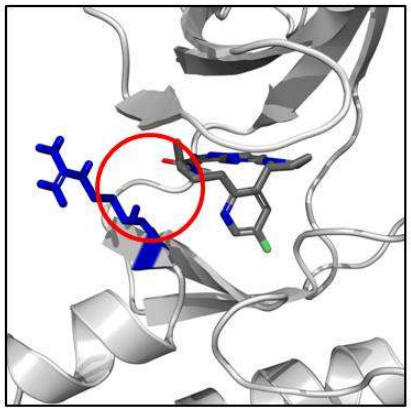
LOXO-195 to Address TRK Acquired Resistance

TRKA G595R

Larotrectinib



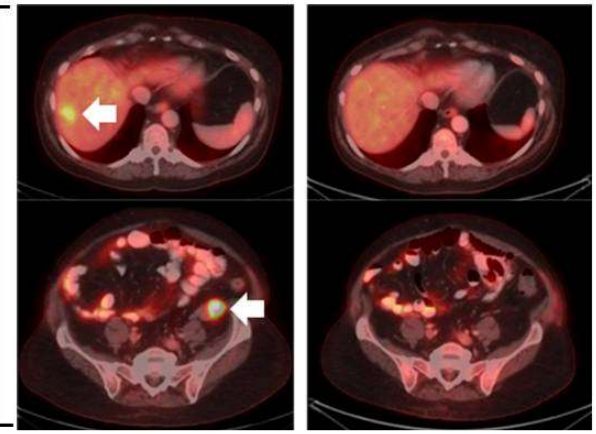
LOXO-195



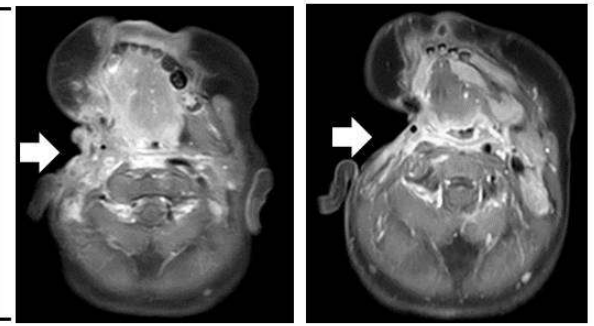
Tumor type	Fusion	Resistance mutation
Colorectal	TPM3-NTRK1	TRKA G595R
Colorectal	LMNA-NTRK1	TRKA G595R
NSCLC	TPR-NTRK1	TRKA G595R
Sarcoma[❖]	TPM3-NTRK1	TRKA G595R
IFS	ETV6-NTRK3	TRKC G623R
Cholangio[❖]	LMNA-NTRK1	TRKA F589L[*] + GNAS Q227H

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.

RET inhibitors

Selpercatinib (Loxo292)

Pralsetinib (Blu 667)

LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with *RET*-altered cancers

Alexander Drilon,[1] Vivek Subbiah,[2] Geoffrey R. Oxnard,[3] Todd M. Bauer,[4] Vamsidhar Velcheti,[5] Nehal J. Lakhani,[6] Benjamin Besse,[7] Keunchil Park,[8] Jyoti D. Patel,[9] Maria E. Cabanillas,[2] Melissa L. Johnson,[4] Karen L. Reckamp,[10] Valentina Boni,[11] Herbert H. F. Loong,[12] Martin Schlumberger,[7] Ben Solomon,[13] Scott Cruickshank,[14] S. Michael Rothenberg,[14] Manisha H. Shah,[15] and Lori J. Wirth[16]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]MD Anderson Cancer Center, Houston, TX; [3]Dana-Farber Cancer Institute, Boston, MA; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [5]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [6]START Midwest, Grand Rapids, MI; [7]Institut Gustave Roussy, Villejuif, France; [8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [9]University of Chicago, Chicago, IL; [10]City of Hope Comprehensive Cancer Center, Duarte, CA; [11]START Madrid CIOCC Hospital Universitario Sanchinarro, Madrid, Spain; [12]The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong; [13]Peter MacCallum Cancer Centre, East Melbourne, Australia; [14]Loxo Oncology, Stamford, CT; [15]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [16]Massachusetts General Hospital Cancer Center, Boston, MA

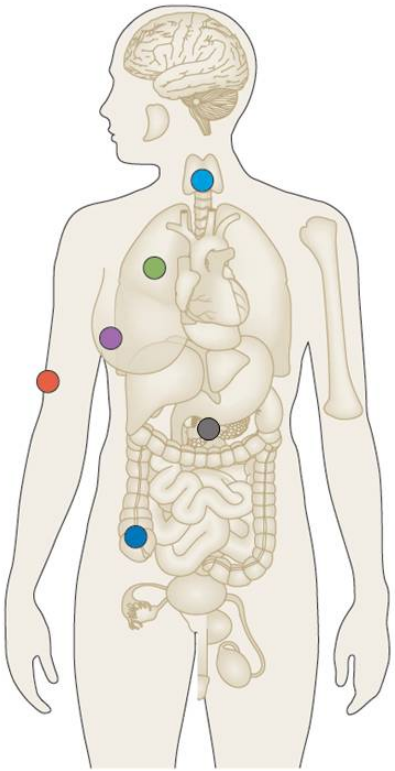
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Dr. Alexander Drilon

Presented By Alexander Drilon at 2018 ASCO Annual Meeting

RET is activated by two major mechanisms in cancer

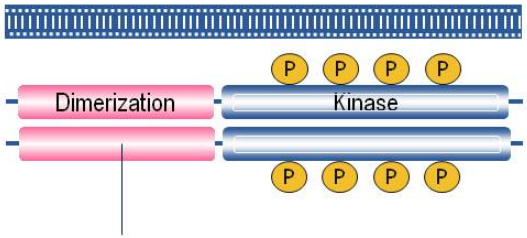
RET fusions



Non-small cell lung cancer (2%)

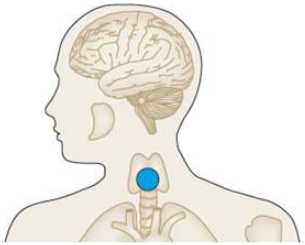
Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



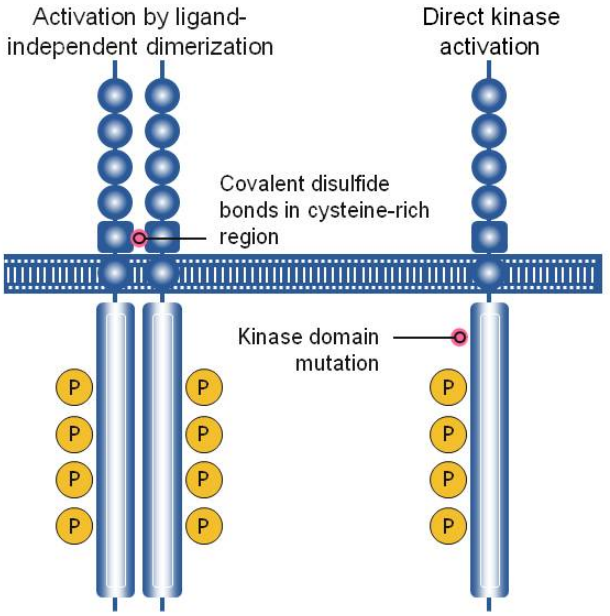
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)



Common mutation: ***RET* M918T**

Drilon et al. Nat Rev Clin Oncol 2018;15:151–67; Kato et al. Clin Cancer Res 2017; 23:1988–97; Pietrantonio et al. Ann Oncol 2018;Mar 10; Su et al. PLoS One 2016;11(11)

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
Fatigue	12%	7%	–	–	20%	–	–	13%
Diarrhea	10%	6%	–	–	16%	–	–	2%
Constipation	13%	1%	–	–	15%	–	–	2%
Dry mouth	12%	–	–	–	12%	–	–	6%
Nausea	9%	4%	–	–	12%	–	–	5%
Dyspnea	7%	2%	1%	–	11%	–	–	–

- Most treatment-emergent AEs were Grade 1 in severity
- Two treatment-related AEs ≥grade 3: grade 3 tumor lysis syndrome (DLT), grade 3 increased ALT
- MTD not reached

AE = adverse event; DLT = dose limiting toxicity; ALT = alanine aminotransferase; MTD = maximum tolerated dose; Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding
April 2, 2018 data cut-off date

Clinical activity of LOXO-292 in *RET*-altered cancers

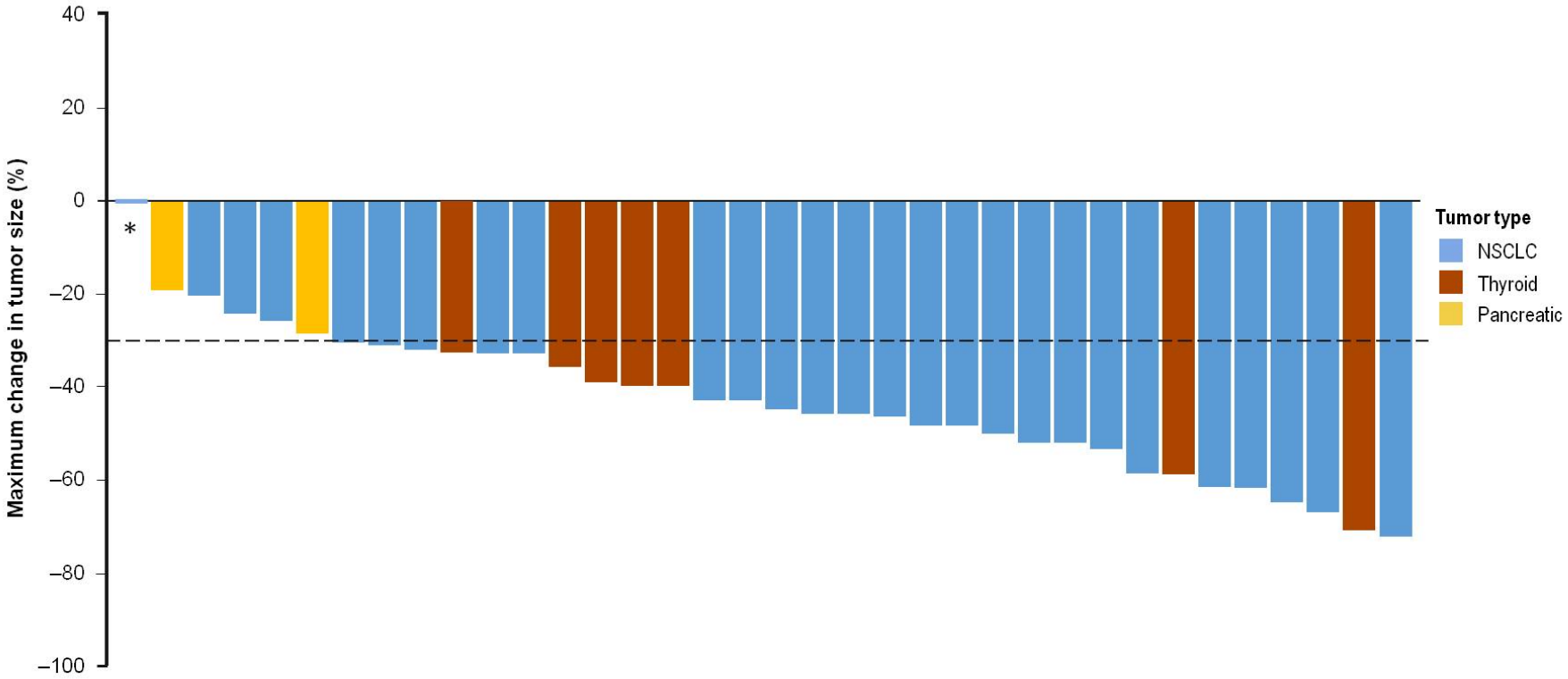
	RET fusion-positive cancers			*RET*-mutant MTC	No known activating *RET* alteration
	All	NSCLC	Other[1]		
Enrolled	49	38	11	29	4
Eligible for response evaluation[2]	39	30	9	22	3
Overall Response Rate (95% CI)[3]	**77% (61% – 89%)**	**77% (58% – 90%)**	**78% (40% – 97%)**	**45% (24% – 68%)**	**0% (0% – 71%)**
Confirmed Overall Response Rate[3,4]	74%	74%	71%	33%	0%
CR	–	–	–	1	–
uCR[5]	–	–	–	1	–
PR	25	20	5	5	–
uPR[5]	5	3	2	3	–
SD	6	4	2	9	2
PD	–	–	–	2	1
Not evaluable[6]	3	3	–	1	–

1. Patients eligible for response evaluation include thyroid cancer (n=7), pancreatic cancer (n=2). 2. Excludes patients recently enrolled that remain on treatment, but have not had a first post-baseline response assessment. 3. Response status per RECIST 1.1. Overall response rate = CR+uCR+PR+uPR. Overall response rate, Confirmed overall response rate: all *RET* fusion-positive (30/39, 25/34), *RET* fusion-positive NSCLC (23/30, 20/27), *RET* fusion-positive other (7/9, 5/7), *RET*-mutant MTC (10/22, 6/18). 4. Excludes patients with unconfirmed CR/PR pending confirmation at time of data cut-off. 5. Unconfirmed responses in patients that remain on treatment awaiting a confirmatory response assessment. 6. Patients that discontinued treatment prior to a first post-baseline response assessment.

NSCLC = non-small-cell lung cancer; MTC = medullary thyroid cancer; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
April 2, 2018 data cut-off date

Presented By Alexander Drilon at 2018 ASCO Annual Meeting

Efficacy of LOXO-292 in *RET* fusion-positive cancers



NSCLC = non-small cell lung cancer
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
April 2, 2018 data cut-off date

Presented By Alexander Drilon at 2018 ASCO Annual Meeting

Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer

Justin F. Gainor[1], Dae Ho Lee[2], Giuseppe Curigliano[3], Robert C. Doebele[4], Dong-Wan Kim[5], Christina S. Baik[6], Daniel Shao-Weng Tan[7], Gilberto Lopes[8], Shirish M. Gadgeel[9], Philippe Alexandre Cassier[10], Matthew H. Taylor[11], Stephen V. Liu[12], Benjamin Besse[13], Michael Thomas[14], Viola Weijia Zhu[15], Hui Zhang[16], Corinne Clifford[16], Michael R. Palmer[16], Christopher D. Turner[16], Vivek Subbiah[17]

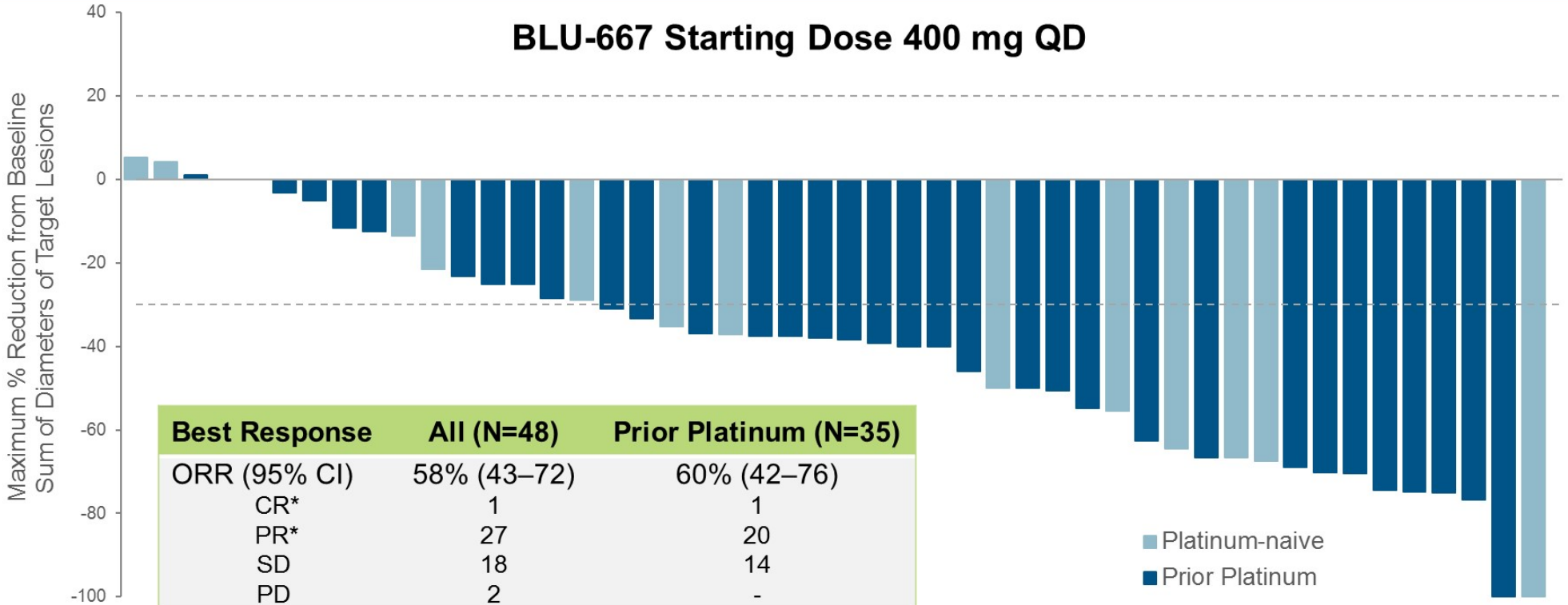
[1]Massachusetts General Hospital, Boston, MA; [2]University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea, Republic of (South); [3]University of Milano, European Institute of Oncology, Division of Early Drug Development, Milan, Italy; [4]University of Colorado Cancer Center, Aurora, CO; [5]Seoul National University Hospital, Seoul, Korea, Republic of (South); [6]Fred Hutchinson Cancer Research Center, Seattle, WA; [7]National Cancer Center, Singapore, Singapore; [8]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; [9]University of Michigan/Rogel Cancer Center, Ann Arbor, MI; [10]Centre Léon-Bérard, Lyon, France; [11]Oregon Health & Science University, Portland, OR; [12]Georgetown University Medical Center, Washington, DC; [13]Paris-Sud University, Orsay and Gustave Roussy, Villejuif, France; [14]Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany; [15]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA; [16]Blueprint Medicines Inc, Cambridge, MA; [17]The University of Texas MD Anderson Cancer Center, Houston, TX

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Justin F. Gainor
PRESENTATION DATE: June 3, 2019

Presented By Justin Gainor at 2019 ASCO Annual Meeting

BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

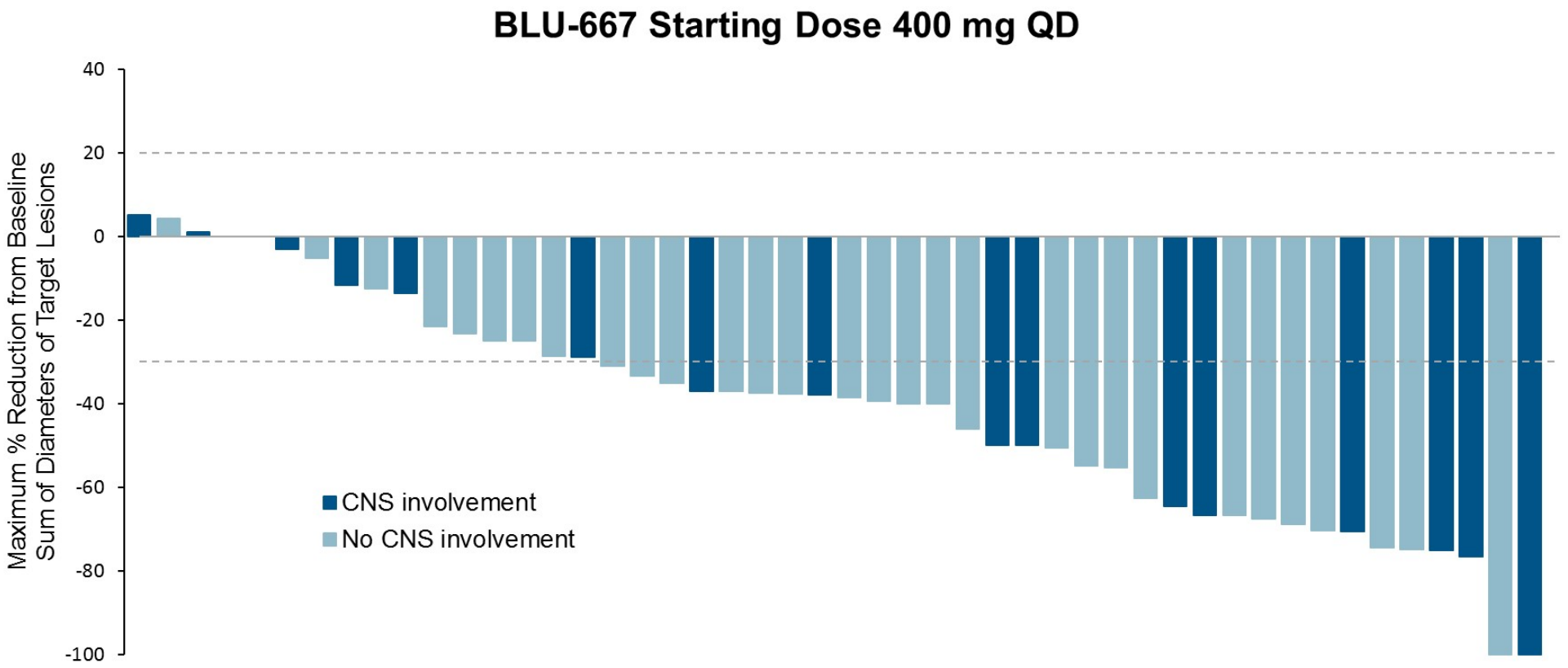
* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

PRESENTED BY: Justin F. Gainor

CI, confidence interval; CR, complete response; DCR, disease control rate (best response of SD or better); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19. Response-evaluable population includes patients with measurable disease at baseline and ≥1 evaluable post-treatment disease assessment, and excludes 4 patients who previously received >1 cycle of a selective RET inhibitor.

BLU-667 is Active Regardless of CNS Involvement



CNS, central nervous system
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 has Activity in Other RET Fusion+ Malignancies

- PR in 2/2 patients with metastatic pancreatic cancer
  - 67 yo male, CCDC6-RET fusion, continues with confirmed PR (53% shrinkage) at ~6 months
  - 31 yo male, TRIM33-RET and JMJD1C-RET fusions, continues treatment after PR (41% shrinkage) at first response assessment
- PR in a patient with intrahepatic bile duct carcinoma
  - 51 yo female, NCOA4-RET fusion, continues with confirmed PR (67% shrinkage) at ~15 months
- ORR 83% (5/6)* in RET-fusion PTC (Abstract 6018 presented June 1, 2019)
- Safety profile similar to what was seen in RET fusion+ NSCLC

* Confirmation of response is pending for two patients. Data cut-off date: 28 Apr 2019.

MET inhibitors

Crizotinib

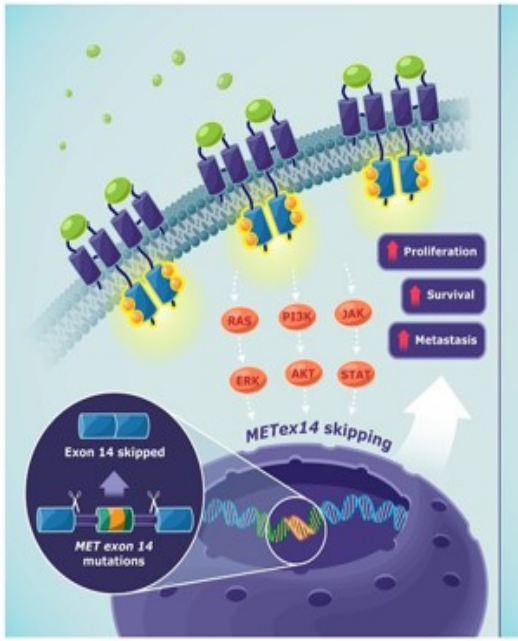
Capmatinib

Tepotinib

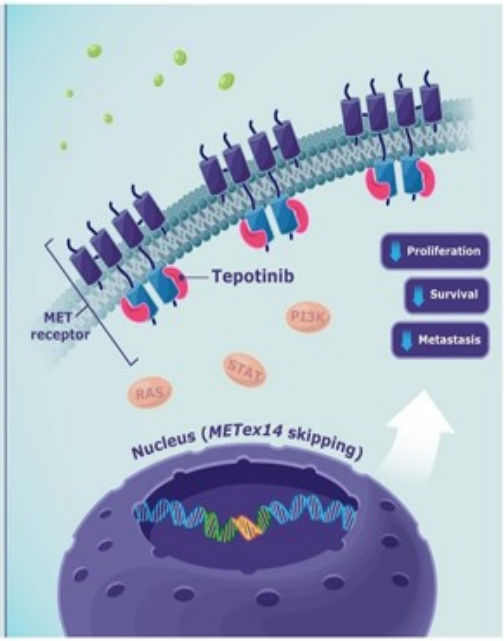
*MET*ex14

- *MET* exon 14 skipping (*MET*ex14) alterations are reported in 3–4% of patients with NSCLC[1]
  - Present in 8–32% of sarcomatoid lung carcinomas[2,3]
- *MET*ex14 alterations can be conveniently detected using liquid biopsy (L+) or tissue biopsy (T+)
- *MET*ex14 alterations lead to aberrant activation of MET kinase, but remain sensitive to MET inhibition
  - MET inhibitors have shown clinical activity in patients with *MET*ex14 alterations[1,4–6]

Effect of *MET*ex14 Skipping Mutations on the Tumor[7,8]



Tepotinib Inhibition of *MET*ex14 Skipping Mutations



1. Paik PK, et al. Cancer Discov. 2015;5:842–9; 2. Shrock AB, et al. J Thorac Oncol. 2016;11:1493–1502; 3. Tong JH, et al. Clin Cancer Res. 2016;22:3048–56; 4. Felip E, et al. WCLC 2018 [abs. OA12.01]; 5. Drilon A, et al. WCLC 2018 [abs. OA12.02]; 6. Wolf J, et al. Ann Oncol. 2018;29(Suppl 8) [abs. LBA52]; 7. Peschard P, et al. J Biol Chem. 2004; 279:29565–71; 8. Ma PC, et al. Cancer Discov. 2015;5:802–5.

NSCLC, non-small cell lung cancer.

PROFILE 1001: Study Design

- Open-label, multicenter phase I trial

Advanced NSCLC with *MET* exon 14 alteration, no prior MET-directed targeted therapy (N = 21) → **Crizotinib** 250 mg BID → ***18 pts evaluable for response in current analysis***

- Tumor response assessed by RECIST v1.0, imaging at baseline and every 8 wks

Drilon AE, et al. ASCO 2016. Abstract 108.

PROFILE 1001: Baseline Characteristics

Characteristic	All Pts (N = 21)
Median age, yrs (range)	68 (53-87)
Female, %	71
Race, % ▪ White/Asian/black/other	 67/19/5/10
Former smoker, %	62
Tumor histology, % ▪ Adenocarcinoma ▪ Sarcomatoid carcinoma ▪ Adenosquamous carcinoma ▪ Squamous cell carcinoma	 76 14 5 5
Prior therapy for advanced disease, % ▪0/1/2/≥ 3	 14/57/14/14

Drilon AE, et al. ASCO 2016. Abstract 108.

PROFILE 1001: Efficacy

Response	Response-Evaluable Pts (n = 18)
ORR, % (95% CI)	44 (22-69)
Best overall response, %	
▪ CR	0
▪ PR	44
▪ SD	50
• Unconfirmed CR/PR	28
▪ PD	0
▪ Indeterminate*	6
Median PFS, mos	NE

*Pt discontinued therapy in cycle 1; response imaging could not be performed but response-evaluable per protocol.

- Median duration of treatment: 5.3 mos (range: 0.2-12.2 mos)
- Median duration of follow-up: 5.7 mos (range: 0.2-12.2 mos)
  - Tumor shrinkage in 14/16 pts with measurable disease at BL
  - Response typically seen within first 2 mos of treatment

Drilon AE, et al. ASCO 2016. Abstract 108.

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Mutation of MET Y1230 as an Acquired Mechanism of Crizotinib Resistance in NSCLC with *MET* Exon 14 Skipping

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56 year old with sarcomatoid NSCLC found to have MET exon 14 and treated with crizotinib with FM we identified a new resistant gene

Clinical Case

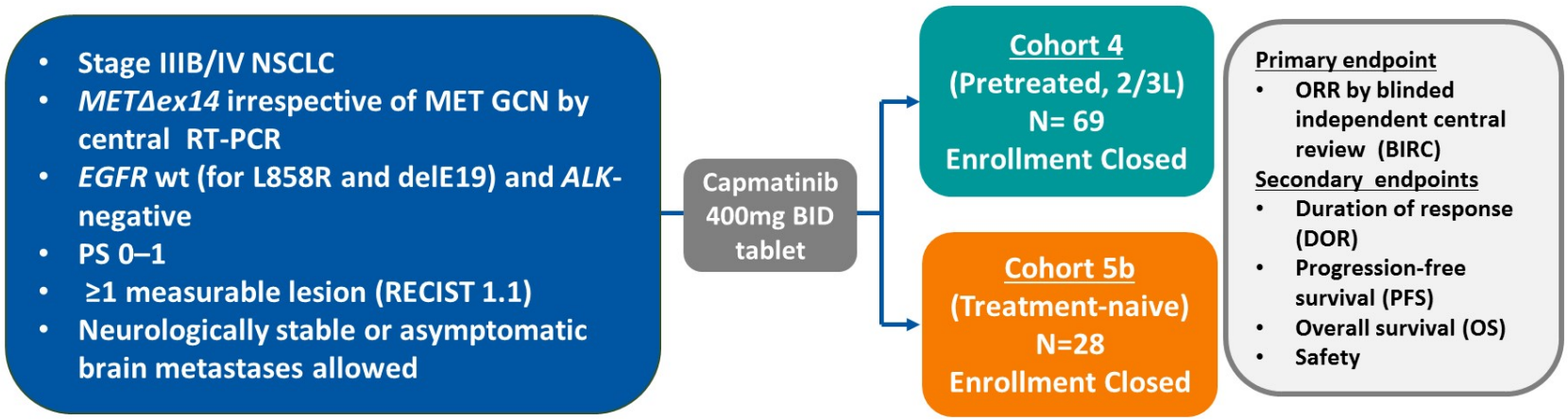
Table 1. Genes Altered: Results of Molecular Diagnostic Assays

Hybrid Capture- Based Tissue CGP

Before Crizotinib	After Crizotinib
MET exon 14 splice site (3020_3028+17del26)	*MET* exon 14 splice site (3020_3028+17del26)
	MET Y1230H
ATM splice site alteration	*ATM* splice site alteration
TP53 S127F	TP53 S127F
	CDKN2A/B loss
	NF1 loss exons 5-53
Tumor mutation burden: 2 mutations per Mb (low)	Tumor mutation burden: 3 mutations per Mb (low)

CGP, comprehensive genomic profiling; *MET*, hepatocyte growth factor receptor gene; *ATM*, ATM serine/threonine kinase gene; *TP53*, tumor protein p53 gene; *CDKN2A/B*, cyclin-dependent kinase inhibitor 2A/B gene; *NF1*, neurofibromin 1 gene; Mb, megabase.

GEOMETRY mono-1: A phase II trial of capmatinib in patients with advanced NSCLC harboring *MET exon14 skipping* mutation



Study methodology:

- Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
- Primary (ORR) and key secondary (DOR) endpoints based on BIRC including 2 parallel independent radiology reviewers (+ additional one for adjudication)
- Efficacy endpoints based on BIRC and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on *MET* mutated patients will be generated in Cohort 6 (2L; N~30) and Cohort 7 (1L; N~27)

Prior therapies

Prior therapies		Cohort 4 (2/3L) N = 69	Cohort 5b (1L) N = 28
Number of prior lines of therapy, n (%)	1 2 3	51 (73.9) 16 (23.2) 2 (2.9)	NA
Prior therapies* (any line), n (%)	Platinum based chemo Immunotherapy Single agent chemo Targeted therapy	61 (88.4) 18 (26.1) 9 (13.0) 3 (4.3)	NA

*pretreated patients were MET inhibitor naïve

Best overall response (pretreated cohort 4)

All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

	Cohort 4 (2/3L) N=69	
	BIRC	**Investigator**
Best overall response, n (%)		
Complete Response	0	1 (1.4)
Partial Response	28 (40.6)	28 (40.6)
Stable Disease	25 (36.2)	22 (31.9)
Non-CR/non-PD	1 (1.4)	2 (2.9)
Progressive Disease	6 (8.7)	7 (10.1)
Not evaluable*	9 (13.0)	9 (13.0)
Overall response rate (ORR) %, (95% CI)	**40.6 (28.9, 53.1)**	**42.0 (30.2, 54.5)**
Disease control rate (DCR) %, (95% CI)	**78.3 (66.7, 87.3)**	**76.8 (65.1, 86.1)**

*not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

Best overall response (treatment naive cohort 5b)

All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

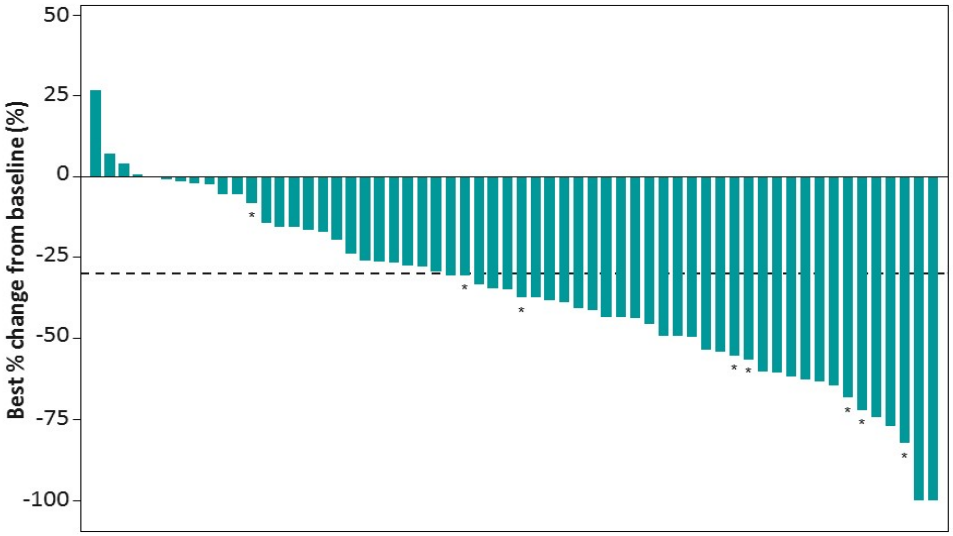
	Cohort 5b (1L) N=28	
	BIRC	**Investigator**
Best overall response, n (%)		
Complete Response	1 (3.6)	0
Partial Response	18 (64.3)	17 (60.7)
Stable Disease	8 (28.6)	10 (35.7)
Progressive Disease	1 (3.6)	1 (3.6)
Overall response rate (ORR) %, (95% CI)	**67.9 (47.6, 84.1)**	**60.7 (40.6, 78.5)**
Disease control rate (DCR) %, (95% CI)	**96.4 (81.7, 99.9)**	**96.4 (81.7, 99.9)**

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

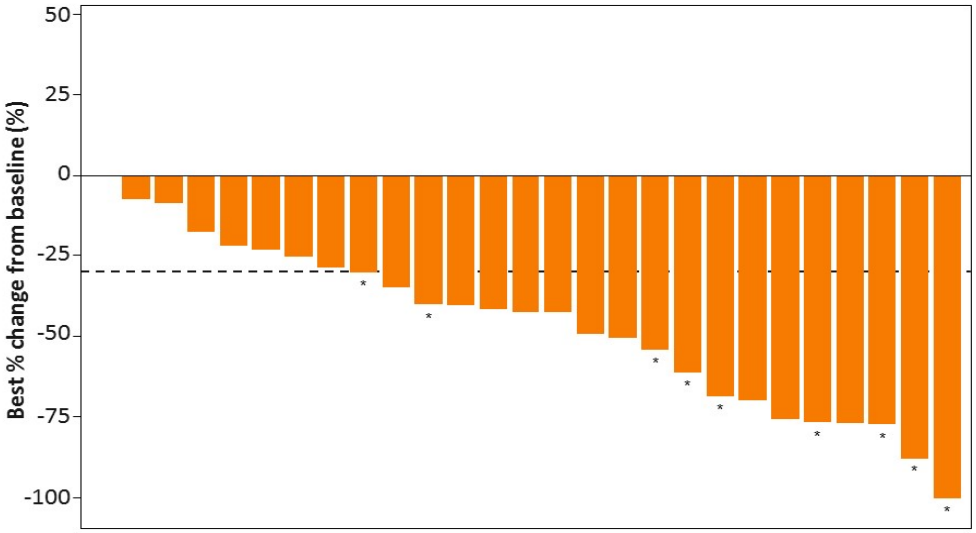
Tumor shrinkage per BIRC

Deep responses observed in a majority of patients across both cohorts

Cohort 4 (2/3L)



Cohort 5b (1L)



*patients still on-treatment

Capmatinib was well tolerated and with a favorable safety profile, consistent with previous reports[1]

Most common treatment-related AEs (≥10%, all grades), n (%)	All patients N=364	
	All grades	Grade 3/4
Any	312 (85.7)	137 (37.6)
Peripheral edema	156 (42.9)	30 (8.2)
Nausea	125 (34.3)	6 (1.6)
Vomiting	68 (18.7)	7 (1.9)
Blood creatinine increased	67 (18.4)	0
Fatigue	50 (13.7)	10 (2.7)
Decreased appetite	45 (12.4)	3 (0.8)
Diarrhea	40 (11.0)	1 (0.3)

- Safety determined in the largest dataset of *MET*-dysregulated NSCLC patients (N=364)
- Median treatment exposure: 15.3 weeks
- The majority of treatment-related AEs were of grades 1 and 2
- Serious AEs suspected to be related to capmatinib occurred in 48 (13.2%) patients
- In total, 83 (22.8%) patients had at least one AE leading to dose reduction
- Treatment-related AEs leading to discontinuation occurred in 39 (10.7%) patients

AE, adverse event; NSCLC, non-small cell lung cancer.

1. Wolf J, et at. *J Clin Oncol.* 2019;37(Suppl 15):abstr 9004.

Capmatinib in patients with high-level *MET*-amplified advanced non–small cell lung cancer (NSCLC): Results from the phase 2 GEOMETRY mono-1 study

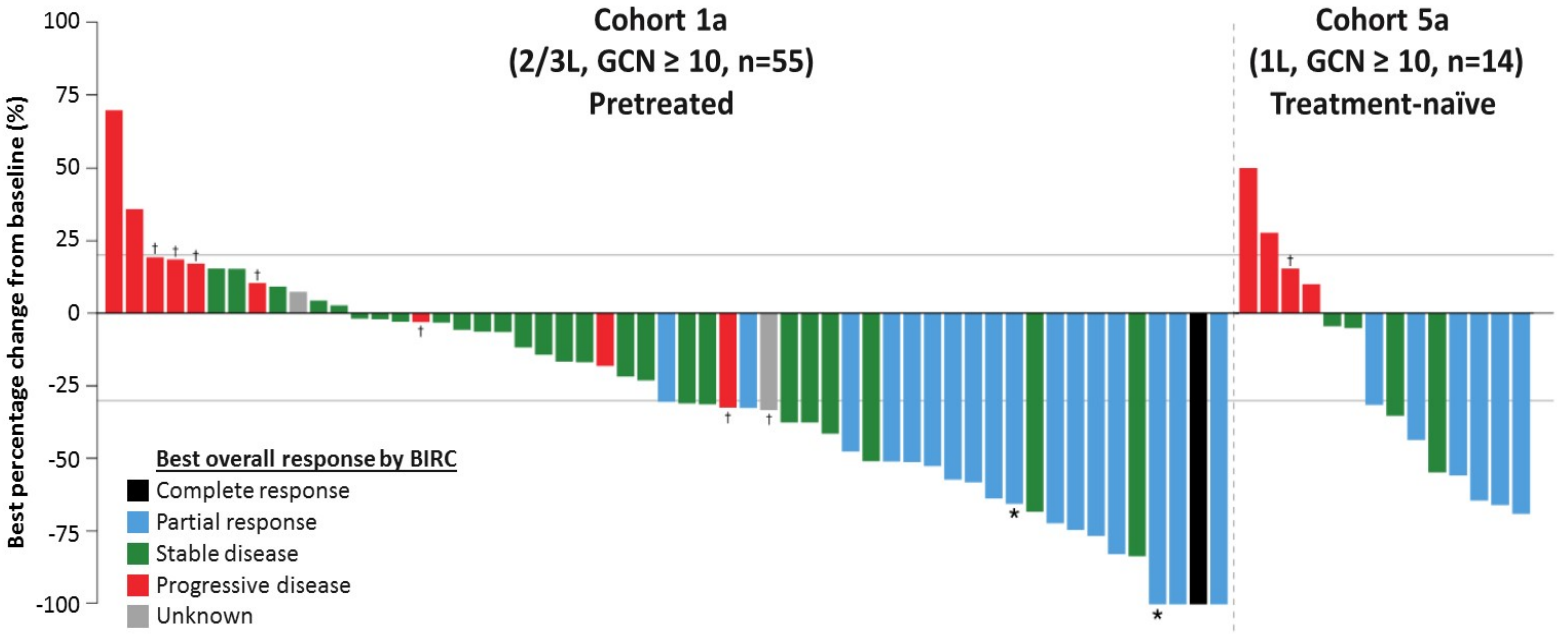
Juergen Wolf,[1] Tobias R. Overbeck,[2] Ji-Youn Han,[3] Maximilian Hochmair,[4] Filippo de Marinis,[5] Kadoaki Ohashi,[6] Egbert F. Smit,[7] Danielle Power,[8] Edward B. Garon,[9] Harry J. M. Groen,[10] Daniel S. W. Tan,[11] Maeve Waldron-Lynch,[12] Sylvie Le Mouhaer,[13] Ngozi Nwana,[14] Monica Giovannini,[14] Rebecca S. Heist[15]

[1]Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; [2]University Medical Center Göttingen, Göttingen, Germany; [3]National Cancer Center, Gyeonggi-do, Republic of Korea; [4]Department of Respiratory and Critical Care Medicine, Vienna North Hospital, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna, Austria; USA; [5] Istituto Europeo di Oncologia IRCCS, Milan, Italy; [6]Okayama University Hospital, Okayama, Japan; [7]Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]Imperial College Healthcare NHS Trust, London, United Kingdom; [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [10]University of Groningen and University Medical Center Groningen, Groningen, The Netherlands; [11]National Cancer Centre Singapore, Singapore; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Pharma S.A.S, Rueil-Malmaison, France; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [15]Massachusetts General Hospital, Boston, MA, USA.

Presented By Juergen Wolf at TBD

Tumor shrinkage assessed by the BIRC

Deep responses observed in the majority of patients across both cohorts

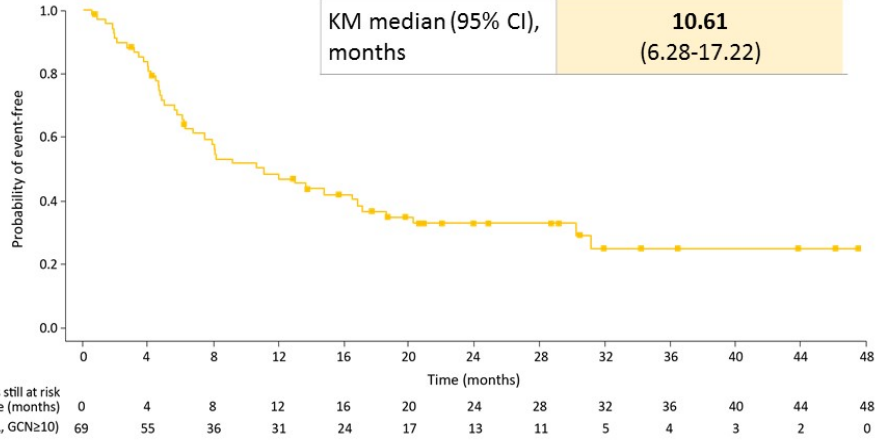


n (number of patients with measurable disease at baseline and ≥1 post-baseline assessment) is used for calculation of percentages.
*Patients still on treatment. †Percentage change in target lesion available but contradicted by overall response = progressive disease or not evaluable. Not evaluable = Unknown as per RESIST 1.1 (All other cases, i.e. not qualifying for confirmed complete response or partial response and without stable disease after more than 6 weeks or progression within the first 12 weeks).
1L/2L/3L, first/second/third-line; BIRC, Blinded Independent Review Committee; GCN, gene copy number.

Overall survival

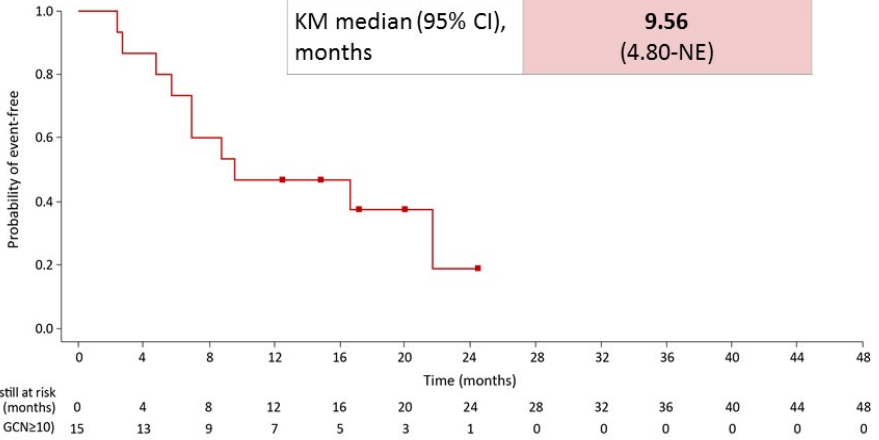
Median OS: 10.61 months in pretreated patients and 9.56 months in treatment-naive patients

	Cohort 1a (2/3L, GCN ≥ 10) (N=69)
No. deaths, n (%)	45 (65.2)
No. censored, n (%)	24 (34.8)
KM median (95% CI), months	**10.61** (6.28-17.22)



No. of patients still at risk Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48
Cohort 1a (2/3L, GCN≥10)	69	55	36	31	24	17	13	11	5	4	3	2	0

	Cohort 5a (1L, GCN ≥ 10) (N=15)
No. deaths, n (%)	10 (66.7)
No. censored, n (%)	5 (33.3)
KM median (95% CI), months	**9.56** (4.80-NE)



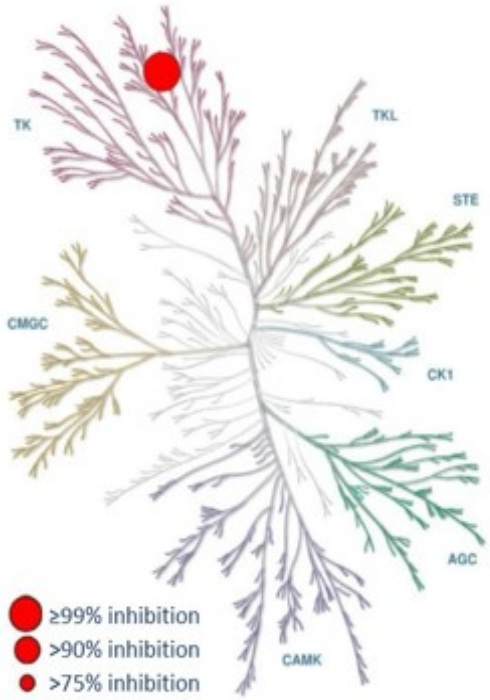
No. of patients still at risk Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48
Cohort 5a (1L, GCN≥10)	15	13	9	7	5	3	1	0	0	0	0	0	0

1L/2L/3L, first/second/third-line; GCN, gene copy number; NE, not estimated; OS, overall survival.

Tepotinib

- Tepotinib is a highly selective, ATP-competitive, reversible, potent MET tyrosine kinase inhibitor (TKI)
  - IC_{50} ~1.7 nM
  - At 1 µM, only MET is inhibited out of a panel of over 300 kinases
- No MTD reached at 1400 mg QD; RP2D is 500 mg QD
- Preclinical brain penetration
  - High binding to rat brain tissue ($f_{u\,br}$ = 0.4%)
  - The $K_{p\,u,u}$ (ratio of free brain vs plasma concentration) in rats was 0.25, i.e. 25% of free tepotinib levels in brain, relative to levels found in plasma
- Complete brain and systemic response lasting almost 1 year in patient with NSCLC harboring MET-RB1 translocation treated with tepotinib as compassionate use (*Dr Marie Florescu, MD, and Dr Raafat Alameddine at CHUM Montreal, Canada*)

Tepotinib kinome[1]



1. Schadt O, Blaukat A. Comprehensive Medicinal Chemistry III. Oxford: Elsevier; 2017. p. 178–203.

$f_{u\,br}$, unbound brain fraction; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; QD, once daily; RB1, retinoblastoma gene; RP2D, recommended phase 2 dose.

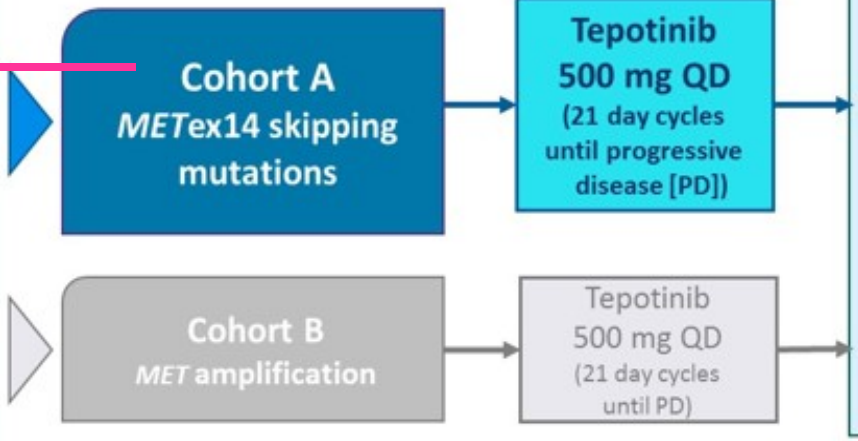
VISION study design

VISION is a single-arm, phase II trial of tepotinib in patients with NSCLC harboring MET alterations (NCT02864992)

Study Design

- **Stage IIIB/IV NSCLC**
  - **All histologies** (including squamous and sarcomatoid)
  - Exclusion of active brain metastases or brain as only measurable lesion
- **Tissue- or blood-based *MET* alterations** (central lab testing)
  - A. *MET*ex14 skipping mutations detected:
    - **Plasma,** LBx (DNA based)
    - **OR**
    - **Tissue,** TBx (RNA based)
  - B. *MET* amplification only
- **1st, 2nd, 3rd line of therapy**
  - Prior anti-MET therapy was not allowed
  - Prior immunotherapy was allowed

N = up to 120



Selected Endpoints

Primary endpoint

- Objective response rate (ORR) by independent review

Secondary endpoints

- ORR by investigator assessment
- Duration of response
- Objective disease control
- Progression-free survival
- Overall survival
- Safety
- Health-related quality of life

The trial aims for an ORR based on independent review in the range of 40–50% with a lower limit of the corresponding exact 2-sided 95% confidence interval (according to Clopper–Pearson) to exceed an ORR of 20%.

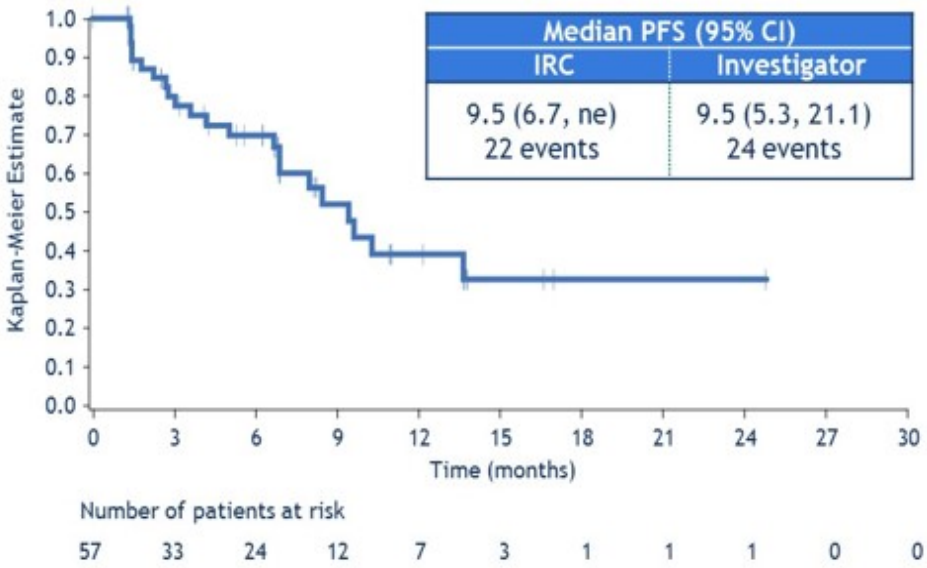
We now report interim data including ORR assessed by independent review and select secondary endpoints

Efficacy: Progression-free survival

PFS across all treatment lines

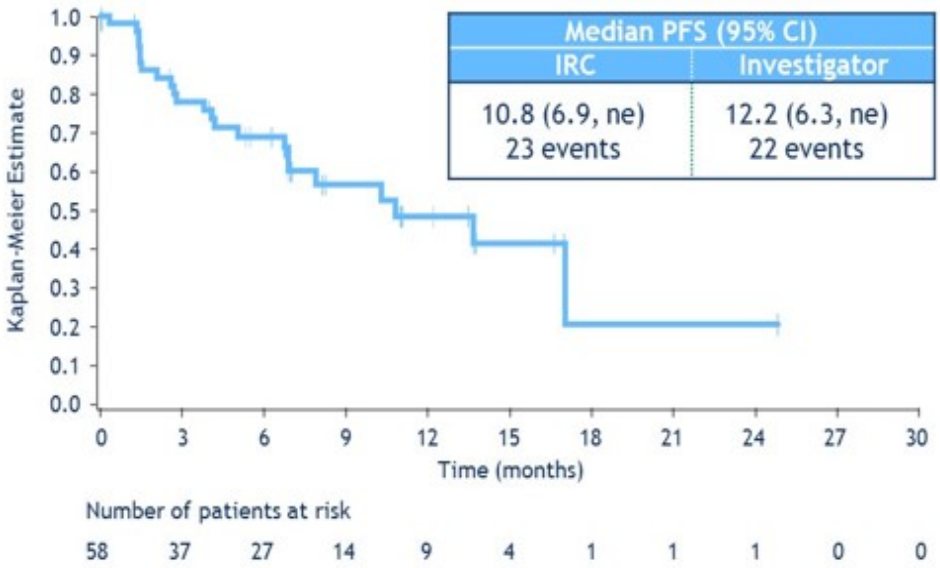
Liquid biopsy (L+) (n=57)

PFS by IRC



Tissue biopsy (T+) (n=58)

PFS by IRC



33/57 L+ patients and 31/58 T+ patients remain on treatment.

Median follow-up for PFS (IRC): 6.9 months (95% CI 5.5, 11.0).

L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.
IRC, independent review committee; ne, not estimable; PFS, progression-free survival.

Conclusion on MET Inhibitors

- Tepotinib has durable clinical activity in patients with NSCLC harboring METex14 mutation and Capmatinib has demonstrated clinically meaningful activity in the same driver mutation population.

	Tepotinib	Capmatinib
ORR (naïve)	L+: 58%; T+:44%	67.9%
ORR (≥2 lines)	L+: 45%; T+:45%	40.6%
DOR (naïve)	14.3 months	11.1 months
DOR (≥2 lines)	L+: 12.4 mo; T+: 12.4 mo	9.7 months
Active in CNS met	Yes	Yes
Safety profile	G3: 19.5%; no G4	G3/4: 35.6%; G4: 4.5%
Discontinuation TRAEs	4.6%	11.1%

- Capmatinib: FDA approved

Memorial Regional Hospital | Memorial Regional Hospital South | Joe DiMaggio Children's Hospital
Memorial Hospital West | Memorial Hospital Miramar |Memorial Hospital Pembroke