Editorial Commentary

Ripretinib inhibits polyclonal drug-resistant KIT oncoproteins: the next step forward in gastrointestinal stromal tumor therapy

Maria Debiec-Rychter[1]^, Piotr Rutkowski[2]^

[1]Department of Human Genetics, KU and University Hospitals Leuven, Leuven, Belgium; [2]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Correspondence to: Maria Debiec-Rychter, MD, PhD. Herestraat 49, 3000 Leuven, Belgium. Email: maria.debiec-rychter@kuleuven.be.

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Genetic alterations in KIT or PDGFRA kinase that are detected in >85% of gastrointestinal stromal tumors (GISTs), constitute the target for the current GISTs therapy (1). The FDA-approved KIT kinase inhibitors crucially improved the treatment of advanced GISTs (2). Yet, primary or secondary resistance to authorized therapies remains a major clinical challenge. The secondary resistance mutations inevitably emerge during targeted therapy, causing disease progression. These mutations usually occur in the kinase switch pocket (encoded by *KIT* exons 13 and 14 or *PDGRA* exons 14 and 15) or in the activation loop domain (encoded by *KIT* exons 17 and 18 and *PDGFRA* exon 18) (3,4). Importantly, most resistance mutations in GIST are quite heterogeneous, with majority of patients acquiring multiple subclonal mutations, with diverse tumor metastases carrying multiple distinct resistant mutations. An inhibitor that blocks only a subset of resistance mutations allows for the selection and growth of other resistant subclones.

A dual "switch-control" tyrosine kinase inhibitor, Ripretinib (formerly known as DCC-2618), was developed to restrain both internal kinase domains, to lock the KIT and PDGFRA kinases in the inactive conformation. As such, it was predicted to be effective against the full spectrum of mutant KIT and PDGFRA kinases found in cancers. Accordingly, ripretinib was a potent inhibitor of both wildtype and a wide range of mutant KIT and PDGFRA kinases, including intrinsically imatinib-resistant *KIT D816V* and *PDGFRA D842V* mutations, in the preclinical *in vitro* studies (5).

The efficacy of ripretinib was evaluated in a pivotal, double-blind, randomized, placebo-controlled, INVICTUS (ClinicalTrials.gov identifier: NCT03353753) phase 3 trial, in patients for whom treatment with so far approved kinase inhibitors had failed. A total of 129 eligible patients were randomized to either ripretinib (n=85) or placebo (n=44) (6). The median progression-free survival (PFS) and median overall survival (OS) for patients receiving ripretinib were significantly longer in comparison with patients receiving a placebo. For patients in the ripretinib arm, 9% had a partial response and 47% had stable disease at 12 weeks, compared with patients in the placebo arm, which showed 0 patients with a partial response and 5% with stable disease. In addition to highly promising efficacy, ripretinib had a well-tolerated safety profile. In May 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced GISTs as a fourth-line or higher therapy (7). Thereafter, ripretinib was approved by EMA in the same indication (8). Thus, ripretinib has raised as a new standard of care for advanced, multi-resistant GIST patients. This constitutes an important step forward in the area of drug development in GIST.

The current report by Bauer and co-workers (9) presented the genomic analysis and the detailed characterization of the complex and extensive heterogeneity of *KIT/PDGFRA* mutations in patients from the INVICTUS phase 3 study.

^ ORCID: Maria Debiec-Rychter: 0000-0001-8183-2105; Piotr Rutkowski, 0000-0002-8920-5429.

Of note, the authors used double approach to reveal tumor genotype, i.e., traditional one, based on sequencing of tumor tissue, and the novel liquid plasma ctDNA analysis. The material for both approaches were collected prior to study enrolment and analyzed by next-generation sequencing.

Notably, combining results from tissue and liquid biopsy, 115 out of 128 (89.9%) patients had detectable *KIT/PDGFRA* mutations. Within 80 patients with detectable *KIT/PDGFRA* mutations in both tissue and liquid biopsies, the high 93.75% concordance rate of primary mutation was observed; notably, liquid biopsy detected most of the mutations found in tissue biopsy and several additional distinctive mutations. Hence, the combination of these two methodologists revealed more complex range of mutations, providing a complete genomic picture of resistance phenotype in tumors of heavily pre-treated GIST patients. Furthermore, efficacy results in the INVICTUS trial were explored by mutation subgroup using combined tissue and liquid biopsy data. Patients were grouped into four subsets based on the presence of any *KIT* exon 9, exon 11, exon 13, and exon 17 mutations. Not adequate sample size did not allow for evaluation of other rare subgroups, such as *KIT* exon 14 or 18 mutations, *PDGFRA* mutations (particularly *D842V* substitution) or tumors without detectable *KIT/PDGFRA* mutations (WT). Importantly, patients receiving ripretinib showed PFS benefit over placebo across all tumors' genotypes [hazard ratio (HR) 0.16, 95% confidence interval (CI): 0.10–0.27] and in all evaluated subsets in Kaplan-Meier PFS analysis.

More information on the activity of ripretinib on earlier stages of GIST and its mechanism of action to different molecular subtypes can give the final results of phase III INTRGUE trial (10), which outcomes published in press release indicate that ripretinib is not superior to sunitinib in a second-line therapy in terms of progression-free survival. Nevertheless, ripretinib had a better safety profile and induced fewer grade 3–4 toxicities, including arterial hypertension.

While ripretinib shows improved progression-free and overall survival in INVICTUS study, which keeps up with its predicted wide range of efficacy, patients continue to show disease progression. Potentially, the efficacy of ripretinib against every secondary *KIT* mutation is not equal and some mutations are insufficiently inhibited in a permanent manner; and/or novel resistant KIT mutations emerge under selective pressure with time. Alternatively, KIT-independent mechanisms may arise or some unknown yet mechanisms reduce the effect of ripretinib. A blend of all these mentioned above mechanisms might also be in place. Importantly, how the tumor dynamics evolve during ripretinib treatment and whether the changing tumor mutational landscape can predict the emerging resistance during treatment is an open question. These can be addressed on account of the cancer DNA samples gathered during the trial. Metastatic GIST is possibly a golden cancer prototype for the clinical application of ctDNA analysis, although not all GISTs shed DNA into the blood at the analytically optimal level (11). In the scenario of INVICTUS study, the results of ctDNA testing during treatment would be particularly interesting and are awaited by a broad research community. These might assist in drawing the firm conclusions on the ripretinib clinical efficacy and prognostic potential on ctDNA based monitoring of patients across this or possible future clinical trials.

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