The development of Potent and Selective RET inhibitors

Rami Rahal, PhD

Blueprint Medicines

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Rami Rahal

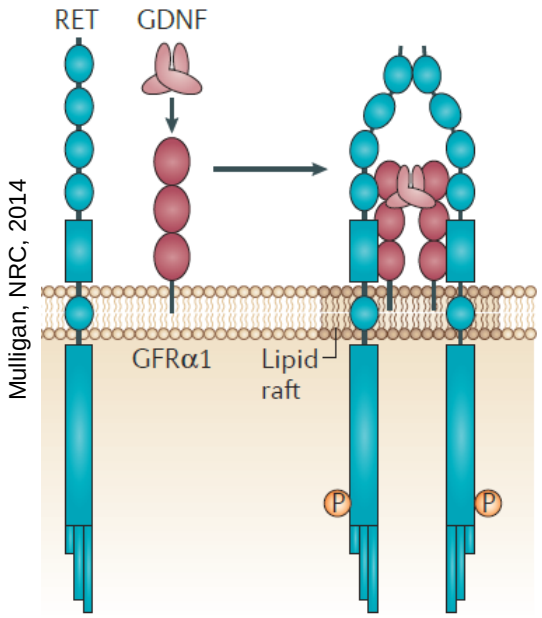
I have the following financial relationships to disclose:

Employee of Blueprint Medicines

-and-

I will not discuss off label use and/or investigational use in my presentation

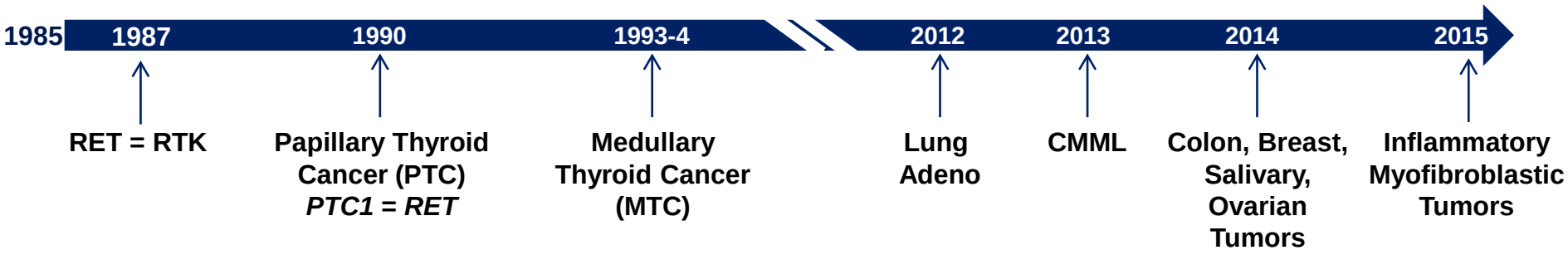
REarranged during Transfection (RET)



Mulligan, NRC, 2014

- Receptor tyrosine kinase that transduces signals from GDNF-family ligands
- **One of the first kinase fusions cloned from an epithelial tumor**

RET Kinase Deregulation in Cancer



Thyroid

Papillary	Follicular	**Medullary**	Anaplastic

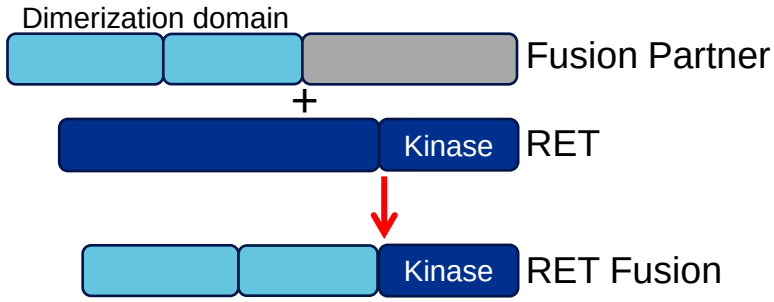
~10% *RET* fusions

RET activating mutations
Extracellular domain mutations
Gatekeeper mutations:
(V804L V804M)
Kinase domain mutations

~50% of MTC patients harbor oncogenic *RET* mutations

NSCLC

- **1-2% of lung adenocarcinomas harbor *RET* kinase fusions**



- Non-overlapping with known driver mutations (e.g. *EGFR*, *ALK* fusions)

Approved Multi-Kinase Inhibitors Targeting KDR Have Been Repurposed for *RET*-Driven Malignancies

- **Broad-kinome activity**
- **Dose limiting toxicities hamper ability to fully inhibit RET**

Compound	Target	KDR Biochem. IC_{50} (nM)	RET Biochem. IC_{50} (nM)	KDR-associated Adverse Events?
Cabozantinib	KDR/MET	1	7	**Yes**
Vandetanib	KDR/EGFR	2	5	**Yes**
Ponatinib	ABL/pan-RTK	2	1	**Yes**
Lenvatinib	KDR	4	2	**Yes**
Sorafenib	RAF/VEGF	21	6	**Yes**

Ideal RET Inhibitor Profile

1. **Potently inhibit RET wild-type fusions (NSCLC & other cancers)**
2. **Potently inhibit oncogenic RET mutants (thyroid cancer)**
3. **Spare KDR in a kinome-selective manner**
4. ***Prevent on-target resistance mutations***

Biochemical IC_{50} (nM)

	RET	KDR	KDR/RET ratio
BLU6864	**1.5**	**73**	**49x**
Ponatinib	2	1	2x
Cabozantinib	7	1	0.14x
Vandetanib	5	2	0.4x

- Greater than 100-fold selective over 95% of the kinome

***KIF5B-RET* Ba/F3 proliferation**

	IC_{50} (nM)
	WT
BLU6864	**167**
Ponatinib	12
Cabozantinib	603
Vandetanib	688

Screens for **resistance mutations** to multi-kinase inhibitors

↓

V804 and Y806 are resistance hotspots

- Similar activity on RET WT and resistance mutants

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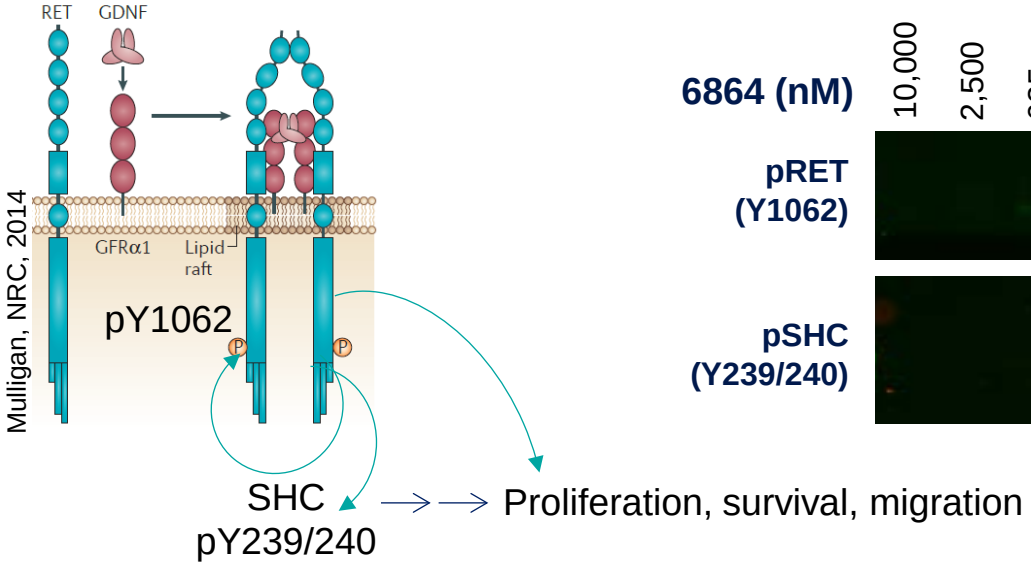
***KIF5B-RET* Ba/F3 proliferation**

	IC_{50} (nM)	Ratio (WT)		
	WT	V804 L	V804 M	V804 E
BLU6864	**167**	**1.2x**	**1.3x**	**1.0x**
Ponatinib	12	10x	32x	122x
Cabozantinib	603	4x	4x	18x
Vandetanib	688	14x	13x	13x

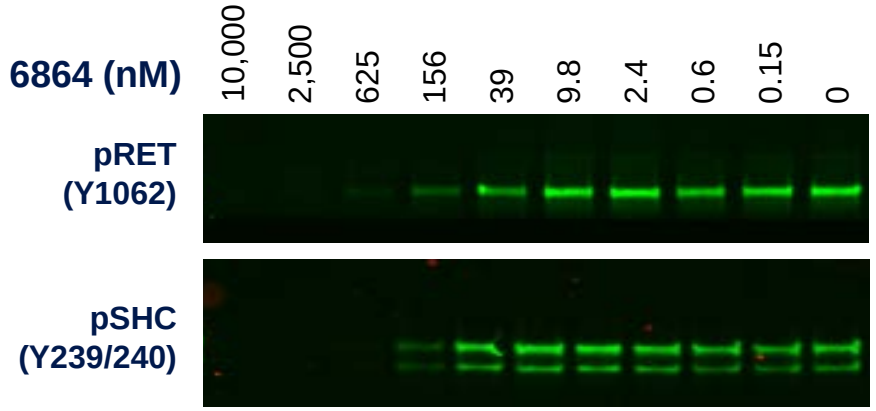
- Similar activity on RET WT and resistance mutants

BLU6864 Potently Inhibits pRET and Suppresses Proliferation of *RET*-Dependent Cancer Cells

Pharmacodynamic Markers



Ba/F3 *KIF5B-RET*

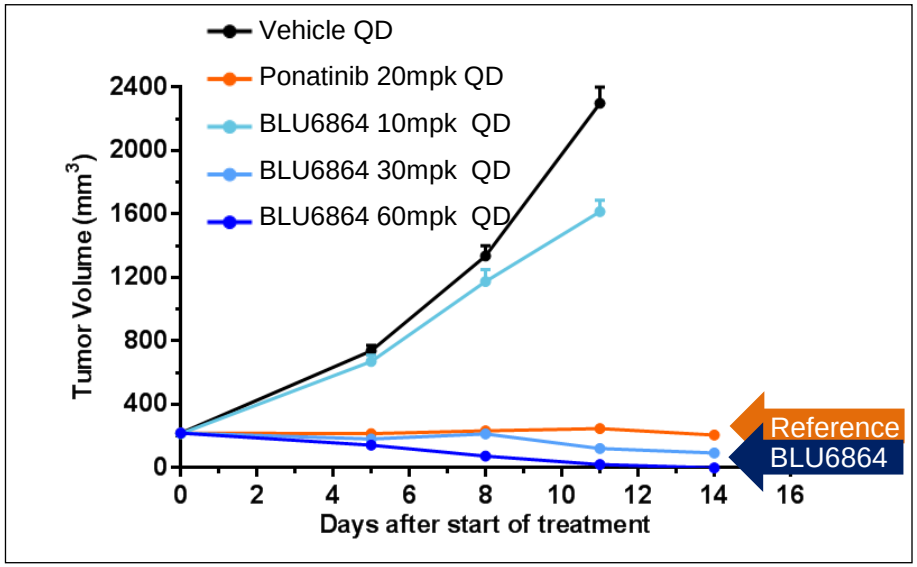


Proliferation IC_{50} (nM)

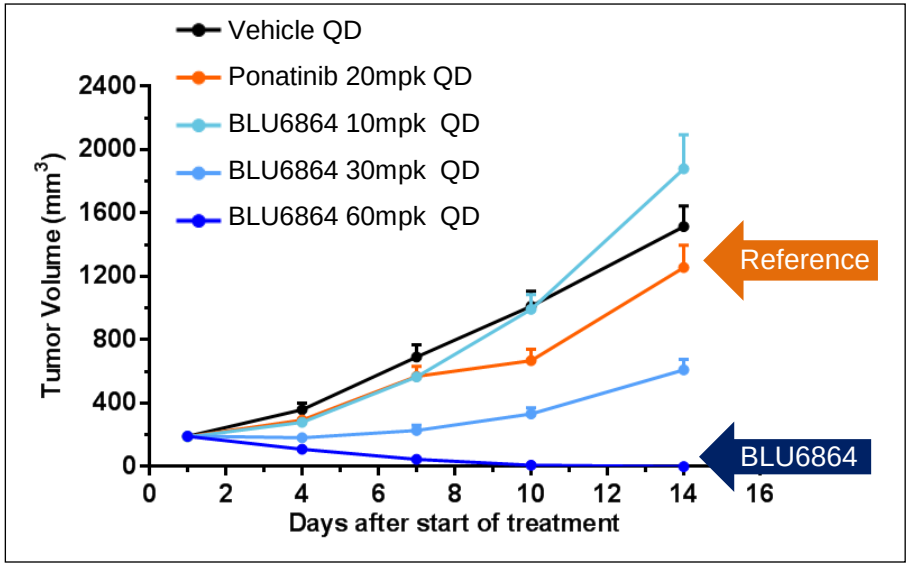
Compound	Ba/F3 KIF5B-RET	LC2/ad (CCDC6-RET)	TT (C634W RET)	MZ-CRC1 (M918T RET)	TPC-1 (CCDC6-RET)
	Fusion	Fusion	Mutant	Mutant	Fusion
BLU6864	167	517	285	138	76
Cabozantinib	603	365	315	97	150
		Lung	Thyroid		

Targeted RET Inhibitors Demonstrate Efficacy on *RET* Fusion WT and V804 Mutant Tumors

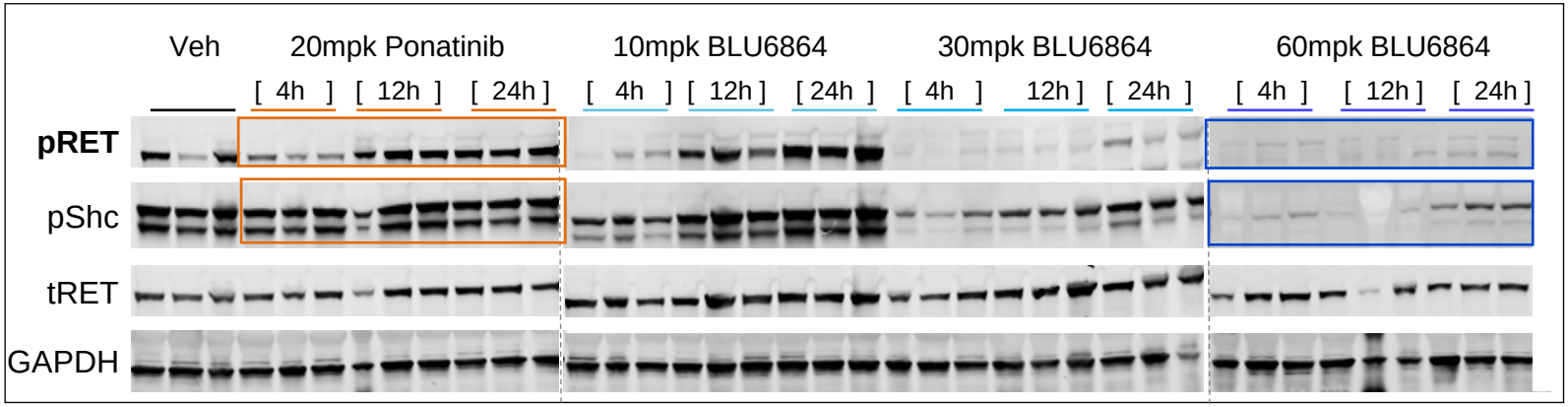
WT *KIF5B-RET* Fusion (Ba/F3)



V804L *KIF5B-RET* Fusion (Ba/F3)

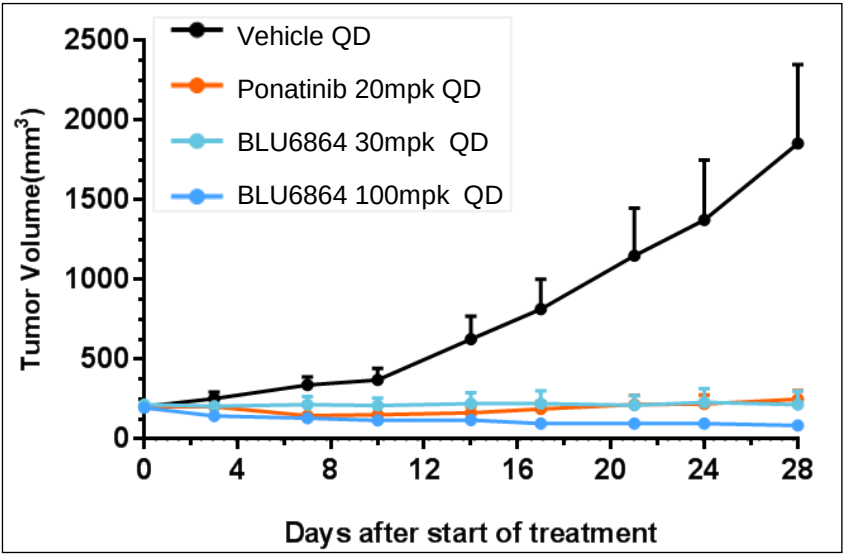


KIF5B-RET Fusion (V804L)

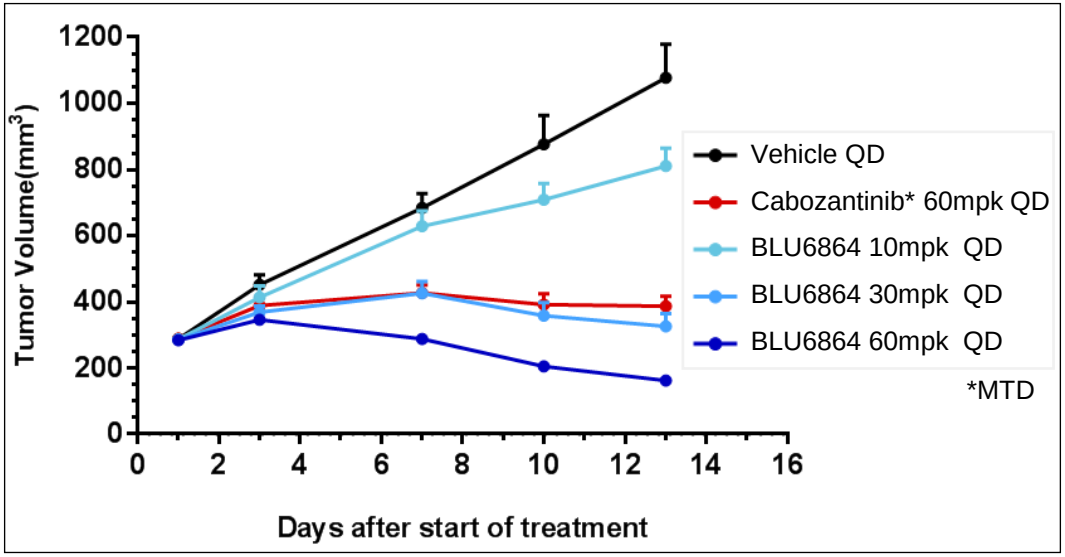


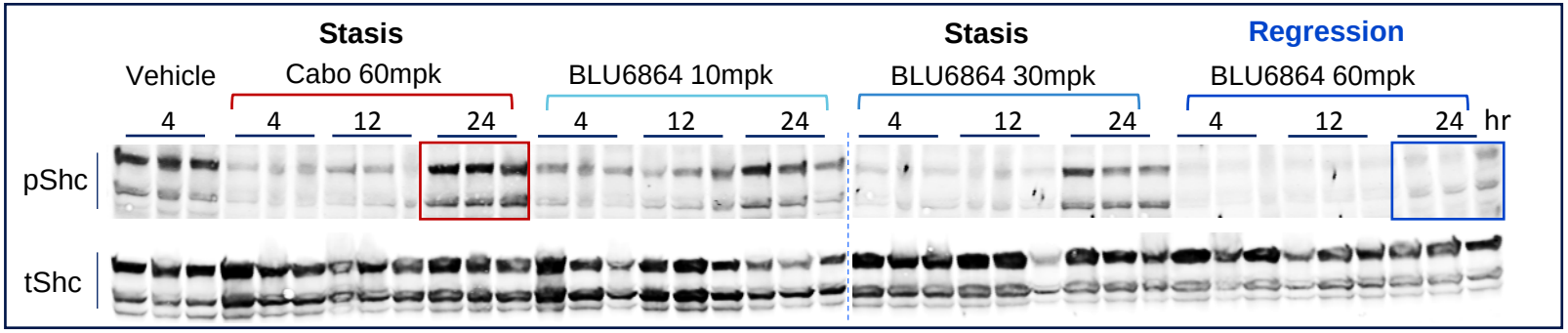
Targeted RET Inhibition Induces Regression in *RET*-Altered Lung and Thyroid Tumor In Vivo Models

Lung Adenocarcinoma PDX *KIF5B-RET* Fusion



Medullary Thyroid Cancer Xenograft Mutant (*RET C634W*)





BLU-667: Targeted RET Inhibitor Optimized for Progression to Clinical Studies

Biochemical IC_{50} (nM)

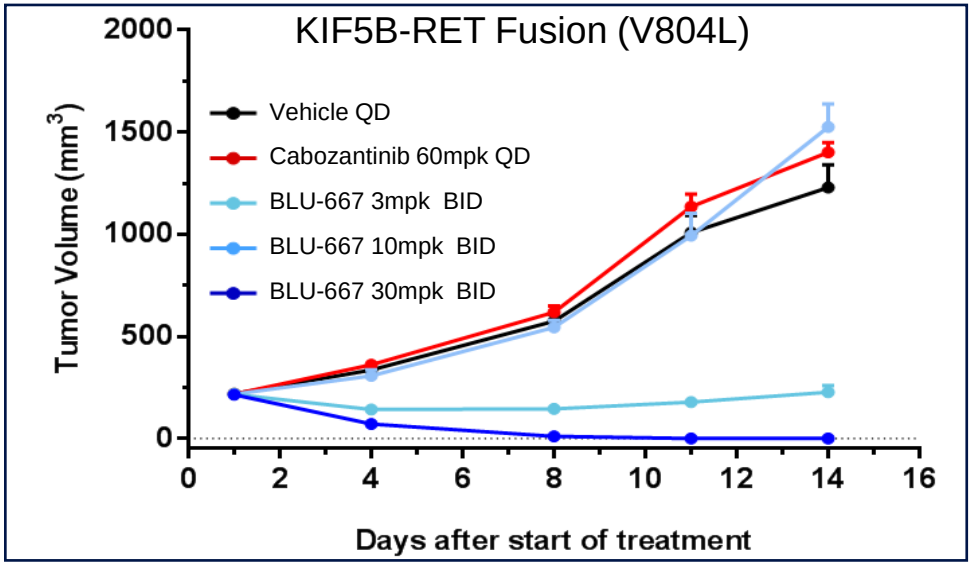
	RET	KDR	KDR/RET ratio
BLU-667	0.5	35	70x
BLU6864	**1.5**	**73**	**49x**
Ponatinib	2	1	2x
Cabozantinib	7	1	0.14x
Vandetanib	5	2	0.4x

***KIF5B-RET* Ba/F3 Proliferation IC_{50} (nM)**

	IC_{50} (nM)	Ratio (WT)	
	WT	V804L	V804E
BLU-667	16	0.9x	1.3x
BLU6864	167	1.2x	1.0x
Ponatinib	12	10x	122x
Cabozantinib	603	4x	18x
Vandetanib	688	14x	13x

Greater than 100-fold selective over 95% of the kinome

BLU-667 currently progressing through IND-enabling studies



Increasing Patient Benefit by Anticipating On-Target Resistance

- On-target resistance remains an issue for targeted therapies

Kinase	Tyrosine Kinase Inhibitor	Drug-Resistant Mutant
BCR-ABL	Imatinib, Dasatinib, Nilotinib	**T315I**
ALK	Crizotinib	L1152R, C1156Y, **V1196M**, G1202R, G1269A
EGFR	Gefitinib, Erlotinib, Osimertinib	**T790M**, C797S
KIT	Imatinib	V654A, **T670I**, N822K, D816V
NTRK	Entrectinib	G595R, G667C,

***Gatekeeper**

BLU-667 Prevents RET Resistance Mutants

Ba/F3 *KIF5B-RET* (WT) → **ENU** (mutagen) → **8x - 64x IC50** 2-3 weeks → **Cell Number** (ATP; Luminescence)

680	1800	2680	2360	2280	2120	1480	720	960	1640	1800	680
1760	4679160	11992160	9725240	9626840	10200080	8318560	1480	2200	8452360	5716120	1440
2080	7121520	2480	3320	10179720	3480	6182800	1800	9287960	2760	2952720	960
1280	4567960	2760	8036600	8070800	10838240	8459720	1360	840	1040	4059880	1240
640	1320	7138520	2802600	1800	4517240	7543360	800	400	1080	4987960	1120
1600	1160	7418120	8945640	1240	4070320	1200	720	880	960	5861160	1000
480	560	960	12560	6600	760	4335120	680	2552400	960	760	480
600	480	440	8520	680	480	680	520	840	480	600	280

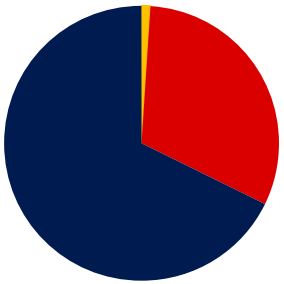
16x IC50 Cabozantinib

400	400	400	360	480	360	480	320	320	280	440	400
480	360	440	480	520	520	440	440	280	480	360	360
440	480	400	400	480	480	400	440	320	320	400	240
400	360	520	560	440	480	440	360	440	400	320	520
400	440	440	400	520	400	360	440	360	360	440	400
400	440	360	640	480	480	440	480	480	440	440	480
440	360	560	440	400	280	400	400	280	360	360	360
440	400	400	400	720	400	600	520	480	480	440	560

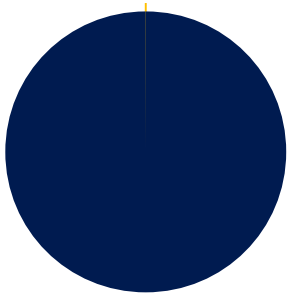
8x IC50 BLU-667

Luminescence

- <10k
- 10k- 100k
- 100k - 1000k
- >1000k



V804E
V804M
V804L
Y806C



BLU-667 allows more potent and selective RET inhibition and decreases the frequency of resistance

Conclusions

- BLU inhibitors
  - Potently inhibit RET wild-type fusions (NSCLC & other cancers)
  - Potently inhibit oncogenic RET mutants (thyroid cancer)
  - Spare KDR in a kinome-selective manner
  - Prevent on-target resistance mutations

- BLU compounds induce tumor regression and a similar dose-efficacy relationship in multiple in vivo models, including
  - Lung adenocarcinoma PDX driven by *KIF5B-RET* fusion
  - Medullary thyroid cancer xenograft models driven by *RET C634W* mutant
  - *KIF5B-RET* Ba/F3 allograft

BLU-667 has the potential to be a transformative medicine for patients with *RET*-driven malignancies

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