Molecular Testing for Precision Medicine

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

@VivekSubbiah

DISCLOSURES

Relationship(s)	Support
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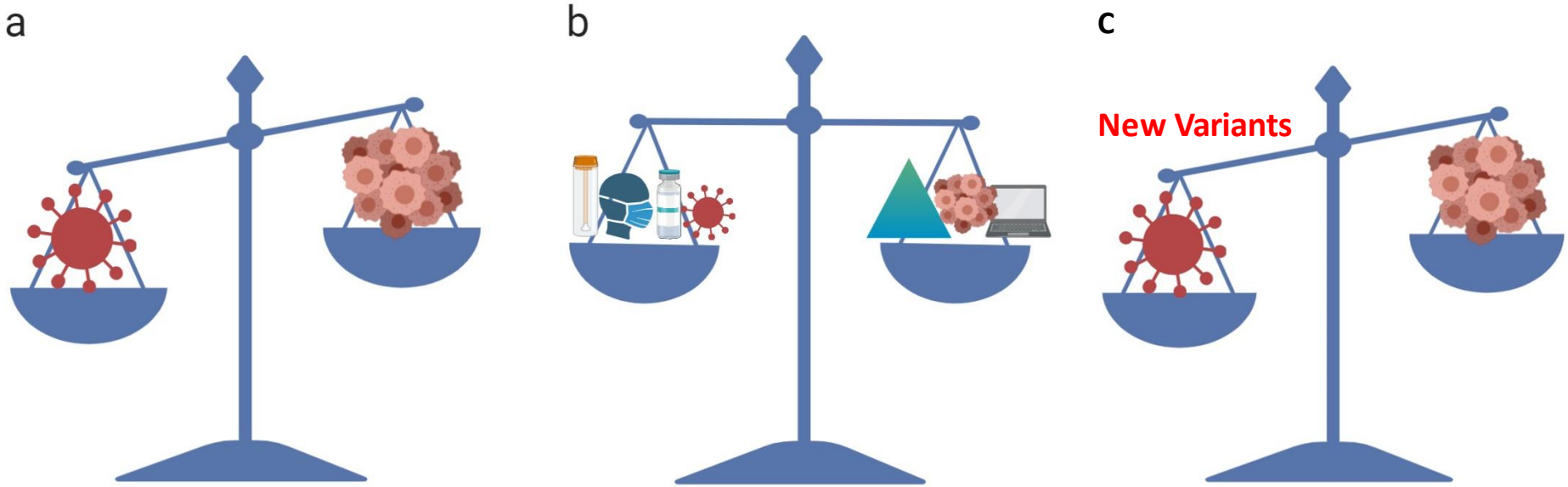
Agenda

- Precision Medicine
- Tumor Agnostic Medicine
- Story of BRAF and RET
- N-of-One
- Resistance mechanisms
- Patient driven precision medicine in the era of social media
- Future outlook

Restoring the balance for cancer care in the COVID-19 era



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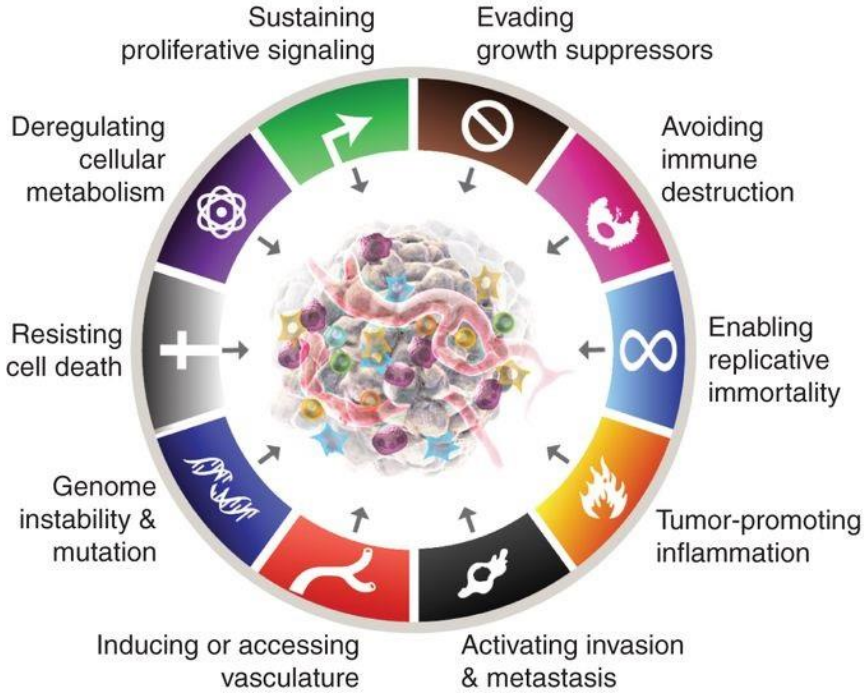
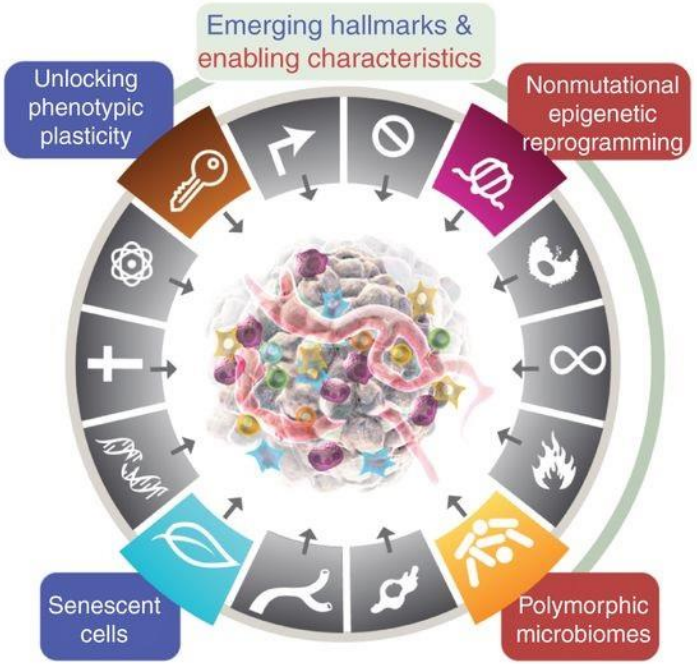
O Alhalabi, V Subbiah, Trends in Cancer 2020

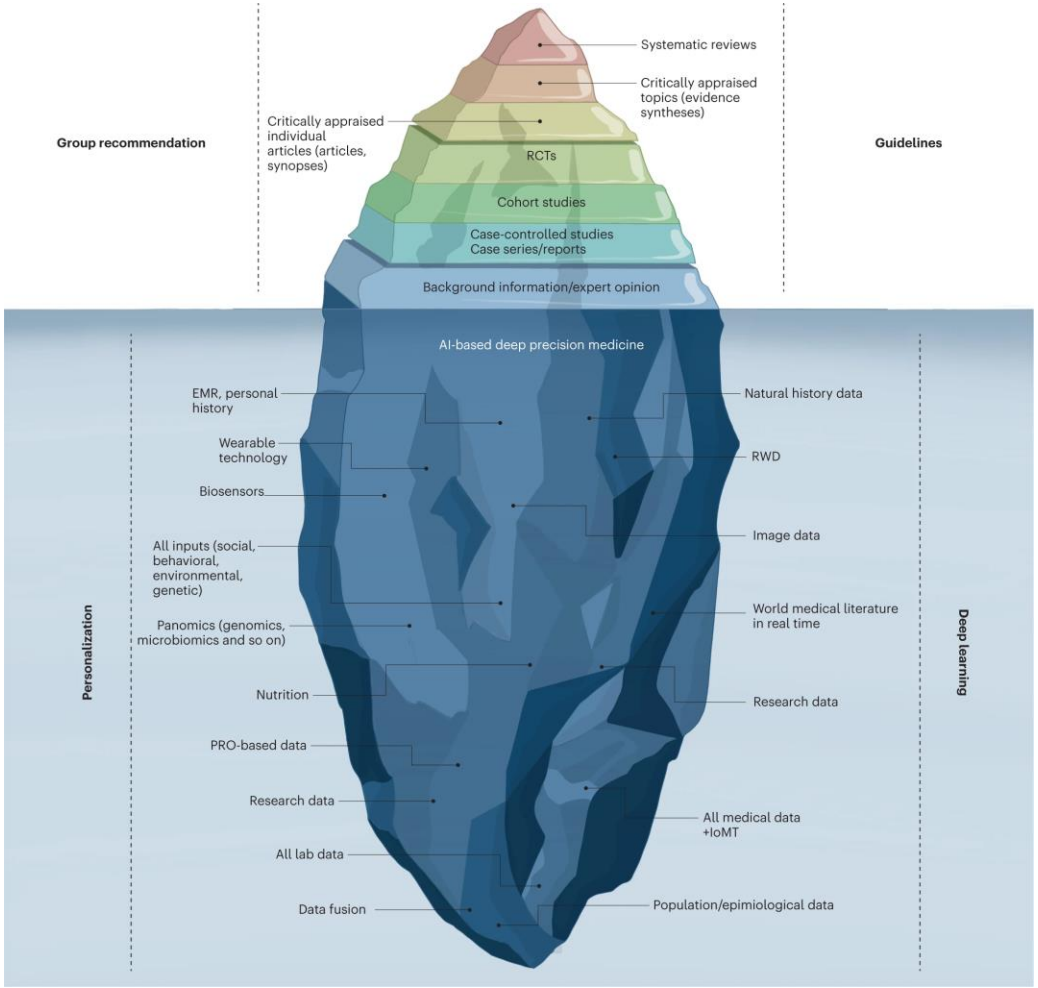
Hallmarks of Cancer: New Dimensions





Hanahan D. Cancer Discov. 2022 Jan;

Evidence-based deep medicine iceberg

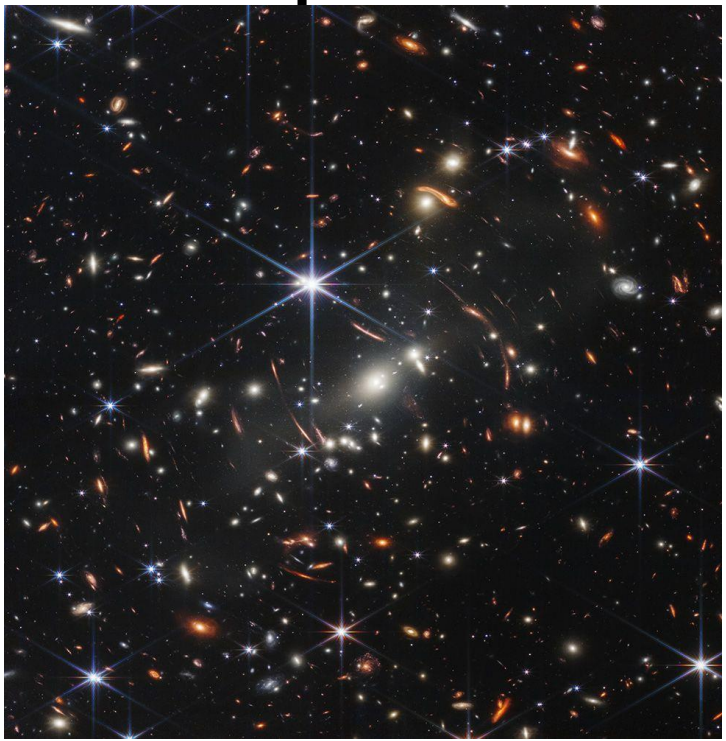


Subbiah V Nature Medicine 2023

HOW DID WE TREAT ADVANCED and METASTATIC CANCERS?

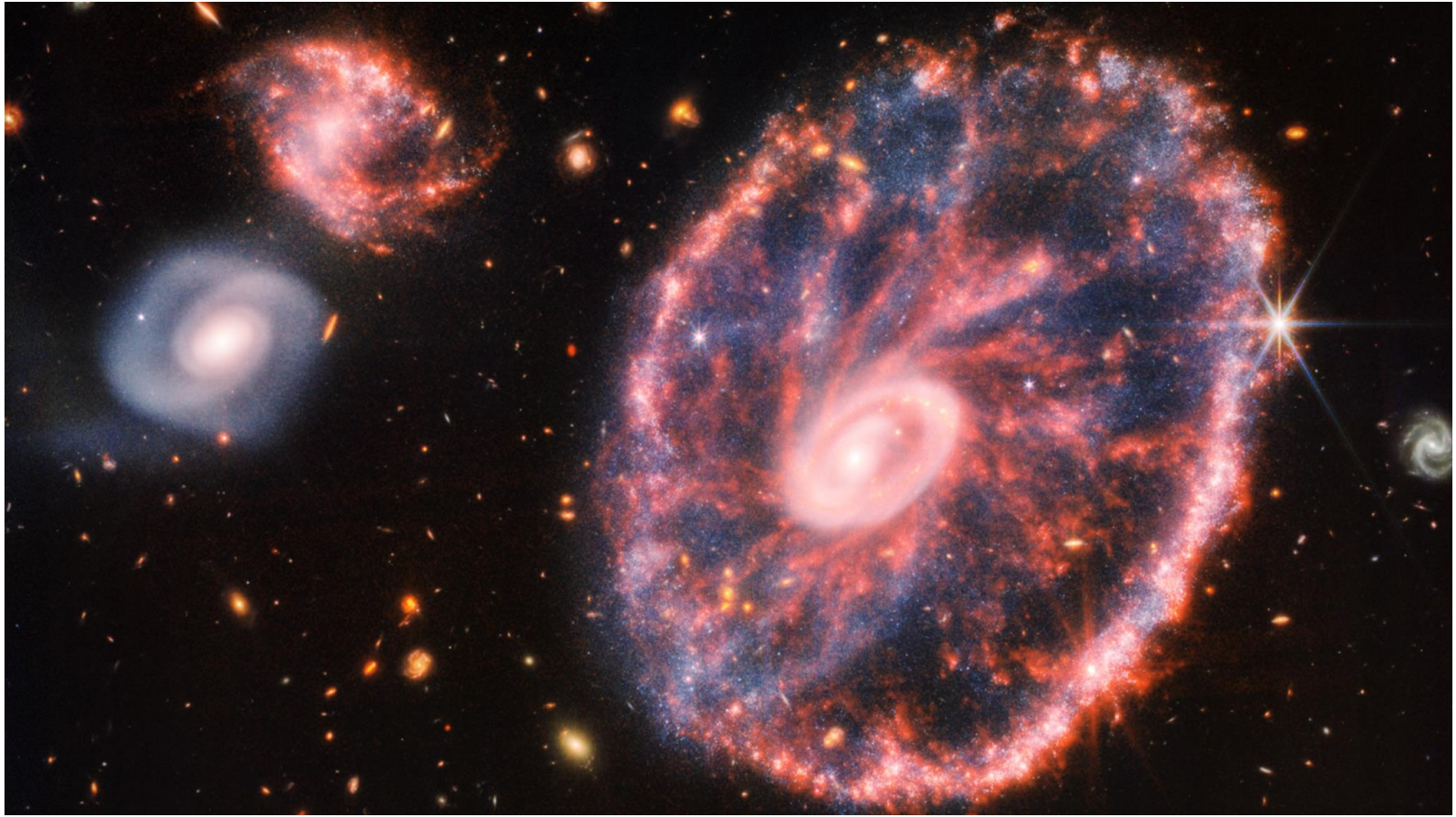
Gallileo Telescope to James Webb telescope

Jupiters moons – similar to what Gallileo saw using an amateur telescope



The telescope's first public image shows a cluster of galaxies called SMACS 0723, which is so heavy it warps and magnifies the light from distant galaxies beyond it.

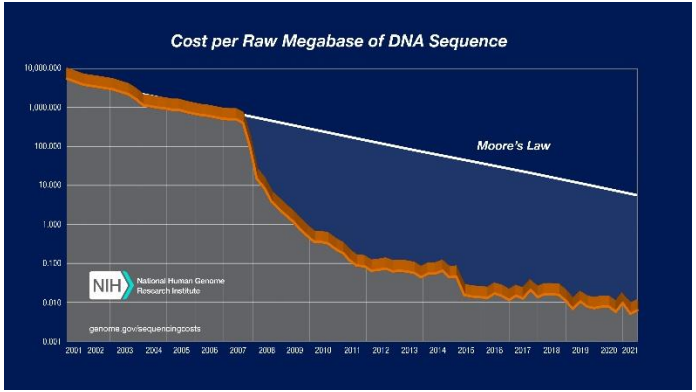
Credit:
NASA, ESA, CSA, and STScI



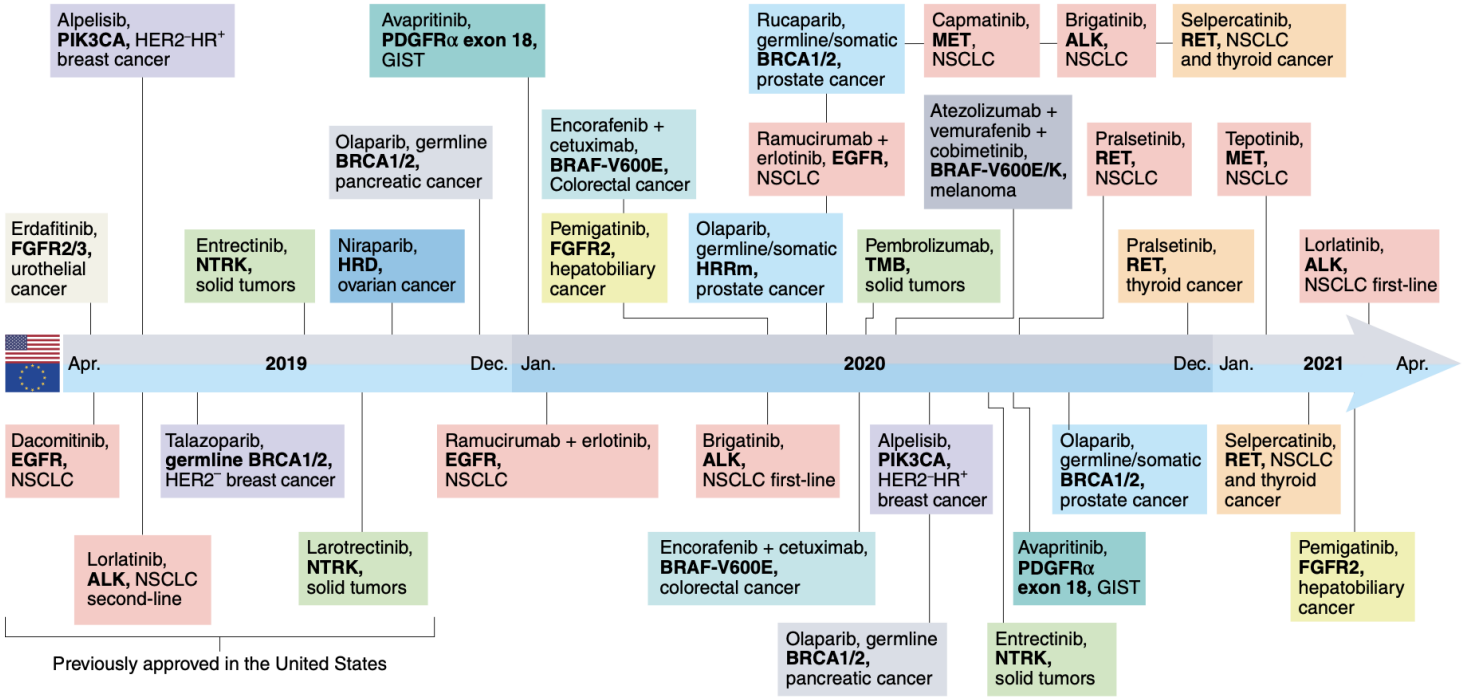
Cartwheel Galaxy - alongside two smaller companion galaxies - which was created as the result of an intergalactic collision Pic: NASA, ESA, CSA, STScI

Light microscope → Molecular microscope

Figure 1



Precision Medicines in Cancer



Adapted from: Mateo et al.; Nat. Medicine 2022

Tumor Agnostic Treatment

- A tumor-agnostic treatment is a drug treatment that is used to treat any kind of cancer, regardless of where in the body it started or the type of tissue from which it developed.
- This type of treatment can be used when the tumor has a very specific molecular alteration that is targeted by a drug likely to work
- Most cancer treatments are developed to treat a cancer that has developed in a specific organ or tissue eg. breast cancer or lung cancer.
- A tumor-agnostic treatment treats any kind of cancer as long as the cancer has the specific molecular alteration targeted by the drug.

New Era of Tissue-agnostic approvals driven by genomics: A Marriage of Genomics and Immunotherapy

- **FDA approves pembrolizumab (anti-PD1)**
- **for solid tumors based on MSI-H (RR ~45%)**

- May 23, 2017

- Tissue agnostic approval
- Approval based on genomic marker
- **Approval based on retrospective/real-world data**

The NTRK fusion story: Picking needles in Haystacks

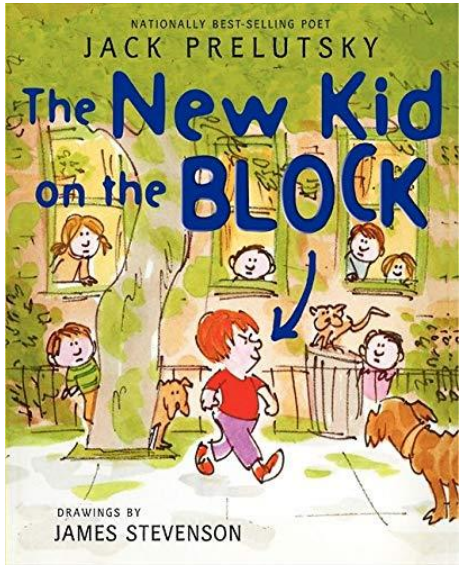
- **Larotrectinib for *NTRK* fusion adult and**
- **pediatric solid tumors**
- FDA approval November 26, 2018

- **Entrectinib for *NTRK* fusion adult**
- **and pediatric solid tumors**
- FDA approval August 16, 2019

The Marriage of Genomics & Immunotherapy: Story continues

- Pembrolizumab for TMB≥10 mutations/mb
- adult and pediatric solid tumors
- FDA approval June 16, 2020

- Dostarlimab (anti-PD1) for
- adult dMMR solid tumors
- FDA approved August 17 2021



And the story continues……

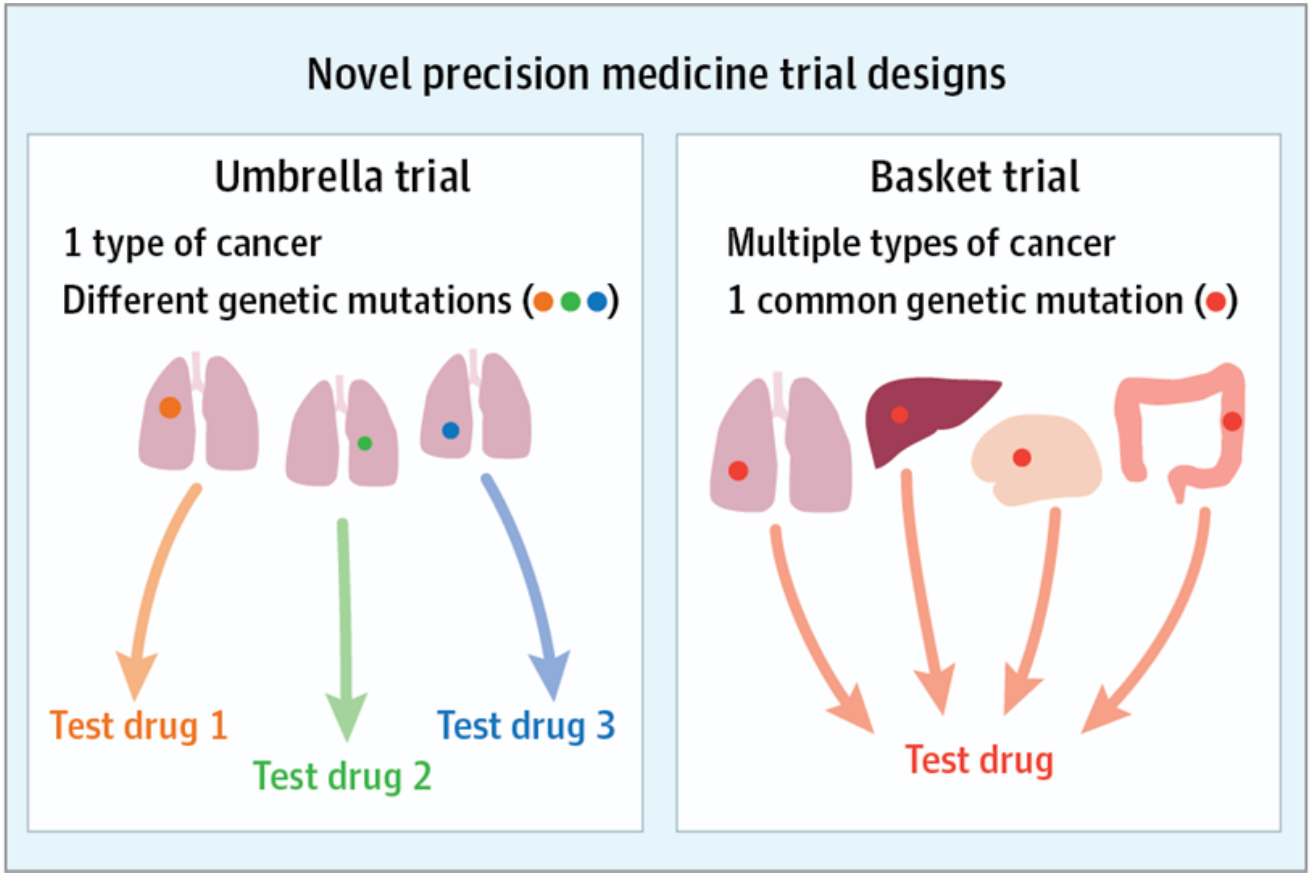
- **Belzutifan** Adults with von Hippel-Lindau (VHL) disease (VHL germline mutations) with renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET)
- FDA approval August 13, 2021

NEW

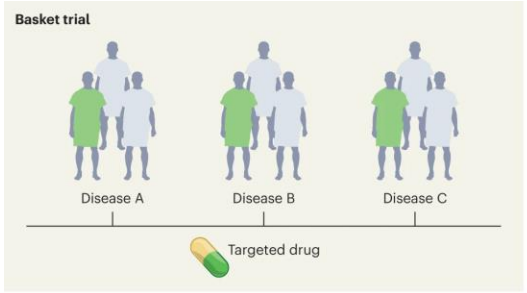
- **Dabrafenib and trametinib** for adult + pediatric patients 6 years or older with unresectable or metastatic BRAF V600E–mutant solid tumors – FDA approved – June 23rd 2022

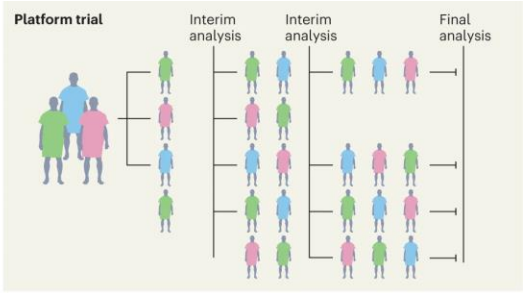
Precision Oncology Paradigm and Rare Cancers- Story of BRAF and RET

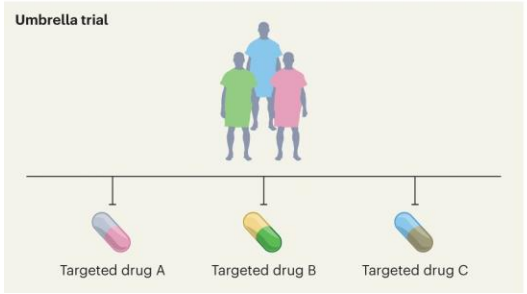
- **Vemurafenib Basket**
- **Rare Cancers Oncology Agnostic Research**
- **RET+ Cancers**

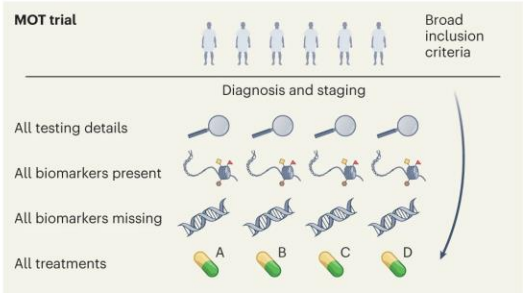

Novel precision medicine trial designs
Umbrella trial
1 type of cancer
Different genetic mutations (●●●)
Test drug 1
Test drug 2
Test drug 3
Basket trial
Multiple types of cancer
1 common genetic mutation (●)
Test drug

Classes of Master Protocols









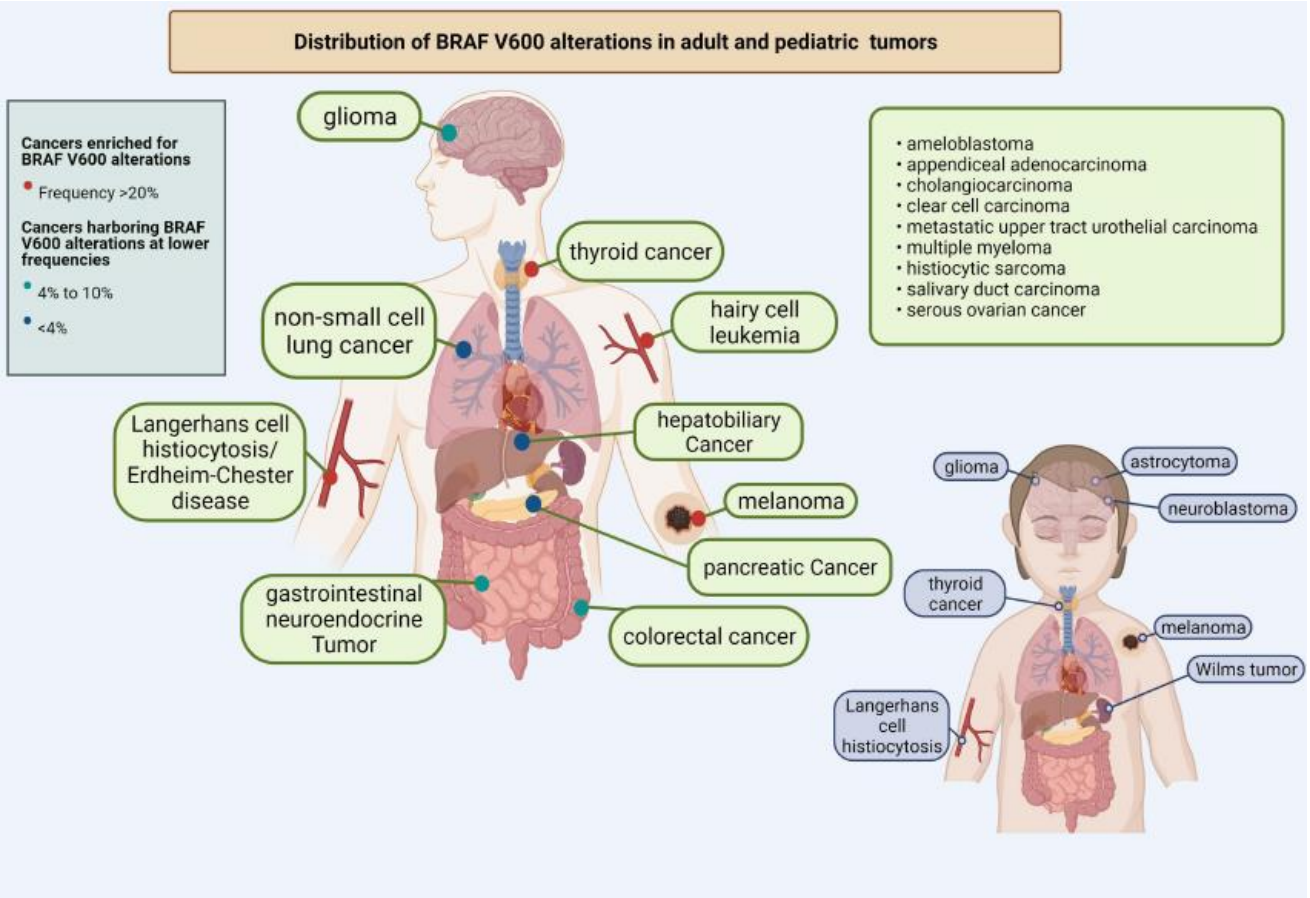
Subbiah V. Nature Medicine 2023

BRAF in Cancer beyond Melanoma

- BRAFmut oncogene - 5-10% of all human malignancies; Most of the tumors that **express BRAF V600E mutations are rare or ultra-rare cancers.**

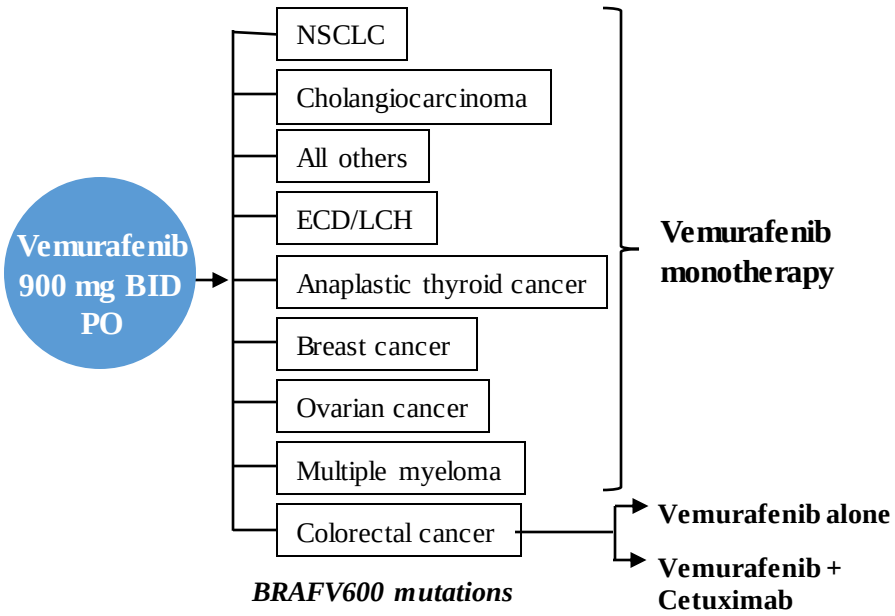
- Constitutive activation of the MAPK pathway

- Most common mutation of BRAF valine-to-glutamic acid substitution at codon 600 (V600E)



Adashek J…Subbiah V Mol. Cancer Ther 2022

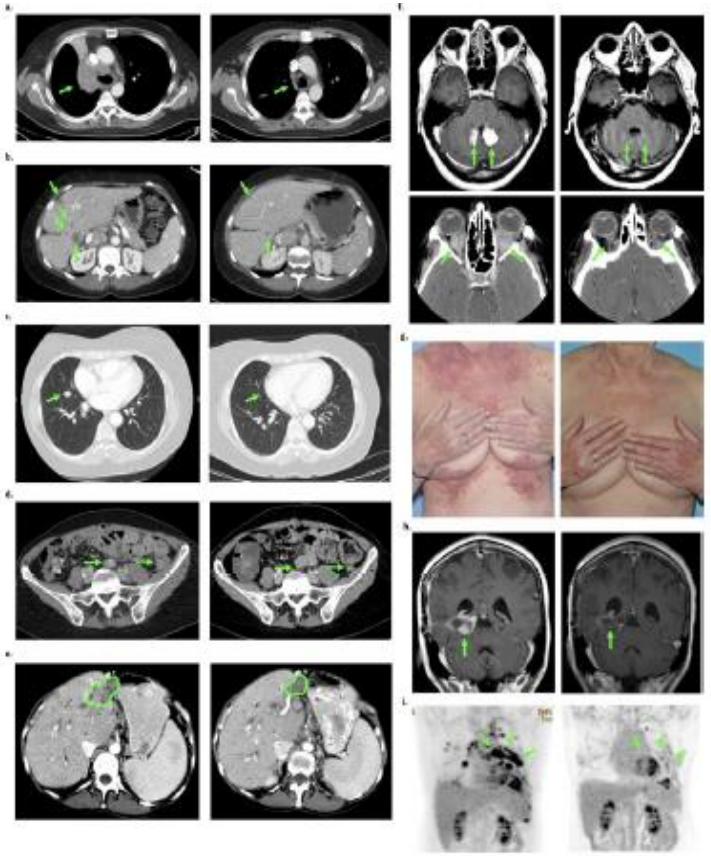
Vemurafenib Basket Trial



- In NSCLC, the response rate was 42%
- **In Erdheim–Chester disease or Langerhans'-cell histiocytosis, the response rate was 43% (FDA approval)**
- Responses in pleomorphic xanthoastrocytoma, anaplastic thyroid cancer, cholangiocarcinoma, salivary-duct cancer, ovarian cancer, and clear-cell sarcoma
- Among patients with colorectal cancer who received vemurafenib and cetuximab.
- Validated BRAF V600 as a therapeutic target beyond melanoma
- Lead to tumor-agnostic sensitivity to vemurafenib with the exception of colorectal cancer

Hyman DM, Puzanov I, Subbiah V, et al. N Engl J Med 2015;373:726-736

BRAF as a Therapeutic Target



- In NSCLC, the response rate was 42%
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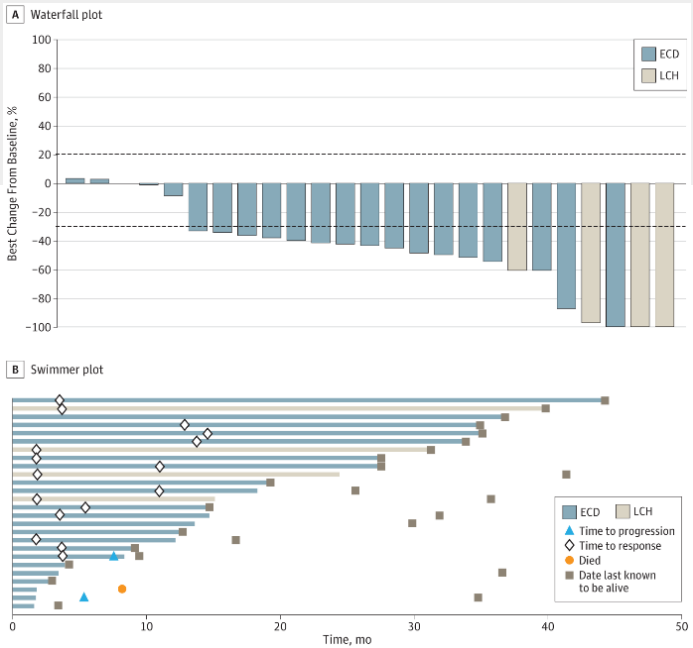
- Responses in pleomorphic xanthoastrocytoma, anaplastic thyroid cancer, cholangiocarcinoma, salivary-duct cancer, ovarian cancer, and clear-cell sarcoma and among patients with colorectal cancer who received vemurafenib and cetuximab.

Hyman*, Puzanov, Subbiah V* et al, *NEJM* 2015

Vemurafenib for BRAF V600–Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study

JAMA Oncol. 2018;4(3):384-388. doi:10.1001/jamaoncol.2017.5029

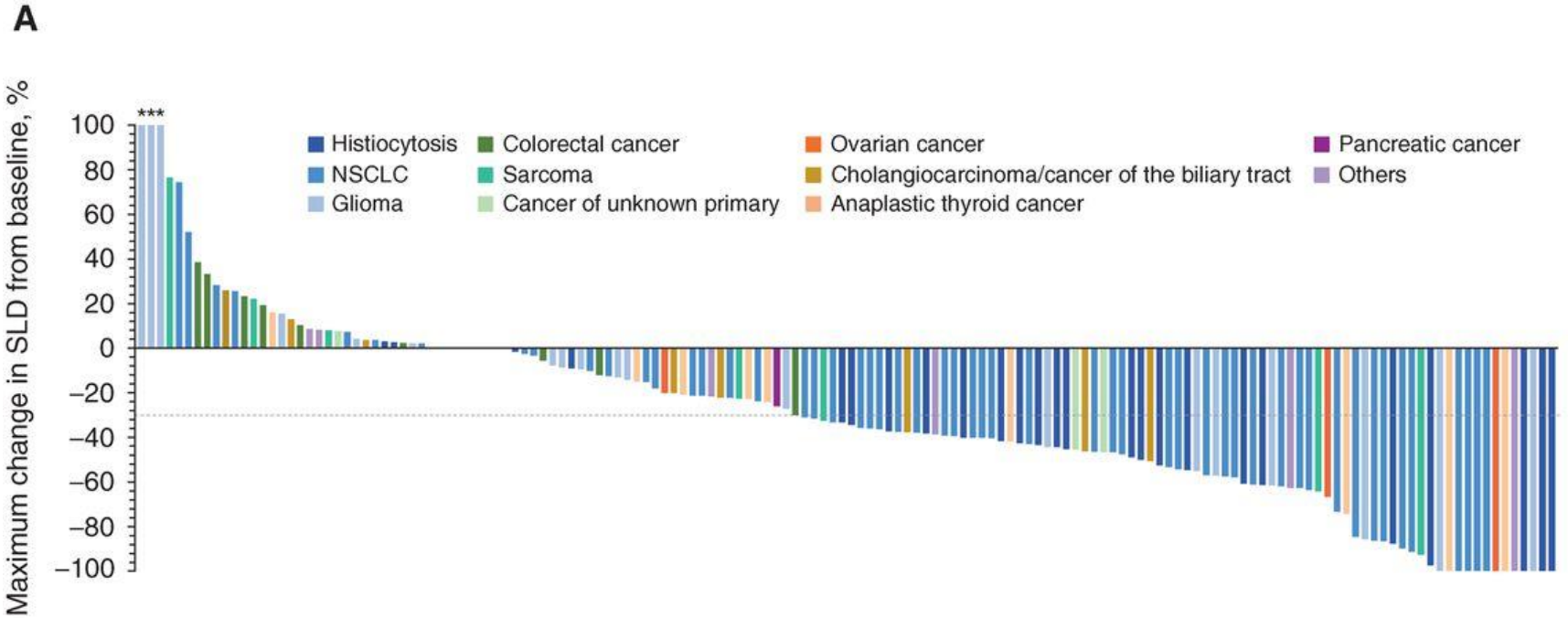


FDA APPROVED

JAMA Network™

Efficacy of Vemurafenib in Individual Patients With BRAF V600–Mutant Erdheim-Chester Disease (ECD) or Langerhans Cell Histiocytosis (LCH)One patient did not have measurable disease at baseline and was thus not evaluable for response but was included in the intention-to-treat analysis as a nonresponder. The line at −30% represents the cutoff for partial response by RECIST criteria (Response Evaluation Criteria in Solid Tumors); the line at +20% demarcates disease progression, which did not occur in any of the patients in this study.

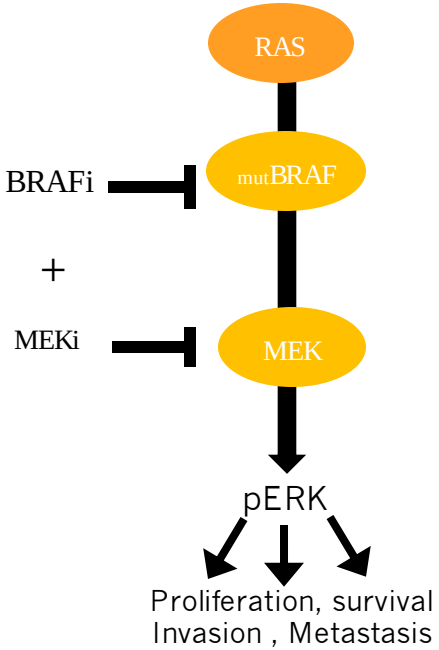
Pan-Cancer Efficacy of Vemurafenib in *BRAF*^{V600}-Mutant Non-Melanoma Cancers



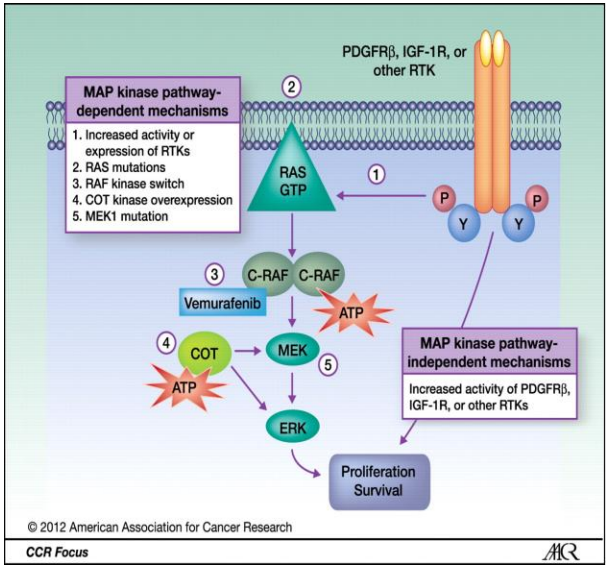
Subbiah V et al Cancer Discov. 2020

Rationale for the BRAF+ MEK Combination

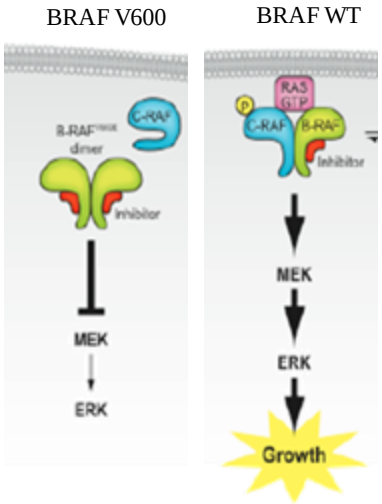
Sustained target inhibition to observe more prolonged and durable anti-tumor effect



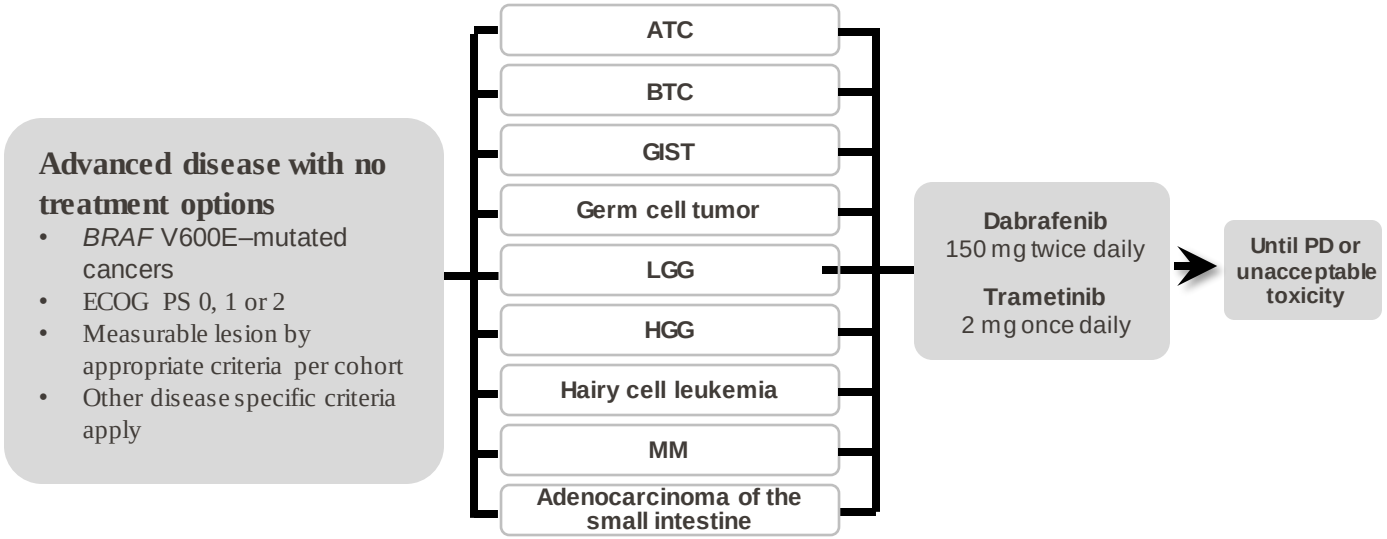
Delay and potentially prevent the development of resistance



Prevent/delay hyperproliferative lesions and secondary malignancies



ROAR Study Design= Rare Oncology Agnostic Research



Primary endpoint: Investigator assessed ORR

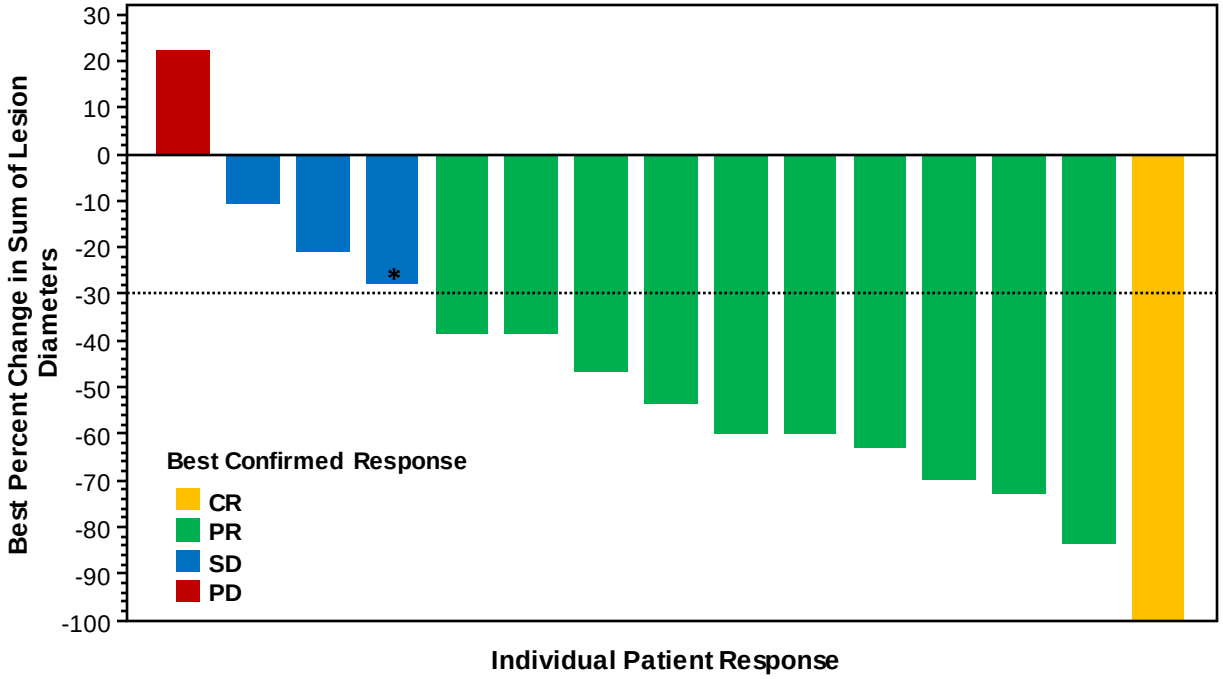
Secondary endpoints: DOR, PFS, OS, safety

Other endpoints: Exploratory Biomarkers, changes from baseline in HRQOL

Subbiah V et al J Clin Oncol 34, 2016 (suppl; abstr TPS2604)

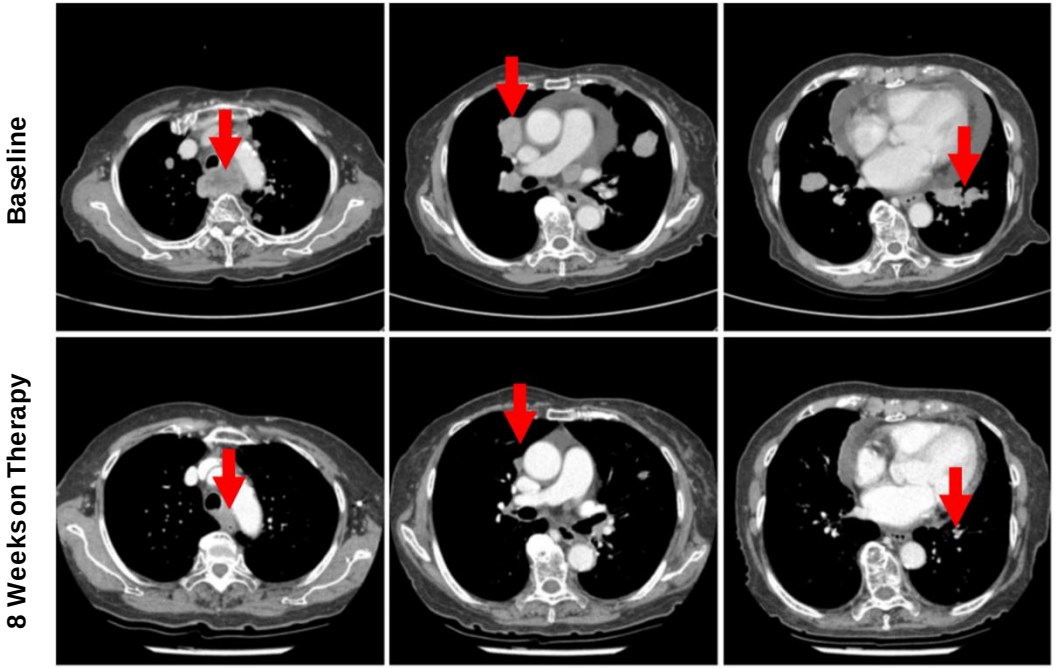
Anaplastic Thyroid Cancer BRAF V600 +

69 % ORR



Subbiah V et al *Journal of Clinical Oncology* 2018 367-13.
DOI: 10.1200/JCO.2017.73.6785

CT scans – Pt with anaplastic thyroid cancer



Subbiah V et al *Journal of Clinical Oncology* 2018 367-13.
DOI: 10.1200/JCO.2017.73.6785

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

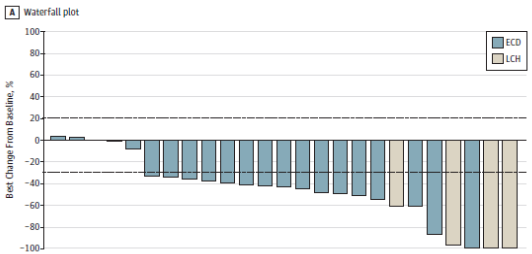
Release

The U.S. Food and Drug Administration approved Tafinlar (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

Successes in Precision Oncology Basket Trials in Rare Cancers

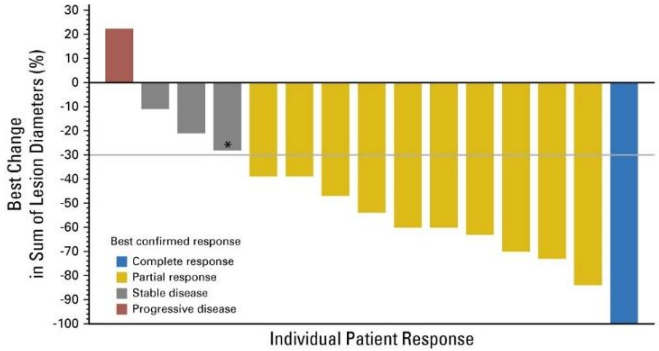
BRAF V600E Erdheim-Chester Disease and Langerhans Cell Histiocytosis



Diamond E, Subbiah V et al, JAMA Oncology 2017

Vemurafenib in Erdheim-Chester

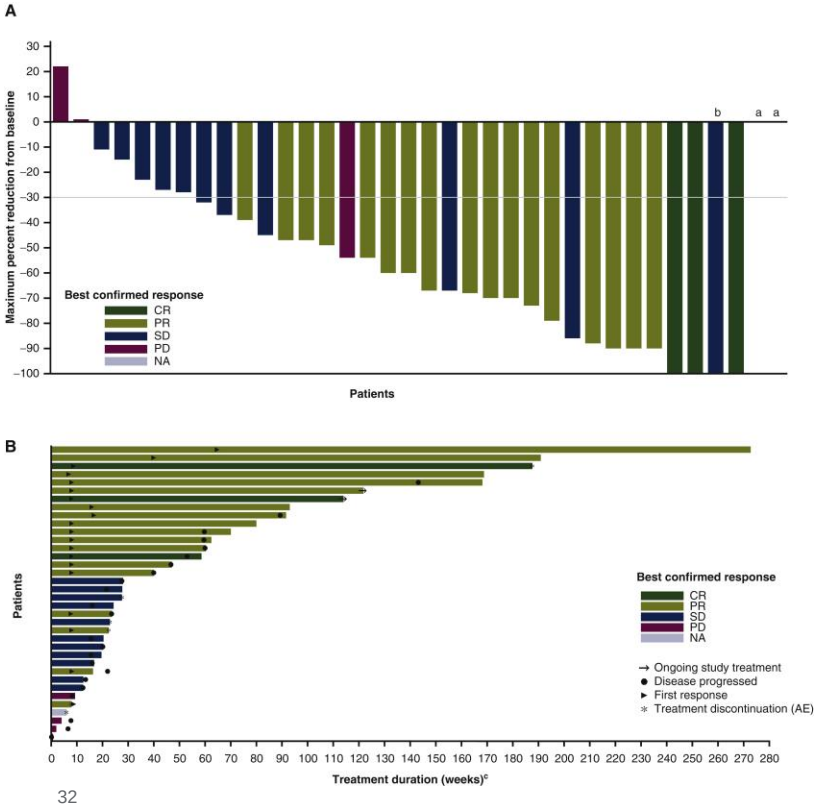
BRAF V600E Anaplastic Thyroid Cancer



- **Dabrafenib/trametinib**
- **Sixteen patients with BRAF V600E-mutated anaplastic thyroid cancer were evaluable**
- **Overall response rate was 69%**

Subbiah V, JCO 2018

Dabrafenib plus trametinib in patients with *BRAF* V600E–mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study



Investigator-assessed responses were observed in 56% of patients, with 50% of responders still in response at 12 months

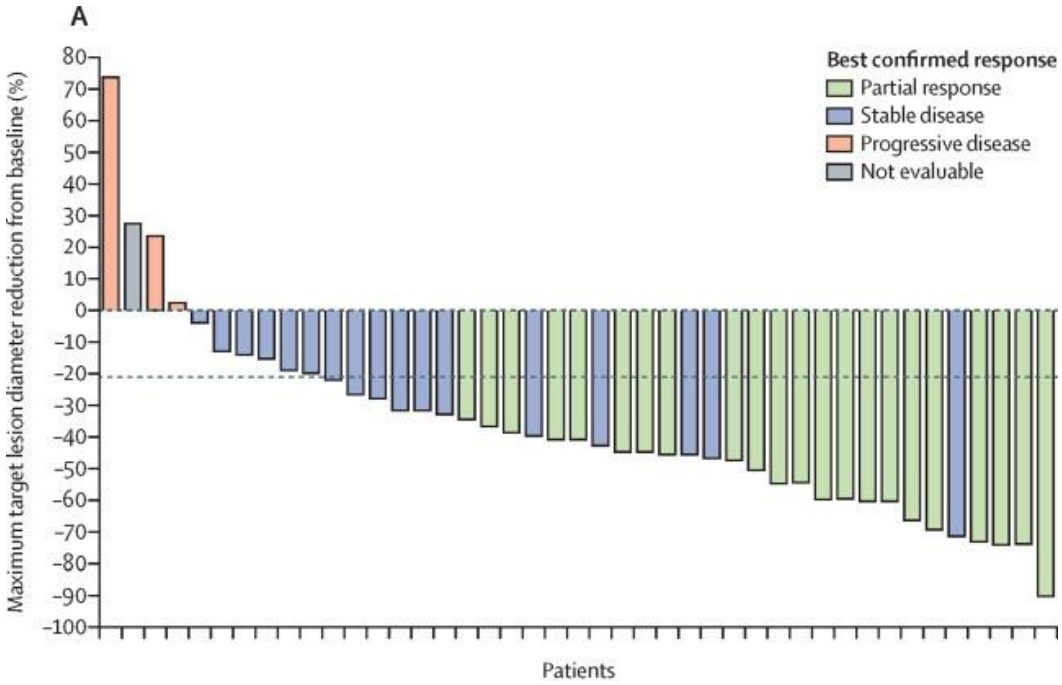
Median OS was 15 months, with the 12-month rate of 52% notable given historic median OS of < 6 months

This updated analysis **confirms the definitive benefit**

Subbiah V et al Jan 2022 , Annals of Oncology *Annals of Oncology*
Volume 33 Issue 4 Pages 406-415 (April 2022)

Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial

Vivek Subbiah, Ulrik Lassen, Elena Élez, Antoine Italiano, Giuseppe Curigliano, Milind Javle, Filippo de Braud, Gerald W Prager, Richard Greil, Alexander Stein, Angelica Fasolo, Jan H M Schellens, Patrick Y Wen, Kert Viele, Aislyn D Boran, Eduard Gasal, Paul Burgess, Palanichamy Ilankumaran, Zev A Wainberg



NCCN GUIDELINES

ORR = 51%, 95% CI 36-67

Implications of all the available evidence

The clinical benefit of dabrafenib plus trametinib supports the use of this combination therapy as a treatment option for patients with *BRAF*^{V600E}-mutated biliary tract cancer. Routine testing for *BRAF*^{V600E} mutations should be considered for all patients with biliary tract cancer.

Subbiah V et al Lancet Oncology 2020

ROAR: dabrafenib plus trametinib in *BRAF* V600E–mutant high-grade + low-grade glioma

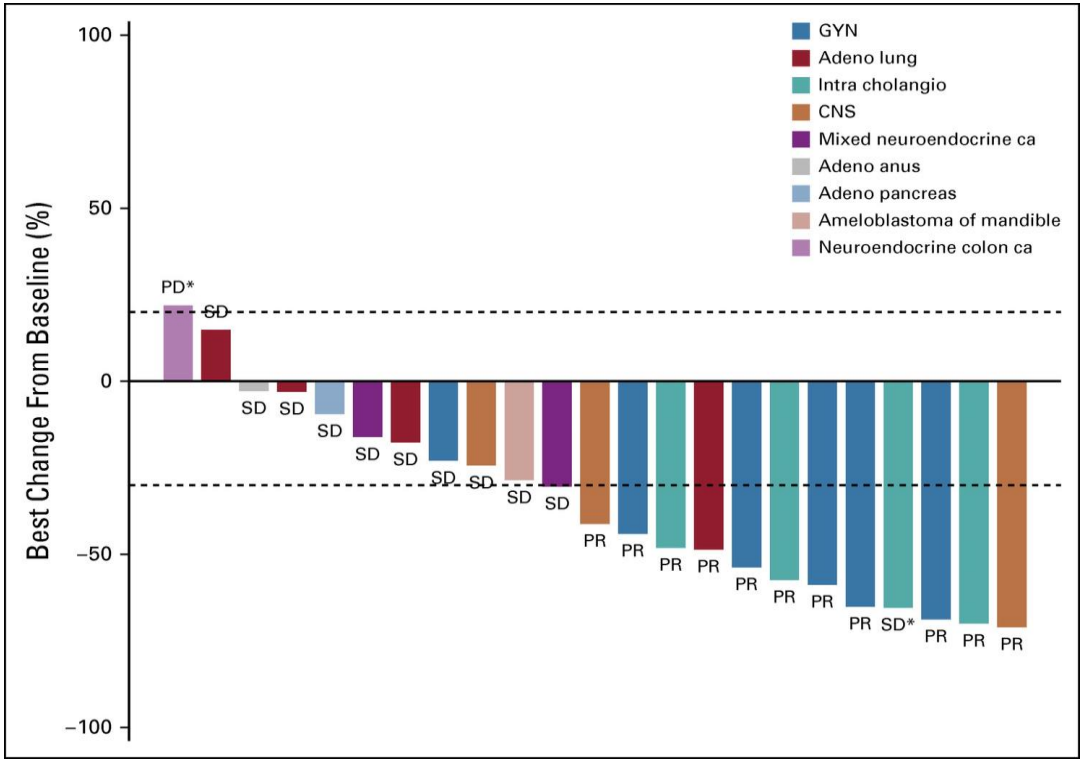
	HGG Cohort[1] (n = 45)		LGG Cohort[2] (n = 13)	
	Investigator-Assessed Total (n = 45)	Independent Radiology Review (n = 45)	Investigator-Assessed Total (n = 13)	Independent Radiology Review (n = 13)
Best response, n (%)				
Complete response	3 (7)	3 (7)	1 (8)	1 (8)
Partial response	12 (27)	11 (24)	6 (46)	6 (46)
Minor response	–	–	2 (15)	2 (15)
Stable disease	10 (22)	5 (11)	3 (23)	2 (15)
Progressive disease	19 (42)	20 (44)	1 (8)	0
Not evaluable	1 (2)	6 (13)	0	2 (15)
ORR (CR + PR), % (95% CI)	33 (20.0-49.0)	31 (18.2-46.6)	–	–
ORR (CR + PR + MR), % (95% CI)	–	–	69 (38.6-90.9)	69 (38.6-90.9)

- In the HGG cohort:
  - The median duration of investigator-assessed response was 36.9 months (95% CI, 7.4-44.2 months)
  - The 24-month DOR rate was 68.8% (95% CI, 36.4%-87.1%)
- In the LGG cohort:
  - The median duration of investigator-assessed response was not reached
  - The estimated 24-month DOR rate was 76.2% (95% CI, 33.2%-93.5%)

CR, complete response; MR, minor response; PR, partial response; RANO, Response Assessment in NeuroOncology.
1. Wen PY, et al. *J Clin Oncol.* 2010;28:1963-1972; 2. van den Bent MJ, et al. *Lancet Oncol.* 2011;12:583-593.

Wen P…..Subbiah V Lancet Onc 2022

Dabrafenib and Trametinib in Patients With Tumors With *BRAF*^{V600E} Mutations: Results of the NCI-MATCH Trial Subprotocol H



April K. S. Salama et al JCO.20.00762

NEW

FDA APPROVED

BRAF+ MEK Tissue Agnostic Approval !

ROAR + NCI-MATCH Arm H + Study X2101 study in pediatric patients with refractory or recurrent solid tumors.

Tumor Type[a]	N	Objective Response Rate (ORR)		Duration of Response (DoR)
		%	95% CI	Range (months)
Biliary tract cancer[b]	48	46	(31, 61)	1.8[d], 40[d]
High grade glioma[c]	48	33	(20, 48)	3.9, 44
Glioblastoma	32	25	(12, 43)	3.9, 27
Anaplastic pleomorphic xanthoastrocytoma	6	67	(22, 96)	6, 43
Anaplastic astrocytoma	5	20	(0.5, 72)	15
Astroblastoma	2	100	(16, 100)	15, 23[d]
Undifferentiated	1	PR	(2.5, 100)	6
Anaplastic ganglioglioma	1	0	NA	NA
Anaplastic oligodendroglioma	1	0	NA	NA
Low grade glioma	14	50	(23, 77)	6, 29[d]
Astrocytoma	4	50	(7, 93)	7, 23
Ganglioglioma	4	50	(7, 93)	6, 13
Pleomorphic xanthoastrocytoma	2	50	(1.3, 99)	6
Pilocytic astrocytoma	2	0	NA	NA
Choroid plexus papilloma	1	PR	(2.5, 100)	29[d]
Gangliocytoma/Ganglioglioma	1	PR	(2.5, 100)	18[d]
Low grade serous ovarian carcinoma	5	80	(28, 100)	12, 42[d]
Adenocarcinoma small intestine	4	50	(7, 93)	7, 8
Adenocarcinoma pancreas	3	0	NA	NA
Mixed ductal / adenoneuroendocrine carcinoma	2	0	NA	NA
Neuroendocrine carcinoma of colon	2	0	NA	NA
Ameloblastoma of mandible	1	PR	(2.5, 100)	30
Combined small cell-squamous carcinoma of lung	1	PR	(2.5, 100)	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1	PR	(2.5, 100)	8
Adenocarcinoma of anus	1	0	NA	NA
Gastrointestinal stromal tumor	1	0	NA	NA

Abbreviations: PR, partial response.

[a] Excludes NSCLC (n=6) and ATC (n=36) (previously approved tumor types for MEKINIST in combination with dabrafenib).

[b] Median DoR 9.8 months (95% CI: 5.3, 20.4).

[c] Median DoR 13.6 months (95% CI: 5.5, 26.7).

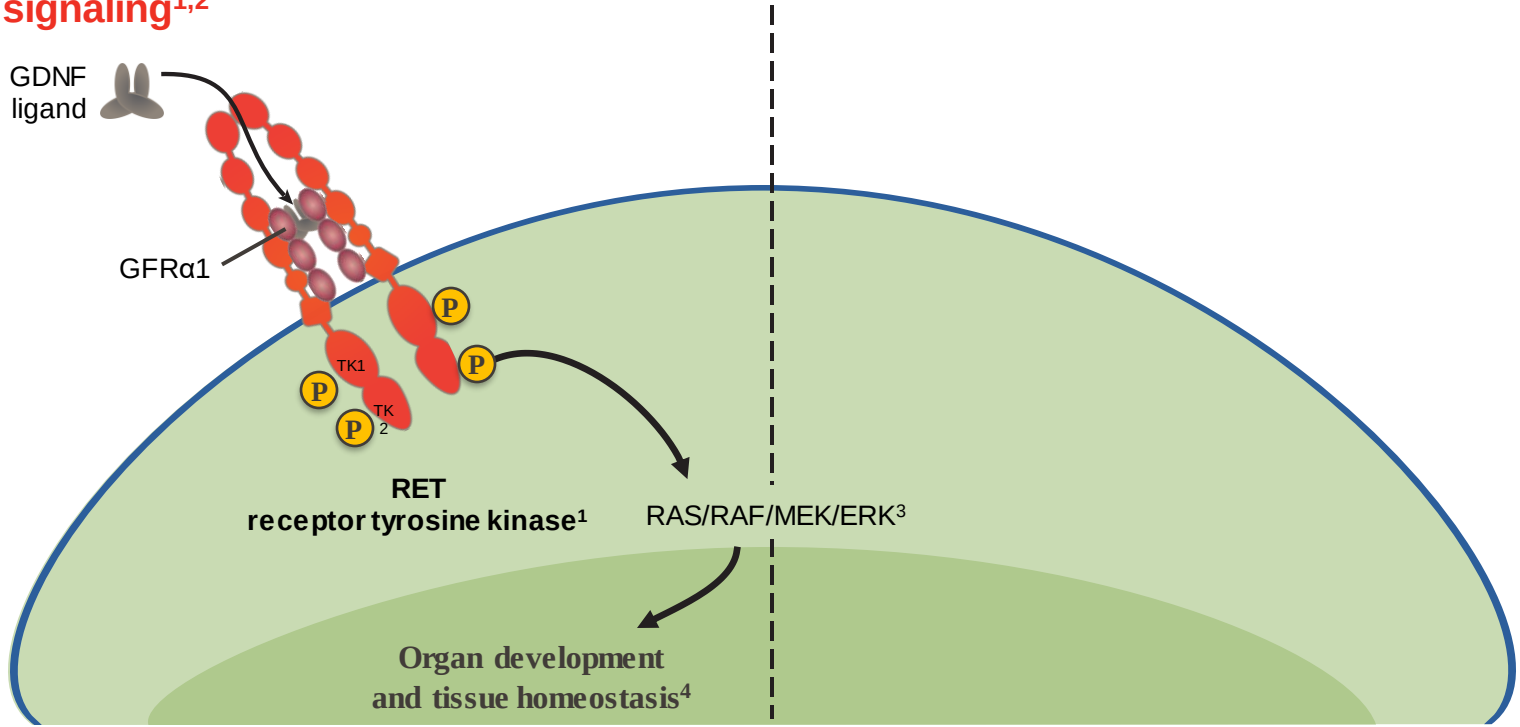
[d] Denotes a right-censored DoR.

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

- RET aberrations in oncology
- RET alterations in NSCLC, RET alterations in MTC and other cancers
- Selective RET inhibitors
- Selpercatinib
- Pralsetinib

RET is an RTK required for normal development[1]

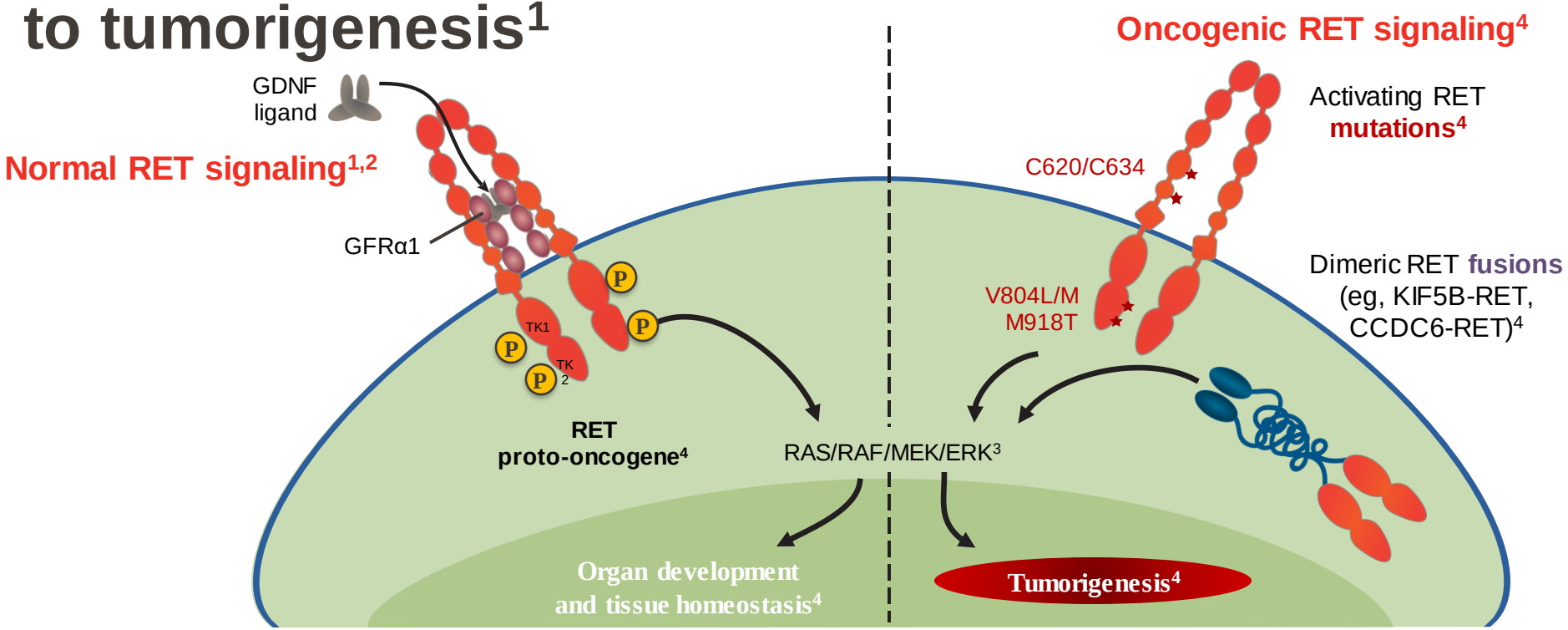
Normal RET signaling[1,2]



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.

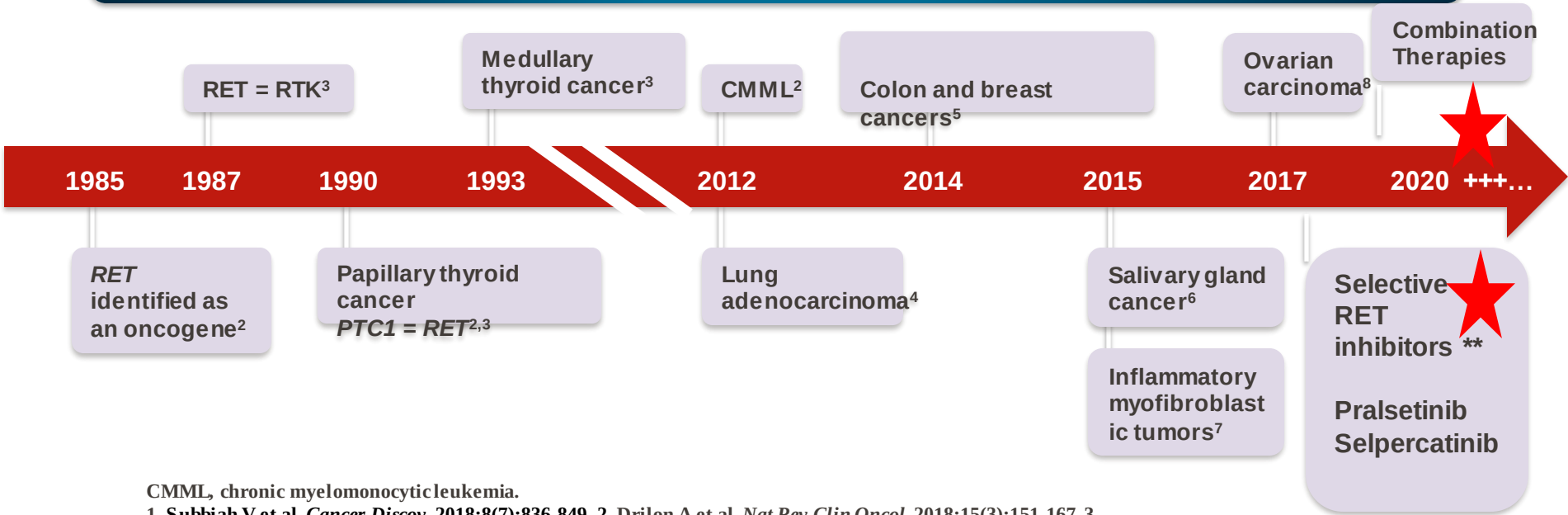
Alterations in RET structure and function can lead to tumorigenesis[1]



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.

Oncogenic *RET* alterations have been identified in numerous cancers[1]

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]**

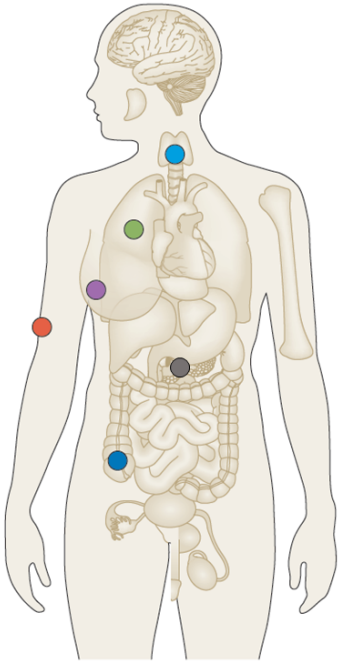


CMML, chronic myelomonocytic leukemia.

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.

RET is activated by two major mechanisms in cancer

RET fusions



Non-small cell lung cancer (2%)

Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)

Salivary gland cancer (<1%)

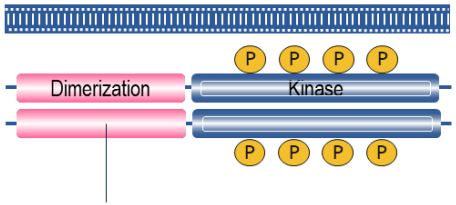
Spitz tumors (<1%)

Colorectal cancer (<1%)

Ovarian cancer (<1%)

Myeloproliferative disorders (<1%)

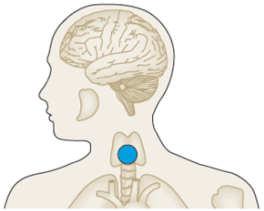
Many others (<1%)



KIF5B (most common in lung cancer)

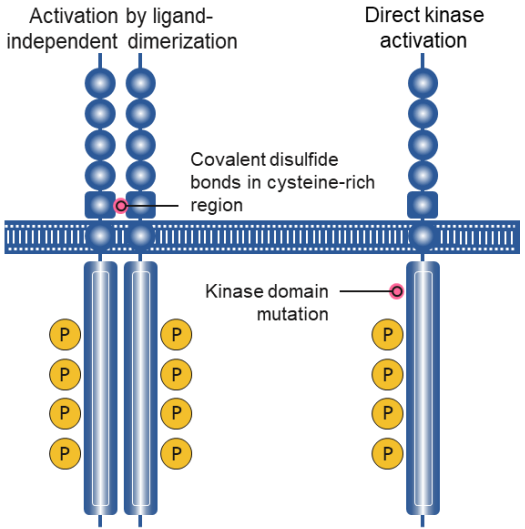
CCDC6 or NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

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



Common mutation: **RET M918T**

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

Sporadic RET M918T/V804M-mutant N-of-1 trial

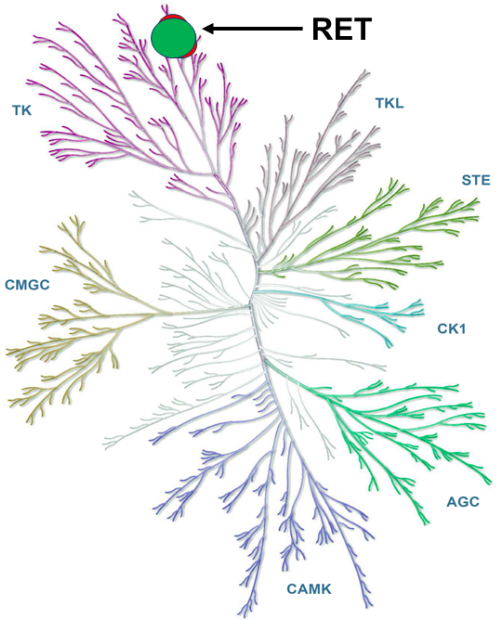
- 49-year old man with advanced MTC s/p total thyroidectomy with RET M918T mutation
- Progressive disease after six MKI treatments over 7 years.
- MKI regimens: **sorafenib** [best response of progressive disease (PD)], **vandetanib** [stable disease (SD)], **cabozantinib** (SD), **MGCD-516** (PD), **RXDX-105** [partial response (PR)], and **vandetanib plus everolimus** (PD).
- Each treatment was discontinued for disease progression in the liver, most recently with hepatomegaly, large-volume ascites, severe fatigue and markedly decreased performance status.
- Cachectic, 30 Bowel movements a day, rapidly declining ECOG PS.
- Molecular analysis of cell-free DNA (Guardant360®) isolated from blood taken before vandetanib plus everolimus treatment identified the founder ***RET M918T*** mutation together with a ***RET V804M*** gatekeeper mutation

- **What would you do next ?**

LOXO-292 or SELPERCATINIB is a potent and selective RET inhibitor

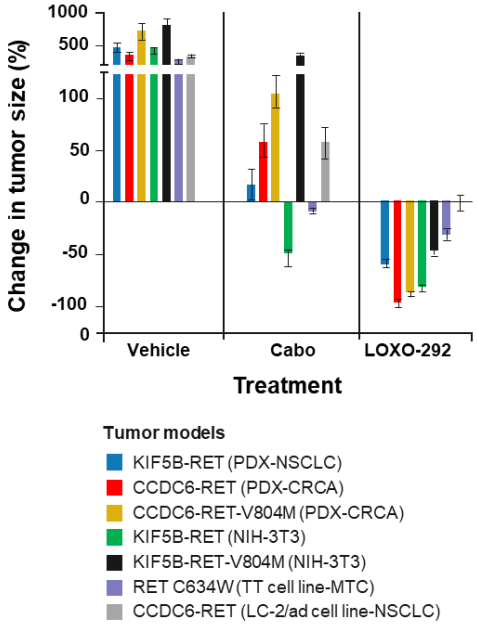
Kinome selectivity

Highly selective for RET



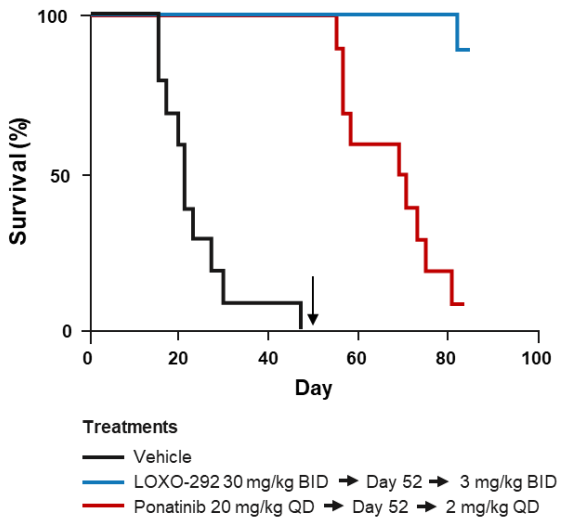
Xenograft models

Multiple fusions/mutations/histologies



Orthotopic brain model

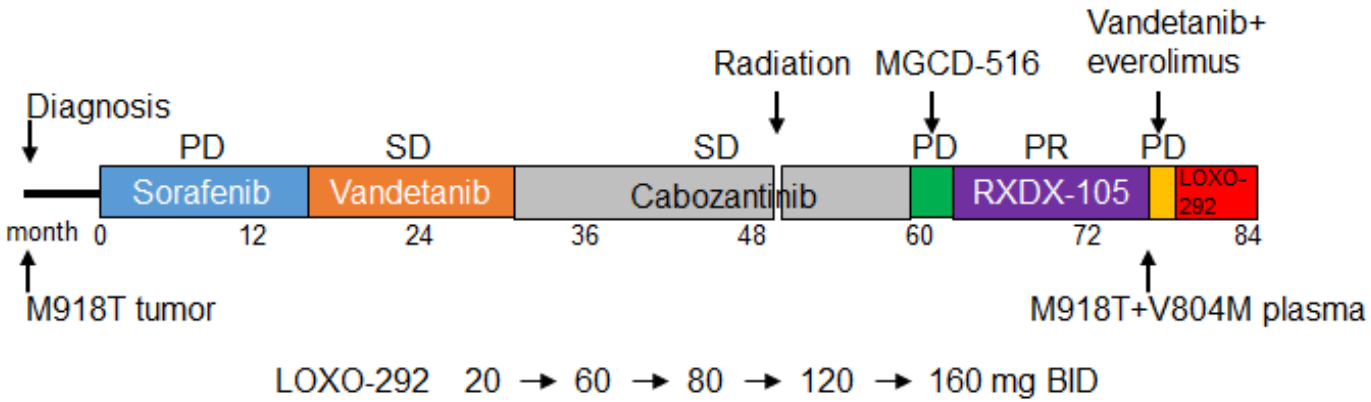
CCDC6-RET orthotopic brain PDX



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

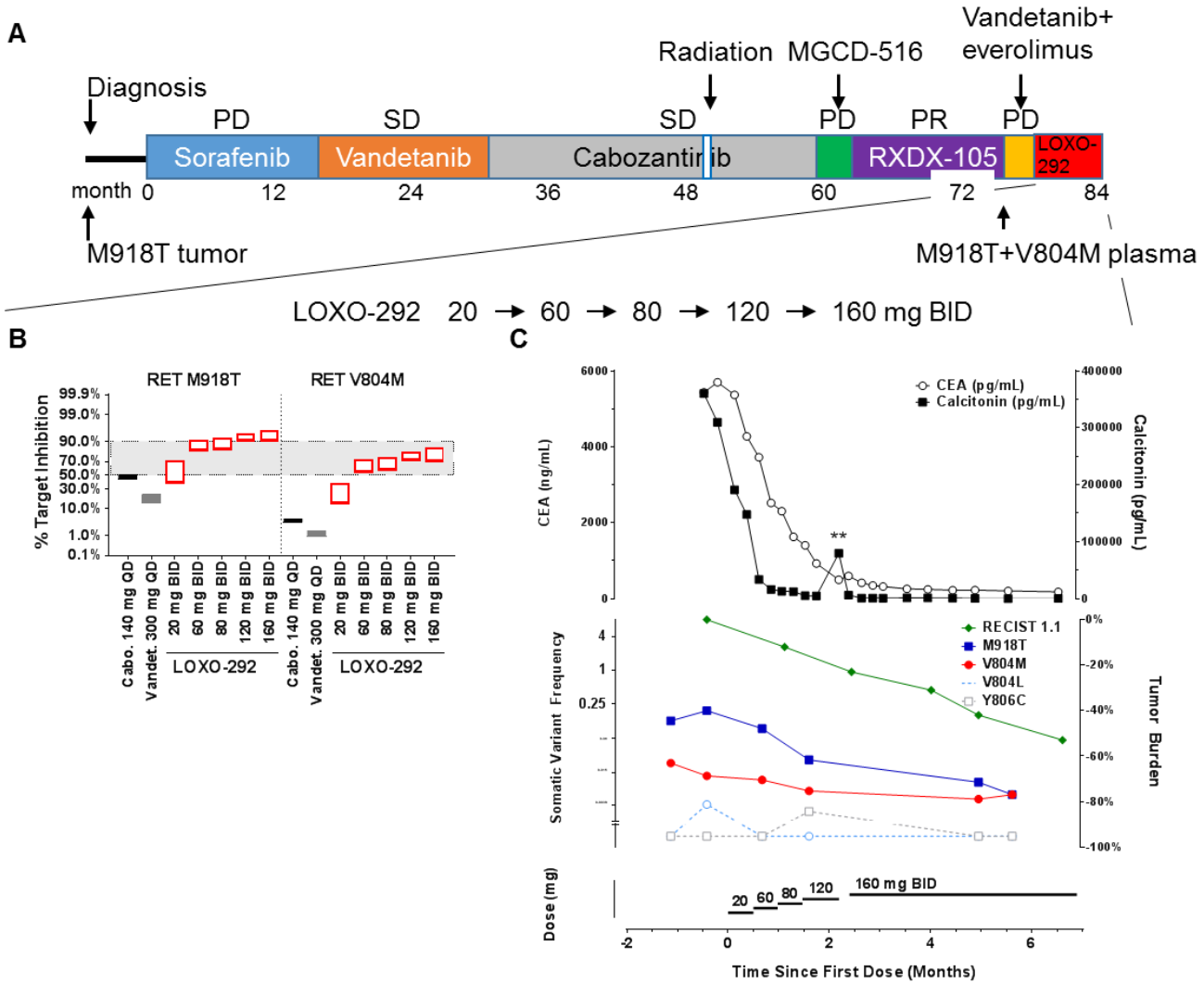
Sporadic RET M918T/V804M-mutant response to Selpercatinib

- **Treated with LOXO-292/ Selpercatinib by *"single patient", N of 1 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")**
- **All side effects grade 1 and have not interrupted dosing of LOXO-292**

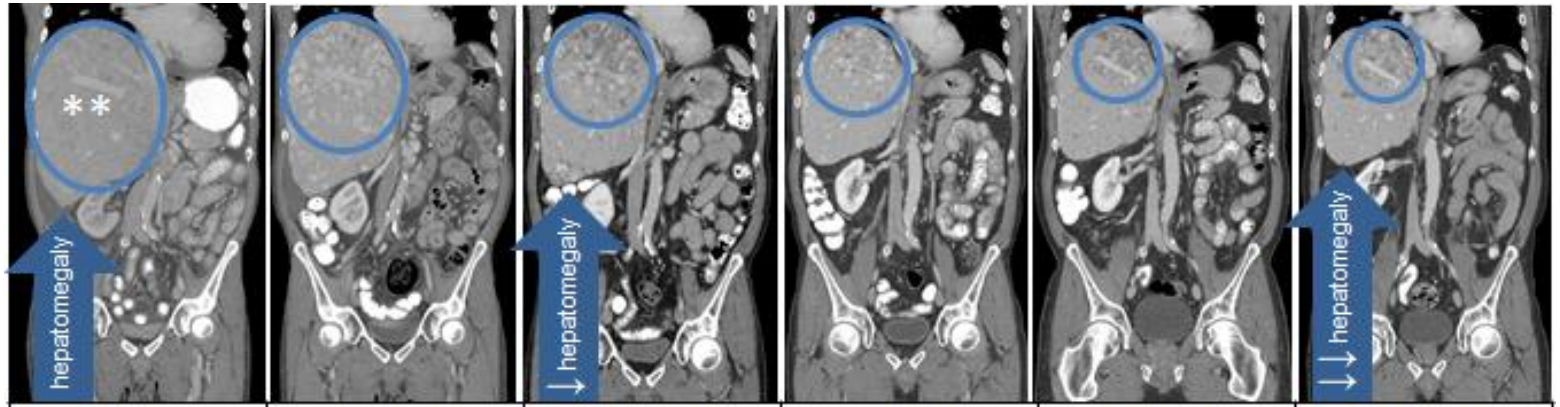


Subbiah V et al, Annals of Oncology 2018 Aug 1;29(8):1869-1876

Sporadic RET M918T/V804M-mutant response to Selpercatinib



Sporadic RET M918T/V804M-mutant response to Selpercatinib



Baseline	1.2 Mo.	2.6 Mo.	4.2 Mo.	5.2 Mo.	6.9 Mo.
25.9x19.5cm	24.3x16.7cm	22.5x15.7cm	20.2x14.5cm	18.8x14.2cm	18.0x13.9cm
↓ Target Lesions (RECIST 1.1)	-12%	-21%	-31% (PR)	-42% (cPR)	-54% (cPR)

Subbiah V et al, Annals of Oncology 2018 Aug 1;29(8):1869-1876

On First Looking into Chapman's Homer

BY JOHN KEATS

Then felt I like some watcher of the skies

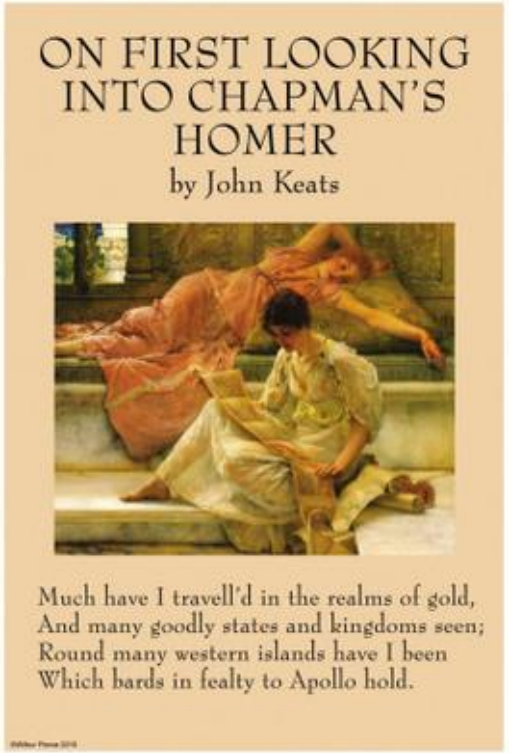
When a new planet swims into his ken;

Or like stout Cortez when with eagle eyes

He star'd at the Pacific—and all his men

Look'd at each other with a wild surmise—

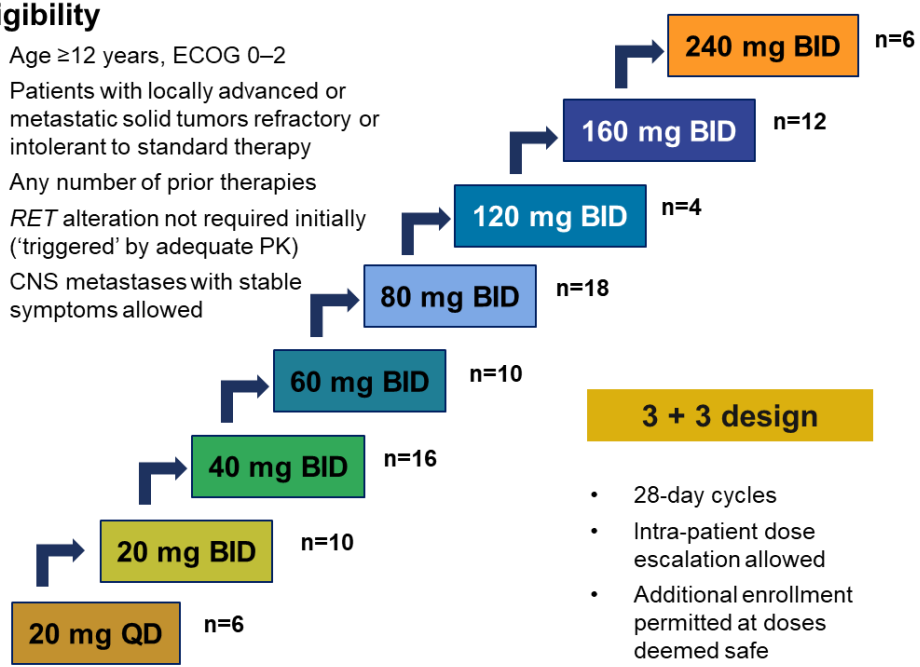
Silent, upon a peak in Darien.



LIBRETTO-001: Selpercatinib phase I dose escalation and pharmacokinetics

Eligibility

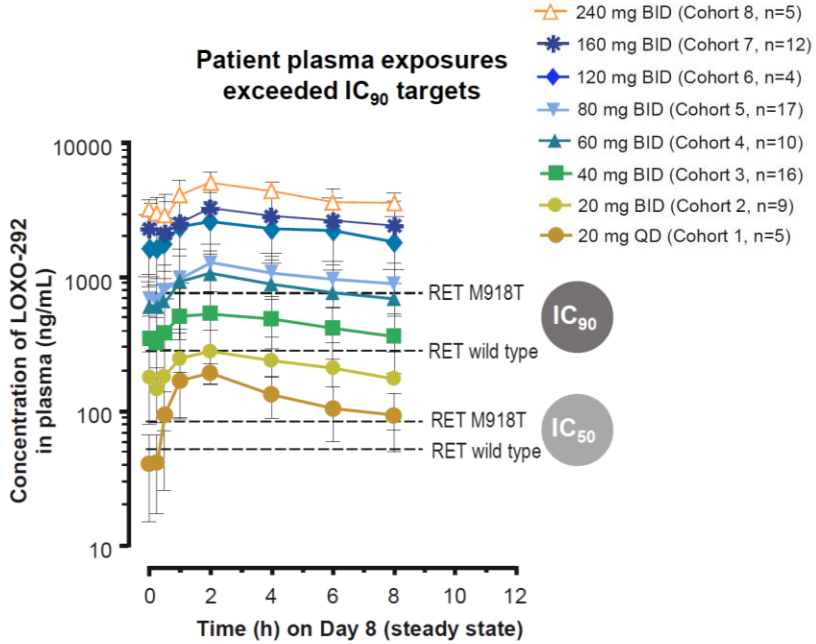
- Age ≥12 years, ECOG 0–2
- Patients with locally advanced or metastatic solid tumors refractory or intolerant to standard therapy
- Any number of prior therapies
- *RET* alteration not required initially ('triggered' by adequate PK)
- CNS metastases with stable symptoms allowed



3 + 3 design

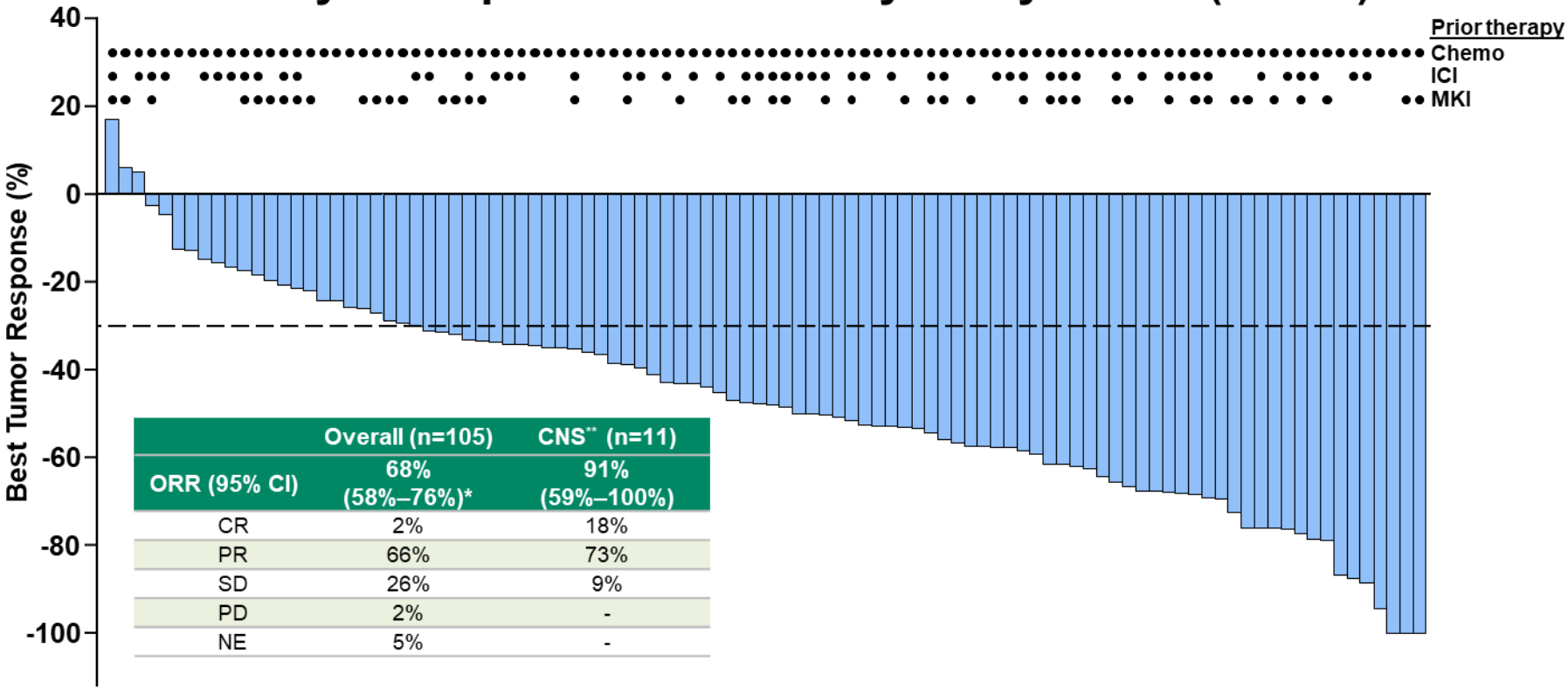
- 28-day cycles
- Intra-patient dose escalation allowed
- Additional enrollment permitted at doses deemed safe

Patient plasma exposures exceeded IC_{90} targets



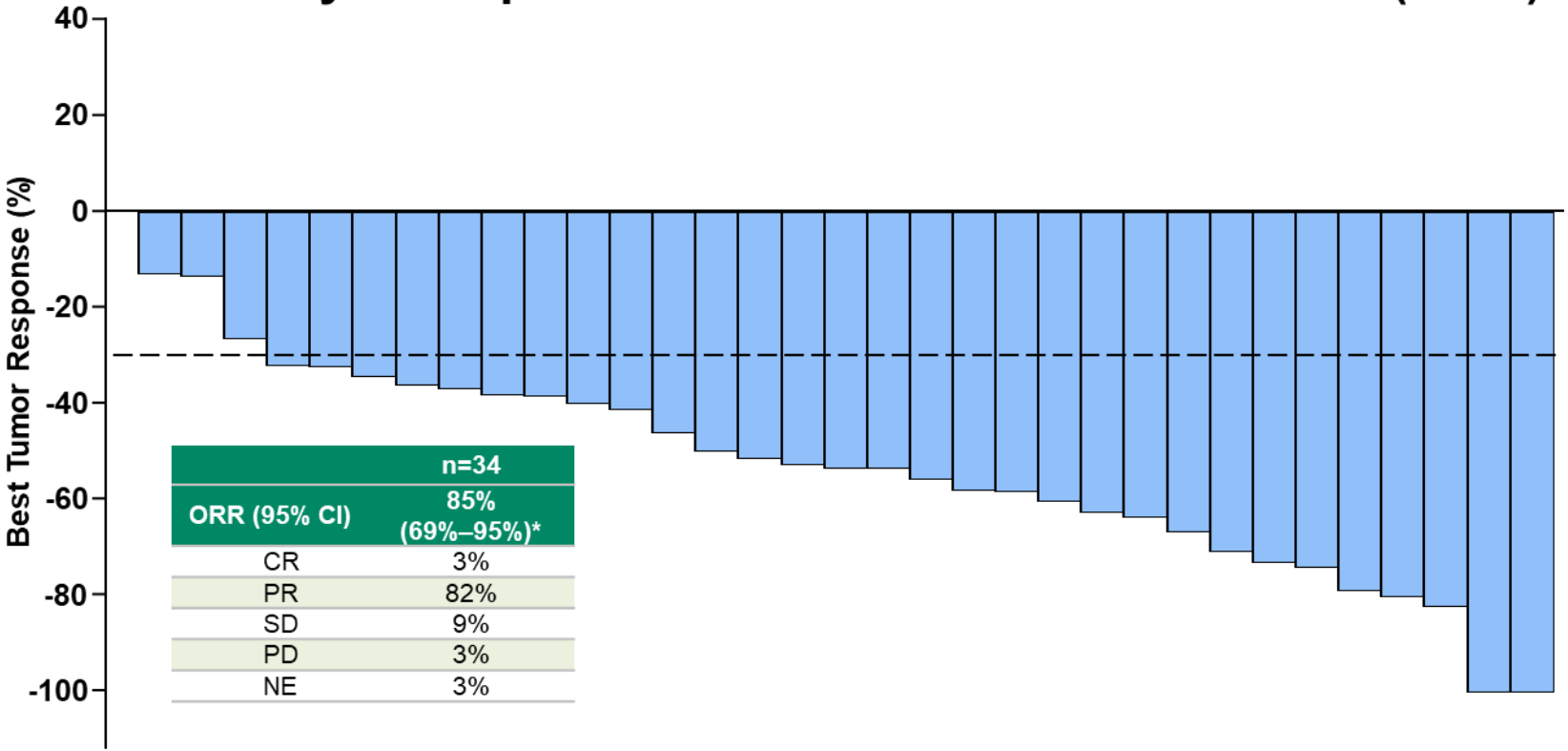
Horizontal lines represent the plasma level at which the unbound LOXO-292 concentration corresponds to IC_{50} or IC_{90} of the indicated target based on cellular assays

Efficacy of Selpercatinib: Primary Analysis Set (n=105)



	Overall (n=105)	CNS** (n=11)
ORR (95% CI)	68% (58%–76%)*	91% (59%–100%)
CR	2%	18%
PR	66%	73%
SD	26%	9%
PD	2%	-
NE	5%	-

Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)



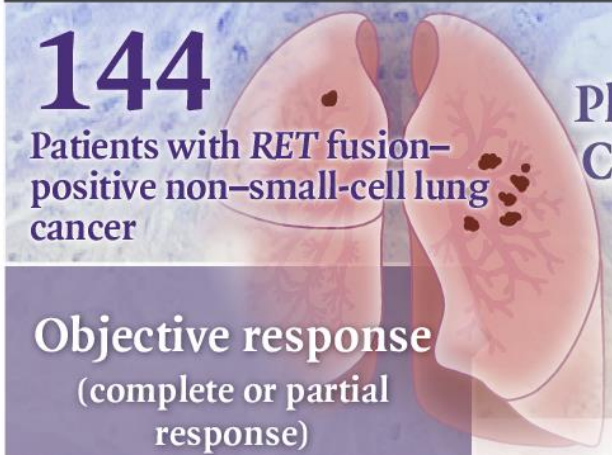
	n=34
ORR (95% CI)	85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy of Selpercatinib in *RET* Fusion–Positive NSCLC

PHASE 1–2 TRIAL

144
Patients with *RET* fusion–positive non–small-cell lung cancer



Objective response
(complete or partial response)

Previous Platinum-Based Chemotherapy	Previously Untreated
(N=105)	(N=39)
64%	85%
(67 patients)	(33 patients)
95% CI, 54 to 73	95% CI, 70 to 94

ENROLLED SEPARATELY

Safety

Twelve of 531 patients in overall cohort (2%) discontinued because of drug-related adverse events.

The median duration of response was 17.5 mo.

A. Drilon et al. 10.1056/NEJMoa2005653

FDA U.S. FOOD & DRUG ADMINISTRATION

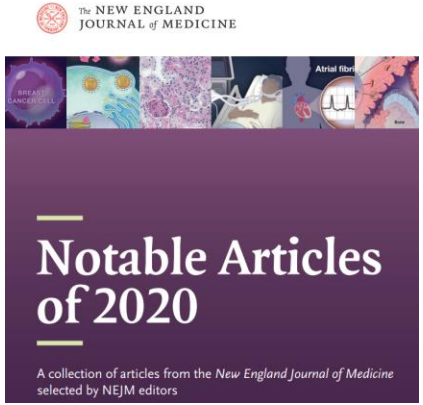
The NEW ENGLAND JOURNAL of MEDICINE

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

FDA APPROVED

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



Selpercatinib now US FDA Approved and in multiple geographies !!!

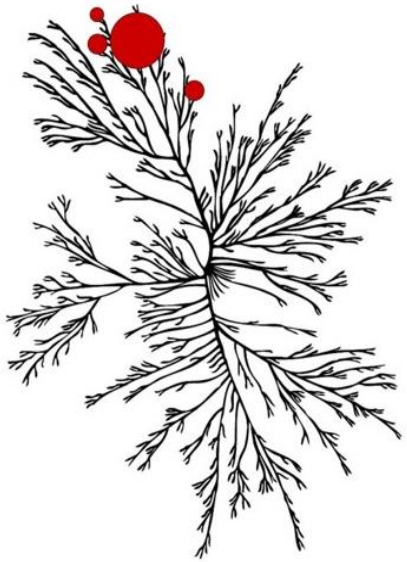
- For the treatment of patients with metastatic ***RET*-fusion positive non-small cell lung cancer (Full FDA approval 2022)**
- **For the treatment of pediatric (> 12 yrs) and adult patients with ***RET*-mutant medullary thyroid cancer (MTC)**
- **For the treatment of pediatric (> 12 yrs) and adult patients with advanced ***RET* fusion-positive thyroid cancer who require systemic therapy.**
- **Line Agnostic approval**
- **EMA approved and approved in multiple geographies**

BLU-667 OR PRALSETINIB - HIGHLY POTENT SELECTIVE RET INHIBITOR

Pralsetinib (BLU-667) is designed to treat *RET*-altered cancers

Pralsetinib potently inhibits RET alterations and resistance mutants while sparing VEGFR2

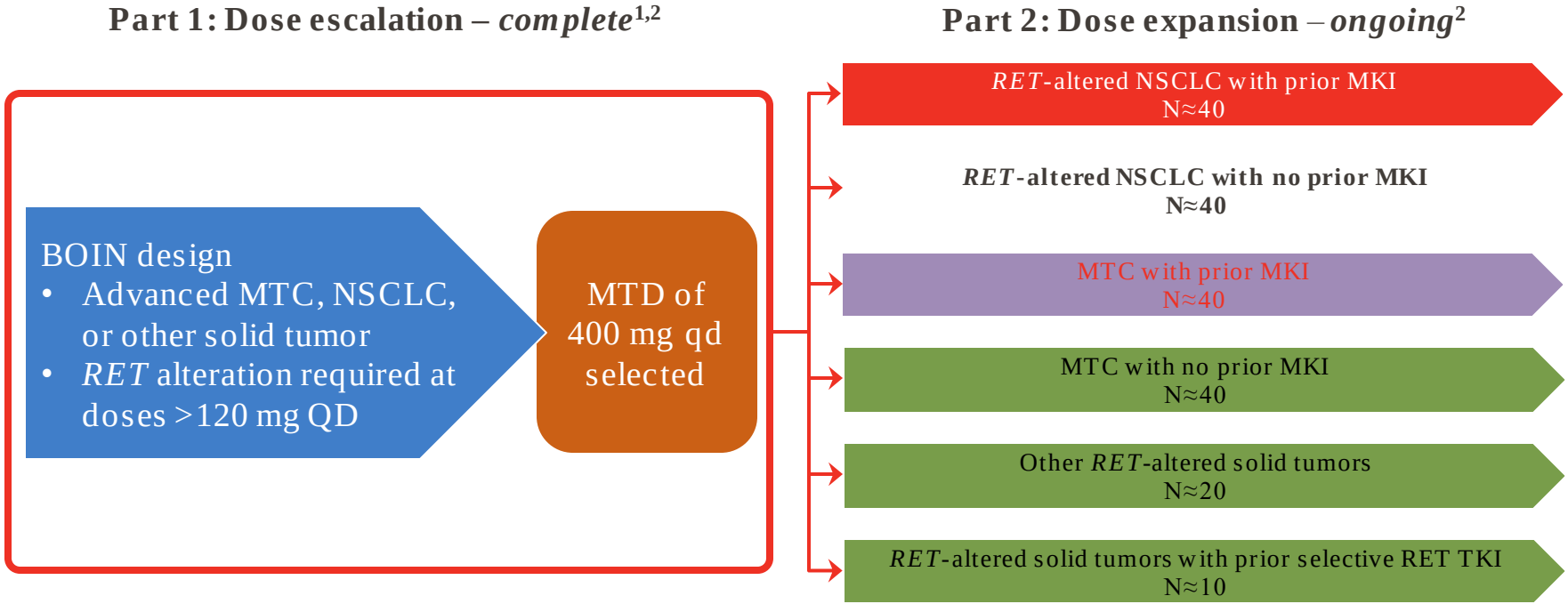
	Biochemical IC50 (nM)			
	RET M918T Most common in MTC	RET V804M Gatekeeper resistance in MTC	CCDC6-RET Occurs in PTC	VEGFR2
BLU-667	0.4	0.4	0.4	35
Cabozantinib	8	45	34	2
Vandetinib	7	3597	20	4
Sorafenib	23	32	ND	21
Lenvatinib	3	360	4	0.7



VEGFR, vascular endothelial growth factor receptor; IC50, half maximal inhibitory concentration; MTC, medullary thyroid cancer; CCDC6, coiled-coil domain containing 6; PTC, papillary thyroid cancer; ND, not determined. Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and the authors and Blueprint Medicines are not responsible for its content

Hu et al. International Thyroid Oncology Group (ITOG) 2018
Subbiah et al. American Association for Cancer Research (AACR) 2018 (clinical trials plenary presentation)
Subbiah et al. Precision Targeted Therapy with BLU-667 for *RET*-Driven Cancers. Cancer Discovery, July 2018

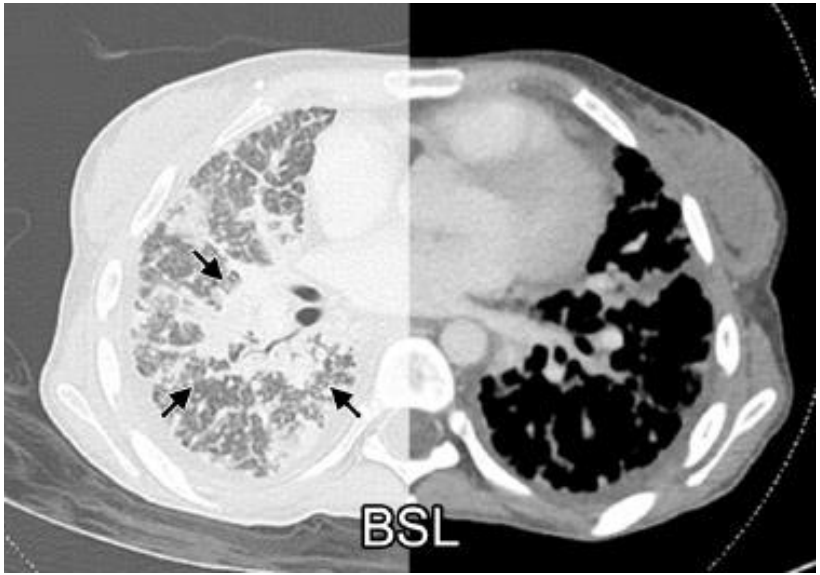
ARROW trial: first-in-human study with Pralsetinib

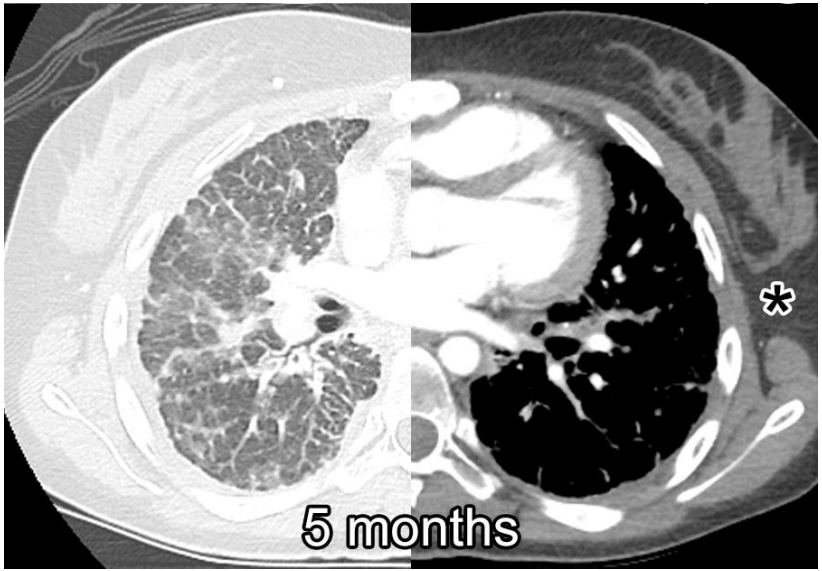


BOIN, Bayesian optimal interval; MTD, maximum tolerated dose.

1. Adapted from data previously presented in April 2018 at AACR Annual Meeting. Data cut-off: April 6, 2018. 2. National Institutes of Health. https://www.clinicaltrials.gov/ct2/show/NCT03037385. Accessed August 22, 2018.

Pralsetinib induced dramatic improvement in young PTC patient





- 23-year-old woman with PTC, sclerosing variant (*CCDC6-RET* fusion) who presented 6 years ago with symptomatic diffuse lung metastases requiring supplemental oxygen (O_2) since diagnosis; treated with I-131 (total activity 351 mCi) with subsequent fibrosis
- Progressed on sorafenib and then on lenvatinib (increasing O_2 needs, pleural effusions and intubated 3 times over 6 wks)
- Initiated BLU-667 at 400 mg once daily → RECIST SD (no target lesion/non-target lymphangitic lung metastases)
- Symptomatic response: O_2 weaned monthly to room air within 5 months, baseline BMI 14.8 steadily increased to 22.3 after 6 mos
- Remains on treatment after 3 yrs and started college, completed college, and searching for a job !

PTC, papillary thyroid cancer; BSL, baseline; CCDC6, coiled-coil domain containing 6; O2, oxygen; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; BMI, body mass index. Patient had non-measurable disease at baseline and is not represented on current waterfall plot. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

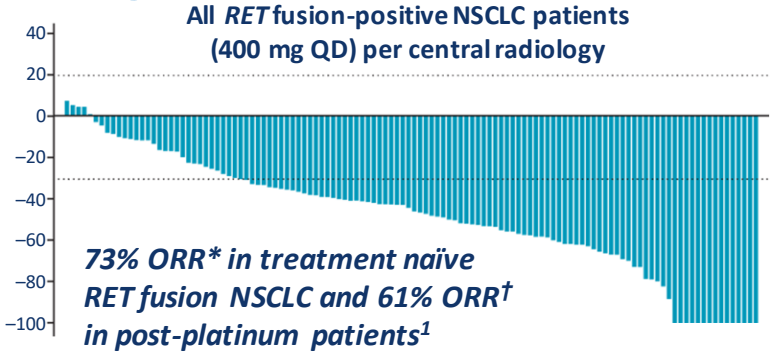
Pralsetinib Phase 1/2 ARROW study

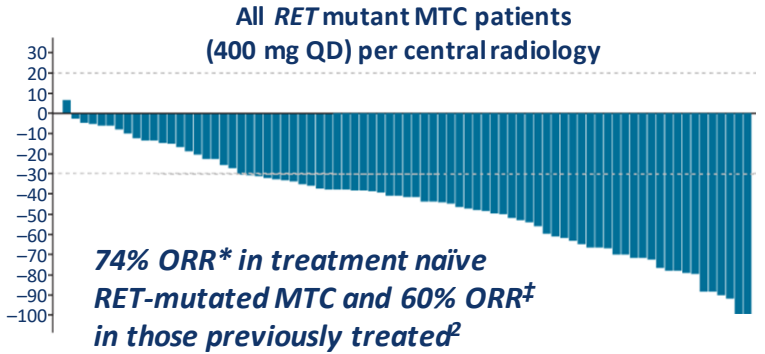
Phase 2 study design

- 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**

1. *Gainor J…**Subbiah V** The Lancet Oncol 2021*
2. ***Subbiah V**, Hu M The Lancet Diab & Endo 2021*

Pralsetinib now FDA approved for RET+ NSCLC and RET+ Thyroid Cancers

- For the treatment of patients with metastatic ***RET*-fusion positive non-small cell lung cancer.**
- For the treatment of pediatric (> 12 yrs) and adult patients with ***RET*-mutant medullary thyroid cancer (MTC)**
- For the treatment of pediatric (> 12 yrs) and adult patients with advanced ***RET* fusion-positive thyroid cancer who require systemic therapy.**
- Line Agnostic approval
- **FDA, EMA approved and approved in multiple geographies**

RET inhibitor super heroes have arrived

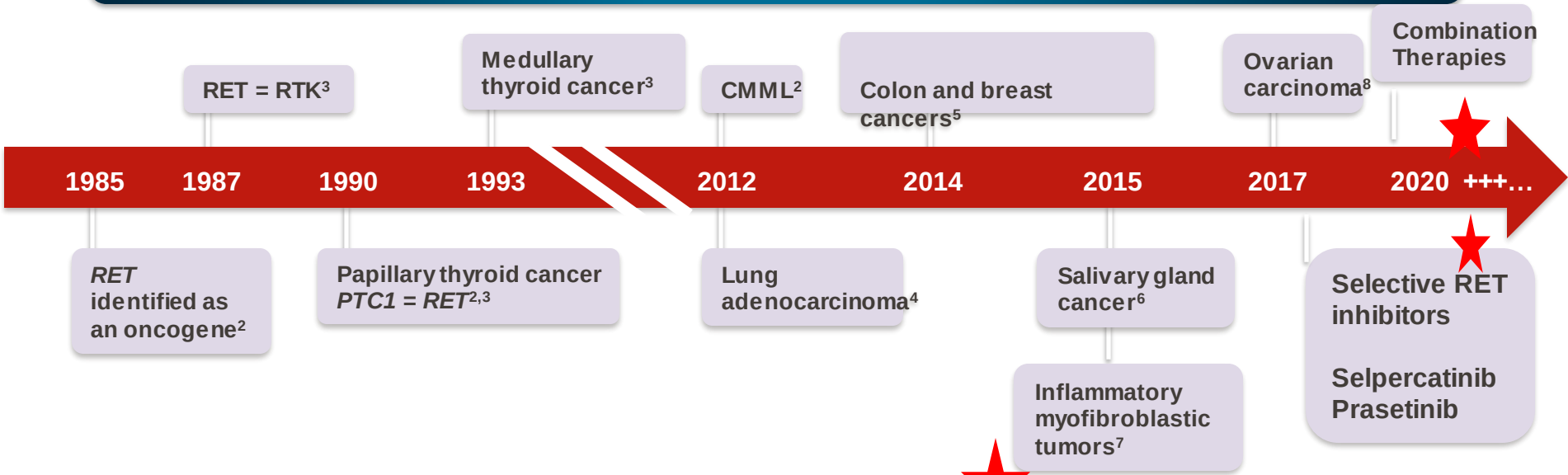
Discovery, pre-clinical and rapid clinical validation with registrational studies leading to FDA approval directly from Phase 1 trials.

- **Responses observed regardless of treatment history, RET fusion partner, RET mutation or CNS involvement and Gatekeeper V804 M coverage.**

US FDA APPROVED

RET inhibitor Timeline for FDA approval

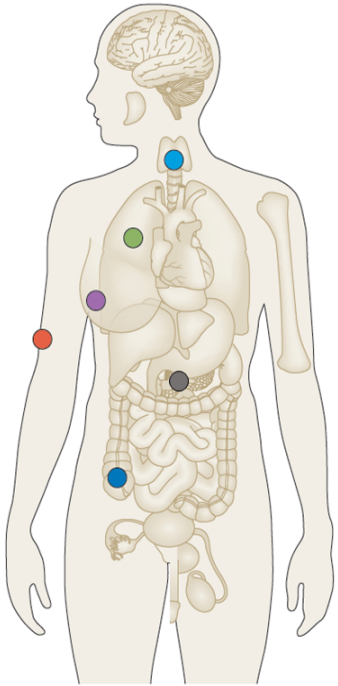
RET **is one of the first oncogenic kinase fusions cloned from an epithelial tumor, and has since been found to be an oncogenic driver primarily in solid tumors[1,2]**



FDA Approval ~ 3 yrs from FIH Phase 1

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.

RET fusions are tissue agnostic targets



***RET* fusions**

Non-small cell lung cancer (2%)

Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)

Salivary gland cancer (<1%)

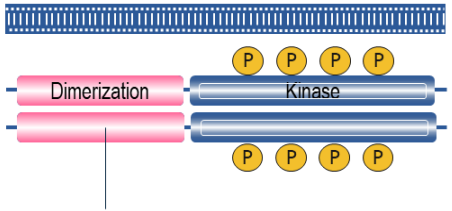
Spitz tumors (<1%)

Colorectal cancer (<1%)

Ovarian cancer (<1%)

Myeloproliferative disorders (<1%)

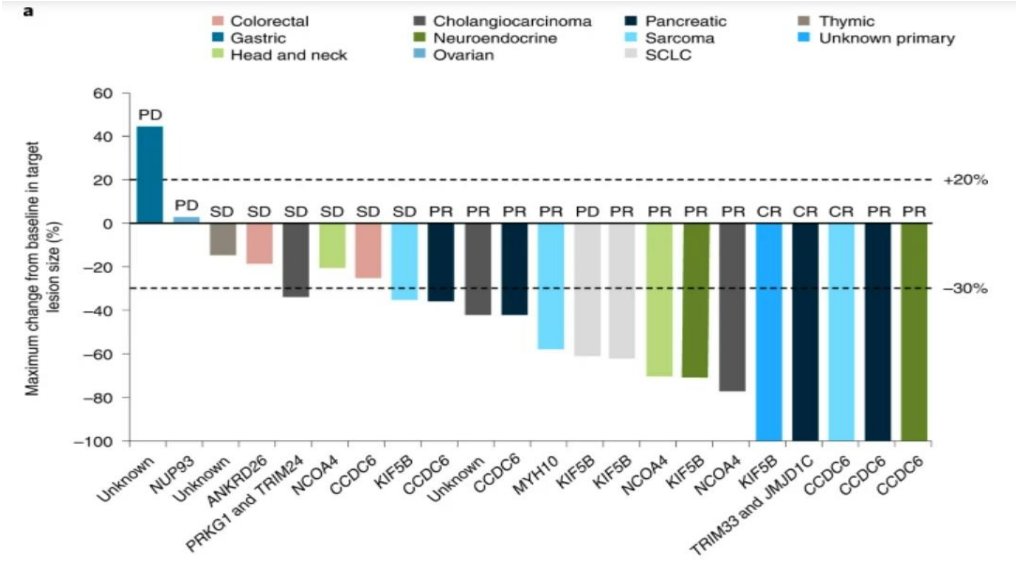
Many others (<1%)

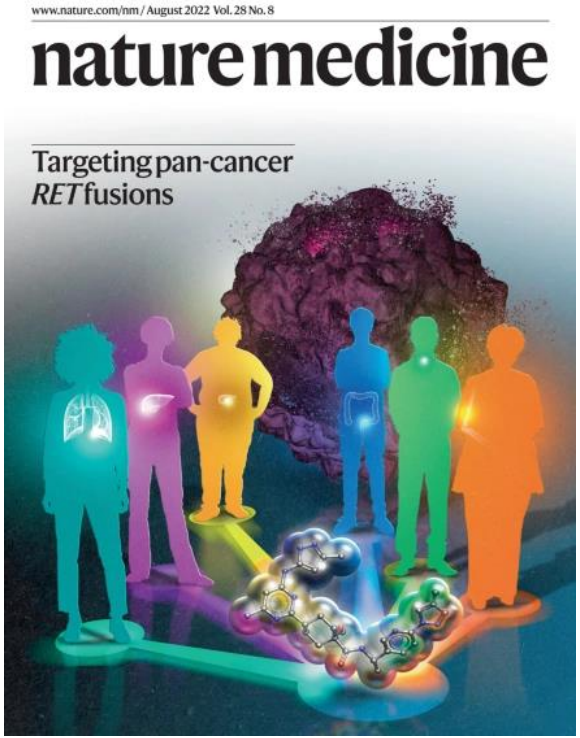


KIF5B (most common in lung cancer)

CCDC6 or NCOA4 (most common in thyroid

Pan-cancer activity of Pralsetinib in RET + Cancers

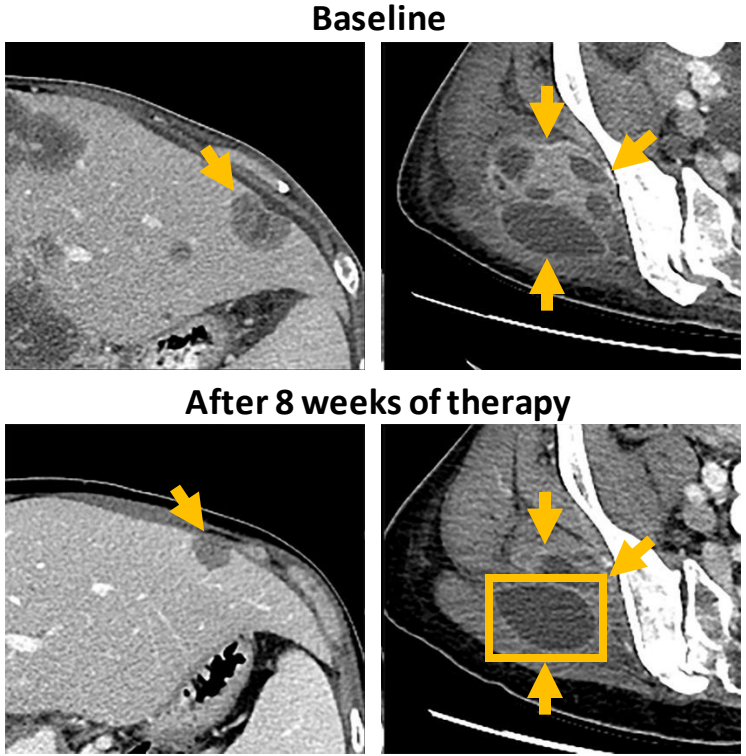




Subbiah V et al. Nature Medicine Aug 2022

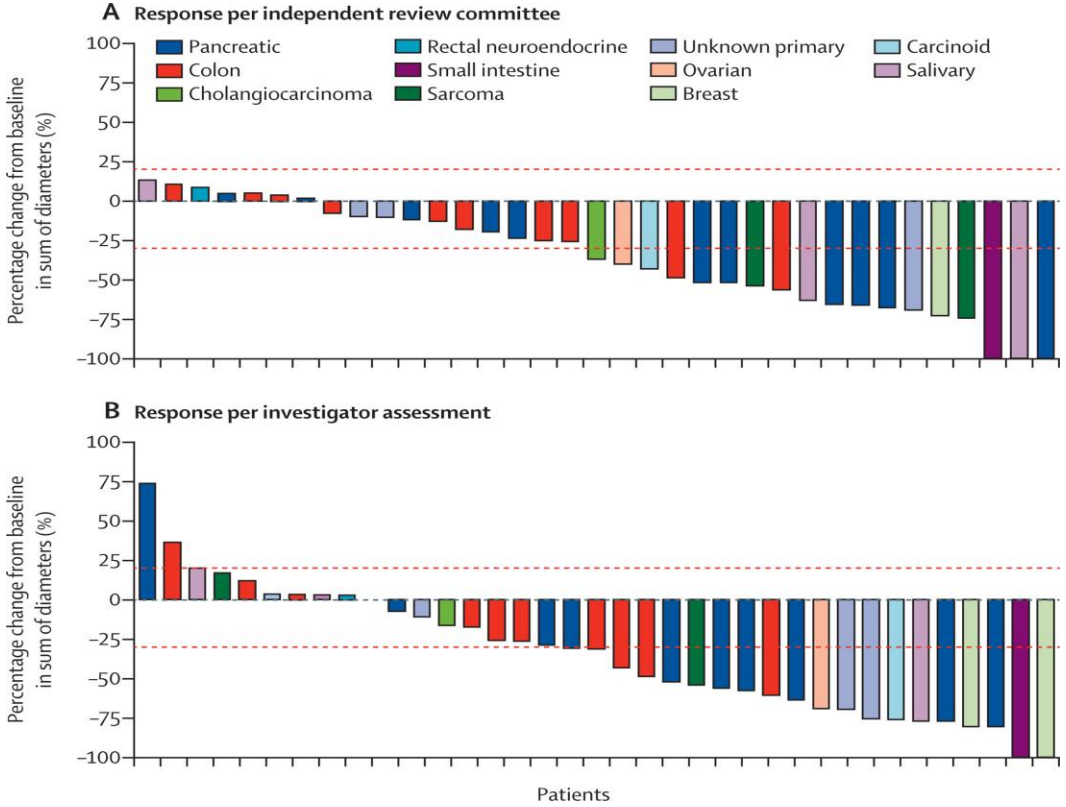
RET + Cholangiocarcinoma

- NCOA4-RET fusion
- Three previous treatments with PD for all (nab-paclitaxel/ gemcitabine/cisplatin; erlotinib/bevacizumab; osimertinib)
- Deep and durable PR with pralsetinib (20 months duration; 64% shrinkage of target lesions)
- At first disease evaluation (8 weeks on treatment):
  - Left hepatic lobe lesion previously measuring 2 x 3 cm decreased to 1.2 x 1.9 cm
  - Prior heterogeneously enhancing soft tissue mass in the right gluteal muscles with decreased size and enhancement, and increased cystic/necrotic components
- Throughout treatment:
  - CA 19-9 reduced from 1,000,000 to 82 U/mL
  - CA 125 reduced from 1591 to 16.4 U/mL
  - Rapid and near-complete clearance of NCOA4-RET fusion ctDNA



Subbiah V et al. Nature Medicine 2022

Tumor Agnostic activity of Selpercatinib in patients with RET+ Cancers



NEW

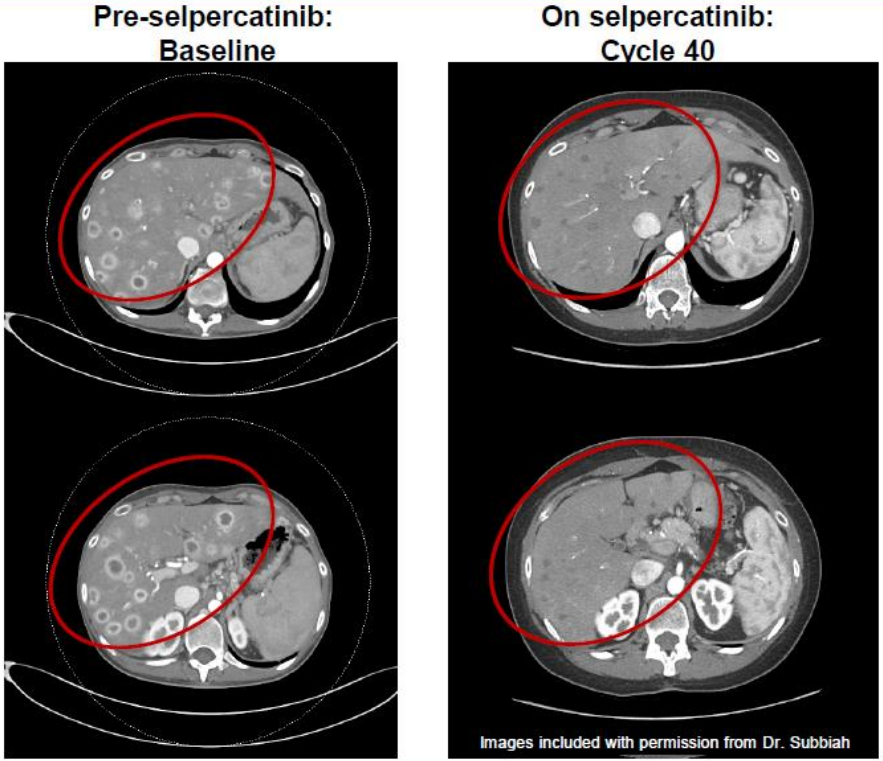
FDA APPROVED

Sept 21st 2022

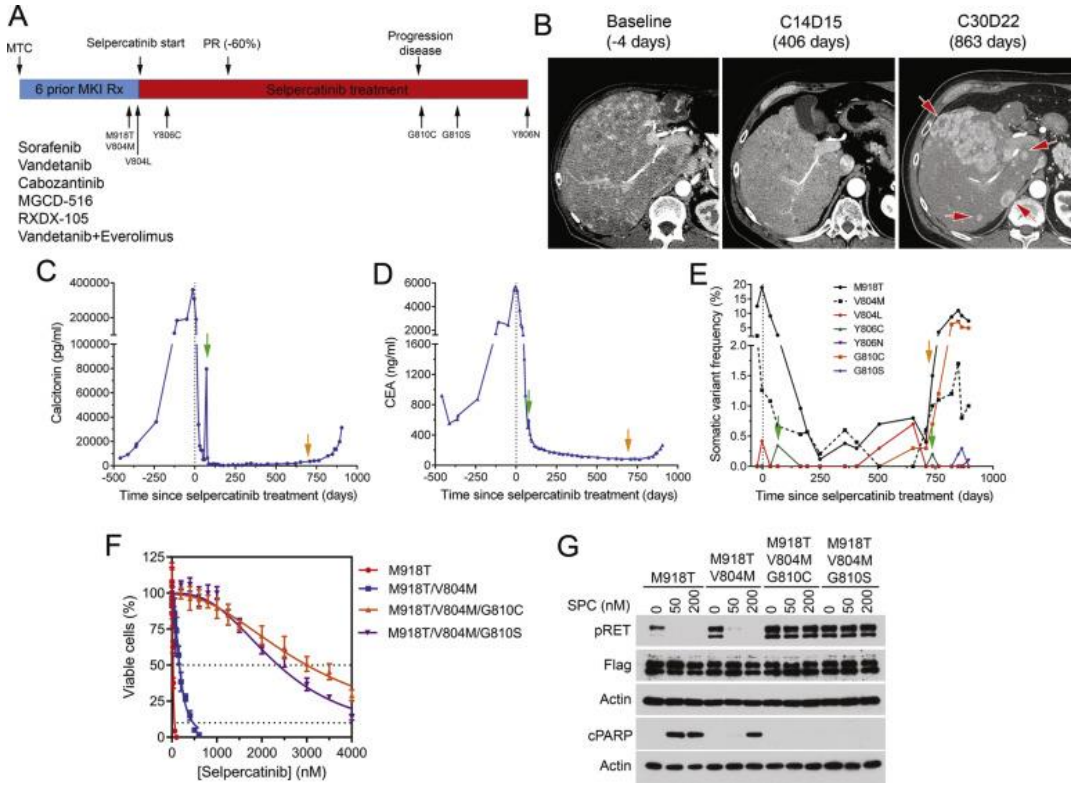
Subbiah V et al. Lancet Oncology Sept 2022

Pancreatic Cancer RET+

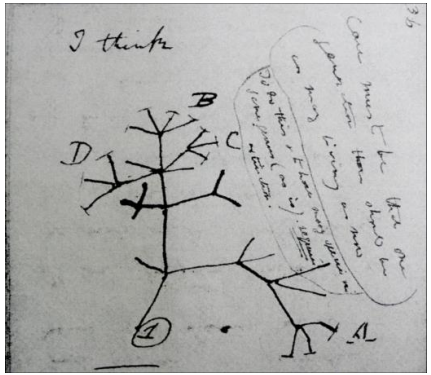
- Pancreatic metastatic ductal adenocarcinoma:
  - *PRKAR1A-RET* fusion
  - Microsatellite stable
  - *KRAS*/*BRAF* wildtype
- Prior therapy:
  - FOLFIRINOX/FOLFIRI, 6 months
  - Discontinued due to PD
- Selpercatinib started:
  - Partial response (-51%)
  - Manageable low-grade AEs
  - Response ongoing at 37 months



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



•Resistance to selpercatinib and pralsetinib are found at the **solvent front and hinge sites** of the RET kinase domain.

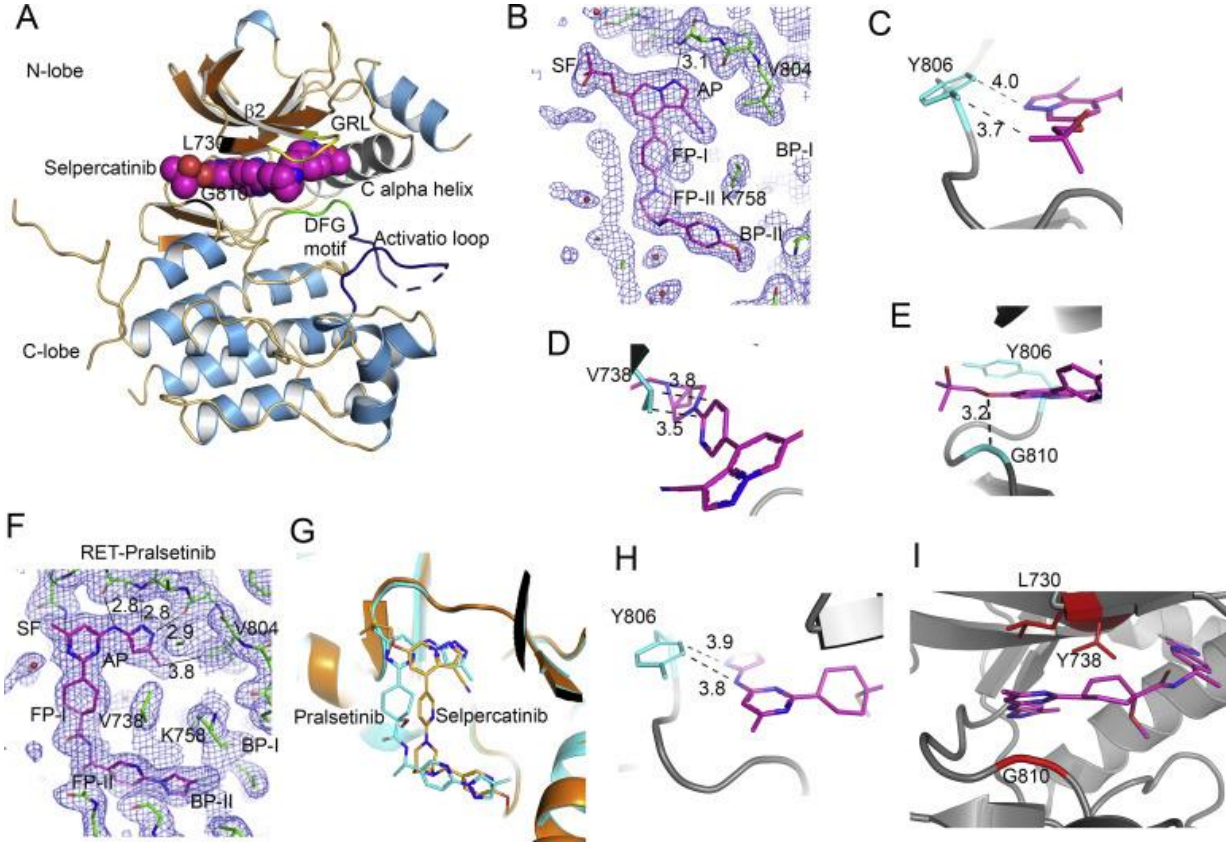


Charles Darwin's sketch on evolution red notebook 'B' precursor of "On the Origin of Species" (1859)

Annals of Oncology 2021 32261-268DOI: (10.1016/j.annonc.2020.10.599)

Subbiah V… Mooers B, Wu J Annals of Oncology Feb 2021

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

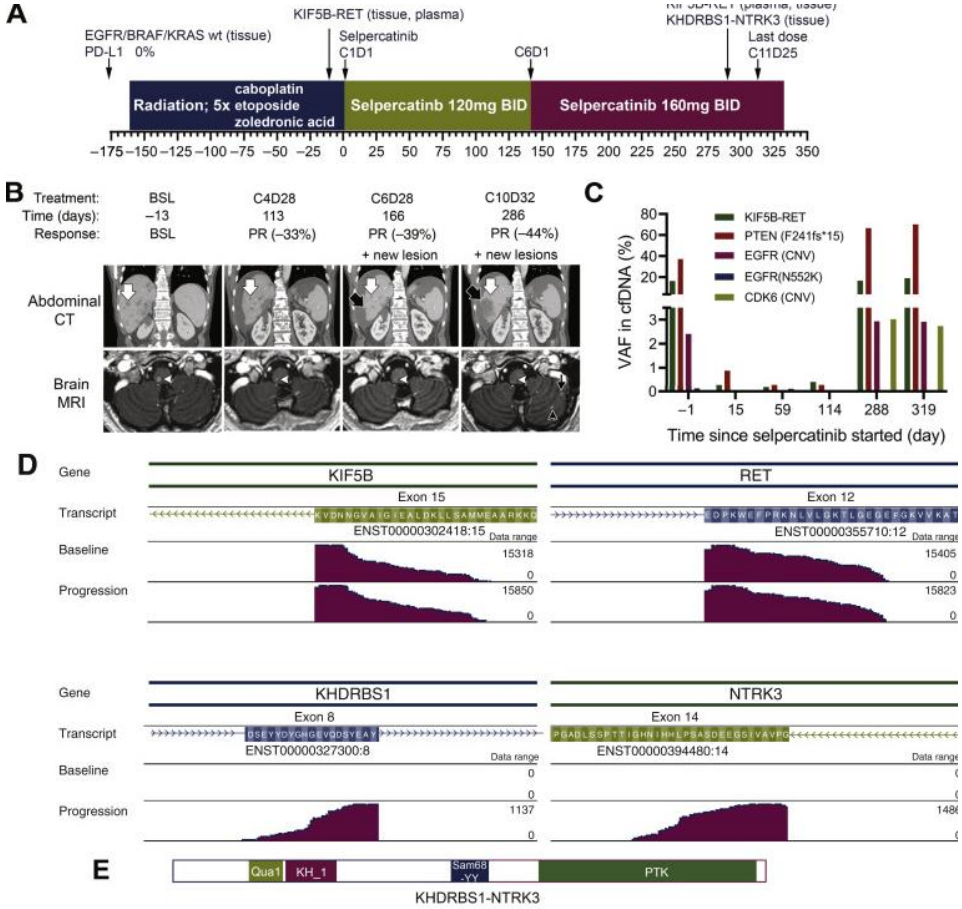


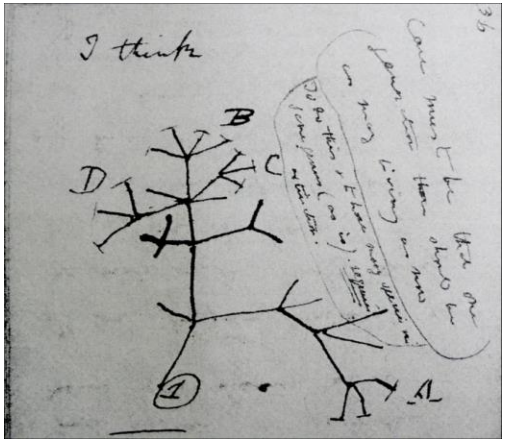
- The identified selpercatinib-resistant RET mutants are cross-resistant to pralsetinib.
- Selpercatinib and pralsetinib use an unprecedented binding mode to dock into the RET kinase.
- Need 2nd generation RET inhibitors that cover gatekeeper and new solvent front mutations

Annals of Oncology 2021 32261-268DOI: (10.1016/j.annonc.2020.10.599)

Subbiah V Annals of Oncology Feb 2021

KHDRBS1–NTRK3 fusion as an acquired resistance mechanism to selpercatinib in RET fusion-positive lung cancer- Off target resistance



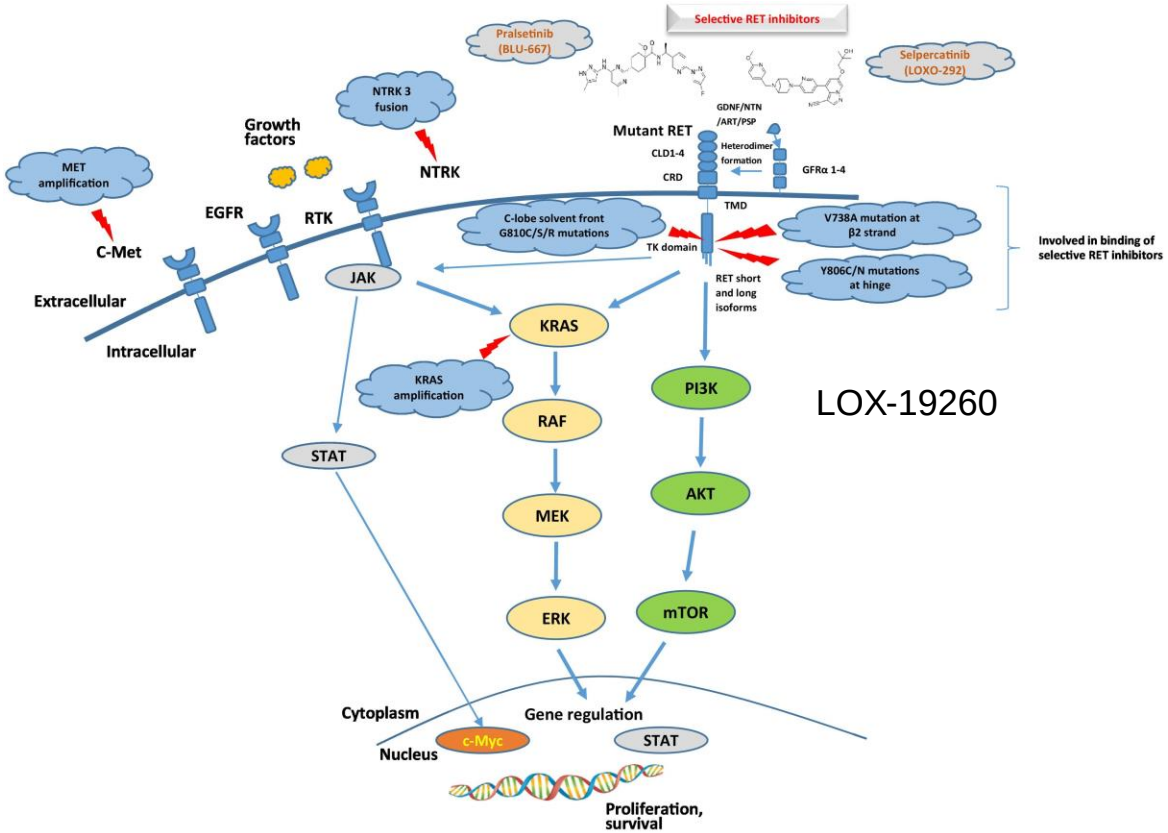


Charles Darwin's sketch on evolution red notebook 'B' precursor of "On the Origin of Species" (1859)

Subbiah V… Mooers B,…… Wu J

Annals of Oncology Feb 2021

Acquired resistance mechanisms (red arrow) to selective RET inhibitors



LOX-19260

Other RET inhibitors in development
Clinical- Phase 1 trials

- LOX-260 (LOXO-19260)
- TAS0953/HM06 (NCT04683250)
- EP0031

Pre-clinical

- Early nonclinical studies with BiDAC™ (bifunctional degradation activating compounds)
- RET inhibitor from C4 therapeutics, and
- 2nd generation selective RET inhibitors from KinaRx and
- 2nd gen RET from LOXO Oncology
- (LOX-18228 and LOX-19260) -

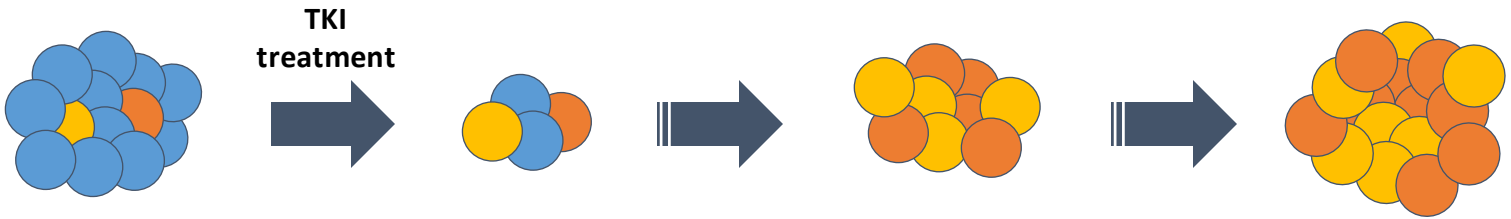
Trends in Cancer DOI: (10.1016/j.trecan.2021.07.003)

Trends in Cancer

Thein KZ, Velcheti V, ***Mooers BHM, Wu J, Subbiah V.***

The emergence of resistance mutations severely impacts the durability of TKI's in cancer

Model of the emergence of TKI-resistant mutant clones[1]



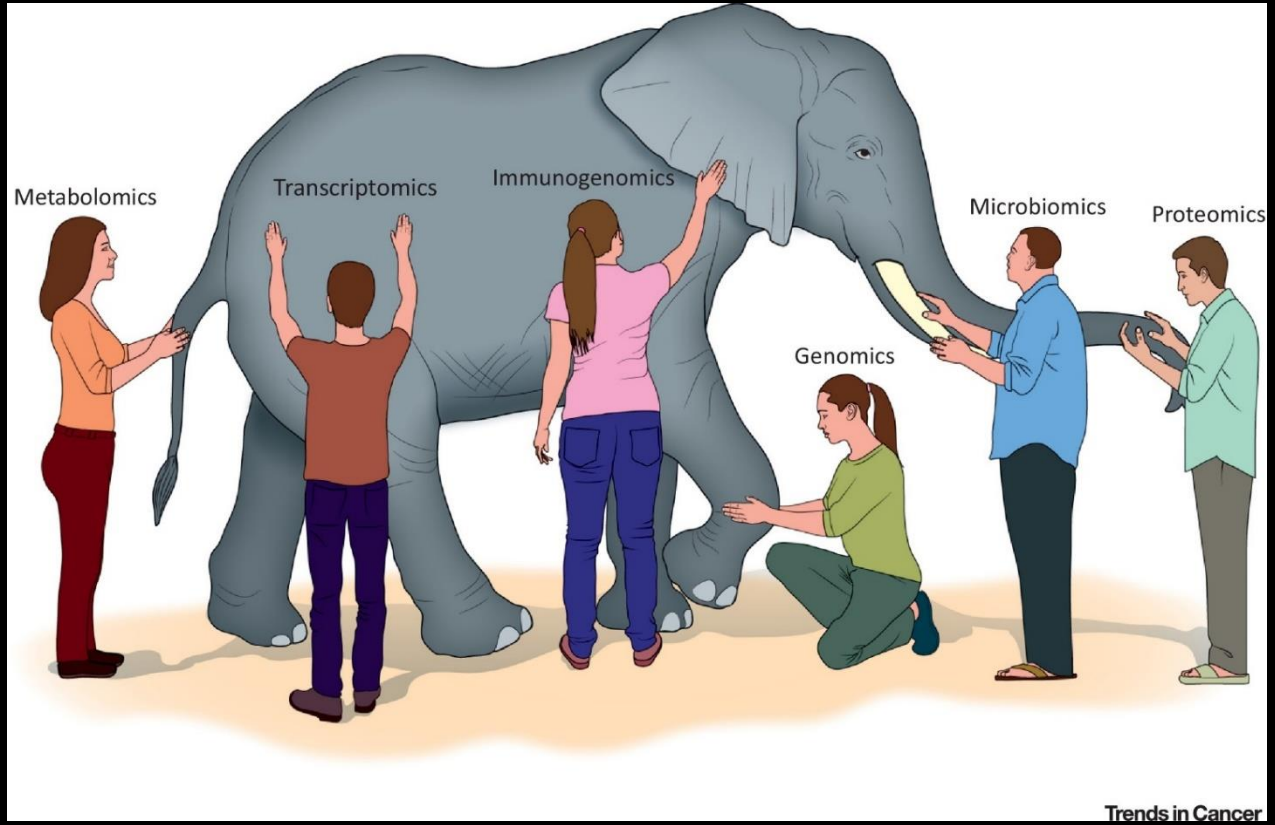
Overcoming resistance mutations in oncogenic drivers is essential for effective precision therapy

Identifying mechanisms of resistance to first generation TKI inhibitors.

Combination therapies, Therapies earlier in the disease course and developing 2nd/3rd/4th generation TKI inbitors

1. Lin JJ, Shaw AT. *Trends Cancer*. 2016;2(7):350-364. 2. Soria J-C et al. *N Engl J Med*. 2018;378(2):113-125.

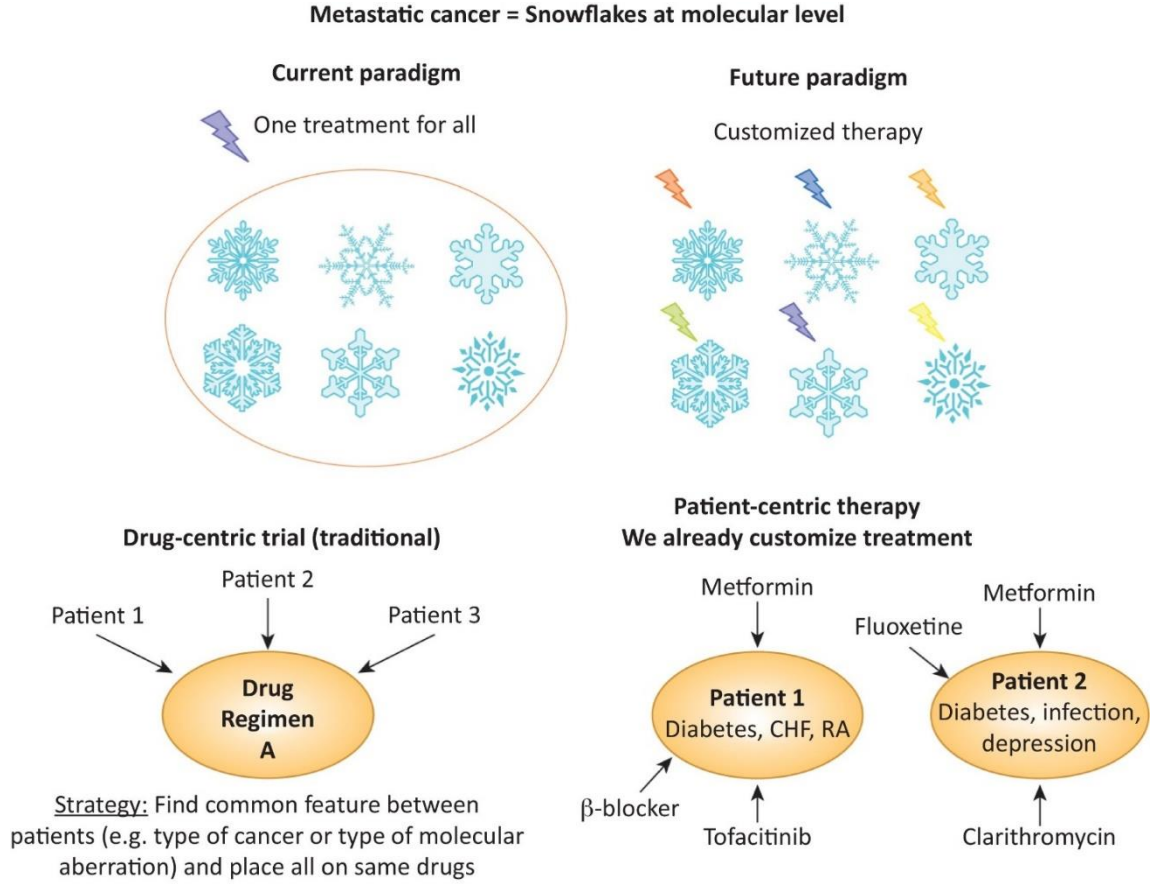
Six Blind Scientists and Elephants



Trends in Cancer 2018 4, 101-109DOI: (10.1016/j.trecan.2017.12.004)

Subbiah V & Kurzrock R

Snowflake Theory and Changing Drug Development Paradigms

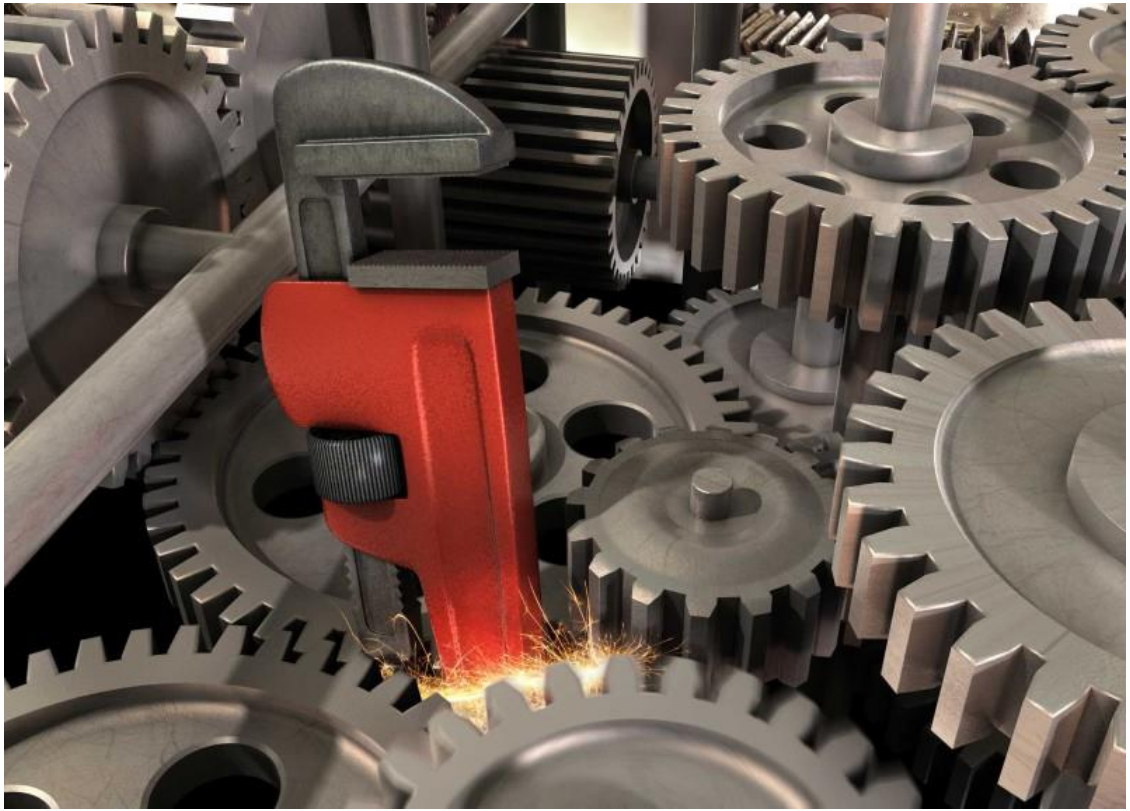


Trends in Cancer

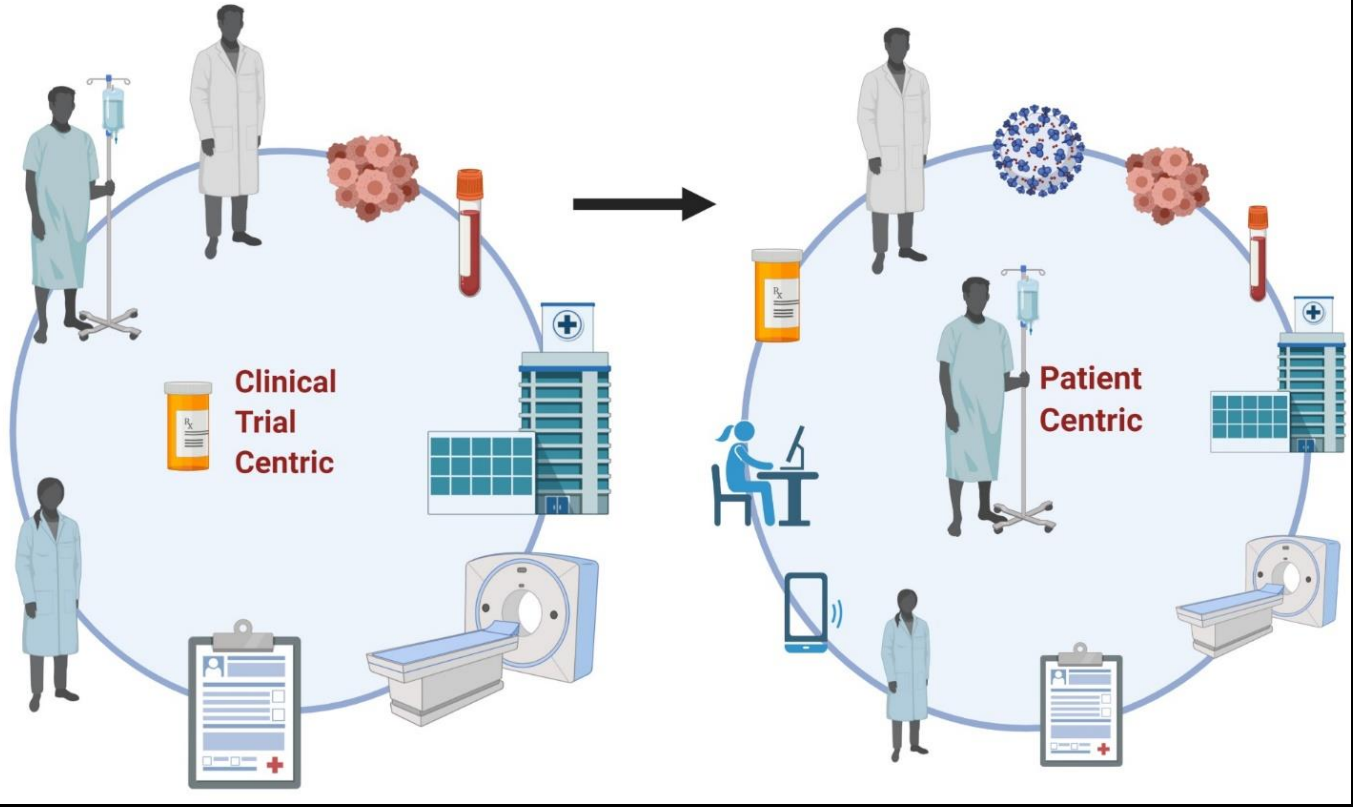
2020

- **The death rate from cancer in the US declined by 29% from 1991 to 2017, including a 2.2% drop from 2016 to 2017, the largest single-year drop ever recorded.**

- **The decline in deaths from lung cancer drove the record drop. Deaths fell from about 3% per year from 2008 - 2013 to 5% from 2013 - 2017 in men and from 2% to almost 4% in women.**

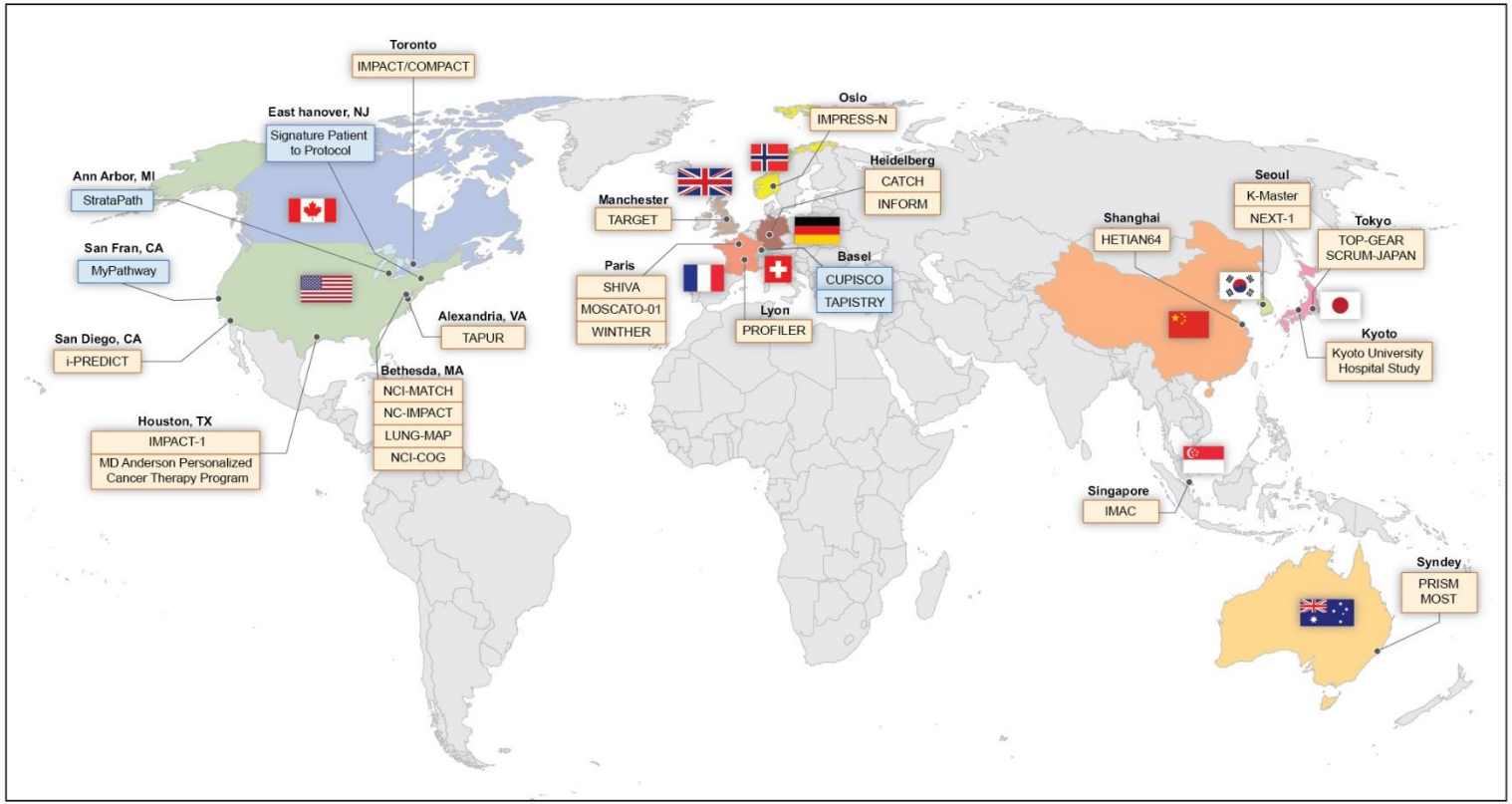


COVID-19 Pandemic & Cancer Clinical Trial Pandemonium: Finding the Silverlining
From Clinical Trial Centric to Patient Centric



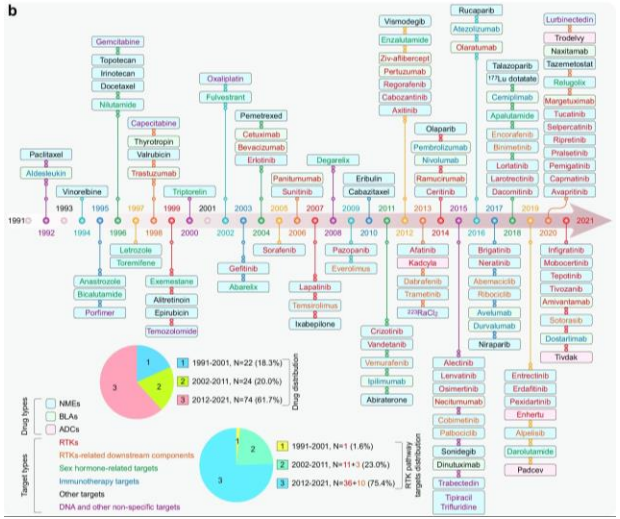
Desai A and Subbiah V, *J Immunother Prec Oncol* 2020.

Globalizing Precision Medicine



Moyers J & Subbiah V. Cancer Discovery 2022

FDA-approved novel therapeutic drugs for solid tumors from 1991 to 2021



Wu Q J Hematol Oncol 2022

nature medicine

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Correspondence | Published: 03 October 2022

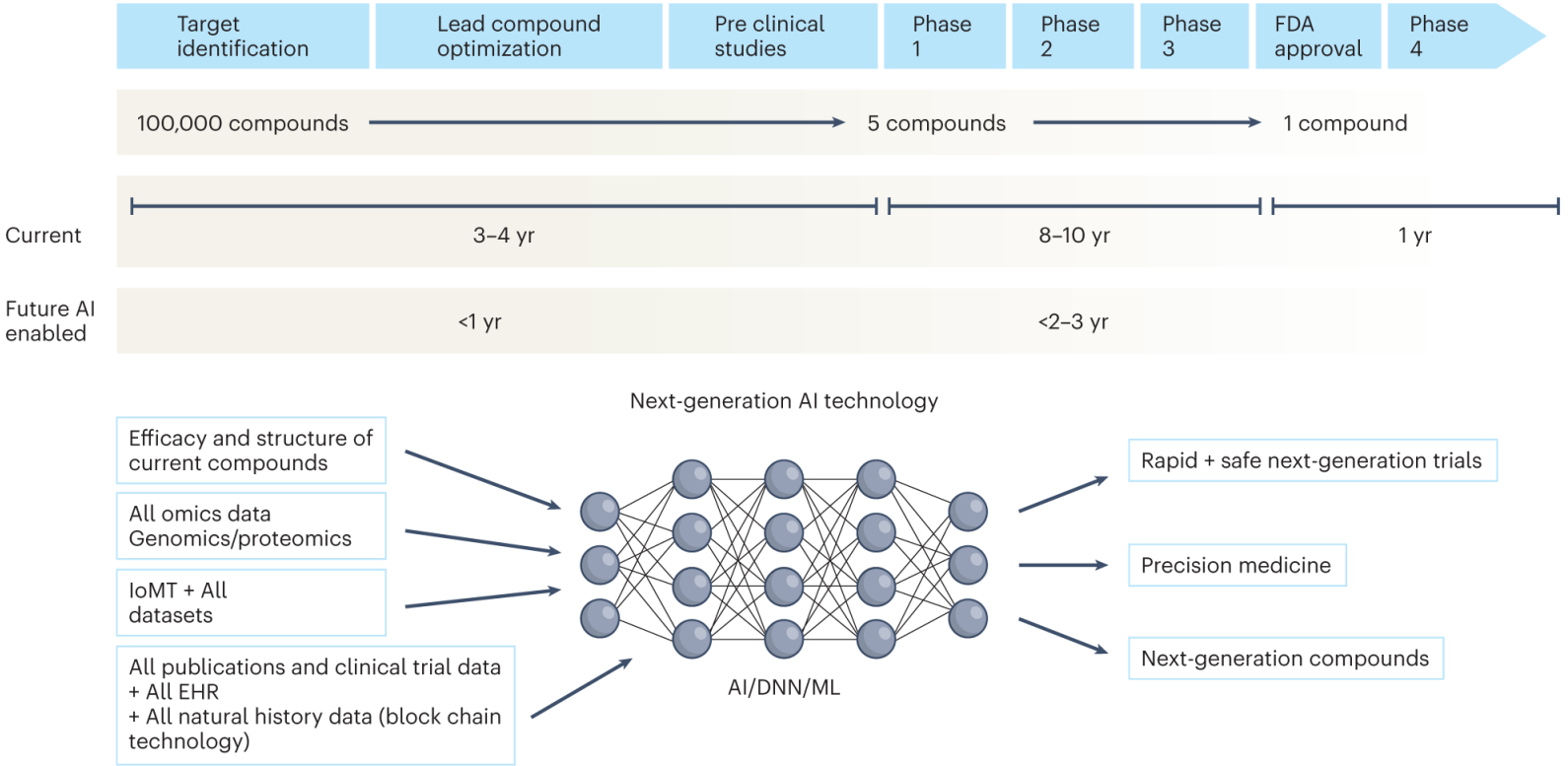
Accelerated approvals hit the target in precision oncology

Vivek Subbiah, Lori J. Wirth, Razelle Kurzrock, Richard Pazdur, Julia A. Beaver, Harpreet Singh & Gautam U. Mehta

Nature Medicine (2022) | Cite this article

Metrics

Timeline of drug development from the present to the future.



Subbiah V Nature Medicine 2023 Jan

RET inhibitor Timeline

NEW

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]**

RET identified as an oncogene[2]

RET = RTK[3]

Papillary thyroid cancer *PTC1* = *RET*[2,3]

Medullary thyroid cancer[3]

CMML[2]

Lung adenocarcinoma[4]

Colon and breast cancers[5]

Salivary gland cancer[6]

Inflammatory myofibroblastic tumors[7]

1st gen RET inhibitors
Loxo-292
BLU-667

Selective RET inhibitors – FDA approved

Selpercatinib
Prasetinib

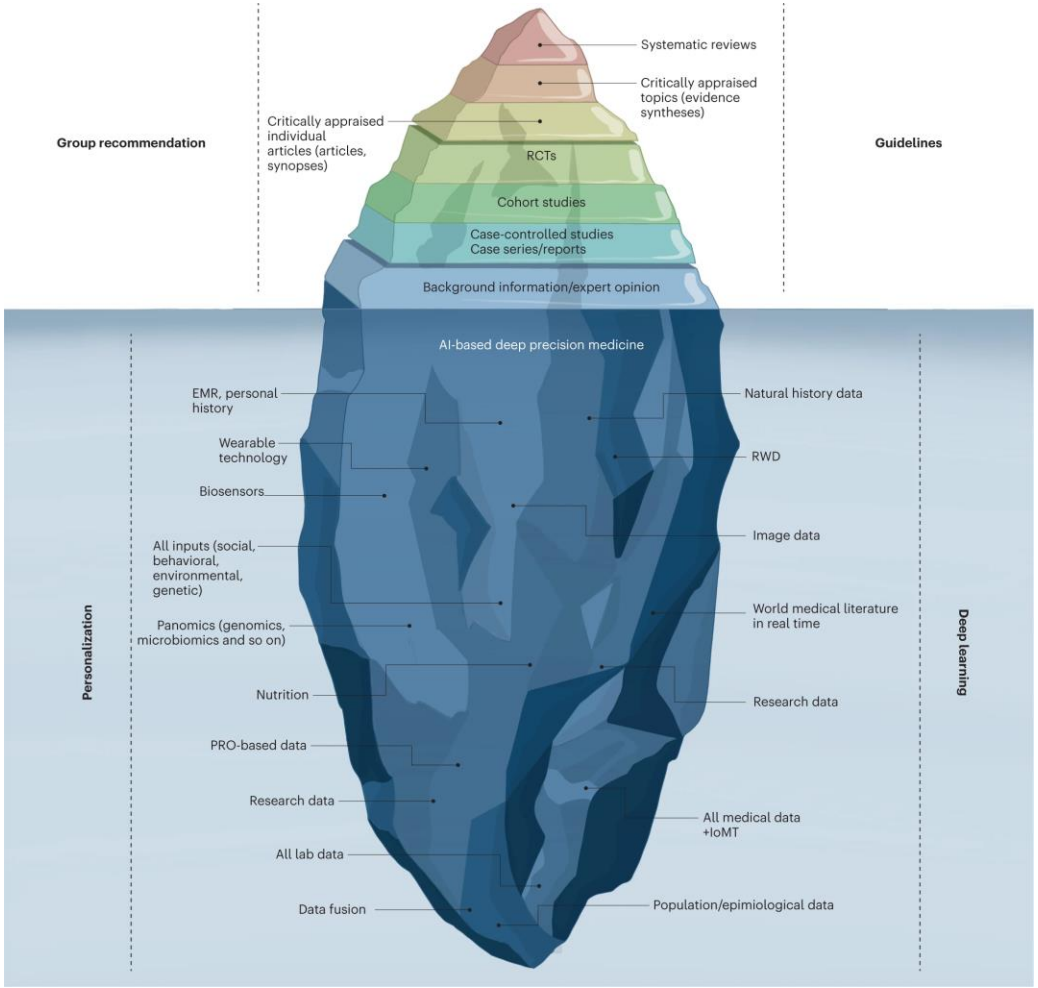
2nd Generation RET inhibitors
LOXO-260
HM06
EP0031

FDA Approval ~ 3 yrs from FIH Phase 1

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.

Evidence-based deep medicine iceberg



Subbiah V Nature Medicine 2023

Summary

- **Revolution in Panomics is here and growing**
- Molecularly driven trials independent of histology
- **Patients will drive clinical trials + drug development**
- Social Media, Search and self-driven molecular testing
- **Future clinical research**
  - Next 1–2 years may determine fundamental pivots for how medicines are developed, giving each stakeholder an opportunity not only to adapt but to shape the future clinical trial paradigm.

Acknowledgements

- We thank the patients and their caregivers for their participation in this study. We thank the study investigators and their support staff at the participating centers and the independent data monitoring committee.
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- V.S. acknowledges support of The Jacquelyn A. Brady Fund. MD Anderson Cancer Center Department of Investigational Cancer Therapeutics is supported by the Cancer Prevention and Research Institute of Texas (RP1100584), the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy, 1U01 CA180964, NCATS Grant UL1 TR000371 (Center for Clinical and Translational Sciences), and the MD Anderson Cancer Center Support Grant (P30 CA016672).

- Contact information:

  - vsubbiah@mdanderson.org
  - **Contact: Twitter @VivekSubbiah**

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- ✓ 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

vsubbiah@mdanderson.org

Contact:

- ➢ Twitter @VivekSubbiah