Highly potent and selective RET inhibitor, BLU-667, achieves proof of concept in ARROW, a phase 1 study of advanced, RET-altered solid tumors

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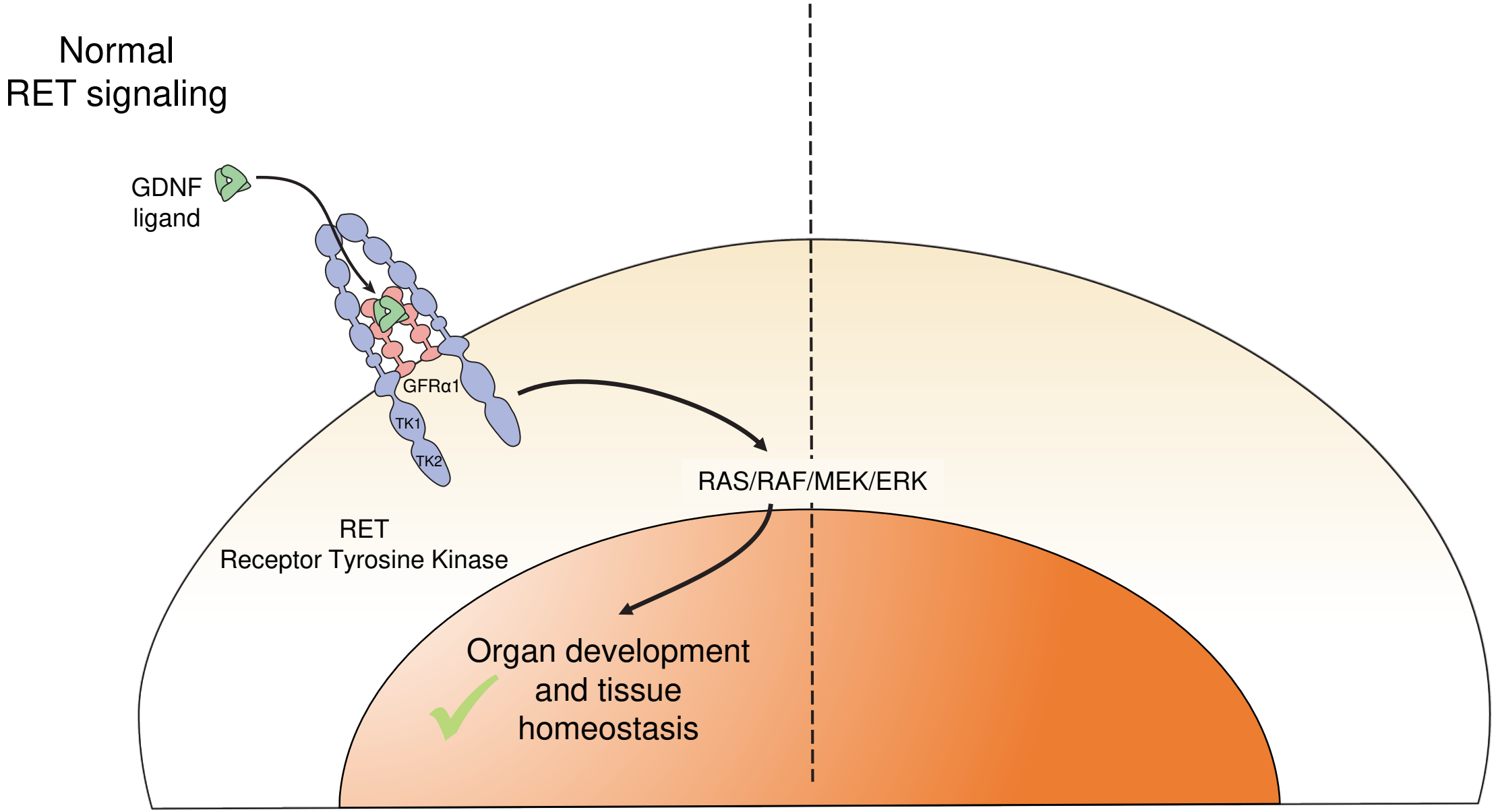
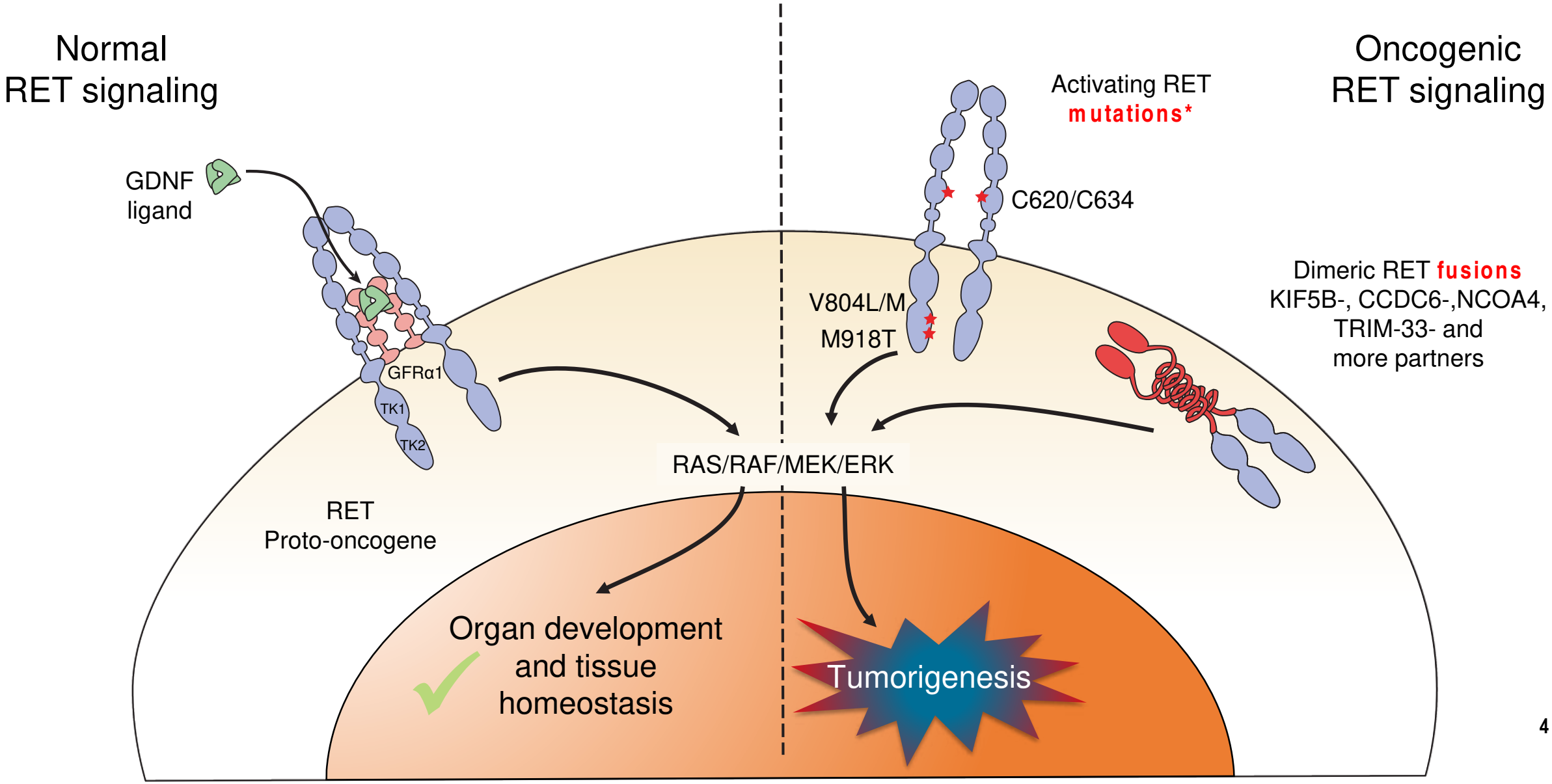
- National Cancer Institute-Cancer Therapy Evaluation Program

BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

Receptor tyrosine kinase, *RE*arranged during *T*ransfection (*RET*)



Receptor tyrosine kinase, *RE*arranged during *T*ransfection (*RET*)



RET is a rare driver of multiple, diverse tumor types[1,2]

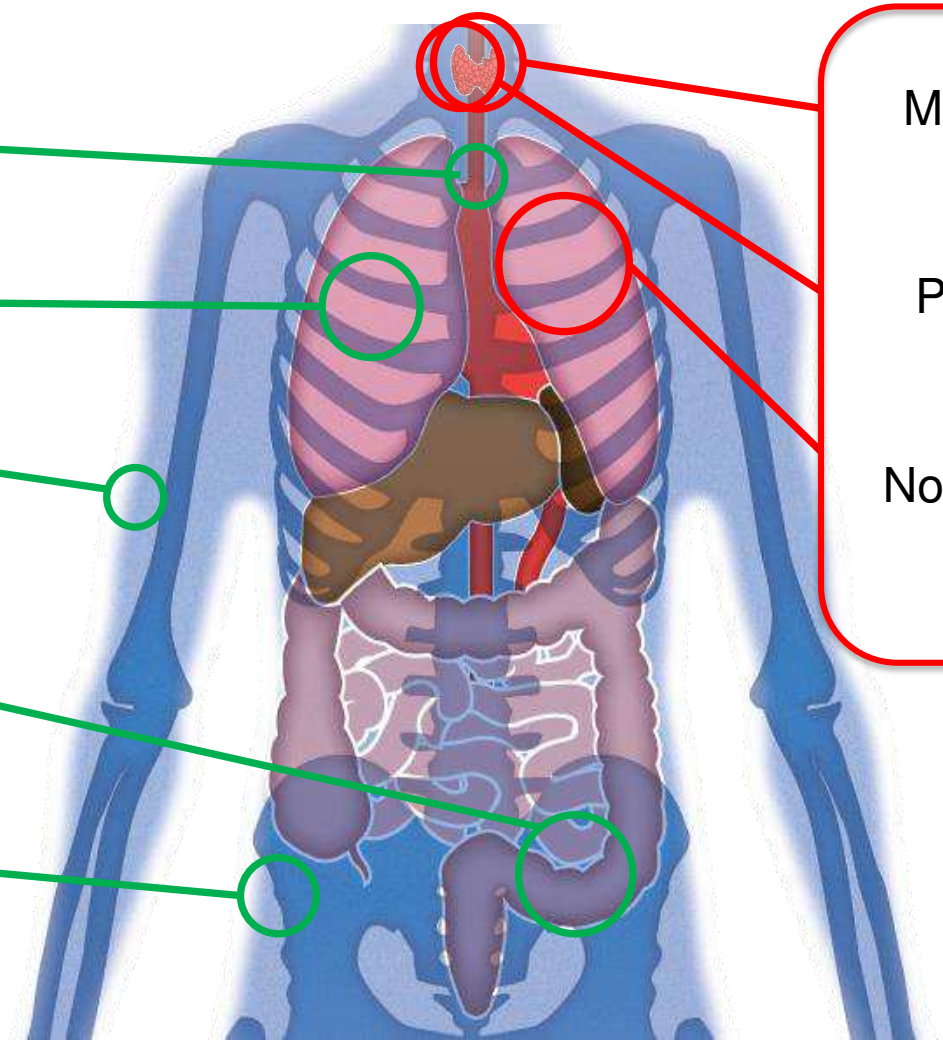
Esophageal cancer

Breast cancer

Melanoma

Colorectal cancer

Leukemia



Other tumor types
≤1% *RET*-altered

Medullary thyroid cancer
>60% *RET*-mutations

Papillary thyroid cancer
~10% *RET*-fusions

Non-small cell lung cancer
~1-2% *RET*-fusions

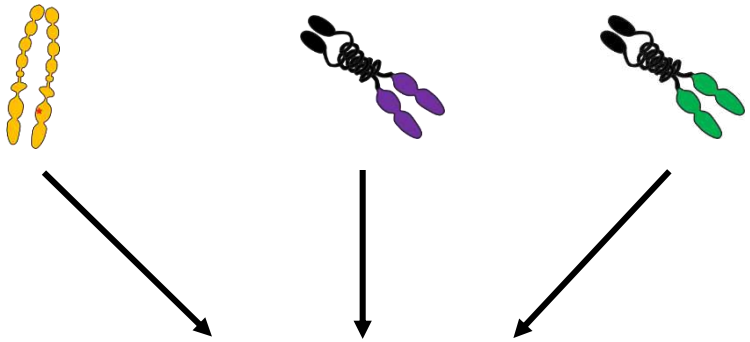
1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

Patients with *RET*-alterations have not benefited from precision oncology

Precision oncology

Non-small cell lung cancer

EGFR mutation | ALK-fusion | ROS-fusion



Selective RTK inhibitors[1]
↑Activity and ↓off-target toxicity

Typical ORR >60%
Typical PFS >9 months
Favorable tolerability

MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

1. Herbst RS et al. *Nature* 2018; 553:446-54; 2. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67.

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Precision oncology

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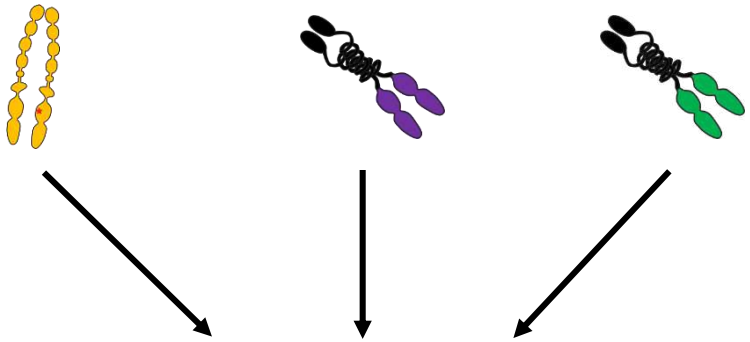
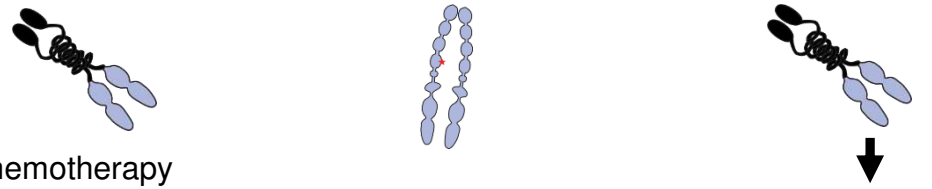


Selective RTK inhibitors[1]
↑Activity and ↓off-target toxicity

Typical ORR >60%
Typical PFS >9 months
Favorable tolerability

Current "non-targeted" paradigms for RET

NSCLC	MTC	Refractory solid tumor
RET- fusion	RET-mutation	RET- fusion



Chemotherapy
Immunotherapy
Multikinase inhibitors

Multikinase inhibitors

No standard of care

Multikinase Inhibitors[2]
↓Activity and ↑off-target toxicity

NSCLC
Typical ORR <30 %
Typical PFS ~4.6 – 7.3 months

MTC
Typical ORR 25-45%
Typical PFS ~11-30 months

MKI have frequent dose reduction/interruption for treatment related toxicity

MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

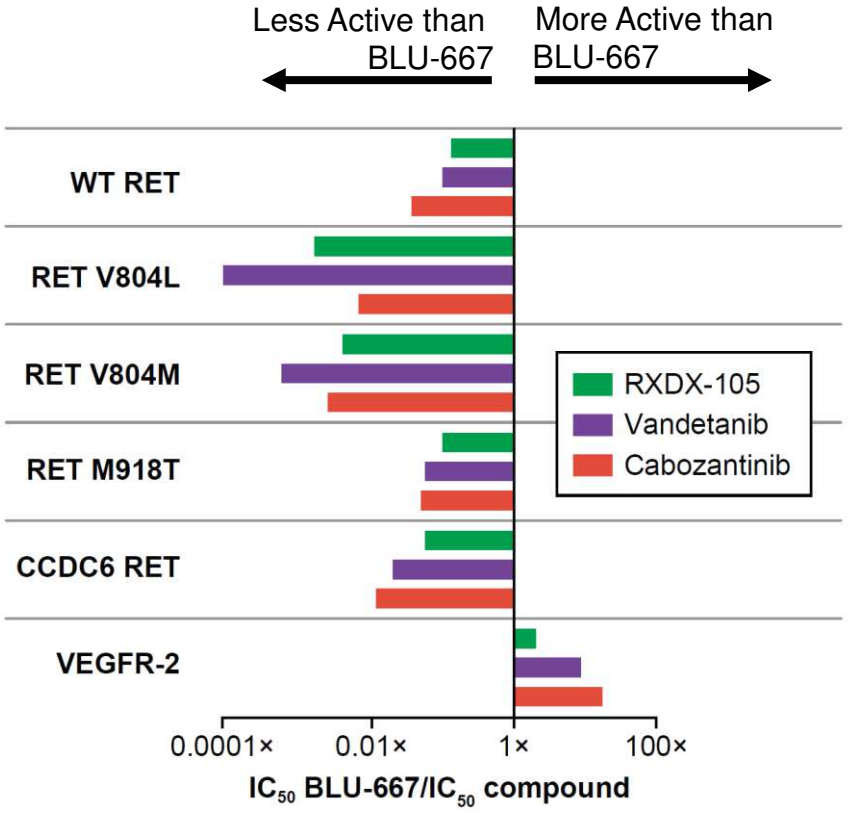
1. Herbst RS et al. *Nature* 2018; 553:446-54; 2. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67.

BLU-667 was designed to treat RET-altered cancers

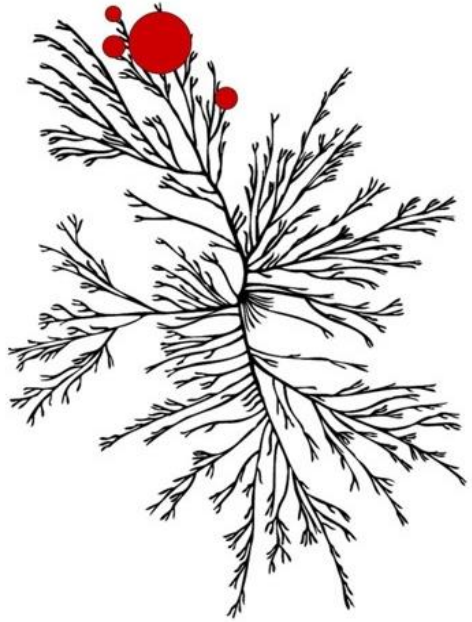
Subnanomolar potency[1]

Variant	Biochemical IC_{50} (nM)
RET wildtype	0.4
RET V804L	0.3
RET V804M	0.4
RET M918T	0.4
CCDC6-RET	0.4

More Potent than MKI

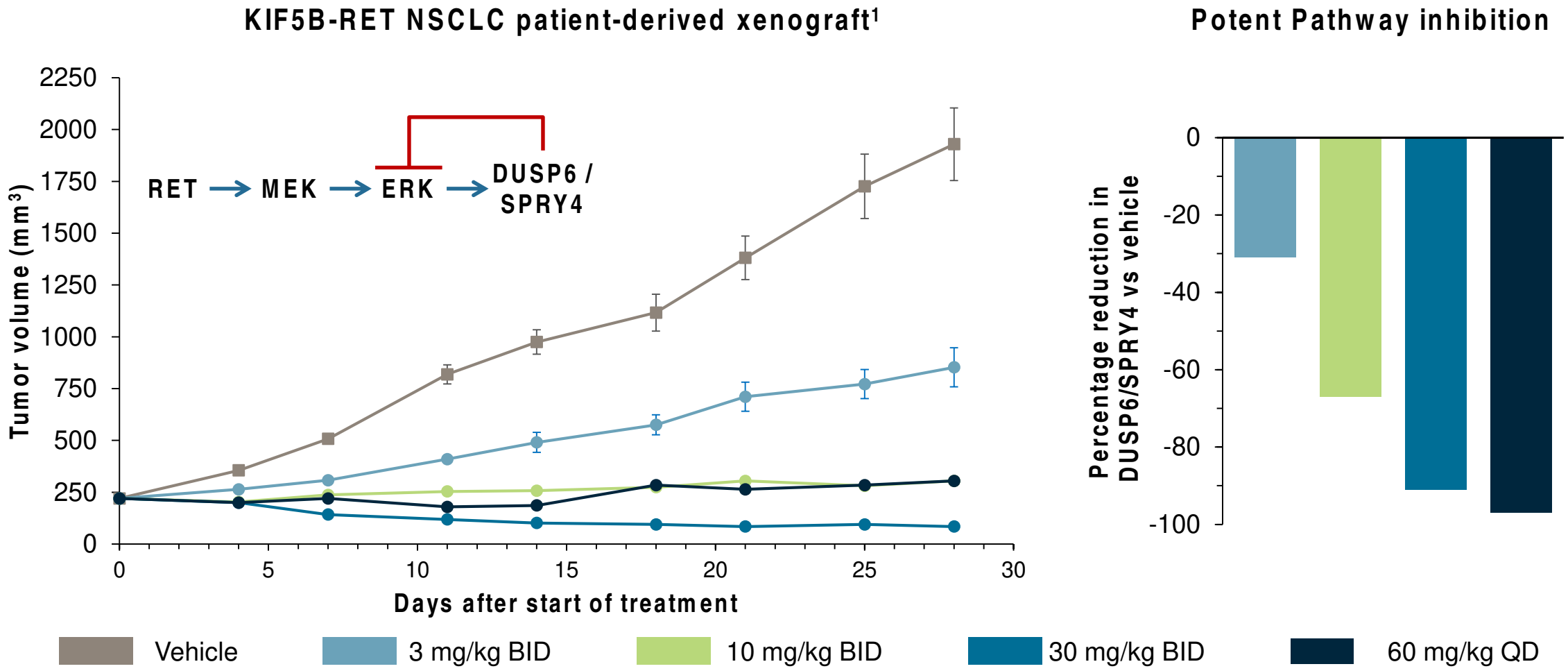


Kinome selectivity for RET



1. Subbiah V et al. *Cancer Discovery* April 15 2018

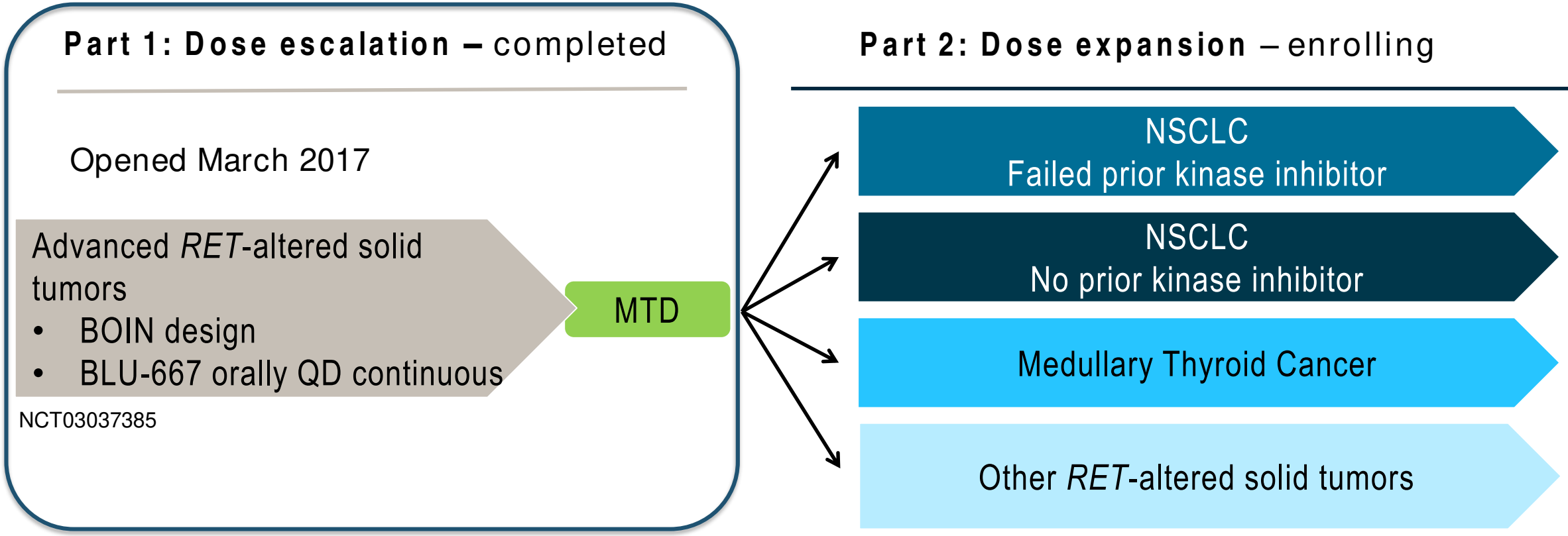
BLU-667 potently inhibits RET-driven tumor growth



BID, two times per day; QD, once daily

1. Subbiah V et al. *Cancer Discovery* April 15 2018

BLU-667 ARROW first-in-human study



Key objectives

- MTD, safety, pharmacokinetics, pharmacodynamics, anti-tumor activity

BOIN, Bayesian optimal interval; MTD, maximum tolerated dose

Demography and baseline characteristics

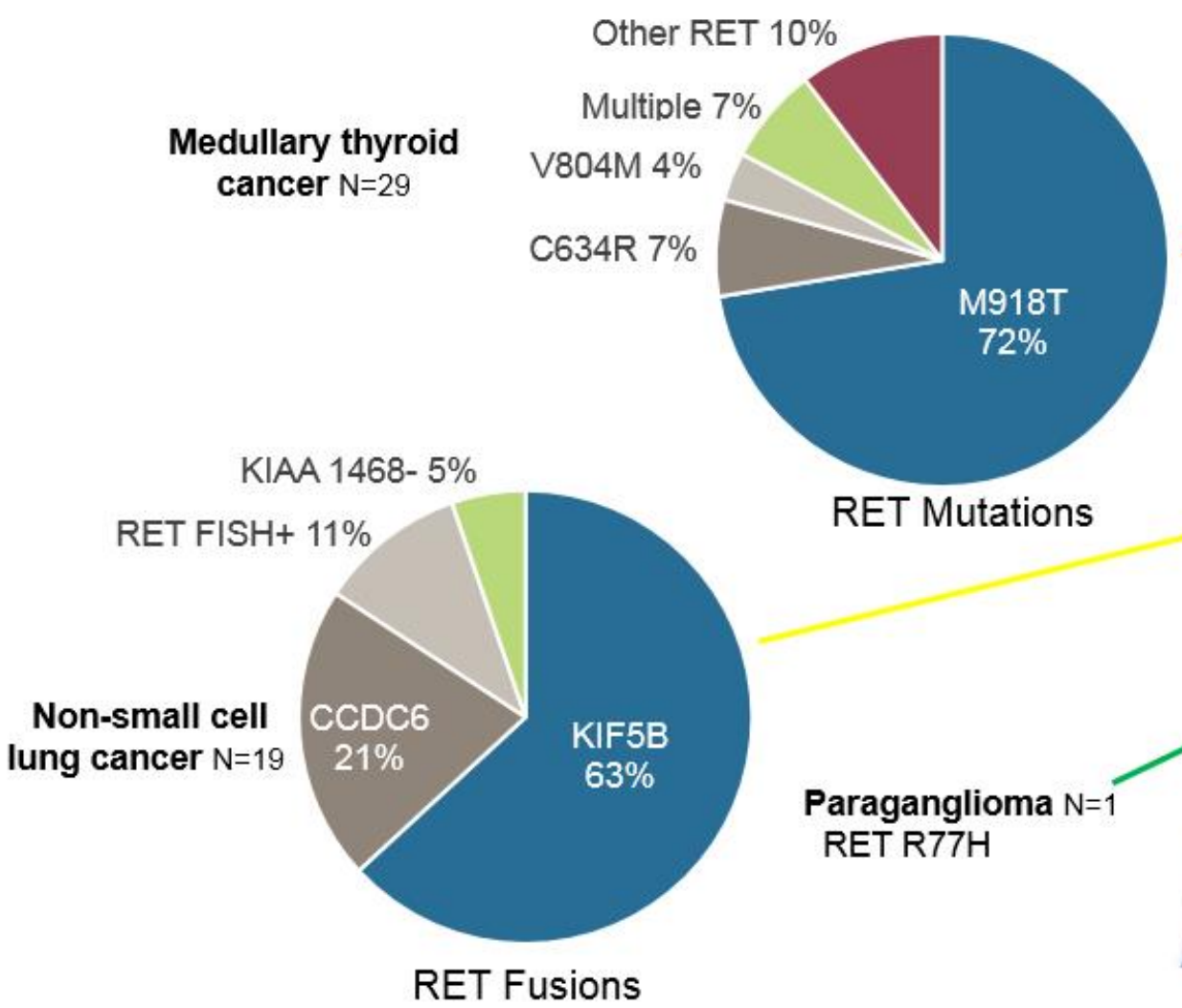
Parameter	(N=53)
Age, years; median (range)	56 (19-83)
Sex, male; n (%)	30 (57)
ECOG PS; n (%)	
0	21 (40)
1	32 (60)
Metastatic disease; n (%)	50 (94)
Tumor type; n (%)	
RET-alteration	51 (96)
Medullary thyroid cancer	29 (55)
Non-small cell lung cancer	19 (36)
Papillary thyroid cancer	2 (4)
Retroperitoneal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

Parameter	(N=53)
Prior systemic therapy; n (%)	41 (77)
Multikinase inhibitor; n (%)	27 (51)
Chemotherapy; n (%)	19 (36)
Immunotherapy; n (%)	18 (34)
# of lines, median (range)	1 (0-8)

ECOG PS, Eastern Cooperative Oncology Group performance score

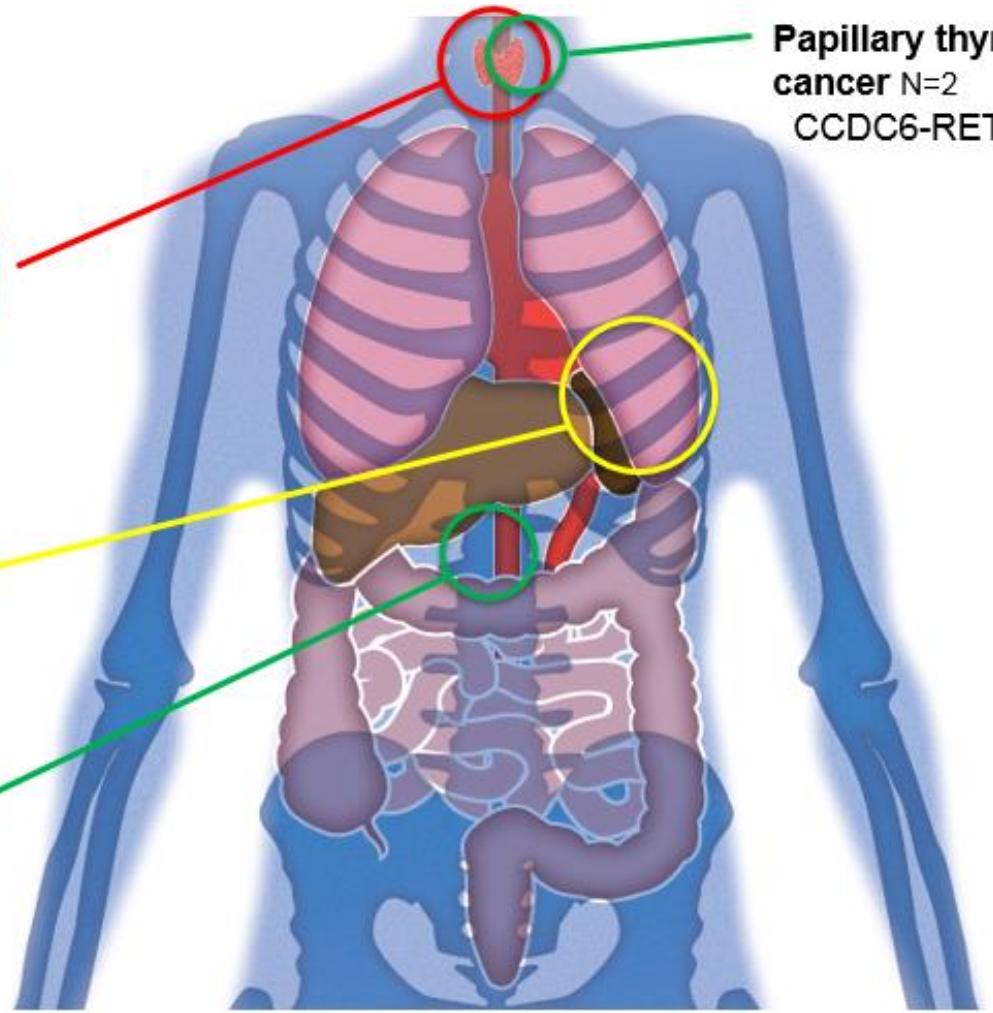
Data cut-off: April 6, 2018

Diverse *RET* genotypes enrolled



Medullary thyroid cancer N=29

Non-small cell lung cancer N=19



Papillary thyroid cancer N=2
CCDC6-RET 100%

Paraganglioma N=1
RET R77H

Data cut-off: April 6, 2018

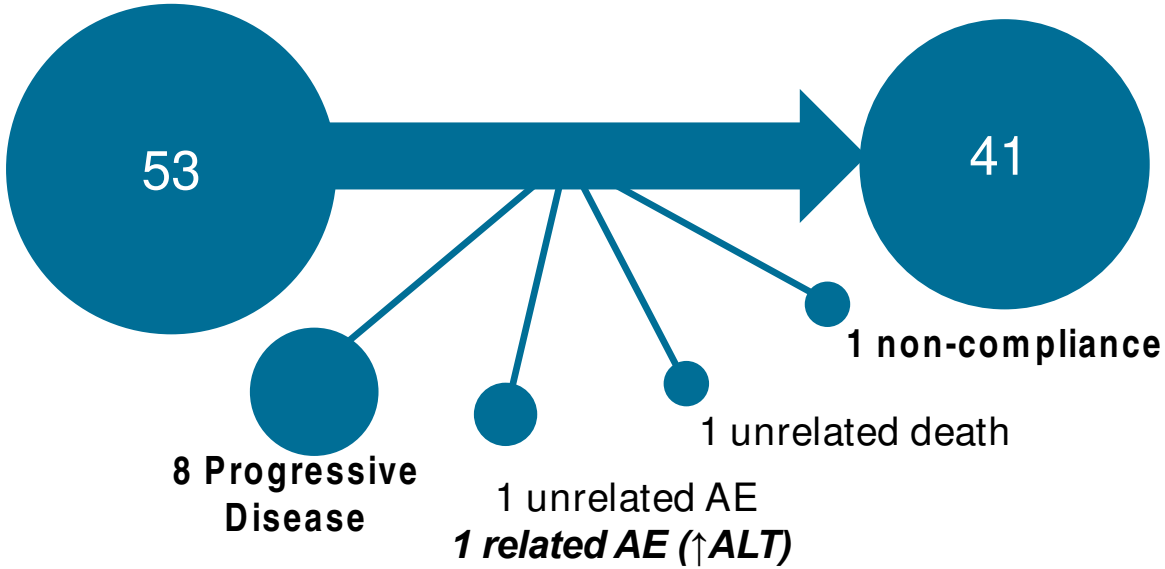
Dose escalation results

Maximum Tolerated Dose – 400 mg QD

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

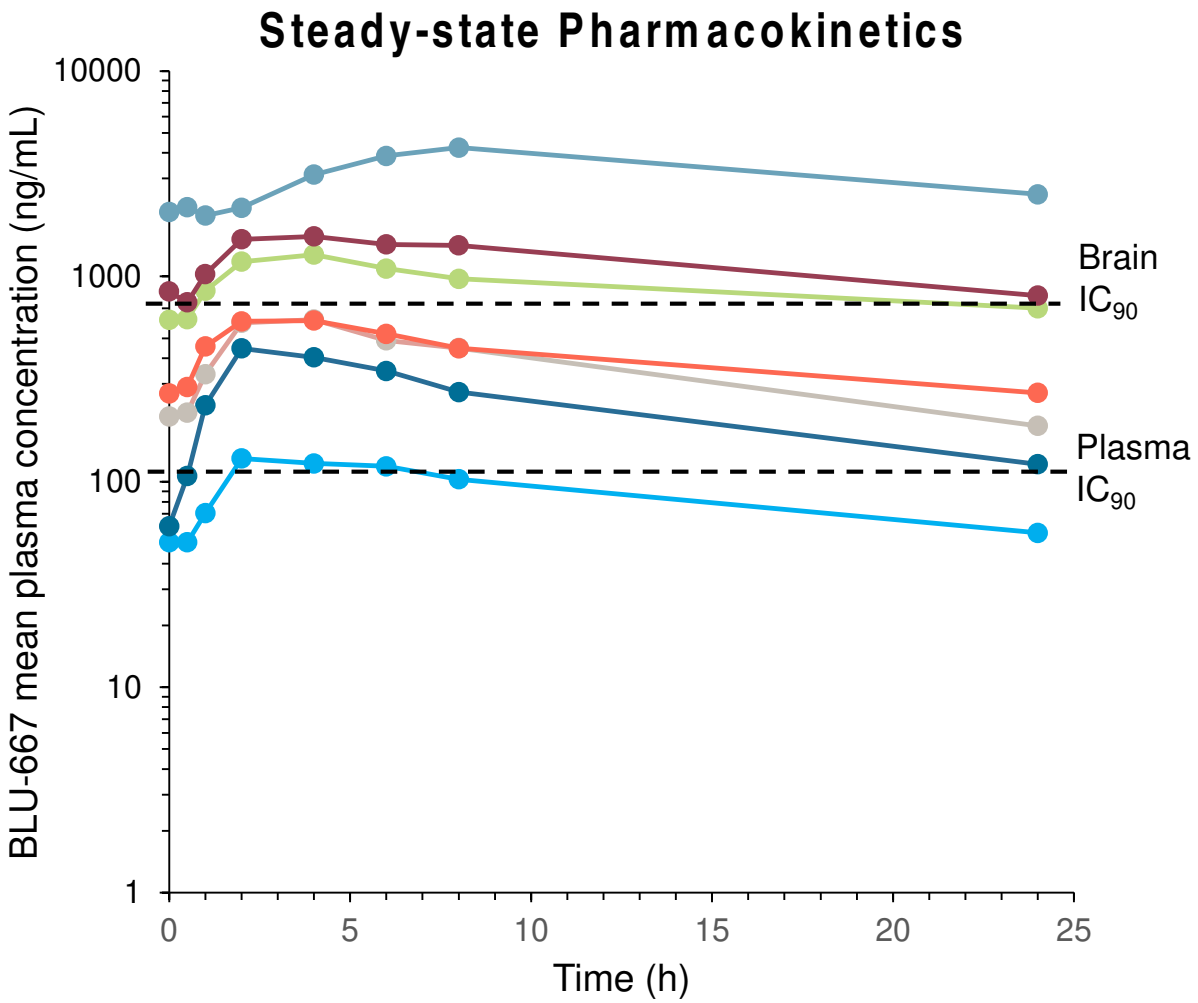
ALT, alanine aminotransferase

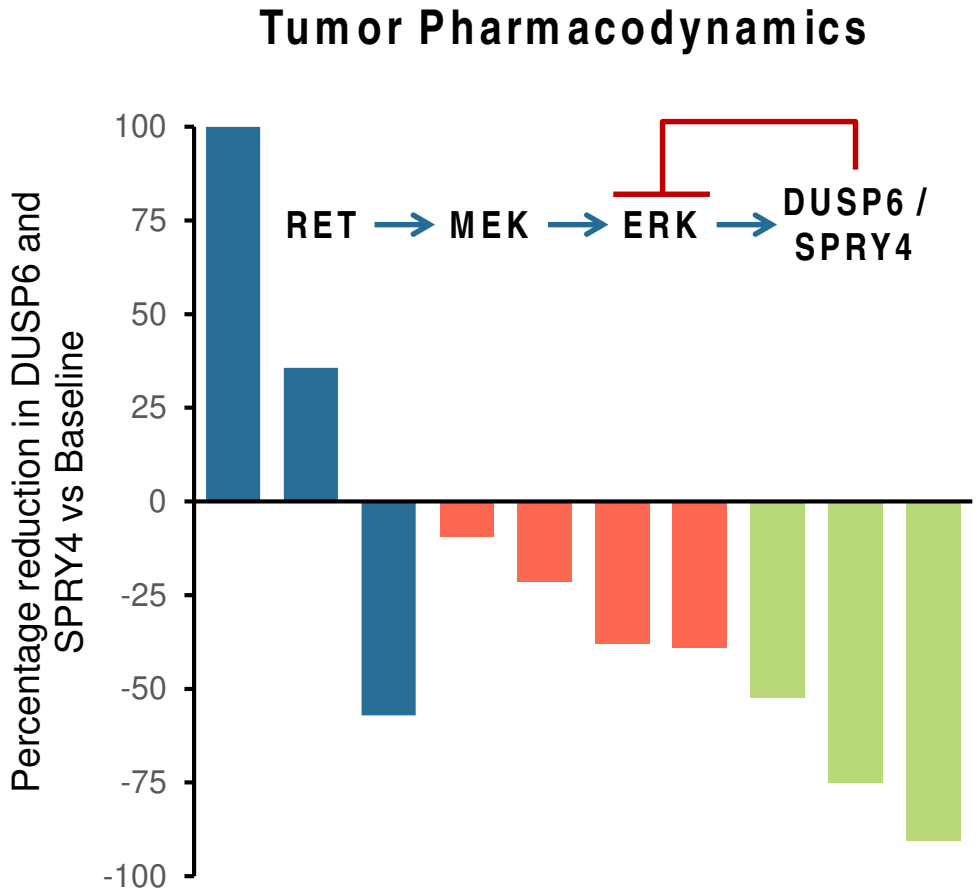
41 of 53
patients remain on treatment
(median 3.9 months [range: 0.3–11.5])



Data cut-off: April 6, 2018

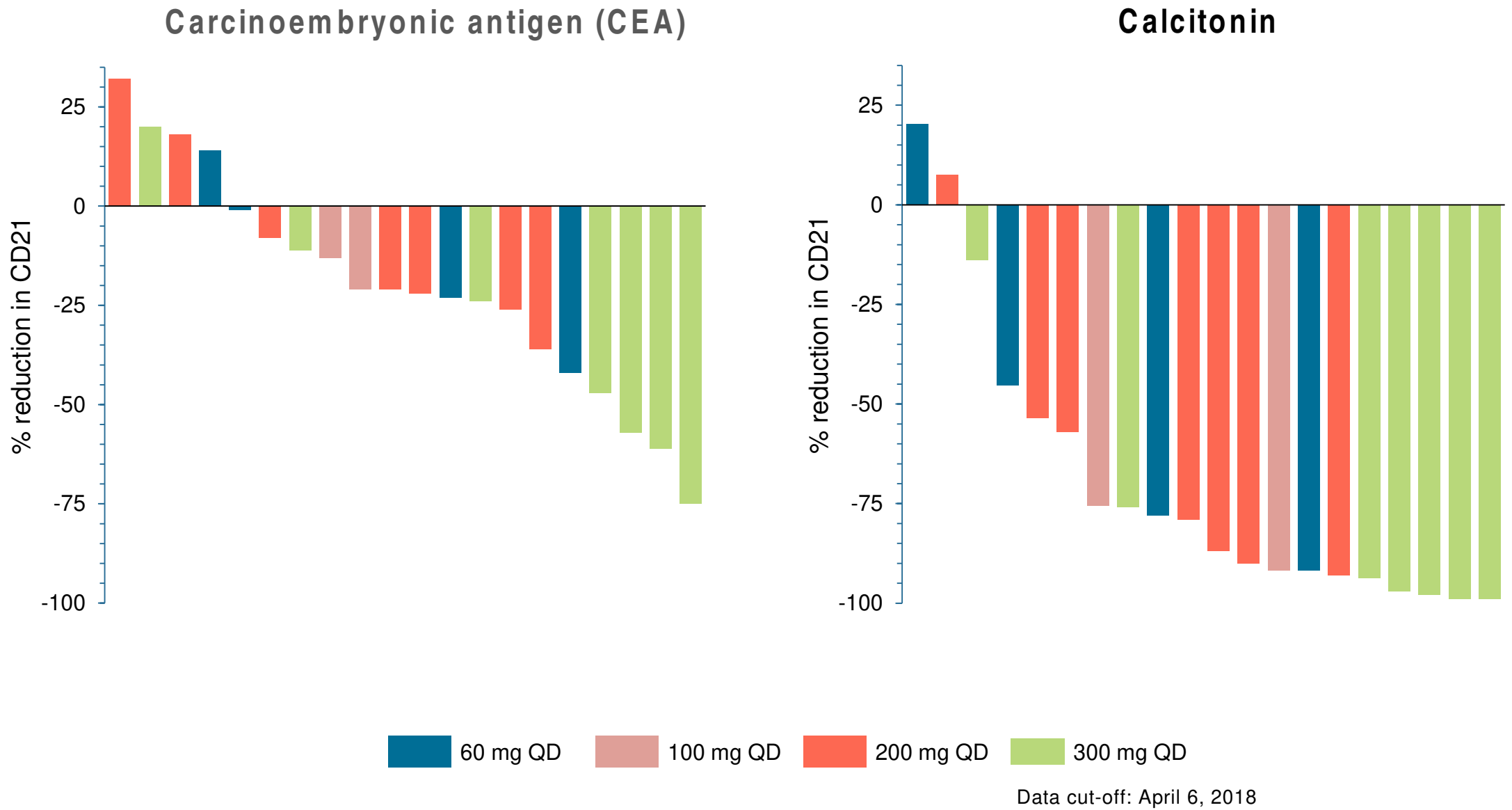
Dose-dependent exposure and RET pathway inhibition





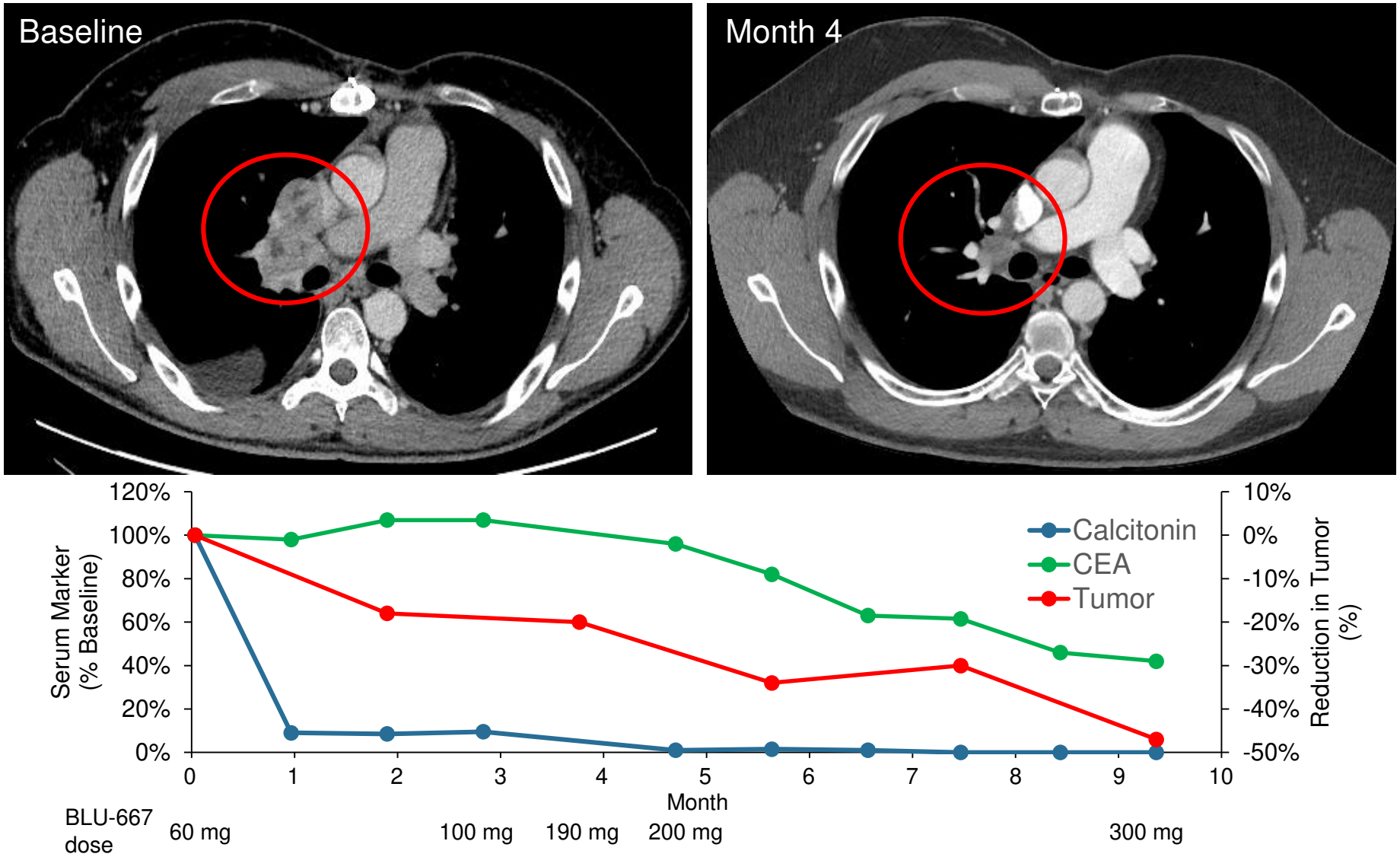
30 mg QD | 60 mg QD | 100 mg QD | 200 mg QD | 300 mg QD | 400 mg QD | 600 mg QD

Dose-dependent decline in MTC tumor markers



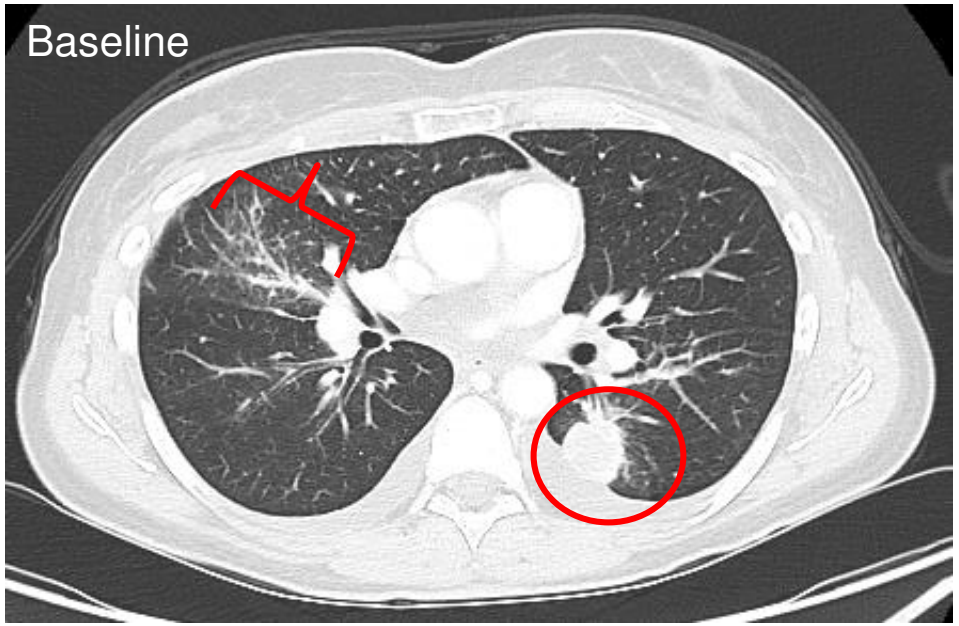
Data cut-off: April 6, 2018

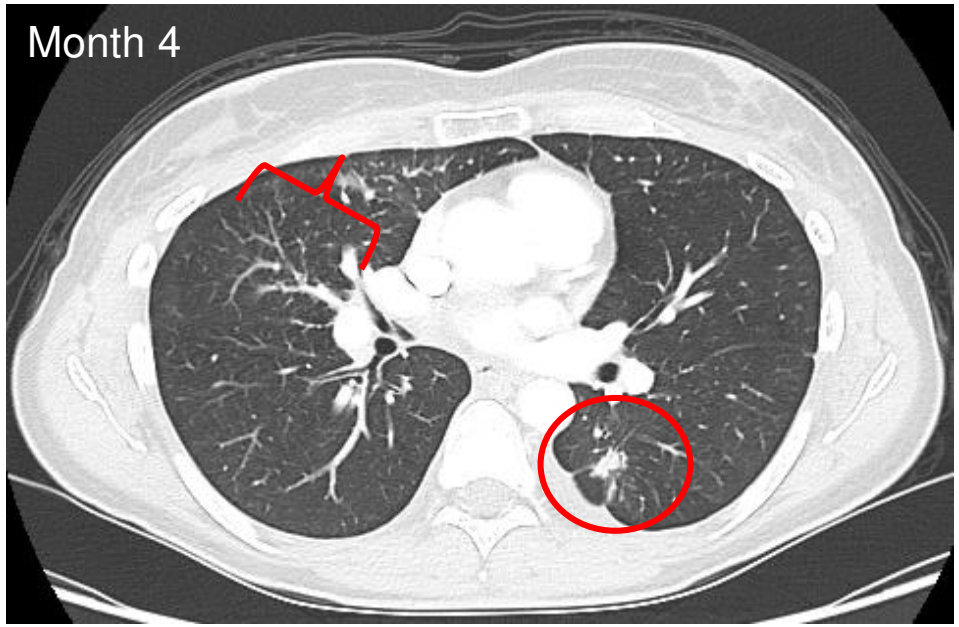
Potent activity against highly invasive *RET*-mutant MTC



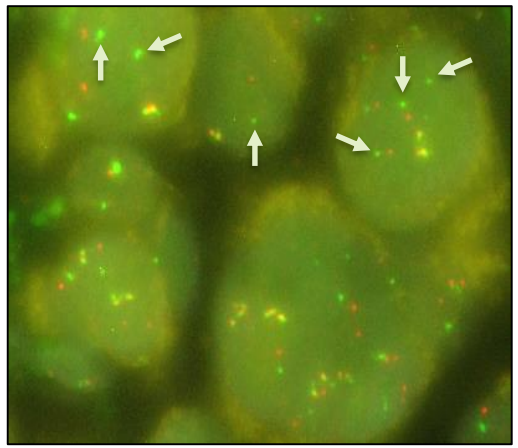
27-year-old male; *RET* L629-D361 Del; initiated at 60 mg; ongoing at 400 mg with confirmed PR

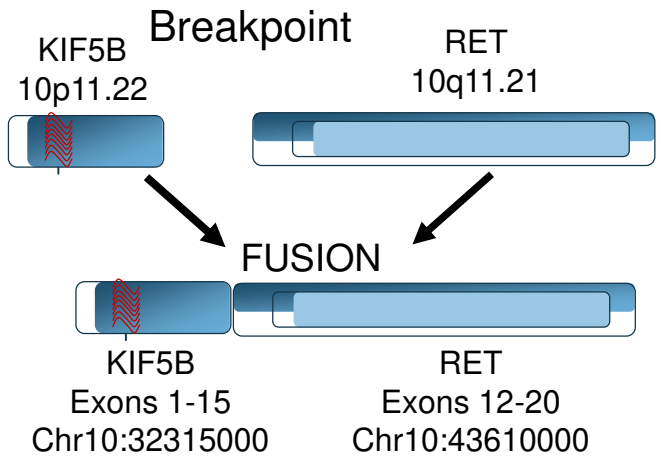
Potent activity against KIF5B-RET NSCLC – post chemotherapy

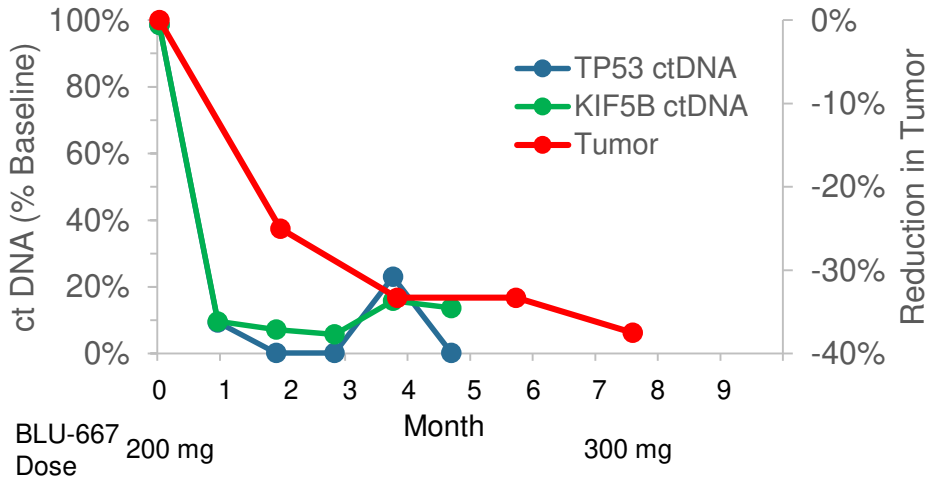




FISH







37-year-old female; ongoing at 400 mg with confirmed PR

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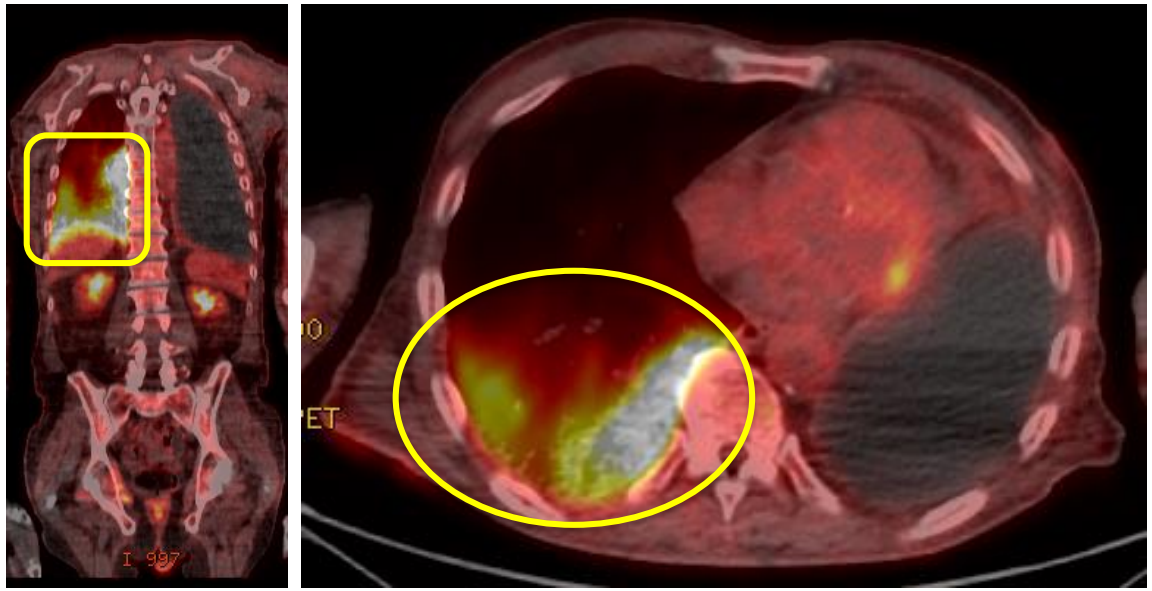
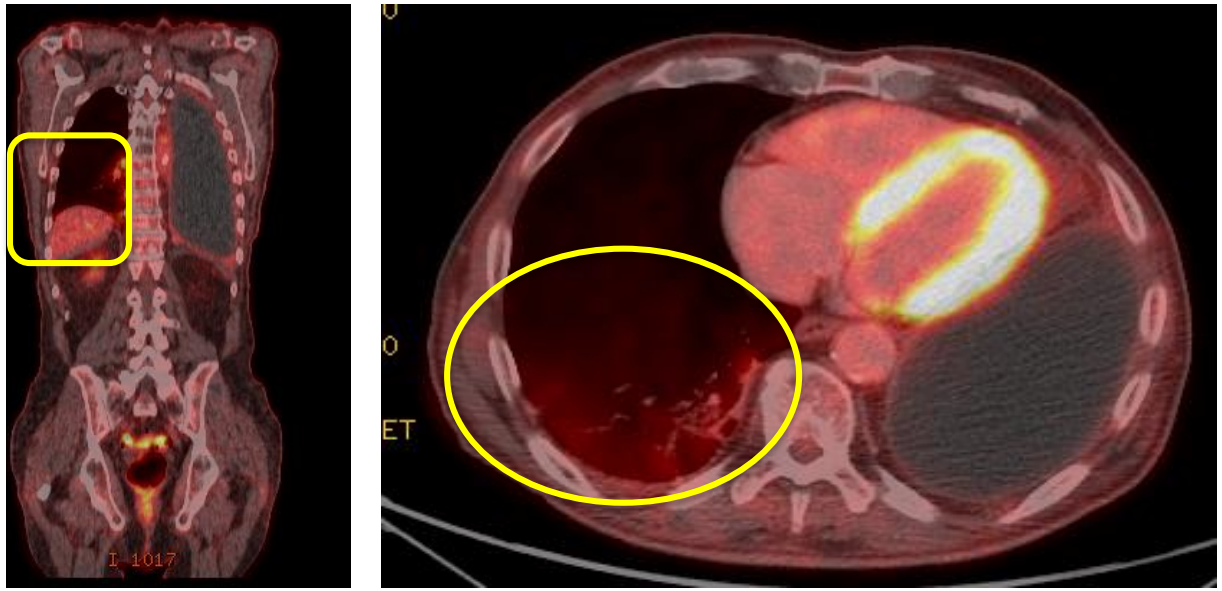
Potent activity against KIF5B-RET NSCLC – post-vandetinib+everolimus

Baseline

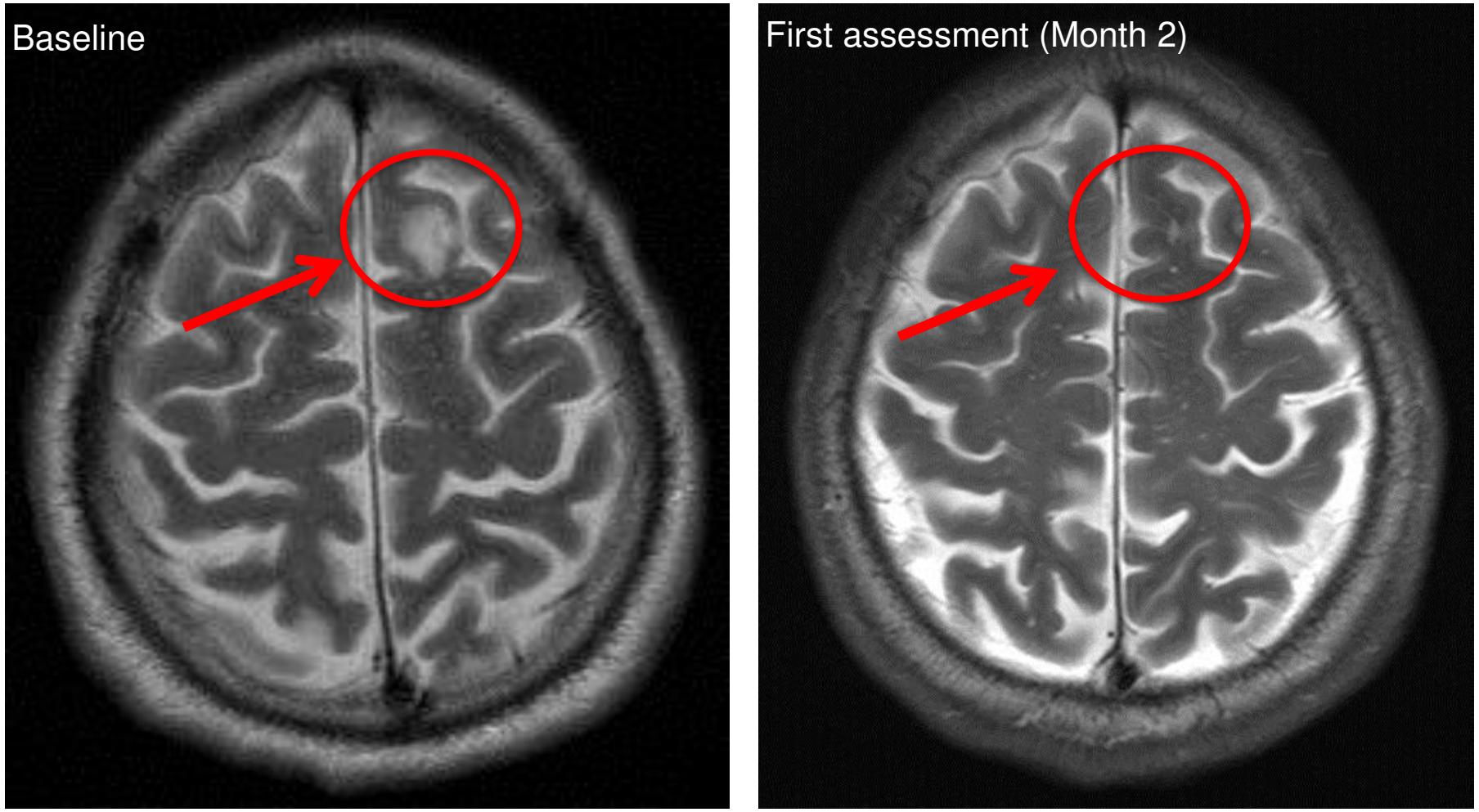


First Assessment (Month 2)



74-year-old male; initiated at 300 mg; ongoing at 400 mg; PR at month 5 pending confirmation Subbiah V et al. *Cancer Discovery* April 15 2018

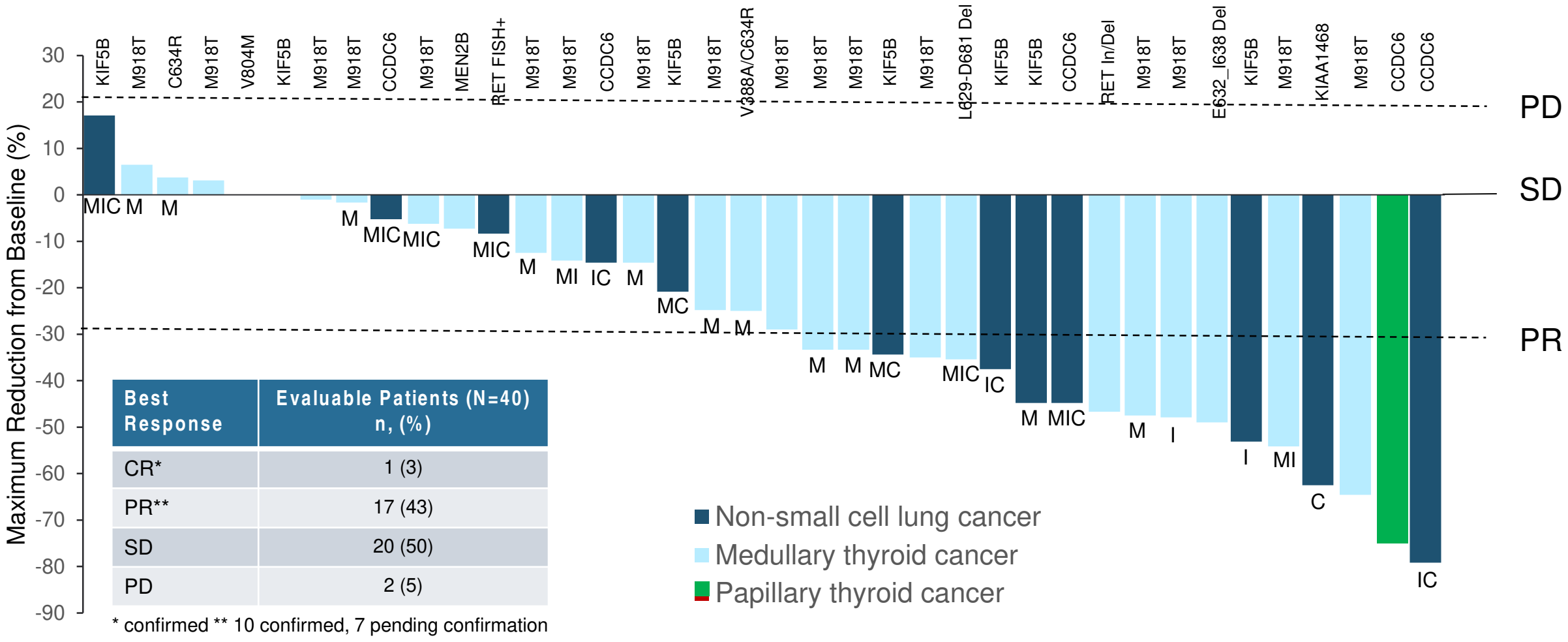
Activity against KIF5B-RET NSCLC brain metastases



69-year-old male; initiated at 400 mg; ongoing at month 4

Images courtesy of Drs of Gainor, J and Lin, J of MGH

BLU-667 has broad anti-tumor activity against RET-altered cancers



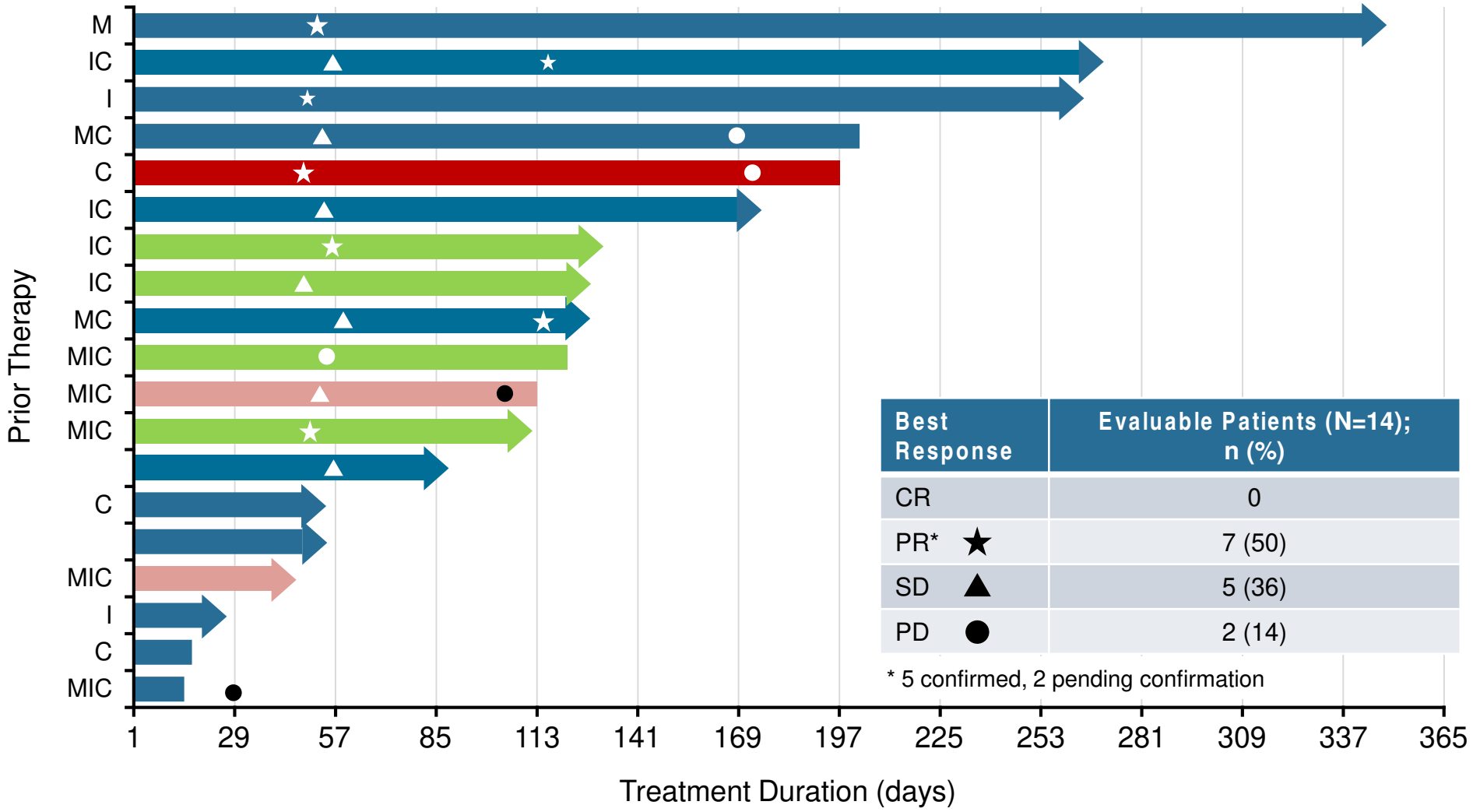
Best Response	Evaluable Patients (N=40) n, (%)
CR*	1 (3)
PR**	17 (43)
SD	20 (50)
PD	2 (5)

* confirmed ** 10 confirmed, 7 pending confirmation

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

Data cut-off: April 6, 2018

BLU-667 has durable activity and high response rate in RET-altered NSCLC



Best Response	Evaluable Patients (N=14); n (%)
CR	0
PR* ★	7 (50)
SD ▲	5 (36)
PD ●	2 (14)

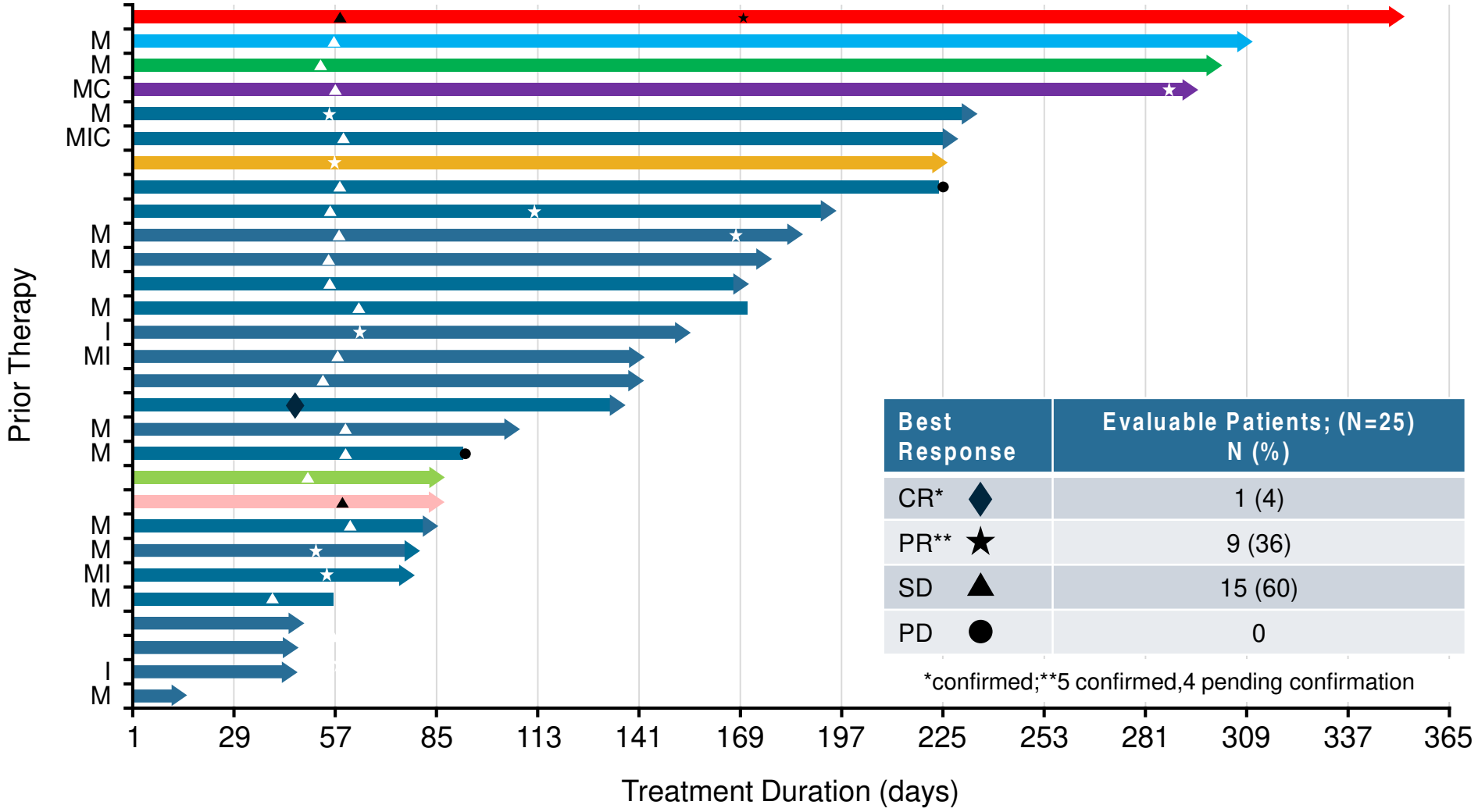
* 5 confirmed, 2 pending confirmation

KIF5B
KIAA1468
CCDC6
RET FISH+

Treatment duration:
Median 3.9 months
Range 0.4–11.4 months
13/19 (68%) on treatment

Data cut-off: April 6, 2018

BLU-667 has durable activity and high response rate in RET-altered MTC



Best Response	Evaluable Patients; (N=25) N (%)
CR*	1 (4)
PR**	9 (36)
SD	15 (60)
PD	0

*confirmed;**5 confirmed,4 pending confirmation

- L629-D361 Del
- V388A/C634R
- C634R
- RET In/Del
- M918T
- E632_1638 Del
- Other RET
- V804M

Treatment duration:
Median 4.7 months
Range 0.5–11.5 months
25/29 (86%) on treatment

Data cut-off: April 6, 2018

BLU-667 is well tolerated

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

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

Most adverse events were Grade 1

8 (16%) patients had Grade 3 treatment-related AE

No Grade 4/5 treatment-related AEs

AE, adverse event; ALP, alkaline phosphatase; ALT, analine aminotransferase;
AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events

Data cut-off: April 6, 2018

Conclusions

- BLU-667 delivers:
  - Potent RET pathway inhibition with favorable tolerability
  - Broad anti-tumor activity regardless of *RET* genotype, indication and prior therapy
  - High preliminary response rates and durable activity
    - ORR: RET-fusion NSCLC 50%
    - ORR: RET-mutant MTC 40%
    - ORR: *RET*-fusions and mutations (NSCLC, MTC and PTC) 45%
    - 41 of 51 *RET*-altered patients remain on treatment
- ARROW dose escalation data validate BLU-667 as a promising precision therapy for *RET*-altered cancers
- ARROW dose expansion is open and enrolling globally
- BLU-667 manuscript published today in Cancer Discovery
  - Foundational preclinical work and clinical translation

Data cut-off: April 6, 2018

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