

BLU-667 is a Potent and Highly Selective RET Inhibitor Being Developed for RET-Driven Cancers



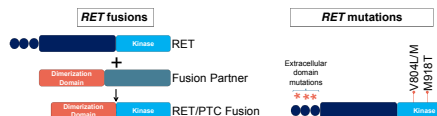
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Poster B151

RET Kinase is Oncogenic in Diverse Cancer Subtypes

Rearranged during transfection (RET) is a highly conserved receptor tyrosine kinase that transduces signaling from the GDNF-family of neurotrophic factors. Activating RET mutations are observed in sporadic medullary thyroid cancer (MTC) and multiple endocrine neoplasia type 2 (MEN2). In other tumor types, chromosomal translocations oncogenically activate RET by fusing the kinase domain to a dimerization domain of another gene, creating RET fusion proteins with constitutive kinase activity. Although RET kinase fusions were initially observed in papillary thyroid cancer (PTC), recent genomic analyses of diverse tumor types identified RET fusions in non-small cell lung cancer (NSCLC), colon, breast, ovary, salivary carcinomas, chronic myelomonocytic leukemia (CMML) and inflammatory myofibroblastic tumors (IMTs).



- 1-2% of NSCLC patients
- 10% of PTC patients
- <1% of patients with colon, ovary, breast, or hematological cancer
- 60% of MTC patients harbor oncogenic RET mutations
- M918T is the most prevalent RET mutation
- Germline V804L or V804M mutations are associated with familial MTC

Frequency of Oncogenic RET Alterations in Solid Tumors

Indication	RET Alteration	Frequency
NSCLC	Fusions	1-2%
MTC	Activating Mutations	60%
PTC	Fusions	10%
Colon, breast, other tumor types	Fusions	<1%

RET-Altered Cancer Patients Have High Medical Need

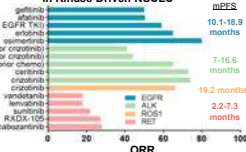
Multikinase inhibitors (mKIs) currently being tested in RET-altered NSCLC patients were not designed to selectively target RET and exhibit:

- Broad kinase activity, often with potent inhibition of VEGFR-2
- Off-target related dose limiting toxicities that hamper their ability to fully inhibit RET
- Dramatically lower ORR and duration of response in NSCLC compared to selective kinase inhibitors targeting other kinase drivers

mKIs Tested in RET-Altered NSCLC Patients

Multi-Kinase Inhibitor	Original Target(s)
Vandetanib	VEGFR-2 / EGFR
Lenvatinib	VEGFR1-2 / FGFR1-3 / PDGFRα / KIT
Sunitinib	VEGFR-2 / pan-RTK
RXDX-105	RAF / RET
Cabozantinib	VEGFR-2 / MET

ORR and mPFS for Kinase Inhibitors in Kinase Driven NSCLC



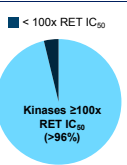
BLU-667 is Designed to Transform Treatment of RET-Altered Cancers

- Crafted to target oncogenic RET fusions and activating mutations
- Highly active against activating and resistance mutations at the gatekeeper (V804) residue
- Kinome selectivity allowing full in vivo RET inhibition at well tolerated doses

BLU-667 is a sub-nanomolar RET inhibitor with ~90 fold selectivity over VEGFR-2

Compound	Biochemical IC ₅₀ (nM)						IC ₅₀ Ratio (VEGFR-2 / RET)
	WT RET	V804L RET	V804M RET	M918T RET	CCDC6-RET	RET	
BLU-667	0.4	0.3	0.4	0.4	0.4	35	88x
Cabozantinib	11	45	162	8	34	2	0.2x
Vandetanib	4	3597	726	7	20	4	1x
RXDX-105	3	188	102	4	7	17	6x

Kinases Inhibited by BLU-667



BLU-667 selectivity was assessed in a biochemical screen of a broad panel of 371 kinases.

BLU-667 is a highly potent RET inhibitor that exhibits $\geq 100x$ selectivity for RET over 96% of kinases tested

BLU-667 is a Potent and Selective Inhibitor of Oncogenic RET Fusions and Mutations

BLU-667 Potently Inhibits RET Autophosphorylation

Compound	pRET IC ₅₀ (nM)	pRET/RET Ratio (vs. BLU-667)
BLU-667	5.0	1x
Cabozantinib	61.9	12x less potent
Vandetanib	833.1	167x less potent
RXDX-105	128.6	26x less potent

BLU-667 Inhibits KIF5B-RET Driven Proliferation and is Active on Gatekeeper (V804) Mutations

Compound	IC ₅₀ (nM)			
	WT	V804L	V804M	V804E
BLU-667	16.5	1.3x	0.3x	1.3x
Cabozantinib	341	9x	16x	36x
Vandetanib	793	12x	11x	11x
RXDX-105	195.8	21x	15x	28x

BLU-667 is More Potent than mKIs on RET Fusions Identified in NSCLC Patients

Cell Line	RET Alteration	Cancer Subtype	BLU-667 IC ₅₀ (nM)	Proliferation IC ₅₀ Relative to BLU-667
Ba/F3	KIF5B-RET	Engineered	16.5	21x
LC2/ad	CCDC6-RET	NSCLC	3.7	89x
				23x
				9x

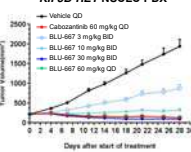
RET Signaling



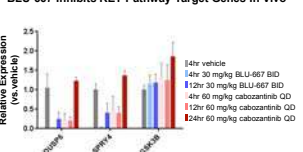
BLU-667 potently inhibited RET fusion-driven cell proliferation, including cell lines harboring a KIF5B-RET fusion, the most prevalent RET fusion identified in RET-rearranged NSCLC patients. Inhibition of cell proliferation was associated with potent downregulation of RET autophosphorylation and downstream signaling. Consistent with these observations, the transcriptional targets of the MAPK pathway DUSP6 and SPRY4 were downregulated by BLU-667 in a dose-dependent manner. Expression of GSK3B, a component of the parallel PI3K/AKT pathway, was not substantially impacted, confirming DUSP6 and SPRY4 as RET pathway biomarkers.

BLU-667 Robustly Suppresses Oncogenic KIF5B-RET Signaling and Tumor Growth Without Functionally Impacting VEGFR-2

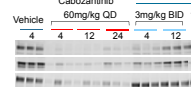
KIF5B-RET NSCLC PDX



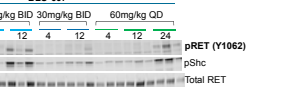
BLU-667 Inhibits RET Pathway Target Genes In Vivo



Cabozantinib 60mg/kg QD



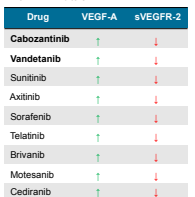
BLU-667



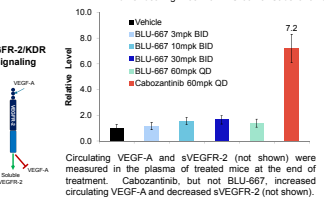
BLU-667 demonstrated dose dependent anti-tumor activity in a KIF5B-RET-driven NSCLC PDX. Modulation of KIF5B-RET activity in tumor lysates was confirmed by decreased pRET and pShc levels. DUSP6 and SPRY4 were also effectively downregulated by RET inhibition in vivo.

Active Doses of BLU-667 Do Not Functionally Impact VEGFR-2 In Vivo

Increased VEGF-A and decreased soluble VEGFR-2 (sVEGFR-2) are class effects of VEGFR-2 inhibitors:



Plasma VEGF-A Levels Following Treatment of KIF5B-RET Tumor-bearing Mice with BLU-667 or Cabozantinib



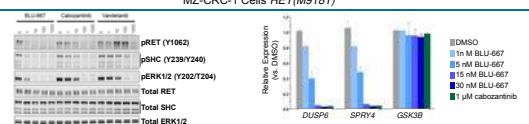
BLU-667, but not cabozantinib, inhibited tumor growth without biomarker evidence of VEGFR-2 inhibition

BLU-667 Inhibits RET Signaling and Cell Proliferation of Thyroid Cancer Cells with Activating RET Alterations

BLU-667 is More Potent than mKIs at Inhibiting RET-Driven Thyroid Cancer Cell Proliferation

Cell Line	RET Alteration	Cancer Subtype	IC ₅₀ (nM)	Proliferation IC ₅₀ Relative to BLU-667
TT	RET (G364W)	MTC	15.4	36x
MZ-CRC-1	RET (M918T)	MTC	4.2	15x
TPC-1	CCDC6-RET	PTC	10.9	31x
				19x
				22x

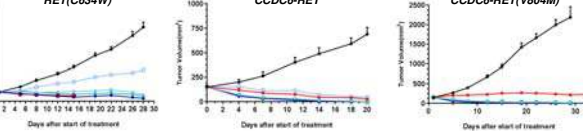
MZ-CRC-1 Cells RET (M918T)



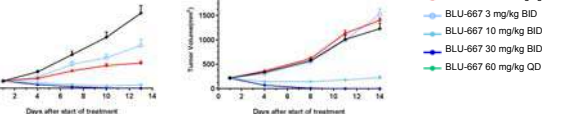
BLU-667 potently inhibited the proliferation of MTC and PTC cell lines harboring oncogenic RET alterations. Downregulation of RET pathway signaling was confirmed by examining pRET, pShc, and pERK1/2 levels. DUSP6 and SPRY4 were potently suppressed by BLU-667, confirming these as lineage independent biomarkers of oncogenic RET signaling.

BLU-667 Has Broad Anti-tumor Activity on Diverse RET-Driven Cancers Including Tumors Harboring Gatekeeper (GK) Mutations

MTC TT Cells RET (G364W), Colorectal Cancer (CRC) PDX MTC CCDC6-RET, and Ponatinib-resistant CRC PDX CCDC6-RET (V804M)



Ba/F3 KIF5B-RET, Cabozantinib-resistant Ba/F3 KIF5B-RET (V804L)



Oral administration of BLU-667 demonstrated dose dependent anti-tumor activity in RET-driven models including an MTC cell line xenograft driven by a RET (G364W) mutation, a CCDC6-RET fusion positive colorectal cancer PDX, as well as a GK mutant CCDC6-RET (V804M) model. BLU-667 was also active in Ba/F3 allograft models expressing either a KIF5B-RET fusion or a KIF5B-RET (V804L) GK mutant. Cabozantinib was administered at the MTD in mice (60 mg/kg QD) and showed antitumor activity similar to BLU-667 in models with a WT RET kinase domain, but not in models driven by GK mutant RET. Moreover, cabozantinib-treated animals suffered a rapid decline in health after 14 days of dosing in the TT and Ba/F3 in vivo studies. BLU-667 was well-tolerated in all models at all doses tested.

BLU-667 Phase 1 Study Initiated and First Patient Enrolled in March 2017

Part 1: Dose escalation Enrolling	Part 2: Dose expansion Planned
Escalation	NSCLC with RET fusion, prior TKI that inhibits RET
MD Anderson General Hospital OHSU UC Irvine U. Pennsylvania Duke	NSCLC with RET fusion, no prior TKI that inhibits RET
	Medullary thyroid cancer
	RET-altered solid tumors other than NSCLC and MTC
	GLOBAL EXPANSION ONGOING

NCT03037385 KEY OBJECTIVES: Identify MTD or RP2D and characterize initial anti-tumor activity

Conclusions

- BLU-667 potently and selectively inhibits oncogenic RET fusions and activating mutations in preclinical models:
 - Broad, robust, anti-tumor activity against multiple RET-driven solid tumor types
 - Highly active against V804 gatekeeper substitutions that are mKI resistant
 - Spares VEGFR-2 at doses that completely inhibit RET
 - DUSP6 and SPRY4 have been identified as robust PD biomarkers of RET activity
- BLU-667 has entered Phase 1 clinical testing in patients with RET-altered NSCLC, thyroid cancer and other solid tumors

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