

Tumor Agnostics in Endocrine Cancers

Vivek Subbiah, MD

**Associate Professor, Department of Investigational Cancer Therapeutics,
Division of Cancer Medicine**

Executive Director, Medical Oncology Research, MD Anderson Cancer Network®

Center Medical Director, Clinical Center For Targeted Therapy

Associate Professor, Division of Pediatrics

The University of Texas MD Anderson Cancer Center

DISCLOSURE INFORMATION

VIVEK SUBBIAH

Vivek Subbiah receives research funding for clinical trials from Novartis, Bayer, GlaxoSmithKline, Nanocarrier, Vegenics, Celgene, Northwest Biotherapeutics, Berghealth, Incyte, Fujifilm, Pharmamar, D3, Pfizer, Multivir, Amgen, Abbvie, Alfa-sigma, Agensys, Boston Biomedical, Idera Pharma, Inhibrx, Exelixis, Blueprint medicines, Loxo oncology, Takeda and Roche/ Genentech, National Comprehensive Cancer Network, NCI-CTEP and UT MD Anderson Cancer Center.

Travel: Novartis, Pharmamar, Astra Zeneca/Medimmune, ASCO, ESMO

Agenda

- Tumor agnostic targets
- BRAF
- NTRK
- RET

BRAF in Cancer

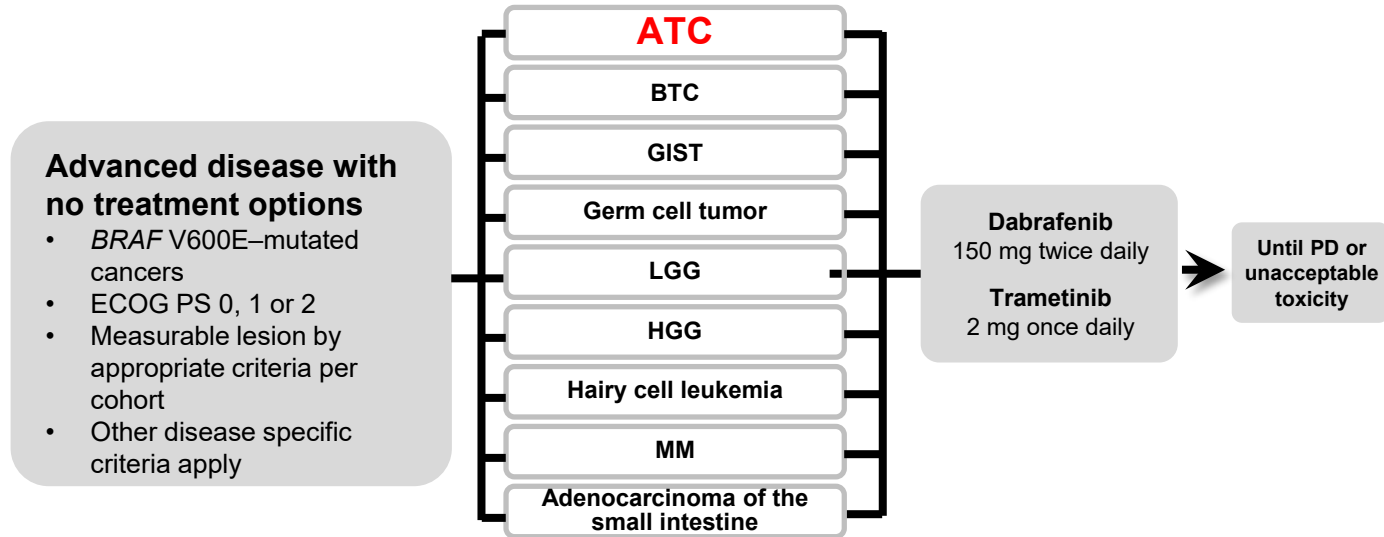
- ❖ BRAFmut oncogene - 5-10% of all human malignancies; Most of the tumors that **express BRAF V600E mutations are rare or ultra-rare cancers.**
- ❖ Constitutive activation of the MAPK pathway
- ❖ Most common mutation of BRAF valine-to-glutamic acid substitution at codon 600 (V600E)
- ❖ Driver mutation in
 - Solid tumors such as melanoma, colorectal cancer, **papillary thyroid cancer**, NSCLC, ovarian cancer and GIST etc.
 - Hematological malignancies such as Multiple myeloma, Langerhans Cell Histiocytosis, Erdheim-Chester Disease, Hairy Cell Leukemia etc
- ❖ Associated with adverse clinical outcomes compared to BRAF wild type tumors in colorectal cancer, melanoma, multiple myeloma, **papillary thyroid cancer and anaplastic thyroid cancer**

BRAF Mutation Incidence in Rare Cancers

| Tumor Type | Sample size | BRAF V600E Mutation Rate (%) | Reference |
|---------------------------------------|-------------------------|------------------------------|---------------------|
| Anaplastic Thyroid Cancer | 94 | 24 | Xing 2005 |
| Biliary Tract Cancer | Cholangiocarcinoma (69) | 16 | Tannapfel 2003 |
| | Gall bladder (21) | 33 | Saetta 2004 |
| Germ Cell Tumor (GCT) | 100 | 1 | Honecker 2009 |
| Adenocarcinoma of the Small Intestine | 35 | 3 | Schonleben 2009 |
| Erdheim-Chester disease | 24 | 54 | Haroche 2012 |
| Langerhans cell histiocytosis | 29 | 38 | Haroche 2012 |
| Ameloblastoma | 24 | 63 | Kurppa 2014 |
| Low-Grade Serous Ovarian Cancer | 65 | 12.3 | Moujaber 2018 |
| Papillary thyroid cancer | 245 | 51 | Kebebew 2007 |



ROAR Study Design



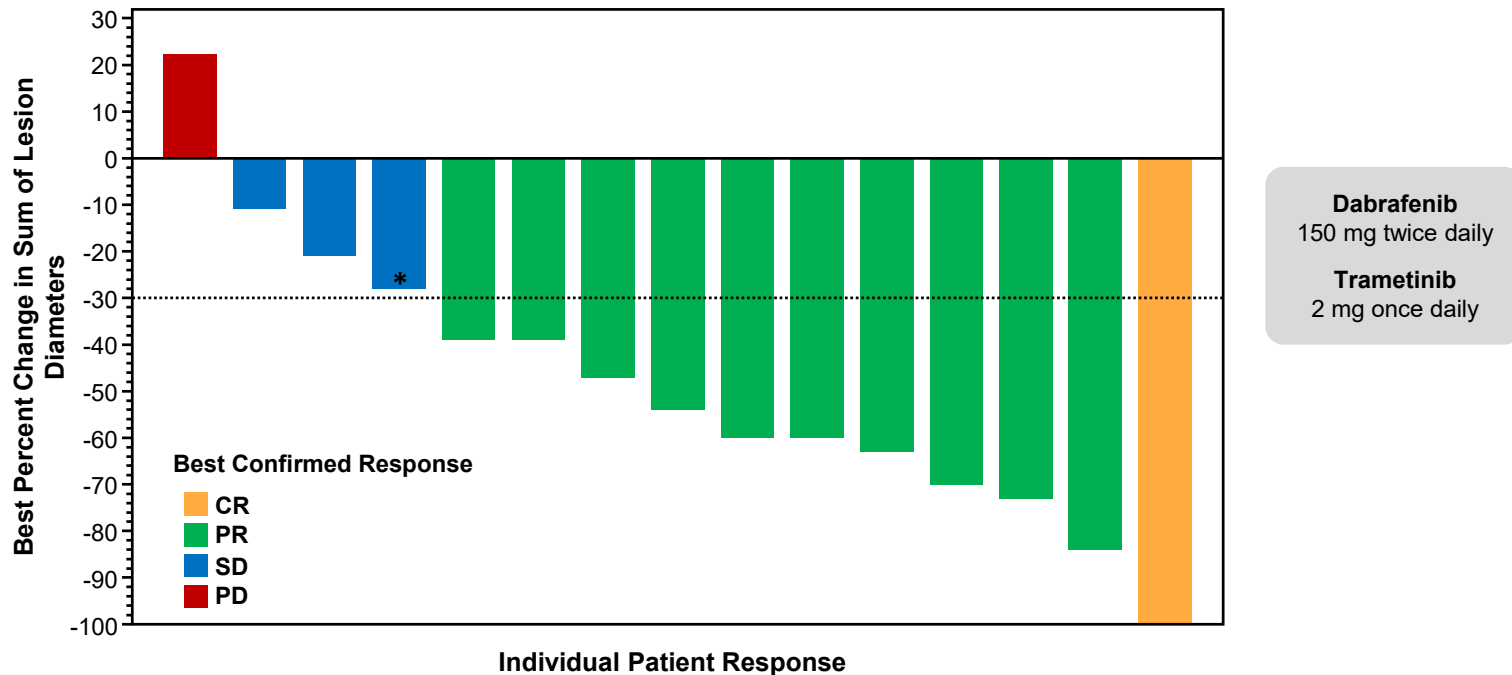
Primary endpoint: Investigator assessed ORR

Secondary endpoints: DOR, PFS, OS, safety

Other endpoints: Exploratory Biomarkers, changes from baseline in HRQOL

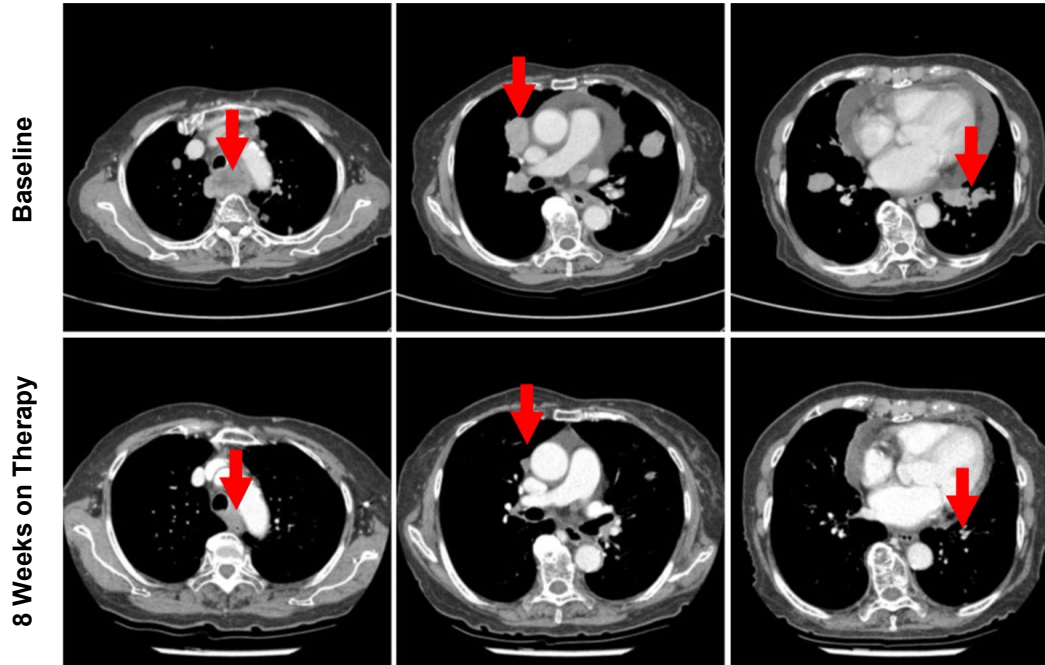
Anaplastic Thyroid Cancer BRAF V600 +

69 % ORR





CT scans – Pt with anaplastic thyroid cancer



Dabrafenib
150 mg twice daily

Trametinib
2 mg once daily

FDA News Release

FDA approves new uses for two drugs administered together for the treatment of BRAF-positive anaplastic thyroid cancer

For Immediate Release

May 4, 2018

Release

The U.S. Food and Drug Administration approved Tafenlar (dabrafenib) and Mekinist (trametinib), administered together, for the treatment of anaplastic thyroid cancer (ATC) that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive).

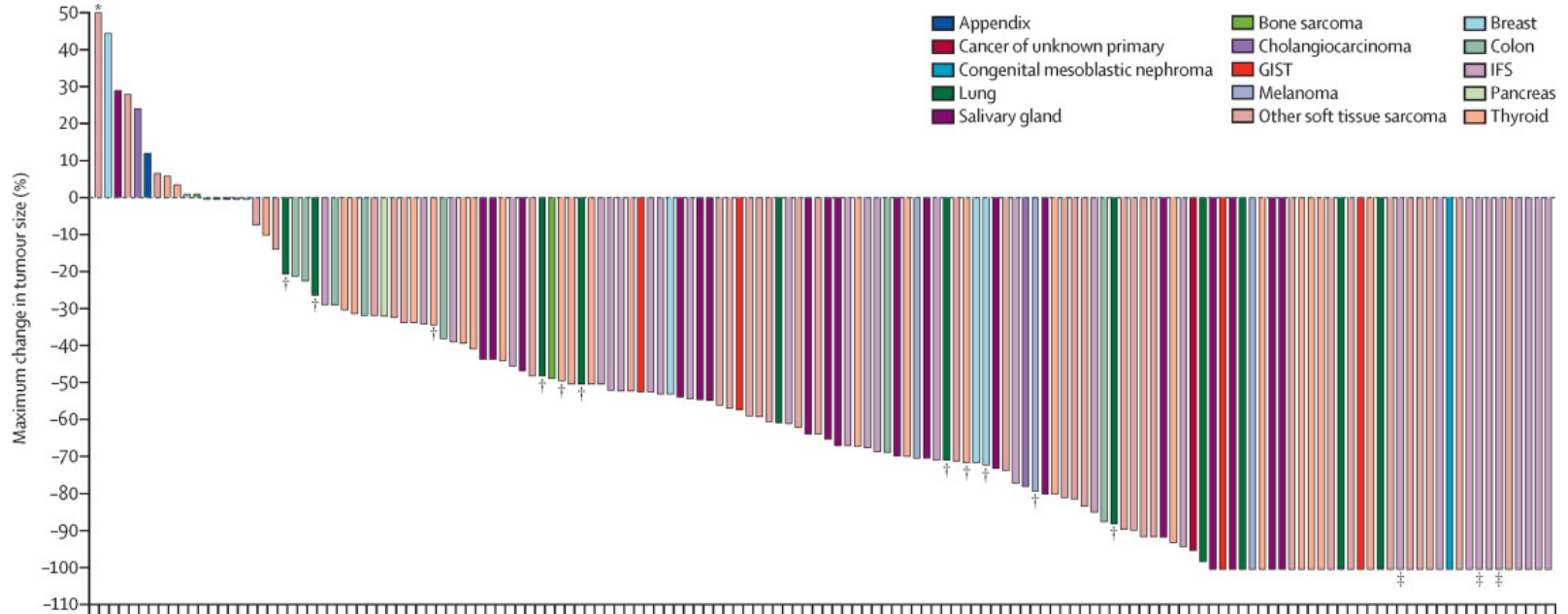
“This is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer, and the third cancer with this specific gene mutation that this drug combination has been approved to treat,” said Richard Pazdur, M.D., director of the FDA’s Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research. “This approval demonstrates that targeting the same molecular pathway in diverse diseases is an effective way to expedite the development of treatments that may help



NTRK in Thyroid cancer

- In thyroid cancer the ETV6-NTRK3 fusion is detected in 1 to 14.5% of thyroid tumors (Stransky, Cerami et al. 2014) (Leeman-Neill, Kelly et al. 2014).
- The incidence of the NTRK3 rearrangement papillary thyroid cancer (PTC) patients with prior exposure to radioactive iodine is 14.5% compared with 2% in sporadic PTC (Leeman-Neill, Kelly et al. 2014).

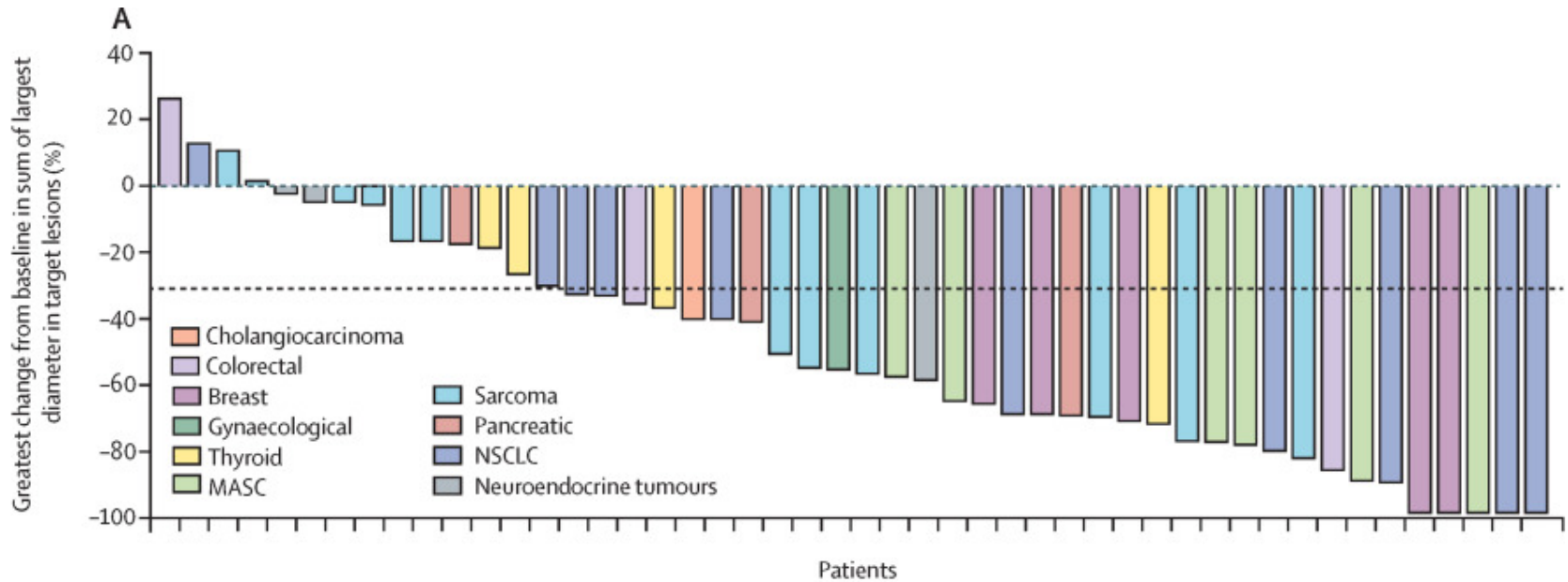
Larotrectinib in patients with TRK fusion-positive solid tumours



Thyroid 24 pts; Responders =19 (79%, 58–93) NE (14·8–NE)



Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours



Thyroid 5 pts (9 %)

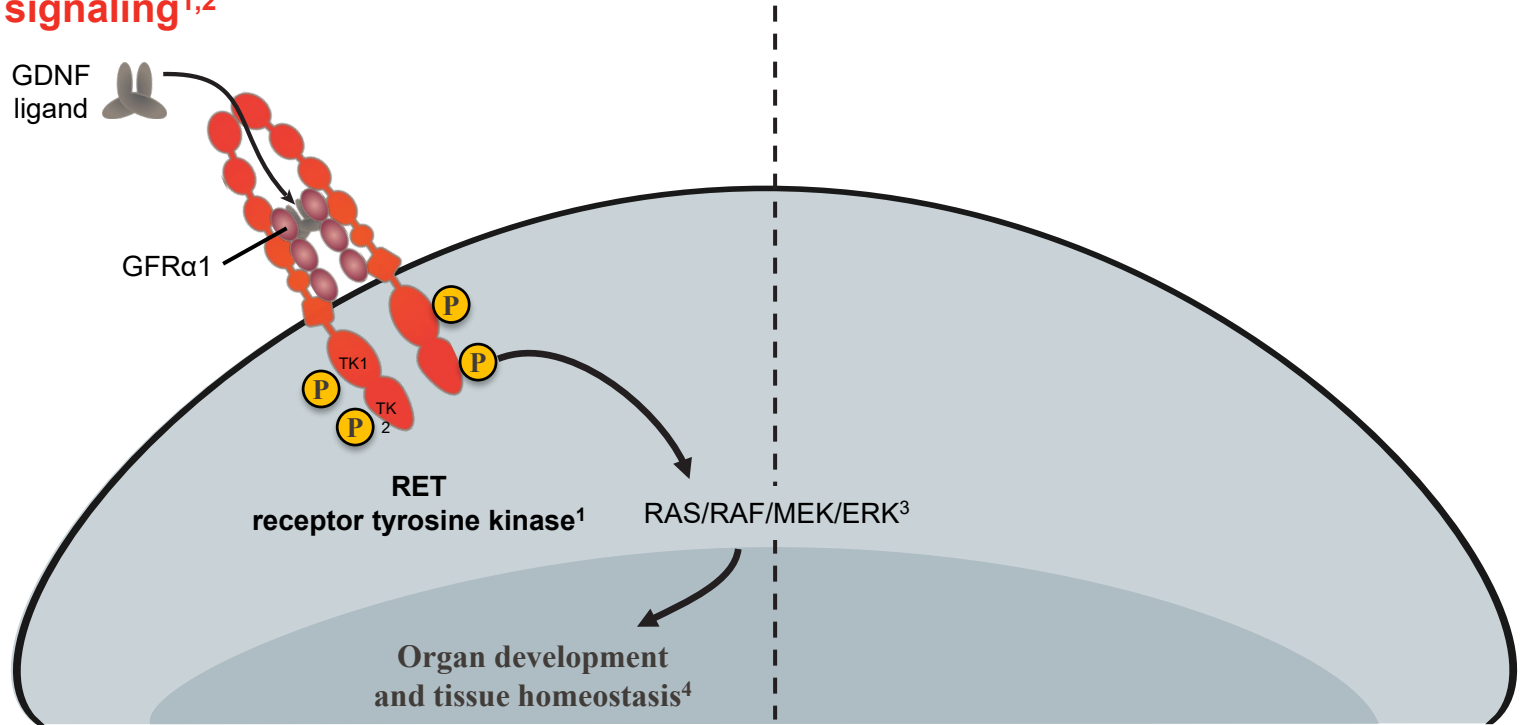
Dooble,R. Lancet Oncol,
Volume 21, Issue 2, 2020

RET inhibitor from Bench → Phase 1/2 → FDA approval



RET is an RTK required for normal development¹

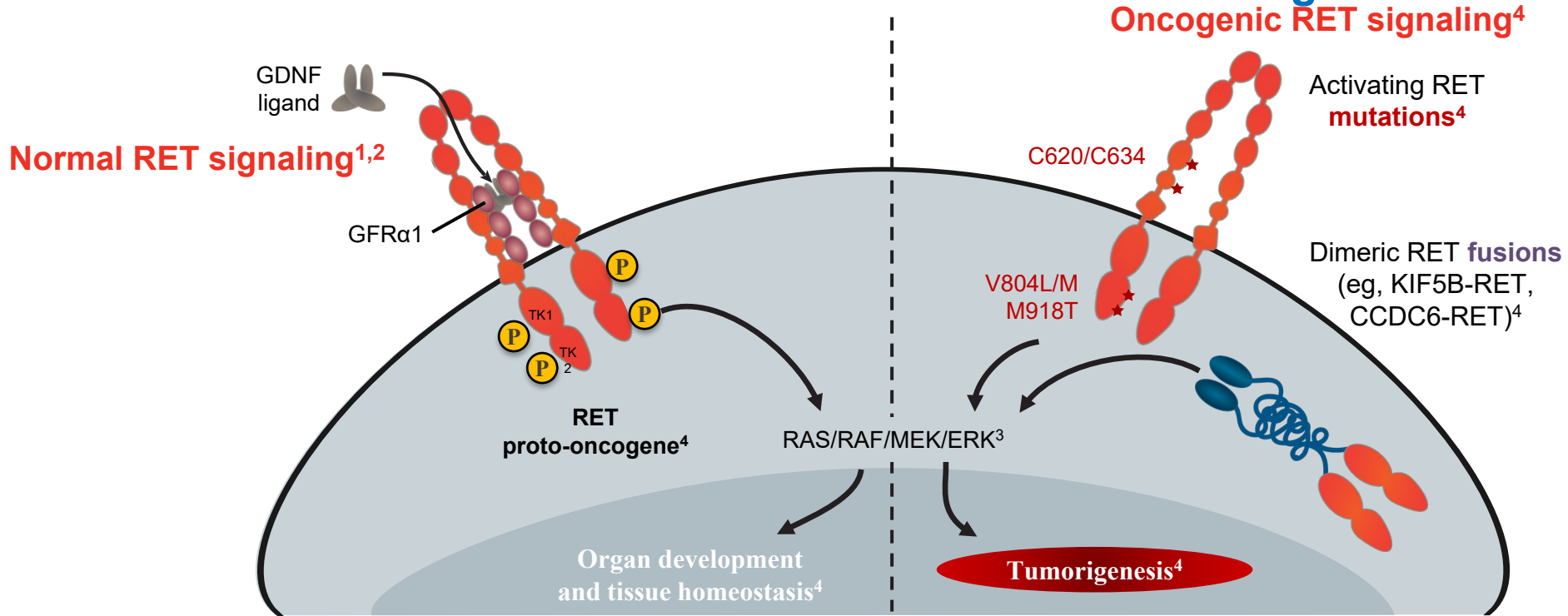
Normal RET signaling^{1,2}



ERK, extracellular signal-regulated kinase; GDNF, glial cell line-derived neurotrophic factor; GFR, GDNF family receptor; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; P, phosphorylation; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RET, rearranged during transfection; RTK, receptor tyrosine kinase; TK, tyrosine kinase.

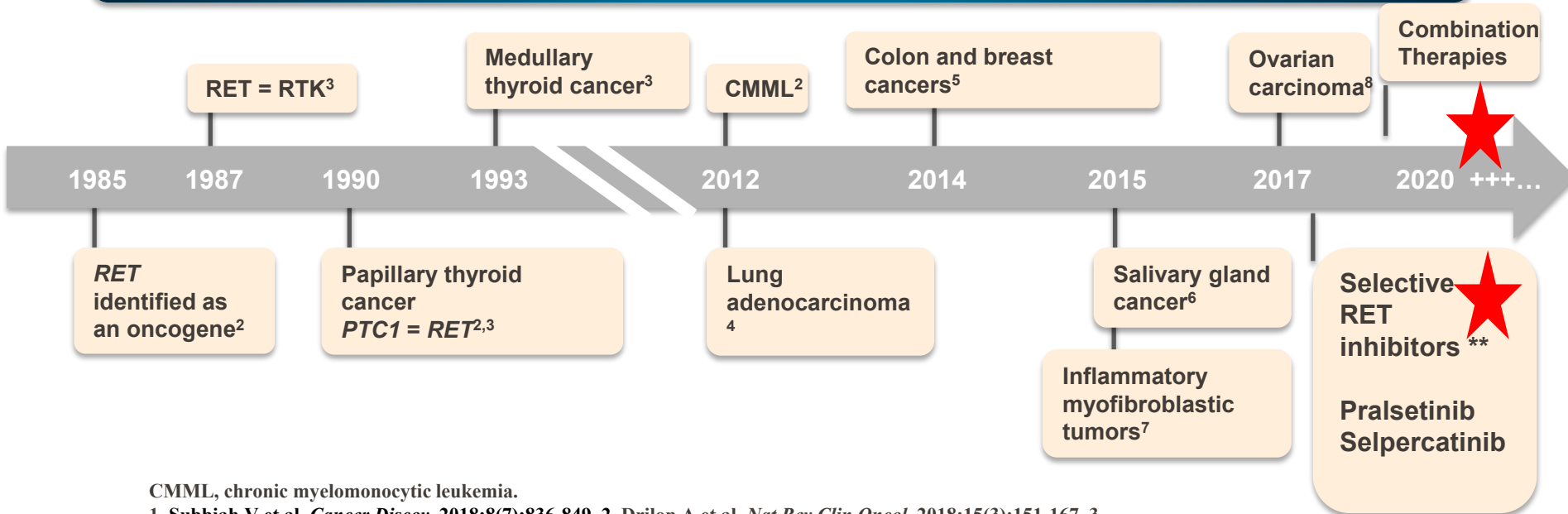
1. Mulligan LM. *Nat Rev Cancer*. 2014;14(3):173-186. 2. Pützer BM et al. In: Diamanti-Kandarakis E, ed. *Contemporary Aspects of Endocrinology*. IntechOpen; 2011. <https://www.intechopen.com/books/contemporary-aspects-of-endocrinology/molecular-diagnostics-in-treatment-of-medullary-thyroid-carcinoma>. Accessed August 23, 2018. 3. Pratilas CA et al. *Proc Natl Acad Sci U S A*. 2009;106(11):4519-4524. 4. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167.

Alterations in RET structure and function can lead to tumorigenesis¹



Oncogenic *RET* alterations have been identified in numerous cancers¹

RET is one of the first oncogenic kinase fusions cloned from an epithelial tumor, and has since been found to be an oncogenic driver primarily in solid tumors^{1,2}

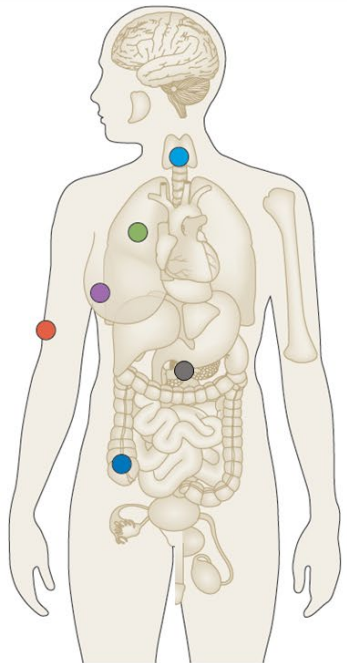


CMML, chronic myelomonocytic leukemia.

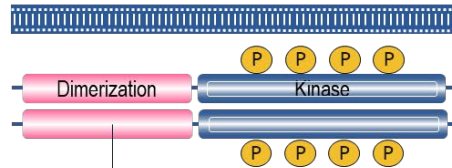
1. Subbiah V et al. *Cancer Discov.* 2018;8(7):836-849.
2. Drlon A et al. *Nat Rev Clin Oncol.* 2018;15(3):151-167.
3. Ibáñez CF. *Cold Spring Harb Perspect Biol.* 2013;5(2):a009134.
4. Ju YS et al. *Genome Res.* 2012;22(3):436-445.
5. Stransky N et al. *Nat Commun.* 2014;5:4846.
6. Grünewald I et al. *Oncotarget.* 2015;6(20):18224-18237.

RET is activated by two major mechanisms in cancer

RET fusions

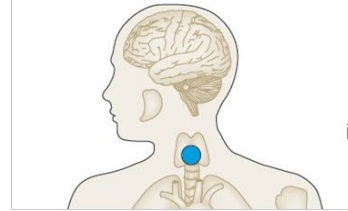


- Non-small cell lung cancer (2%)
 - Papillary and other thyroid cancers (10–20%)
 - Pancreatic cancer (<1%)
 - Salivary gland cancer (<1%)
 - Spitz tumors (<1%)
 - Colorectal cancer (<1%)
 - Ovarian cancer (<1%)
 - Myeloproliferative disorders (<1%)
 - Many others (<1%)

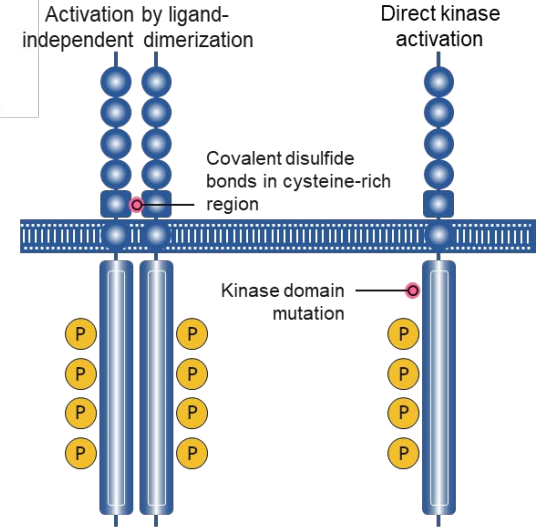


KIF5B (most common in lung cancer)
CCDC6 or NCOA4 (most common in thyroid cancer)

RET mutations



- Medullary thyroid cancer
 - sporadic (>60%)
 - hereditary (>90%)



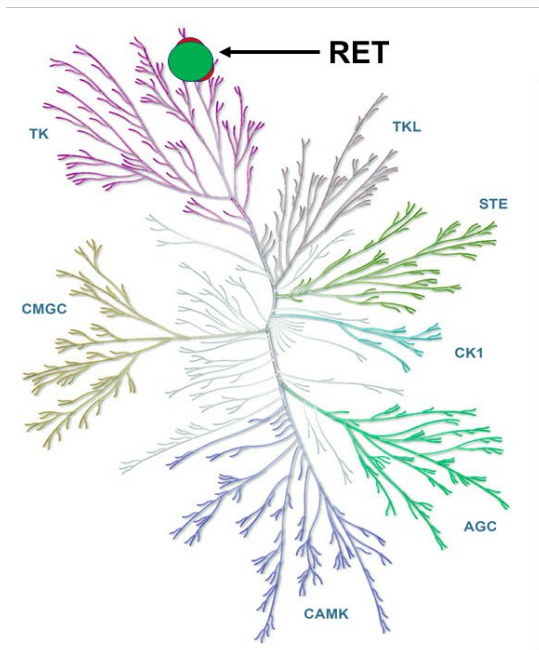
Common mutation: **RET M918T**



SELPERCATINIB is a potent and selective RET inhibitor

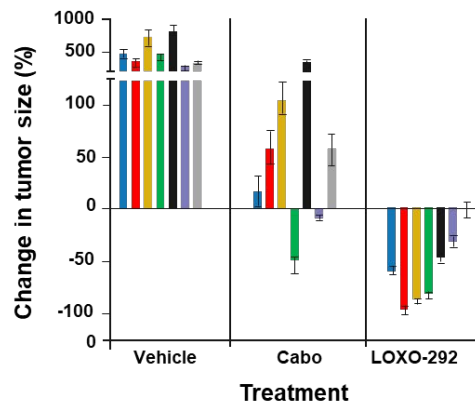
Kinome selectivity

Highly selective for RET



Xenograft models

Multiple fusions/mutations/histologies

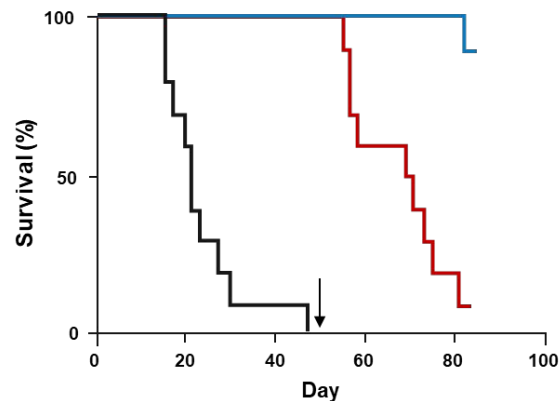


Tumor models

- 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



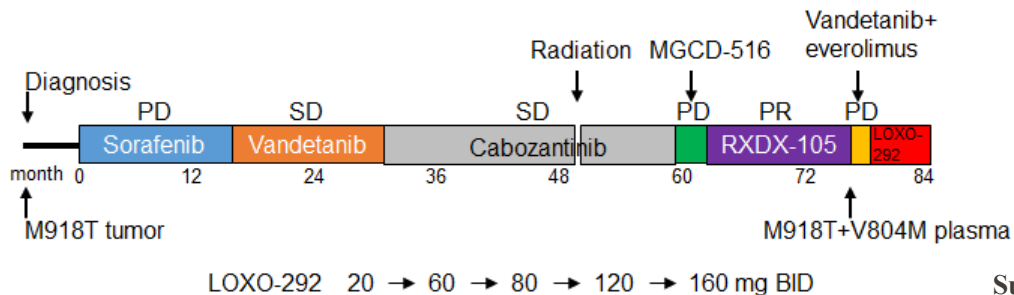
Treatments

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

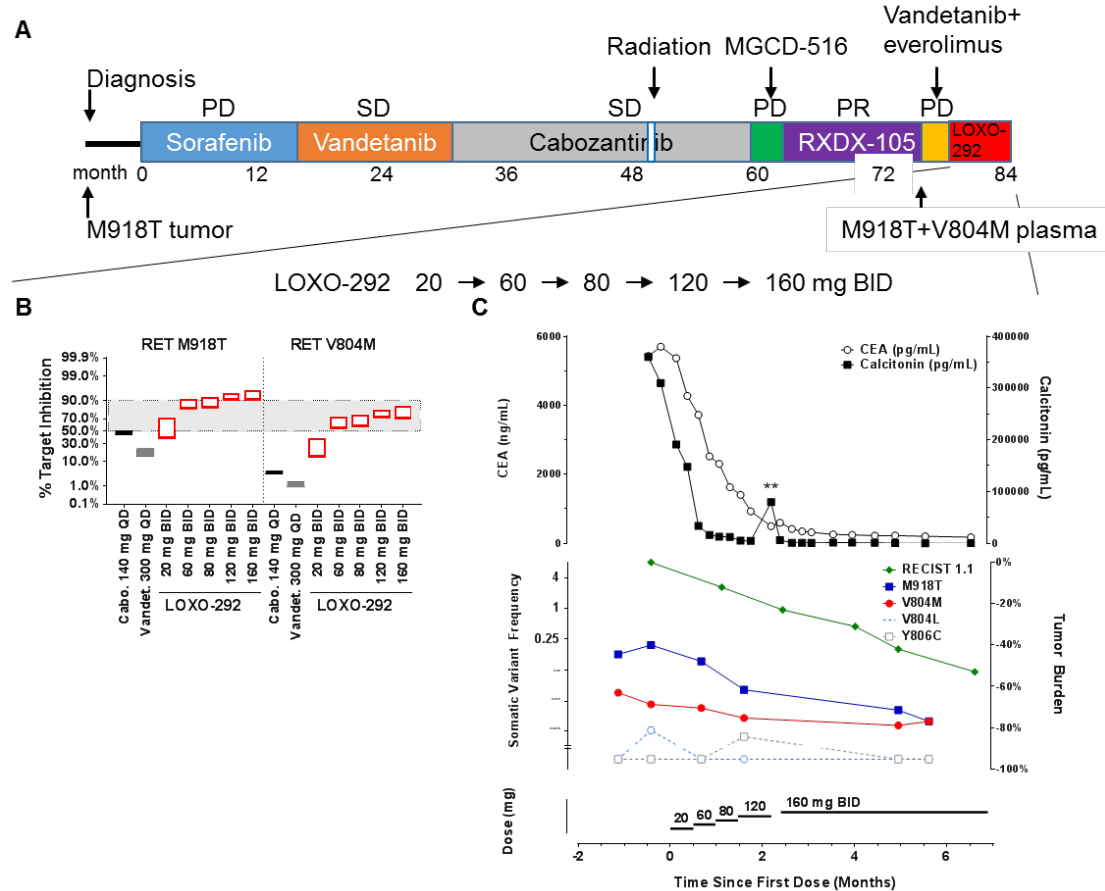
Subbiah V et al. Ann Oncol 2018; Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily

Sporadic RET M918T/V804M-mutant response to Selpercatinib

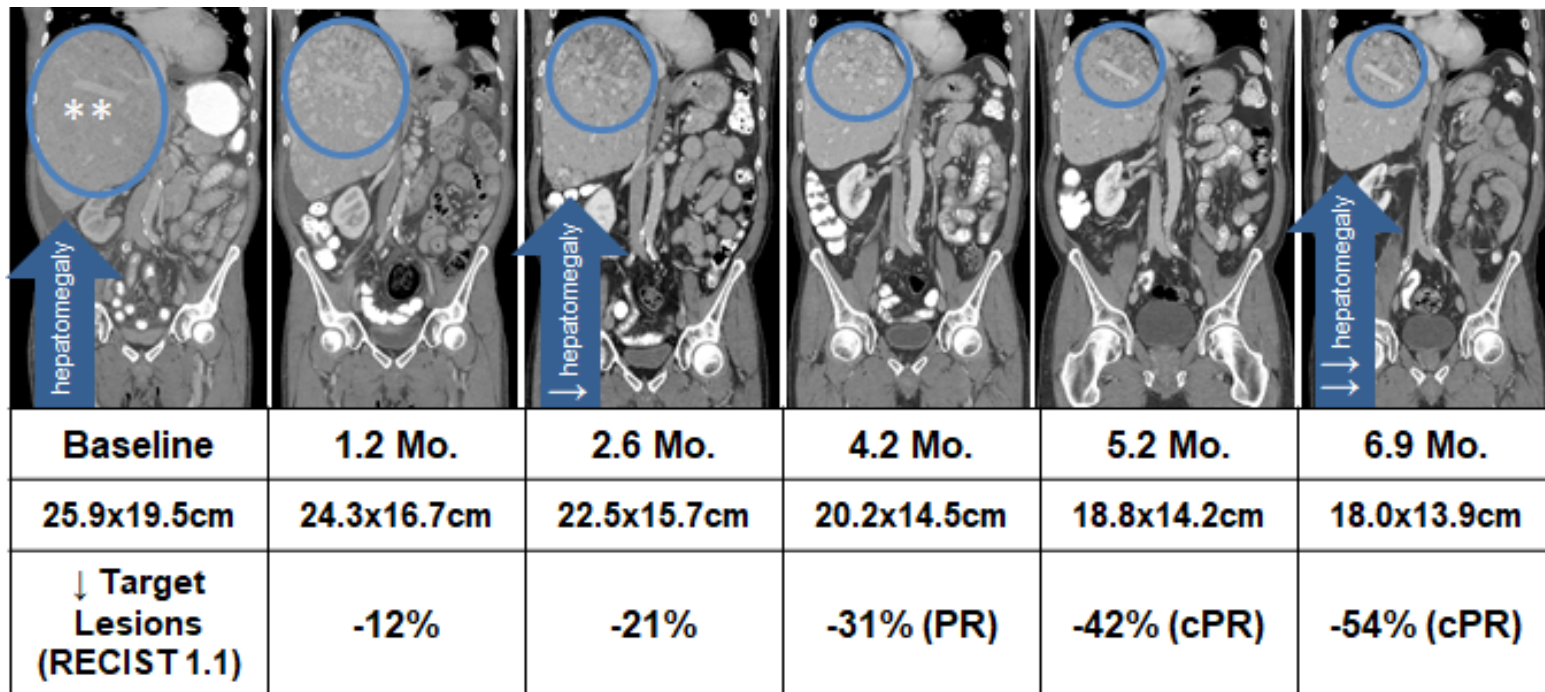
- 49-year old man with advanced MTC with RET M918T mutation
- Progressive disease after six MKI treatments over 7 years
- Prior to treatment: poor performance status, 30 BMs per day, pain from liver enlargement. Acquire resistance mutation: V804M “gatekeeper”
- Treated with LOXO-292 by “*single patient*”, *compassionate use protocol*
- Resolution of diarrhea and pain in first week
- Calcitonin (360,000 pg/mL) and CEA (5700 ng/mL) became normal
- Reduction in tumor size by -54% (“confirmed PR”)



Sporadic RET M918T/V804M- mutant response to Selpercatinib



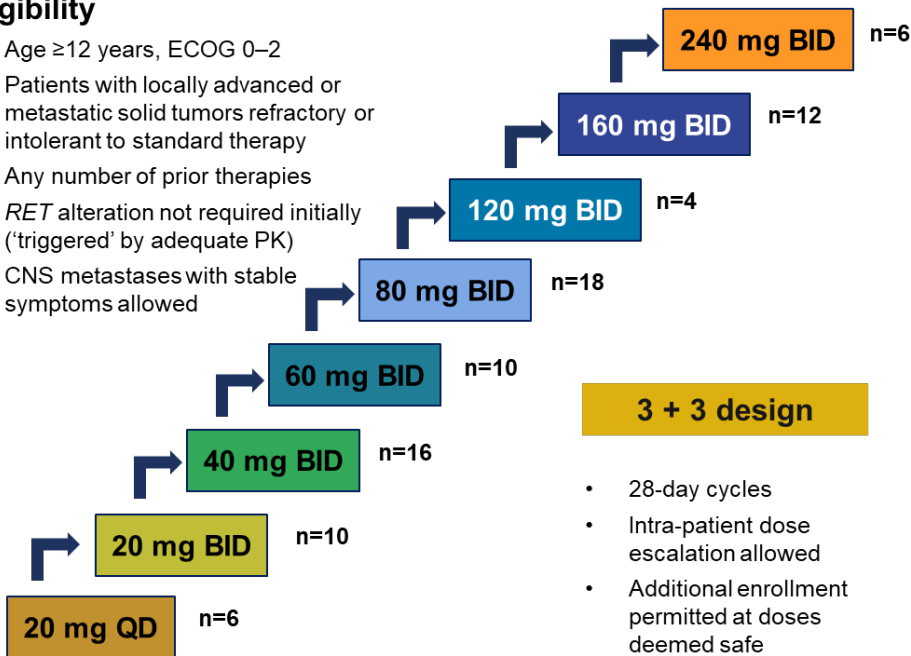
Sporadic RET M918T/V804M-mutant response to Selpercatinib



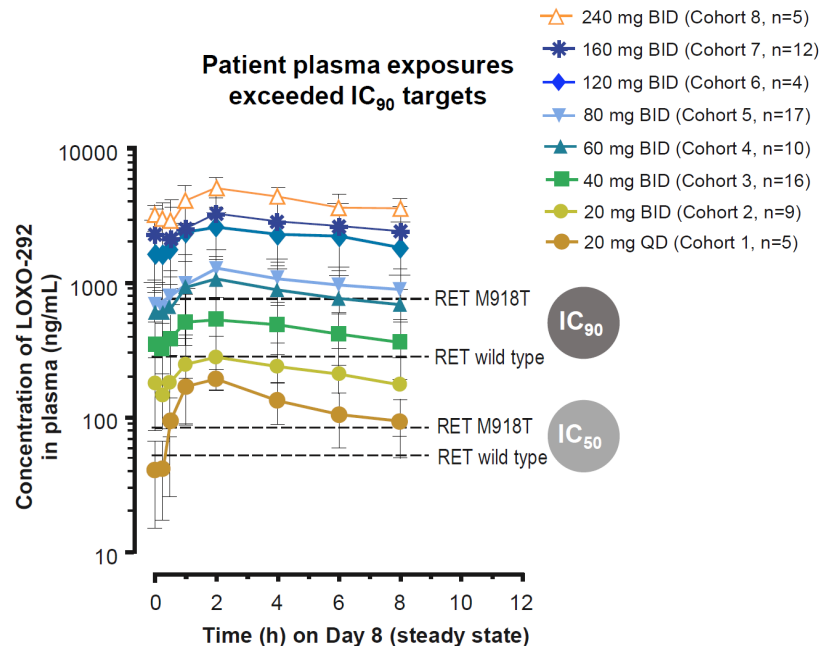
LIBRETTO-001: phase I dose escalation and pharmacokinetics

Eligibility

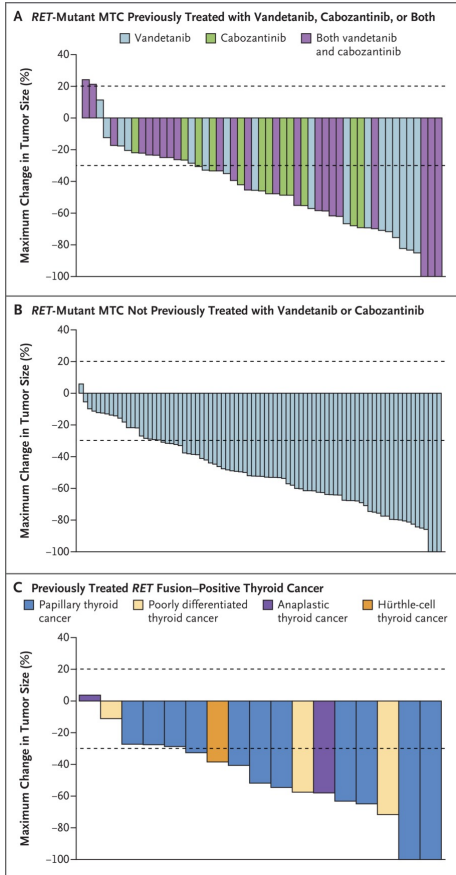
- Age ≥ 12 years, ECOG 0–2
- Patients with locally advanced or metastatic solid tumors refractory or intolerant to standard therapy
- Any number of prior therapies
- *RET* alteration not required initially ('triggered' by adequate PK)
- CNS metastases with stable symptoms allowed



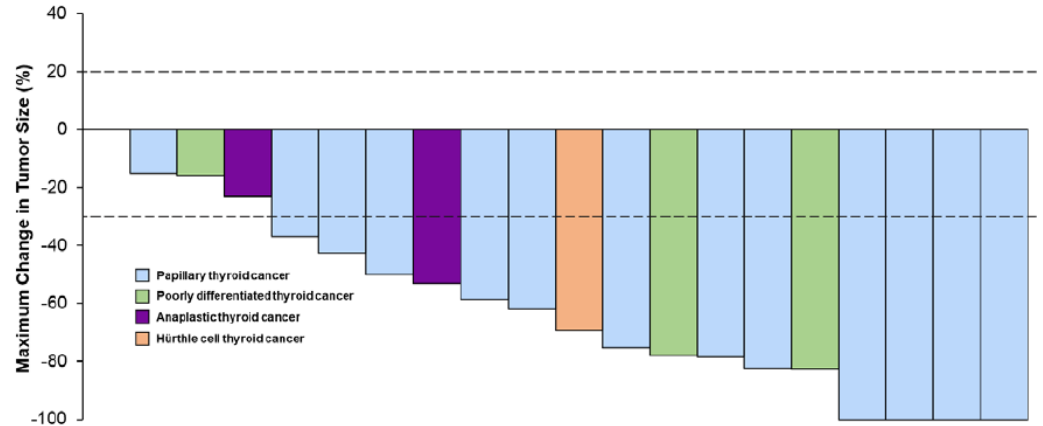
Patient plasma exposures exceeded IC_{90} targets



Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers



Waterfall plot of the maximum change in tumor size in *RET* fusion positive thyroid cancer patients as assessed by blinded independent review committee (n=19)



Waterfall Plots of the Maximum Change in Tumor Size.

Wirth et al 2020 NEJM

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

Table 2. Efficacy.*

| Response | <i>RET</i> -Mutant MTC Previously Treated | | <i>RET</i> -Mutant MTC Not Previously Treated | | Previously Treated <i>RET</i> Fusion-Positive Thyroid Cancer | |
|---|---|--------------------------------|---|--------------------------------|--|--------------------------------|
| | Independent Review (N=55) | Investigator Assessment (N=55) | Independent Review (N=88) | Investigator Assessment (N=88) | Independent Review (N=19) | Investigator Assessment (N=19) |
| Objective response — % (95% CI) | 69 (55–81) | 62 (48–75) | 73 (62–82) | 71 (60–80) | 79 (54–94) | 58 (34–80) |
| Best response — no. (%) | | | | | | |
| Complete response | 5 (9) | 3 (5) | 10 (11) | 3 (3) | 1 (5) | 0 |
| Partial response | 33 (60) | 31 (56) | 54 (61) | 59 (67) [†] | 14 (74) | 11 (58) |
| Stable disease | 14 (25) | 16 (29) | 20 (23) | 24 (27) | 4 (21) | 7 (37) |
| Progressive disease | 1 (2) | 3 (5) | 2 (2) | 0 | 0 | 0 |
| Could not be evaluated | 2 (4) [‡] | 2 (4) [‡] | 2 (2) | 2 (2) | 0 | 1 (5) |
| Duration of response | | | | | | |
| No. of patients with objective response | 38 | 34 | 64 | 59 [§] | 15 | 11 |
| Data censored — no. (%) | 32 (84) | 25 (74) | 60 (94) | 56 (95) | 9 (60) | 8 (73) |
| Median (95% CI) — mo | NE (19.1–NE) | NE (18.4–NE) | 22.0 (NE–NE) [¶] | 22.0 (NE–NE) [¶] | 18.4 (7.6–NE) | NE (9.5–NE) |
| Median follow-up — mo | 14.1 | 14.8 | 7.8 | 8.0 | 17.5 | 17.5 |
| Progression-free survival | | | | | | |
| Data censored — no. (%) | 42 (76) | 33 (60) | 80 (91) | 82 (93) | 11 (58) | 12 (63) |
| Median (95% CI) — mo | NE (24.4–NE) | 27.4 (13.7–NE) | 23.6 (NE–NE) [¶] | 23.6 (23.6–NE) [¶] | 20.1 (9.4–NE) | NE (10.0–NE) |
| Median follow-up — mo | 16.7 | 16.7 | 11.1 | 11.1 | 13.7 | 19.3 |
| Prevalence at 1 yr (95% CI) — % | 82 (69–90) | 68 (54–79) | 92 (82–97) | 95 (86–98) | 64 (37–82) | 61 (33–81) |

* Percentages may not total 100 because of rounding. For *RET*-mutant MTC, “previously treated” indicates previously treated with vandetanib, cabozantinib, or both, and “not previously treated” indicates not previously treated with vandetanib or cabozantinib. NE denotes could not be estimated.

[†] Included are three patients with unconfirmed partial responses pending confirmation.

[‡] Included is one patient who died before the first response assessment.

[§] Included are confirmed responses only.

[¶] The median is unstable because it is based on less than 10% of the total number of events.

Wirth et al 2020 NEJM

Selpercatinib or RETEVMO now US FDA Approved in May 2020 !!!

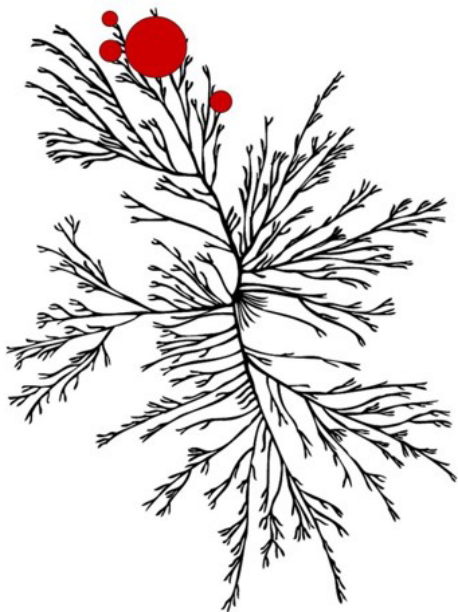


- ❖ For the treatment of patients with metastatic RET-fusion positive non-small cell lung cancer.
- ❖ For the treatment of patients with RET-mutant medullary thyroid cancer (MTC)
- ❖ For the treatment of patients with advanced RET fusion-positive thyroid cancer who require systemic therapy.
- ❖ Line Agnostic approval

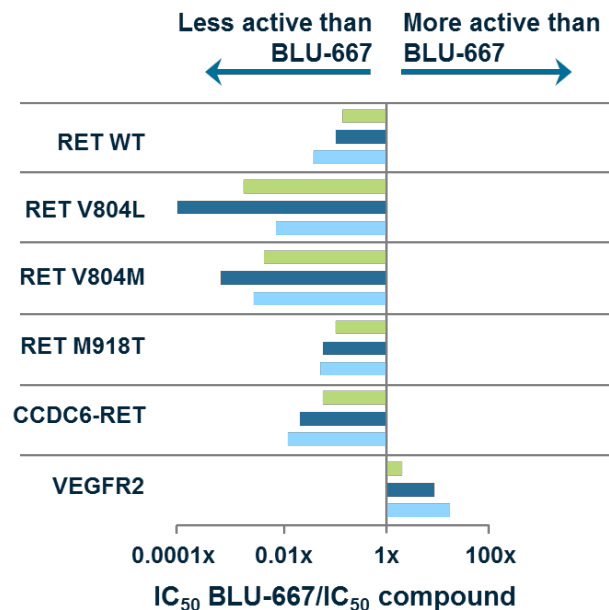
BLU-667 OR PRALSETINIB OR GAVRETO - HIGHLY POTENT SELECTIVE RET INHIBITOR

Pralsetinib - designed to treat *RET*-altered cancers

High kinome selectivity for *RET*^{1,2}



More potent and selective than MKIs^{1,2}



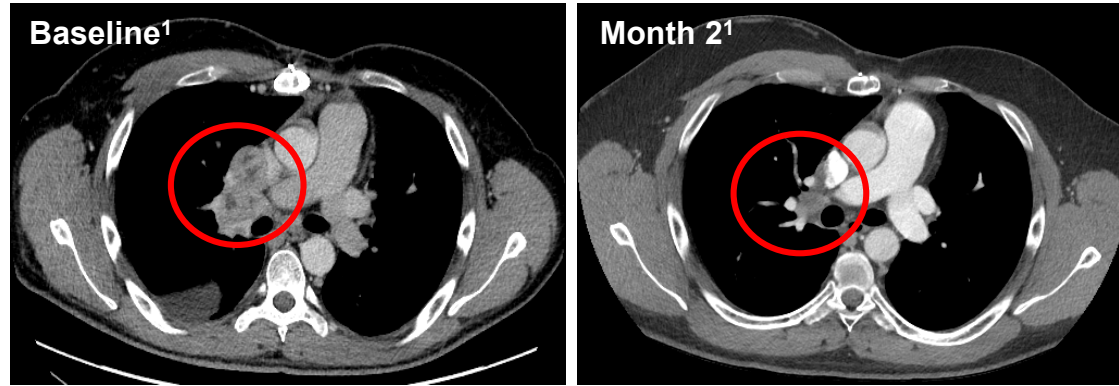
IC₅₀, half maximal inhibitory concentration; WT, wild-type.

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) (www.cellsignal.com).

The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

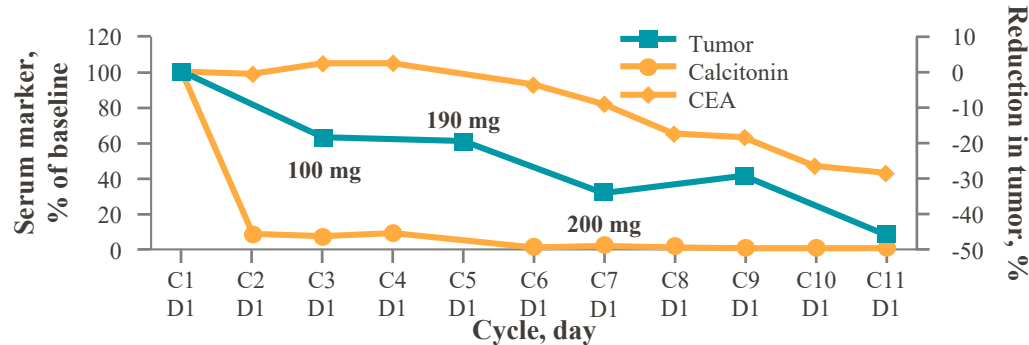
Subbiah V et al. *Cancer Discov.* 2018;8(7):836-849.

BLU-667 demonstrates potent activity against highly invasive *RET*-mutant MTC



27-year-old male^{1,2}

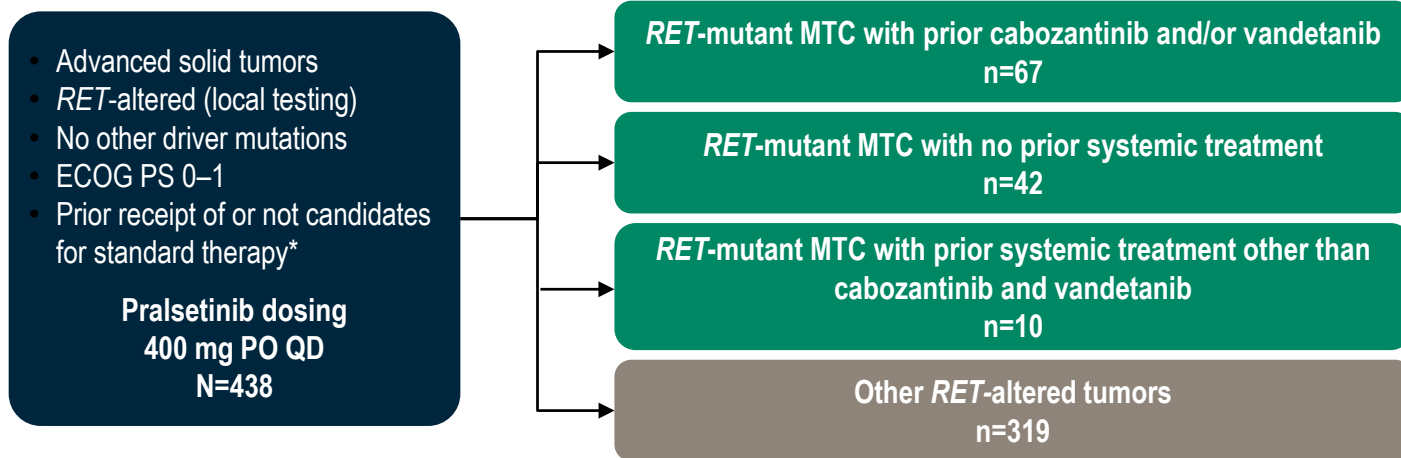
- *RET* L629-D361 Del
- Initiated at 60 mg
- Ongoing at 400 mg with confirmed PR



PR, partial response.

1. Subbiah V et al. *Cancer Discov.* 2018;8(7):836-849. 2. Data previously presented in April 2018 at AACR Annual Meeting. Data cut-off: April 6, 2018.

Registrational phase 1/2 study of pralsetinib in patients with solid tumors (ARROW)



Key endpoints

- Blinded, independent central review ORR and DOR per RECIST v1.1
- Safety

ARROW (NCT03037385) is an ongoing, international multicenter phase 1/2 study across 84 sites in 11 countries

*Until protocol amended in July 2019 to allow enrollment of treatment-naïve, standard therapy-eligible patients. Data cutoff February 13, 2020.

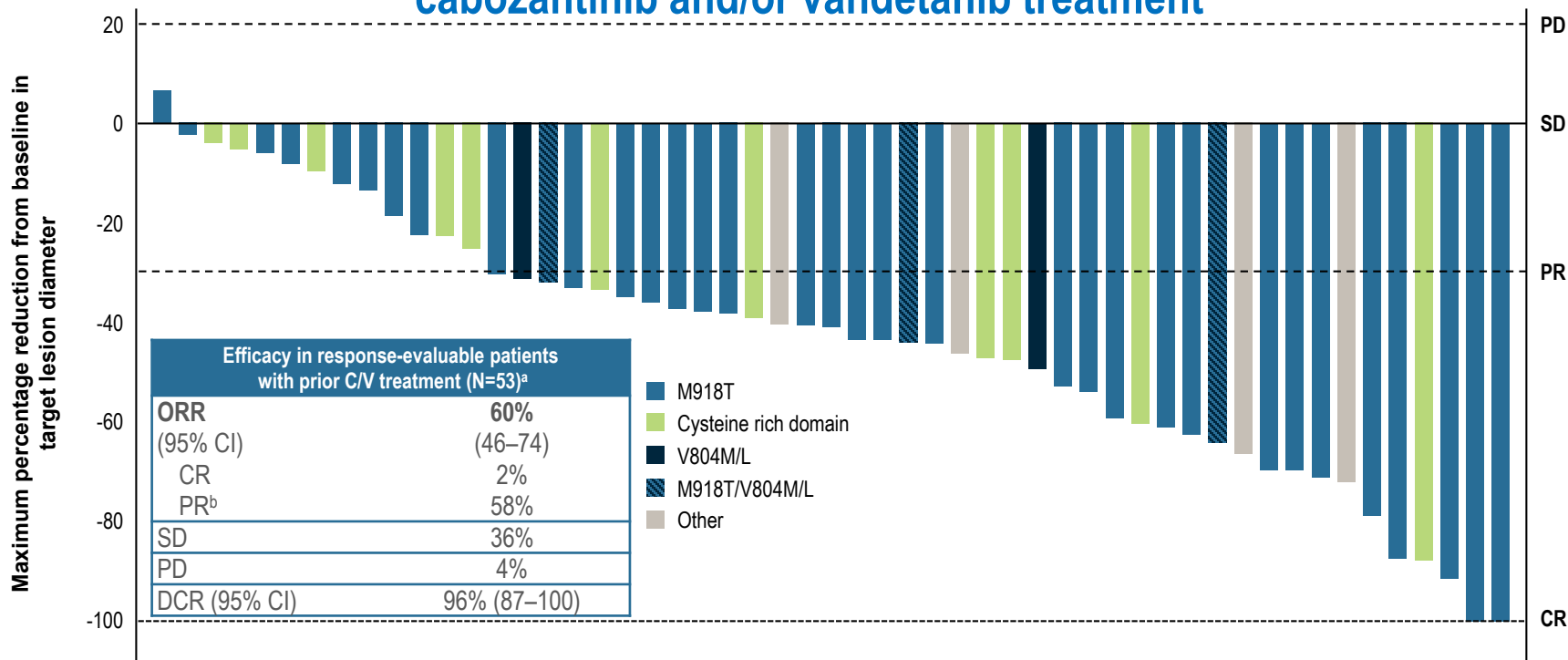
ECOG PS, Eastern Cooperative Oncology Group performance score; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, overall response; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Baseline demographics and disease characteristics in *RET*-mutant MTC population

| Characteristic | All 400 mg pralsetinib (N=92) ^a | Prior cabozantinib and/or vandetanib treatment (n=61) | No prior systemic treatment (n=22) |
|--|--|---|--|
| Median age (range), years | 59 (19–83) | 58 (25–83) | 60 (19–81) |
| Male, n (%) | 63 (68) | 41 (67) | 16 (73) |
| ECOG PS, n (%) | | | |
| 0 | 37 (40) | 17 (28) | 15 (68) |
| 1–2 ^b | 55 (60) | 44 (72) | 7 (32) |
| History of CNS/brain metastases, n (%) | 9 (10) | 5 (8) | 3 (14) |
| <i>RET</i> mutation | 92 (100) | 61 (100) | 22 (100) |
| M918T | 56 (61) | 41 (67) ^c | 8 (36) |
| Cysteine rich domain ^d | 27 (29) | 14 (23) | 11 (50) |
| V804M/L | 3 (3) | 2 (3) | 1 (5) |
| Other ^e | 6 (7) | 4 (7) | 2 (9) |

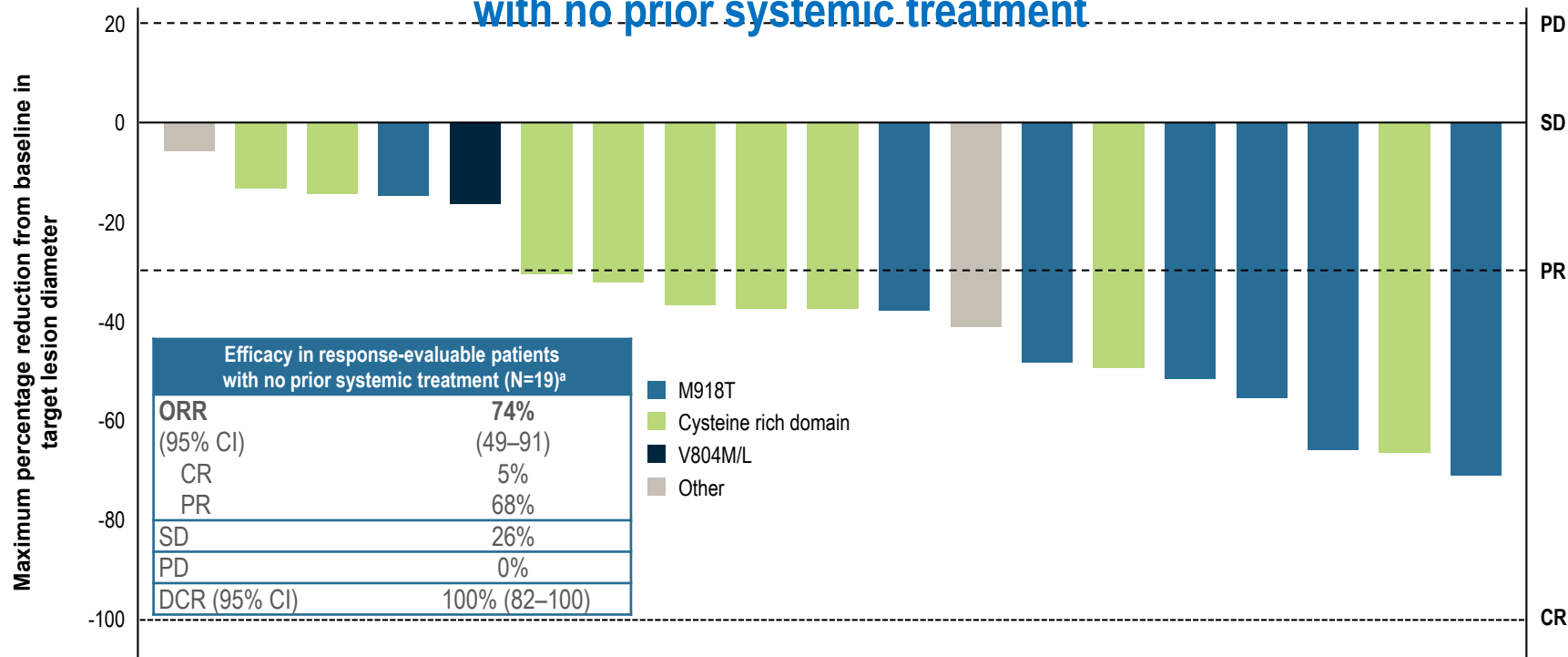
^aIncludes patients enrolled by July 11, 2019, data cutoff February 13, 2020. Patients enrolled by this date either received standard therapy or were not candidates for standard therapy; 9 patients received prior systemic therapy other than cabozantinib or vandetanib. ^bECOG PS of 2 was allowed prior to a protocol amendment. ^cThree patients classified with M918T as the primary mutation also had a V804L or V804M mutation. ^dCysteine rich domain includes: C609, C611, C618, C620, C630 and/or C634. ^eOther includes: D898_E901del (1), L790F (1), A883F (2), K666E (1) and R844W (1). CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score.

Clinical response to pralsetinib in patients with prior cabozantinib and/or vandetanib treatment



^aBlinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. Six patients without measurable disease at baseline on central review, and 2 patients without a post-baseline tumor response assessment were not response evaluable. ^b1 PR pending confirmation. C/V, cabozantinib and/or vandetanib; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Clinical response to pralsetinib in patients with no prior systemic treatment



^aBlinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. Two patients without measurable disease at baseline on central review and 1 patient who experienced major protocol violation were not response evaluable.

Pralsetinib Phase 1/2 ARROW study

Phase 2 study design

- Advanced solid tumors
- RET-altered (local testing)
- No other driver mutations
- ECOG PS 0-1

**Pralsetinib dosing:
400 mg PO QD**

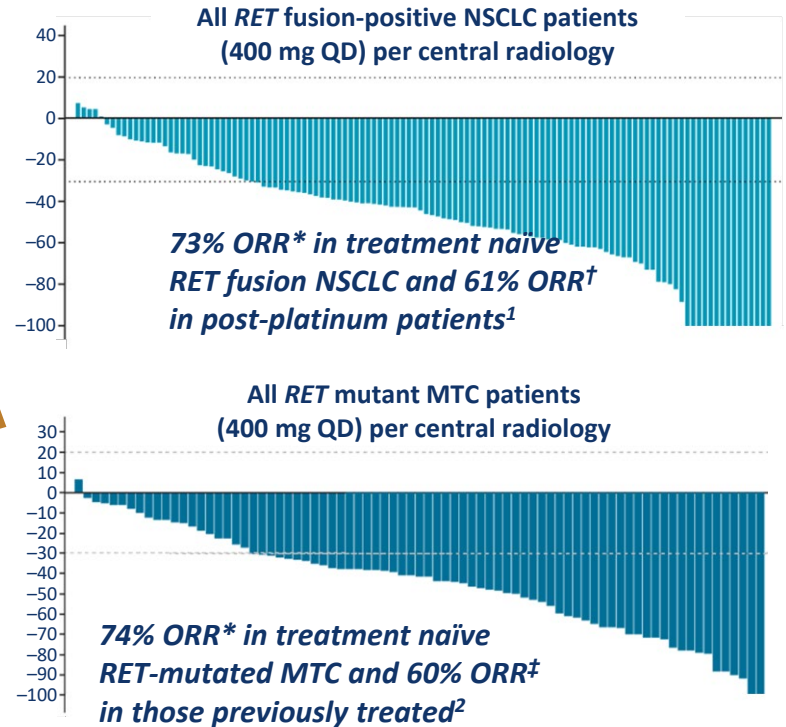
RET fusion-positive
NSCLC

RET mutation-positive
MTC

RET fusion-positive
other tumors

Primary endpoints

- Centrally reviewed ORR per RECIST v1.1
- Safety

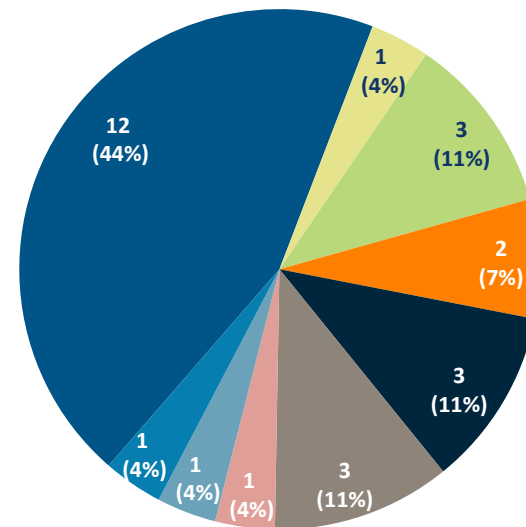


ARROW is registered with clinicaltrials.gov (NCT03037385). Data cutoff, November 18, 2019. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance score; MTC, medullary thyroid cancer; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; ORR, overall response rate; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection. Data shown for response evaluable population. *All responses confirmed. †Two responses pending confirmation. ‡One response pending confirmation.

1. Phase 1/2 ARROW trial data in patients with *RET* fusion-positive NSCLC reported on January 8, 2020. Data cutoff: November 18, 2019. 2. Phase 1/2 ARROW trial data in patients with *RET*-mutated MTC reported on April 1, 2020. Data cutoff: February 13, 2020.

| | | RET fusion thyroid (n=13)* | Other RET fusion tumor types (N=14)† |
|---------------------------------------|----------------------------|----------------------------|--------------------------------------|
| Median age (range), years | | 63 (23–74) | 54 (31–71) |
| Male, n (%) | | 7 (54) | 6 (43) |
| ECOG performance status, n (%) | 0 | 4 (31) | 5 (36) |
| | 1 | 8 (62) | 9 (64) |
| | 2‡ | 1 (8) | 0 |
| Disease stage, n (%) | III | 0 | 1 (7) |
| | IV | 13 (100) | 13 (93) |
| Brain metastasis, n (%) | | 5 (38) | 2 (14) |
| Prior therapies, n (%) | Any prior systemic therapy | 12 (92) | 14 (100) |
| | Radioactive iodine | 12 (92) | 0 |
| | Lenvatinib/Sorafenib | 7 (54) | 0 |
| | Cabozantinib/Vandetanib | 2 (15) | 1 (7) |
| | Chemotherapy | 0 | 14 (100) |
| | Other anticancer therapy | 0 | 7 (50) |
| Fusion partners, n (%) | CCDC6 | 6 (46) | 4 (29) |
| | KIF5B | 0 | 3 (21) |
| | NCOA4 | 4 (31) | 2 (14) |
| | Other | 3 (23) | 1 (7) |
| | Unknown | 0 | 4 (29) |

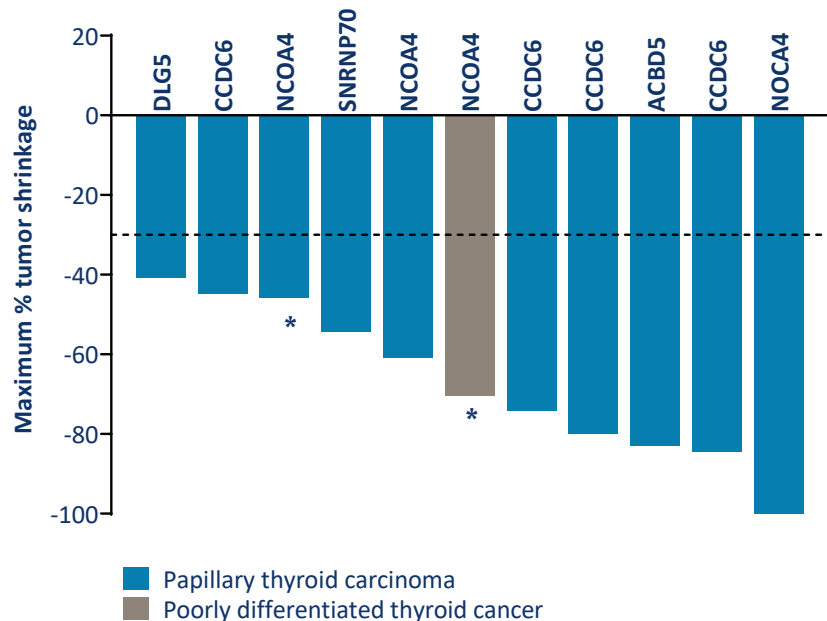
RET fusion tumor types (N=27)



- Papillary thyroid carcinoma
- Poorly differentiated thyroid cancer
- Pancreatic
- Cholangiocarcinoma
- Thymus
- Colon
- Mixed histology lung
- Ovarian
- Neuroendocrine (unknown primary)

*Enrolled by July 11, 2019. †Enrolled by November 19, 2019. ‡ECOG performance status of 2 was permitted prior to a protocol amendment. ECOG, Eastern Cooperative Oncology Group; KIF5B, kinesin family member 5b; NCOA4, nuclear receptor coactivator 4; RET, rearranged during transfection.

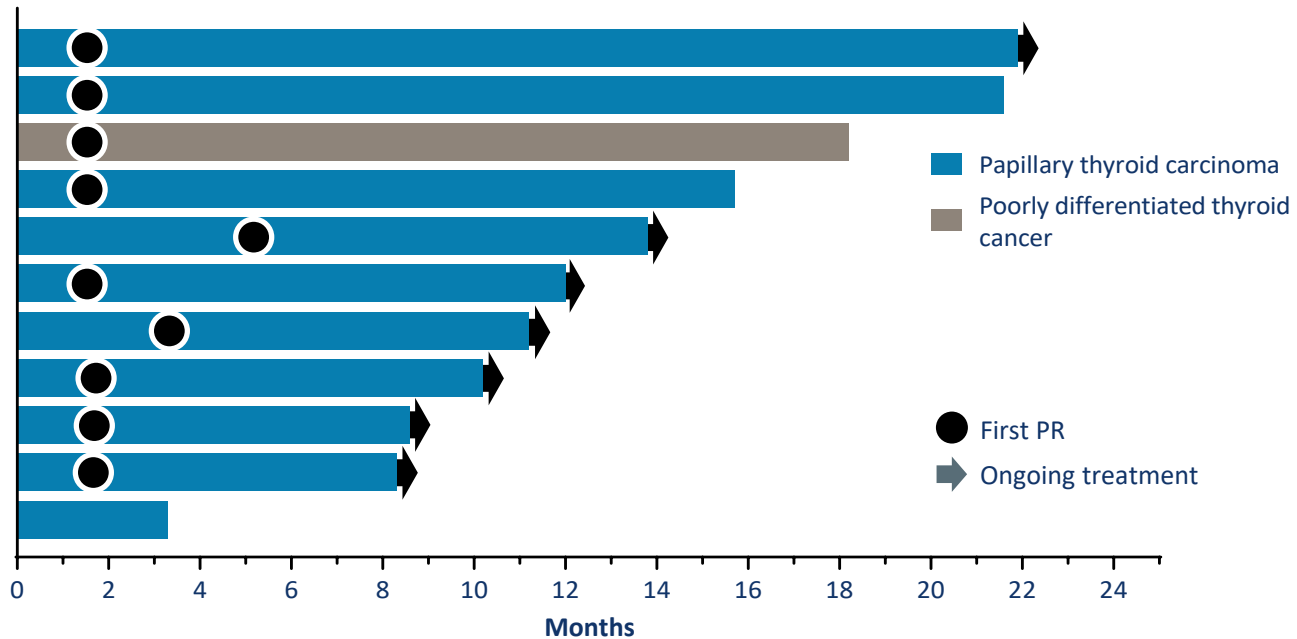
Activity of pralsetinib in *RET* fusion-positive thyroid tumors



| Best response, (response evaluable), % | RET fusion-positive thyroid cancer (n=11) [†] |
|--|--|
| ORR | 91 |
| (95% CI) | (59–100) |
| PR | 91 |
| SD | 9 |
| PD | 0 |
| DCR | 100 |
| (95% CI) | (72–100) |

Blinded independent central review of tumor response; response-evaluable patients enrolled by Jul 11, 2019, as of a data cut-off Feb 13, 2020. *Patients initially received alternate pralsetinib starting doses in the dose-escalation study portion, but subsequently transitioned to 400 mg QD. [†]Response-evaluable population excludes two patients with papillary thyroid carcinoma without measurable disease at baseline per blinded central review. These two patients were assessed with CR and SD, and continue treatment at 12.9 and 23.3 months, respectively. CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease.

Pralsetinib treatment duration in patients with *RET* fusion-positive thyroid cancer



Blinded independent central review of tumor response; response-evaluable patients enrolled by Jul 11, 2019, as of a data cut-off Feb 13, 2020. PR, partial response.



Case study: 66-year-old man with poorly differentiated thyroid cancer

NCOA4-RET fusion; no previous treatments

Deep and durable PR with pralsetinib (18 months duration; 94% shrinkage of target lesions)

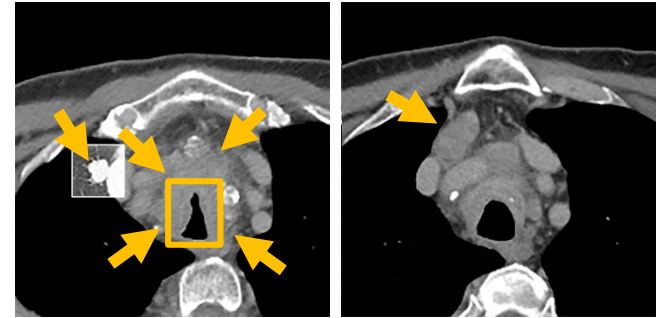
At first disease evaluation (8 weeks on treatment):

- Spiculated mass in the right upper pulmonary lobe previously measuring 6.3 cm resolved with residual scar
- Infiltrative mass previously surrounding and compressing the upper thoracic trachea lost definition and decreased in size
- Superior mediastinal lymph node decreased from 1.6 to 0.6 cm in short-axis dimension

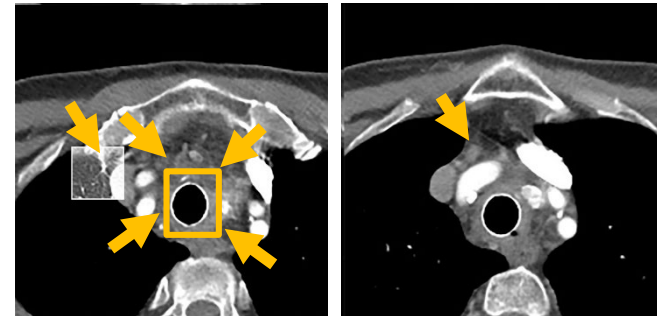
Throughout treatment:

- Thyroglobulin antibodies reduced from 1411 IU/mL to <1 IU/mL
- Complete clearance of NCOA4-RET fusion ctDNA

Baseline



After 8 weeks of therapy

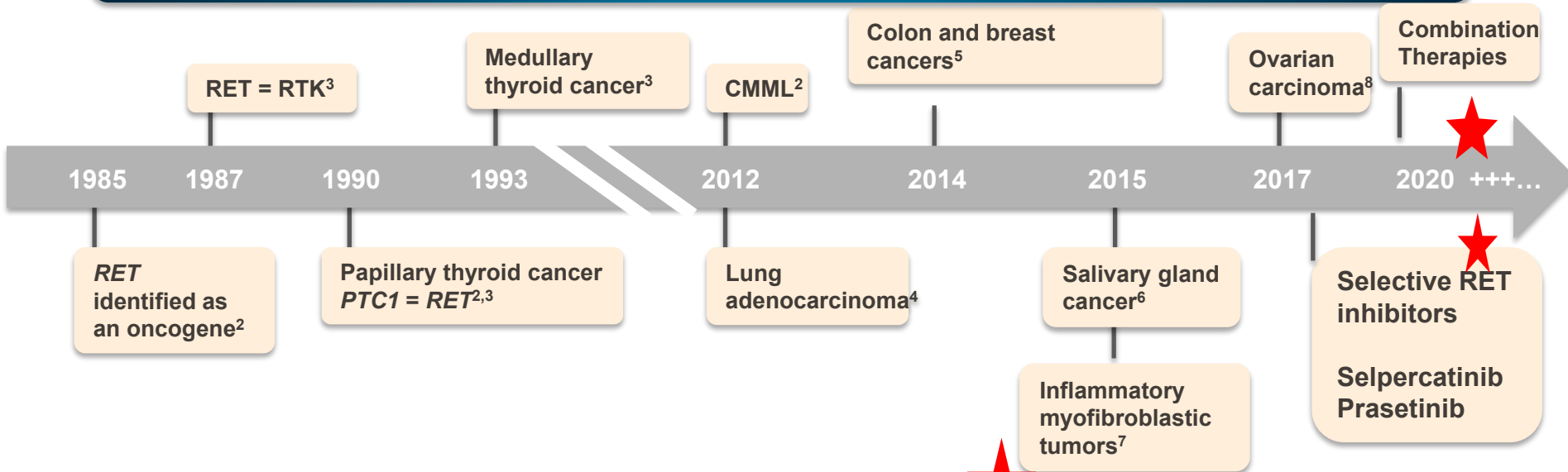


Pralsetinib now FDA approved for RET+ NSCLC

- Pralsetinib has FDA in RET fusion+ Non-small cell Lung cancer as of Sept 4th 2020
- Line agnostic indication
- Pralsetinib has Breakthrough therapy designation granted for RET-mutated MTC and New drug application has been filed.

RET inhibitor Timeline for FDA approval

RET is one of the first oncogenic kinase fusions cloned from an epithelial tumor, and has since been found to be an oncogenic driver primarily in solid tumors^{1,2}

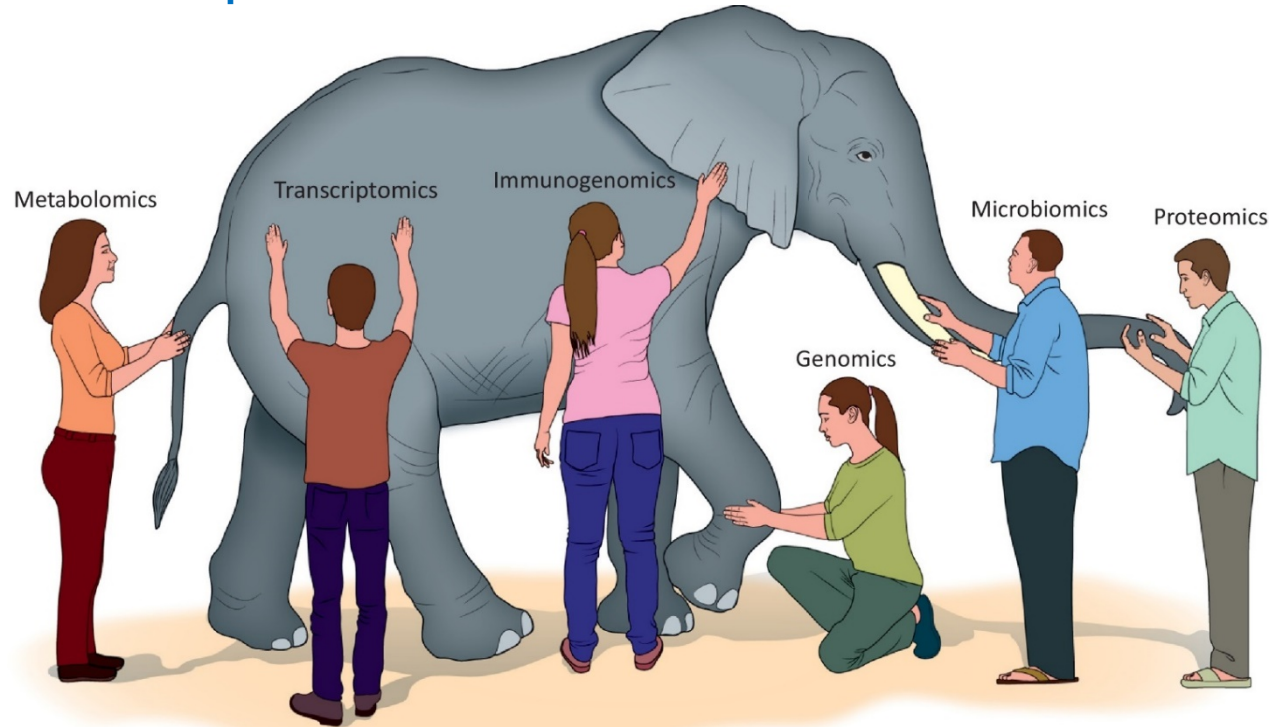


CMML, chronic myelomonocytic leukemia.

1. Subbiah V et al. *Cancer Discov.* 2018;8(7):836-849. 2. Drilon A et al. *Nat Rev Clin Oncol.* 2018;15(3):151-167. 3. Ibáñez CF. *Cold Spring Harb Perspect Biol.* 2013;5(2):a009134. 4. Ju YS et al. *Genome Res.* 2012;22(3):436-445. 5. Stransky N et al. *Nat Commun.* 2014;5:4846. 6. Grünewald I et al. *Oncotarget.* 2015;6(20):18224-18237.

**FDA Approval ~ 3 yrs from
FIH Phase 1**

Six Blind Men and Elephants





- ✓ **Patients and families who enrolled on the clinical trials**
- ✓ **Investigators, & staff at MD Anderson Cancer Center and world wide collaborating sites for the clinical trials**

Contact:

- **Email: vsubbiah@mdanderson.org**
- **Twitter [@VivekSubbiah](https://twitter.com/VivekSubbiah)**