



A new promising quinazoline-derived Pan-KIT mutant inhibitor for the gastrointestinal stromal tumors (GIST) management

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors commonly located in stomach (60%) and small intestine (25%), but they can also be found in other parts of the gastrointestinal tract (1). GISTs are characterized by hotspot mutations in *KIT* and *PDGFRA* oncogenes. These oncogenes codify type III receptor tyrosine kinase which, after binding to the ligand [stem cell factor (SCF) and platelet-derived growth factor (PDGF), respectively], results in receptor homodimerization and kinase activation (2,3). The presence of activating mutations of *KIT* and *PDGFRA* causes ligand-independent kinase and downstream signaling pathways activation, including MAPK, PI3k/AKT, and STAT3 pathways (1,4).

Approximately 80% of GISTs harbor *KIT* mutations, including in-frame deletions, insertions, substitutions, or combinations thereof (1,2). Most mutations affect the juxtamembrane (JM) domain, encoded by exon 11, and disrupt the normal juxtamembrane secondary structure responsible for maintaining the KIT inactive conformation (1,2). Importantly, shorter progression-free and overall survivals are associated with deletions when compared with the other exon 11 mutations (1,5). Specifically, deletions in codons 557 and/or 558 are related to malignant behavior (1,5). In addition to exon 11 mutations, about 10% of *KIT* mutations occur in exon 9, followed by exon 17 and exon 13, that occur in a very

low percentage (1). In about 10% of cases, mutations in the *PDGFRA* are found and often associated with low-risk GIST (4). *PDGFRA* is activated in GISTs with mutations specially in exon 18, followed by mutations in exon 12 and 14 that are rarer (2). In a subset of 10% *KIT*/*PDGFRA* wild-type GIST, somatic *BRAF* mutations and germinative *SDHx* mutations are described (2,6)

In 2002, the tyrosine kinase inhibitor (TKI) imatinib was FDA-approved as first-line treatment for GIST patients (1,2,5). Imatinib inhibits *KIT* kinase by directly binding to the ATP pocket and competitively inhibiting the ATP binding. Additionally, *PDGFRA*, *ABL*, *FLT3* (Fms-like tyrosine kinase 3), and *CSF1R* (macrophage colony-stimulating-factor receptor) are also imatinib key molecular targets (5). Despite the imatinib efficacy, it is known that about 10% of patients have primary resistance (tumor progression within the first 6 months of treatment) specially in cases with D842V *PDGFRA* mutation, followed by wild-type and, exon 9-mutant *KIT* (1). In addition, most of the patients will develop secondary resistance (within two years) due to new, or secondary, mutation in *KIT* or *PDGFRA* (1).

Most GIST patients who develop secondary resistance to imatinib are treated with another TKI, sunitinib, as second line therapy. Sunitinib received FDA approval in 2006 and targets *KIT*, *PDGFRA*, *VEGFR* and *RET* receptors (5). Nevertheless, its activity against secondary imatinib-

resistant kinase mutations was shown to be suboptimal resulting in a progression-free survival of approximately 6.5 months (5,7). Most recently, regorafenib, another generation of TKI, was approved by the FDA as third line therapy, targeting KIT, PDGFRA, RET, RAF1, BRAF, VEGFR 1–3, and FGFR receptors (5,7). Several alternative TKIs as nilotinib, masatinib, sorafenib, dovitinib, pazopanib, and others have been studied in GIST resistant cases, but so far have shown disappointing results (8).

In a recent publication, Kettle and co-authors reported a new promising quinazoline-derived pan-KIT mutant inhibitor for GIST treatment (9). To identify this novel inhibitor, the authors optimized an existing kinase scaffold from several phenoxyquinazoline and quinoline structures related to TKI inhibitors previously described (9). They identified AZD3229, a multitargeted agent able to promote growth inhibition of a series of mutant KIT-Ba/F3 derived cell lines, with good margin to KDR (VEGFR2)-driven effects and kinome selectivity presenting the same performance as other successful approved GIST agents (9).

Quinazolines moieties are noteworthy in medicinal chemistry due to the wide range of biological properties (10). These compounds were found to be inhibitors of not only EGFR [e.g., gefitinib (Iressa[®])], but many other tyrosine kinase receptors as well (11). Several studies of the quinazolinone ring structure activity revealed that substituents at different positions could improve antimicrobial activities (12). Moreover, a dimethoxyquinazoline, known as prazosin, belongs to the class of alpha-adrenergic blockers and is used to treat high blood pressure (13). This point should be highlighted, considering that hypertension consists of one of the most common side effects of TKIs, resulting particularly from the KDR inhibition. Thus, these studies greatly extend the knowledge for quinazolines biological importance such as anticancer and antihypertensive activities and provide a basis for new potential therapeutic targets.

Kettle's group demonstrated that AZD3229, through C7 methoxyethoxy group modification, compared to others compounds with different substituents at quinazolinone ring positions tested, have a great equilibrium between KIT mutant potency and KDR selectivity able to limit the hypertension potential frequently seen in GIST therapies (9). Therefore, these substitutions show significant improvements in physicochemical and ADME (absorption, distribution, metabolism, and excretion) properties (9).

Kettle and colleagues also evaluated the broad KIT mutant inhibition profile compared to current standard

clinical agents (imatinib, sunitinib, and regorafenib) and agents in clinical trials [ripretinib (DCC-2618) and avapritinib (BLU-285)] and assessed an extended panel of human kinase binding assays through general kinome selectivity (9). Interestingly, AZD3229 presented a broad selectivity suchlike as observed for imatinib and avapritinib, presenting lower amplitude of inhibition. As expected for multitargeted kinases, both sunitinib and regorafenib showed a greater activity across the panel, and ripretinib presented an intermediate activity spectrum. These evidences open up a wider profile of AZD3229 potential (9). However, it must be taken into account that even though many patients tolerate TKIs better than cytotoxic chemotherapy, they could develop adverse effects arising from on-target and off-target effects (14). Therefore, particularly in GISTs, benefits have been associated with drug-dependent off-target effects, such as modulation of immune responses, and angiogenesis (15). Thus, a complete characterization of on-target and off-target effects as well as the elucidation of the mechanisms of action may be required from complementary approaches.

Finally, the authors also showed *in vivo* efficacy of AZD3229 compared to imatinib, sunitinib and regorafenib of relevance to each mutant using Ba/F3 cell lines (9). They showed that AZD3229 at a dose of 20 mg/kg b.i.d induces tumor volume regression more effectively than regorafenib at a dose of 100 mg/kg q.d and imatinib. On the other hand, in an exon 11 del/V654A allograft AZD3229 at a dose of 2 and 20 mg/kg b.i.d induces tumor volume regression. Sunitinib, revealed great regressions at 80 mg/kg q.d as expected with its clinical practice experience and when compared to AZD3229 at a dose of 20 mg/kg b.i.d (9). Although Kettle's group provides important evidence of AZD3229 efficacy *in vivo*, its clinical application still has a long way to go. Voskoglou-Nomikos and colleagues reported that the clinical translatability of models containing murine allograft is frequently poor compared to human cell models (16). Thus, despite differences of *in vivo* models, each offers vulnerabilities as well as advantages and disadvantages and may be addressed by these findings in other models like patient-derived models of acquired resistance that can better recapitulate the original patient-tumor complexity (17).

In conclusion, the results published by Kettle and colleagues are exciting and suggest that a structure-based design of quinazoline derived pan-KIT mutant inhibitor is promising. Now, a refined clinical application of this inhibitor is needed, using other robust *in vivo* models as well

as to define on-targets and off-targets activities, in order to provide maximal impact in cancer treatment and provide patients with the greatest chance of valuable benefit.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Corless CL. Gastrointestinal stromal tumors: what do we know now? *Mod Pathol* 2014;27 Suppl 1:S1-16.
2. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour. *Lancet* 2013;382:973-83.
3. Campanella NC, de Oliveira AT, Scapulatempo-Neto C, et al. Biomarkers and novel therapeutic targets in gastrointestinal stromal tumors (GISTs). *Recent Pat Anticancer Drug Discov* 2013;8:288-97.
4. Rubin BP, Heinrich MC. Genotyping and immunohistochemistry of gastrointestinal stromal tumors: An update. *Semin Diagn Pathol* 2015;32:392-9.
5. Li K, Cheng H, Li Z, et al. Genetic progression in gastrointestinal stromal tumors: mechanisms and molecular interventions. *Oncotarget* 2017;8:60589-604.
6. Doyle LA, Hornick JL. Gastrointestinal stromal tumours: from KIT to succinate dehydrogenase. *Histopathology* 2014;64:53-67.
7. Garcia del Muro X. Nilotinib, imatinib, and GIST therapy. *Lancet Oncol* 2015;16:483-4.
8. Wozniak A, Gebreyohannes YK, Debiec-Rychter M, et al. New targets and therapies for gastrointestinal stromal tumors. *Expert Rev Anticancer Ther* 2017;17:1117-29.
9. Kettle JG, Anjum R, Barry E, et al. Discovery of N-(4-[[5-Fluoro-7-(2-methoxyethoxy)quinazolin-4-yl] amino]phenyl)-2-[4-(propan-2-yl)-1H-1,2,3-triazol-1-yl]acetamide (AZD3229), a Potent Pan-KIT Mutant Inhibitor for the Treatment of Gastrointestinal Stromal Tumors. *J Med Chem* 2018;61:8797-810.
10. Hameed A, Al-Rashida M, Uroos M, et al. Quinazoline and quinazolinone as important medicinal scaffolds: a comparative patent review (2011-2016). *Expert Opin Ther Pat* 2018;28:281-97.
11. Ravez S, Castillo-Aguilera O, Depreux P, et al. Quinazoline derivatives as anticancer drugs: a patent review (2011 - present). *Expert Opin Ther Pat* 2015;25:789-804.
12. Jafari E, Khajouei MR, Hassanzadeh F, et al. Quinazolinone and quinazoline derivatives: recent structures with potent antimicrobial and cytotoxic activities. *Res Pharm Sci* 2016;11:1-14.
13. Yadav MR, Naik PP, Gandhi HP, et al. Design and synthesis of 6,7-dimethoxyquinazoline analogs as multi-targeted ligands for alpha1- and AII-receptors antagonism. *Bioorg Med Chem Lett* 2013;23:3959-66.
14. Cabanillas ME, Hu MI, Durand JB, et al. Challenges associated with tyrosine kinase inhibitor therapy for metastatic thyroid cancer. *J Thyroid Res* 2011;2011:985780.
15. Bellora F, Dondero A, Corrias MV, et al. Imatinib and Nilotinib Off-Target Effects on Human NK Cells, Monocytes, and M2 Macrophages. *J Immunol* 2017;199:1516-25.
16. Voskoglou-Nomikos T, Pater JL, Seymour L. Clinical predictive value of the in vitro cell line, human xenograft, and mouse allograft preclinical cancer models. *Clin Cancer Res* 2003;9:4227-39.
17. Gould SE, Junttila MR, de Sauvage FJ. Translational value of mouse models in oncology drug development. *Nat Med* 2015;21:431-9.

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