THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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Hot news in Lung cancer: Targeting RET and BRAF

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The University of Texas MD Anderson Cancer Center

DISCLOSURE INFORMATION

VIVEK SUBBIAH

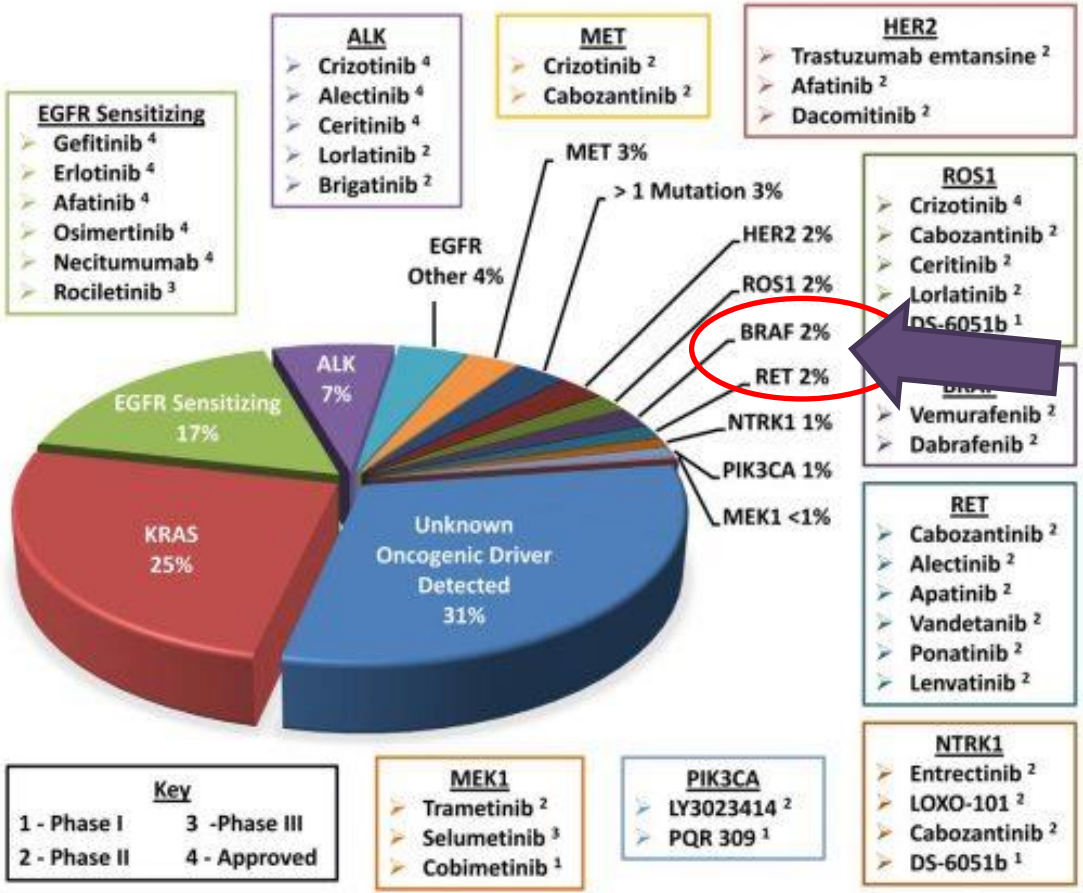
Personal financial interests & Institutional financial interests:

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

- BRAF basket trials
- BRAF therapy in NSCLC
- RET pathway
- RET inhibitors in RET fusion + NSCLC

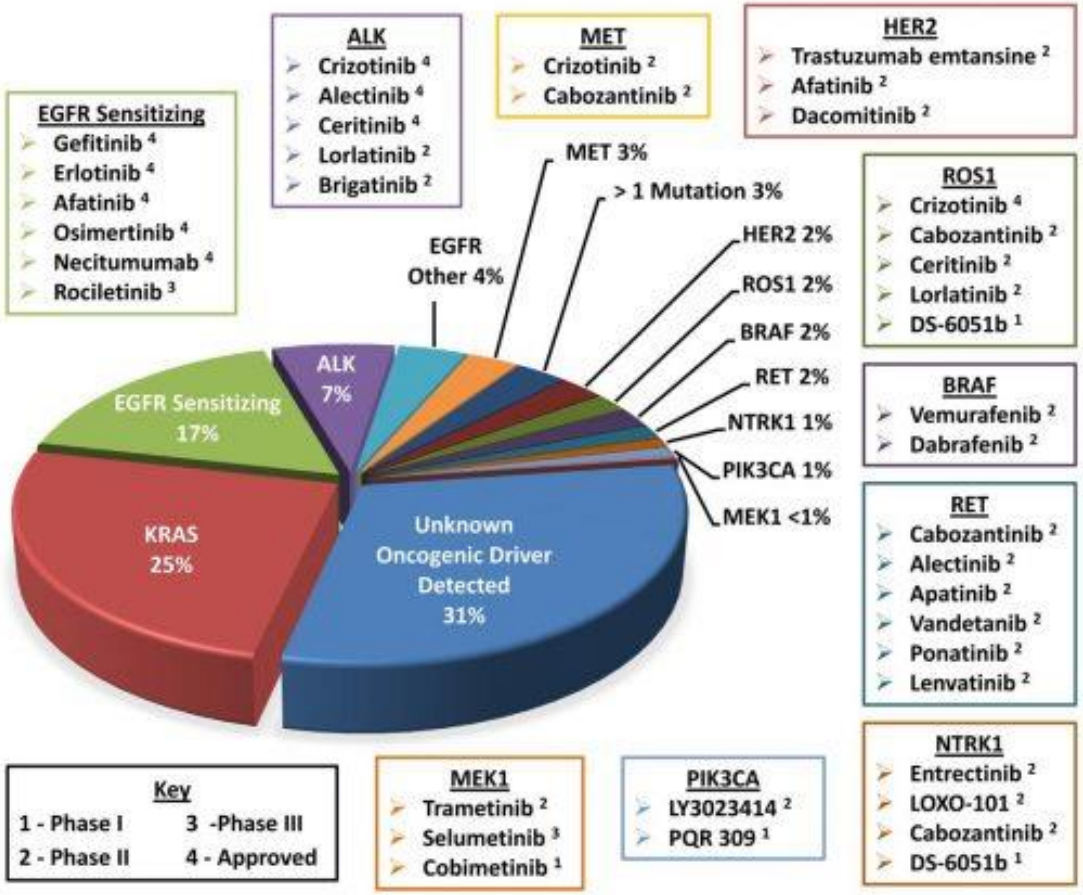

EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET
Crizotinib 2
Cabozantinib 2
HER2
Trastuzumab emtansine 2
Afatinib 2
Dacomitinib 2
ROS1
Crizotinib 4
Cabozantinib 2
Ceritinib 2
Lorlatinib 2
DS-6051b 1
Vemurafenib 2
Dabrafenib 2
RET
Cabozantinib 2
Alectinib 2
Apatinib 2
Vandetanib 2
Ponatinib 2
Lenvatinib 2
NTRK1
Entrectinib 2
LOXO-101 2
Cabozantinib 2
DS-6051b 1
PIK3CA
LY3023414 2
PQR 309 1
MEK1
Trametinib 2
Selumetinib 3
Cobimetinib 1
Key
1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved
EGFR Sensitizing 17%
ALK 7%
KRAS 25%
Unknown Oncogenic Driver Detected 31%
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%

BRAF in Cancer

- BRAFmut oncogene - 5-10% of all human malignancies.
- 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 malignanices such as Multiple myeloma, Langerhans Cell Histiocytosis, Erdheim-Chester Disease, Hairy Cell Leukemia etc

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
Gastrointestinal Stromal Tumor	321	2 to 5	Hostein 2010
Germ Cell Tumor (GCT)	100	1	Honecker 2009
Low grade glioma (adult)	Pilocytic astrocytoma (22)	9	Schindler 2011
	Oligodendroglioma (62)	2	
	Pleomorphic xanthoastrocytoma (38)	63	
	Ganglioglioma (53)	21	
High grade glioma (adult)	Anaplastic ganglioglioma (5)	40	Schindler 2011
	Secondary glioblastoma (18)	6	
	Giant cell glioblastoma (15)	7	
Hairy Cell Leukemia	47	100	Tiacci 2011
Multiple Myeloma	22	4	Walker 2012
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
Endometrial Adenocarcinoma	28	10.7	Mai 2013
Colorectal Cancer	519	8.7	Tol 2009


ALK
Crizotinib 4
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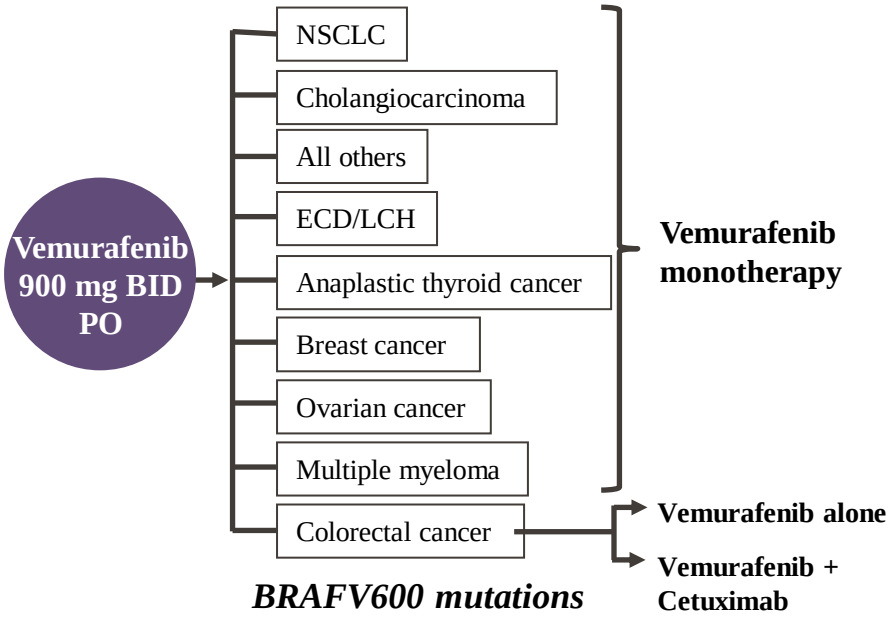
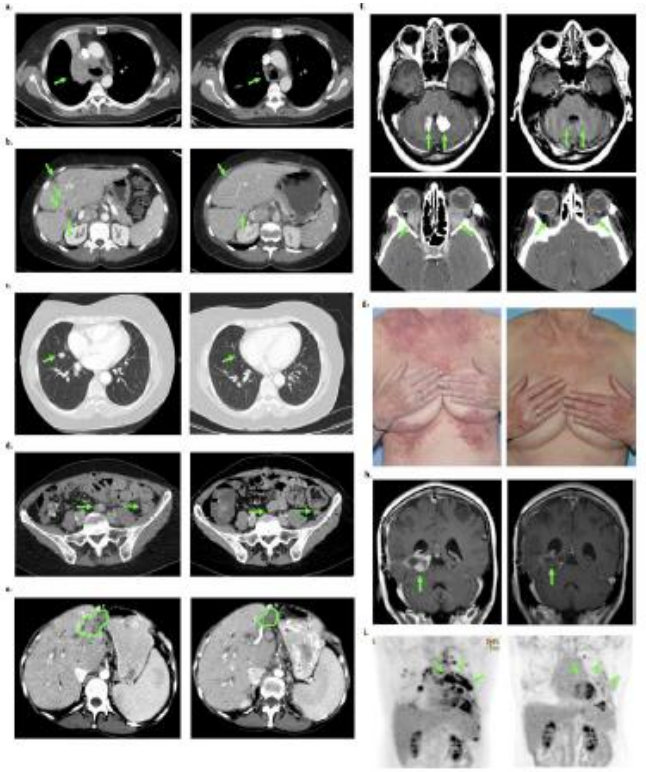
Vemurafenib Basket Trial



- 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%**
- **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 and among patients with colorectal cancer who received vemurafenib and cetuximab.**

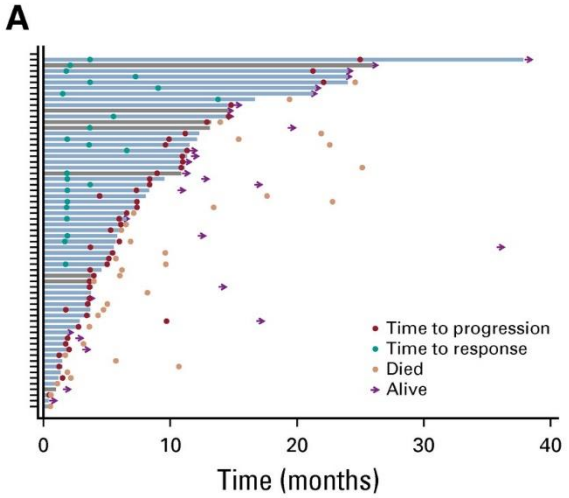
Hyman*, Puzanov, Subbiah V* et al, *NEJM* 2015

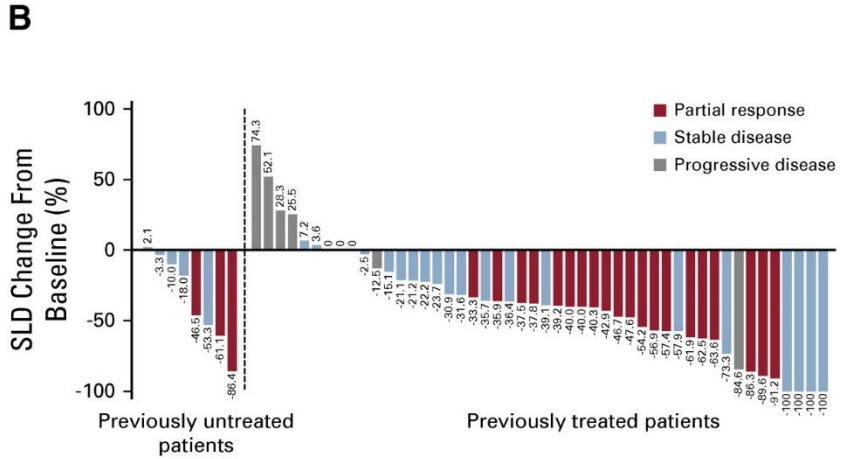
original report

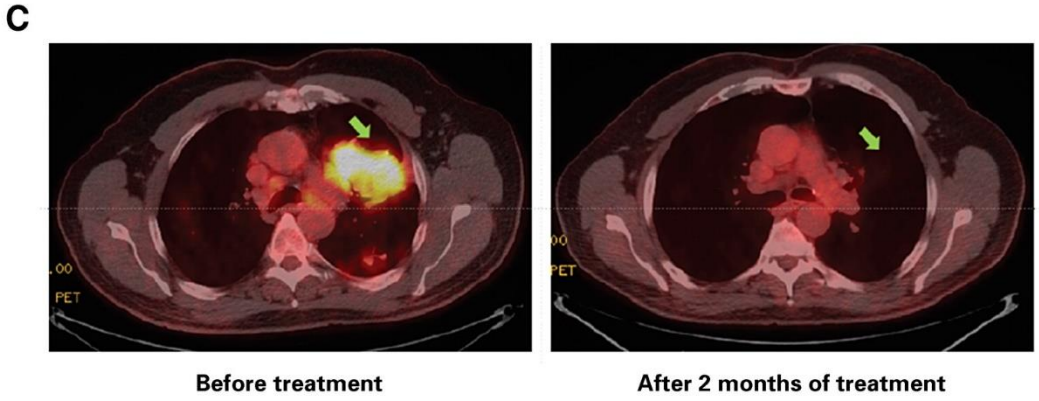
Efficacy of Vemurafenib in Patients With Non–Small-Cell Lung Cancer With *BRAF* V600 Mutation: An Open-Label, Single-Arm Cohort of the Histology-Independent VE-BASKET Study

Vivek Subbiah, MD[1]; Radj Gervais, MD[2]; Gregory Riely, MD, PhD[3]; Antoine Hollebecque, MD[4]; Jean-Yves Blay, MD, PhD[5]; Enriqueta Felip, MD, PhD[6]; Martin Schuler, MD[7]; Anthony Gonçalves, MD, PhD[8]; Antonio Italiano, MD, PhD[9]; Vicki Keedy, MD[10]; Ian Chau, MD[11]; Igor Puzanov, MD[12]; Noopur S. Raje, MD[13]; Funda Meric-Bernstam, MD[1]; Martina Makrutzki, MD[14]; Todd Riehl, PharmD[15]; Bethany Pitcher, MMath[16]; Jose Baselga, MD, PhD[3,17]; and David M. Hyman, MD[3,17]

- **Objective Response Rate was 37.1% (95% CI, 25.2% to 50.3%) overall**
- **Median progression-free survival was 6.5 months (95% CI, 5.2 to 9.0 months),**
- **Median overall survival was 15.4 months (95% CI, 9.6 to 22.8 months).**



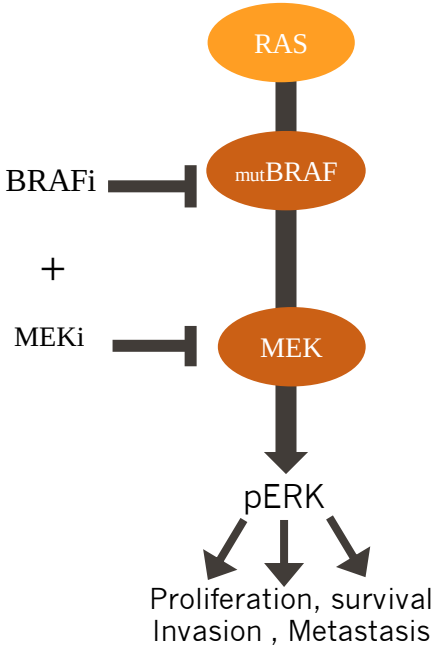




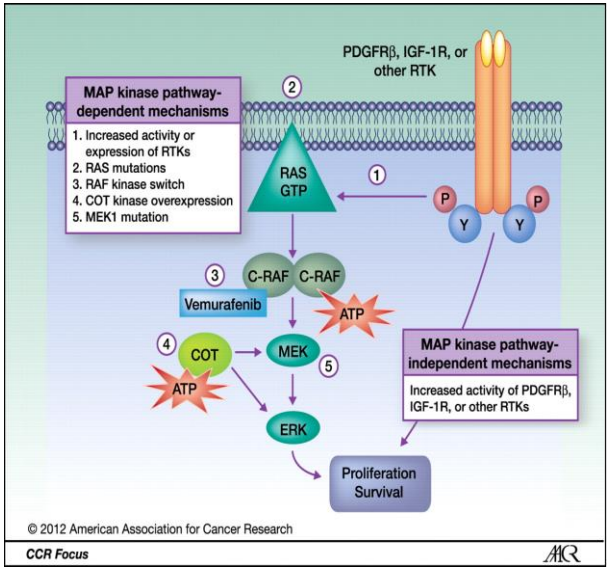
Published in: Vivek Subbiah et al; *JCO Precision Oncology* 2019 31-9.
DOI: 10.1200/PO.18.00266

Rationale for the TAF/MEK Combination

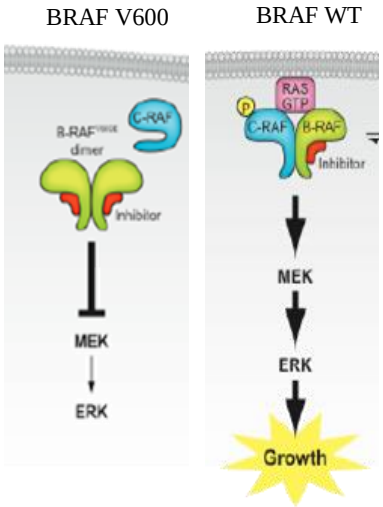
Sustained target inhibition to observe more prolonged and durable anti-tumor effect



Delay and potentially prevent the development of resistance



Prevent/delay hyperproliferative lesions and secondary malignancies



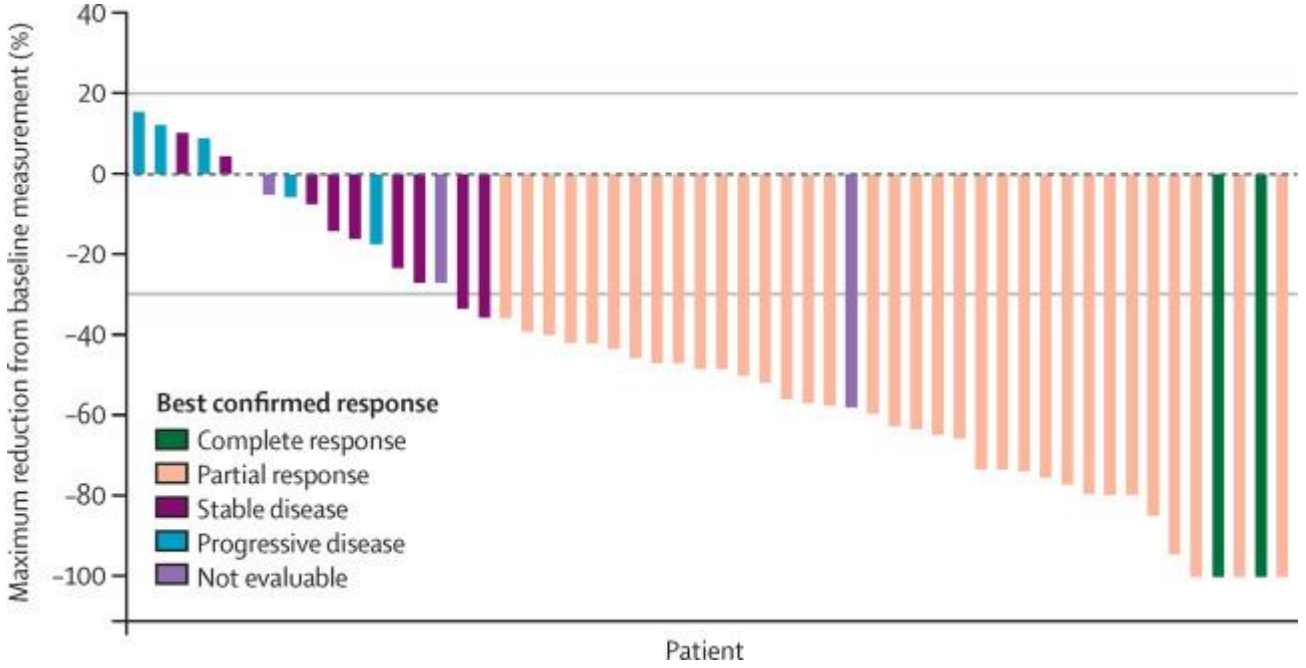
Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, Tae Min Kim, Julien Mazieres, Silvia Novello, James R Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

- **ORR = 63 % NSCLC.**
- **Median progression-free survival of 9.7 months,**

***Lancet Oncol* 2016; 17: 984–93**

Dabrafenib plus trametinib in patients with previously treated *BRAF*V600E-mutant metastatic NSCLC



Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

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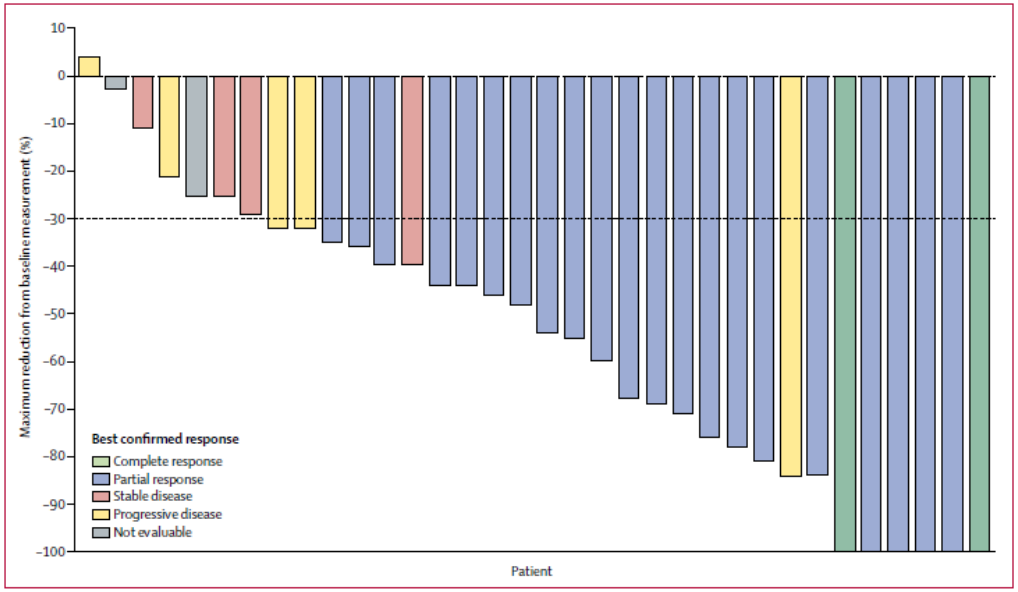
- **ORR = 64%, 95% CI 46–79)**
- **Median PFS =10·9 months (95% CI 7·0–16·6),**
- **6-month progression-free survival = 72%**

***Lancet Oncol* 2017; 18: 1307–16**

Dabrafenib + trametinib in patients with previously untreated *BRAF*V600E-mutant metastatic NSCLC



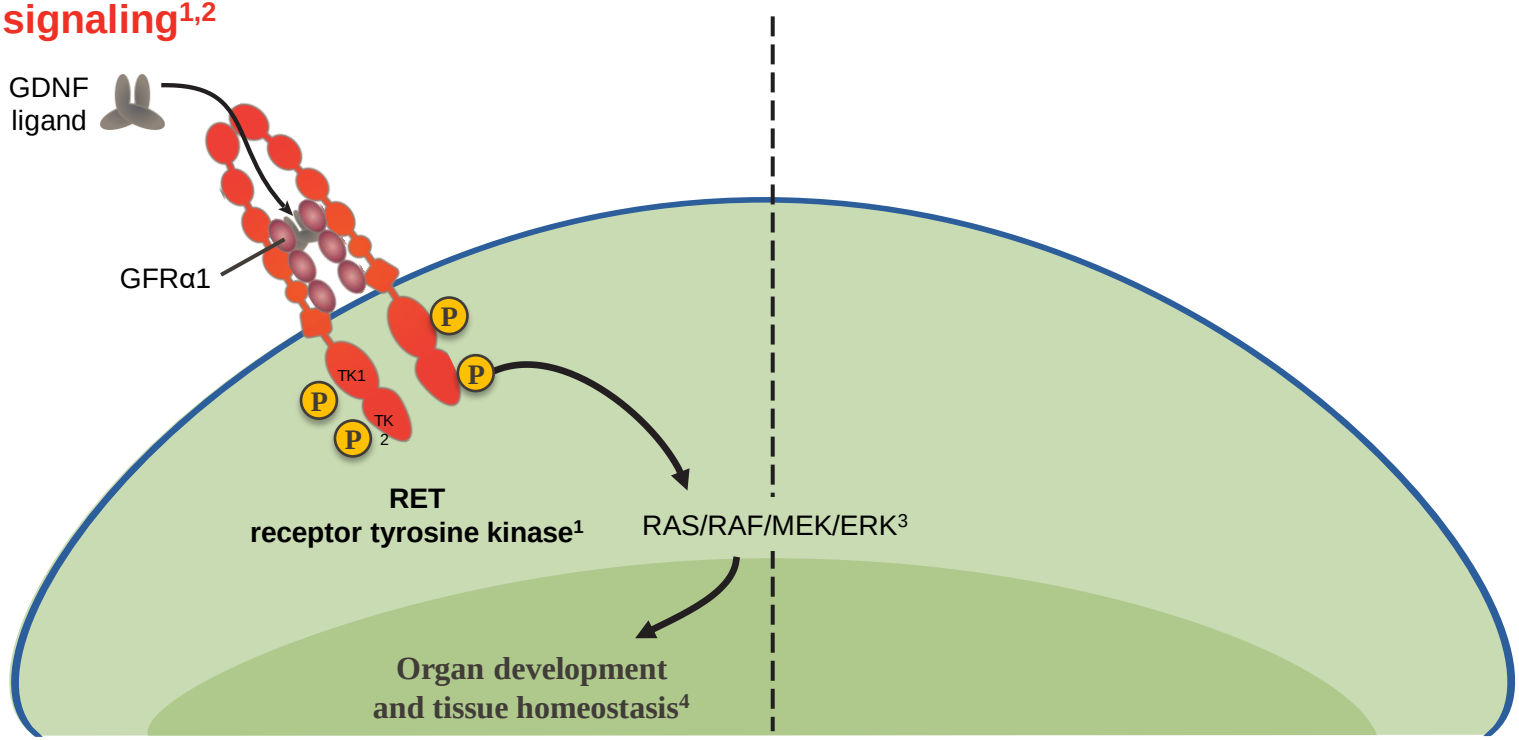
- ORR = 64%, 95% CI 46–79)
- Median PFS =10·9 months (95% CI 7·0–16·6),
- 6-month progression-free survival = 72%

RET targeting

- RET aberrations in oncology
- RET alterations in NSCLC
- Multi-kinase drugs
- Selective RET inhibitors
- LOXO-292
- BLU-667
- Future directions

RET is an RTK required for normal development[1]

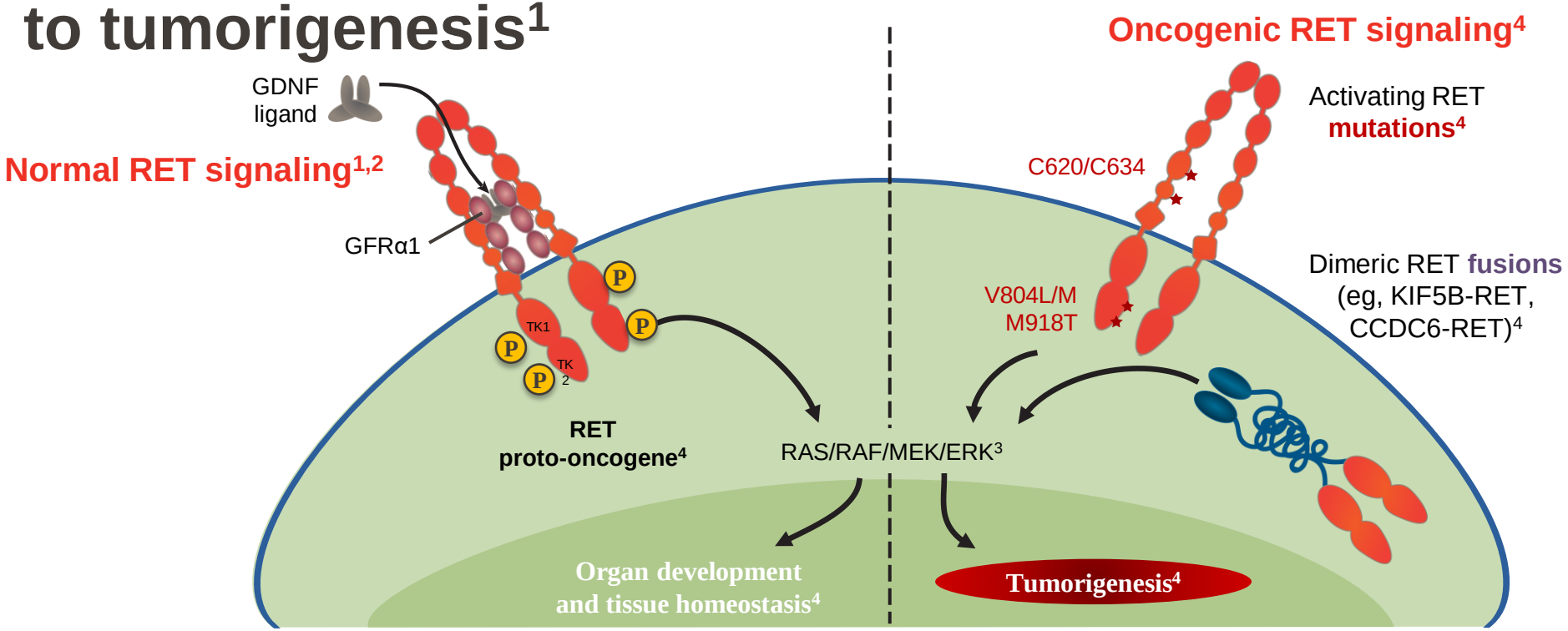
Normal RET signaling[1,2]



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.

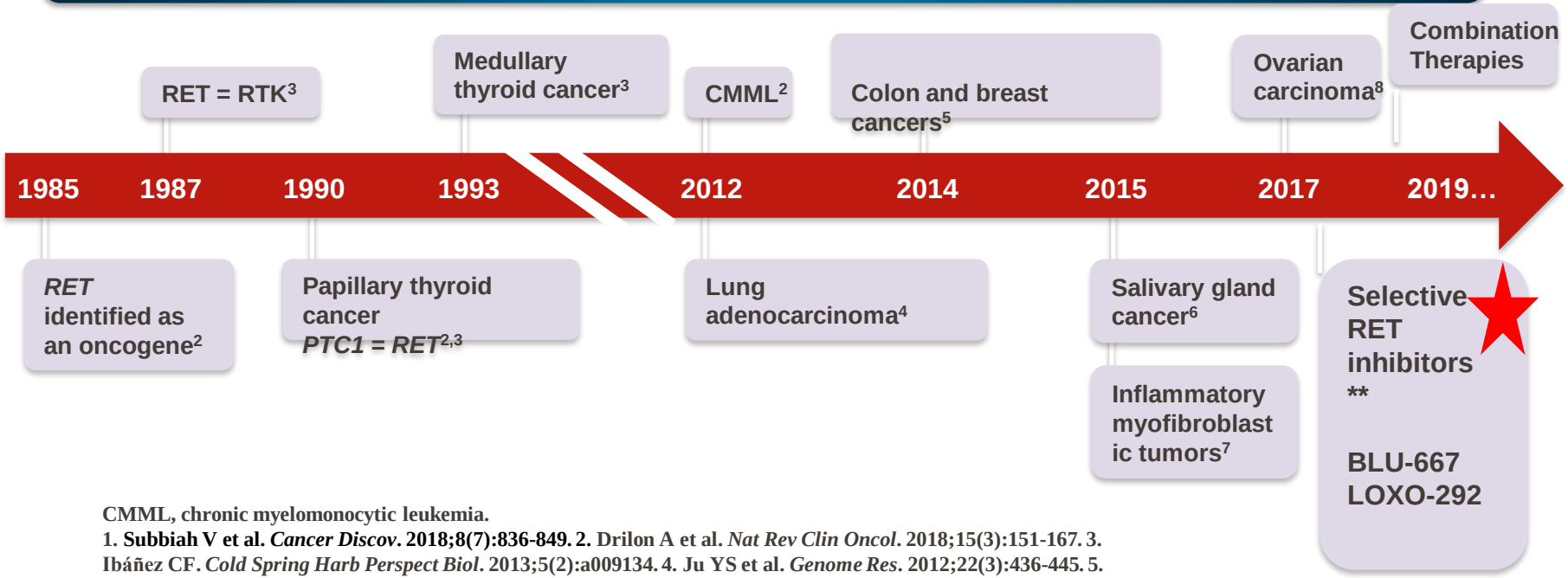
Alterations in RET structure and function can lead to tumorigenesis[1]



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]**

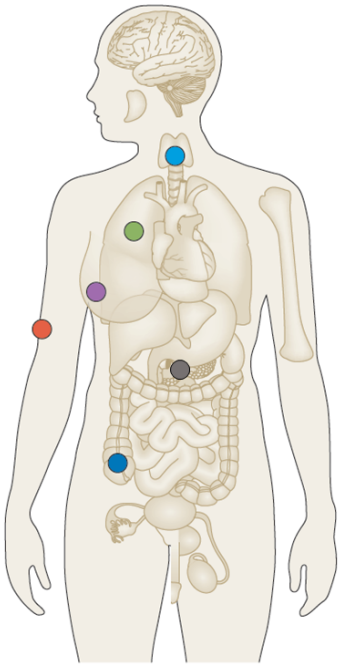


CMML, chronic myelomonocytic leukemia.

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%)

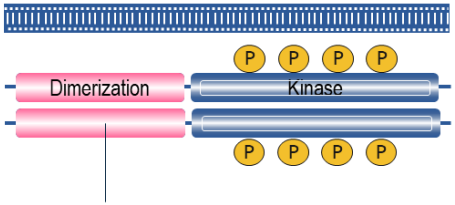
Spitz tumors (<1%)

Colorectal cancer (<1%)

Ovarian cancer (<1%)

Myeloproliferative disorders (<1%)

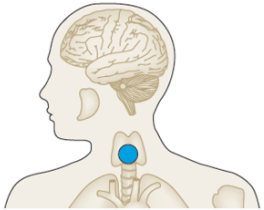
Many others (<1%)



KIF5B (most common in lung cancer)

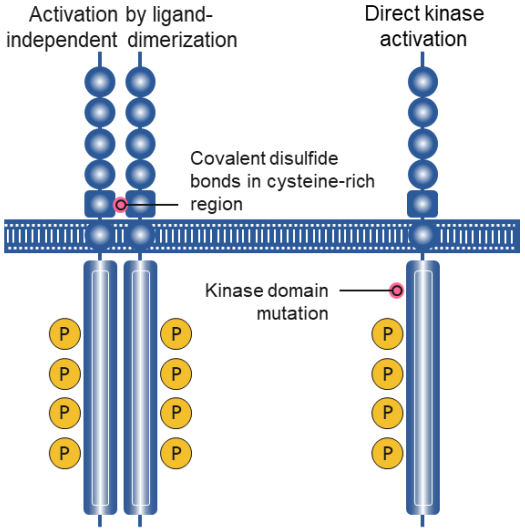
CCDC6 or NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

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

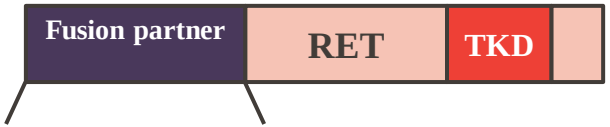


Common mutation: **RET M918T**

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)

A number of oncogenic RET fusions and activating point mutations have been identified to date

RET fusions[1]



KIF5B	NCOA	TBLXR1
CCDC6	GOLGA5	FGFR1OP
NCOA4	TRIM24	EML4
TRIM33	TRIM27	EPHA5
CUX1	KTN1	SQSTM1
KIAA1217	RFG9	PARD3
FRMD4A	ERC1	PICALM
KIAA1468	HOOK3	AFAP1L2
PRKAR1A	PCM1	PPFIBP2
FKBP15	AKAP13	ACBD5
	SPECC1L	MYH13

Most common RET fusion partners in:
- **NSCLC[2]:** KIF5B, CCDC6, NCOA4
- **PTC[3]:** CCDC6, NCOA4

Activating RET point mutations[1]

C634F/G/R/S/W/Y	C630R/Y	M918T	Y806C
G533C	D631Y	L790F	A883F
C609F/G/R/S/Y	K666E	Y791F	S891A
C611F/G/S/Y/W	C620F/R/S	V804M	E768D
C618F/R/S		V804L	

ATA category for risk of aggressive MTC[4]

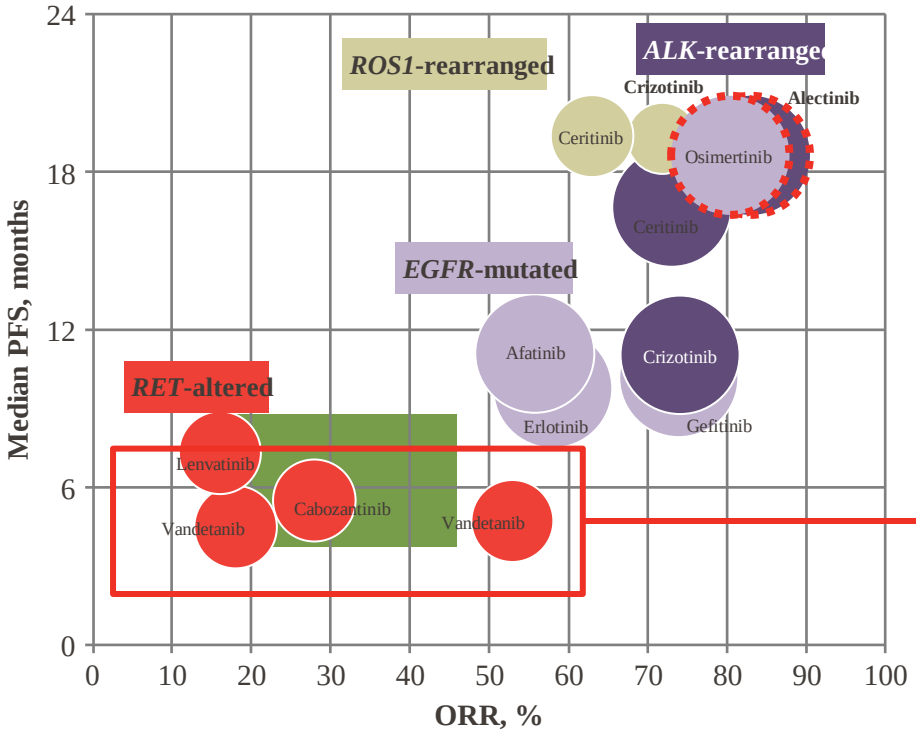
Unknown	Moderate	High	Highest

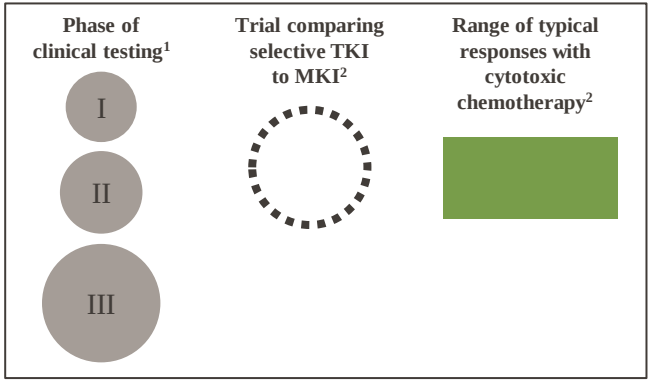
Most common RET mutations in:
- **MTC[5]:** C634F/G/R/S/W/Y, M918T, V804M, L790F, Y791F

ATA, American Thyroid Association; CCDC, coiled-coil domain containing; KIF, kinesin family member; NCOA, nuclear receptor coactivator.

1. Iams WT, Lovly CM. *Cancer Discov*. 2018;8(7):797-799. 2. Farago AF, Azzoli CG. *Transl Lung Cancer Res*. 2017;6(5):550-559.
3. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. 4. Wells SA Jr et al. *Thyroid*. 2015;25(6):567-610. 5. Romei C et al. *Nat Rev Endocrinol*. 2016;12(4):192-202.

Patients with *RET*-altered NSCLC have not yet achieved the promise of precision therapy





ORR and PFS achieved with MKIs in *RET*-altered NSCLC are:

- Notably lower than those achieved in *ALK*-, *ROS1*-, and *EGFR*-mutated NSCLC[1]
- Similar to those achieved with cytotoxic chemotherapy[2]

PFS, progression-free survival; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. 2. Herbst RS et al. *Nature*. 2018;553(7689):446-454.

Drug-related toxicity due to non-selectivity greatly limits the efficacy of MKIs in *RET*-altered cancers

Many MKIs have greater potency on several off-target kinases across the kinome, such as VEGFR2[1]

Potential toxicities due to MKI off-target activity include[1,2]:

- Hypertension
- Hand-foot syndrome
- Proteinuria
- Hypopigmentation
- QT prolongation
- Thrombosis
- Hemorrhage

Results from several clinical studies of MKIs in patients with NSCLC and thyroid cancers demonstrate high rates of dose reduction and drug discontinuation[1]

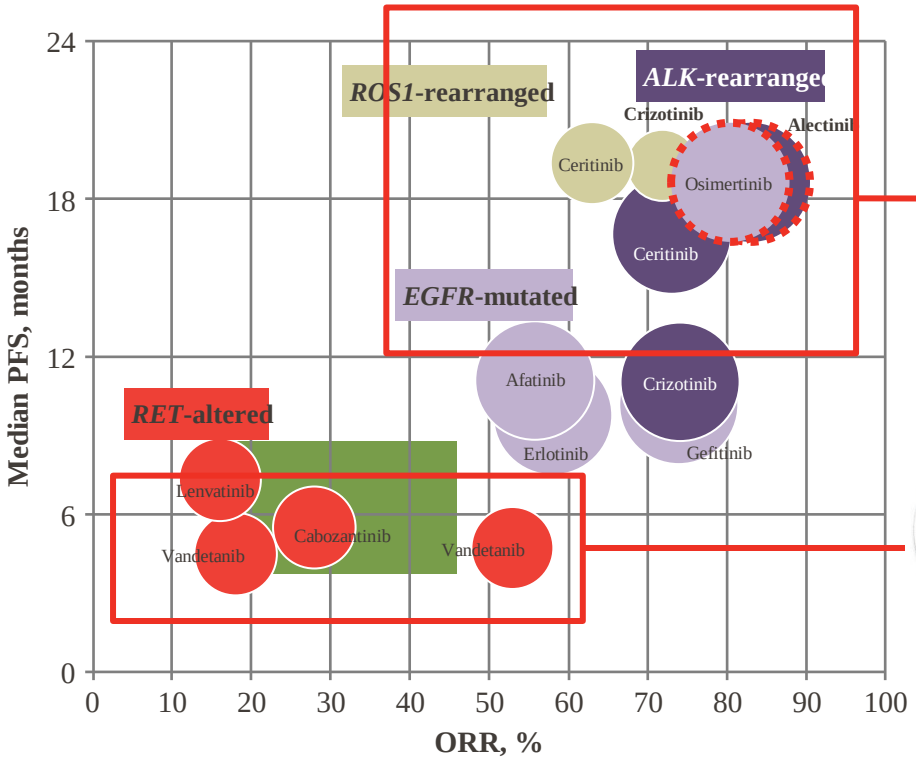
Cancer type[1]	MKI[1]	Dose reduction rate[1]	Discontinuation rate[1]
NSCLC	Cabozantinib, vandetanib, lenvatinib, sorafenib	23% to 73%	8% to 33%
Thyroid cancer	Cabozantinib, vandetanib, lenvatinib, sorafenib, sunitinib, dovitinib, motesanib	19% to 79%	6% to 24%

VEGFR, vascular endothelial growth factor receptor.

1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. 2. Iams WT, Lovly CM. *Cancer Discov*. 2018;8(7):797-799.

In search of Super Heroes for RET inhibition !

Patients with *RET*-altered NSCLC have not yet achieved the promise of precision therapy



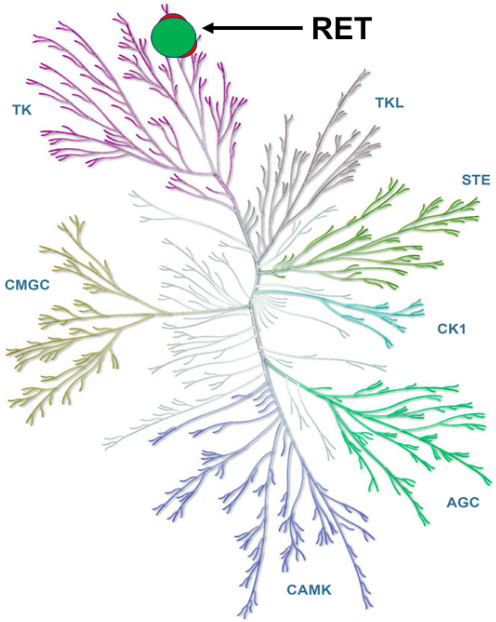
PFS, progression-free survival; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. 2. Herbst RS et al. *Nature*. 2018;553(7689):446-454.

LOXO-292 (SELPERCATINIB) is a potent and selective RET inhibitor

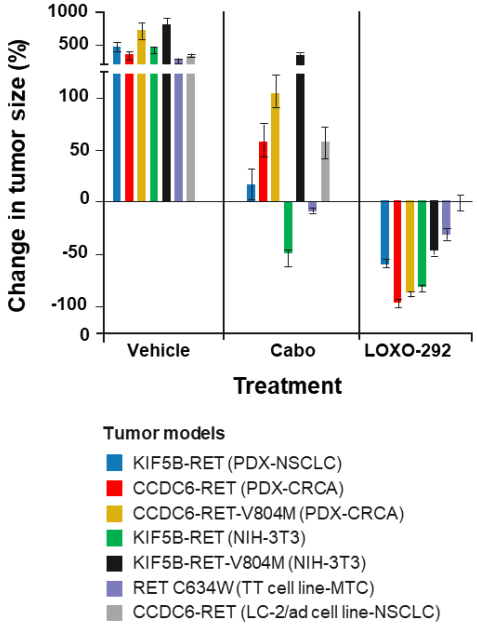
Kinome selectivity

Highly selective for RET



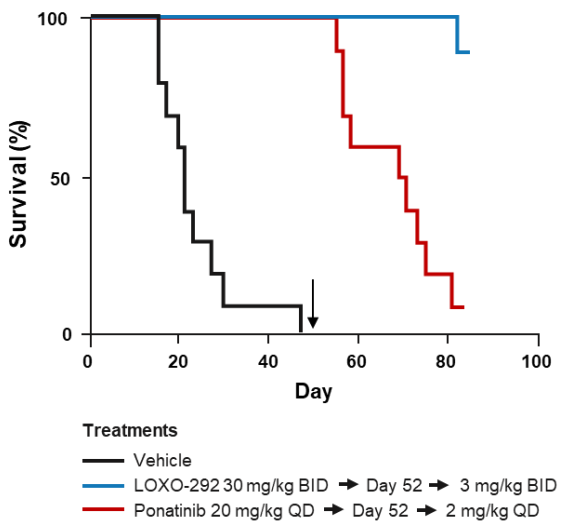
Xenograft models

Multiple fusions/mutations/histologies



Orthotopic brain model

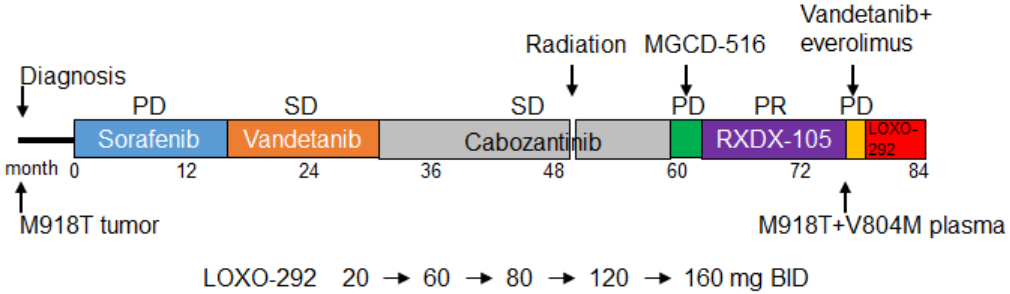
CCDC6-RET orthotopic brain PDX



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

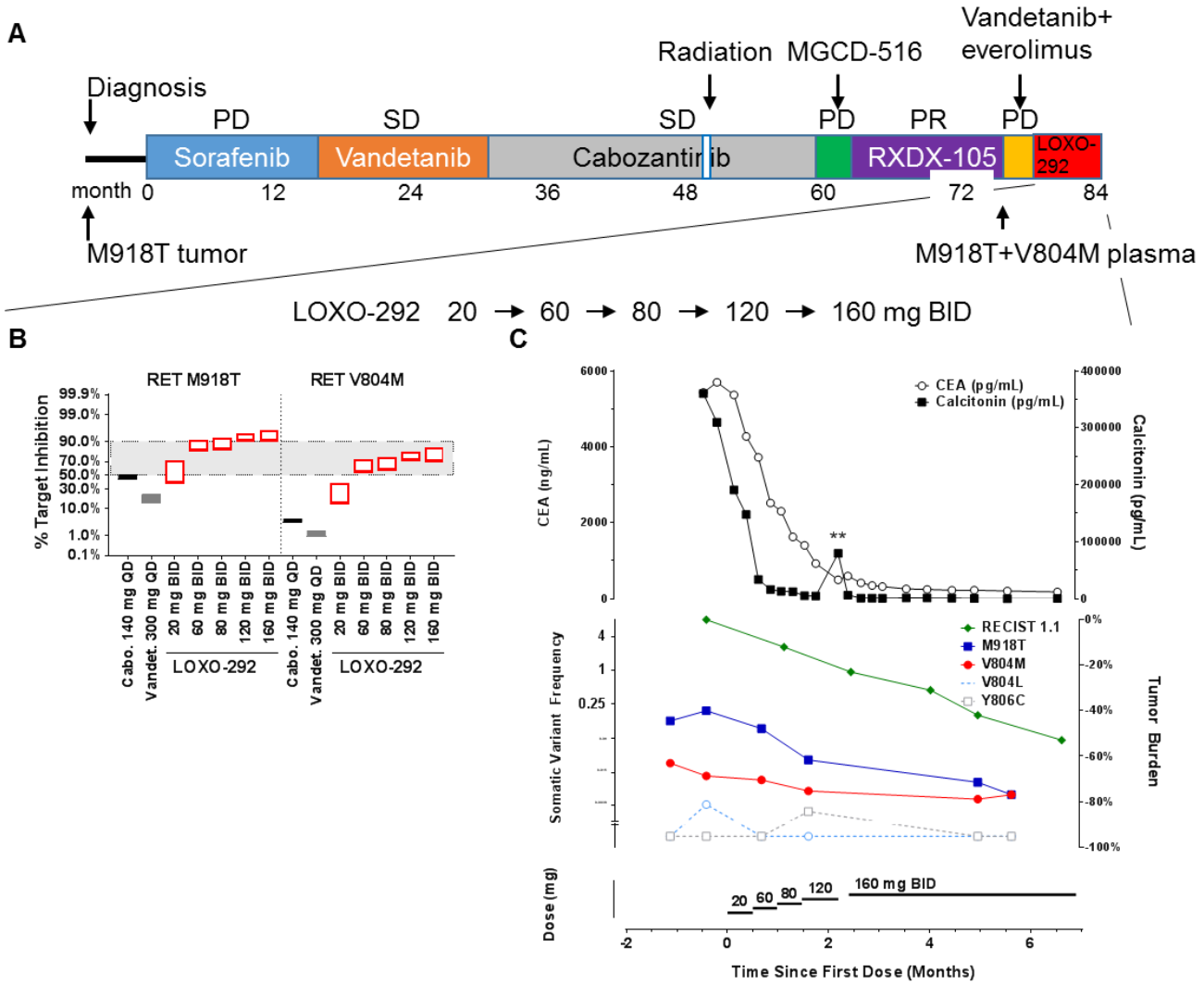
Sporadic RET M918T/V804M-mutant response to LOXO-292

- 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")
- Remains on treatment for 24 months
- All side effects grade 1 and have not interrupted dosing of LOXO-292

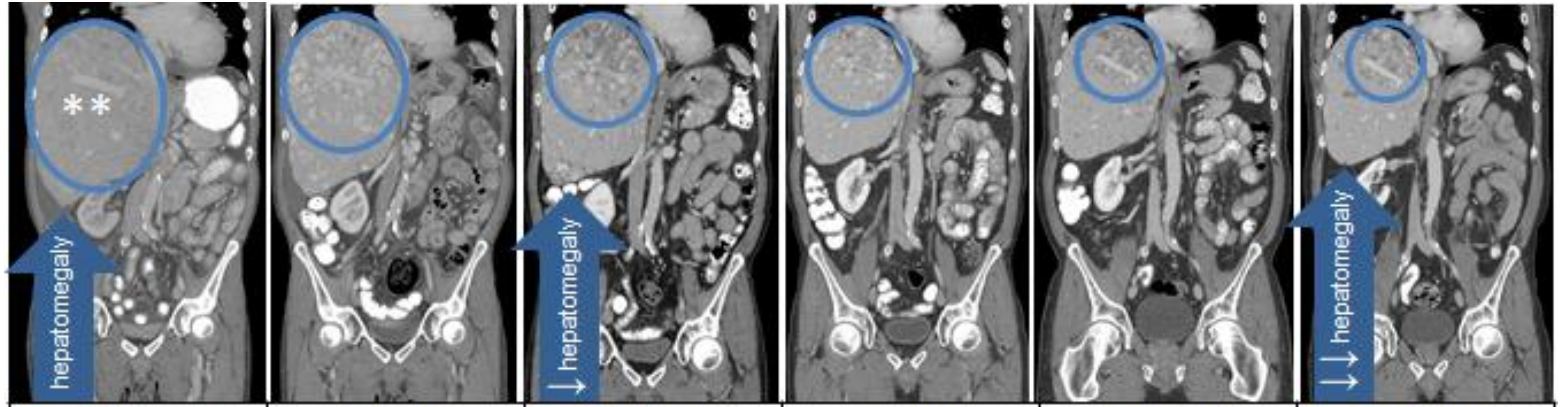


Subbiah V et al, Annals of Oncology 2018 Aug 1;29(8):1869-1876

Sporadic RET M918T/V804M-mutant response to LOXO-292



Sporadic RET M918T/V804M-mutant response to LOXO-292



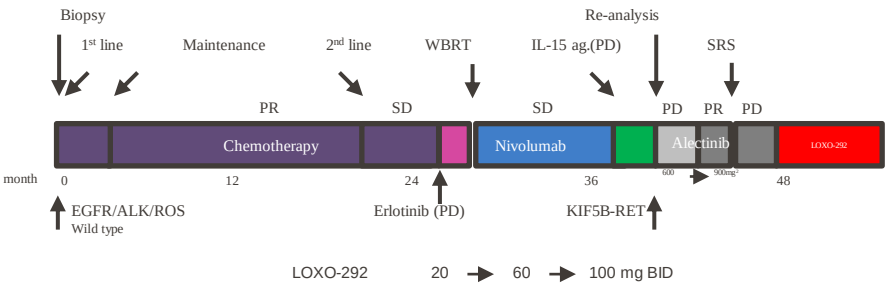
Baseline	1.2 Mo.	2.6 Mo.	4.2 Mo.	5.2 Mo.	6.9 Mo.
25.9x19.5cm	24.3x16.7cm	22.5x15.7cm	20.2x14.5cm	18.8x14.2cm	18.0x13.9cm
↓ Target Lesions (RECIST 1.1)	-12%	-21%	-31% (PR)	-42% (cPR)	-54% (cPR)

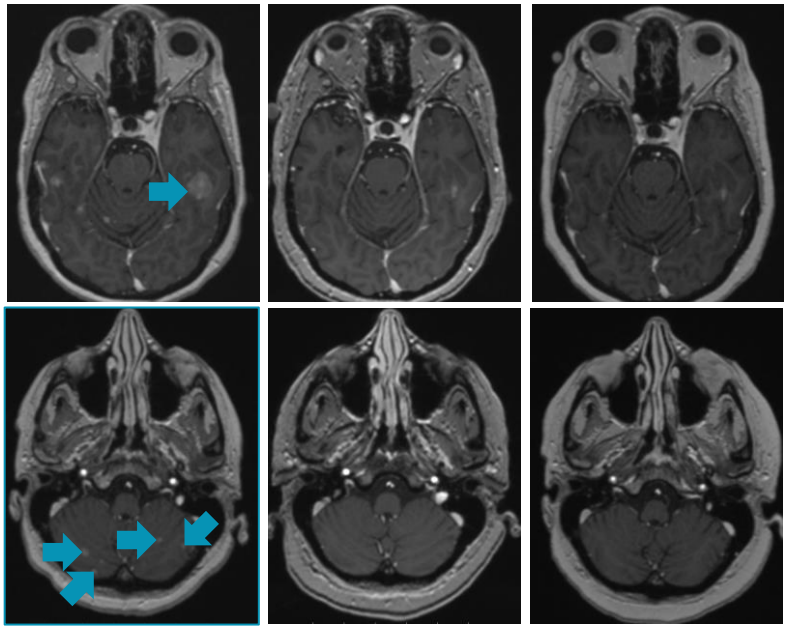
Subbiah V et al, **Annals of Oncology 2018 Aug 1;29(8):1869-1876**

KIF5B-RET fusion-positive NSCLC response to LOXO-292

40 year-old woman with *KIF5B-RET*+ NSCLC

- **Chemotherapy, immunotherapy, WBRT, alectinib → progressive symptomatic brain metastases**
- **Rapid clinical response to LOXO-292 with ↓ gait imbalance resolution of confusion and gait imbalance**
- **Confirmed RECIST response (best -67% extdracranially and no residual) and shrinkage of multiple brain metastases**
- **No AEs attributed to LOXO-292**
- **Patient discontinued treatment against medical advice**





Baseline	2 Mo.	5 Mo.
↓ Target Lesions (RANO-BM)	-89% (PR)	-100% (cPR)

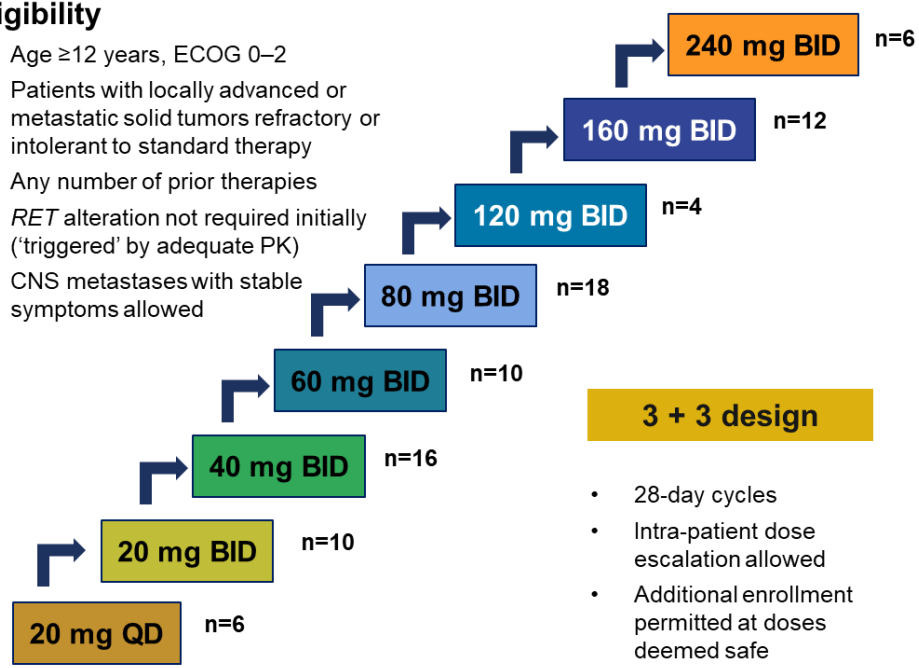
Subbiah V et al, Annals of Oncology 2018 Aug 1;29(8):1869-1876

LIBRETTO-001: phase I dose escalation and pharmacokinetics

- **82 patients enrolled across 8 dose levels**

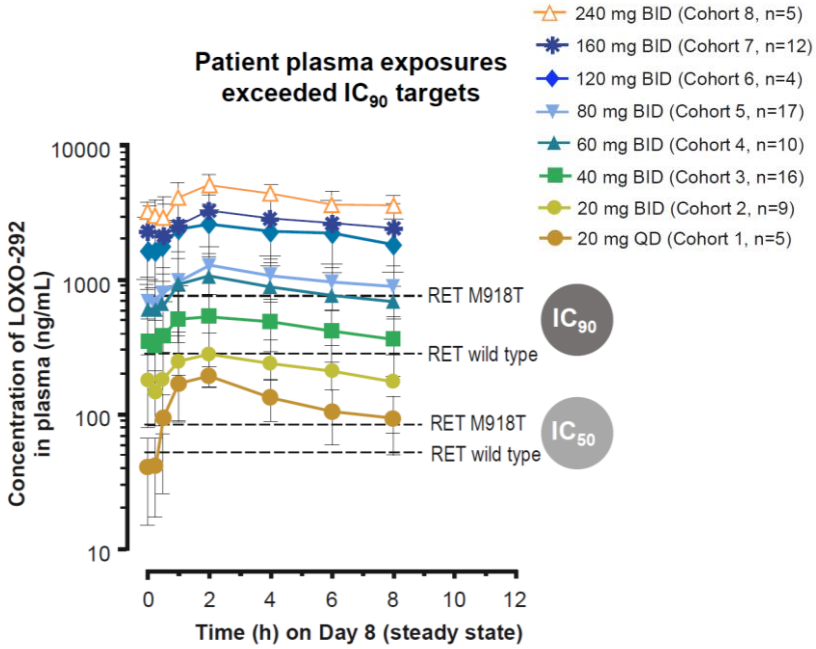
Eligibility

- 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

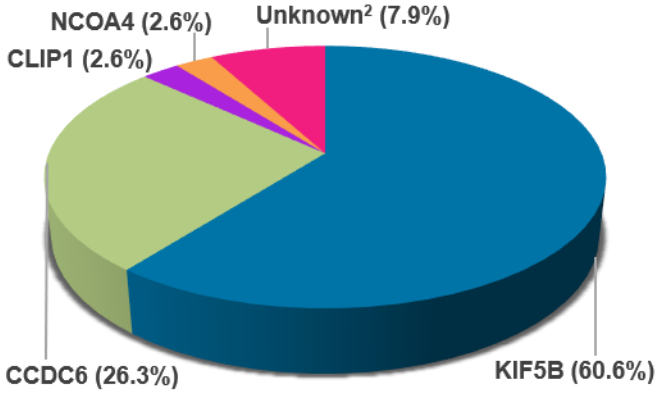


Horizontal lines represent the plasma level at which the unbound LOXO-292 concentration corresponds to IC_{50} or IC_{90} of the indicated target based on cellular assays

RET-altered cancers

Tumor type, n (%)	Total (n=82)
RET fusion-positive NSCLC	38 (46%)
RET fusion-positive thyroid cancer	9 (11%)
RET fusion-positive pancreatic cancer	2 (2%)
RET-mutant MTC	29 (35%)
No known activating *RET* alteration	4 (5%)

RET fusion partner[1]



RET-fusion positive NSCLC

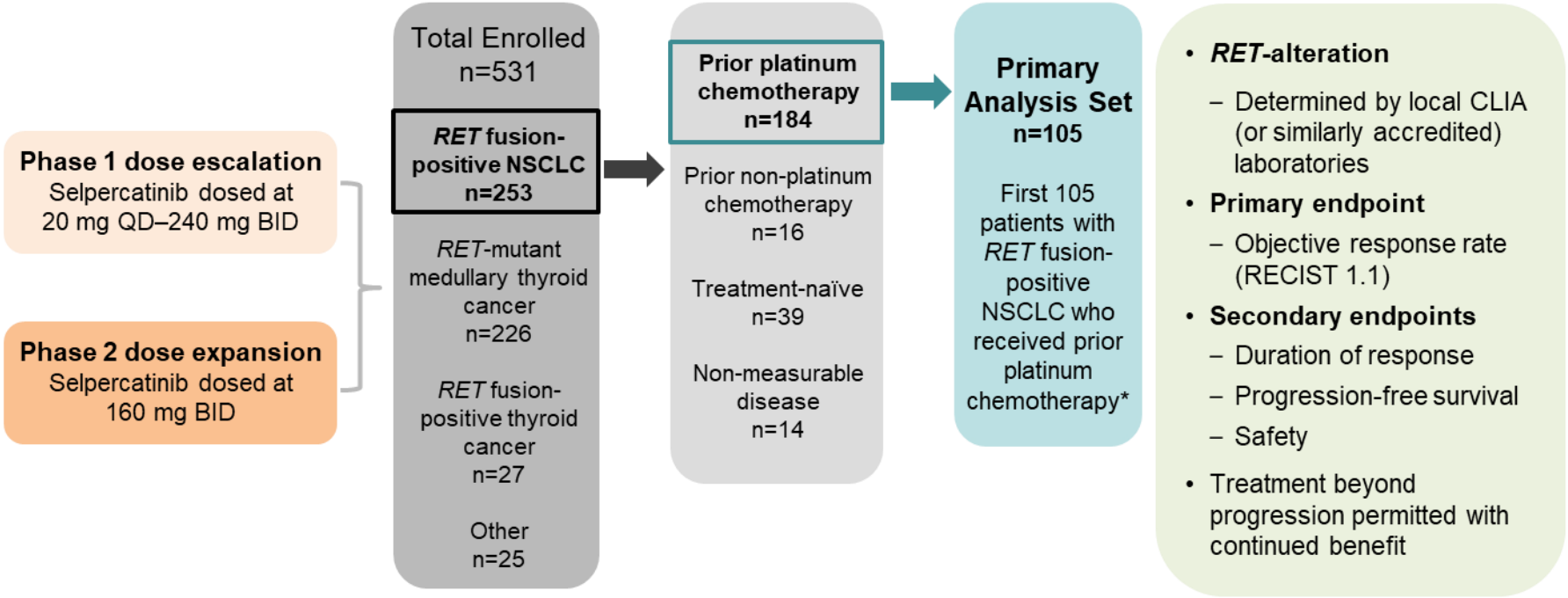
Characteristic	Total (n=38)
Female / Male, n (%)	22 (58) / 16 (42)
Median age (range), years	62.5 (36–80)
ECOG performance status, n (%)	
0	6 (16)
1	32 (84)
Median prior systemic regimens (range)	3 (1–9)
Prior multikinase inhibitor (MKI), n (%)[3]	
0	17 (45)
≥1	21 (55)
Prior chemotherapy or immunotherapy, n (%)	33 (87)
Prior chemotherapy and immunotherapy, n (%)	15 (39)
Brain metastases, n (%)	8 (21)

Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of Selpercatinib (LOXO-292) in Patients with *RET* Fusion-Positive Lung Cancers

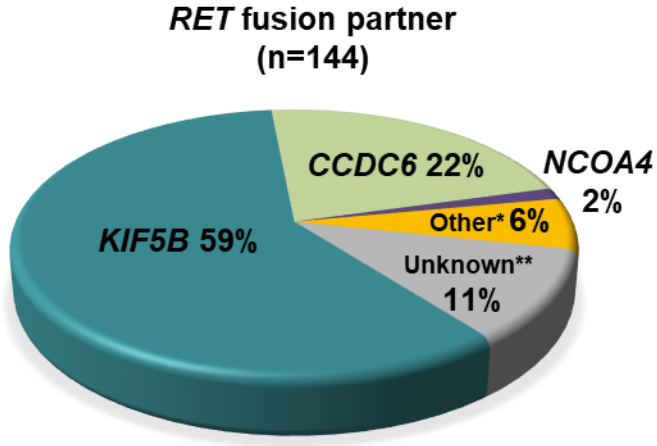
A. Drilon[1], G. Oxnard[2], L. Wirth[3], B. Besse[4], O. Gautschi[5], S.W.D. Tan[6], H. Loong[7], T. Bauer[8], Y.J. Kim[9], A. Horiike[10], K. Park[11], M. Shah[12], C. McCoach[13], L. Bazhenova[14], T. Seto[15], M. Brose[16], N. Pennell[17], J. Weiss[18], I. Matos[19], N. Peled[20], B.C. Cho[21], Y. Ohe[22], K. Reckamp[23], V. Boni[24], M. Satouchi[25], G. Falchook[26], W. Akerley[27], H. Daga[28], T. Sakamoto[29], J. Patel[30], N. Lakhani[31], F. Barlesi[32], M. Burkard[33], V. Zhu[34], V. Moreno Garcia[35], J. Medioni[36], M. Matrana[37], C. Rolfo[38], D.H. Lee[39], H. Nechushtan[40], M. Johnson[41], V. Velcheti[42], M. Nishio[43], R. Toyozawa[44], K. Ohashi[45], L. Song[46], J. Han[47], A. Spira[48], M.Duca[49], K. Staal Rohrberg[50], S. Takeuchi[51], J. Sakakibara[52], S. Waqar[53], H. Kenmotsu[54], F. Wilson[55], B.Nair[56], E. Olek[56], J. Kherani[56], K. Ebata[56], E. Zhu[56], M. Nguyen[56], L. Yang[56], X. Huang[56], S. Cruickshank[56], S. Rothenberg[56], B. Solomon[57], K. Goto[58], V. Subbiah[59]

1.Memorial Sloan Kettering Cancer Center, New York, NY/United States of America. 2. Dana-Farber Cancer Institute, Boston, MA/United States of America. 3. Massachusetts General Hospital, Boston, MA/United States of America. 4. Institut Gustav Roussy, Villejuif/France. 5. Luzerner General Hospital, Luzern/Switzerland. 6. National Cancer Centre, Singapore/Singapore. 7. Prince of Wales Hospital, Shatin/Hong Kong PRC. 8. Sarah Cannon Research Institute, Nashville, TN/United States of America. 9. Seoul National University Bundang Hospital, Gyeonggido/Democratic People's Republic of Korea. 10. The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo/Japan. 11. Samsung Medical Center, Seoul/Democratic People's Republic of Korea. 12. The Ohio State University, Columbus, OH/United States of America. 13. University of California, San Francisco, CA/United States of America. 14. University of California San Diego, Moores Cancer Center, La Jolla, CA/United States of America. 15. National Hospital Organization Kyushu Cancer Center, Fukuoka/Japan. 16. University of Pennsylvania, Philadelphia, PA/United States of America. 17. Cleveland Clinic, Cleveland, OH/United States of America. 18. University of North Carolina, Chapel Hill, NC/United States of America. 19. Vall d' Hebron Institute of Oncology, Barcelona/Spain. 20. Soroka Medical Center, Beer Sheva/Israel. 21. Severance Hospital, Yonsei University Health System, Seoul/ Democratic People's Republic of Korea. 22. National Cancer Center Hospital, Tokyo/Japan. 23. City of Hope Comprehensive Cancer Center, Duarte, CA/United States of America. 24. START Madrid-CIOCC, Madrid/Spain. 25. Hyogo Cancer Center, Akashi/Japan. 26.Sarah Cannon Research Institute, Denver, CO/United States of America. 27. Huntsman Cancer Institute, Salt Lake City, UT/United States of America. 28. Osaka City General Hospital, Osaka/Japan. 29. Tottori University Hospital, Yonago/Japan. 30. University of Chicago, Chicago, IL/United States of America. 31. South Texas Accelerated Research Therapeutics (START) Midwest, Grand Rapids, MI/United States of America. 33. University of Wisconsin - Carbone Cancer Center, Madison, WI/United States of America. 34 University of California - Irvine Medical Center, Irvine, CA/United States of America. 35. Fundacion Jimenez Diaz, START-Madrid-FJD, Madrid/Spain. 36. Hopital Europeen Georges Pompidou, Paris/France. 37. Ochsner Clinic Foundation, New Orleans, LA/United States of America. 38. University of Maryland Medical Center, Baltimore, MD/United States of America. 39. Asan Medical Center, Seoul/ Democratic People's Republic of Korea. 40. Hadassah Hebrew University Medical Center Ein Karem, Jerusalem/Israel. 41. Tennesse Oncology/Sarah Cannon Research Institute, Nashville, TN/United States of America. 42. NYU Langone Cancer Center, New York, NY/United States of America. 43. Cancer Institute Hospital of JFCR, Tokyo/Japan. 44. National Hospital Organization Kyushu Cancer Center, Fukuoka/Japan. 45. Okayama University Hospital, Okayama/Japan. 46. Kaiser Permanente - Santa Clara, CA/ United States of America. 47. National Cancer Center, Democratic People's Republic of Korea. 48. Virginia Cancer Specialists, VA/United States of America. 49. Istituto Nazionale Tumori - National Cancer Institute, Milan, Italy. 50. The Finsen Centre, Rigshospitalet, Denmark. 51. Kanazawa University Hospital, Kanazawa, Japan. 52. Hokkaido University Hospital, Hokkaido, Japan. 53. Washington University School of Medicine, Missouri/United States of America. 54. Shizuoka Cancer Center, Nagaizumi, Japan. 55. Yale University School of Medicine - Yale Cancer Center, CT/United States of America. 56. Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company, Stamford, CT/United States of America. 57. Peter MacCallum Cancer Center, Melbourne, ACT/Australia. 58. National Cancer Center Hospital East, Kashiwa/Japan. 59. MD Anderson Cancer Center, Houston, TX/United States of America

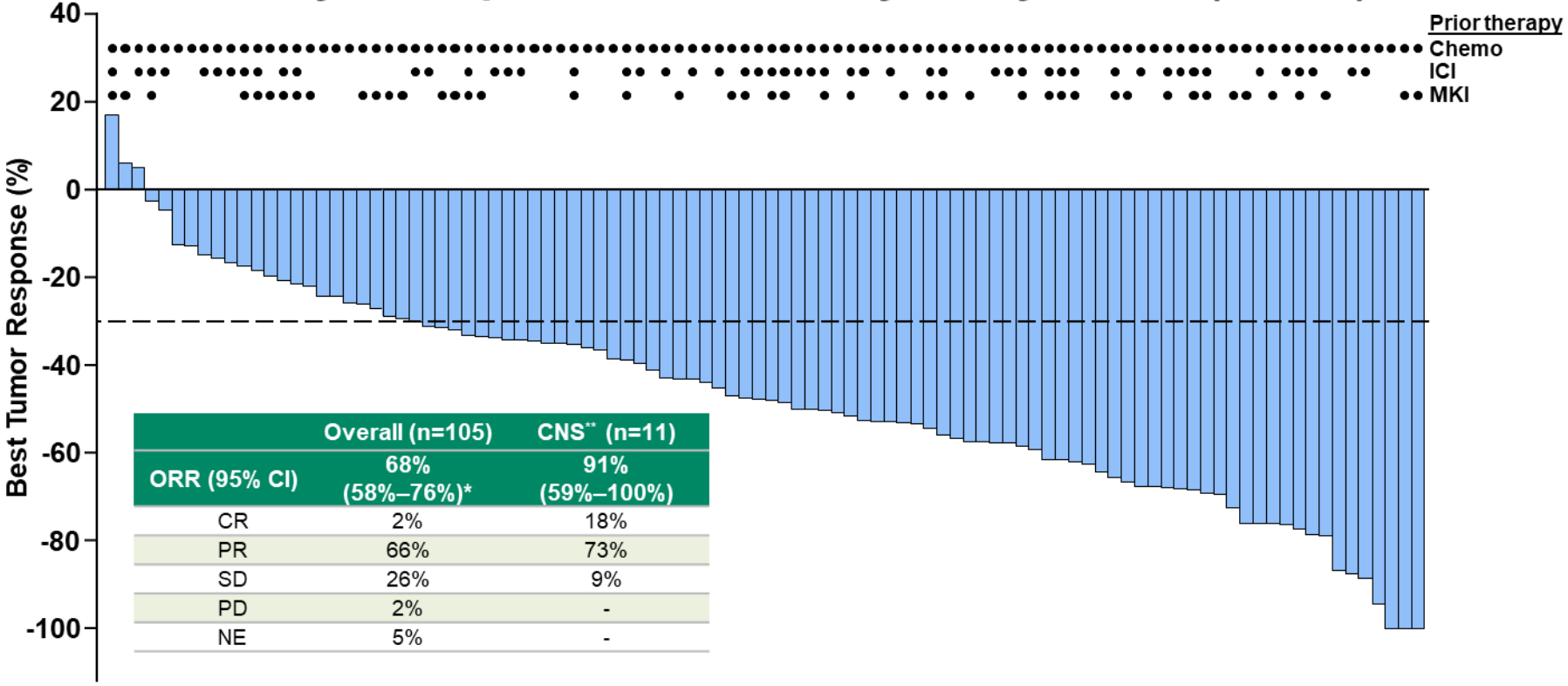
LIBRETTO-001: Selpercatinib in *RET*-altered cancers



Patient Characteristics	PAS (n=105)	Treatment-naïve (n=39)
Female / Male, n (%)	62 (59) / 43 (41)	22 (56) / 17 (44)
Median age (range), years	61 (23–81)	61 (23–86)
ECOG performance status, n (%)		
0	31 (30)	19 (49)
1	72 (69)	20 (51)
2	2 (2)	0
Median prior systemic regimens (range)	3 (1–15)	0
Prior platinum-based chemotherapy, n (%)	105 (100)	-
Prior PD-1/PD-L1 inhibitor, n (%)	58 (55)	-
Concurrent with platinum-based chemotherapy	9 (9)	-
Sequential to platinum-based chemotherapy	49 (47)	-
Prior multikinase inhibitor (MKI), n (%)	50 (48)	-
1	37 (35)	-
≥2	13 (12)	-
Brain metastases, n (%)‡	37 (35)	7 (18)
Measurable disease	104 (99)	39 (100)

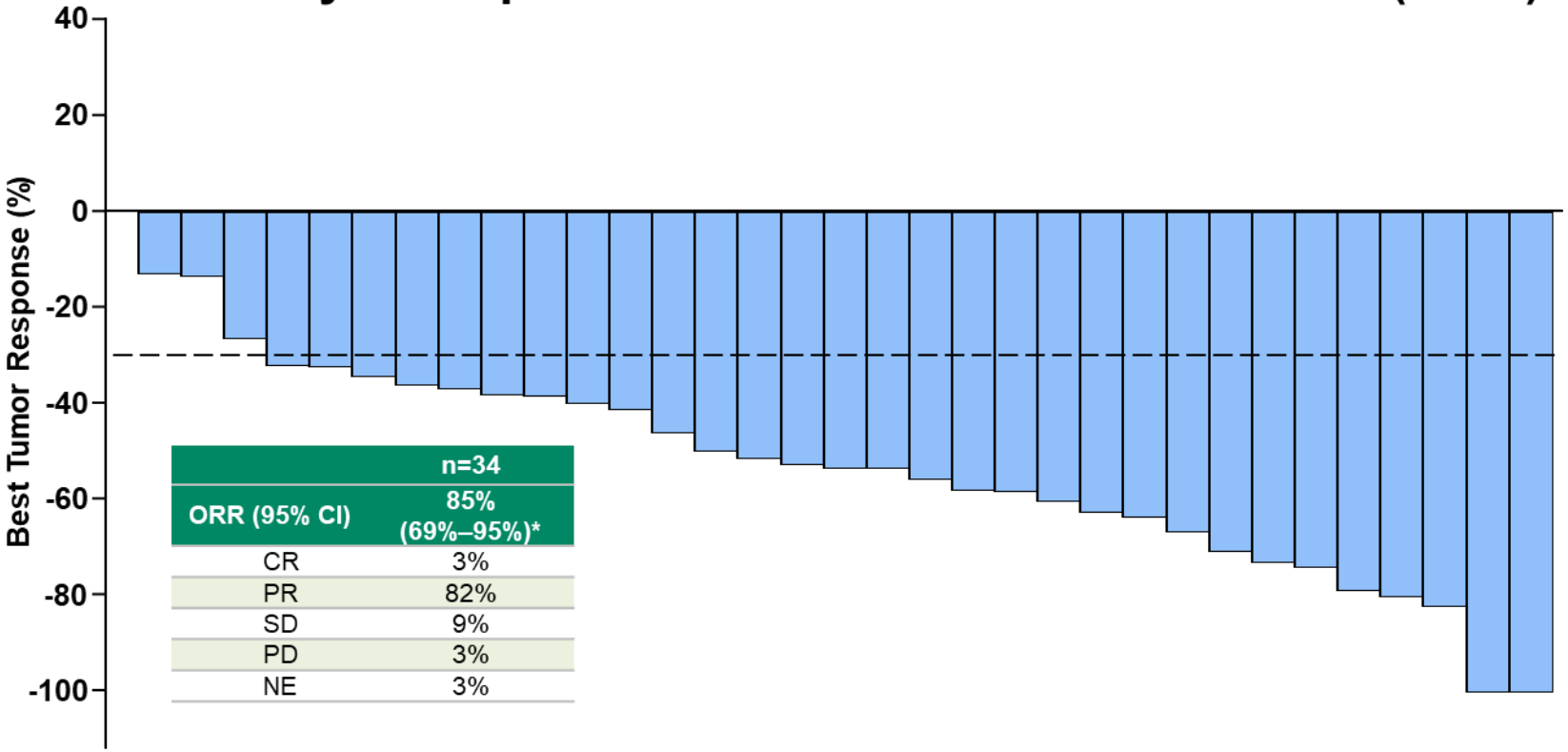


Efficacy of Selpercatinib: Primary Analysis Set (n=105)



	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%	-

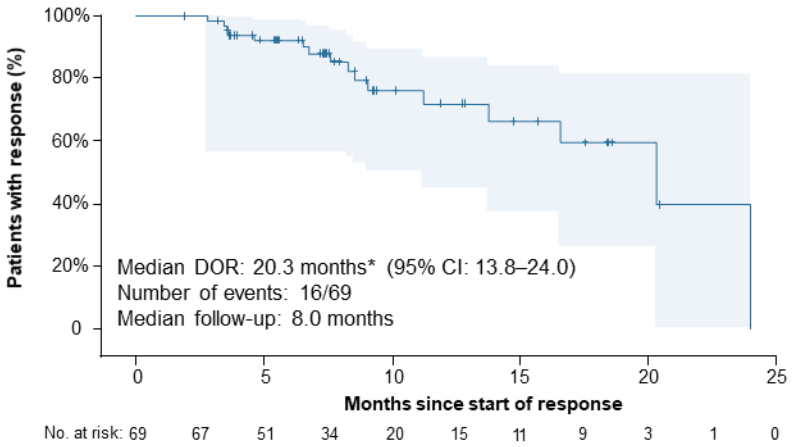
Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)



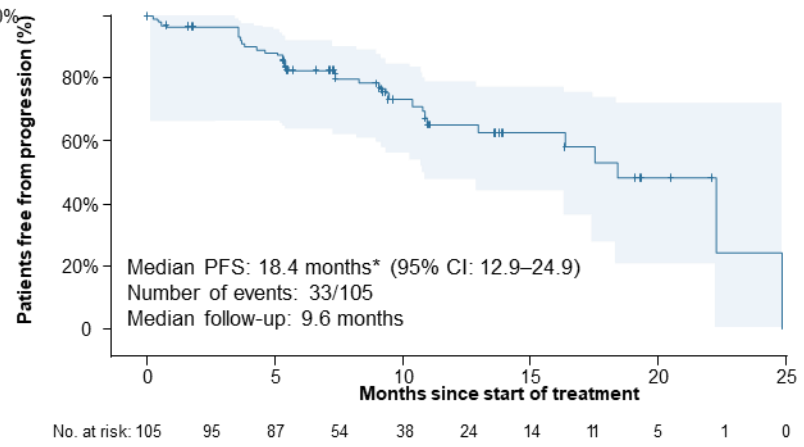
ORR (95% CI)	n=34 85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

Durability of Selpercatinib Efficacy: Primary Analysis Set

Duration of response



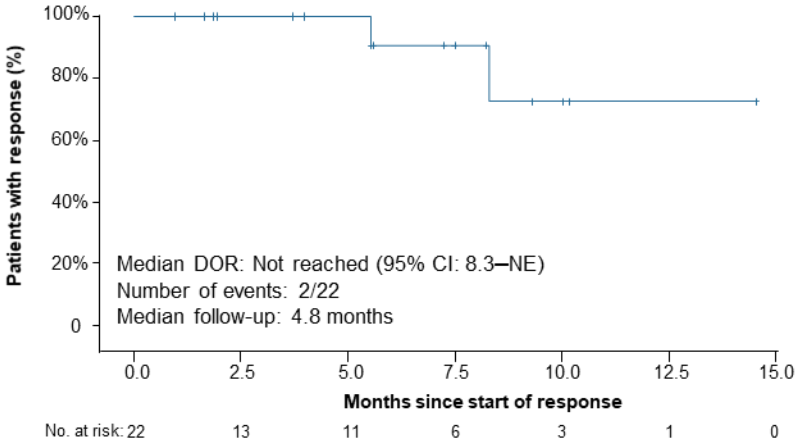
Progression-free survival



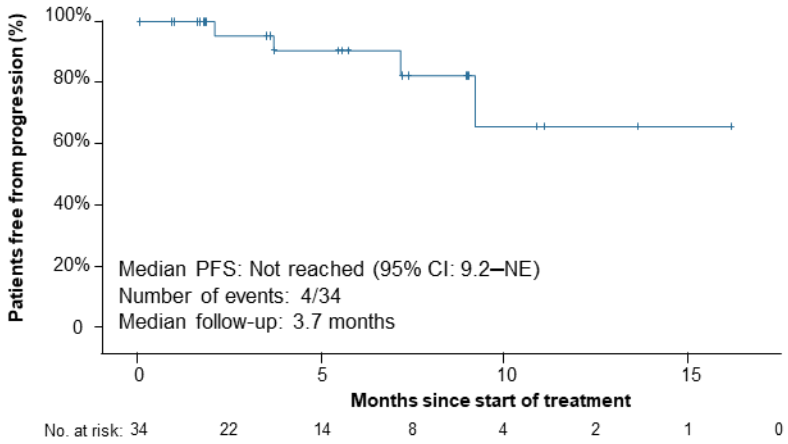
- Of 28 patients in the PAS that progressed, 23 continued treatment post-progression, for 0.2–16.4+ months
- ORR, DOR, PFS similar regardless of prior therapy (e.g. anti-PD-1/PD-L1, MKIs)

Durability of Selpercatinib Efficacy: Treatment-Naïve

Duration of response



Progression-free survival



Selpercatinib Safety Profile

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

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

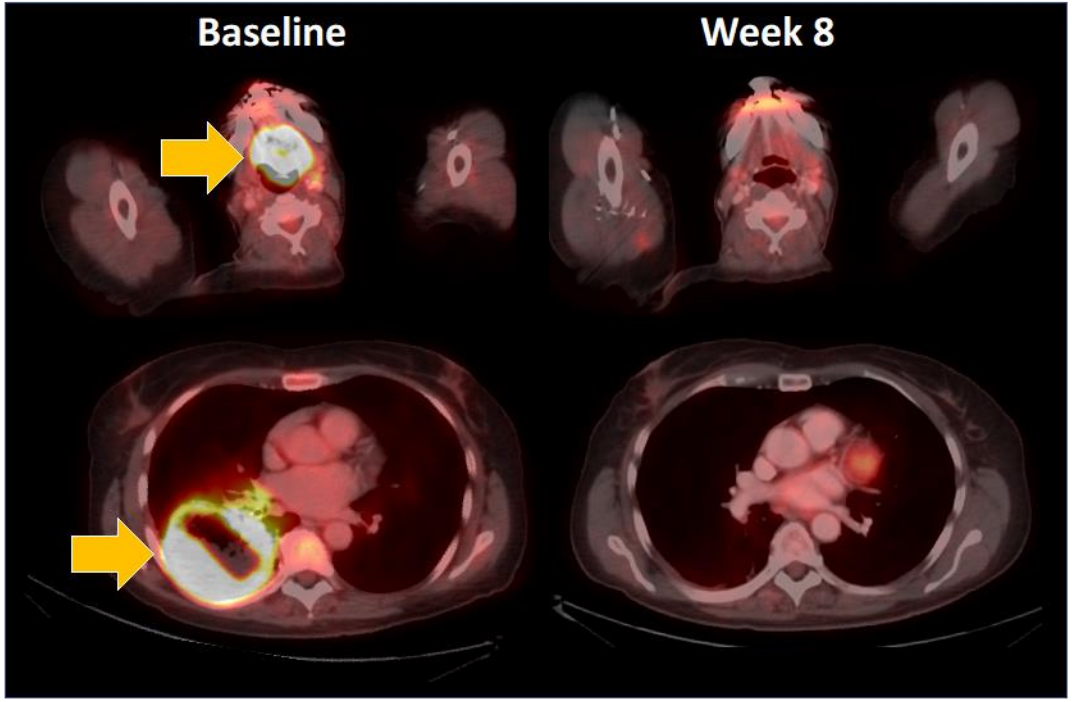
Selpercatinib Response in the Treatment-Naïve Setting

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

- Metastatic disease to the base of tongue, lungs, and bone

Initiated selpercatinib at 160 mg BID as first systemic therapy

- Brisk, durable, and confirmed PR by RECIST 1.1
- Remains on treatment at 10 months



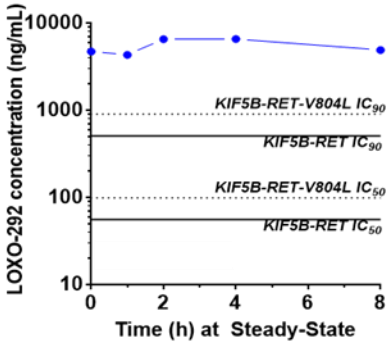
Data cut-off: June 17th, 2020. Images courtesy of A. Drilon.

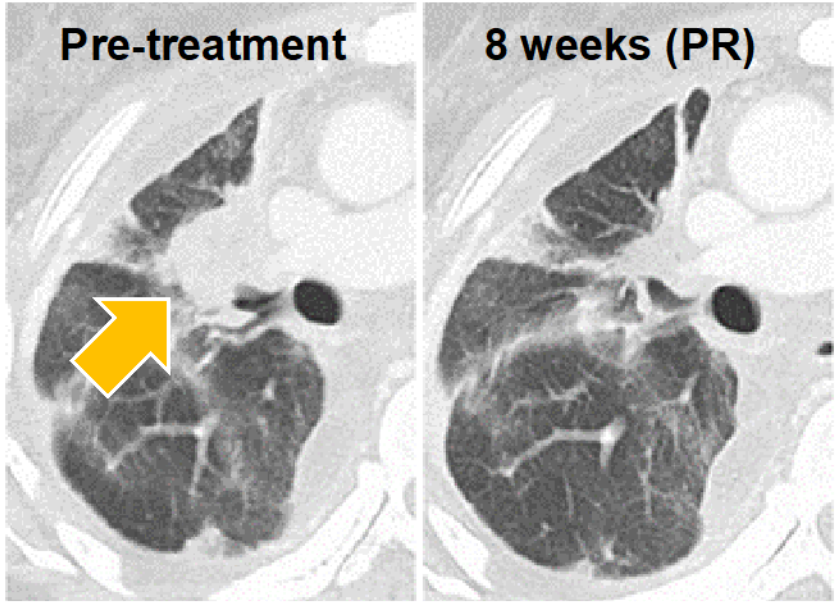
Selpercatinib Overcomes Acquired Gatekeeper Resistance

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

- **Selpercatinib demonstrated robust and durable anti-tumor activity in *RET* fusion-positive NSCLC**
  - Prior platinum doublet (n=105):
    - ORR 68% (95% CI: 58–76), CNS ORR 91% (95% CI: 59–100)
    - Median DOR 20.3 months (95% CI: 13.8–24.0), median PFS 18.4 months (95% CI: 12.9–24.9)
    - Heavily pre-treated population (median of 3 prior systemic therapies)
  - Treatment-naïve (n=34): ORR 85% (95% CI 69–95), median DOR, PFS not reached
- **Favorable safety profile**
  - Safety database (n= 531):
    - Most AEs low grade and unrelated to selpercatinib
    - Only 1.7% discontinued therapy for treatment-related AEs

- Outcomes consistent with other potent, selective, and CNS-active targeted therapies for genomically-driven lung cancers (e.g. *EGFR*/*ALK*)
- **New Drug Application (NDA) submission planned by the end of 2019**
- **Randomized, global phase 3 trial:** selpercatinib vs. platinum-pemetrexed ± pembrolizumab in treatment-naïve *RET* fusion-positive NSCLC (in the coming months)

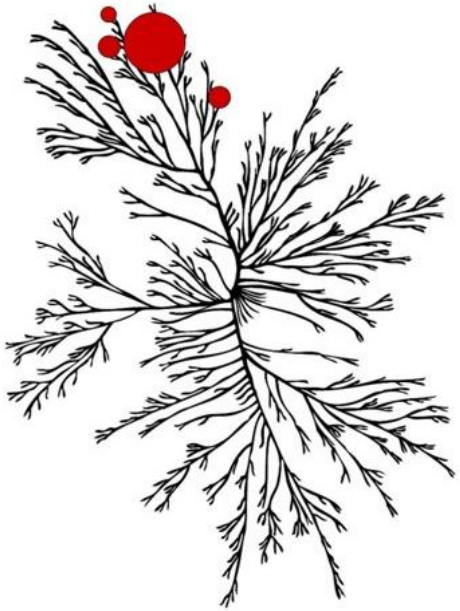
LOXO-292 has US FDA Breakthrough Therapy Designation for three indications:

- **For the treatment of patients with metastatic *RET*-fusion positive non-small cell lung cancer who require systemic therapy, and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy**

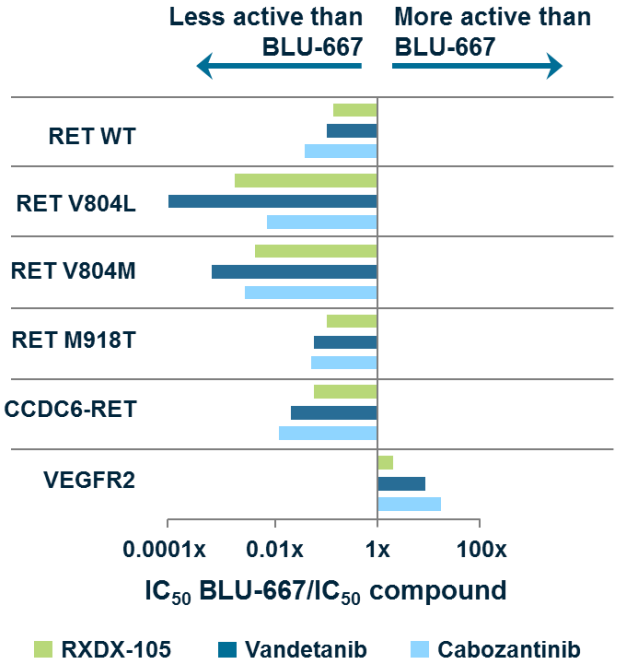
BLU-667- HIGHLY POTENT SELECTIVE RET INHIBITOR

BLU-667 - designed to treat *RET*-altered cancers

High kinome selectivity for RET[1,2]



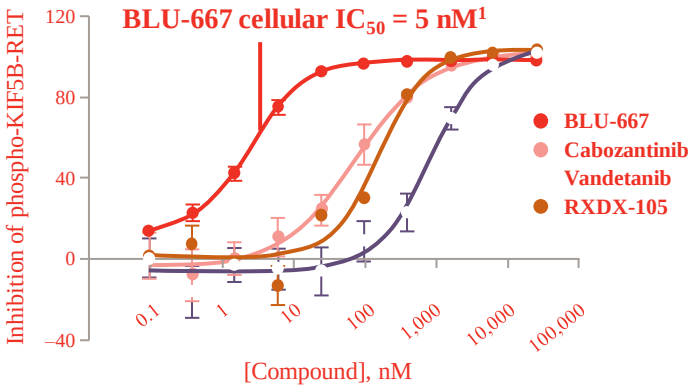
More potent and selective than MKIs[1,2]



IC_{50}, 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 potently inhibits the most common oncogenic *RET* alterations found in diverse tumor types



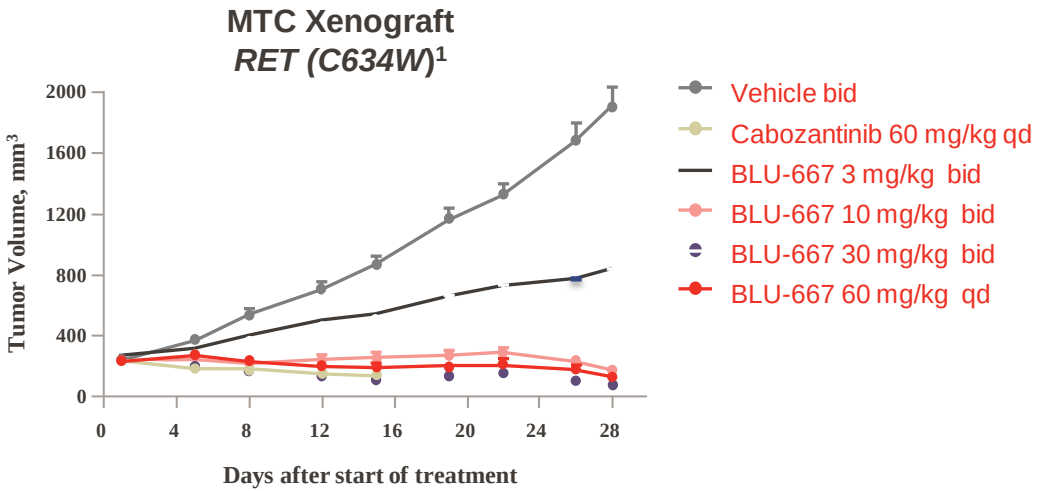
- BLU-667 inhibits autophosphorylation of KIF5B-RET fusion **≥10 times more potently** than cabozantinib, vandetanib, and RXDX-105[1]
- BLU-667 potently inhibits RET M918T activating mutation, CCDC6-RET fusion, and V804L/M gatekeeper resistance mutants while sparing VEGFR2[1]

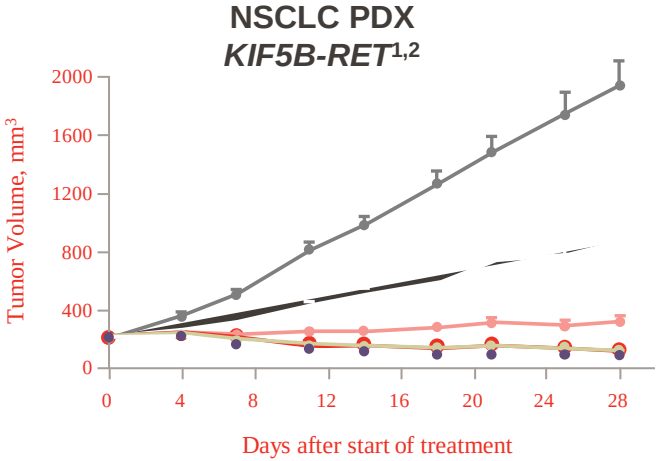
Biochemical IC_{50} (nM)[2]

Compound	WT RET	RET V804L	RET V804M	RET M918T	CCDC6-RET	VEGFR2
BLU-667	**0.4**	**0.3**	**0.4**	**0.4**	**0.4**	**35**
Cabozantinib	11	45	162	8	34	2
Vandetanib	4	3,597	726	7	20	4
RXDX-105	3	188	102	4	7	17

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

BLU-667 suppresses tumor growth and inhibits RET signaling in *RET*-altered MTC and NSCLC human tumor xenografts

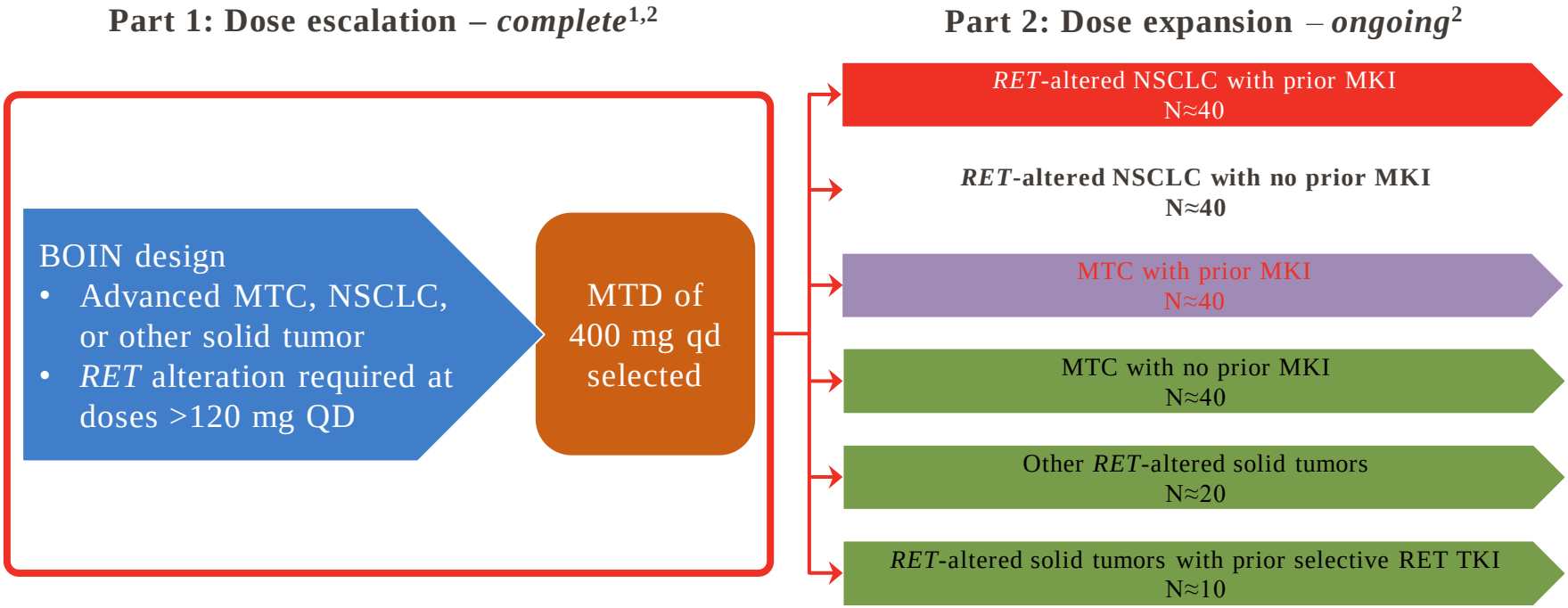




PDX, patient-derived xenograft.

1. Subbiah V et al. *Cancer Discov*. 2018;8(7):836-849. 2. Data previously presented in October 2017 at AACR-NCI-EORTC Annual Meeting.

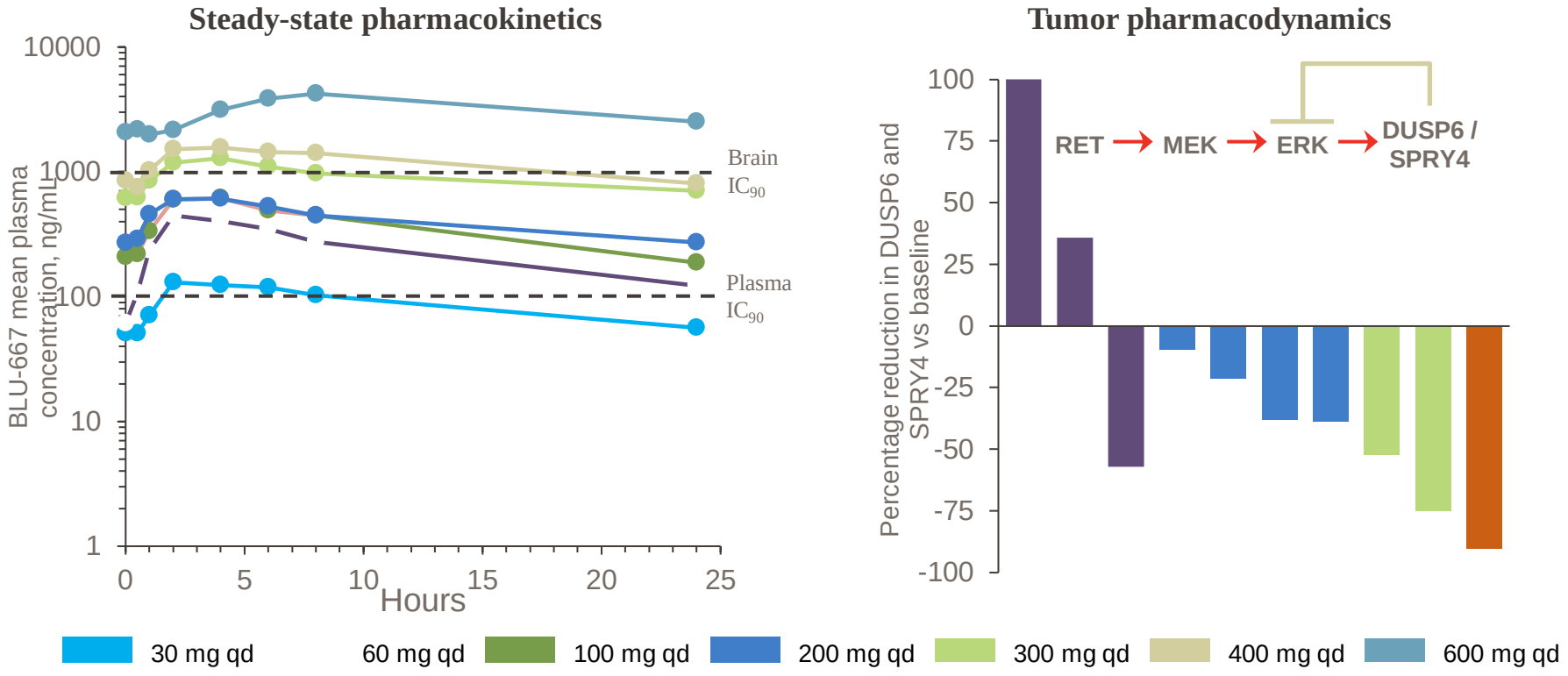
ARROW trial: first-in-human study with BLU-667



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

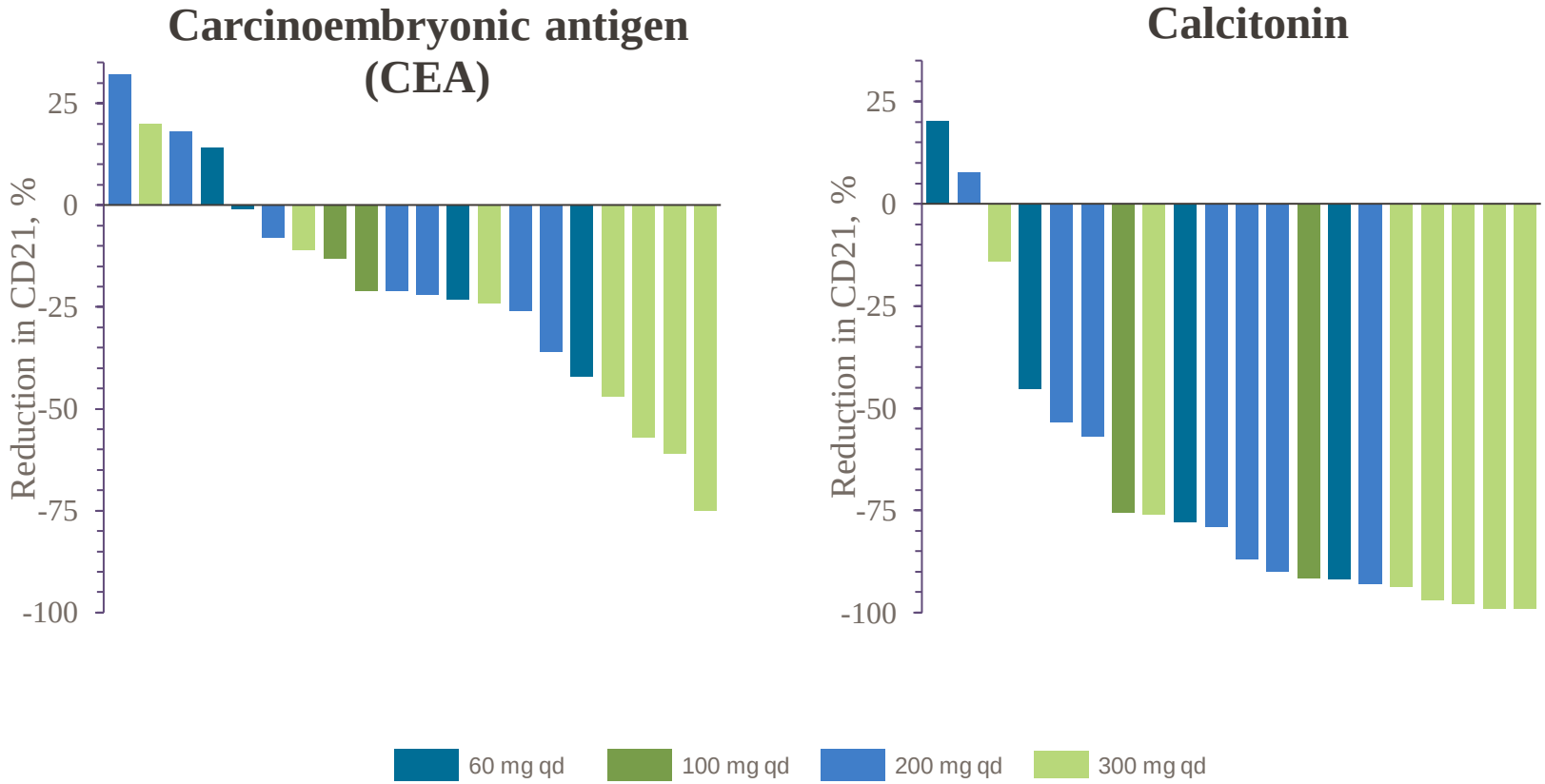
1. Adapted from data previously presented in April 2018 at AACR Annual Meeting. Data cut-off: April 6, 2018. 2. National Institutes of Health. https://www.clinicaltrials.gov/ct2/show/NCT03037385. Accessed August 22, 2018.

Dose-dependent exposure and RET pathway inhibition



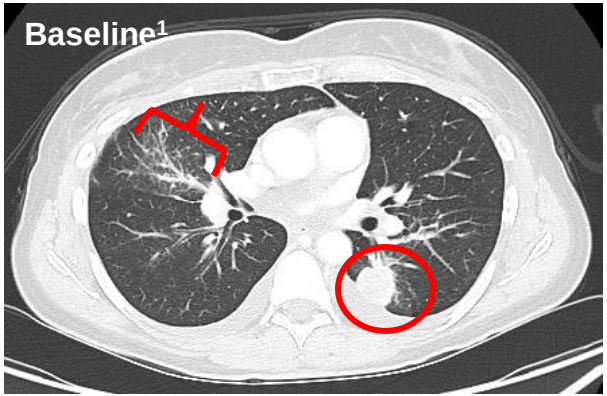
Data previously presented in April 2018 at AACR Annual Meeting. Data cut-off: April 6, 2018.

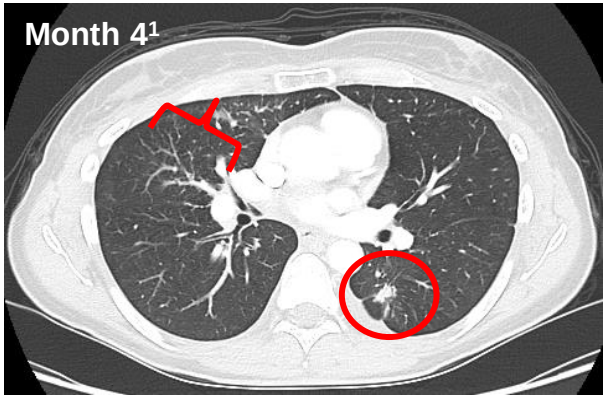
Dose-dependent decline in MTC tumor markers



Data previously presented in April 2018 at AACR Annual Meeting. Data cut-off: April 6, 2018.

BLU-667 demonstrates potent activity against *KIF5B-RET* NSCLC after chemotherapy

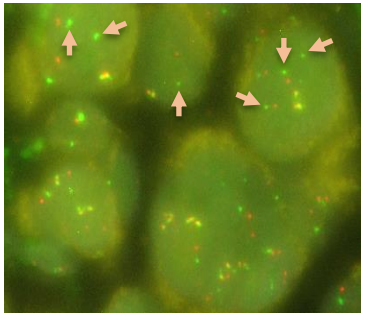




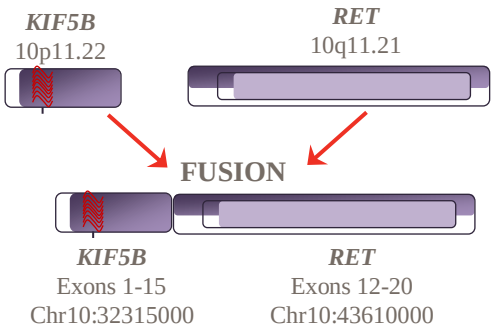
37-year-old female[1,2]

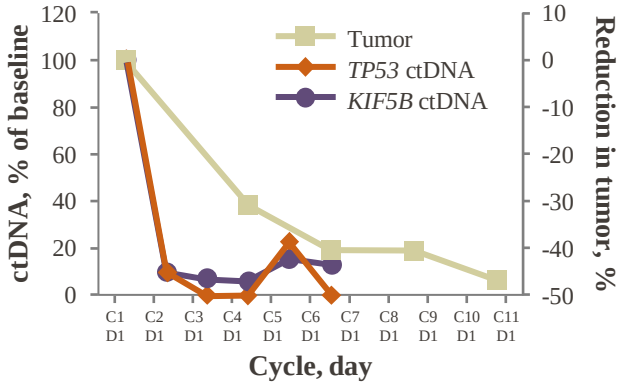
- Ongoing at 400 mg with confirmed PR

FISH[2]



Break point[2]



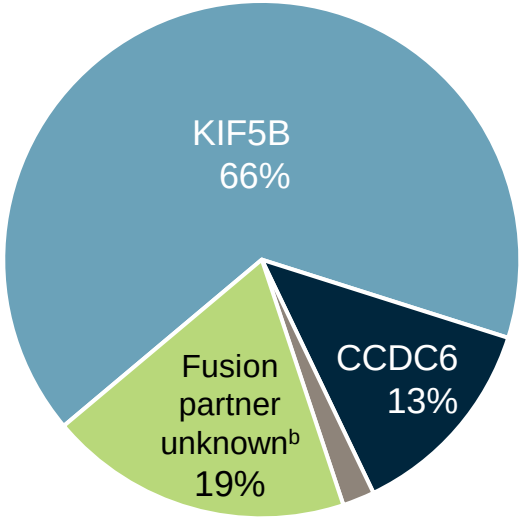


ctDNA, circulating tumor DNA.

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.

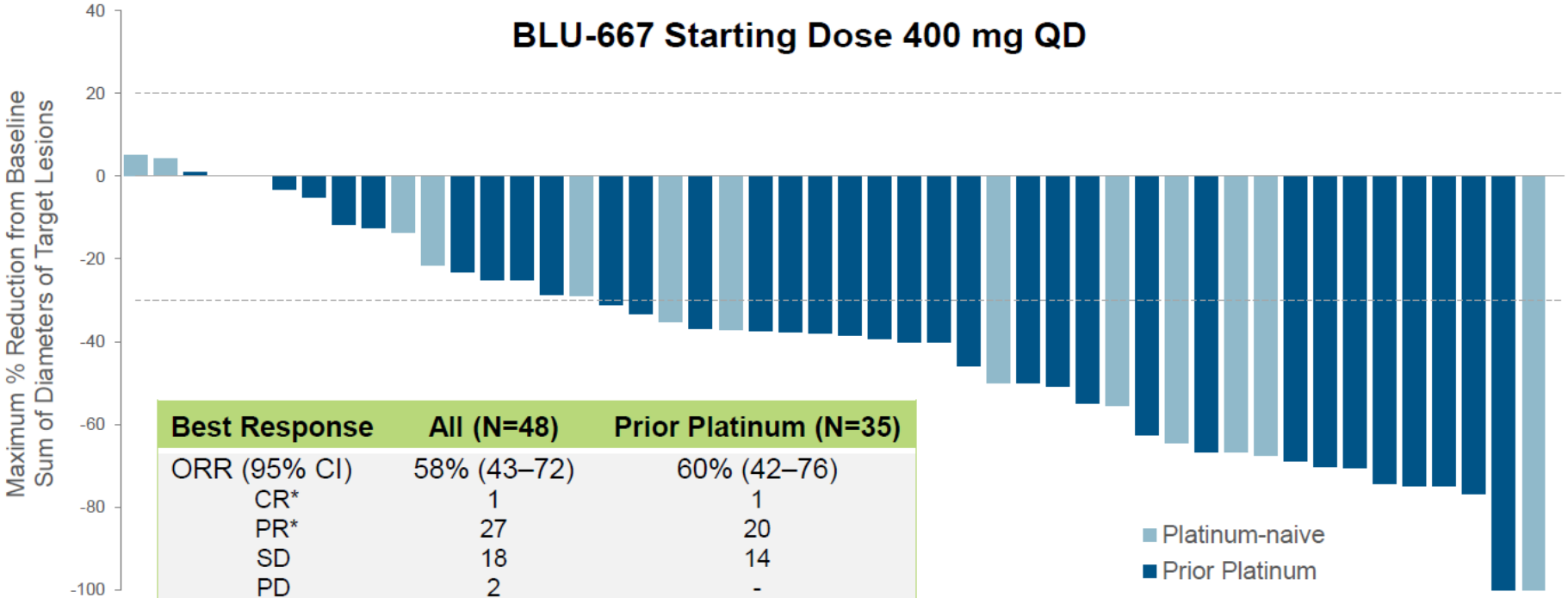
Baseline Characteristics
RET Fusion+ Advanced NSCLC Patients

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)



ECOG PS, Eastern Cooperative Oncology Group Performance Status. [a]Smoking history is unknown for one patient. [b]Includes RET fusion+ by fluorescence *in situ* hybridization (FISH); RET fusion partner to be determined via central analysis. Data cut-off date: 28 Apr 2019.

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



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

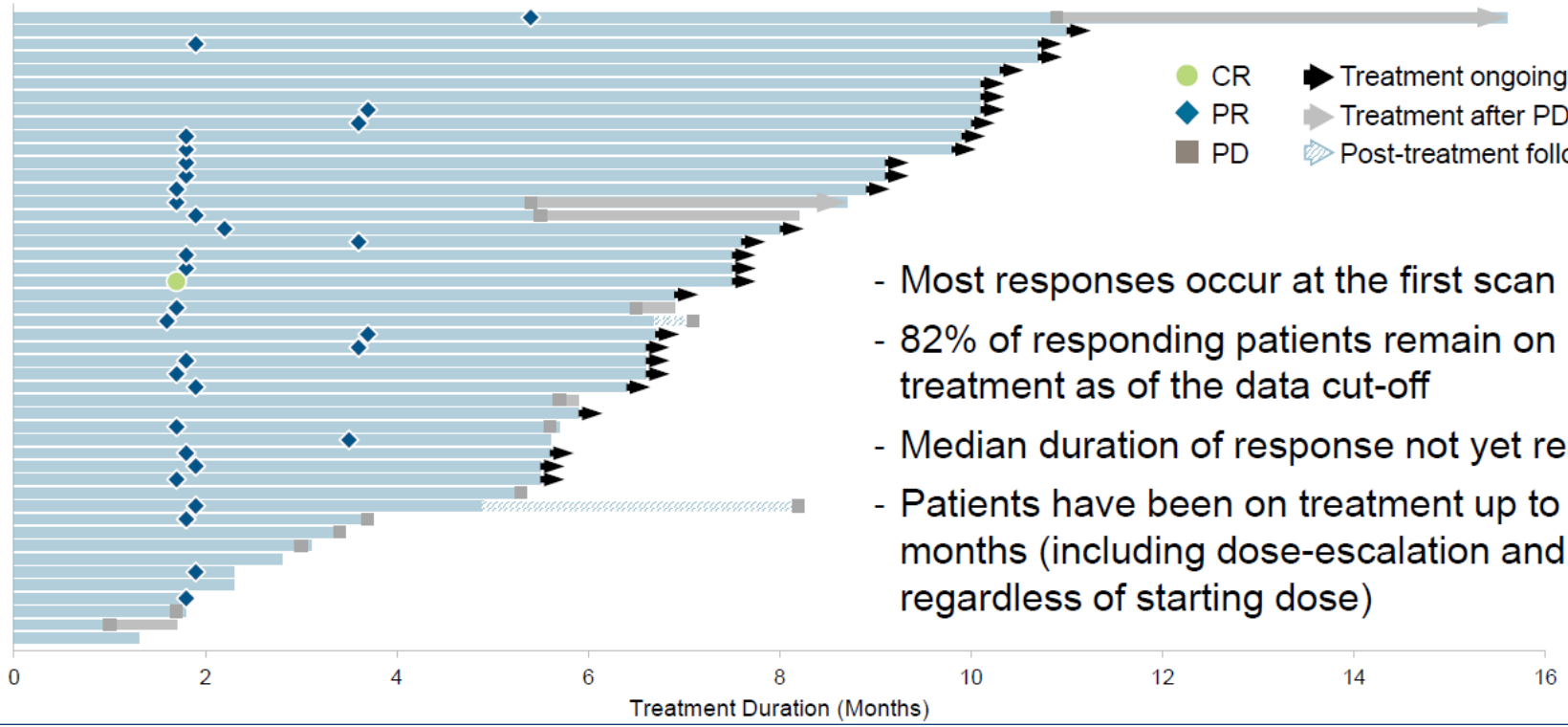
* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

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

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

BLU-667 Induces Rapid and Durable Responses in RET Fusion+ Advanced NSCLC

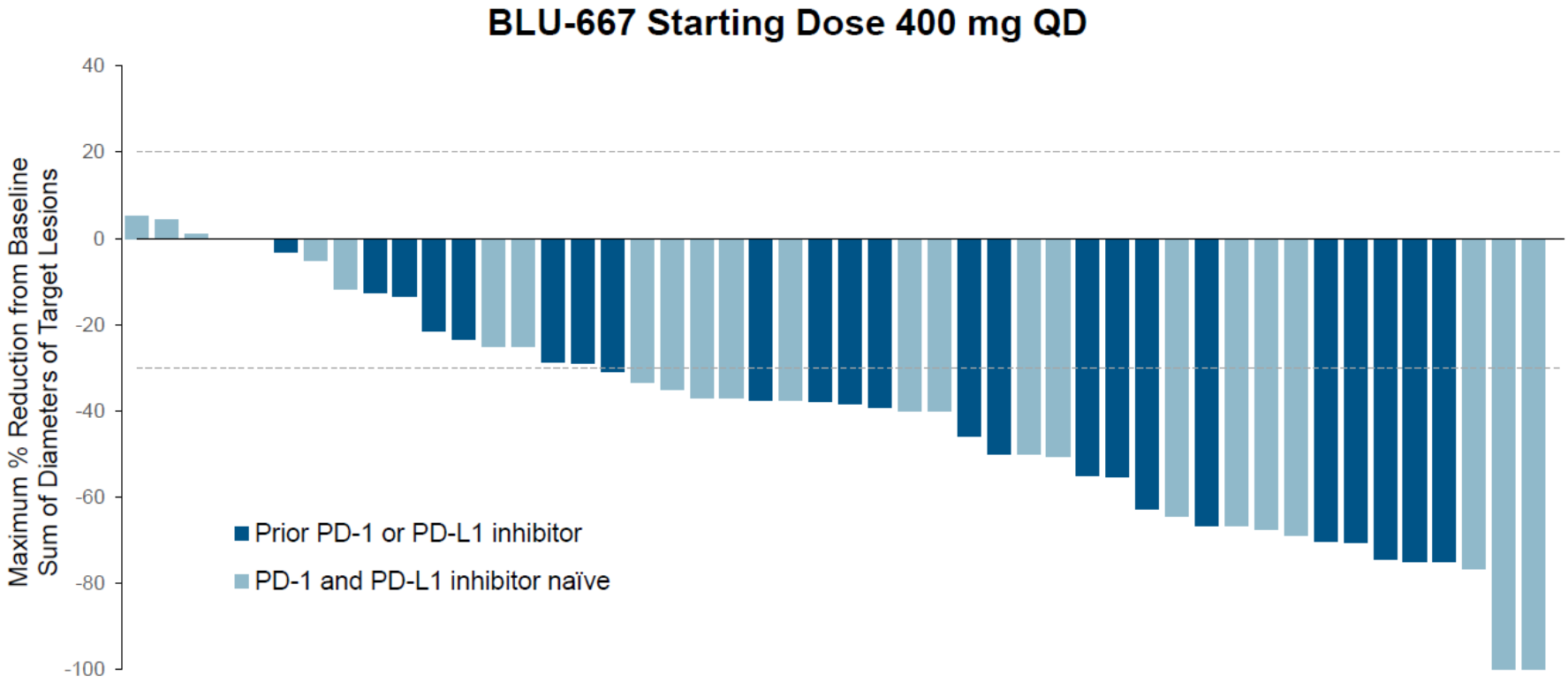
Duration of Treatment and Response: BLU-667 Starting Dose 400 mg QD



- Most responses occur at the first scan (week 8)
- 82% of responding patients remain on treatment as of the data cut-off
- Median duration of response not yet reached
- Patients have been on treatment up to 24 months (including dose-escalation and regardless of starting dose)

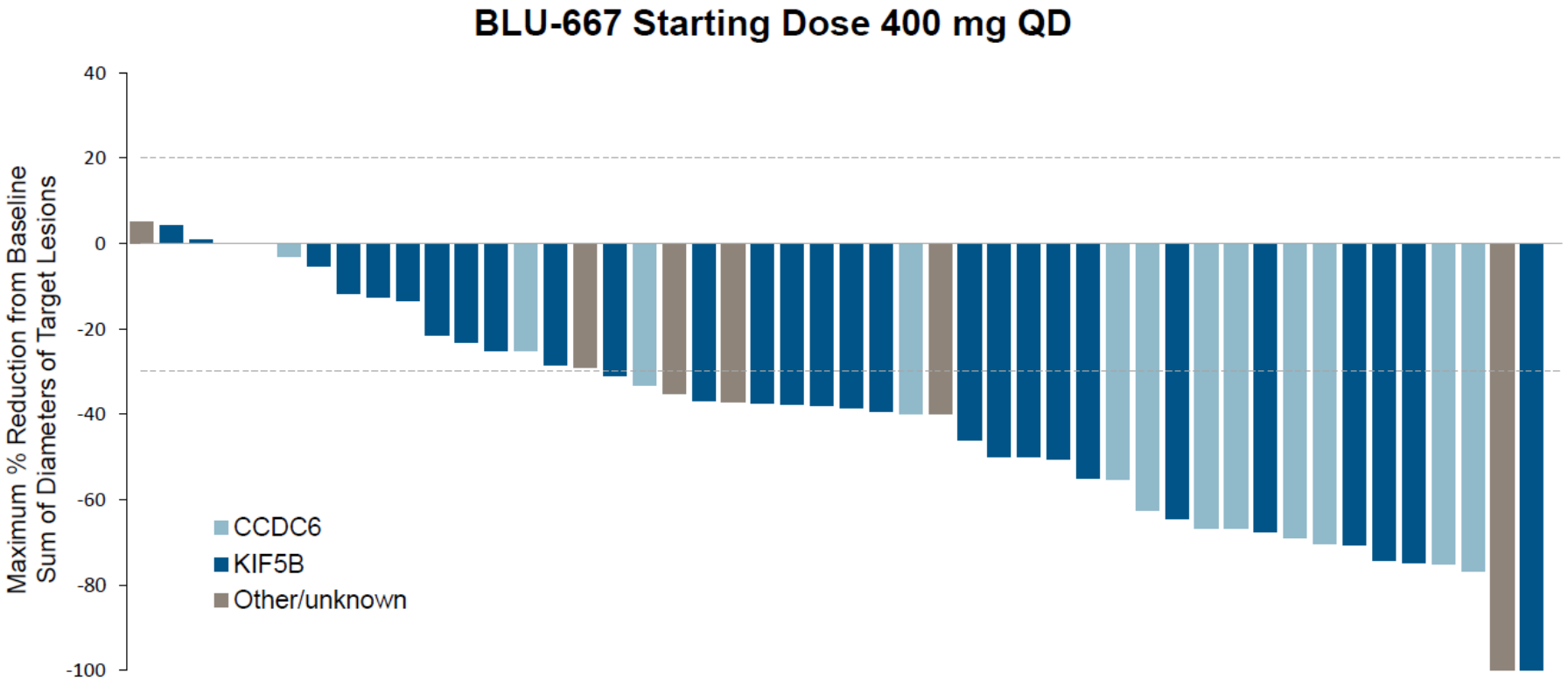
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Regardless of Prior Checkpoint Treatment



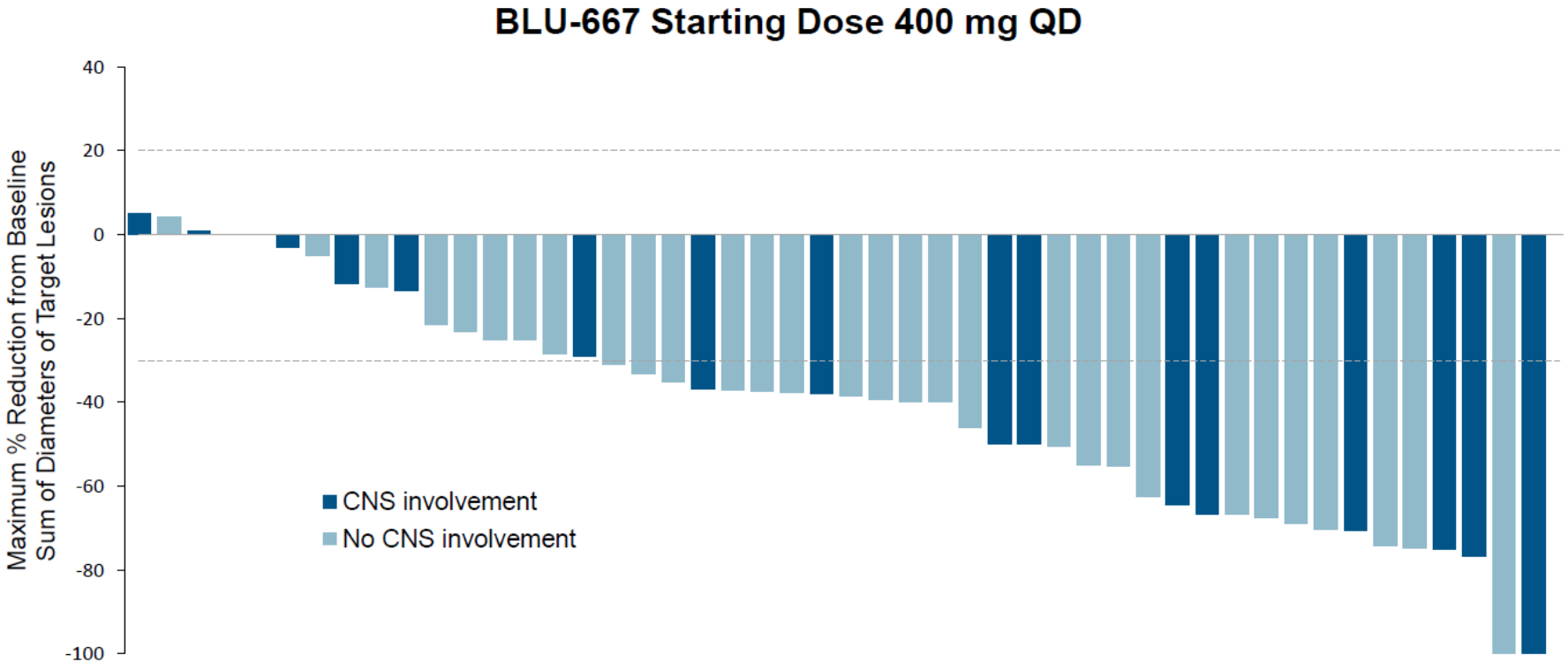
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Across RET Fusion Genotypes



Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Regardless of CNS Involvement



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

BLU-667 is Well Tolerated by Patients with RET Fusion+ Advanced NSCLC

Adverse Events	RET Fusion+ Advanced NSCLC 400 mg QD Starting Dose (N=120)			
	Treatment-Emergent (≥15% overall)		Treatment-Related	
	All	Grade ≥3	All	Grade ≥3
Constipation	30%	2%	17%	2%
Neutropenia[a]	26%	13%	26%	13%
AST increased	24%	5%	20%	2%
Fatigue	21%	3%	13%	3%
Hypertension	20%	13%	13%	10%
Anemia	18%	7%	11%	4%
Diarrhea	18%	2%	9%	-
Pyrexia	18%	-	2%	-
ALT increased	17%	3%	13%	2%
Cough	17%	-	3%	-
Dry mouth	17%	-	12%	-

Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopenia[b] (3%).

[a]Combined term including decreased neutrophils and neutropenia. [b]Combined term including leukopenia and white blood cell count decreased. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase. Data cut-off date: 28 Apr 2019.

BLU- 667 has US FDA Breakthrough Therapy Designation

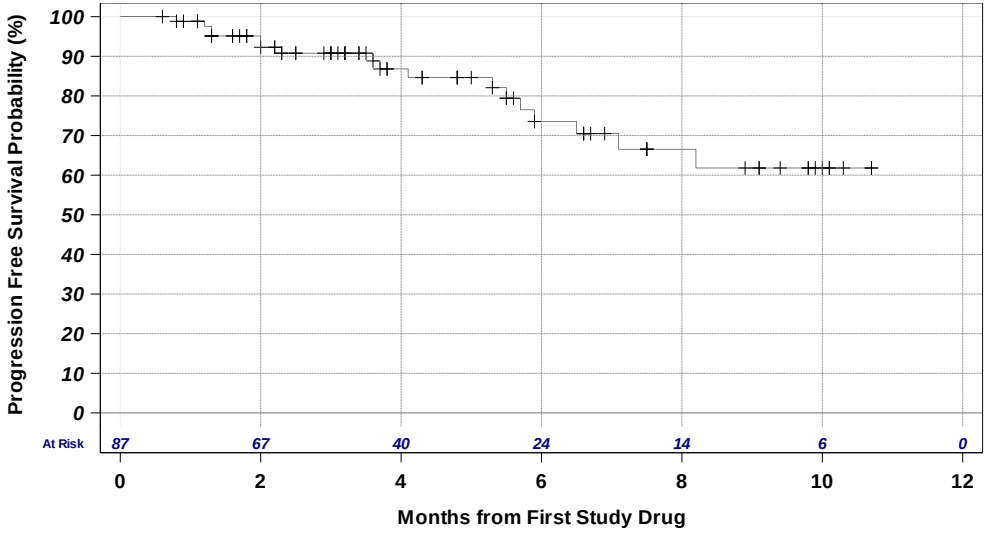
- BLU-667 has FDA breakthrough therapy designation in RET fusion+ NSCLC that progressed following platinum based chemotherapy

Preliminary PFS for BLU-667 in previously treated NSCLC supports advancing development into first-line setting

ARROW trial – BLU-667

RET fusion+ NSCLC previously treated with platinum-based chemo[1]

Median PFS not reached



Alectinib – ALK+ NSCLC	Median PFS
Previously treated with crizotinib[2]	8.9 months
Previously untreated[3]	25.7 months

Osimertinib – EGFR+ NSCLC	Median PFS
Previously treated with systemic therapy[4]	10.1 months
Previously untreated[4]	18.9 months

[1] BLU-667 PFS analysis. Data cut-off: April 28, 2019. [2] Ou, et al. ASCO presentation, 2015. [3] Alectinib prescribing information. [4] Osimertinib prescribing information. PFS, progression free survival.

Selective RET inhibitors

- **LIBRETTO-001** and **ARROW** trials show potent RET pathway inhibition with favorable tolerability
- Broad antitumor activity regardless of *RET* genotype
- High preliminary response rate and durable activity.
- Dose-escalation + expansion data validate selective RET inhibition as a promising precision therapy for *RET*-altered cancers

Summary-RET inhibitor super heroes have arrived

Discovery, pre-clinical and rapid clinical validation with registrational intent of selective RET inhibitor trials in the RET space.

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

US FDA Breakthrough Designations.

RET aberrant patients → Enrolled in RET trials.

Medical Decision-Support

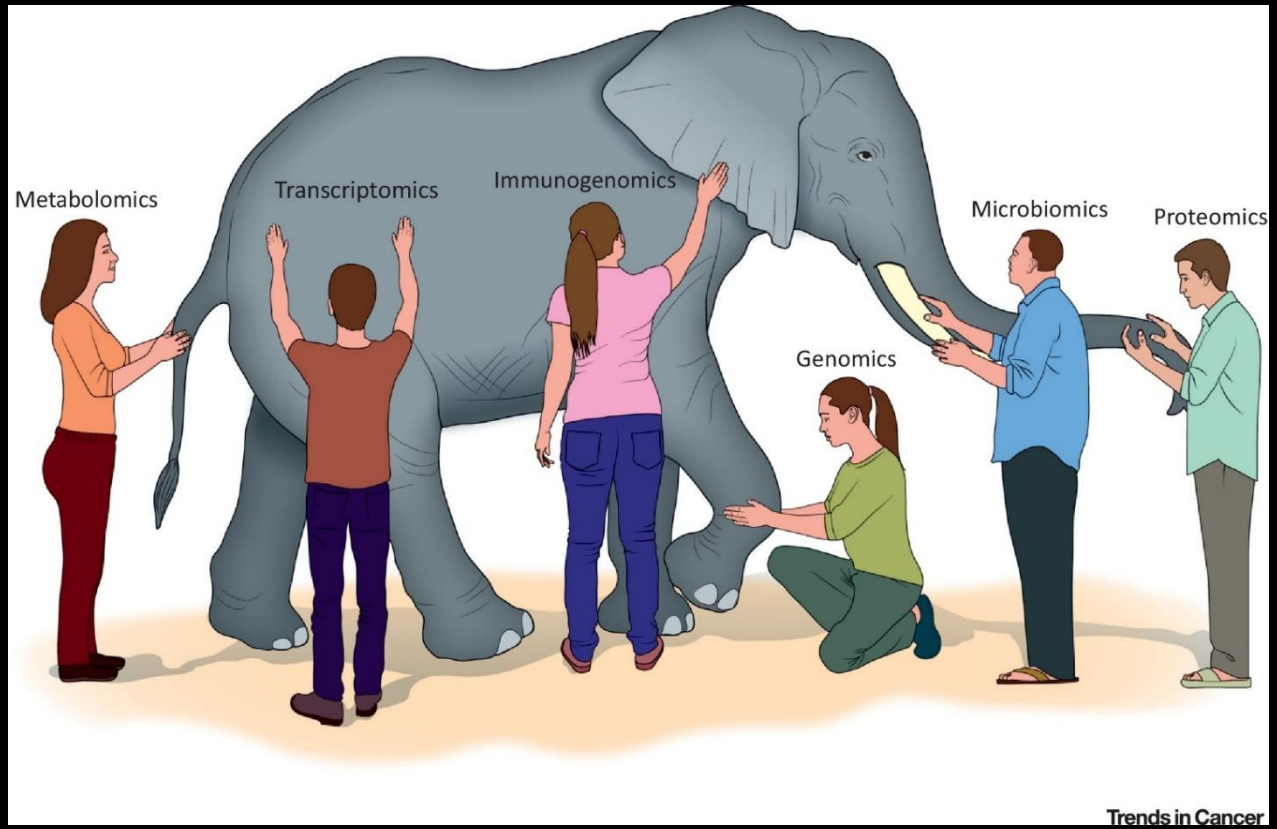
The Light Microscope
Invented in 1590
Still used to diagnose and classify cancer

Universal Genomic Testing Needed to Win the War Against Cancer

Genomics IS the Diagnosis

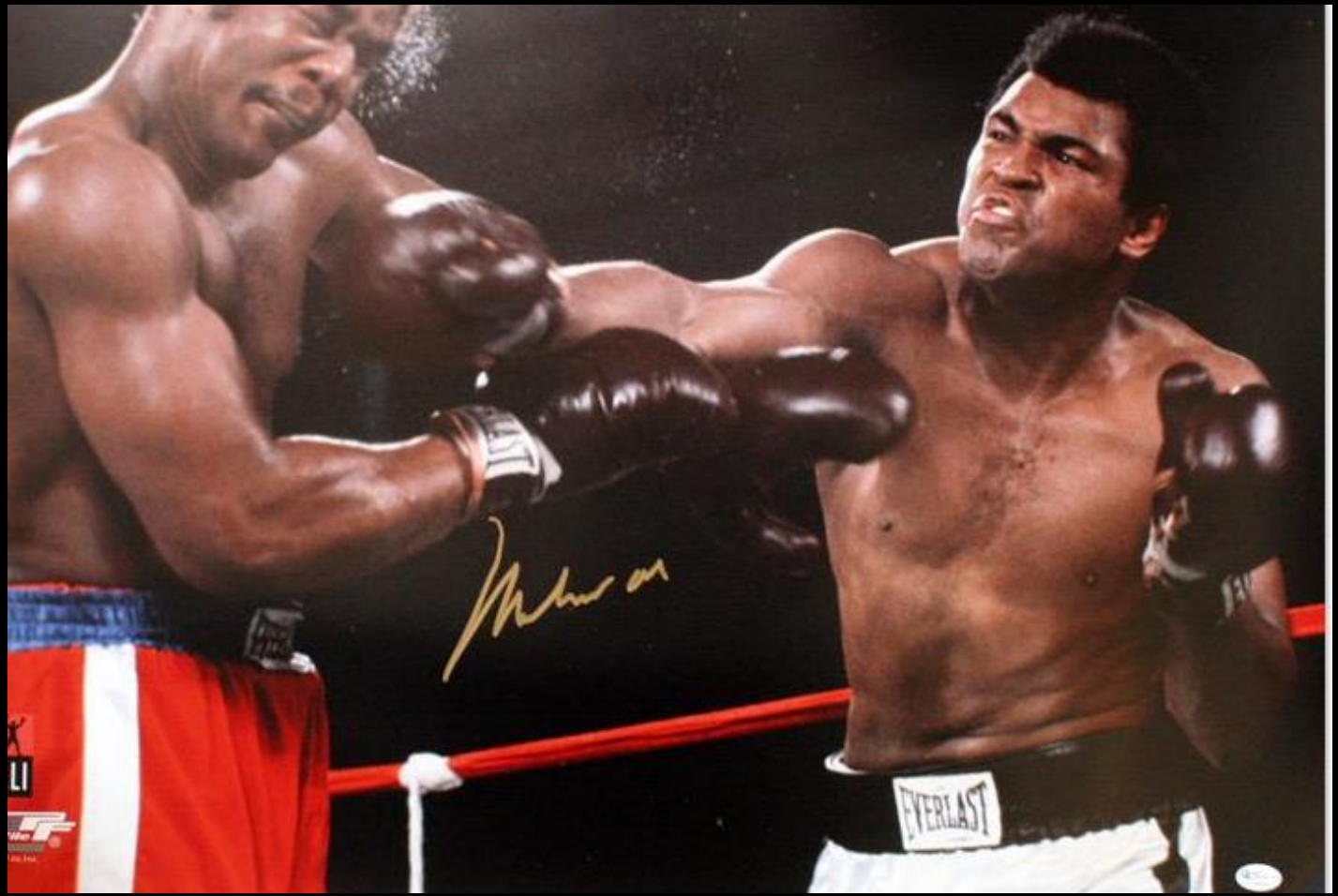
Subbiah V et al JAMA Oncology 2016

Six Blind Men and Elephants



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

Subbiah V et al


EVERLAST

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.**

THE TIME IS NOW

Together we will end cancer

Acknowledgements

- ✓ **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**
- ✓ **Blueprint medicines**
- ✓ **LOXO Oncology / Eli Lilly & Company**

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