

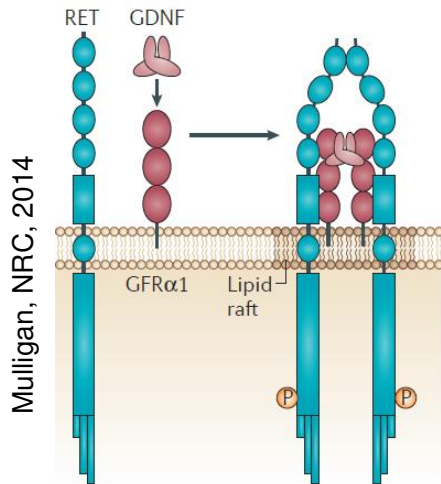


**BLU-667 is a potent and highly selective
RET inhibitor in development for
RET-driven thyroid cancers**

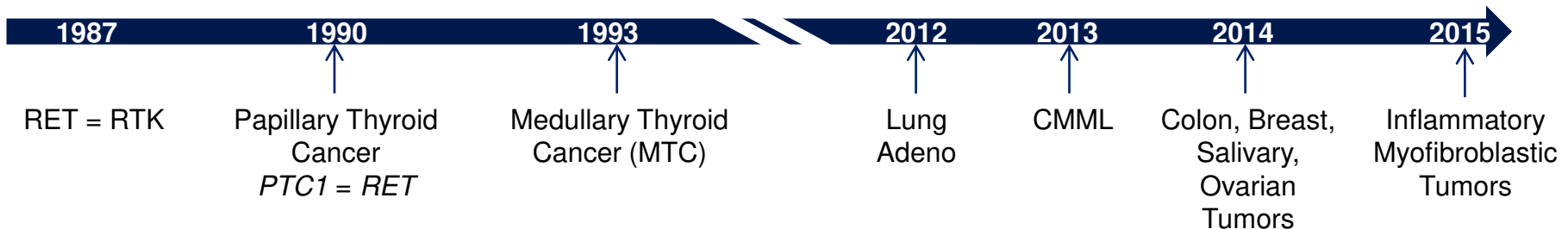
Rami Rahal, PhD
Blueprint Medicines
July 30, 2017

- Employee and shareholder of Blueprint Medicines
- BLU-667 is an investigational agent currently in development by Blueprint Medicines

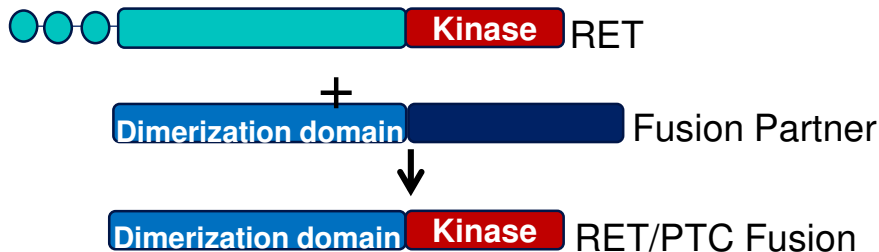
REarranged during Transfection (RET)



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



RET fusions



- ~10% of papillary thyroid cancer patients
- 1-2% of NSCLC patients
- <1% of patients with colon, ovary, breast, or hematological cancer

RET mutations



- ~60% of medullary thyroid cancer (MTC) patients harbor oncogenic *RET* mutations
- M918T is the most prevalent *RET* mutation

Kinase Inhibitors Approved for Treating MTC were Not Designed to Selectively Inhibit RET

- **Broad kinome activity with potent inhibition of VEGFR-2**
- **Off-target related dose limiting toxicities hamper ability to inhibit fully RET**

Compound (Trade Name)	Intended Target(s)	VEGFR-2 Biochem. IC ₅₀ (nM)	RET Biochem. IC ₅₀ (nM)	Serious adverse events	Overall Response Rate in MTC
Cabozantinib (Cometriq)	VEGFR-2 / MET	2	11	Perforations and fistulas; hemorrhage	27%
Vandetanib (Calpresa*)	VEGFR-2 / EGFR	4	4	QT prolongation; Torsades de pointes; sudden death	44%

*Only available through Calpresa REMS due to safety concerns

BLU-667: a Highly Potent and Selective RET Inhibitor

1. Potently inhibit RET wild-type fusions (PTC, NSCLC & other cancers)
2. Potently inhibit oncogenic RET mutants (MTC)
3. Spare VEGFR-2 in a kinome-selective manner
4. *Potently inhibit resistance mutations to existing multi-kinase inhibitors*

Biochemical IC₅₀ (nM)

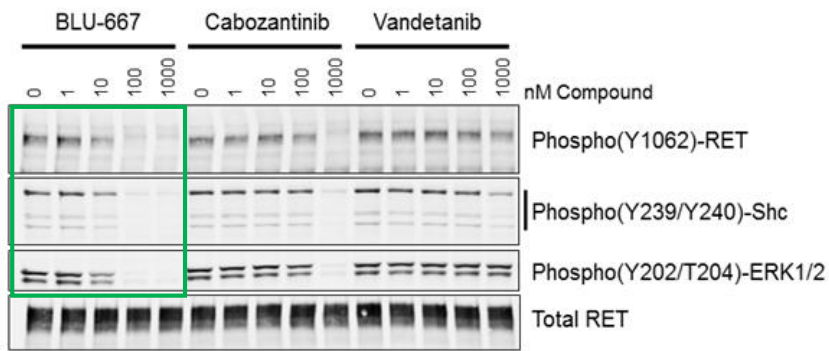
	RET	VEGFR-2	VEGFR-2 / RET ratio
BLU-667	0.4	35	88x
Cabozantinib	11	2	0.2x
Vandetanib	4	4	1x

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

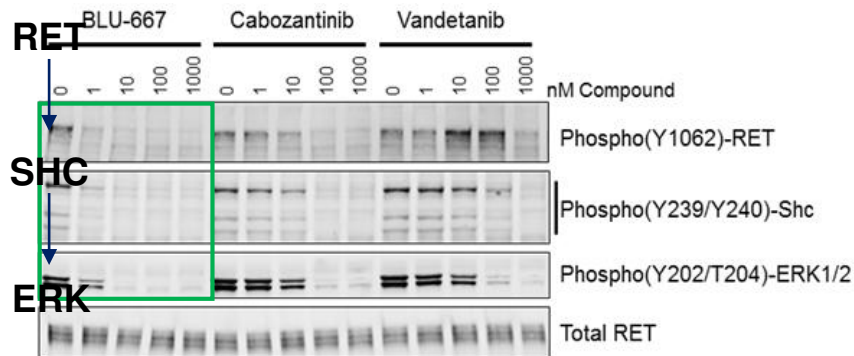
BLU-667 is currently being evaluated in a phase 1 trial for patients with MTC and other advanced solid tumors harboring oncogenic *RET* alterations

BLU-667 inhibits RET signaling and *RET*-driven proliferation of thyroid cancer cell lines

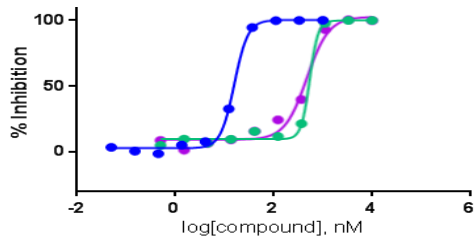
TT Cells *RET*(C634W)



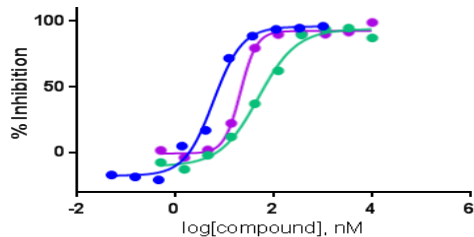
MZ-CRC-1 Cells *RET*(M918T)



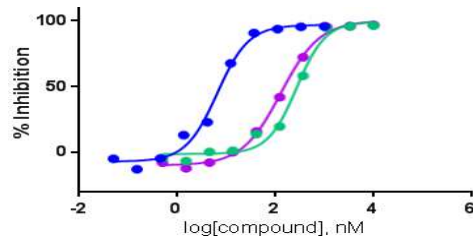
TT (MTC) *RET*(C634W)



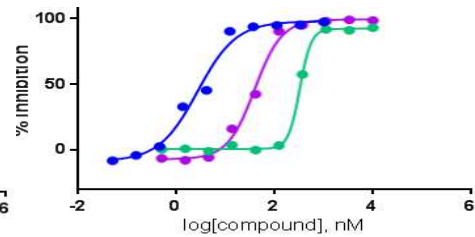
MZ-CRC-1 (MTC) *RET*(M918T)



TPC-1 (PTC) *CCDC6-RET*

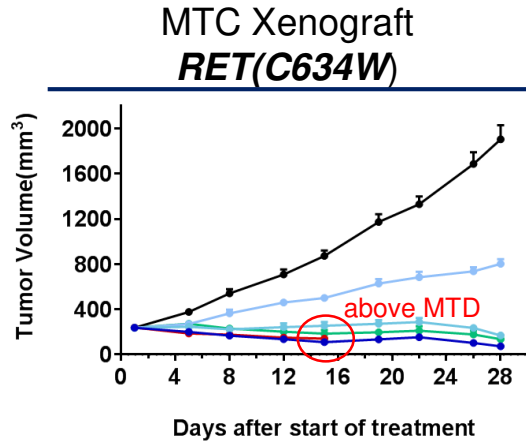


LC2/ad (NSCLC) *CCDC6-RET*

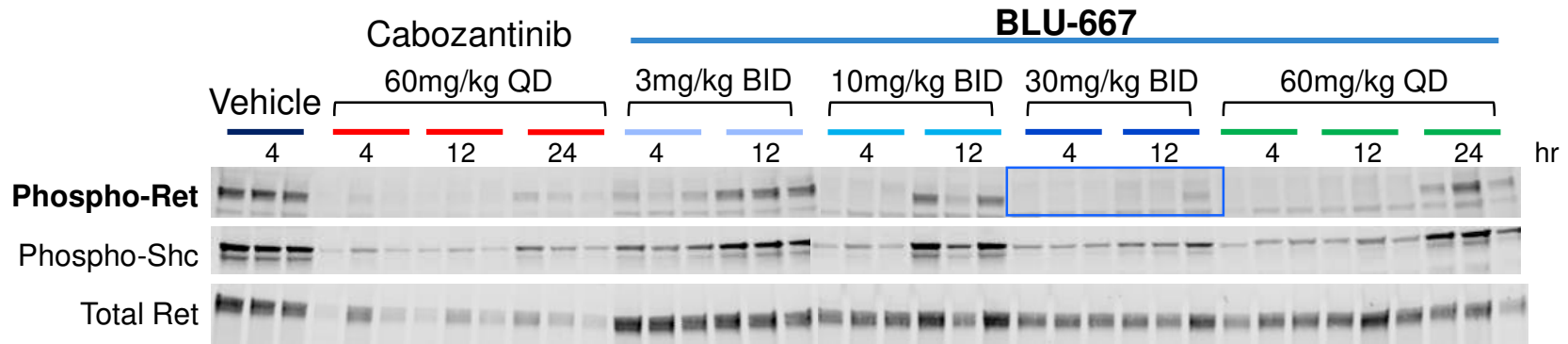
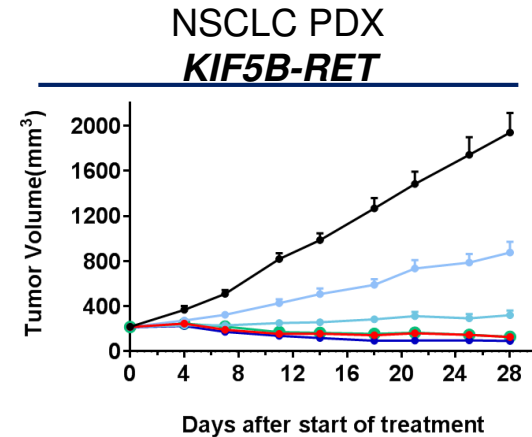


● BLU-667 ● Cabozantinib ● Vandetanib

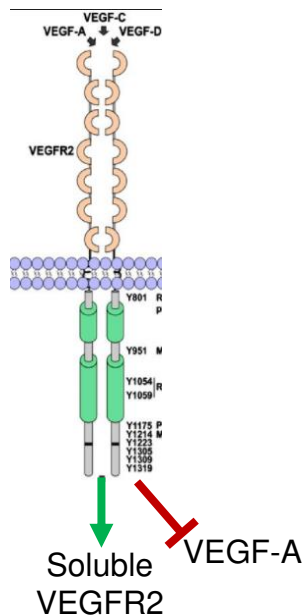
BLU-667 suppresses tumor growth and inhibits RET signaling in *RET*-altered thyroid and NSCLC tumors



Effects of BLU-667 and cabozantinib on VEGFR-2 in vivo?



***KIF5B-RET* NSCLC PDX tumor lysates**



Drug	VEGF-A	sVEGFR-2
Cabozantinib	↑	↓
Vandetanib	↑	↓
Sunitinib	↑	↓
Axitinib	↑	↓
Sorafenib	↑	↓
Telatinib	↑	↓
Brivanib	↑	↓
Motesanib	↑	↓
Cediranib	↑	↓

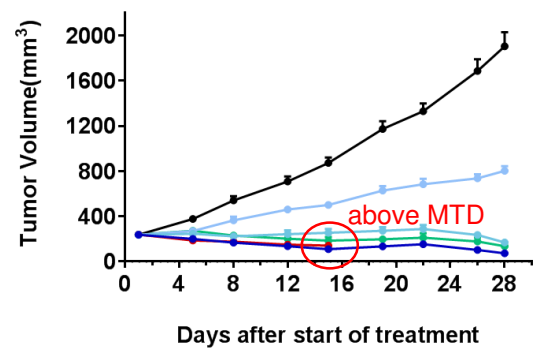
Class effect of VEGFR-2 inhibitors:

- **increased VEGF-A**
- **decreased sVEGFR-2**

Adapted from Ebos et al, PNAS (2007)
Murukesh et al, British Journal of Cancer (2010)
Tolaney et al, The Oncologist (2017)

BLU-667 suppresses tumor growth without significantly impacting VEGFR-2

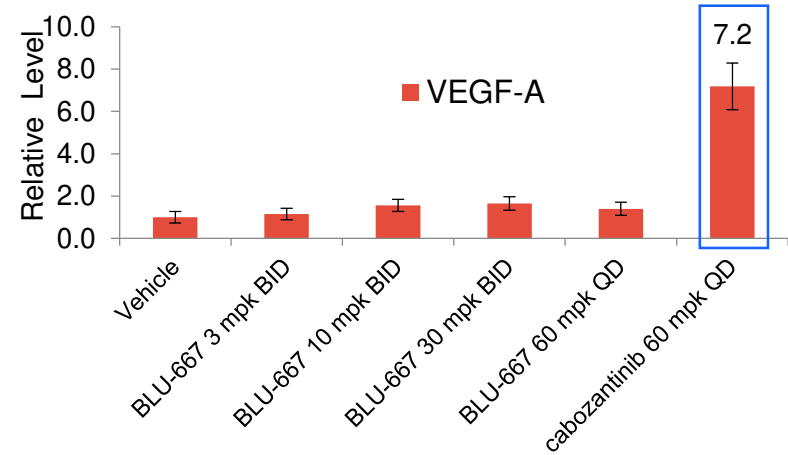
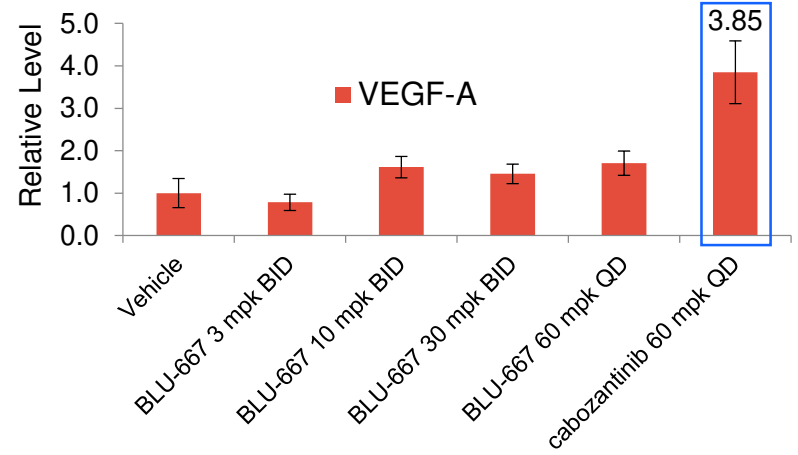
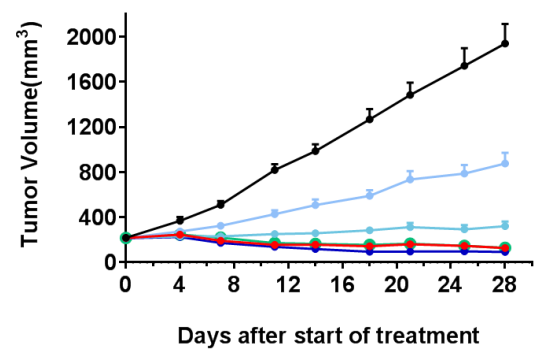
MTC Xenograft
RET(C634W)



Biomarkers of VEGFR-2 inhibition:

- increased VEGF-A
- decreased sVEGFR-2

NSCLC PDX
KIF5B-RET

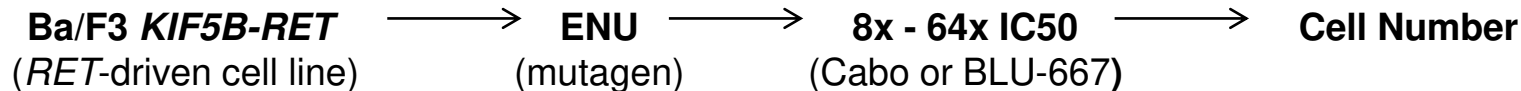


- On-target resistance remains an issue for targeted therapies

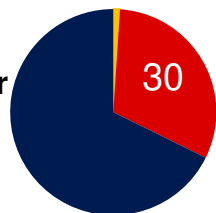
Kinase	Tyrosine Kinase Inhibitor	Drug-Resistant Mutant
BCR-ABL	Imatinib, Dasatinib, Nilotinib	T315I
ALK	Crizotinib	L1152R, C1156Y, V1196M , G1202R, G1269A
EGFR	Gefitinib, Erlotinib, Osimertinib	T790M , C797S
KIT	Imatinib	V654A, T670I , N822K, D816V
NTRK	Entrectinib	G595R, G667C,

***Gatekeeper**

BLU-667 Prevents RET Resistance Mutants in Preclinical Studies

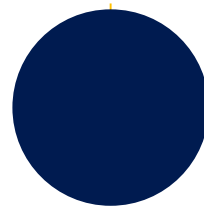


~30% wells harbor resistant clones



V804E
V804M
V804L
Y806C

No wells harbored resistant clones



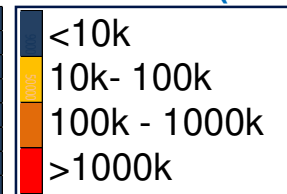
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1760	4679160	11992160	9725240	9626840	10200080	8318560	1480	2200	8452360	5716120	1440
2080	7121520	2480	3320	10179720	3480	6182800	1800	9287960	2760	2952720	960
1280	4567960	2760	8036600	8070800	10838240	8459720	1360	840	1040	4059880	1240
640	1320	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	480	600	520	480	440	440	560

8x IC50 BLU-667

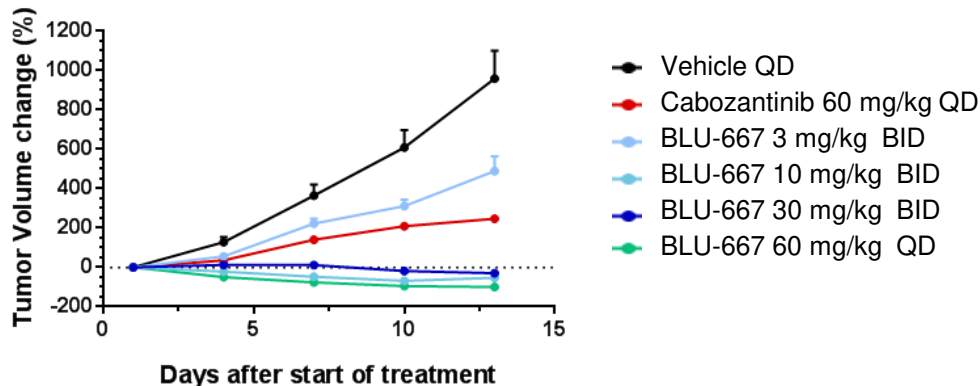
Cell Number (ATP)



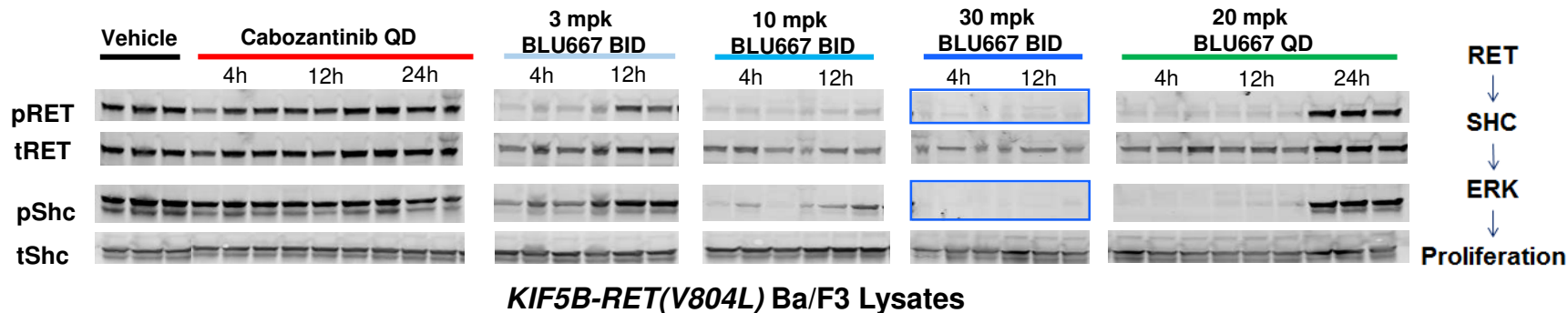
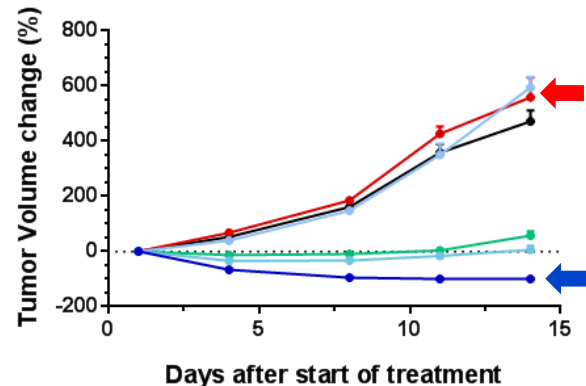
Selective and potent inhibition of RET with BLU-667 decreases the frequency of resistance

BLU-667 Induces Dose Dependent Regression and pRET Inhibition in *RET* V804L-Driven Allograft

KIF5B-RET Ba/F3



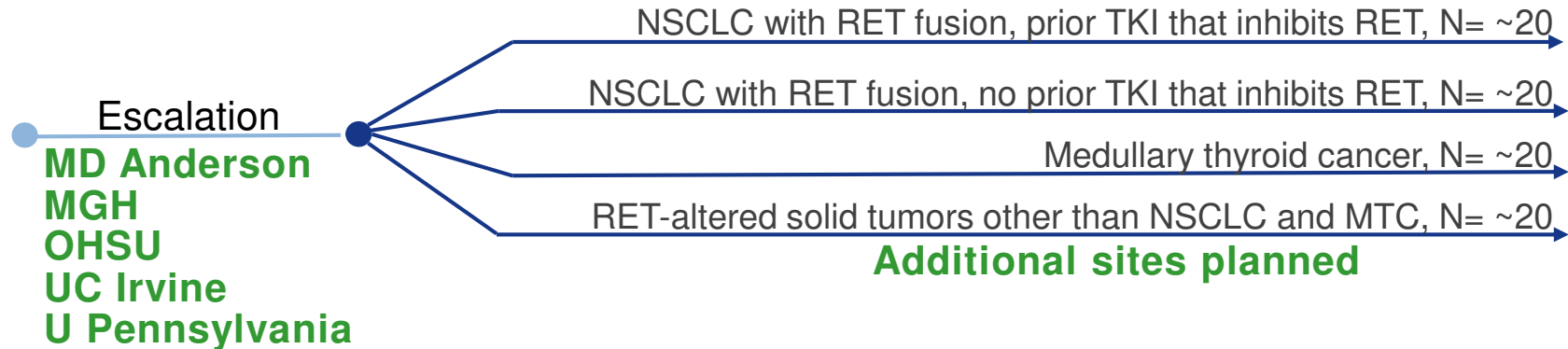
KIF5B-RET(V804L) Ba/F3



Phase 1 study initiated and first patient enrolled in March, 2017

Part 1: Dose escalation
Enrolling

Part 2: Dose expansion
Planned



KEY OBJECTIVES

- **Part 1:** MTD and RP2D, anti-tumor activity, pharmacokinetics, pharmacodynamics
- **Part 2:** Response rate, duration of response, *RET* gene status in plasma and tumor tissue

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

- In preclinical studies, BLU-667:
 - Potently inhibits RET wild-type fusions & oncogenic RET mutants
 - Spare VEGFR-2 in a kinome-selective manner
 - Prevents on-target resistance mutations
 - Induces robust tumor growth inhibition in multiple in vivo models of MTC and NSCLC
- BLU-667 is currently being evaluated in a phase 1 trial for patients with MTC, NSCLC and other advanced solid tumors harboring oncogenic *RET* alterations

RET project team members



- Terri Alvarez-Diez
- Jim Baker
- Andy Boral
- Natasja Brooijmans
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- Erica Evans
- Paul Fleming
- Tim Guzi
- Wei Hu
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- Tim LaBranche
- Debra Mazaik
- Patrick McNamara
- Michelle Maynard
- Stephen Miller
- Michael Nest
- Michael Palmer
- Rami Rahal
- Sherwin Sattarzadeh
- Hongliang Shi
- Grace Silva
- Teghi Singh
- Dawna Smith
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- Gordon Wilkie
- Doug Wilson
- Kevin Wilson
- Ben Wolf
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