



Published in final edited form as:

Cancer Discov. 2018 July ; 8(7): 797–799. doi:10.1158/2159-8290.CD-18-0489.

Stop fRETting the Target: Next-Generation RET Inhibitors Have Arrived

Wade T. Iams¹ and Christine M. Lovly²

¹Division of Hematology/Oncology, McGaw Medical Center of Northwestern University, Chicago, Illinois.

²Vanderbilt-Ingram Cancer Center, Nashville, Tennessee.

Summary

BLU-667 is a next-generation RET inhibitor that maximizes on-target and minimizes off-target effects. It is an exemplar of genotype-driven drug development followed by multi-histology basket trial validation that is becoming a paradigm for precision oncology. *Cancer Discov*; 8(7); 797–9. ©2018 AACR.

The identification and successful pharmacologic inhibition of oncogenic, constitutively active cellular kinases has been life-changing for many patients with cancer. Oncogenic kinase alterations occur in multiple ways, including point mutations, insertions/deletions, amplifications, and chromosomal rearrangements. Examples include point mutations in receptor tyrosine kinases (RTK) such as the EGFR point mutations in intracellular kinases such as BRAF, amplifications in RTKs such as HER2, and chromosomal rearrangements in RTKs such as BCR-ABL, anaplastic lymphoma kinase (ALK), and ROS1.

In patients with non-small cell lung cancer (NSCLC), the step-wise refinement of drug development against the oncogenic kinases EGFR and ALK has demonstrated notable clinical benefits. For example, the recently reported FLAURA trial revealed that first-line therapy with the third-generation, mutant-selective EGFR tyrosine kinase inhibitor (TKI) osimertinib more than doubles progression-free survival (PFS) compared with earlier-generation EGFR inhibitors in patients with advanced treatment-naïve *EGFR*-mutant NSCLC (1). Similarly, the ALEX trial demonstrated that first-line therapy with the “second-generation” ALK inhibitor alectinib more than doubled PFS compared with treatment with the “first-generation” ALK inhibitor crizotinib (25 months vs. 10 months, respectively; ref. 2). Similar drug development paradigms are under way for other targets, including ROS1, NTRK1/2/3, and RET. In this issue of *Cancer Discovery*, Subbiah and colleagues describe the development of a “next-generation” RET inhibitor, BLU-667, that is entering the

Corresponding Author: Christine M. Lovly, Vanderbilt-Ingram Cancer Center, 2220 Pierce Avenue South, 777 PRB, Nashville, TN 37232. Phone: 615-936-3457; Fax: 615-343-2973; christine.lovly@vanderbilt.edu.

Disclosure of Potential Conflicts of Interest

C.M. Lovly reports receiving commercial research support from Novartis, Xcovery, and AstraZeneca and is a consultant/advisory board member for Cepheid, Foundation Medicine, Takeda, Pfizer, Ariad, AstraZeneca, Novartis, Clovis, and Genoptix. No potential conflicts of interest were disclosed by the other author.

analogous field of increasing the specificity of target kinase inhibition in patients with *RET*-driven malignancies (3).

The *RET* gene encodes for an oncogenic RTK found in a variety of cancers (4). Constitutive activation of RET can occur through point mutations, either in the extracellular domain or in the kinase domain, or through chromosomal rearrangements. In patients with medullary thyroid cancer (MTC), *RET* is characteristically altered by activating point mutations, whereas in patients with NSCLC and papillary thyroid cancer (PTC), *RET* is characteristically altered through chromosomal rearrangements (Fig. 1). Pharmacologic inhibition of RET is currently achieved with multikinase inhibitors (MKI), such as vandetanib and cabozantinib, in patients with *RET*-driven MTC, PTC, and NSCLC.

Subbiah and colleagues describe the strategic development and initial clinical deployment of a novel, next-generation *RET*-selective inhibitor, BLU-667 (3). Starting with a chemical library screen encompassing >10,000 kinase inhibitors of >60 different chemical scaffolds, the lead compound, BLU-667, was selected to maximize on-target efficacy against wild-type and oncogenic RET while maintaining selectivity toward the target. In subsequent studies in NSCLC and MTC cell lines, BLU-667 exhibited superior potency *in vitro* against various oncogenic *RET* alterations compared with the MKIs vandetanib, cabozantinib, and RXDX-105. The authors focused their *in vitro* toxicity evaluation on inhibition of VEGFR2, as excess VEGFR2 inhibition can result in hypertension, thrombosis, and hemorrhage. BLU-667 achieved greater selectivity for RET over VEGFR2 compared with vandetanib, cabozantinib, and RXDX-105.

Following their *in vitro* drug potency analyses, the authors show that BLU-667 inhibits MAPK signaling better than vandetanib, cabozantinib, and RXDX-105 in both murine and human cell line models of *RET*-driven cancer mediated by both chromosomal rearrangements and point mutations, including the common MKI *RET* resistance mutations V804L and V804M. The authors proceed to quantify the *in vivo* antitumor efficacy of BLU-667 in allografts and patient-derived xenografts (PDX) of *RET*-driven cancer mediated by both chromosomal rearrangements and point mutations, again including the common MKI *RET* resistance mutation V804L and one PDX from a patient with *CCDC6-RET*-positive colorectal cancer. The authors trace the antitumor effects to on-target MAPK pathway inhibition in on-treatment tumor lysates in the PDX model of *KIF5B-RET* fusion NSCLC. To evaluate off-target effects, in the *KIF5B-RET* fusion NSCLC PDX model the authors demonstrate that BLU-667 has significantly less anti-VEGFR2 effect than cabozantinib.

Building on their preclinical studies, the authors describe a phase I “basket” trial (NCT03037385) treating patients with advanced, unresectable *RET*-altered tumors with BLU-667. The authors describe antitumor responses in 4 patients, including a 47% tumor reduction after 11 months in a patient with TKI-naïve MTC, a 47% tumor reduction after 8 months in a patient with MTC who had progressed after vandetanib, a >30% tumor reduction after 16 weeks in a patient with TKI-naïve *KIF5B-RET* fusion NSCLC, and a 34% tumor reduction after 16 weeks in a patient with *KIF5B-RET* fusion NSCLC who had progressed on vandetanib and everolimus. These patients experienced grade 1 toxicities,

including nausea, leukopenia, hyperphosphatemia, constipation, dry skin, and rash. In one of the patients with MTC, RET pathway inhibition was demonstrated by decreased *DUSP6* and *SPRY4* mRNA expression in on-treatment tumor biopsies after 28 days of therapy. We await publication of the full clinical data for a complete efficacy and toxicity evaluation.

This addition to the arsenal for managing *RET*-altered cancers is noteworthy in several regards. First, the authors describe a compelling story of tailored drug development for an area of need, *RET*-driven malignancies, with detailed preclinical analysis supporting the compound's development. Second, the authors document initial clinical activity in patients with *RET*-driven tumors across histology (MTC, NSCLC) and different types of *RET* alterations (activating point mutations, rearrangements). Third and most notably, the strategic design of this drug, focusing on minimizing VEGFR2 "off-target" inhibition, is anticipated to decrease the frequency and severity of vascular toxicities (hypertension, thrombosis, hemorrhage) which have been particularly problematic with the MKIs that target both RET and VEGFR2. For example, in one study with vandetanib, grade 3 or higher hypertension affected over half of patients (5). However, it is crucial that this is validated in a larger dataset, because only 4 patients are reported in this article.

These findings also raise interesting questions for ongoing and future studies. First, as "next-generation" RET inhibitors are developed, what is the optimal sequence of RET TKI therapy? In addition to BLU-667, other, more selective inhibitors are being developed, including LOXO-292 (NCT03157128). Will response rates and resistance mechanisms change based on the line of therapy in which a specific RET TKI is received? Will there be a role for earlier-generation MKIs, which target RET and possibly other kinases that allow therapeutic escape?

Second, will the efficacy of BLU-667 and other "next-generation" RET inhibitors cross all histologies of *RET*-altered tumors? The more common *RET*-altered tumors were studied here, including MTC and NSCLC; however, *RET* alterations are found at low frequency across a broad variety of tumor types (Fig. 1). As oncologic care is rapidly integrating site-agnostic therapies, such as the recent FDA approval of pembrolizumab in microsatellite-unstable tumors (6) and breakthrough therapy designation for entrectinib in patients with *NTRK-rearranged* malignancies (7), it is still critical to consider tumor site of origin. We make particular note of *BRAF*^{V600E} mutations, which are also found across a variety of tumor types. *BRAF*^{V600E} inhibitors, such as vemurafenib and dabrafenib, achieve high response rates in *BRAF*-mutant melanoma (8). In contrast, similar responses are not observed in *BRAF*-mutant colorectal cancer, where upstream EGFR can provide primary resistance to *BRAF* inhibitors (9). Time will tell whether tissue site of origin will be critical in mediating the efficacy of RET inhibitors.

Third, will all genomic *RET* alterations be equally inhibited by BLU-667 and other "next-generation" RET inhibitors? When the clinical context of a target includes multiple genomic alteration types, such as chromosomal rearrangements and point mutations, it is critical to prove drug efficacy in preclinical development in all scenarios before proceeding to broad human testing. Although differences in drug efficacy based on different mutations have been demonstrated in patients with *EGFR*-mutant NSCLC, differences in drug efficacy based on

chromosomal rearrangement fusion partners remain inadequately understood, as demonstrated by the remaining controversy in patients with *ALK*-rearranged NSCLC (10). The initial studies presented herein suggest that BLU-667 retains broad sensitivity against both *RET* mutations and *RET* fusions; however, more nuanced differences regarding degrees of sensitivity across different alterations within this target remain to be defined. It is also likely that mechanisms of acquired resistance to BLU-667 will differ based on the genomic and potentially histologic context.

In conclusion, next-generation TKIs applied in patients with *EGFR*- and *ALK*-driven NSCLC have shown impressive improvements in efficacy and acceptable toxicity profiles compared with earlier-generation inhibitors. We remain optimistic that a similar paradigm will play out for next-generation *RET* inhibitors such as BLU-667 in patients with *RET*-driven cancers.

Acknowledgments

C.M. Lovly was supported by a Damon Runyon Clinical Investigator Award, a LUNgevity Career Development Award, a V Foundation Scholar-in-Training Award, an AACR-Genentech Career Development Award, a LCFA/IASLC Lori Monroe Scholarship, and by the NIH and NCI R01CA121210, U10CA180864, P01CA129243, and P30CA068485.

References

1. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113–25. [PubMed: 29151359]
2. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017;377:829–38. [PubMed: 28586279]
3. Subbiah V, Gainor JF, Rahal R, Brubaker JD, Kim JL, Maynard M, et al. Precision targeted therapy with BLU-667 for *RET*-driven cancers. *Cancer Discov* 2018;8:836–49. [PubMed: 29657135]
4. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. *RET* aberrations in diverse cancers: next-generation sequencing of 4,871 patients. *Clin Cancer Res* 2017;23:1988–97. [PubMed: 27683183]
5. Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H, et al. Vandetanib in patients with previously treated *RET*-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir Med* 2017;5:42–50. [PubMed: 27825616]
6. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–13. [PubMed: 28596308]
7. Drlon A, Siena S, Ou SI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov* 2017;7:400–9. [PubMed: 28183697]
8. Zhu Z, Liu W, Gotlieb V. The rapidly evolving therapies for advanced melanoma - towards immunotherapy, molecular targeted therapy, and beyond. *Crit Rev Oncol Hematol* 2016;99:91–9. [PubMed: 26708040]
9. Corcoran RB, Andre T, Atreya CE, Schellens JHM, Yoshino T, Bendell JC, et al. Combined BRAF, EGFR, and MEK inhibition in patients with BRAF(V600E)-mutant colorectal cancer. *Cancer Discov* 2018;8:428–43. [PubMed: 29431699]
10. Lin JJ, Shaw AT. Differential sensitivity to crizotinib: Does EML4-ALK fusion variant matter? *J Clin Oncol* 2016;34:3363–5. [PubMed: 27458283]

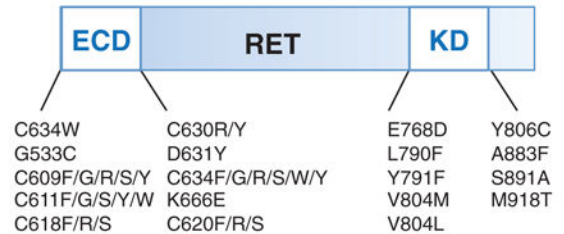
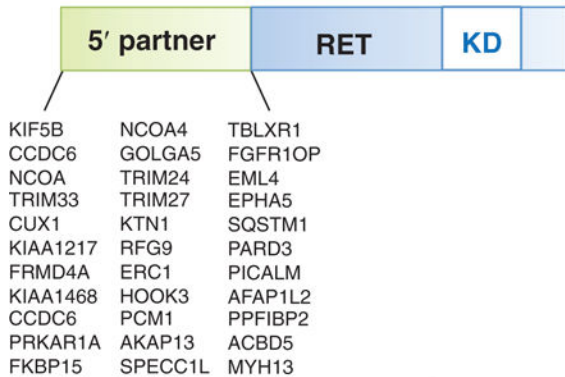
RET-driven cancers

RET fusions

NSCLC (~1%–2%)⁴
 PTC (~10%)⁴
 Pancreatic cancer (<1%)³

RET mutations

MTC (>60%)⁴
 Breast cancer (<1%)³
 Endometrial cancer (<1%)³
 Merkel cell carcinoma (<1%)³
 Colorectal cancer (<1%)³
 Sarcoma (<1%)³
 Melanoma (<1%)³
 Gastric cancer (<1%)³



RET inhibitors

<u>MKIs that target RET</u>		<u>"Next-generation"</u> <u>RET inhibitors</u>
Vandetanib	Alectinib	BLU-667
Cabozantinib	Ponatinib	LOXO-292
RXDX-105	Regorafenib	
Lenvatinib	Nintedanib	
Sorafenib	Apatinib	
Sunitinib	Motesanib	
Dovitinib		

Figure 1. *RET* alterations by histology and mutation type with current *RET* Inhibitors. *RET*-driven cancers tend to harbor either chromosomal rearrangements or point mutations in the *RET* extracellular domain or tyrosine kinase domain. A variety of multikinase inhibitors have been applied in patients with *RET*-driven cancer; however, BLU-667 and LOXO-292 are two next-generation *RET* inhibitors now being broadly applied to patients whose tumors harbor these oncogenic *RET* alterations.