## One tumour, many faces: Optimising testing, targeting and monitoring oncogene-addicted NSCLC beyond EGFR

# RET-fused NSCLC: State of the art treatment of advanced disease, including sanctuary sites

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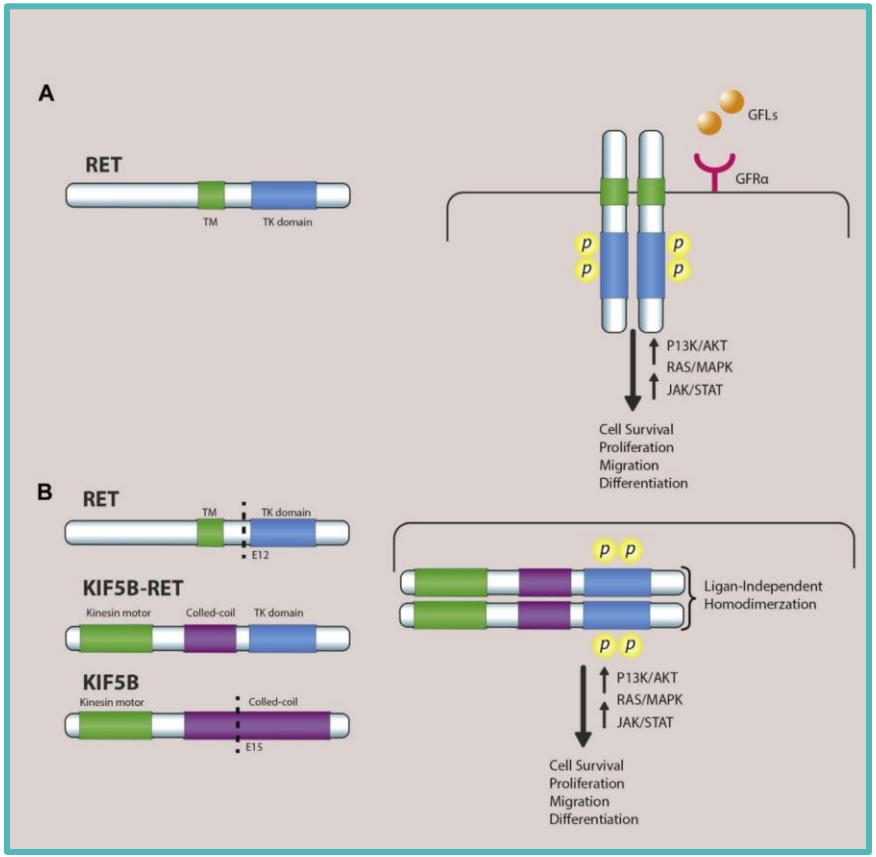
# Scenario in 2022


| EGFR | ALK | ROS1 | BRAF | RET | HER2 | EGFRex20 | MET ex 14 | NTRK | KRAS | CLIP1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | Alectinib | Crizotinib | Dabrafenib | Selpercatinib | Trastuzumab | Mobocertinib | Tepotenib | Larotrectinib | Sotorasib | Lorlatinib |
| Gefitinib | Crizotinib | Entrectinib | Trametinib | Pralsetinib | Deruxtecan | Amivantanab | Capmatinib | Entrectinib | Adagrasib | |
| Erlotinib | Brigatinib | Lorlatinib | | | | Poziotinib | | | | |
| Afatinib | Lorlatinib | Repotrectinib | | | | Mobocertinib | | | | |
| Patritumab | Ceritinib | | | | | | | | | |
| Deruxtecan | Ensartinib | | | | | | | | | |
| Amivantanab/Lazertinib | | | | | | | | | | |

# RET (REarranged during Transfection) gene

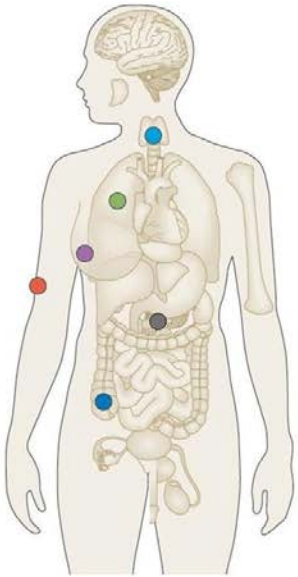



- Identified In 1985 as a novel transforming gene as result of transfection of the NIH 3T3 cell with high molecular weight DNA of a human T-cell lymphoma
- Maps on chromosome 10q11.2 and encodes a RTK consisting of three domains (extracellular, transmembrane domain and intracellular kinase)
- The primary RET ligands belong to the glial-derived neurotrophic factor (GDNF) family, including GDNF, artemin, neurturin, and persephin
- Ligand binding activates RET through the formation of homodimers and autophosphorylation of the kinase dom.
- Downstream pathways (RAS/MAPK/ERK, PI3K/AKT, and JAK/STAT) are associated with cellular proliferation, migration and differentiation
- RET is expressed in neurons, sympathetic and parasympathetic ganglia, thyroid C cells, adrenal medullary cells, urogenital tract cells, and testis germ cells
- Plays an important role in organogenesis and development of the enteric nervous system

Takahashi et al, Cell 1985; Ferrara R et al. J Thorac Oncol 2017

# RET activation in cancer

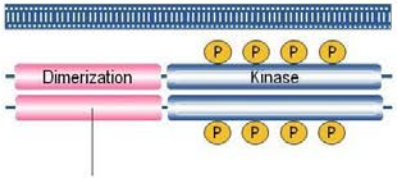
## *RET* fusions



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

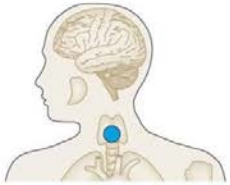
**Papillary and other thyroid cancers (10–20%)**

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



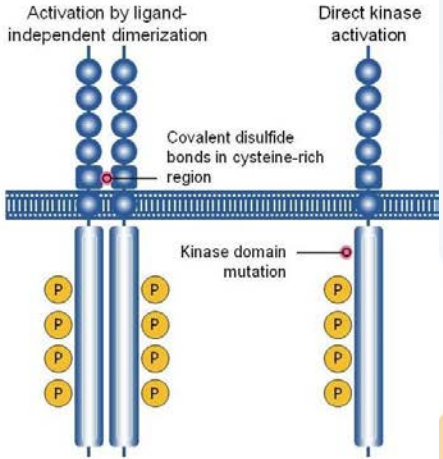

***KIF5B*** (most common in lung cancer)
***CCDC6* or *NCOA4*** (most common in thyroid cancer)

## *RET* mutations



**Medullary thyroid cancer**

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



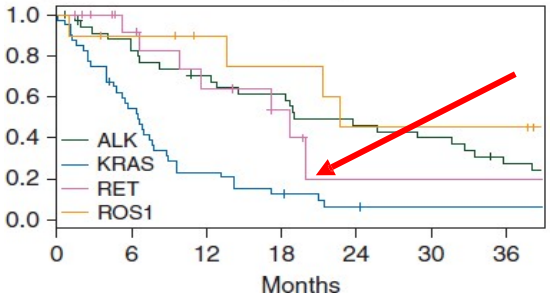

Common mutation: ***RET*** **M918T**

# RET+ NSCLC:
# Clinical and pathological characteristics

- Median age < 60 years
- Never smokers
- Women
- Often metastatic at diagnosis also with a small primary
- Frequent brain mets
- Adenocarcinoma
- Radiological presentation: GGO, pneumonitis, multiple bilateral micronodules, pleural effusions
- Chemo-sensitive (platinum-pemetrexed)
- Poorly responsive to immunotherapy

# RET+ NSCLC and chemotherapy

Progression free survival (PFS)

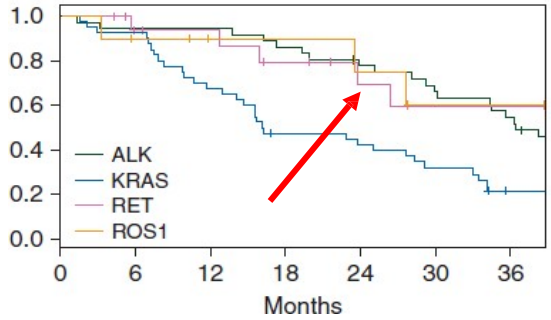



| | n | Median PFS | (95% CI) |
|---|---|---|---|
| *RET* | 18 | 19 mo | (12–NR) |
| *ROS1* | 10 | 23 mo | (14–NR) |
| *ALK* | 36 | 19 mo | (15–36) |
| *KRAS* | 40 | 6 mo | (5–9) |

| | |
|---|---|
| *KRAS* vs *ALK* | $P < 0.001$ |
| *KRAS* vs *ROS1* | $P = 0.002$ |
| *KRAS* vs *RET* | $P = 0.005$ |
| *ALK* vs *ROS1* vs *RET* | $P = 0.57$ |
| All | $P < 0.001$ |

NR: not reached

Overall survival




| | n | Median OS | (95% CI) |
|---|---|---|---|
| *RET* | 18 | NR | (24–NR) |
| *ROS1* | 10 | NR | (24–NR) |
| *ALK* | 36 | 37 mo | (30–63) |
| *KRAS* | 40 | 16 mo | (14–33) |

| | |
|---|---|
| *KRAS* vs *ALK* | $P < 0.001$ |
| *KRAS* vs *ROS1* | $P = 0.08$ |
| *KRAS* vs *RET* | $P = 0.004$ |
| *ALK* vs *ROS1* vs *RET* | $P = 0.43$ |
| All | $P < 0.001$ |

NR: not reached

| Patients | ORR (PR) | DCR (PR + SD) |
|---|---|---|
| *RET*-rearranged | 45% ($n = 5/11$) | 91% ($n = 10/11$) |
| *ROS1*-rearranged | 78% ($n = 7/9$) | 90% ($n = 8/9$) |
| *ALK*-rearranged | 50% ($n = 14/28$) | 93% ($n = 26/28$) |
| *KRAS*-mutant | 26% ($n = 9/35$) | 86% ($n = 30/35$) |
| *P* value | 0.02 | 0.91 |

The overall response rate (ORR) and disease control rate (DCR) with pemetrexed-based systemic therapy in 83 patients with evaluable disease are summarized. These outcomes were compared between patient groups, with the *P* values reflecting an overall comparison of the four molecular subgroups listed. Only partial responses (PR) and no complete responses were observed.
SD, stable disease.

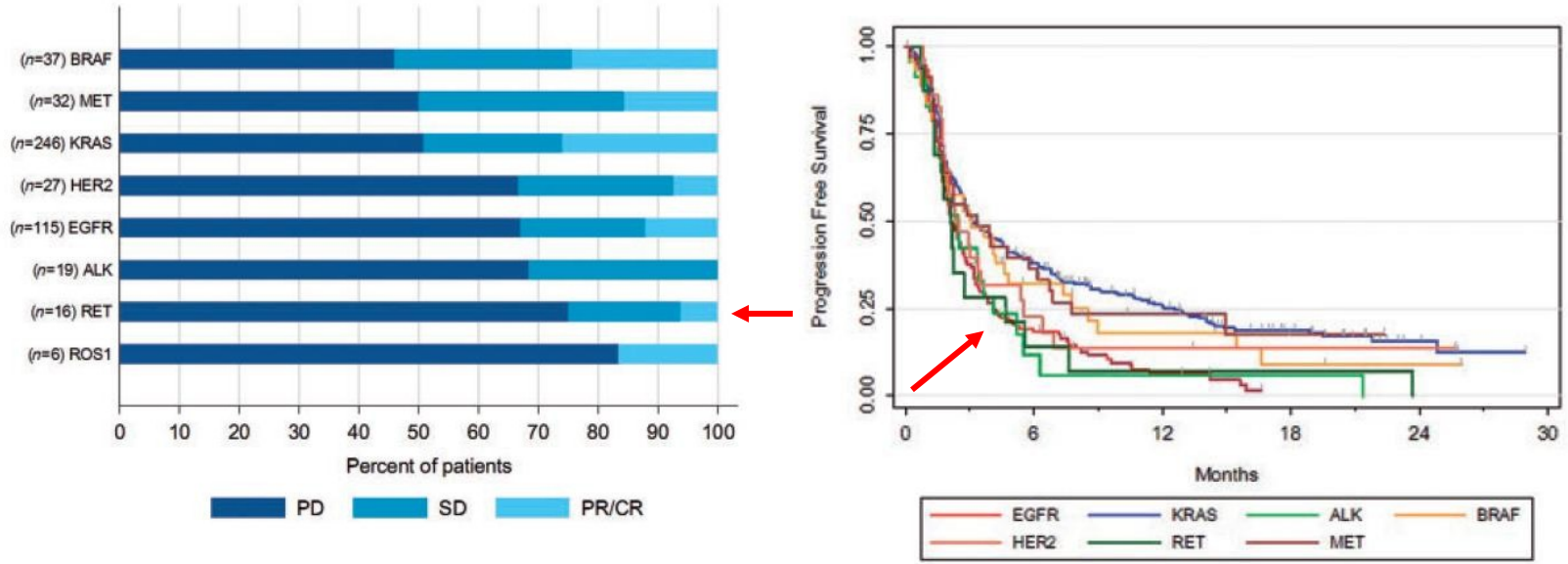
Drilon, Ann Oncol 2016

**Table 4.** Clinical Outcomes With First-Line Chemotherapy

| Outcome | All Chemotherapy Agents (n = 108) | Platinum Doublet (n = 84) | Platinum + Pemetrexed (n = 66) |
|---|---|---|---|
| Best response (95% CI) | 52% (39.8 to 64.4) 36 of 69 evaluable | 51% (38.1 to 63.4) 33 of 65 evaluable | 49% (35.4 to 62.9) 27 of 55 evaluable |
| Disease control rate (95% CI) | 75% (63.5 to 84.9) 52 of 69 evaluable | 75% (63.1 to 85.2) 49 of 65 evaluable | 75% (61.0 to 85.3) 41 of 55 evaluable |
| Median PFS (95% CI) | 6.6 months (5.1 to 9.3) | 7.8 months (5.3 to 10.2 months) | 6.4 months (4.3 to 8.8 months) |
| Median OS (95% CI) | 23.6 months (13.6 to 30.8) | 24.8 months (13.6 to 32.3 months) | 23.6 months (13.4 to 33.2 months) |

NOTE. The best response, disease control rate, median PFS, and median OS of patients with advanced non–small-cell lung cancer and first-line chemotherapy are summarized.
Abbreviations: OS, overall survival; PFS, progression-free survival.

# Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry




Mazieres, Ann Oncol'19

# Multi-TKIs in RET+ NSCLC

| Drug | Phase | n. | Screening assays | ORR (%) | PFS (months) | mOS/1-year OS |
|---|---|---|---|---|---|---|
| Vandetanib[1,2,3] | II | 19 | RT-PCR/FISH | 47 | 4.7 | 11.1 mo/47% |
| | II | 18 | RT-PCR/FISH | 18 | 4.5 | 11.6 mo/33% |
| | Registry | 11 | RT-PCR/FISH/NGS# | 18 | 2.9 | 10.2/NA |
| Cabozantinib[3,4] | II | 26 | FISH/NGS | 28 | 5.5 | 9.9 mo/38% |
| | Registry | 31 | # | 33 | 3.6 | 4.9 mo/NA |
| Lenvatinib[3,5] | II | 25 | FISH or RT-PCR/NGS | 16 | 7.3 | NR |
| | Registry | 2 | # | 50 | NA | NA |
| Sunitinib[3] | Registry | 10 | # | 22 | 2.2 | 6.8 mo/NA |

[1] Yoh K, Lancet Respir Med 2017; [2] Lee SH, Ann Oncol 2017; [3] Gautschi O, J Clin Oncol 2017; [4] Drilon A, Lancet Oncol 2016; [5] Hida T, Lung Cancer 2019;

# NEW RET Tyrosine Kinase Inhibitors

- Pralsetinib (Blu-667)
- Selpercatinib (Loxo 292)

# Pralsetinib versus Selpercatinib in NSCLC cell lines

## Selectivity for VEGFR-2

*Cellular activity against p-VEGFR-2 ($IC_{50}$, nM)*

| Anti-target | p-VEGFR-2 |
|---|---|
| Pralsetinib | 65 nM |
| Loxo-292 | 54 nM |

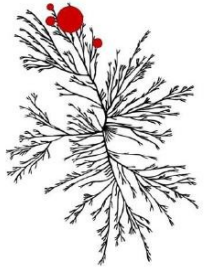
## Inhibition of gatekeeper mutations predicted to drive resistance

*Cellular anti-proliferative activity against KIF5B-RET the most common RET fusion in NSCLC [IC50, nM (fold difference)]*

| RET fusion | KIF5B-RET | KIF5B-RET V804L | KIF5B-RET V804M | KIF5B-RET V804E |
|---|---|---|---|---|
| Pralsetinib | 10.1 nM (1x) | 8.1 nM (0.8x) | 14.1 nM (1.4x) | 8.1 nM (0.8x) |
| Loxo-292 | 10.5 nM (1x) | 28.4 nM (2.7x) | 78.8 nM (7.5x) | 126 nM (12x) |

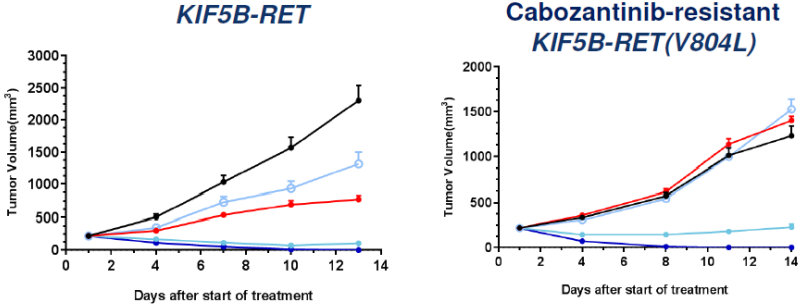
# BLU-667: activity and tolerability in RET+ NSCLC

**BLU-667: High kinome selectivity for RET[a]**



BLU-667 vs. pharmacologically relevant kinases:

- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

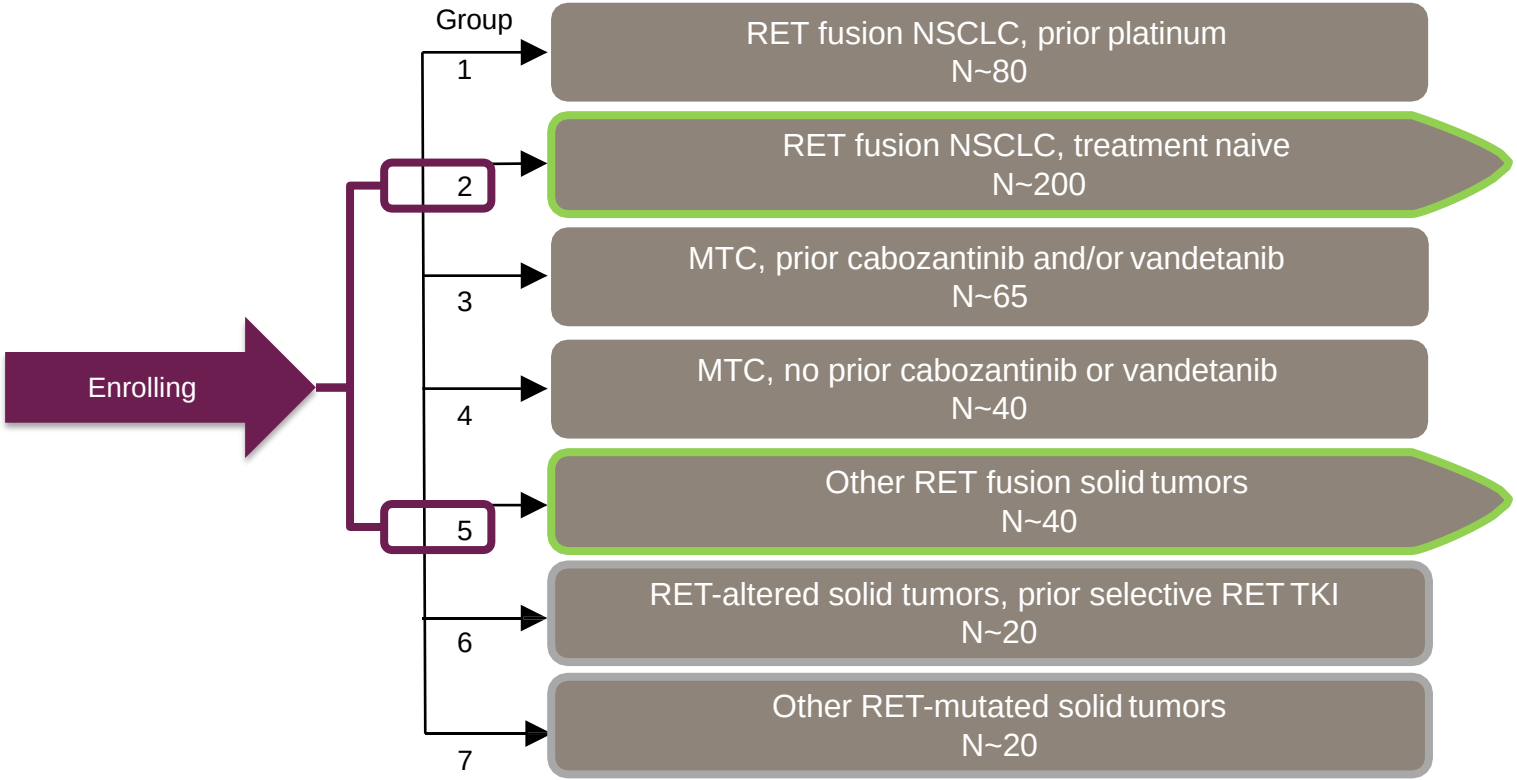



*In vivo* models of implanted, engineered Ba/F3 cells[1]

| | Pralsetinib $IC_{50}$ | Cabozantinib $IC_{50}$ | Vandetanib $IC_{50}$ |
|---|---|---|---|
| **Wild-type RET** | 0.4 | 11 | 4 |
| **RET V804L** Gatekeeper resistance | 0.3 | 45 | 3597 |
| **RET V804M** Gatekeeper resistance | 0.4 | 162 | 726 |
| **RET M918T Mutation** | 0.4 | 8 | 7 |
| **CCDC6-RET Fusion** | 0.4 | 34 | 20 |
| **VEGFR2** Anti-target | 35 | 2 | 4 |

Subbiah V et al, Cancer Discov 2018

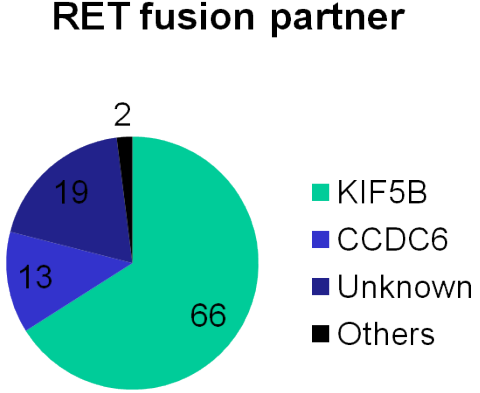
# ARROW study progress
## Phase 2, dose-expansion, N~465, ongoing




Gainor J, Lancet Oncology 2021

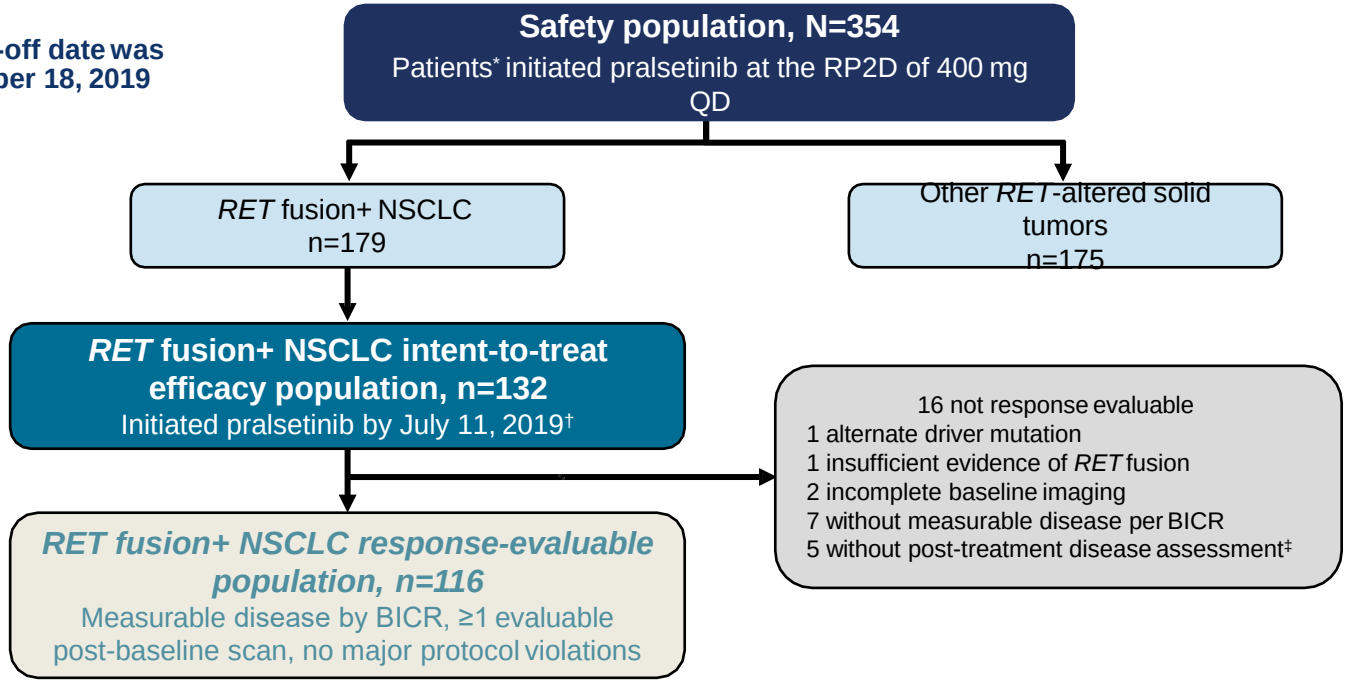
# Patient characteristics (NSCLC cohort)

| Characteristic | RET-Fusion+ Advanced NSCLC 400 mg QD Starting Dose | |
|---|---|---|
| | All (N=120) | Prior Platinum (N=91) |
| Age (years), median (range) | 60 (28-87) | 60 (28-85) |
| Male, n (%) | 59 (49) | 45 (49) |
| ECOG PS, n (%) | | |
| 0 | 46 (38) | 33 (36) |
| 1-2 | 74 (62) | 58 (64) |
| Brain metastases, n (%) | 48 (40) | 36 (40) |
| Prior systemic regimens, median (range) | 2 (0-11) | 2 (1-11) |
| Any prior anticancer treatment | 101 (84) | 91 (100) |
| Chemotherapy, n (%) | 92 (77) | 91(100) |
| PD-1 or PD-L1 inhibitor, n (%) | 47 (39) | 41 (45) |
| Chemotherapy + PD-(L)1 combination, n (%) | 41 (34) | 41 (45) |
| Multikinase inhibitor, n (%) | 21 (18) | 20 (22) |
| Smoking history[a] | | |
| Current/Prior | 41 (34) | 33 (36) |
| Never | 78 (65) | 57 (63) |
| Histology | | |
| Adenocarcinoma | 114 (95) | 87 (96) |
| Other | 6 (5) | 4 (4) |



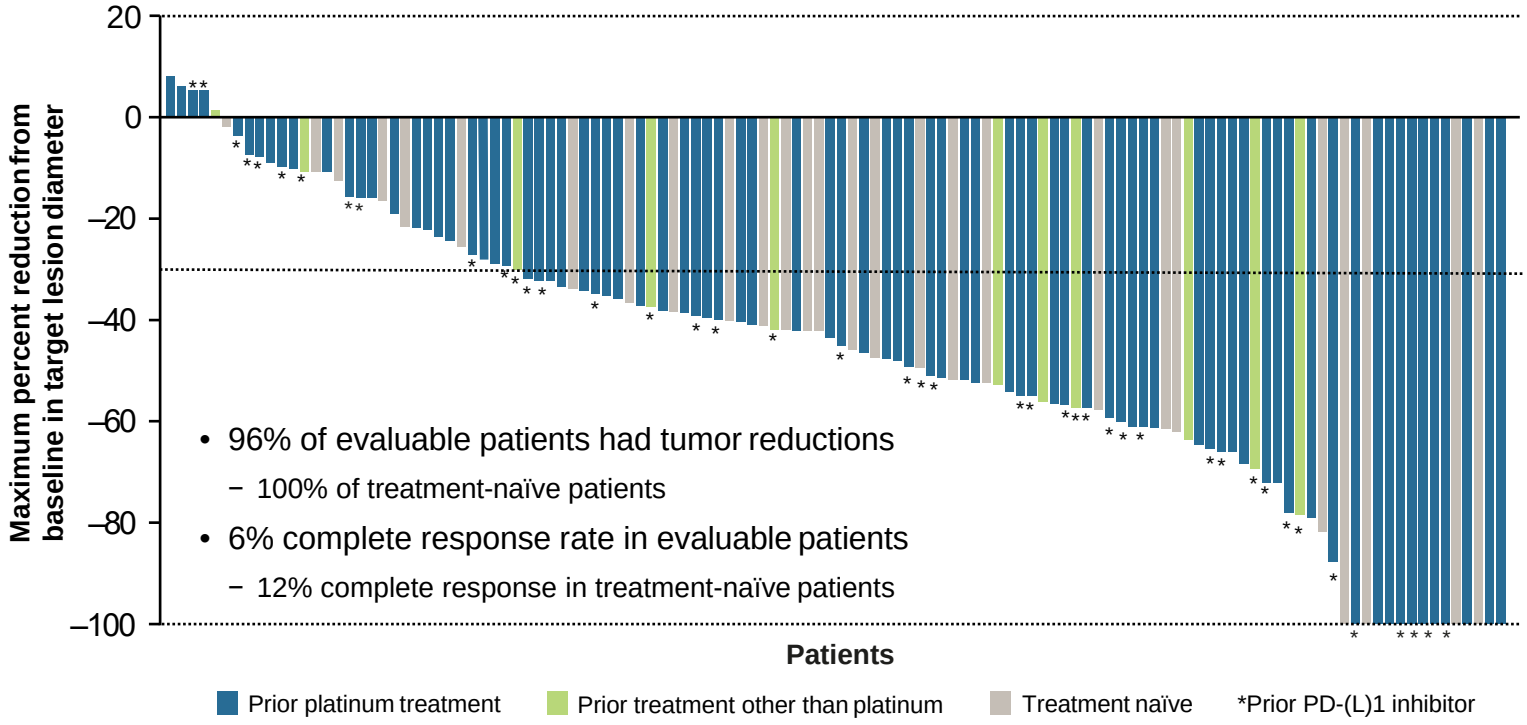
# ARROW: Patient disposition/analysis population

**Data cut-off date was November 18, 2019**




Gainor J, Lancet Oncology 2021

# ARROW: Tumor shrinkage (Blinded Independent Centralized Review) RET Fusion Positive NSCLC (400mg starting dose)




Gainor J, Lancet Oncology 2021

# Safety and efficacy of pralsetinib in NSCLC: Update Arrow

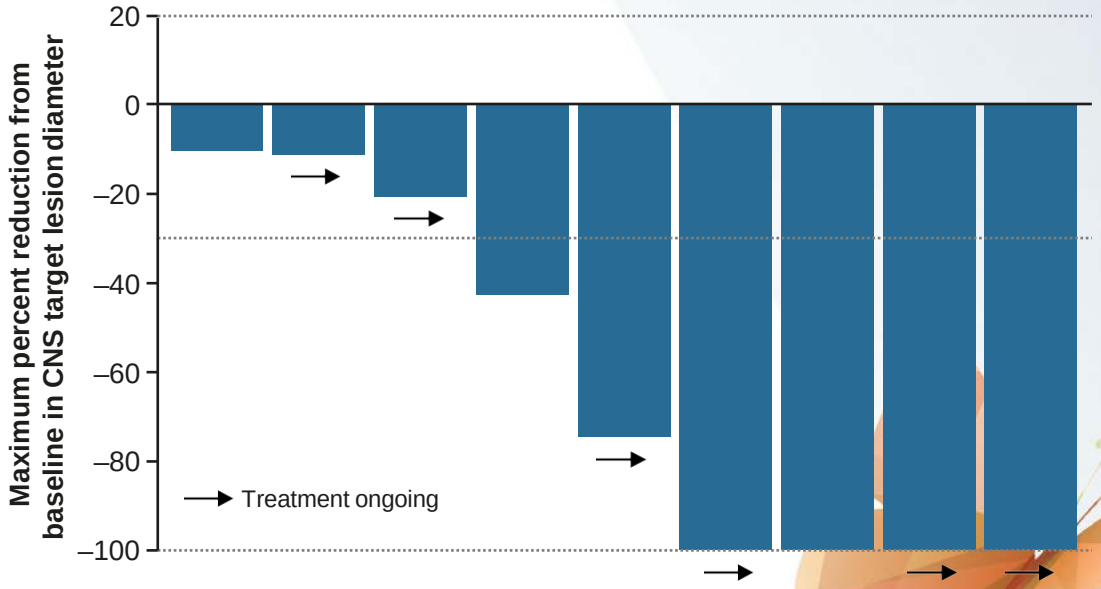
## Key results

| | RET fusion+ NSCLC (n=216) | Treatment naïve | | | Prior treatment | |
|---|---|---|---|---|---|---|
| | | All (n=68) | Pre-eligibility revision (n=43) | Post eligibility revision (n=25) | Prior platinum (n=126) | Prior non-platinum (n=22) |
| ORR, % (95%CI) | 69 (62, 75) | 79 (68, 88) | 74 (59, 87) | 88 (69, 98) | 62 (53, 70) | 73 (50, 89) |
| BOR, n (%) | | | | | | |
| CR | 9 (4) | 4 (6) | 4 (9) | 0 (0) | 5 (4) | 0 (0) |
| PR | 139 (64) | 50 (74) | 28 (65) | 22 (88) | 73 (58) | 16 (73) |
| SD | 50 (23) | 9 (13) | 7 (16) | 2 (8) | 37 (29) | 4 (18) |
| PD | 10 (5) | 3 (4) | 3 (7) | 0 (0) | 5 (4) | 2 (9) |
| NE | 8 (4) | 2 (3) | 1 (2) | 1 (4) | 6 (5) | 0 (0) |
| DCR, % (95%CI) | 92 (87, 95) | 93 (84, 98) | 91 (78, 97) | 96 (80, 100) | 91 (85, 96) | 91 (71, 99) |
| CBR, % (95%CI) | 77 (71, 82) | 82 (71, 91) | 79 (64, 90) | 88 (69, 98) | 74 (65, 81) | 77 (55, 92) |
| Median DoR, months (95%CI) | 22.3 (15.1, NR) | NR (9.0, NR) | 11.0 (7.4, NR) | NR (NR, NR) | 22.3 (15.1, NR) | NR (9.2, NR) |
| mPFS, months (95%CI) | 16.4 (11.0, 24.1) n=233 | 13.0 (9.1, NR) n=75 | 10.9 (7.7, NR) n=47 | NR (NR, NR) n=28 | 16.5 (10.5, 24.1) n=136 | 12.8 (9.1, NR) n=22 |

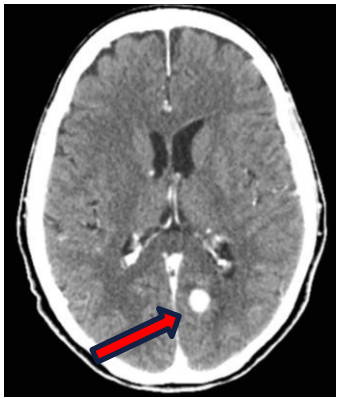
Curigliano G, et al. J Clin Oncol 2021;39(suppl):Abstr 9089

# ARROW: CNS activity (Blinded Independent Centralized Review)
# RET Fusion Positive NSCLC (400mg starting dose)

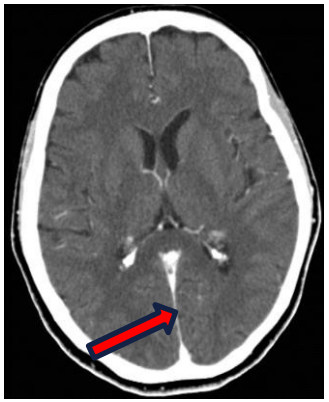
- Intracranial overall response rate in 9 patients with measurable CNS metastases at baseline was 56%
- Three patients (33%) with intracranial complete response



# ARROW: CNS activity (Blinded Independent Centralized Review)
# RET Fusion Positive NSCLC (400mg starting dose)



Baseline



After 8 months

- 71 year-old female previous smoker with *RET-CCDC6* fusion-positive metastatic NSCLC
- No response and disease progression at 6 months on prior pembrolizumab monotherapy
- Metastatic disease in brain, bone, adrenal gland, and lymph nodes at study entry
- Complete resolution of a 12.6 mm brain target lesion observed at 1.6 months on pralsetinib
- As of May 1, 2020, continues pralsetinib for 10+ months with ongoing overall partial response

Courtesy of G. Curigliano

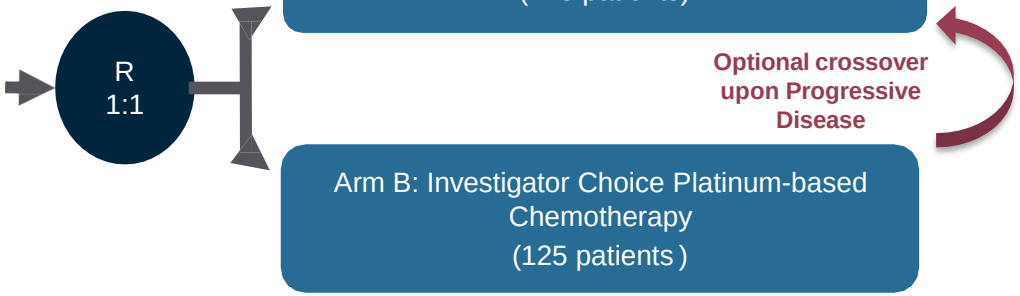
# ARROW: Safety
## All ARROW patients (400 mg starting dose)

- Pralsetinib 400 mg QD had a treatment duration between 0.1- 22.3 months and median (range) dose intensity of 92% (18–100)
- Only 4% of patients discontinued due to treatment-related adverse events

| Treatment-related adverse events in ≥10% of patients | All patients (N=354)* | |
|---|---|---|
| **AE preferred term** | **Any grade** | **Grade ≥3** |
| AST increased | 31 | 2 |
| Anemia | 22 | 8 |
| ALT increased | 21 | 1 |
| Constipation | 21 | 1 |
| **Hypertension** | **20** | **10** |
| **Neutropenia** | **19** | **10** |
| Diarrhea | 14 | 1 |
| White blood cell count decreased | 14 | 3 |
| Dysgeusia | 13 | 0 |
| Blood creatinine increased | 12 | 0 |
| Fatigue | 12 | 1 |
| Neutrophil count decreased | 12 | 4 |
| Dry mouth | 11 | 0 |
| Hyperphosphatemia | 11 | <1 |
| Asthenia | 10 | 1 |

# AcceleRET Phase 3 Study Design

- RET-fusion positive
- Metastatic NSCLC
- No prior systemic treatment
- Open Label
- N=250



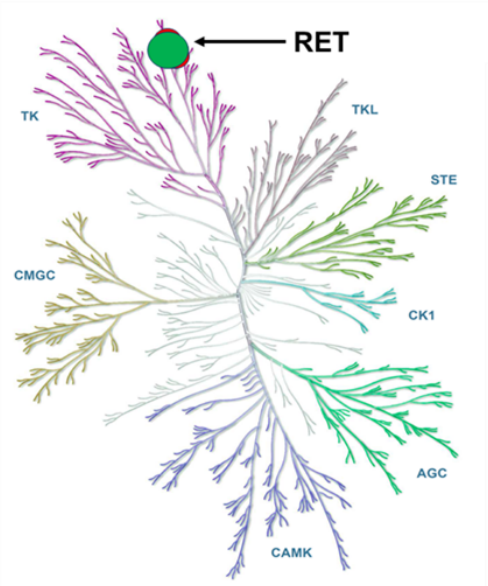

**Primary Endpoint** : Progression Free Survival (PFS)
**Key Secondary Endpoints** : Overall Response Rate (ORR), CNS ORR, Overall Survival (OS), and Safety

- Investigator's choice includes:
  - (1) **Non-Squamous histology:** Carboplatin or cisplatin / pemetrexed (with opt. pemetrexed maintenance)
    - Investigator's choice as above with pembrolizumab
  - (2) **Squamous histology:** carboplatin or cisplatin / gemcitabine

# Selpercatinib* (LOXO-292) is a Potent and Selective RET Inhibitor

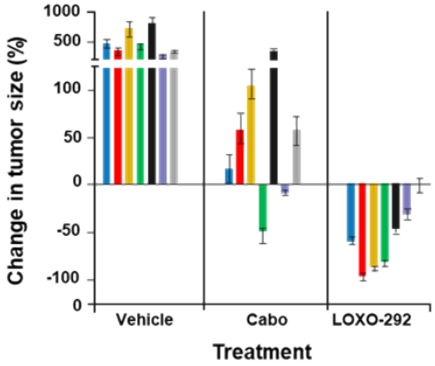
## Kinome selectivity

Highly selective for RET




## Xenograft models

Multiple fusions/mutations/histologies

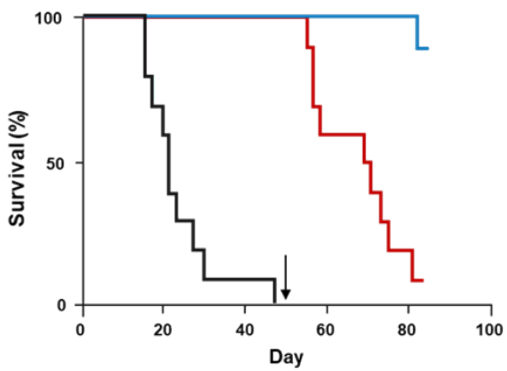



Tumor models

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

## Orthotopic brain model

*CCDC6-RET* orthotopic brain PDX



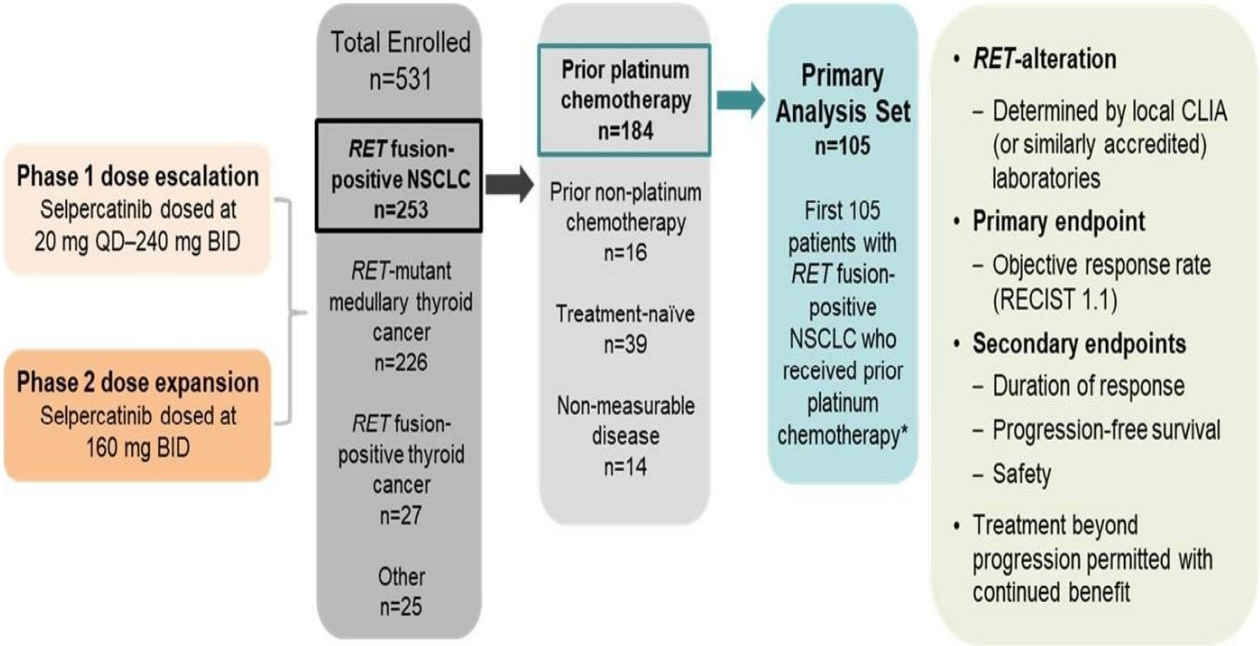

Treatments

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

Subbiah V, et al. *Ann Oncol* 2018;29:1869-1876. *PRN, pending USAN approval.

Subbiah V et al, Ann Oncol 2018

# LIBRETTO-001: Selpercatinib in RET-altered cancers

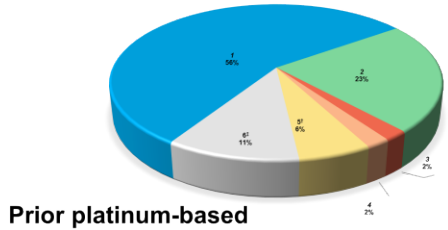



Drilon A et al, NEJM 2020

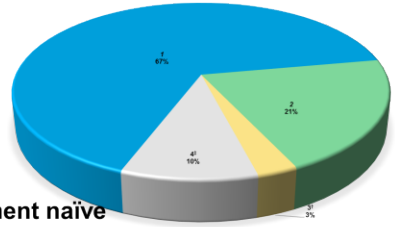
# Baseline Patient Characteristics

| Characteristic (%, unless otherwise stated) | Prior Platinum-based Chemotherapy (n=105) | Treatment Naïve (n=39) |
|---|---|---|
| **Age, median (range), years** | 61 (23–81) | 61 (23–86) |
| **Sex** | | |
| Female | 62 (59) | 22 (56) |
| Male | 43 (41) | 17 (44) |
| **Race** | | |
| White | 55 (52) | 28 (72) |
| Asian | 40 (38) | 7 (18) |
| Black or African American | 5 (5) | 3 (8) |
| Other | 3 (3) | 1 (3) |
| Missing | 2 (2) | 0 |
| **Smoking status** | | |
| Never smoker | 75 (71) | 29 (74) |
| Former smoker | 29 (28) | 9 (23) |
| Current smoker | 1 (1) | 1 (3) |
| **ECOG performance status** | | |
| 0 | 31 (30) | 18 (46) |
| 1 | 72 (69) | 21 (54) |
| 2 | 2 (2) | 0 |
| **NSCLC histological subtype** | | |
| Adenocarcinoma | 90 (86) | 34 (87) |
| Large cell neuroendocrine carcinoma | 2 (2) | 0 |
| Squamous cell carcinoma | 1 (1) | 0 |
| Not otherwise specified | 12 (11) | 5 (13) |
| **Prior systemic regimens, median (range)** | 3 (1–15) | 0 |
| **Prior platinum-based chemotherapy** | 105 (100) | – |
| **Prior anti-PD-1/PD-L1 therapy** | 58 (55) | – |
| **Prior multitargeted kinase inhibitor*** | 50 (48) | |
| 1 | 37 (74) | – |
| ≥2 | 13 (26) | |
| **Brain metastases** | 38 (36) | 7 (18) |
| **Measurable disease** | 104 (99) | 39 (100) |

***RET* Gene Fusion**

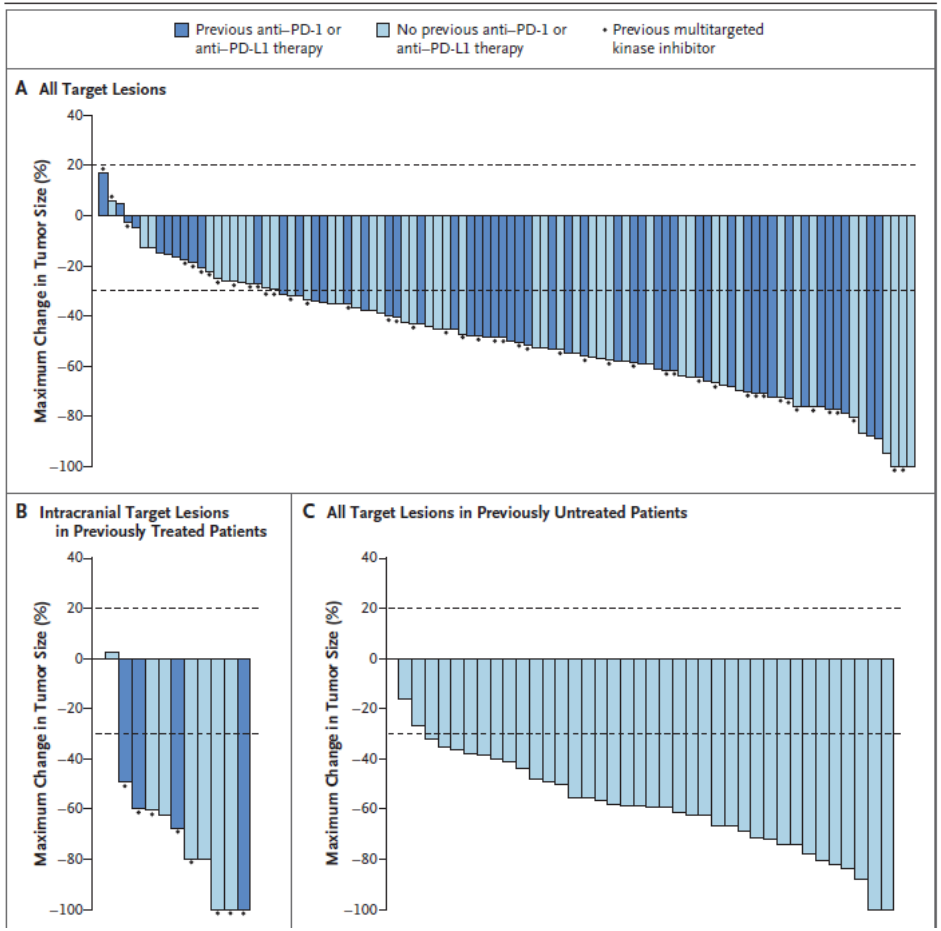



**Prior platinum-based chemotherapy**




**Treatment naïve**

*Multitargeted kinase inhibitors (MKIs) administered included cabozantinib (16 patients), vandetanib (8), lenvatinib (7), and others (36). Patients may have received more than one MKI. †Other fusions identified in single tumors included *CLIP1-RET*, *RBPMS-RET* and *DOCK1-RET*, *ARHGAP12-RET, CCDC88C-RET, TRIM24-RET, PRKAR1A-RET* and *ERC1-RET*. ‡*RET* fusion indicated by molecular analysis but fusion partner not identified. Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating greater disability. Total % may be different than the sum of the individual components due to rounding. Abbreviations: NSCLC, non-small-cell lung cancer.




The NEW ENGLAND JOURNAL of MEDICINE

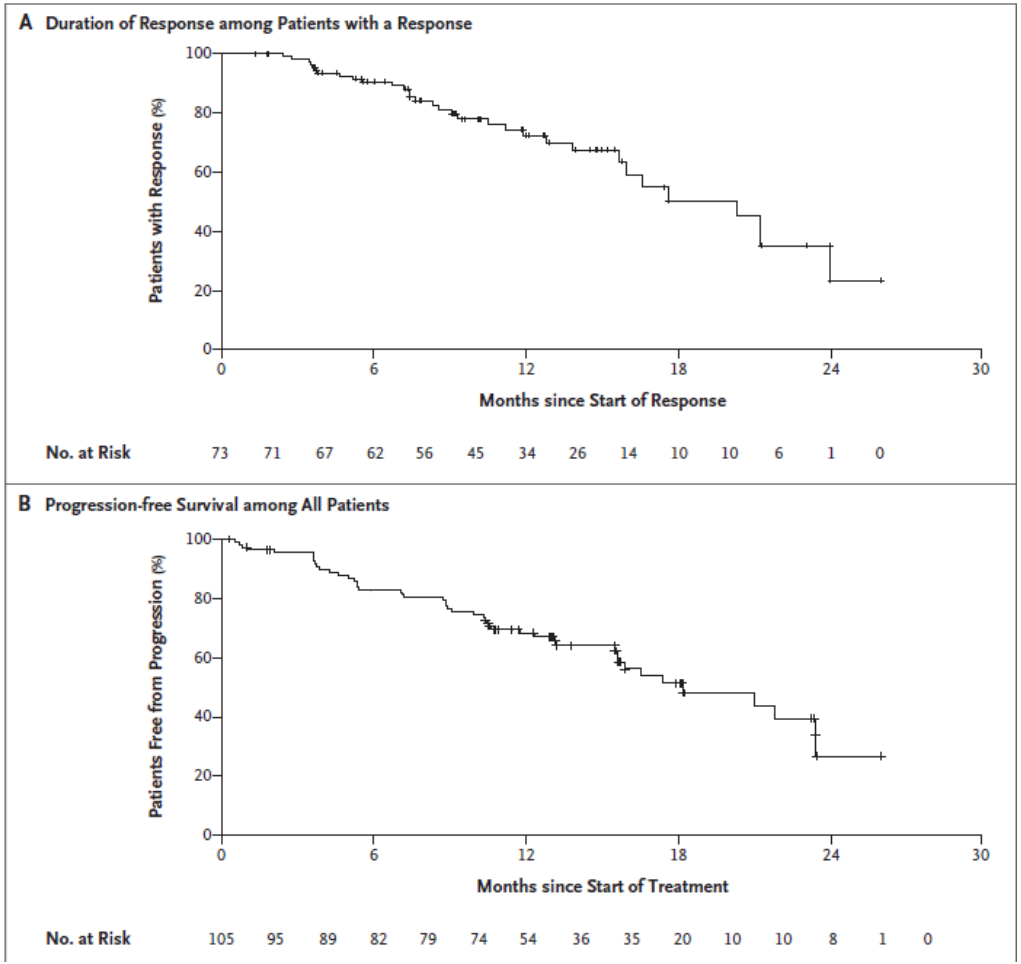
ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

# Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

| | Pre-treated # 105 | Untreated # 39 |
|---|---|---|
| OR # (%) | 67 (64) | 33 (85) |
| mDOR (mo) | 17.5 | NE |

| | |
|---|---|
| Time to OR (mo) | 1.8 |
| CNS OR% (#11) | 91 |

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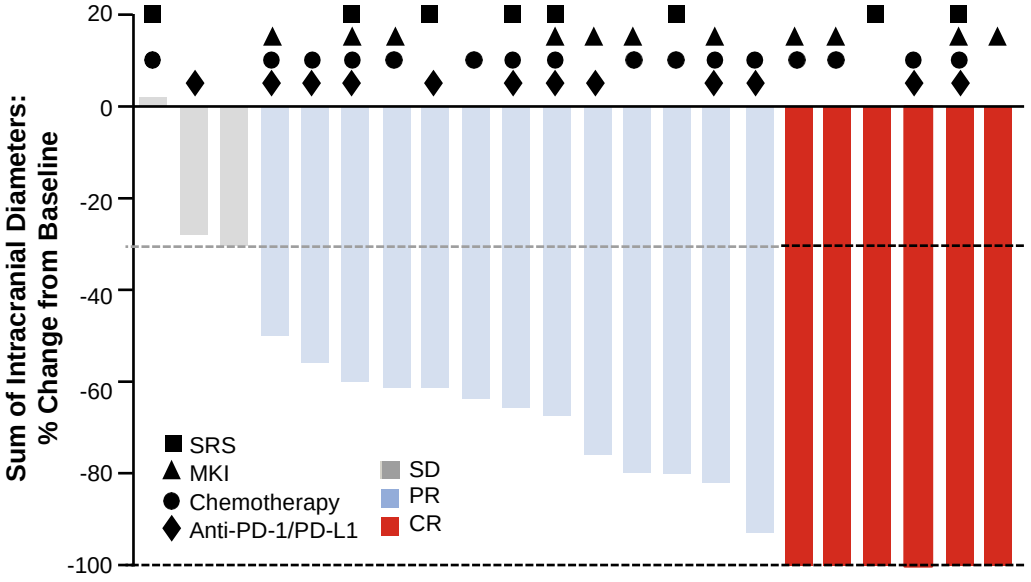
| | All patients # 105 |
|---|---|
| 1Y PFS | 66 % |
| mPFS (mo) | 16.5 |

# Intracranial Responses were Observed Across a Variety of Prior Treatment Histories

| Measurable baseline intracranial metastatic disease (n=22) | |
|---|---|
| Intracranial response | |
| **ORR (95% CI), %** | **82 (60-95)** |
| Best intracranial response, n (%) | |
| CR | 5 (23) |
| PR | 13 (59) |
| SD | 4 (18) |
| PD | 0 |
| Intracranial DCR, n (%) | 22 (100) |




Subbiah V, et al. Clin Cancer Res 2021; 27(15):4160-4167. Intracranial Efficacy of Selpercatinib in RET Fusion-Positive Non-Small Cell Lung Cancers on the LIBRETTO-001 Trial.

# Intracranial Responses Occurred Regardless of Prior Cranial Radiotherapy in Patients with Measurable Disease

| | Measurable baseline intracranial metastatic disease (n=22) | | |
|---|---|---|---|
| | All patients (n=22) | Patients without prior intracranial radiotherapy (n=14) | Patients with prior intracranial radiotherapy (n=8)[a] |
| Intracranial response | | | |
| ORR, n (%) | 18 (82) | 12 (86) | 6 (75) |
| 95% CI | 60-95 | 57-98 | 35-97 |
| Best intracranial response, n (%) | | | |
| CR | 5 (23) | 4 (29) | 1 (13) |
| PR | 13 (59) | 8 (57) | 5 (63) |
| SD | 4 (18) | 2 (14) | 2 (25) |
| PD | 0 | 0 | 0 |

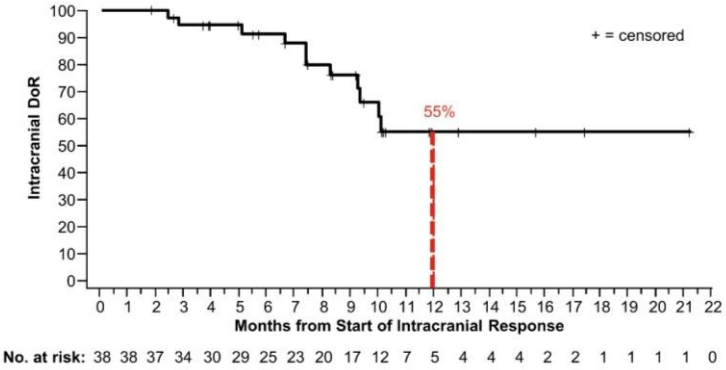
- Intracranial responses, including CRs, occurred regardless of prior history of cranial radiotherapy in patients with measurable baseline intracranial metastatic disease

Subbiah V, et al. Clin Cancer Res 2021; 27(15):4160-4167.

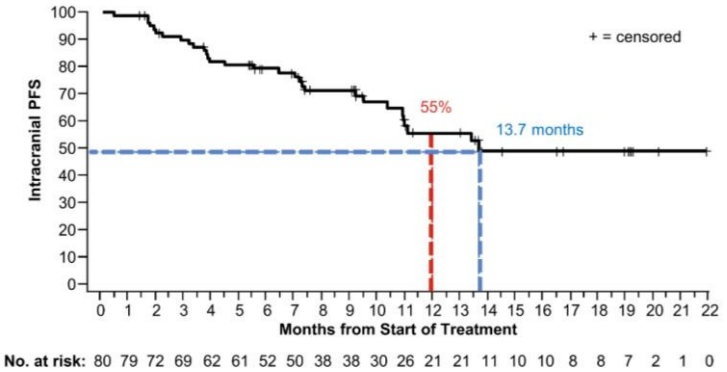
# Intracranial Duration of Response and PFS

- There were a total of 38 intracranial responders
  - 18 patients with measurable baseline intracranial metastatic disease who achieved CR or PR
  - 20 patients with nonmeasurable baseline intracranial metastatic disease who achieved CR
- At 1-year, 55% of intracranial responses were ongoing
- The median PFS is immature due to limited follow-up time and limited number of events

| Intracranial responders (n=38)[a] | |
|---|---|
| **Intracranial DoR** | |
| Median follow-up, mo (IQR) | 9.5 (5.7-12.0) |
| **Median DoR, mo (95% CI)** | **NE (9.3-NE)** |
| **12-month DoR rate, % (95% CI)** | **55 (32-73)** |




| All patients with baseline intracranial metastatic disease (n=80) | |
|---|---|
| **Intracranial PFS** | |
| Median follow-up, mo (IQR) | 11.0 (7.4-16.5) |
| **Median PFS, mo (95% CI)** | **13.7 (10.9-NE)** |
| **12-month PFS rate, % (95% CI)** | **55 (41-67)** |



# Safety profile

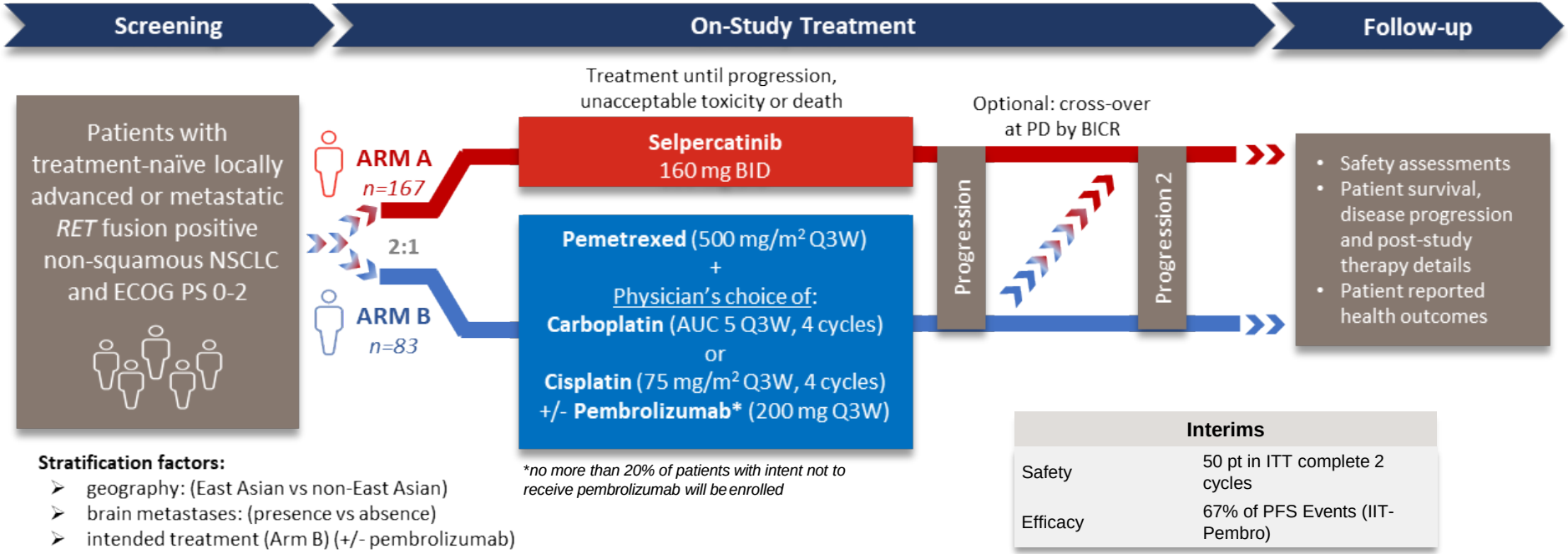
+ Hypersensitivity reactions 7%
Mc Coach, JTO 2021

| | 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% |

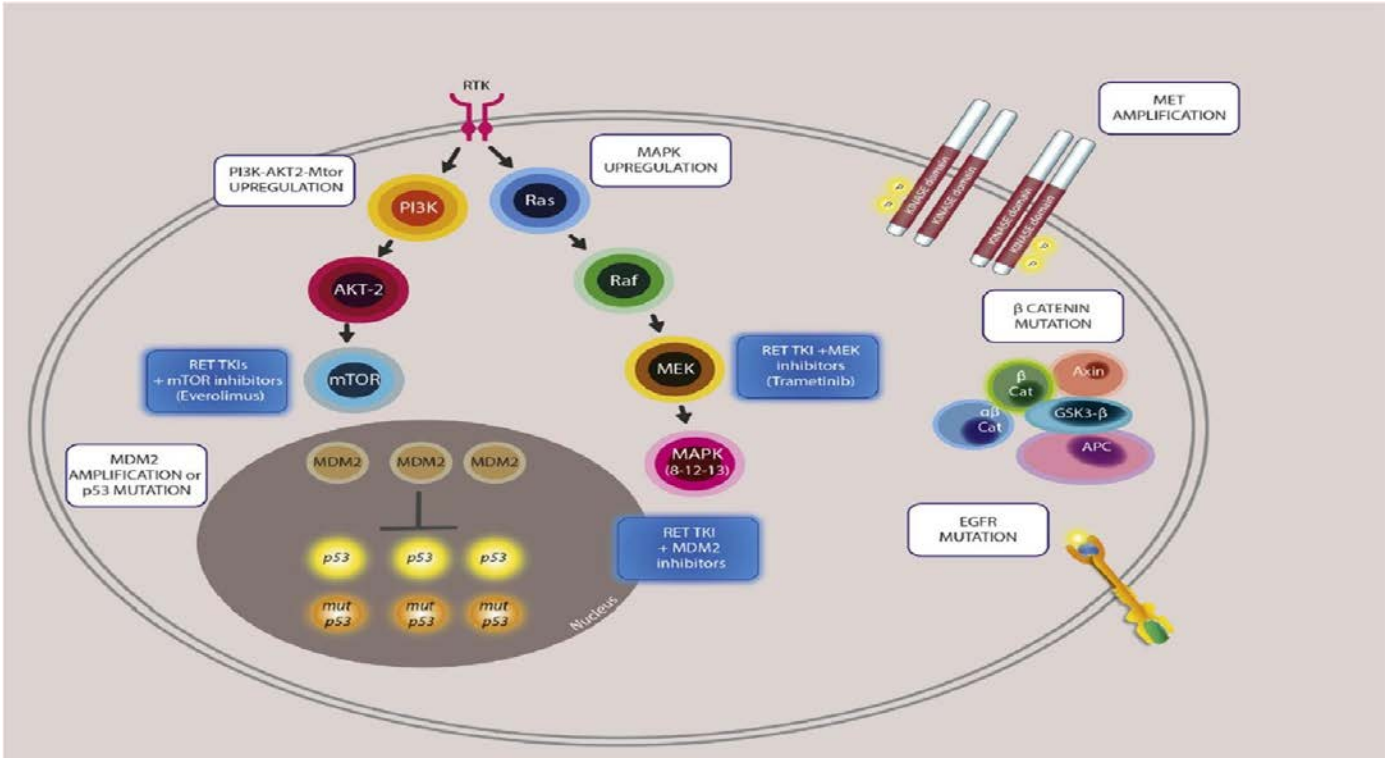
9 patients (1.7%) discontinued due to treatment-related AEs

Drilon A et al, WCLC 2019

# LIBRETTO 431 - Study Design



# Escape mechanisms to rearranged during transfection proto-oncogene (RET) inhibition




elcc European Lung Cancer Congress

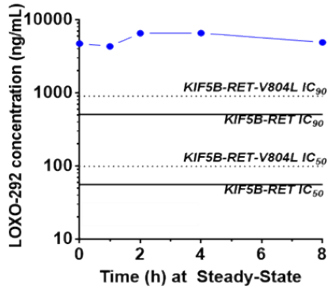
# Overcoming Acquired RET Gatekeeper Resistance

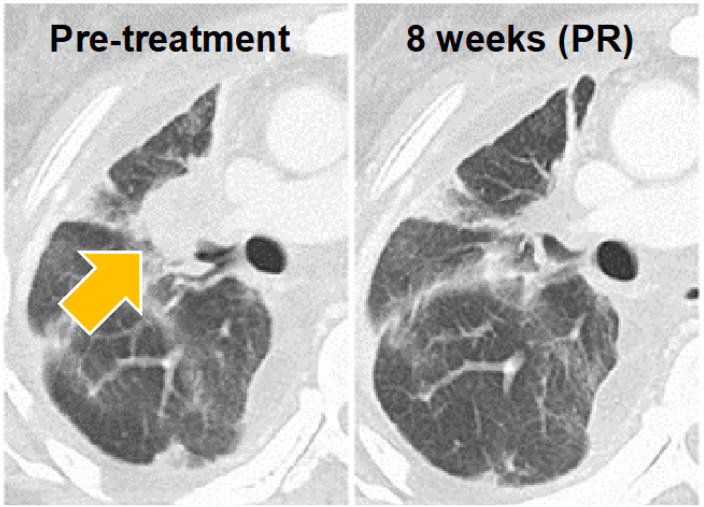
## Selpercatinib Overcomes Acquired Gatekeeper Resistance

42-year-old woman with *KIF5B-RET* fusion-positive NSCLC

- 15 prior systemic therapy regimens
  - chemotherapy, immunotherapy, and investigational kinase inhibitors
- Acquired **RET V804L gatekeeper mutation** post-vandetanib therapy

Initiated selpercatinib at 160 mg BID




Decreased shortness of breath
Confirmed PR by RECIST 1.1
Remains on treatment at 11 months

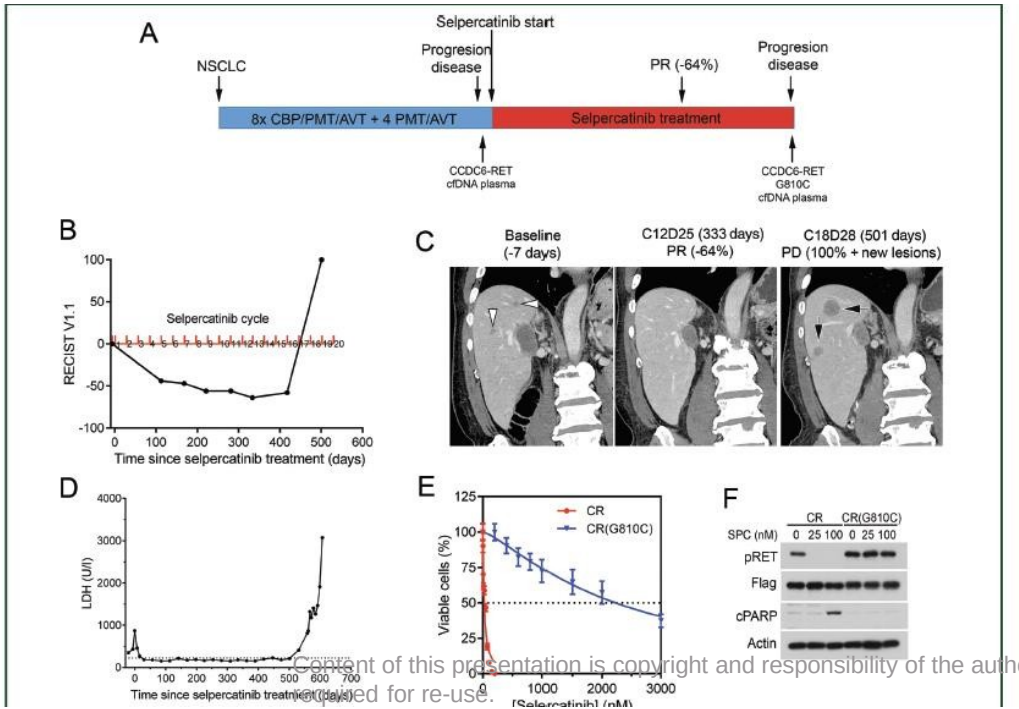
Data cut-off: June 17th, 2019; Wirth et al, JCO Precision Oncology, In Press. Images courtesy of K. Goto.

ORIGINAL ARTICLE

# Structural basis of acquired resistance to selpercatinib and pralsetinib mediated by non-gatekeeper RET mutations

V. Subbiah[1*†], T. Shen[2,3†], S. S. Terzyan[4,5†], X. Liu[2,3†], X. Hu[2,3], K. P. Patel[6], M. Hu[7], M. Cabanillas[7], A. Behrang[8], F. Meric-Bernstam[1], P. T. T. Vo[2], B. H. M. Mooers[2,4,5*] & J. Wu[2,3*]

[1]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Center, Houston; [2]Peggy and Charles Stephenson Cancer Center; Departments of [3]Pathology; [4]Biochemistry and Molecular Biology; and [5]Laboratory of Biomolecular Structure and Function, University of Oklahoma Health Sciences Center, Oklahoma City; [6]Molecular Diagnostics Laboratory; [7]Endocrine and Neoplasia; and [8]Musculoskeletal Imaging, Division of Diagnostic Imaging, the University of Texas MD Anderson Cancer Center, Houston, USA



# Conclusions

- RET fusions are driver alterations in 1-3% NSCLC (mutations are in thyroid ca)
- More frequent in non smokers and with younger age
- Poorly responsive to immunotherapy
- Selpercatinib and Pralsetinib are RET TKIs with remarkable and long lasting activity
- Demonstrated anti-cranial activity
- Toxicity is mild (of note hypertension and hypersensitivity reactions)
- Mechanisms of resistance are almost unknown (gatekeeper and non gatekeeper)

**TEST TEST TEST**