
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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Disclosures

I have the following financial relationships to disclose:

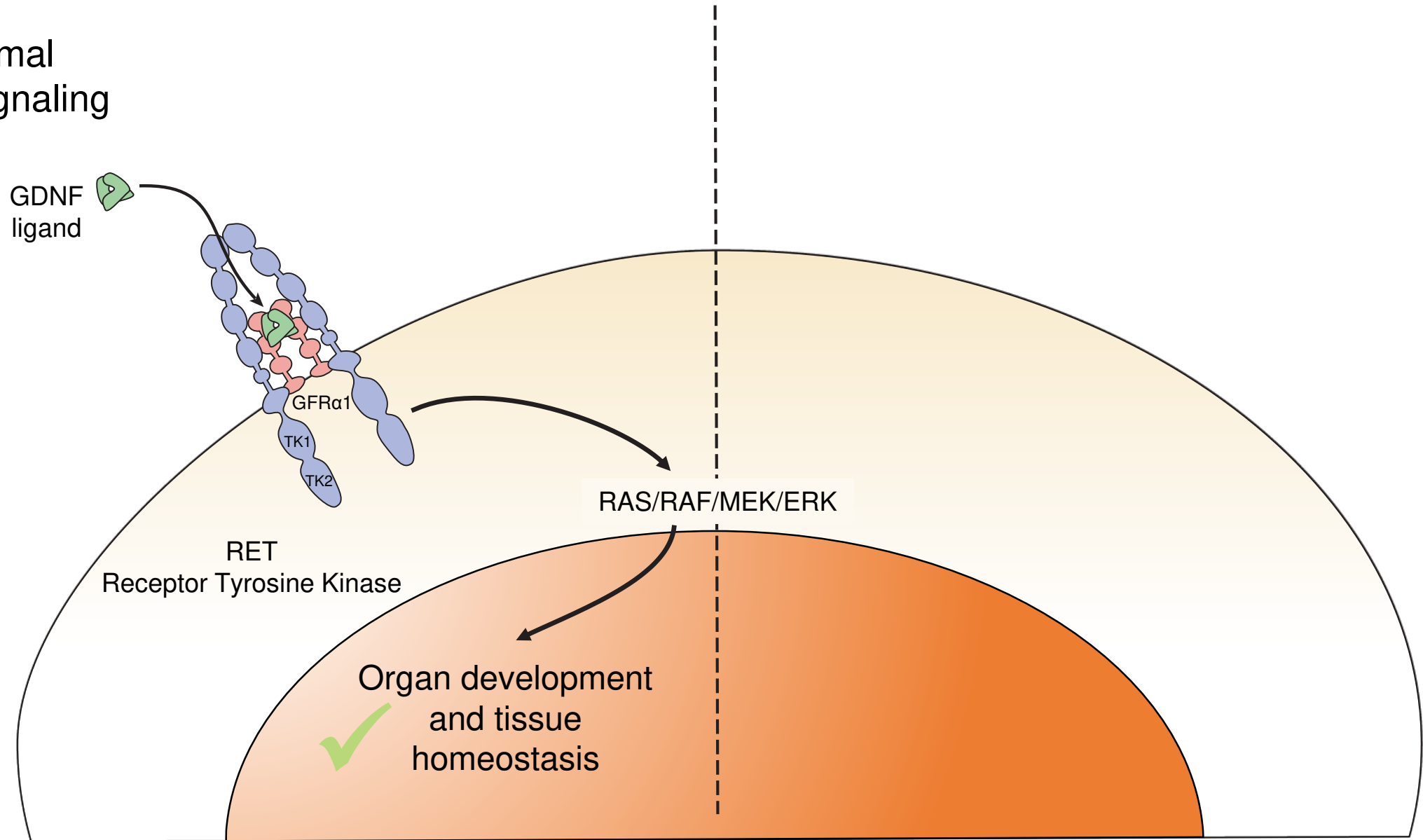
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- National Comprehensive Cancer Network
- National Cancer Institute-Cancer Therapy Evaluation Program

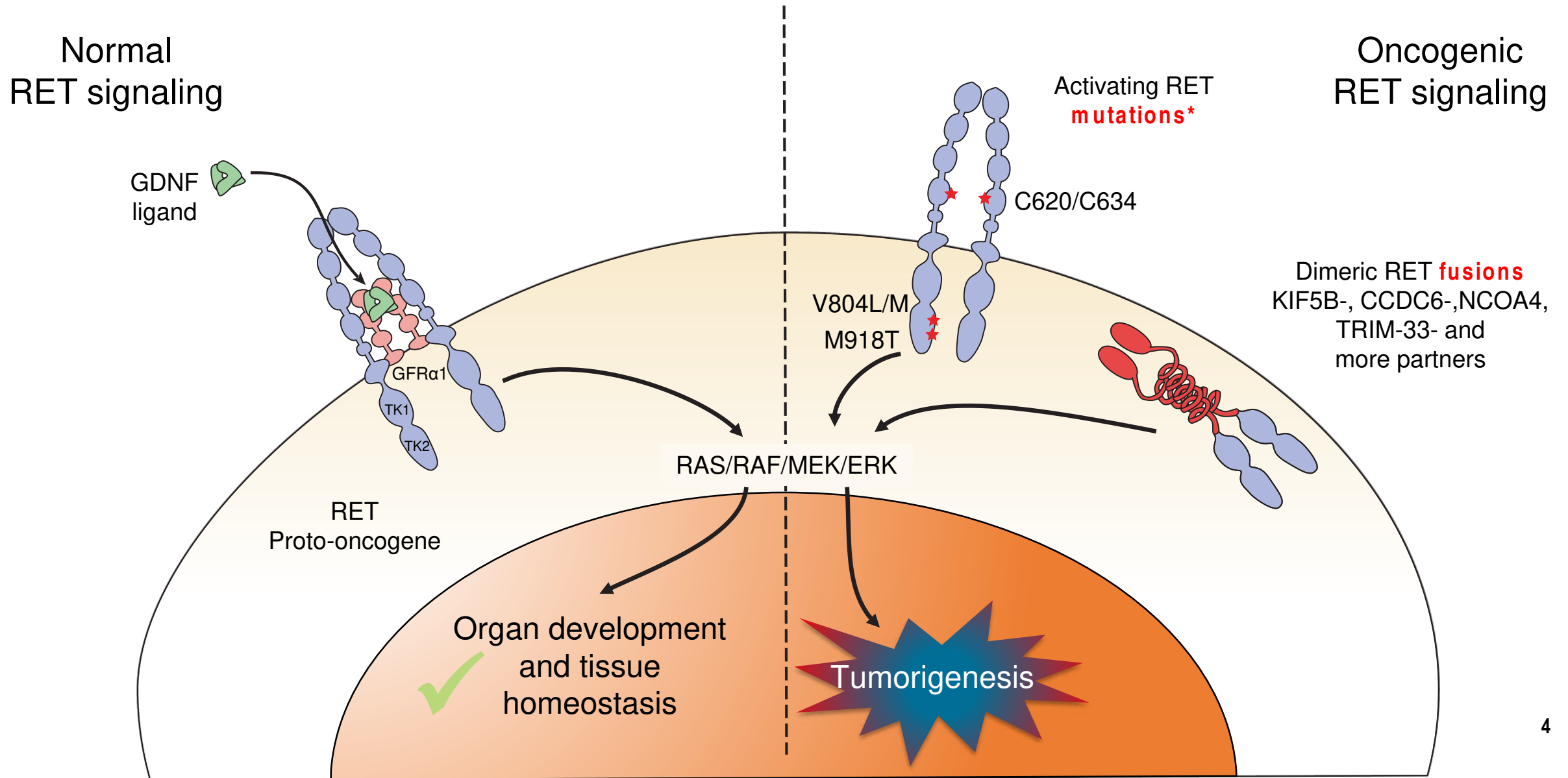
BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

Receptor tyrosine kinase, REarranged during Transfection (RET)

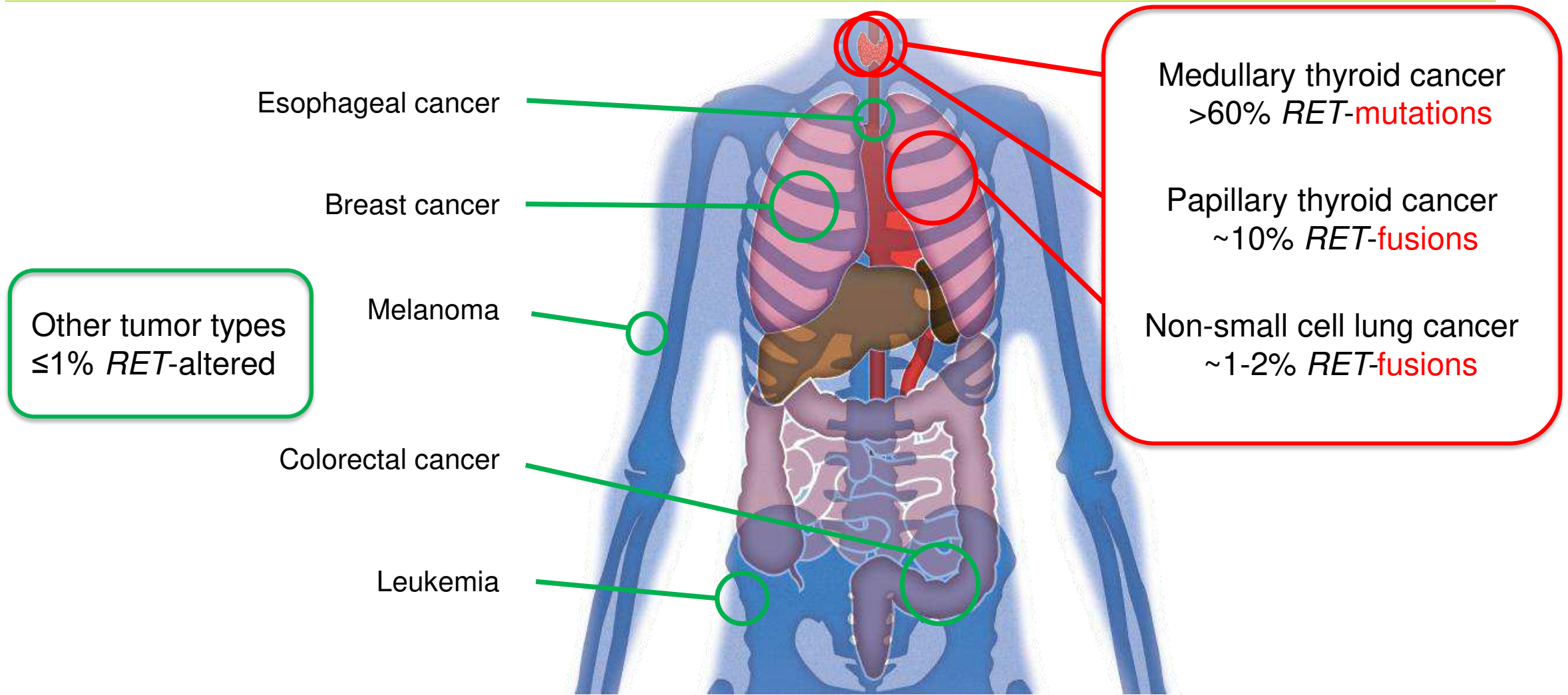
Normal
RET signaling



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



RET is a rare driver of multiple, diverse tumor types^{1,2}

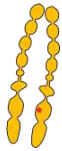


Patients with *RET*-alterations have not benefited from precision oncology

Precision oncology

Non-small cell lung cancer

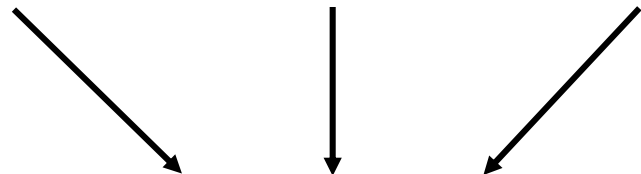
EGFR mutation



ALK-fusion



ROS-fusion



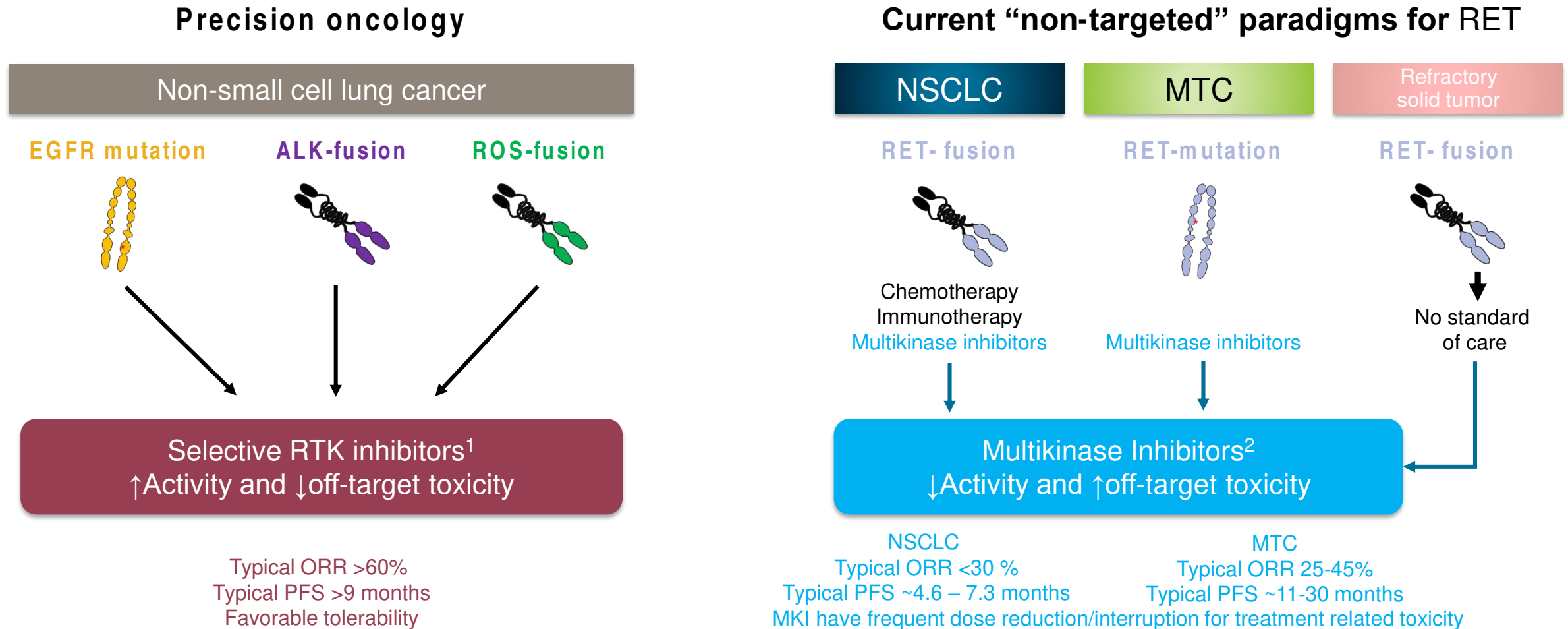
Selective RTK inhibitors¹
↑Activity and ↓off-target toxicity

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.

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



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.

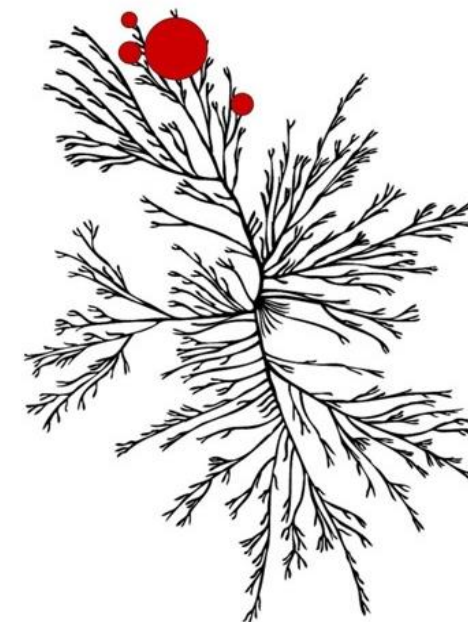
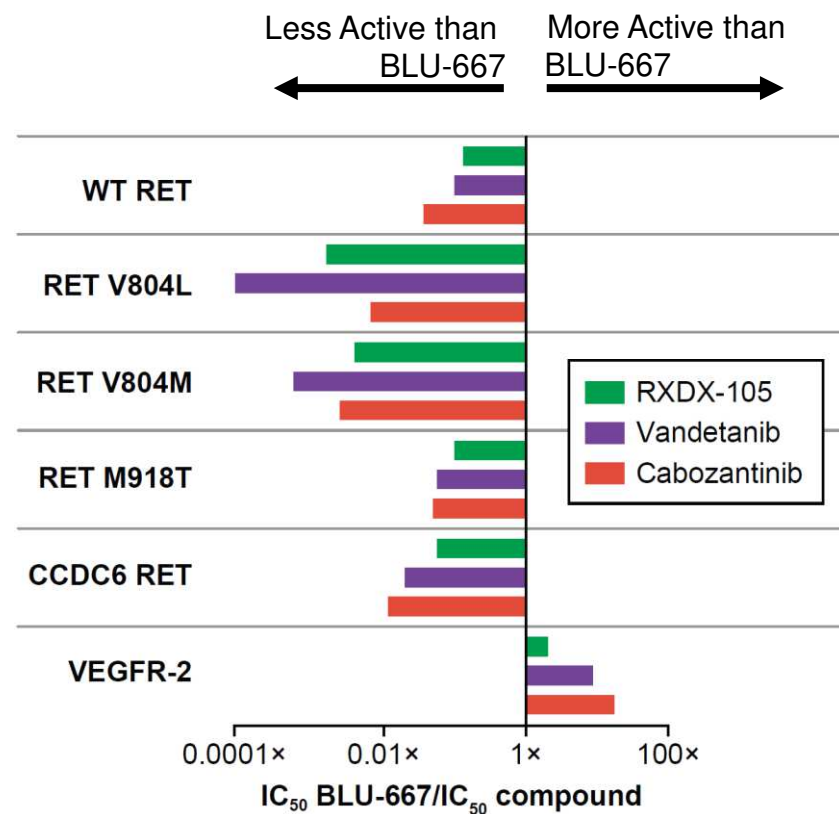
BLU-667 was designed to treat RET-altered cancers

Subnanomolar potency¹

More Potent than MKI

Kinome selectivity for RET

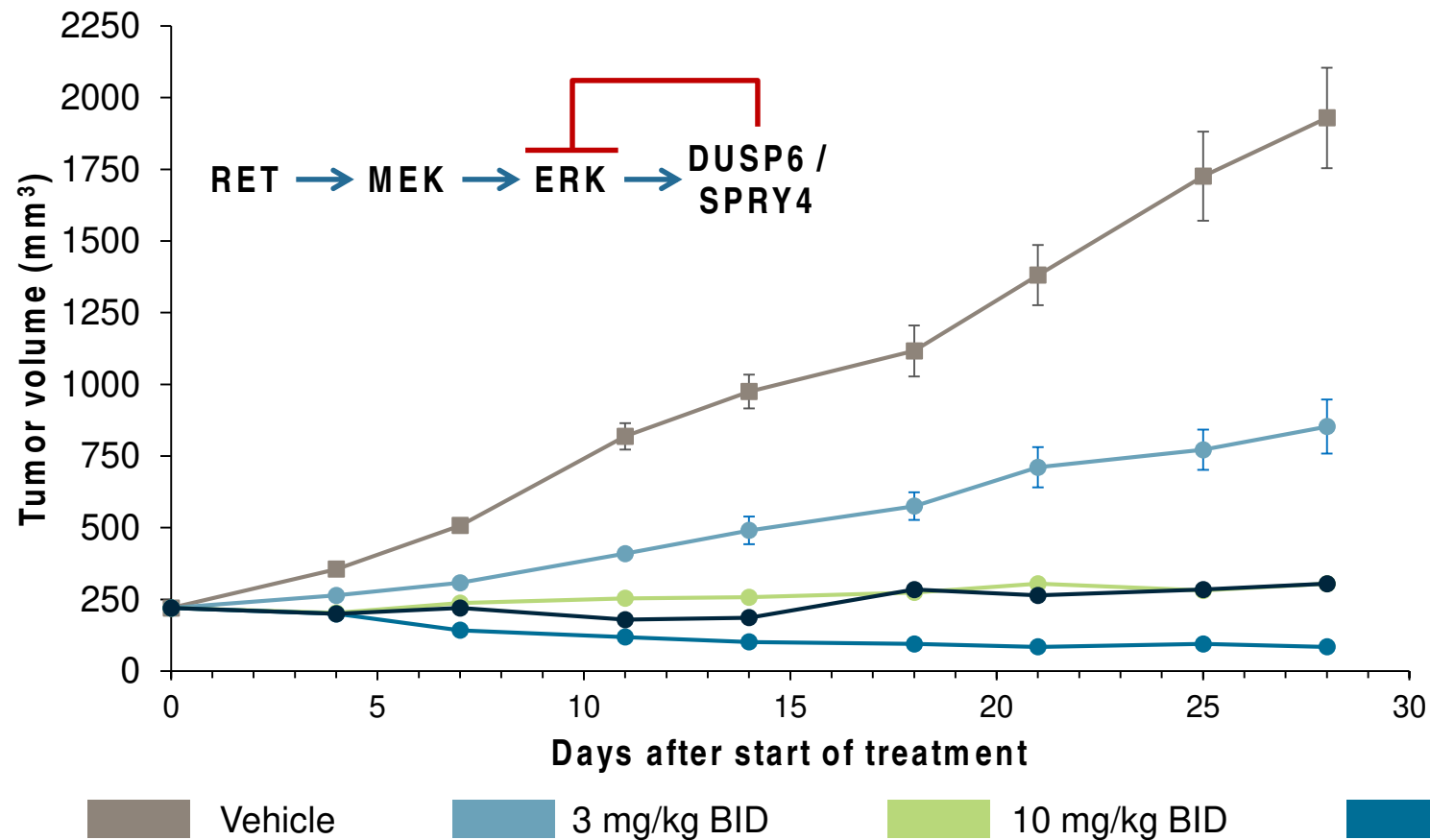
Variant	Biochemical IC ₅₀ (nM)
RET wildtype	0.4
RET V804L	0.3
RET V804M	0.4
RET M918T	0.4
CCDC6-RET	0.4



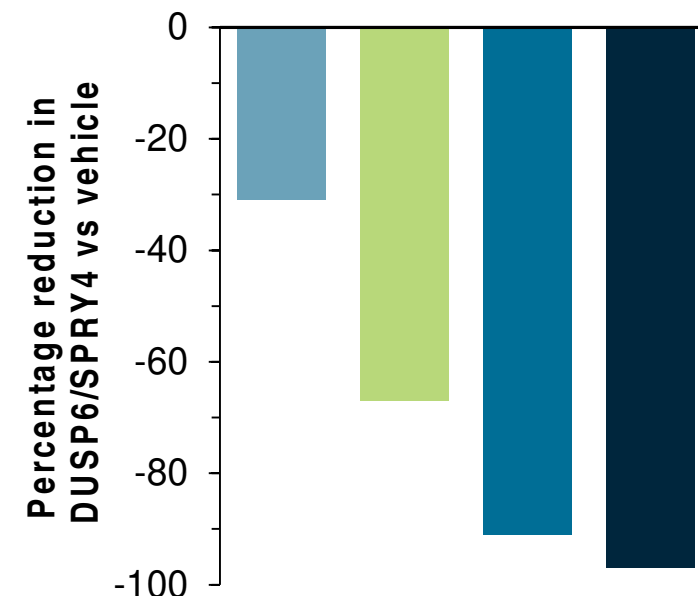
1. Subbiah V et al. *Cancer Discovery* April 15 2018

BLU-667 potently inhibits RET-driven tumor growth

KIF5B-RET NSCLC patient-derived xenograft¹



Potent Pathway inhibition



BLU-667 ARROW first-in-human study

Part 1: Dose escalation – completed

Opened March 2017

Advanced *RET*-altered solid tumors

- BOIN design
- BLU-667 orally QD continuous

MTD

NCT03037385

Part 2: Dose expansion – enrolling

NSCLC
Failed prior kinase inhibitor

NSCLC
No prior kinase inhibitor

Medullary Thyroid Cancer

Other *RET*-altered solid tumors

Key objectives

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

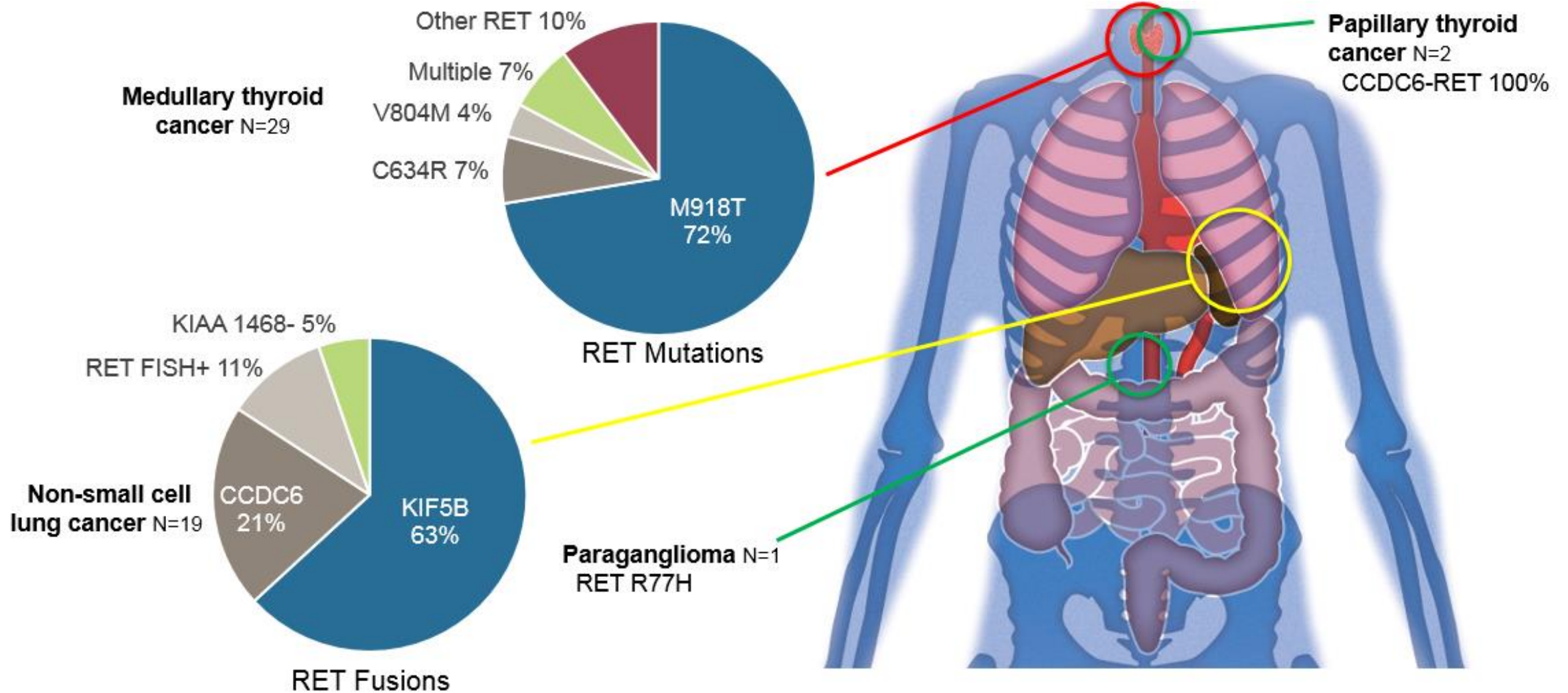
Demography and baseline characteristics

Parameter	(N=53)	Parameter	(N=53)
Age, years; median (range)	56 (19-83)	Prior systemic therapy; n (%)	41 (77)
Sex, male; n (%)	30 (57)	Multikinase inhibitor; n (%)	27 (51)
ECOG PS; n (%)		Chemotherapy; n (%)	19 (36)
0	21 (40)	Immunotherapy; n (%)	18 (34)
1	32 (60)	# of lines, median (range)	1 (0-8)
Metastatic disease; n (%)	50 (94)		
Tumor type; n (%)			
<i>RET</i> -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- <i>RET</i> altered solid tumor	2 (4)		

ECOG PS, Eastern Cooperative Oncology Group performance score

Data cut-off: April 6, 2018

Diverse *RET* genotypes enrolled



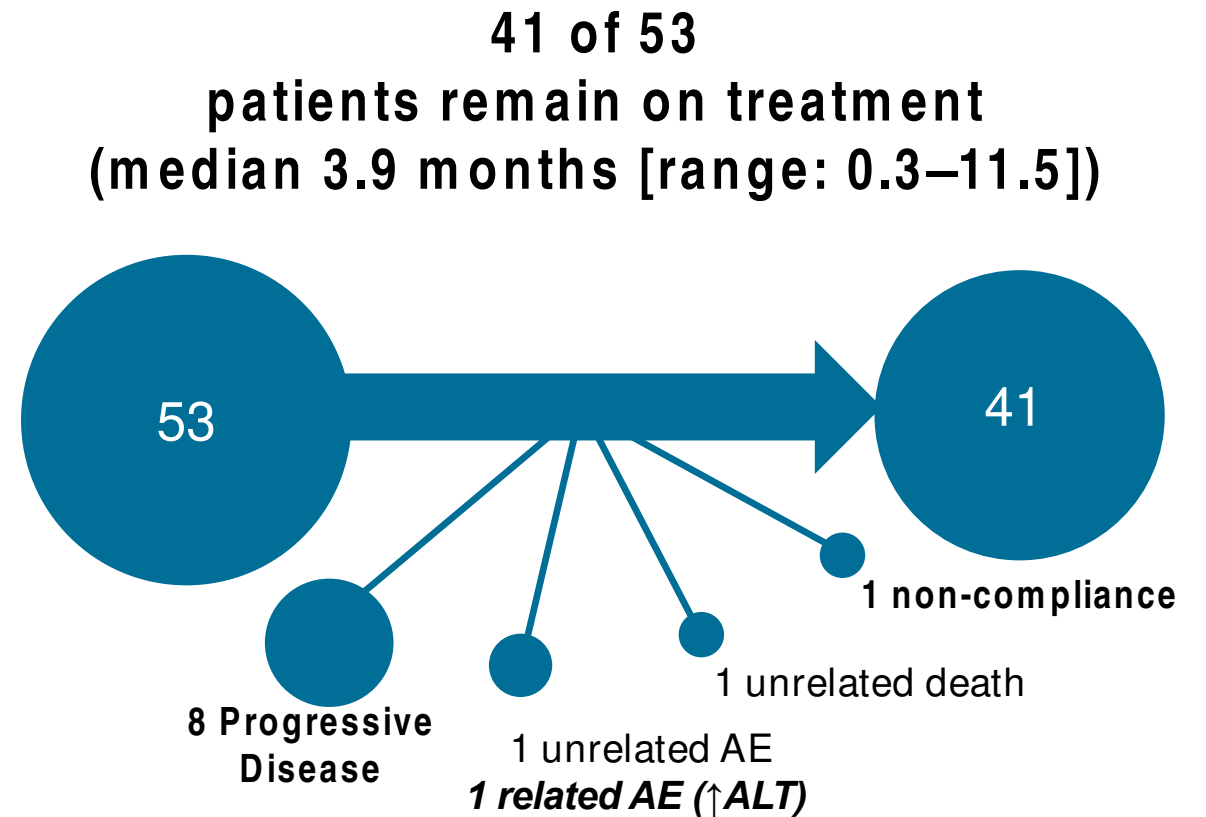
Data cut-off: April 6, 2018

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)

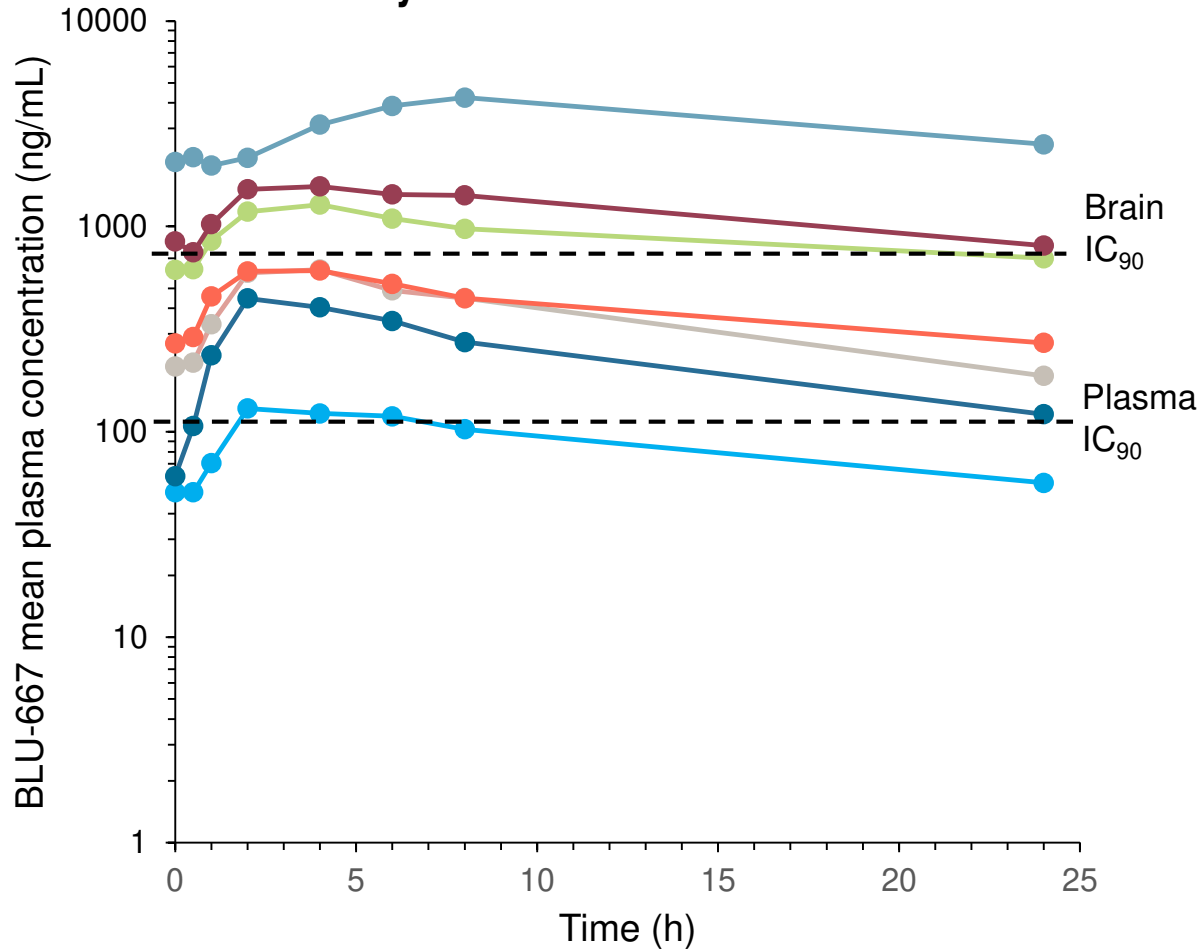
ALT, alanine aminotransferase



Data cut-off: April 6, 2018

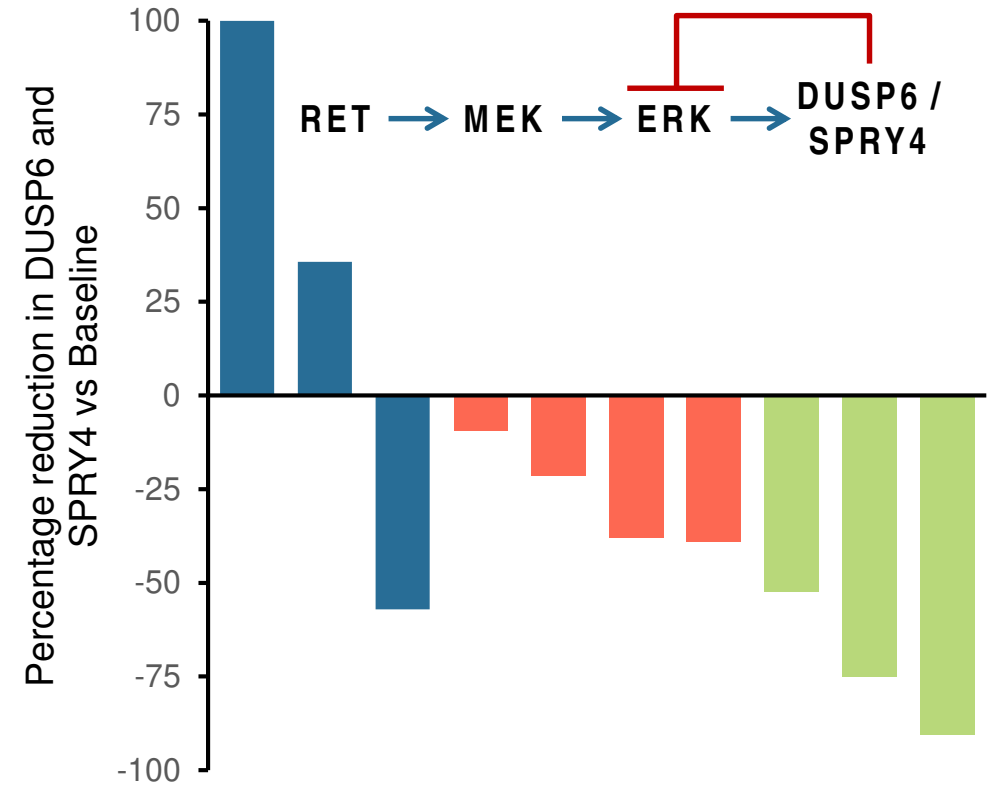
Dose-dependent exposure and RET pathway inhibition

Steady-state Pharmacokinetics



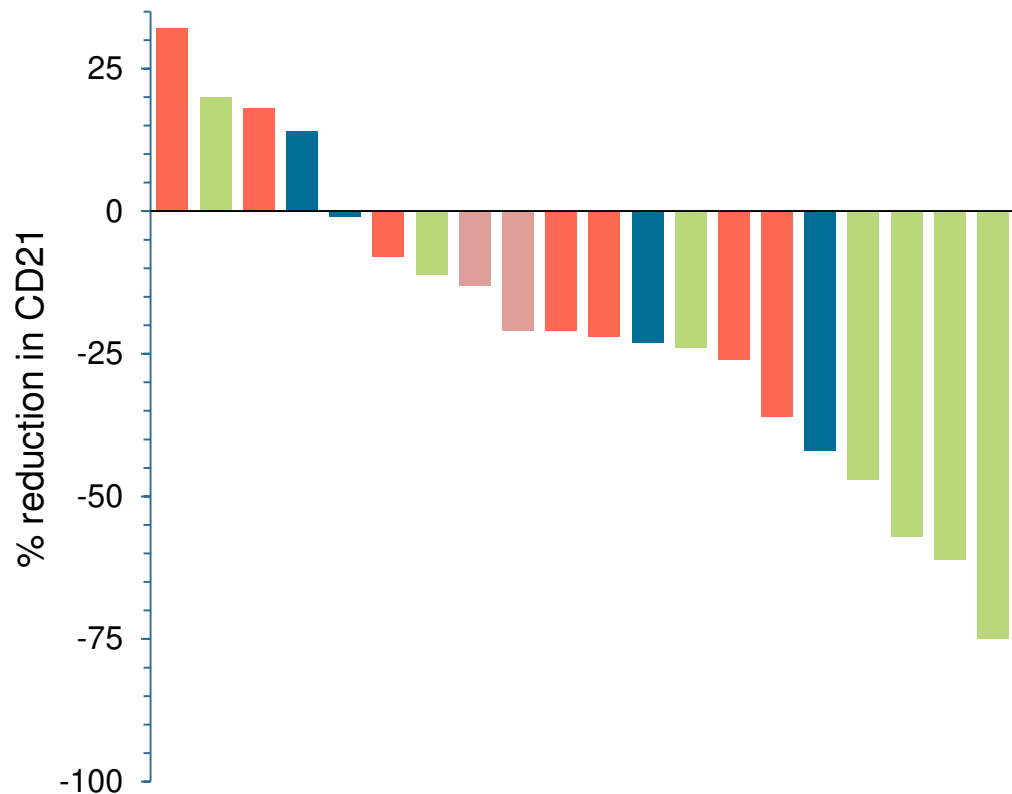
■ 30 mg QD
 ■ 60 mg QD
 ■ 100 mg QD
 ■ 200 mg QD
 ■ 300 mg QD
 ■ 400 mg QD
 ■ 600 mg QD

Tumor Pharmacodynamics

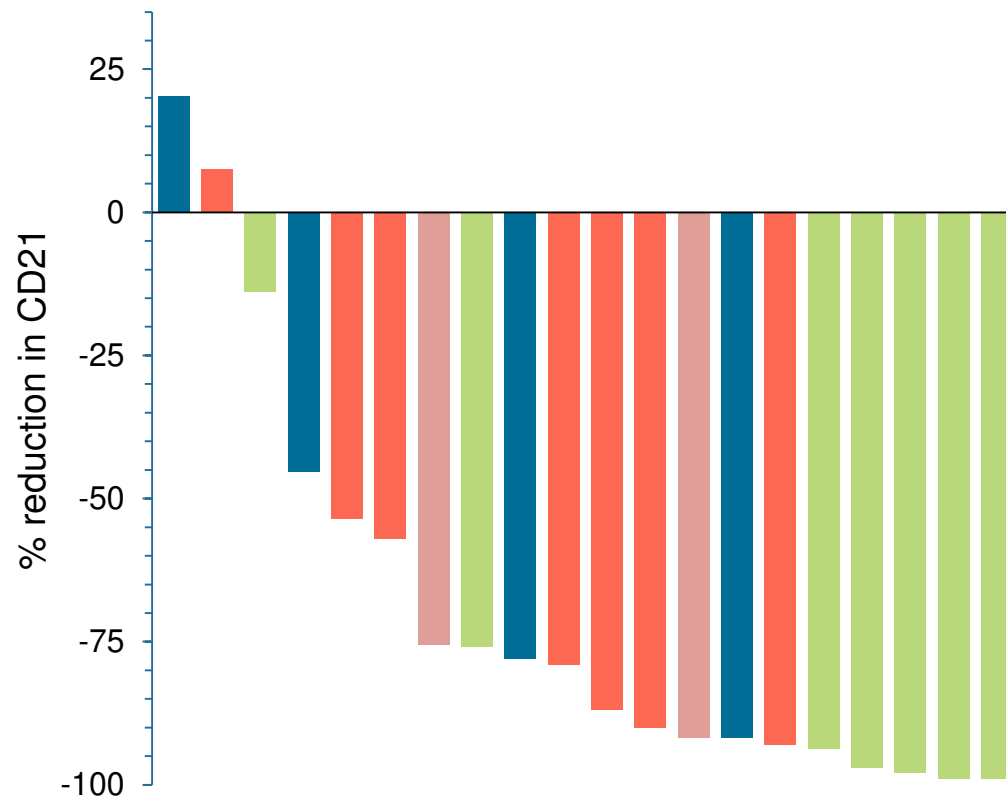


Dose-dependent decline in MTC tumor markers

Carcinoembryonic antigen (CEA)



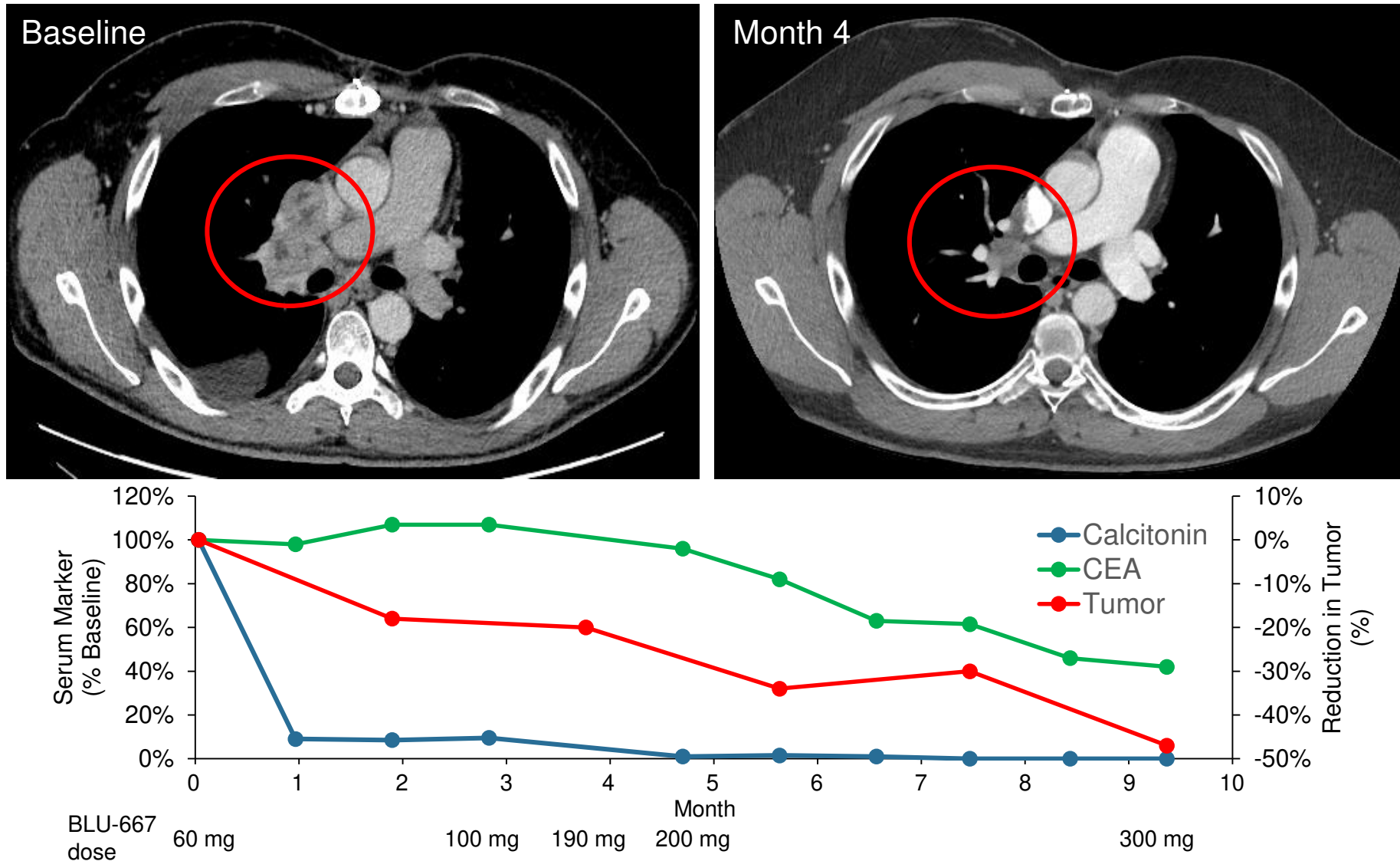
Calcitonin



60 mg QD 100 mg QD 200 mg QD 300 mg QD

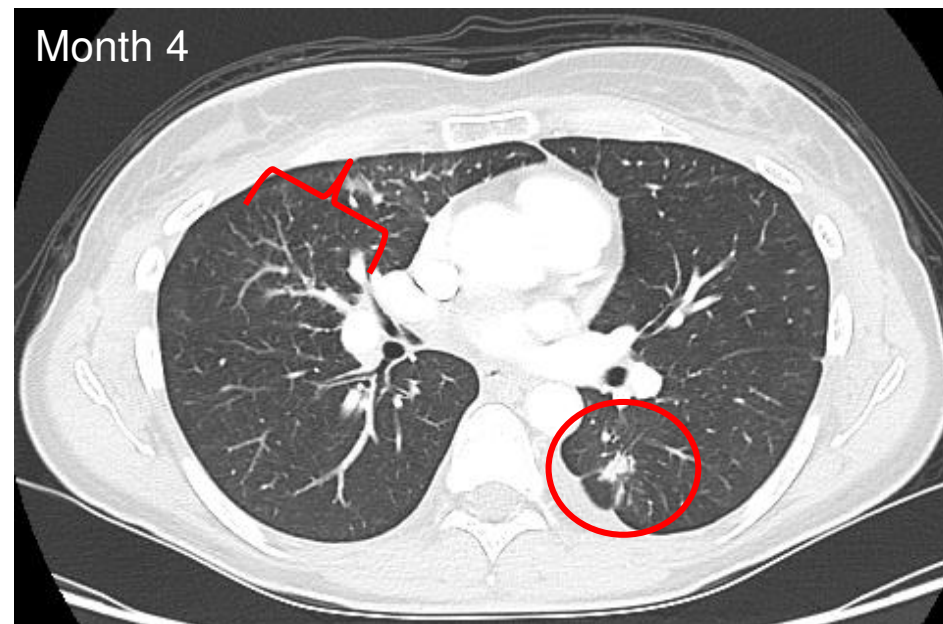
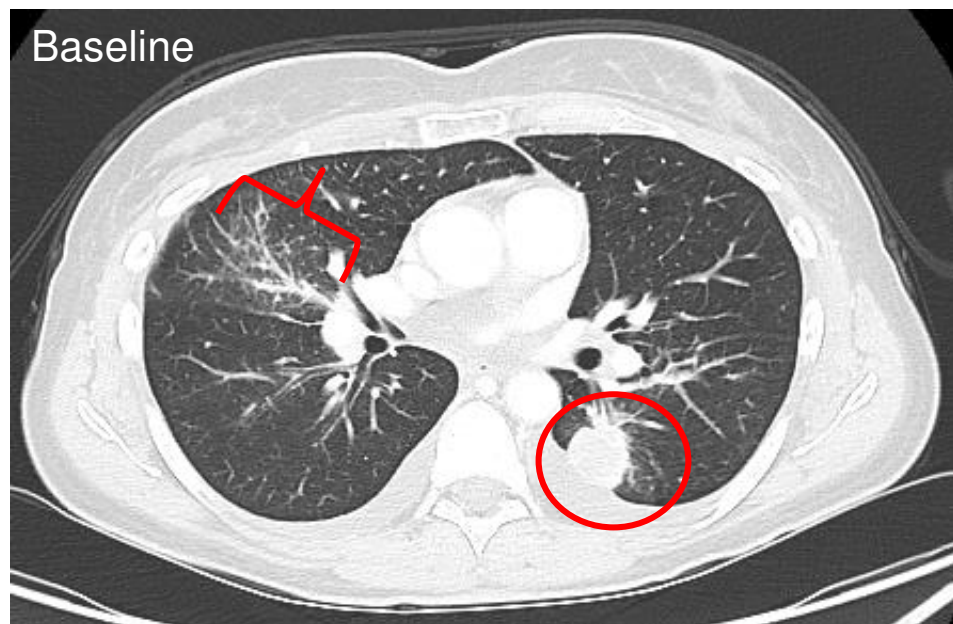
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Potent activity against highly invasive *RET*-mutant MTC

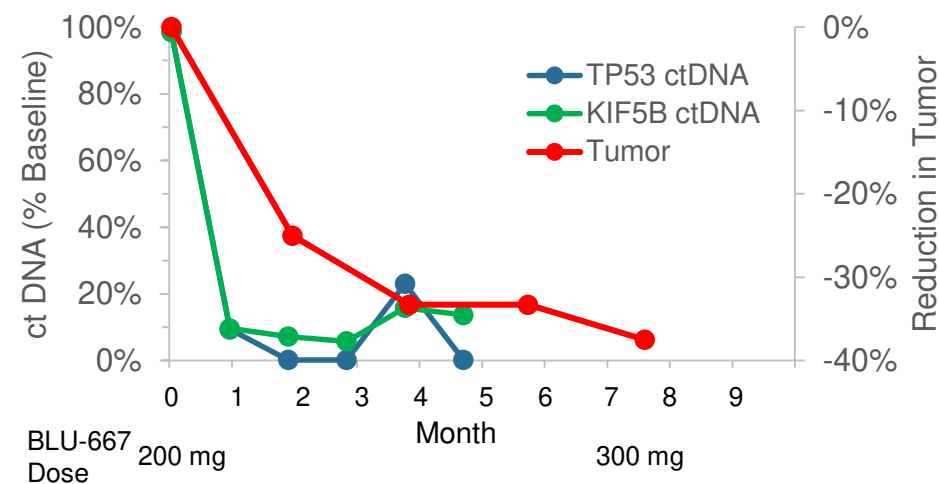
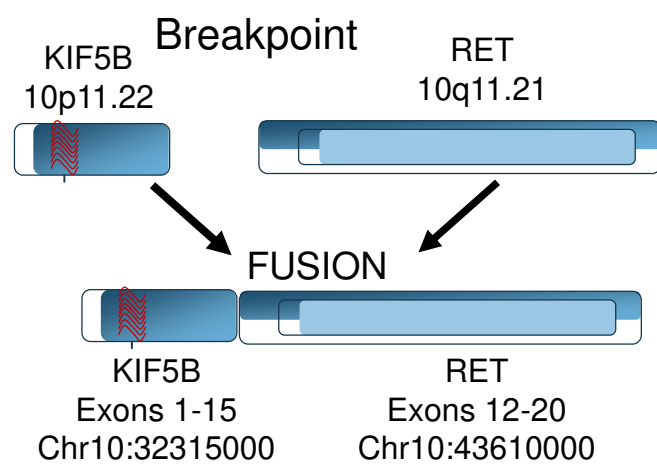
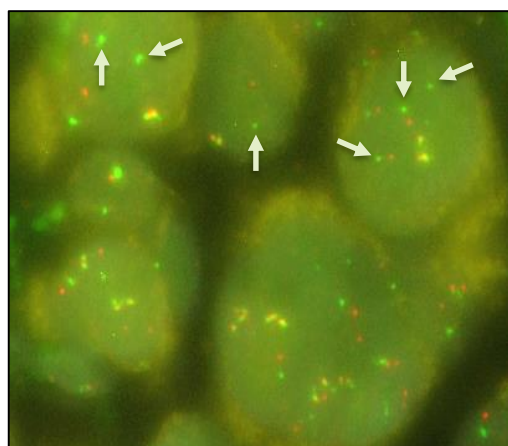


27-year-old male; *RET* L629-D361 Del; initiated at 60 mg; ongoing at 400 mg with confirmed PR

Potent activity against KIF5B-RET NSCLC – post chemotherapy

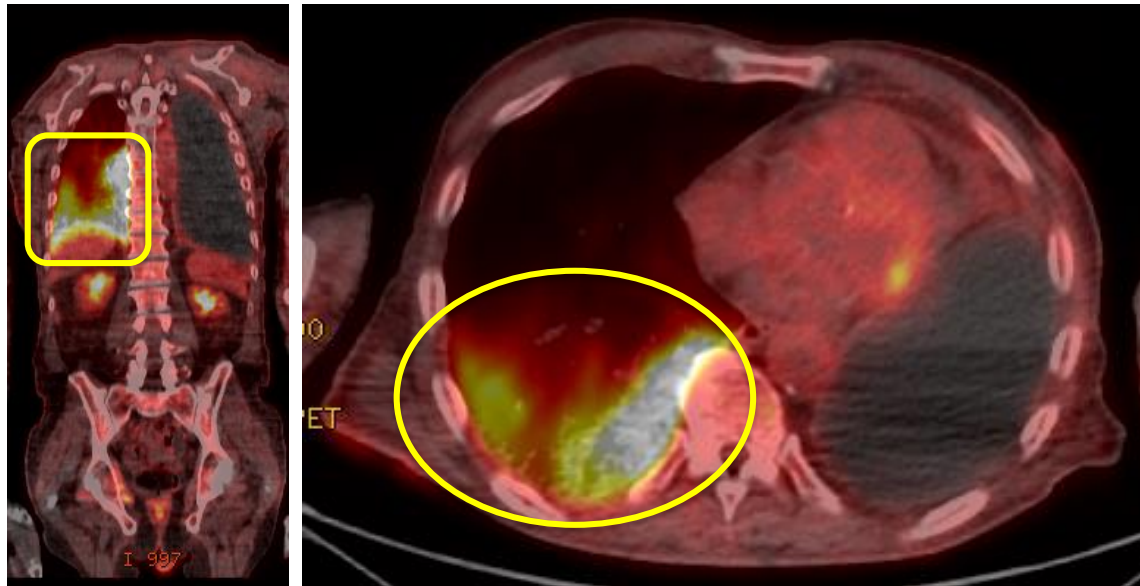


FISH

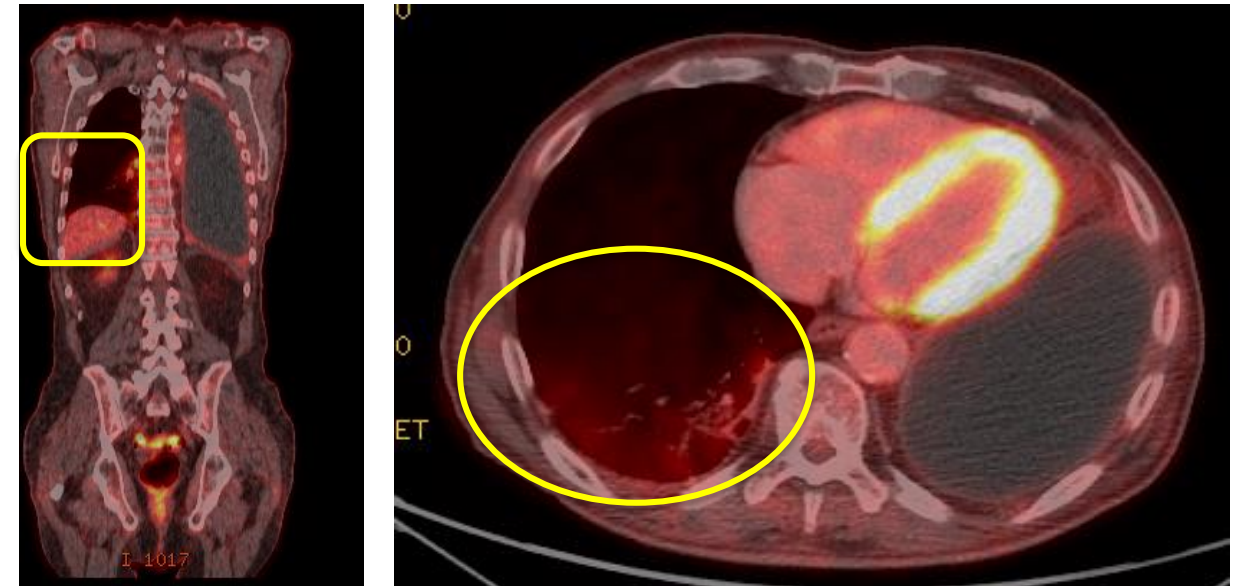


Potent activity against KIF5B-RET NSCLC – post-vandetinib+everolimus

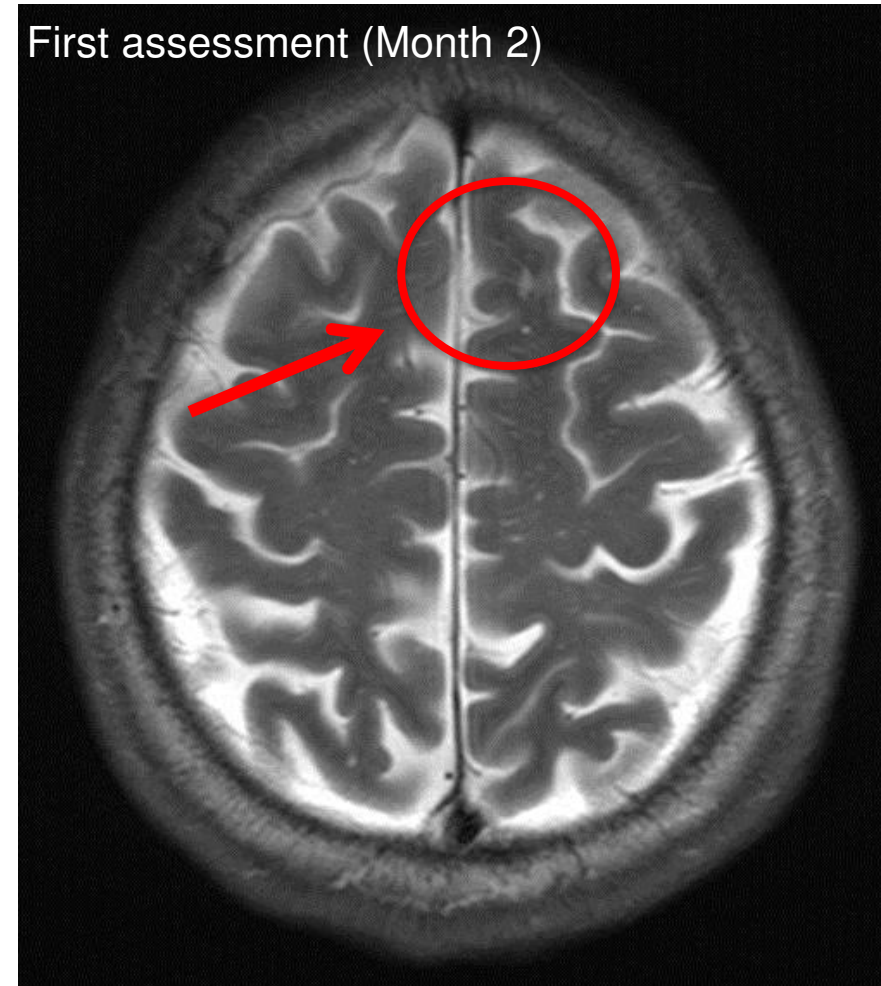
Baseline



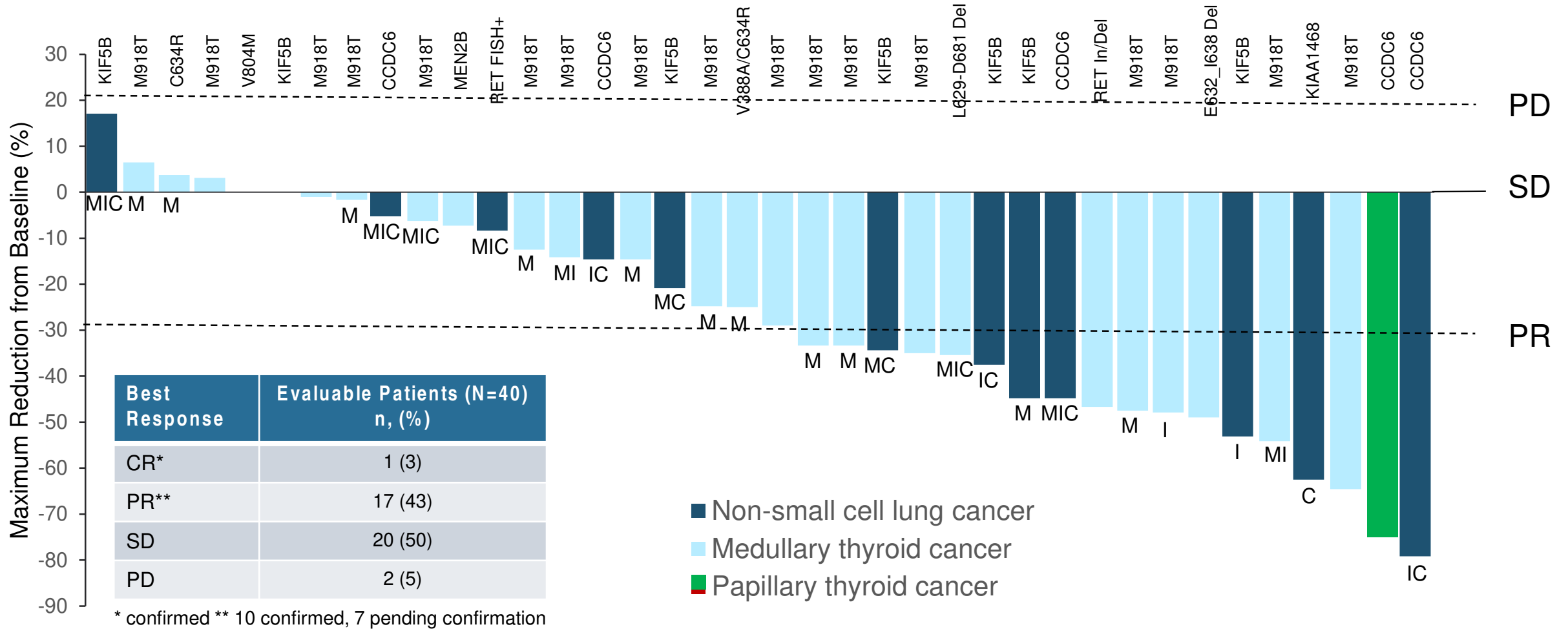
First Assessment (Month 2)



Activity against KIF5B-RET NSCLC brain metastases



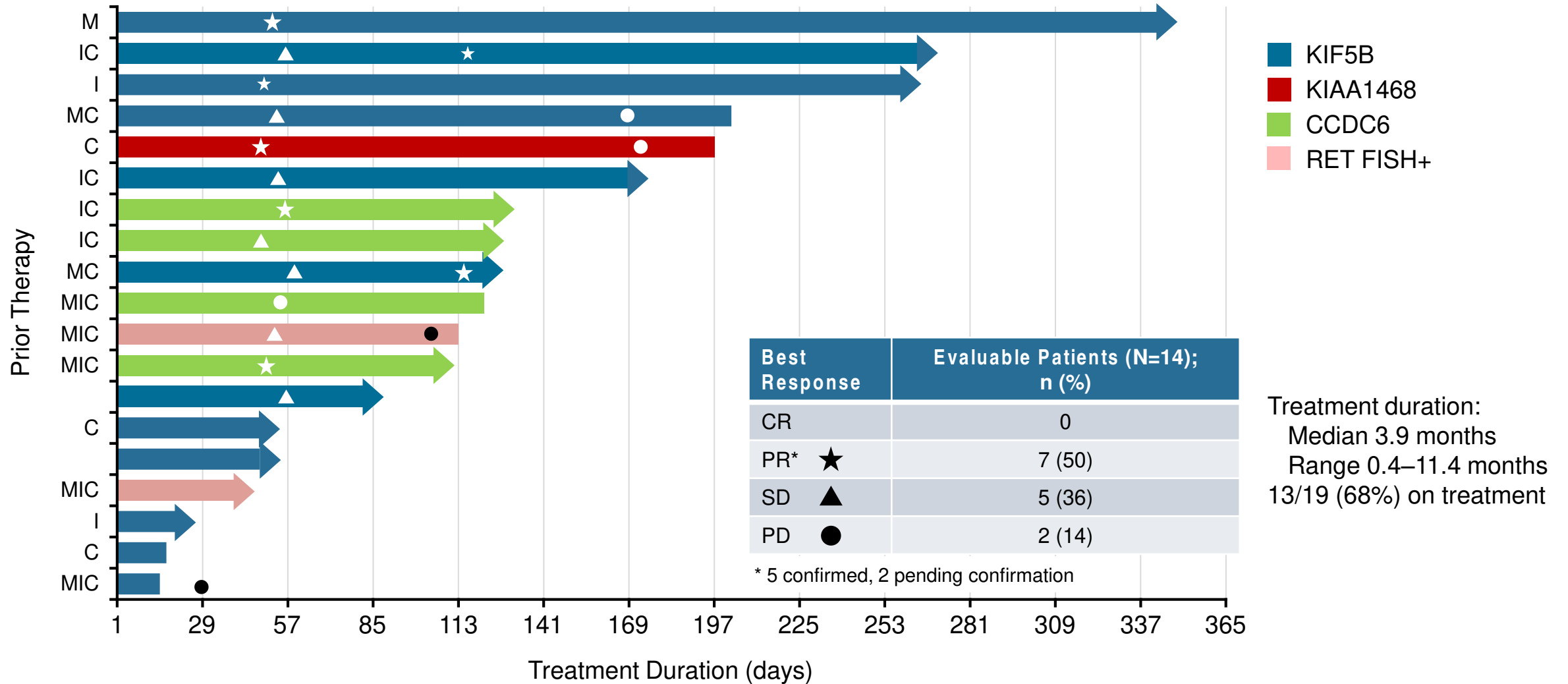
BLU-667 has broad anti-tumor activity against RET-altered cancers



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

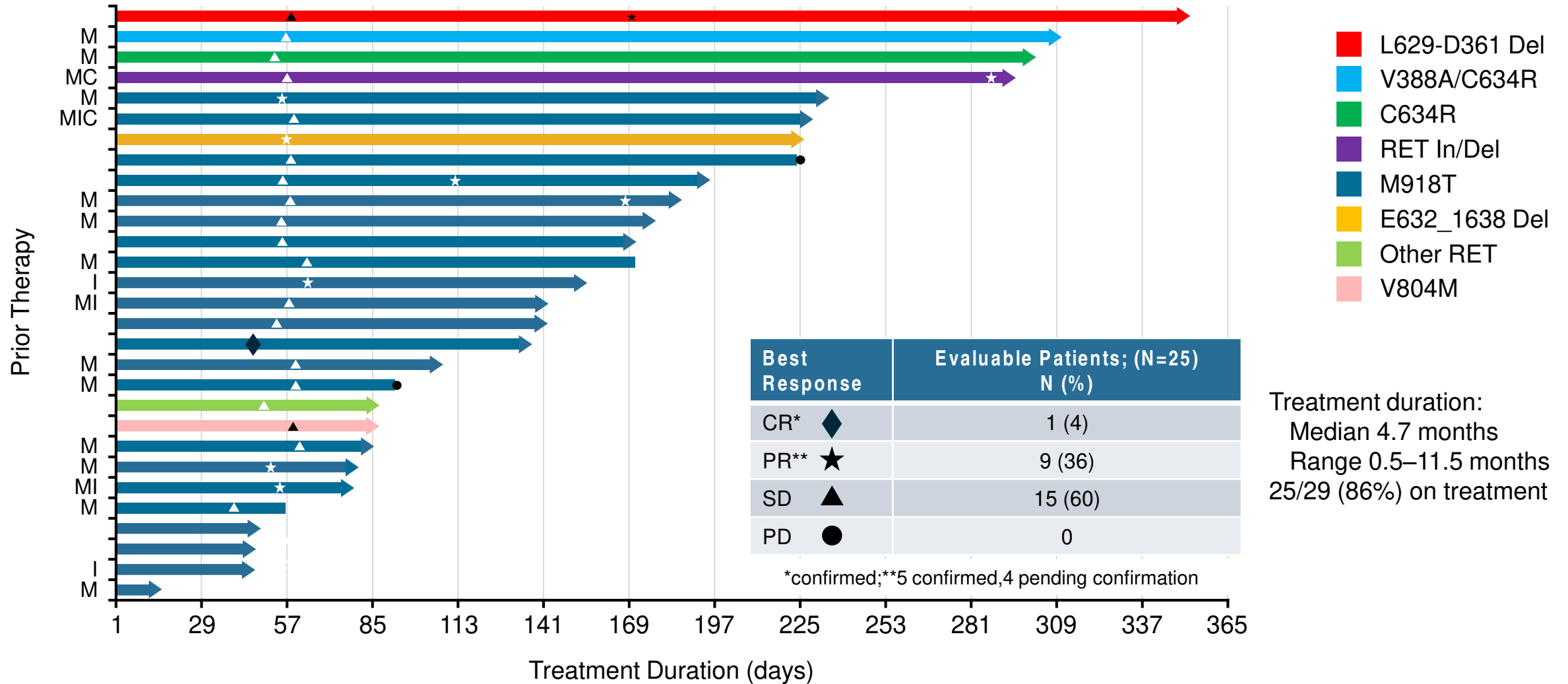
Data cut-off: April 6, 2018

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



Data cut-off: April 6, 2018

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



Data cut-off: April 6, 2018

BLU-667 is well tolerated

Treatment-emergent Adverse Events $\geq 10\%$ 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, alanine aminotransferase;
AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events

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

Acknowledgements

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 - Chao Family Comprehensive Cancer Center University of California Irvine Medical Center, United States
 - Abramson Cancer Center, University Of Pennsylvania, United States
 - Vall d'Hebron Institute of Oncology Vall d'Hebron University Hospital, Barcelona, Spain