# Targeting *RET* Fusions in Lung Cancer

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# Disclosures

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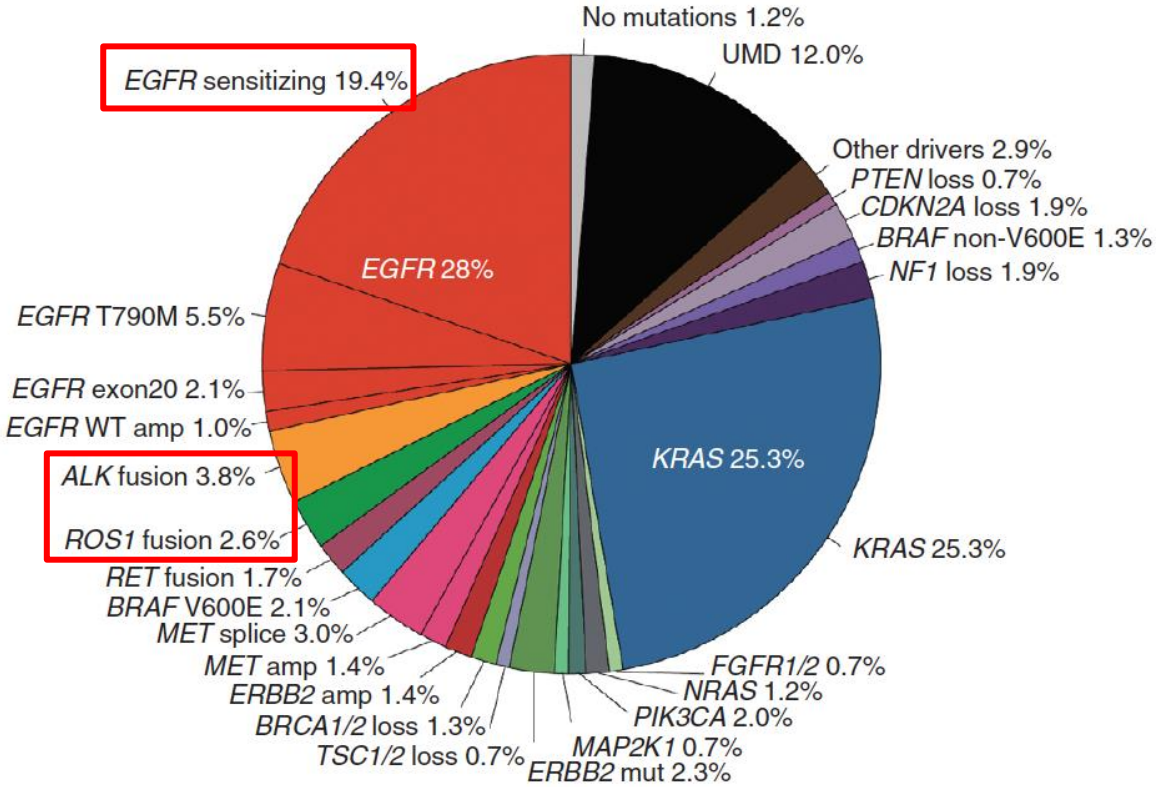
Travel: Pfizer
CME support: OncLive

# Oncogenic Driver Alterations in NSCLC




Jordan EJ et al., Cancer Discov 2017;7:596-609

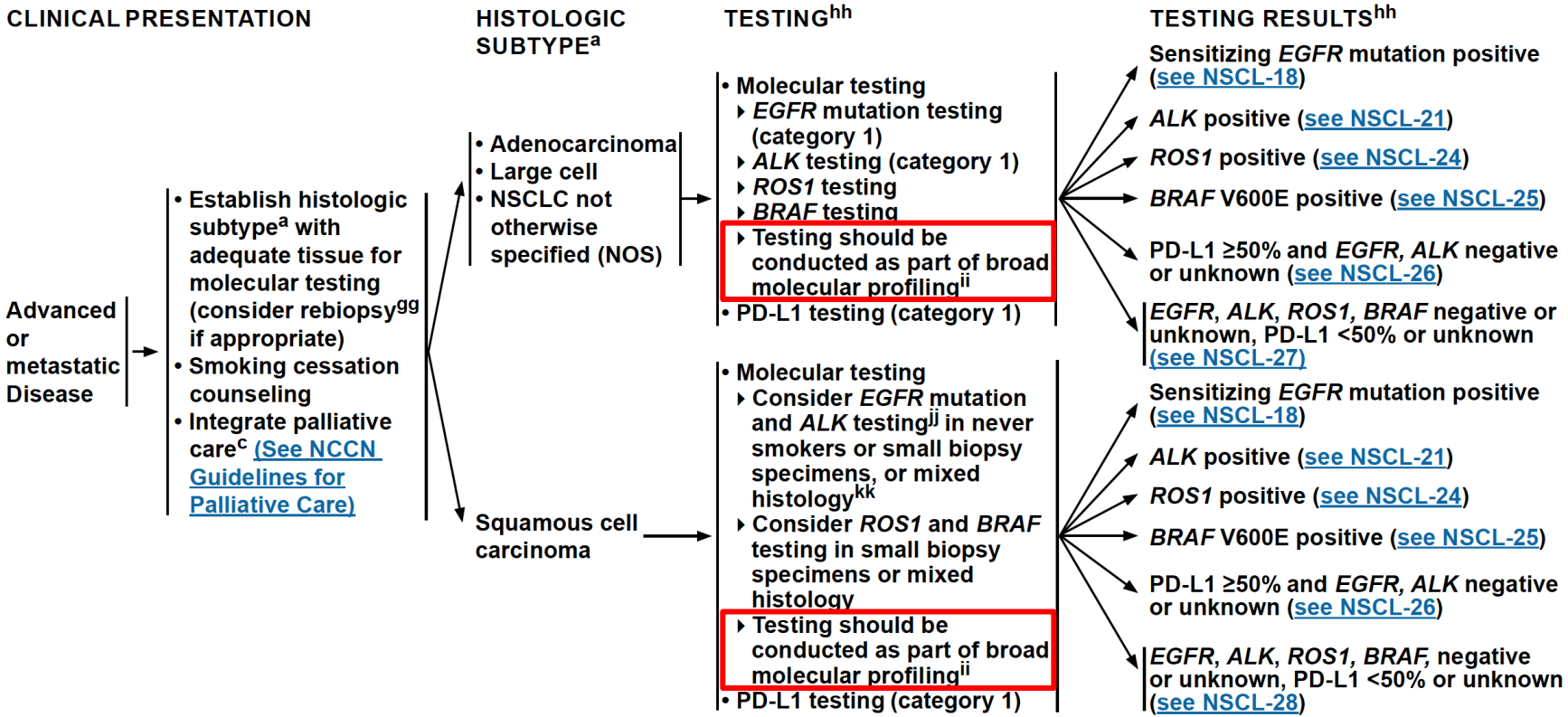
# Matching Tyrosine Kinase Inhibitors (TKIs) to Targets in Advanced Oncogene-Driven NSCLC

| EGFR | ALK | ROS1 | BRAF | NTRK |
|---|---|---|---|---|
| • Erlotinib | • Crizotinib | • Crizotinib | • Dabrafenib + Trametinib | • Larotrectinib |
| • Gefitinib | • Ceritinib | • Entrectinib | • Vemurafenib | • Entrectinib |
| • Afatinib | • Alectinib | • Ceritinib | • Encorafenib + binimetinib | • Repotrectinib |
| • Osimertinib | • Brigatinib | • Brigatinib | • LXH254 + LTT462 or trametinib | • LOXO-195 |
| | • Ensartinib | • Lorlatinib | | |
| | • Lorlatinib | • Cabozantinib | | |
| | | • DS-6051b | | |
| | | • Repotrectinib | | |

FDA-approved TKIs are shown in blue.

Not all drugs in clinical development are shown; monoclonal antibodies or antibody-drug conjugates are not shown.

# Recommendations for Broad Molecular Profiling at Initial Diagnosis of Advanced NSCLC

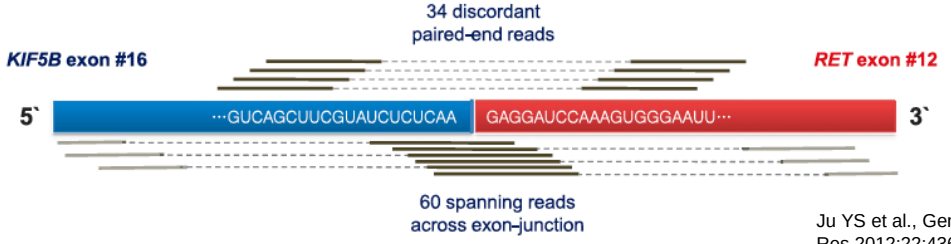


# *RET* Fusion in NSCLC

A transforming *KIF5B* and *RET* gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing

Young Seok Ju,[1,2] Won-Chul Lee,[1,3] Jong-Yeon Shin,[1,4] Seungbok Lee,[1,3] Thomas Bleazard,[1] Jae-Kyung Won,[5] Young Tae Kim,[6,7] Jong-Il Kim,[1,3,4,8] Jin-Hyoung Kang,[9] and Jeong-Sun Seo[1,2,3,4,8,10]

[1]Genomic Medicine Institute (GMI), Medical Research Center, Seoul National University, Seoul 110-799, Korea; [2]Macrogen Inc., Seoul 153-781, Korea; [3]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul 110-799, Korea; [4]Psoma Therapeutics Inc., Seoul 153-781, Korea; [5]Molecular Pathology Center, Seoul National University Cancer Hospital, Seoul 110-744, Korea; [6]Department of Thoracic and Cardiovascular Surgery, Clinical Research Institute, Seoul National University Hospital, Seoul 110-799, Korea; [7]Cancer Research Institute, Seoul National University College of Medicine, Seoul 110-799, Korea, [8]Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine, Seoul 110-799, Korea; [9]Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University, Seoul 137-040, Korea




Ju YS et al., Genome Res 2012;22:436-45

RET, ROS1 and ALK fusions in lung cancer

Kengo Takeuchi[1,2], Manabu Soda[3], Yuki Togashi[1,2], Ritsuro Suzuki[4], Seiji Sakata[1], Satoko Hatano[1], Reimi Asaka[1,2], Wakako Hamanaka[2], Hironori Ninomiya[2], Hirofumi Uehara[5], Young Lim Choi[6], Yukitoshi Satoh[5,7], Sakae Okumura[5], Ken Nakagawa[5], Hiroyuki Mano[3,6] & Yuichi Ishikawa[2]

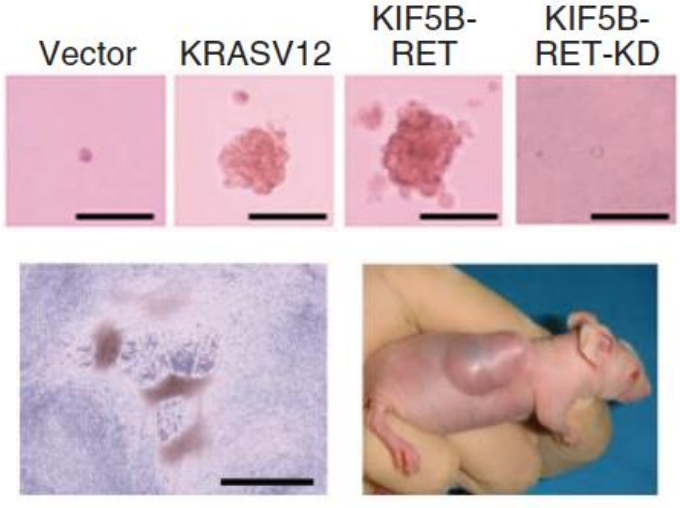
Identification of new *ALK* and *RET* gene fusions from colorectal and lung cancer biopsies

Doron Lipson[1,9], Marzia Capelletti[2,9], Roman Yelensky[1], Geoff Otto[1], Alex Parker[1], Mirna Jarosz[1], John A Curran[1], Sohail Balasubramanian[1], Troy Bloom[1], Kristina W Brennan[1], Amy Donahue[1], Sean R Downing[1], Garrett M Frampton[1], Lazaro Garcia[1], Frank Juhn[1], Kathy C Mitchell[1], Emily White[1], Jared White[1], Zac Zwirko[1], Tamar Peretz[3], Hovav Nechushtan[3], Lior Soussan-Gutman[4], Jhingook Kim[5], Hidefumi Sasaki[6], Hyeong Ryul Kim[7], Seung-il Park[7], Dalia Ercan[2], Christine E Sheehan[8], Jeffrey S Ross[1,8], Maureen T Cronin[1], Pasi A Jänne[2] & Philip J Stephens[1]

*KIF5B-RET* fusions in lung adenocarcinoma

Takashi Kohno[1,15], Hitoshi Ichikawa[2,15], Yasushi Totoki[3], Kazuki Yasuda[4], Masaki Hiramoto[4], Takao Nammo[4], Hiromi Sakamoto[2], Koji Tsuta[5], Koh Furuta[5], Yoko Shimada[1], Reika Iwakawa[6], Hideaki Ogiwara[1], Takahiro Oike[6], Masato Enari[7], Aaron J Schetter[8], Hirokazu Okayama[6,8], Aage Haugen[9], Vidar Skaug[9], Suenori Chiku[10], Itaru Yamanaka[11], Yasuhito Arai[3], Shun-ichi Watanabe[12], Ikuo Sekine[13], Seishi Ogawa[14], Curtis C Harris[8], Hitoshi Tsuda[5], Teruhiko Yoshida[2], Jun Yokota[6] & Tatsuhiro Shibata[3]

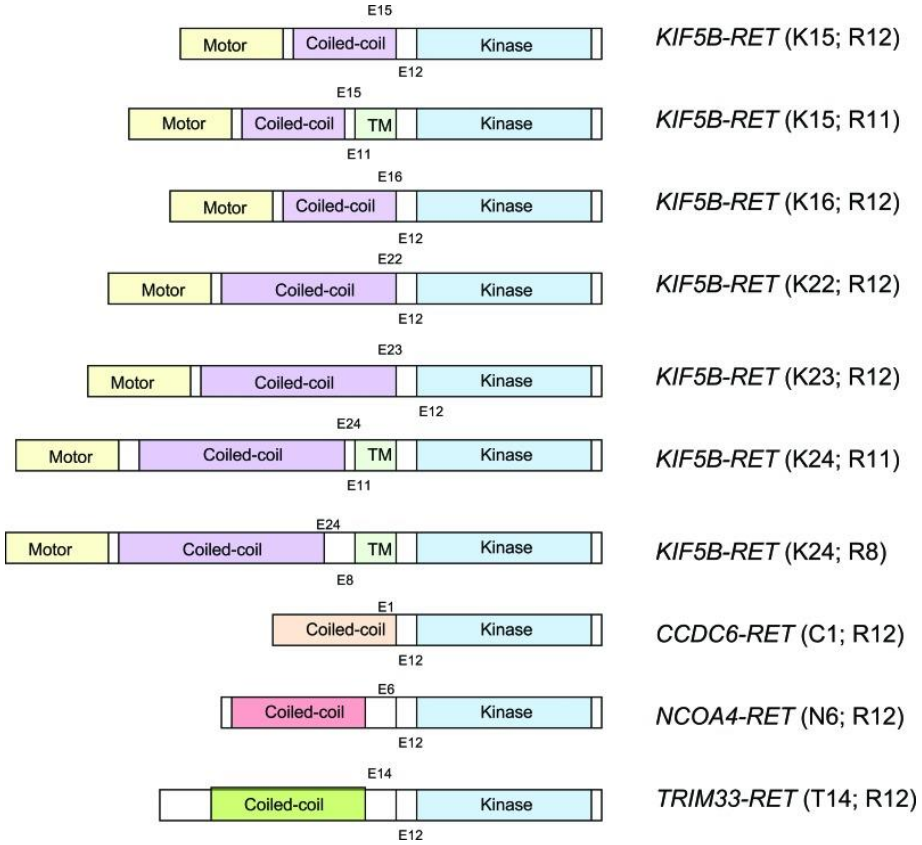
## *KIF5B-RET* is transforming




Kohno T et al., Nat Med 2012;18:375-7

Takeuchi K et al., Nat Med 2012;18:378-81

# The Most Common *RET* Fusions in NSCLC



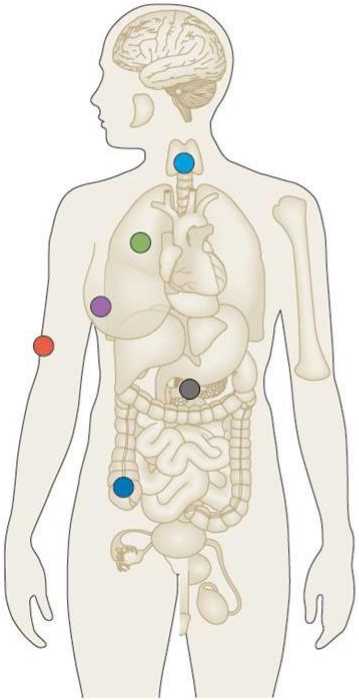

**RET**

- Transmembrane glycoprotein RTK
- Encoded by the Rearranged during Transfection gene on chromosome 10q11.2
- Role in the normal development of the kidney, enteric nervous system, and homeostasis of neural, neuroendocrine, hematopoietic, male germ cell tissues

Gainor and Shaw, Oncologist 2013;18:865-75

# Activating *RET* Alterations Across Solid Tumors

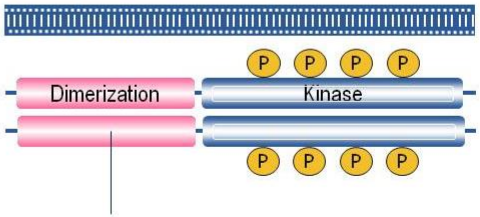
## *RET* fusions



**Non-small cell lung cancer (2%)**

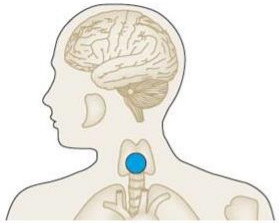
**Papillary and other thyroid cancers (10–20%)**

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



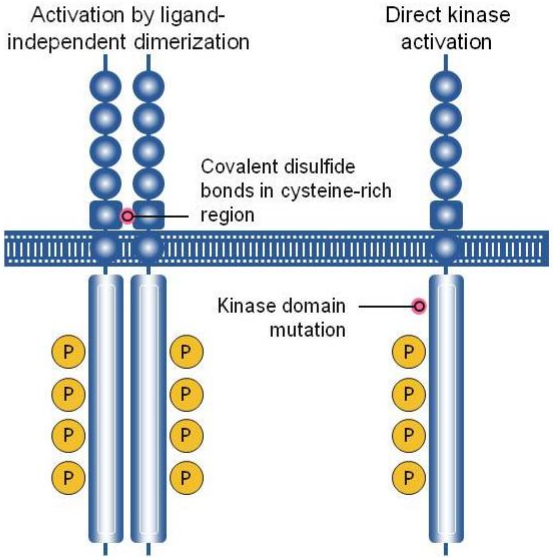

***KIF5B*** (most common in lung cancer)
***CCDC6* or *NCOA4*** (most common in thyroid cancer)

## *RET* mutations



**Medullary thyroid cancer**

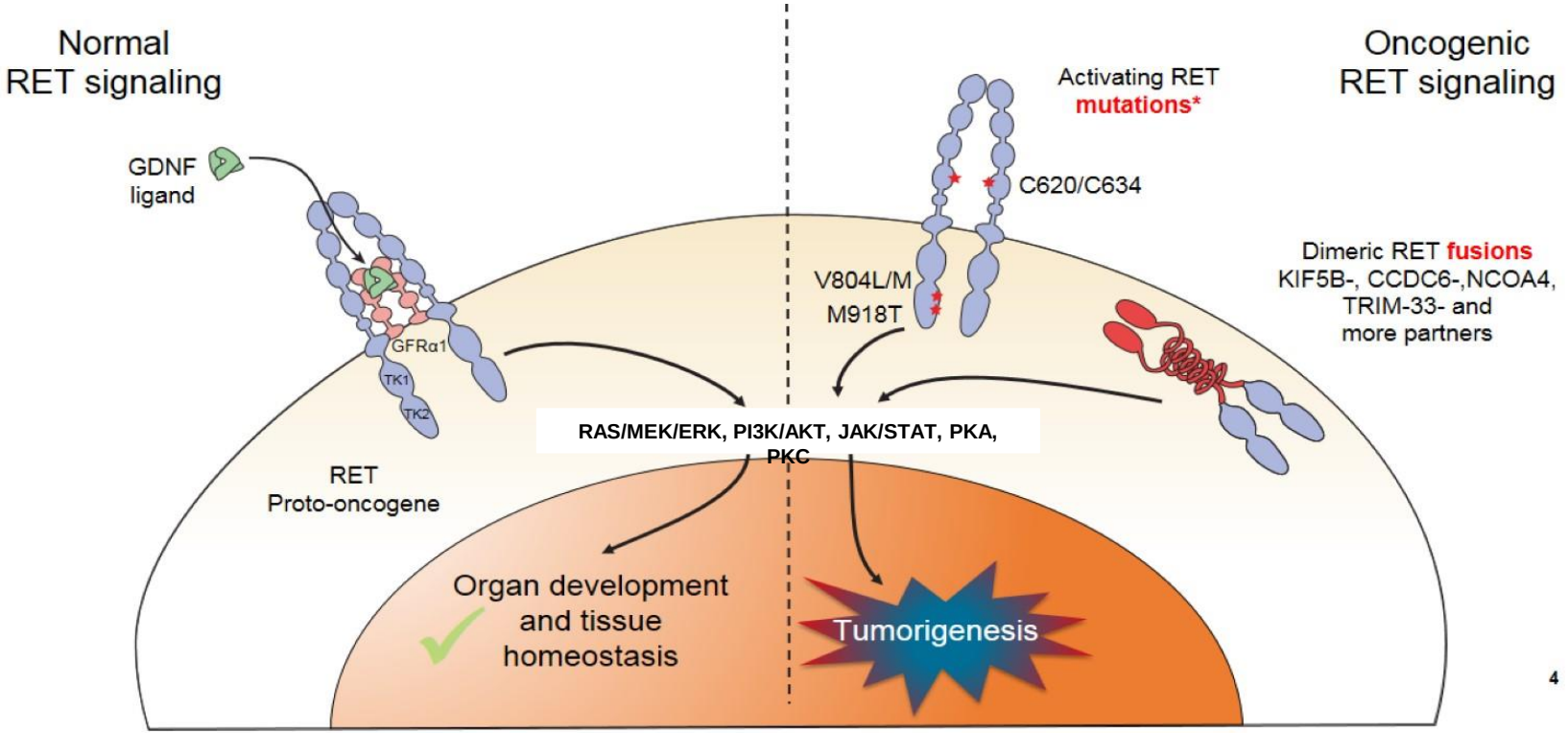
**sporadic (>60%)**
**hereditary (>90%)**




Common mutation: ***RET* M918T**

Drilon A et al. ASCO 2018

# Oncogenic RET Signaling




Subbiah V et al. AACR 2018

# Clinicopathologic Features of *RET*-Rearranged NSCLC

*Global, multi-center RET registry*

Associated with baseline patient/tumor characteristics of:

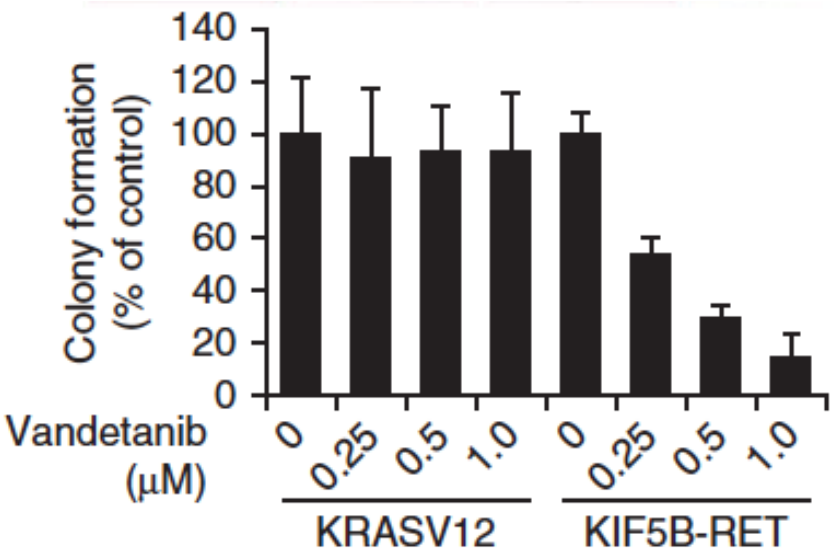
- Never or minimal smoking history
- Adenocarcinoma tumor histology

| Characteristic | n (%) [N = 165] |
|---|---|
| **Age, years** | |
| Median (range) | 61 (28-89) |
| < 70 | 126 (76) |
| **Gender** | |
| Male | 79 (48) |
| Female | 86 (52) |
| **Smoking history** | |
| Never | 103 (62) |
| Former/current/unknown | 62 (38) |
| **Tumor histology** | |
| Adenocarcinoma | 158 (96) |
| Squamous/NOS/unknown | 7 (4) |
| ***RET* fusion gene partner** | |
| *KIF5B* | 58 (35) |
| Other | 23 (14) |
| Unknown | 84 (51) |
| **Stage at diagnosis** | |
| I-III/unknown | 48 (29) |
| IV | 117 (71) |

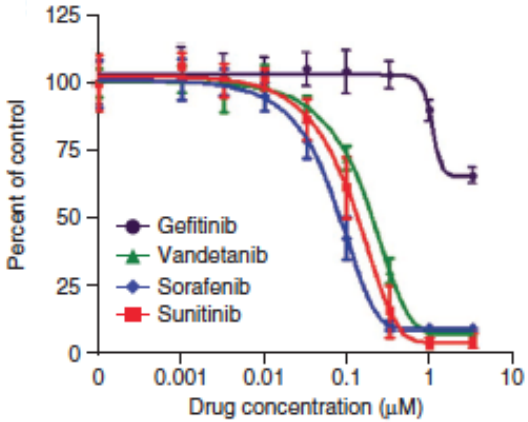
Gautschi O et al., J Clin Oncol 2017;35:1403-10

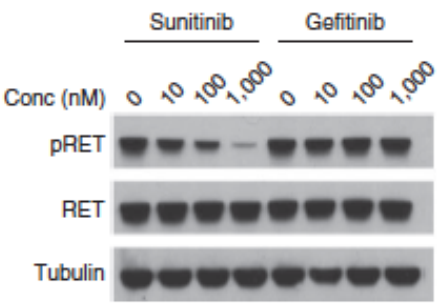
# Targeting RET

*KIF5B-RET*-expressing NIH3T3 cells are sensitive to vandetanib




*KIF5B-RET*-expressing Ba/F3 cells are sensitive to MKIs that inhibit RET




Kohno T et al., Nat Med 2012;18:375-7;
Lipson D et al., Nat Med 2012;18:382-4

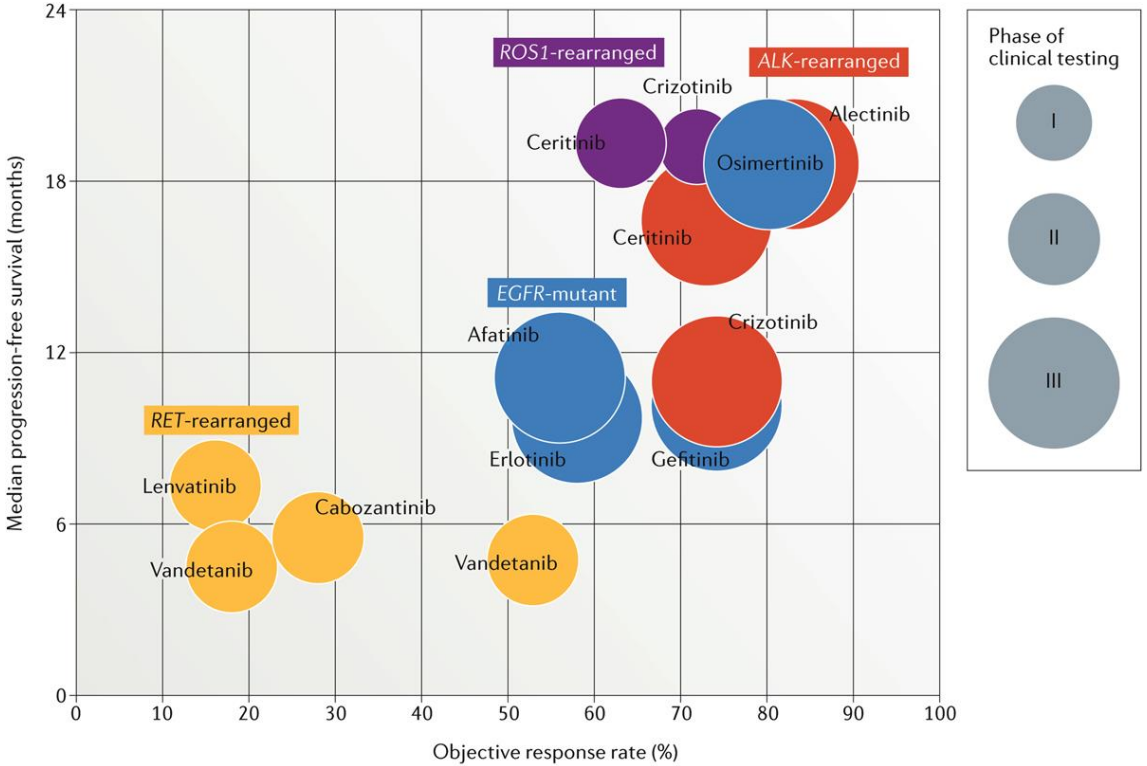
# Multikinase Inhibitors Have Suboptimal Clinical Activity in *RET*-Rearranged Non-Small Cell Lung Cancer

| Drug | Clinical Trial | ORR | Median PFS |
|---|---|---|---|
| Cabozantinib | Phase II (n = 26; 25 evaluable for response)[1] | 7/25 (28%) | 5.5 months |
| Vandetanib | Phase II (n = 17) [2] | 3/17 (18%) | 4.5 months |
| | Phase II (n = 19) [3] | 9/19 (47%) | 4.7 months |
| Lenvatinib | Phase II (n = 25) [4] | 4/25 (16%) | 7.3 months |
| Sorafenib | Phase II (n = 3) [5] | 0/3 (0%) | |
| RXDX-105 | Phase Ib (n = 40) [6] | 6/40 (15%) | |

Multikinase inhibitors reported to have activity in *RET*-rearranged NSCLC based on retrospective series (e.g., sunitinib, alectinib, ponatinib) are not shown in this table.

[1]Drilon A et al., Lancet Oncol 2016;17:1653-60. [2]Lee SH et al., Ann Oncol 2017;28:292-7. [3]Yoh K et al., Lancet Respir Med 2017;5:42-50. [4]Velcheti V et al., Ann Oncol 2016;27:1204PD. [5]Horiike A et a., Lung Cancer 2016;93:43-6. [6]Drilon A et al., Cancer Discov 2018

# Prior RET-Targeted TKIs Compared to TKIs in Other Oncogene-Driven NSCLCs




Drilon A et al., Nat Rev Clin Oncol 2018;15:150

# Multikinase Inhibitors Have Been Limited by Toxicities Related to Non-RET Activity

| Drug | Clinical Trial | Dose Reduction Rate | Drug Discontinuation Rate |
|---|---|---|---|
| Cabozantinib | Phase II (n = 26)[1] | 19/26 (73%) | 2/26 (8%) |
| Vandetanib | Phase II (n = 17) [2] | 4/17 (23%) | NA |
| | Phase II (n = 19) [3] | 10/19 (53%) | 4/19 (21%) |
| Lenvatinib | Phase II (n = 25) [4] | 16/25 (64%) | 5/25 (20%) |
| Sorafenib | Phase II (n = 3) [5] | 1/3 (33%) | NA |
| RXDX-105 | Phase Ib (n = 62)[6] | 19/62 (31%) | 8/62 (13%) |

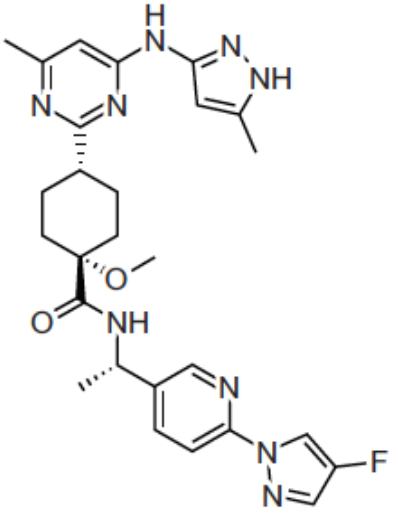
[1]Drilon A et al., Lancet Oncol 2016;17:1653-60. [2]Lee SH et al., Ann Oncol 2017;28:292-7. [3]Yoh K et al., Lancet Respir Med 2017;5:42-50. [4]Velcheti V et al., Ann Oncol 2016;27:1204PD. [5]Horiike A et a., Lung Cancer 2016;93:43-6. [6]Drilon A et al., Cancer Discov 2018

*Entering the New Chapter of Treating RET+ NSCLC and Other RET-Altered Solid Tumors:*

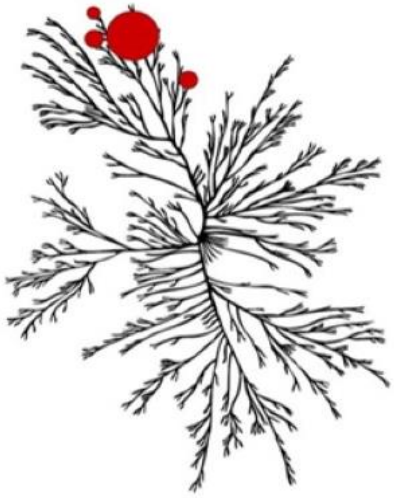
# Novel Oral, Potent RET-Selective TKIs

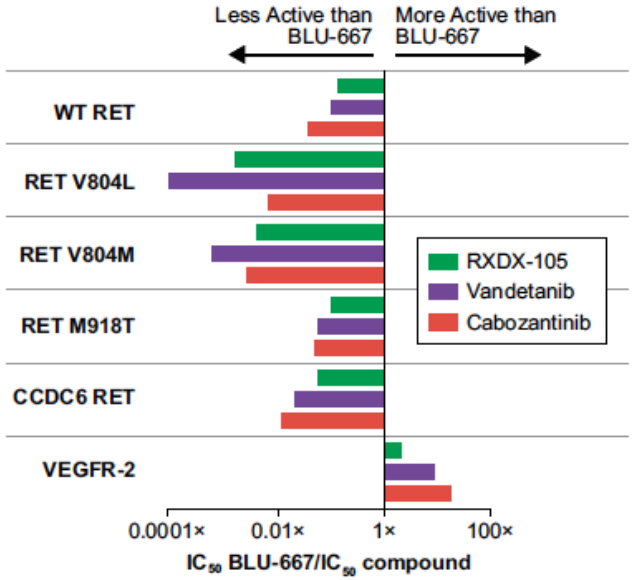
# BLU-667: A RET-Selective Tyrosine Kinase Inhibitor

BLU-667



Kinome selectivity

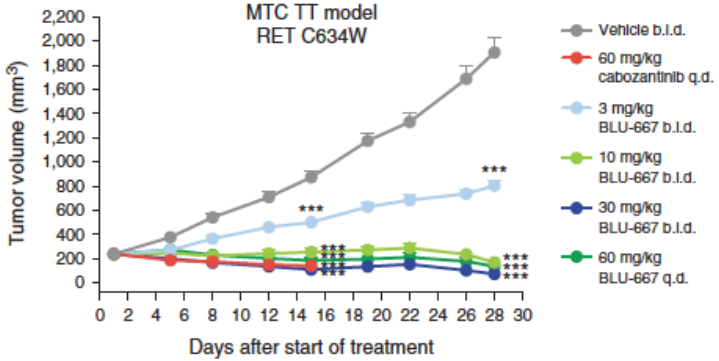


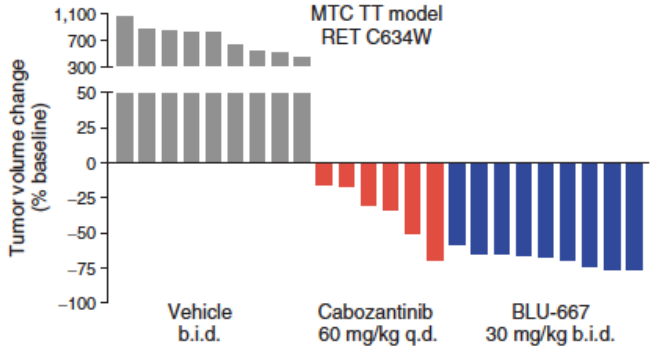



| | Biochemical $IC_{50}$, nmol/L | | | | | |
|---|---|---|---|---|---|---|
| Compound | WT RET | RET V804L | RET V804M | RET M918T | CCDC6-RET | VEGFR2 |
| BLU-667 | 0.4 | 0.3 | 0.4 | 0.4 | 0.4 | 35 |
| Cabozantinib | 11 | 45 | 162 | 8 | 34 | 2 |
| Vandetanib | 4 | 3,597 | 726 | 7 | 20 | 4 |
| RXDX-105 | 3 | 188 | 102 | 4 | 7 | 17 |

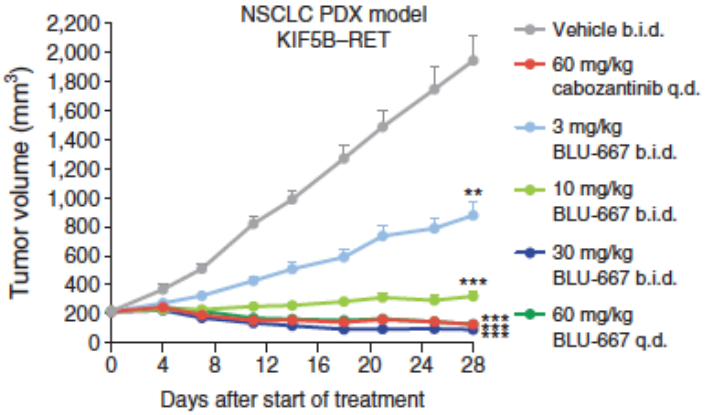
Subbiah V et al., Cancer Discov 2018;8:836-49

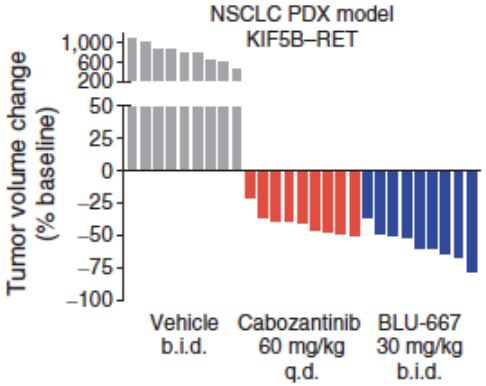
# BLU-667: Preclinical Data




Anti-tumor activity of BLU-667 compared with cabozantinib in ***RET* C634W MTC** xenograft




Anti-tumor activity of BLU-667 compared with cabozantinib in ***KIF5B-RET* NSCLC** patient-derived xenograft

Subbiah V et al., Cancer Discov 2018;8:836-49

# Phase I Study of BLU-667 (ARROW)

| Parameter | (N=53) |
|---|---|
| Age, years; median (range) | 56 (19-83) |
| Sex, male; n (%) | 30 (57) |
| ECOG PS; n (%) | |
| 0 | 21 (40) |
| 1 | 32 (60) |
| Metastatic disease; n (%) | 50 (94) |
| Tumor type; n (%) | |
| *RET*-alteration | 51 (96) |
| Medullary thyroid cancer | 29 (55) |
| Non-small cell lung cancer | 19 (36) |
| Papillary thyroid cancer | 2 (4) |
| Retroperitoneal Paraganglioma | 1 (2) |
| Non-*RET* altered solid tumor | 2 (4) |

| Parameter | (N=53) |
|---|---|
| Prior systemic therapy; n (%) | 41 (77) |
| Multikinase inhibitor; n (%) | 26 (49) |
| Chemotherapy; n (%) | 19 (36) |
| Immunotherapy; n (%) | 18 (34) |
| # of lines, median (range) | 1 (0-8) |

Subbiah V et al., AACR 2018

# BLU-667 Safety Profile

Maximum Tolerated Dose – 400 mg QD

| Dose (mg QD) | # Evaluable (N=49) | Dose limiting toxicity |
|---|---|---|
| 30 | 1 | None |
| 60 | 6 | None |
| 100 | 5 | Alanine transaminase increased (1) |
| 200 | 12 | None |
| 300 | 11 | Tumor lysis syndrome (1)<br>Hypertension (1) |
| 400 | 10 | Asthenia (1)<br>Hypertension (1) |
| 600 | 4 | Hyponatremia (1)<br>Hypertension (1) |

Treatment-emergent Adverse Events ≥10% per CTCAE
(30-400 mg Safety Population, N=49)

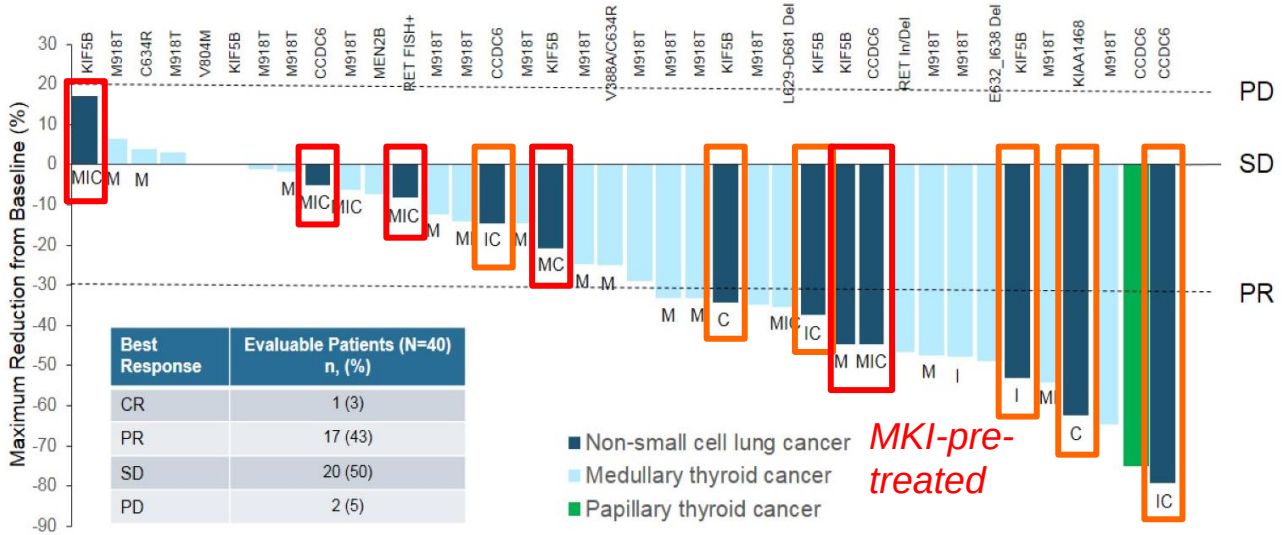
| Adverse event, n (%) | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Constipation | 10 (20) | 2 (4) | 0 |
| ALT increased | 10 (20) | 0 | 1 (2) |
| AST increased | 8 (16) | 2 (4) | 0 |
| Hypertension | 2 (4) | 2 (4) | 4 (8) |
| Fatigue | 5 (10) | 1 (2) | 1 (2) |
| Edema peripheral | 6 (12) | 1 (2) | 0 |
| Diarrhea | 4 (8) | 1 (2) | 1 (2) |
| Blood creatinine increased | 6 (12) | 0 | 0 |
| Hyperphosphatemia | 4 (8) | 2 (4) | 0 |
| Headache | 5 (10) | 1 (2) | 0 |
| Leukopenia | 5 (10) | 0 | 0 |
| Neutropenia | 2 (4) | 1 (2) | 2 (4) |
| White blood cell decreased | 2 (4) | 2 (4) | 1 (2) |
| Insomnia | 5 (10) | 0 | 0 |
| Cough | 3 (6) | 2 (4) | 0 |

Subbiah V et al., AACR 2018

# BLU-667 in *RET*-Altered Cancers including NSCLC

Responses to BLU-667 seen in TKI-pre-treated and -naïve lung and thyroid cancer patients

**ORR in *RET*-rearranged NSCLC: 50%**



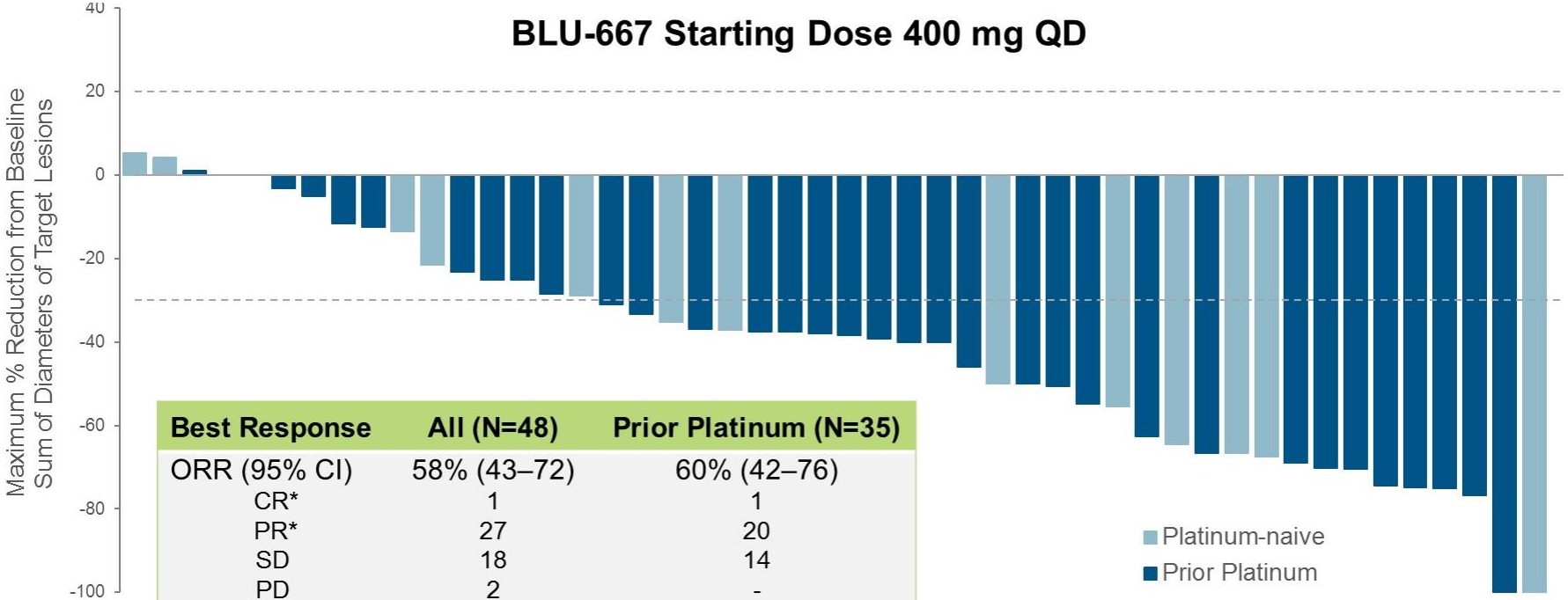

| Best Response | Evaluable Patients (N=40) n, (%) |
|---|---|
| CR | 1 (3) |
| PR | 17 (43) |
| SD | 20 (50) |
| PD | 2 (5) |

C, prior chemotherapy; CR, complete response; I, prior immunotherapy; M, prior MKI therapy; MKI, multikinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease

Data cut-off: April 6, 2018

Subbiah V et al., AACR 2018

# BLU-667 (Pralsetinib) in *RET*+ NSCLC



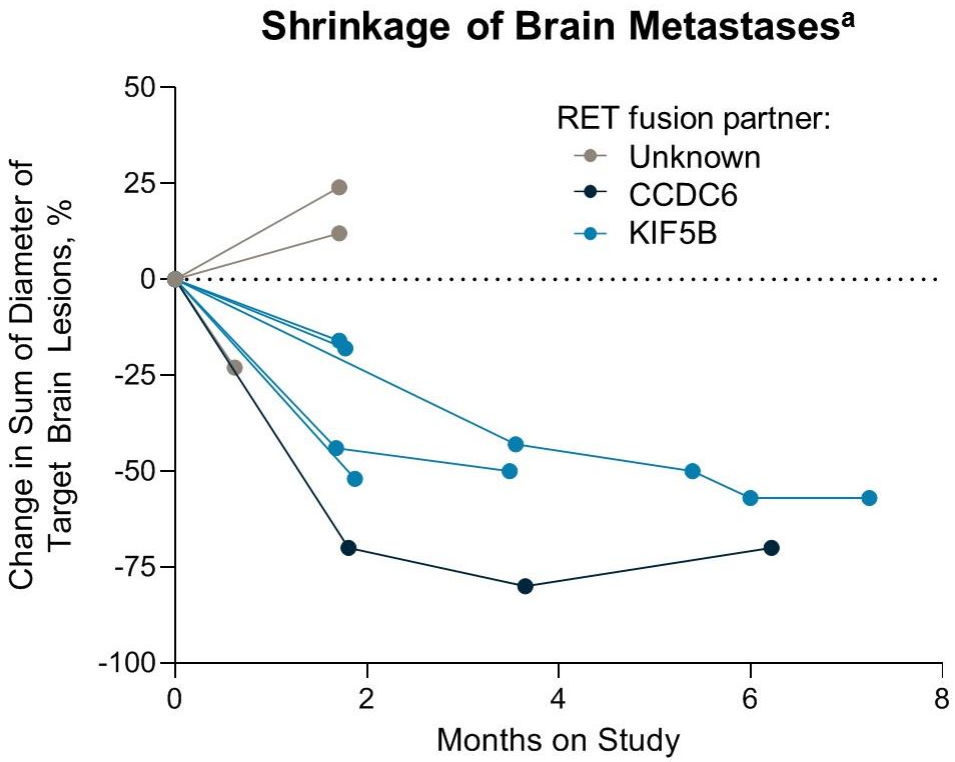

| Best Response | All (N=48) | Prior Platinum (N=35) |
|---|---|---|
| ORR (95% CI) | 58% (43–72) | 60% (42–76) |
| CR* | 1 | 1 |
| PR* | 27 | 20 |
| SD | 18 | 14 |
| PD | 2 | - |
| DCR (95% CI) | 96% (86–99) | 100% (90–100) |

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

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

Data cut-off: April 28, 2019
Gainor JF et al., ASCO 2019

# CNS Activity of BLU-667

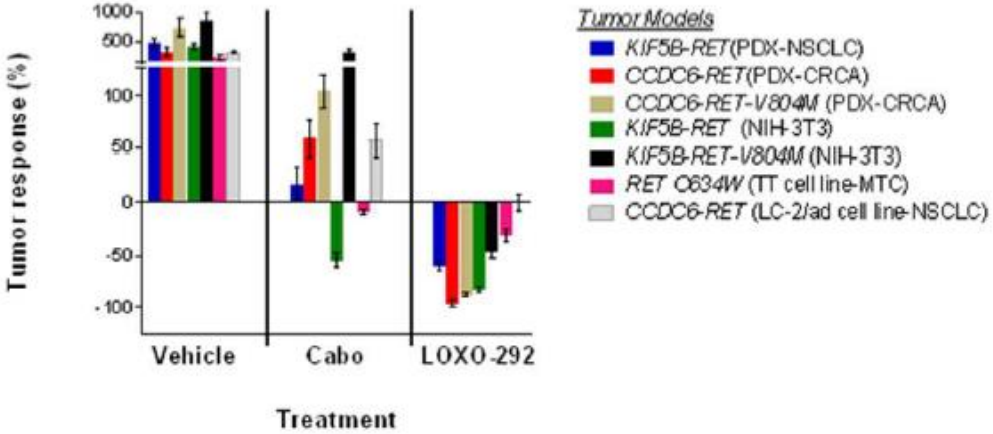



**7 of 9 (78%) patients** with measurable brain metastases had shrinkage of brain lesions on BLU-667

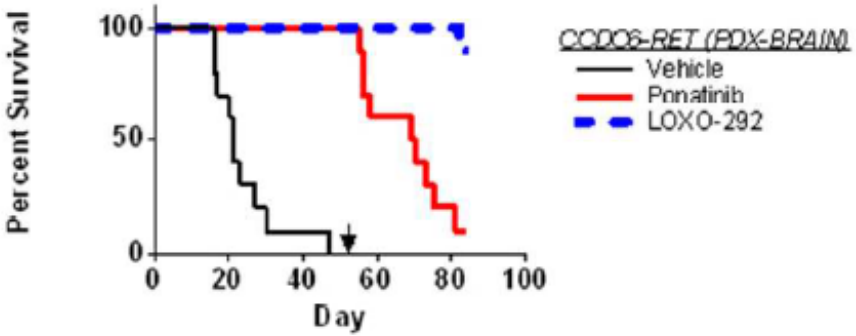
Data cut-off: April 28, 2019
Gainor JF et al., ASCO 2019

# LOXO-292: Another Oral RET-Selective TKI

Anti-tumor activity of LOXO-292 compared with cabozantinib in ***RET*-mutant and *RET*-rearranged mouse tumor models**

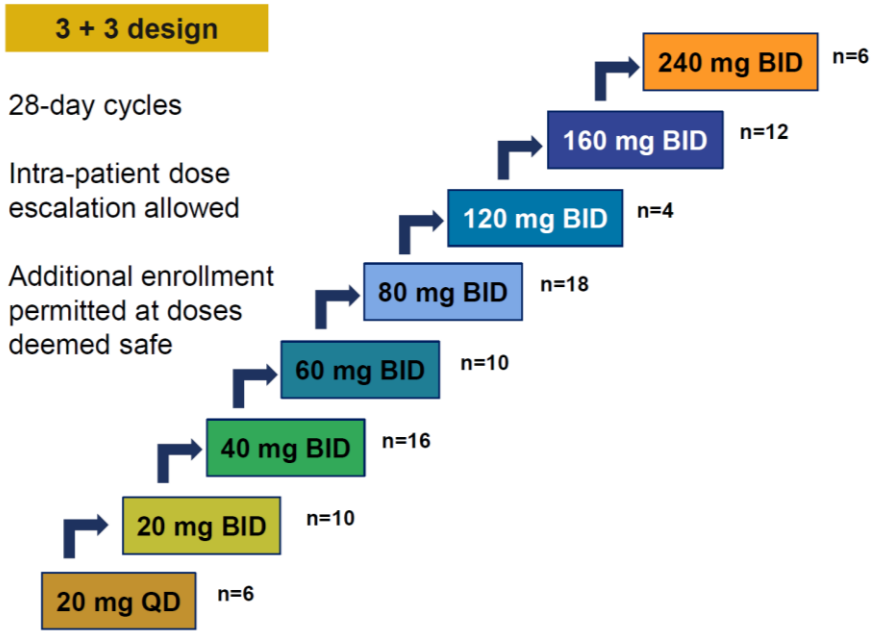



**Preclinical CNS activity** of LOXO-292




Subbiah V et al., Ann Oncol 2018;29:1869-76

# Phase I Study of LOXO-292 (LIBRETTO-001)



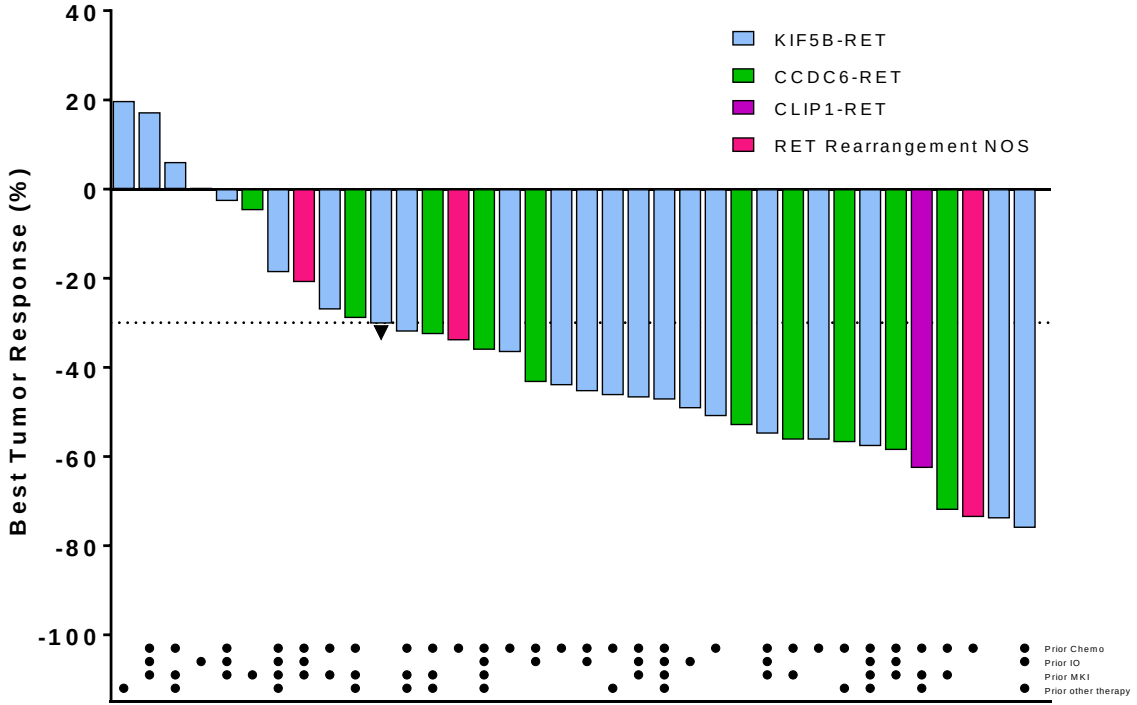

| Characteristic | Total (n=82) |
|---|---|
| **Female / Male, n (%)** | 40 (49%) / 42 (51%) |
| **Median age (range), years** | 61 (17–88) |
| **ECOG performance status, n (%)** | |
| 0 | 21 (26%) |
| 1 | 58 (71%) |
| 2 | 3 (4%) |
| **Tumor type, n (%)** | |
| *RET* fusion-positive NSCLC | 38 (46%) |
| *RET* fusion-positive thyroid cancer | 9 (11%) |
| *RET* fusion-positive pancreatic cancer | 2 (2%) |
| *RET*-mutant MTC | 29 (35%) |
| Other | 4 (5%) |
| **Median prior systemic regimens (range)** | 3 (1–9) |
| **≥1 prior multikinase inhibitor (MKI), n (%)[1]** | **54 (66%)** |
| 0 | 28 (34%) |
| 1 | 30 (37%) |
| ≥2 | 24 (29%) |
| **Prior chemotherapy regimen, n (%)** | **38 (46%)** |
| **Prior immunotherapy regimen, n (%)** | **20 (24%)** |
| **Brain metastases, n (%)[2]** | **12 (15%)** |

Drilon A et al., ASCO 2018

# LOXO-292 in *RET*-Rearranged NSCLC: Preliminary Activity Seen in the Dose Escalation Part

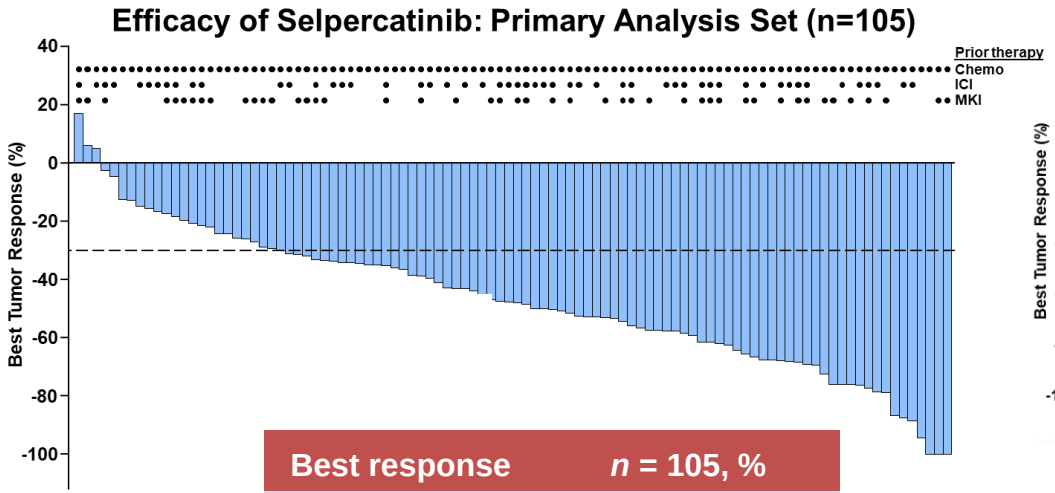
Responses to LOXO-292 seen in TKI-pre-treated and -naïve lung cancer patients

**Confirmed ORR in *RET*-rearranged NSCLC: 68%** (25/37) (95% CI, 50-82%)



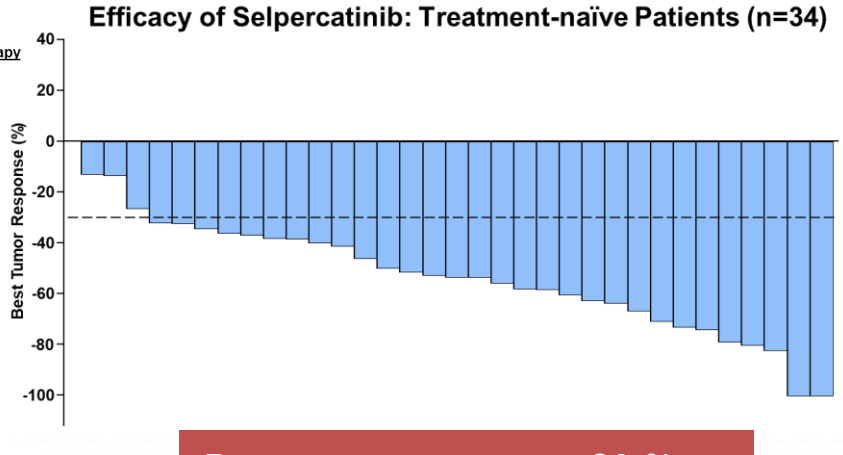

Oxnard GR et al., WCLC 2018

# LOXO-292 (Selpercatinib) in *RET*+ NSCLC




| Best response | *n* = 105, % |
|---|---|
| **PR/CR** | **68%** |
| SD | 26% |
| PD | 2% |
| NE | 5% |

**Median PFS: 18.4 months** (95% CI, 12.9-24.9)
Median follow-up: 9.6 months




| Best response | *n = 34, %* |
|---|---|
| **PR/CR** | **85%** |
| SD | 9% |
| PD | 3% |
| NE | 3% |

**Median PFS: not reached** (95% CI, 9.2-NE)
Median follow-up: 3.7 months

Primary analysis set = first 105 patients with *RET* fusion-positive NSCLC who received prior platinum chemotherapy

Drilon A et al., WCLC 2019

# LOXO-292 (Selpercatinib) safety profile

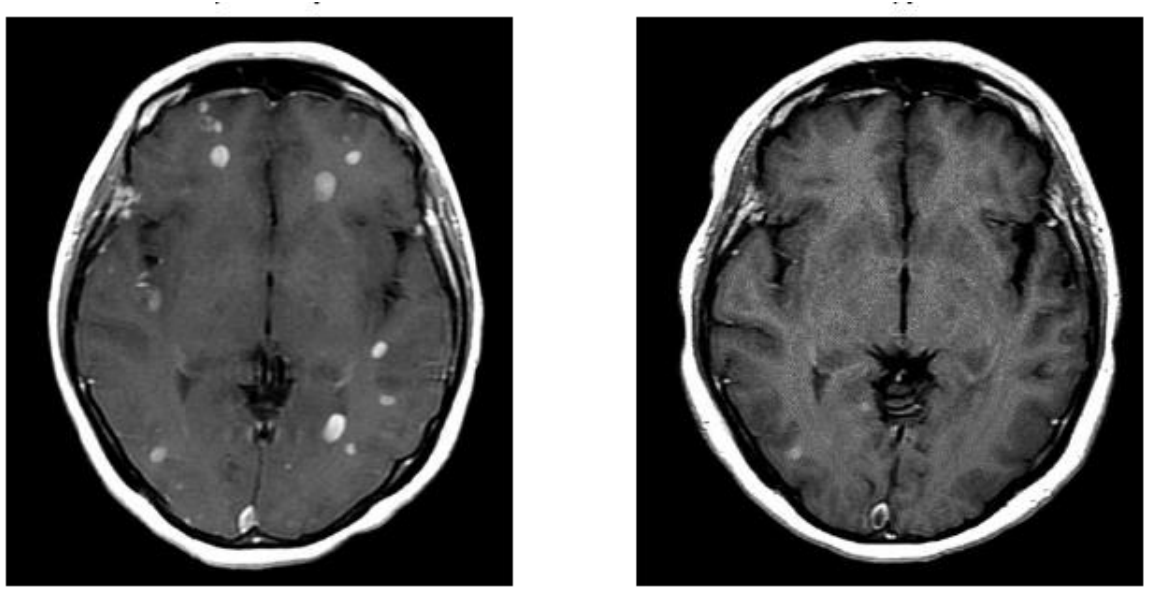
| | LIBRETTO-001 Safety Database, n=531 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Treatment-emergent AEs (≥15% overall) | | | | | Treatment-related AEs | | |
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total | Grade 3 | Grade 4 | Total |
| Dry mouth | 29% | 4% | – | – | 32% | – | – | 27% |
| Diarrhea | 21% | 8% | 2% | – | 31% | 1% | – | 16% |
| Hypertension | 4% | 11% | 14% | <1% | 29% | 8% | <1% | 18% |
| Increased AST | 17% | 5% | 6% | 1% | 28% | 4% | 1% | 22% |
| Increased ALT | 13% | 4% | 7% | 1% | 26% | 6% | 1% | 21% |
| Fatigue | 15% | 9% | 1% | – | 24% | <1% | – | 14% |
| Constipation | 19% | 3% | <1% | – | 22% | <1% | – | 11% |
| Headache | 15% | 4% | 1% | – | 20% | <1% | – | 7% |
| Nausea | 15% | 4% | <1% | – | 19% | <1% | – | 8% |
| Peripheral edema | 16% | 4% | <1% | – | 19% | – | – | 10% |
| Increased creatinine | 14% | 4% | – | <1% | 18% | – | – | 10% |

9 patients (1.7%) discontinued due to treatment-related AEs

Drilon A et al., WCLC 2019

# LOXO-292 CNS activity

Example of intracranial response to LOXO-292 in a patient with *RET* fusion-positive NSCLC



Baseline

Week 4

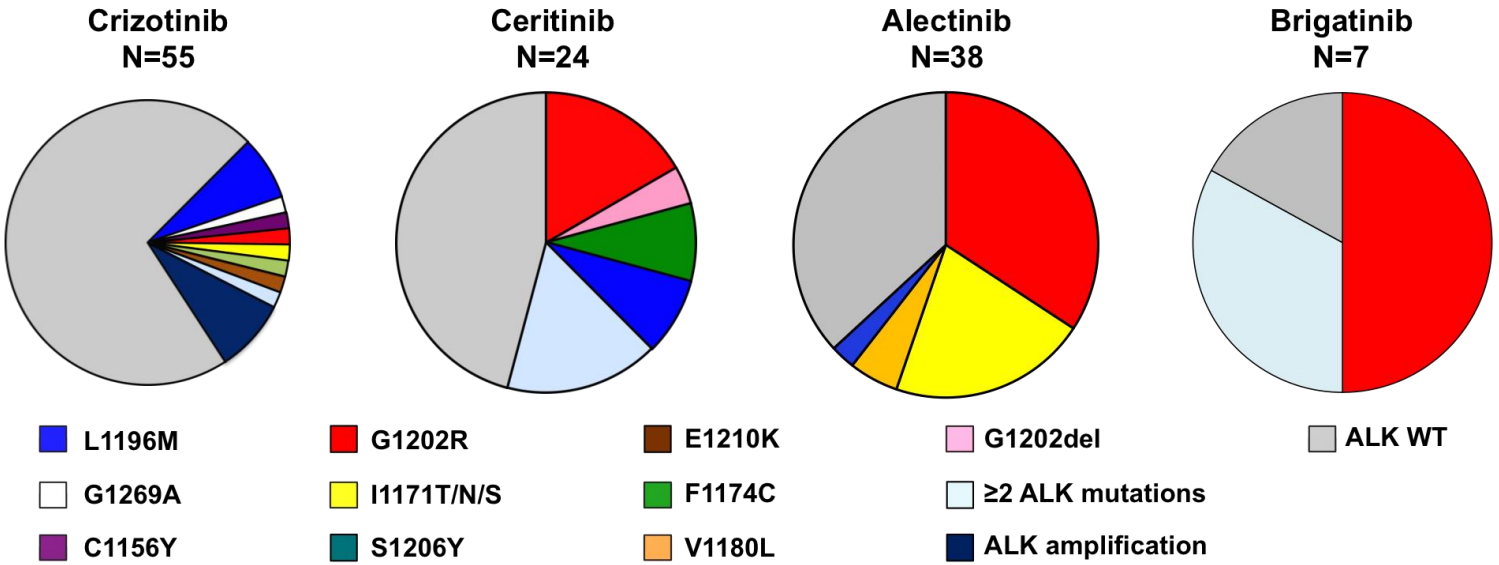
Drilon A et al., WCLC 2019

# Resistance to RET Inhibition in RET+ NSCLC

1. What mechanisms will drive resistance to RET-selective TKIs such as BLU-667 and LOXO-292 in clinic?

2. How could these resistance mechanisms be targeted in patients as we go forward?

# The Issue of Acquired Resistance to Targeted Therapy:
## Example of Resistance to 1st- and 2nd-Generation ALK TKIs Mediated by Distinct *ALK* Resistance Mutations in ALK+ NSCLC

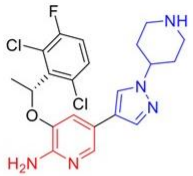



Gainor JF et al., Cancer Discov 2017;6:1118-1133
Lin JJ et al., ASCO 2018

# Multiple Generations of ALK TKIs in ALK+ NSCLC

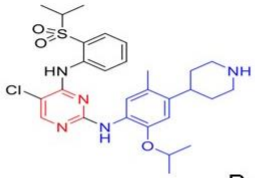
**First-Generation**

Crizotinib

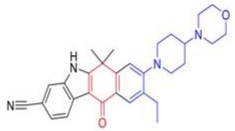


**Second-Generation**

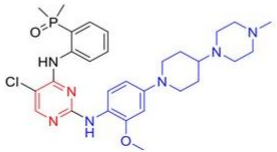
Ceritinib



Alectinib

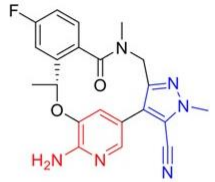


Brigatinib



**Third-Generation**

Lorlatinib



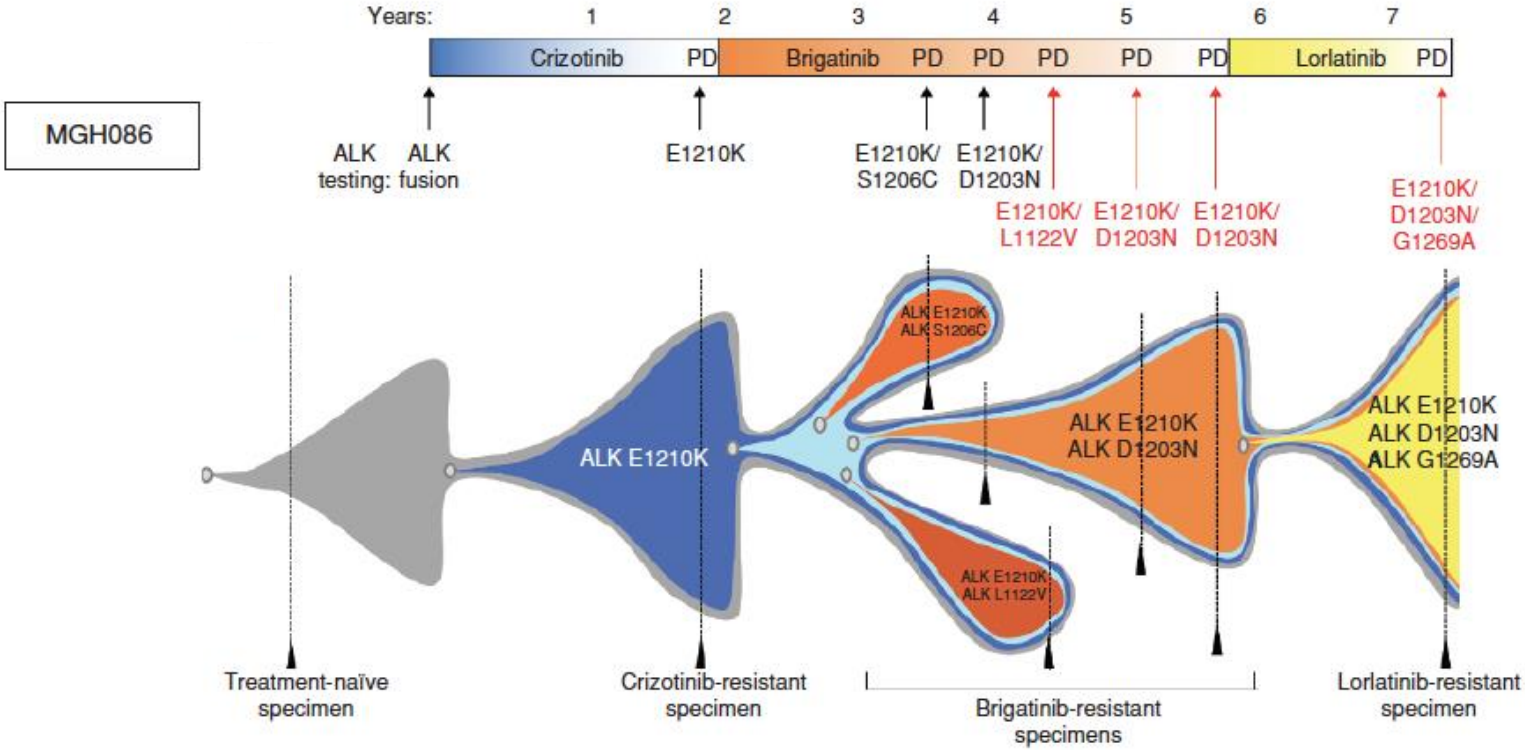
With each successive generation of ALK inhibitors:

1. Enhanced **potency** against the target (ALK)
2. Improved **CNS activity**
3. Broader activity against secondary ***ALK* resistance mutations**

| ALK TKI | Cellular IC50 |
|---|---|
| Crizotinib | 38.6 |
| Ceritinib | 4.9 |
| Alectinib | 11.4 |
| Brigatinib | 10.7 |
| Lorlatinib | 2.3 |

Gainor JF et al., Cancer Discov 2017;6:1118-1133
Modified from Gainor JF et al., ASCO 2019

# Emergence of Compound *ALK* Resistance Mutations with Sequential ALK TKI Therapy

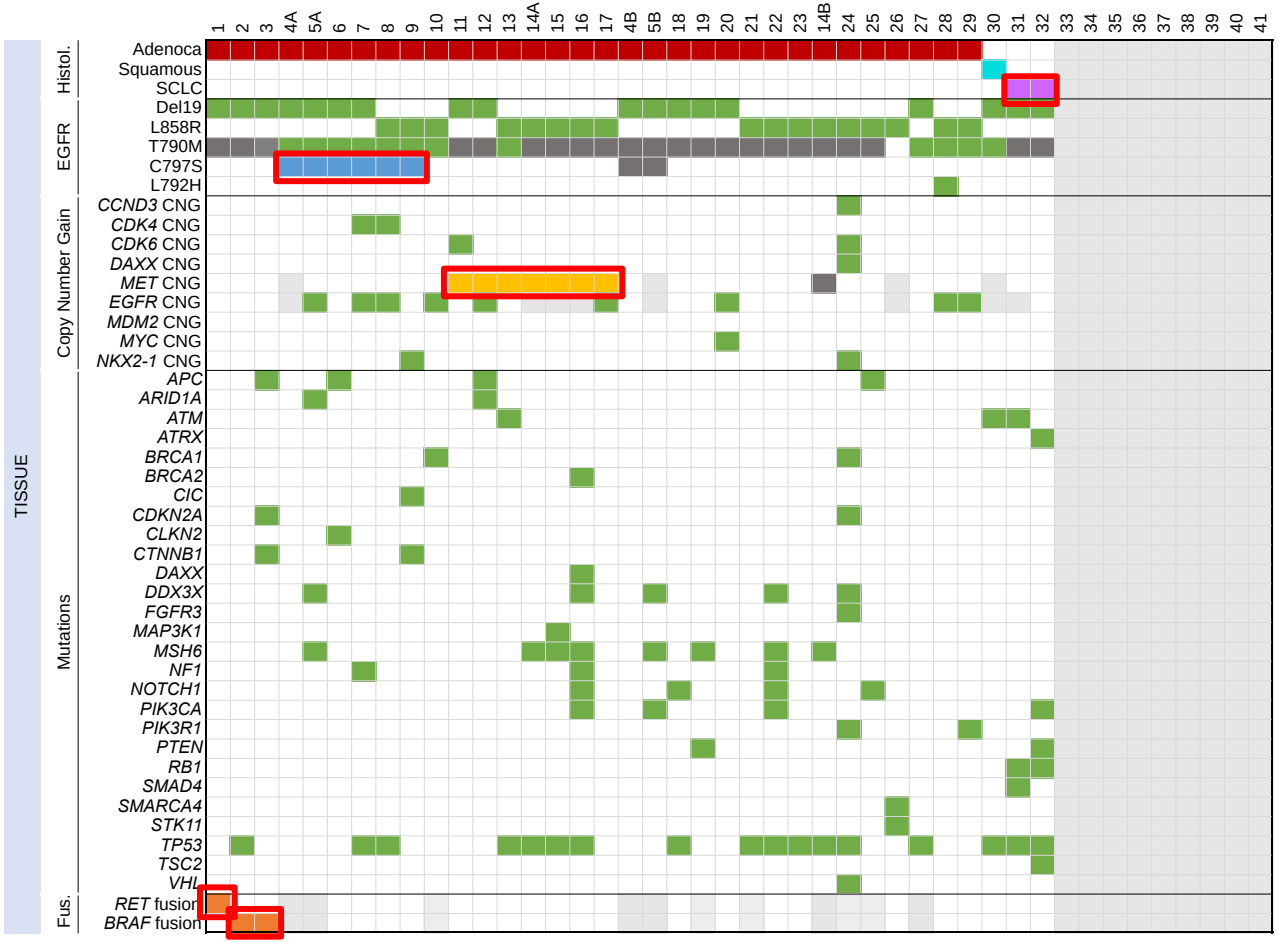



Yoda S et al., Cancer Discov 2018;8(6):714-29

# Resistance to RET Inhibition in RET+ NSCLC:
## Currently Available Evidence Focusing on Multikinase Inhibitors

| Resistance Mechanism | Multikinase Inhibitor | Level of Evidence | Reference |
|---|---|---|---|
| **RET V804L** | Cabozantinib | Preclinical | Huang et al., Mol Cancer Ther 2016;15:2521-9 |
| **RET V804M** | Cabozantinib<br>**Vandetanib** | Preclinical<br>**Clinical** | Plenker et al., Sci Transl Med 2017;9(394)<br>Dagogo-Jack et al., J Thorac Oncol 2018;13:e226-7 |
| **RET G810A** | Vandetanib | Preclinical | Huang et al., Mol Cancer Ther 2016;15:2521-9 |
| **RET I788N** | AD80 | Preclinical | Plenker et al., Sci Transl Med 2017;9(394) |
| **RET S904F** | **Vandetanib** | **Clinical** | Nakaoku et al., Nat Commun 2018;9:625 |
| **RAS/MAPK activation** | Ponatinib | Preclinical | Nelson-Taylor et al., Mol Cancer Ther 2017;16:1623-33 |
| **EGFR activation** | Various TKIs (foretinib, vandetanib, sorafenib, sunitinib) | Preclinical | Vaishnavi et al., Cancer Res 2017;77:3551-63<br>Chang et al., Yonsei Med J 2017;58:9-18 |
| **MDM2 amplification** | **Cabozantinib** | **Clinical** | Somwar et al., ASCO 2016 |

# RET fusions as a Resistance Mechanism in Other Oncogene-Driven Lung Cancers: Osimertinib-Resistant, *EGFR*-Mutant NSCLC Tumor Biopsies




Adenocarcinoma
Squamous cell carcinoma
Small cell lung cancer

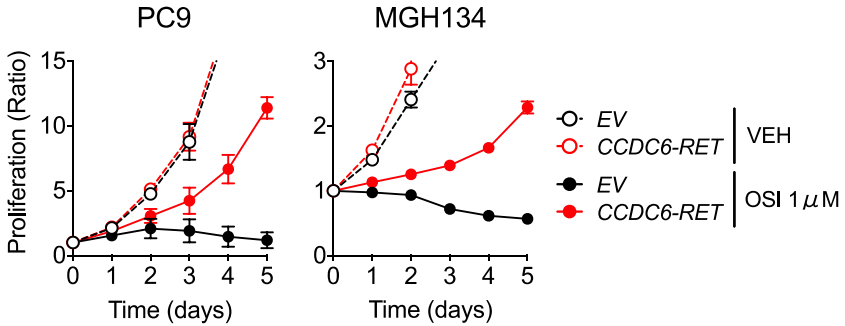
C797S
MET amplification
Gene fusion

Alteration present
Alteration previously detected on tissue/plasma, but no longer present
Testing not performed

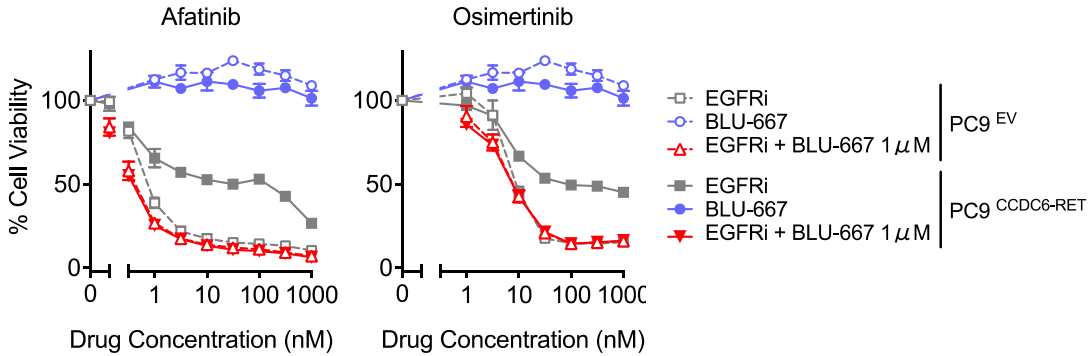
Piotrowska Z et al., Cancer Discov 2018;8:1529-39

# *CCDC6-RET* Fusion Confers Resistance to EGFR-TKIs and Can Be Overcome by EGFRi + RETi

*CCDC6-RET* expression in *EGFR*-mutant NSCLC cells is sufficient to confer resistance to osimertinib




Afatinib or osimertinib in combination with BLU-667 suppress the cell viability of PC9$^{CCDC6\text{-}RET}$

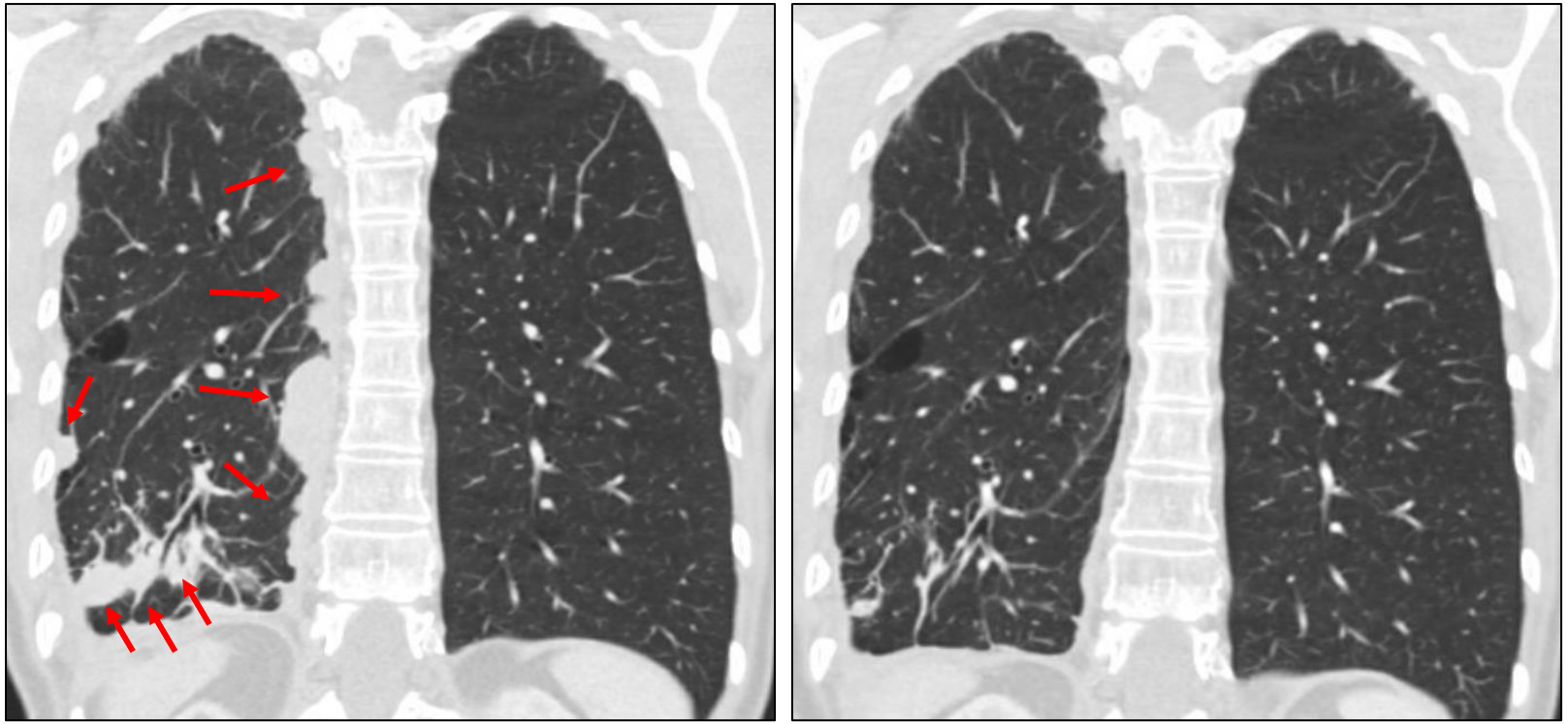



Piotrowska Z et al. Cancer Discovery 2018;8:1529-39

# Treatment of an Osimertinib-Resistant, *CCDC6-RET*-Rearranged Tumor with EGFRi + RETi

*Baseline*

*PR after 8 weeks of Osimertinib + BLU-667*



Piotrowska Z et al. Cancer Discovery 2018;8:1529-39

# Summary

- *RET* fusions represent a distinct, targetable molecular subset of lung cancer
- Activating *RET* alterations are found in a diverse spectrum of malignancies
- Previously available multi-kinase inhibitors targeting RET have been limited by modest anti-RET efficacy and substantial toxicities
- RET-selective TKIs (BLU-667, LOXO-292) are now available, with promising safety profile and preliminary efficacy across *RET*-altered solid tumors demonstrated in phase I studies
- Future studies are needed to characterize mechanisms of resistance to the RET TKIs, and to develop strategies for overcoming these mechanisms

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**Patients and Families**