Editorial Commentary

Gastrointestinal stromal tumor (GIST): molecular heterogeneity and current challenges

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The majority of gastrointestinal stromal tumors (GISTs) harbour an activating mutation in the receptor tyrosine kinase domains of either the KIT (approximately 80%) or platelet-derived growth factor receptor alpha (PDGFRA) (approximately 10%) genes. The remainder are a heterogeneous group that are KIT/PDGFRA wild type (1,2). A proportion of these patients will have mutations in succinate dehydrogenase (SDH) or rarer mutations in genes such as BRAF or NF-1 (3,4). The use of first-generation tyrosine kinase inhibitors (TKIs) (imatinib, sunitinib and regorafenib) used in the first, second- and third-line settings respectively, has significantly improved patient outcomes (5-8). However, resistance to these first generation TKIs is inevitable (9). When resistance occurs, disease control remains a significant clinical challenge and next-generation TKIs or other molecules with novel mechanisms of action have been or are being developed to overcome these challenges.

Avapritinib is a selective inhibitor of KIT and PDGFRA tyrosine kinases. It is highly potent against the KIT D816V–mutant and PDGFRA D842V–mutant kinases (10). As fourth or later line of therapy, avapritinib had demonstrated impressive objective response rates (ORR) of 21% in patients with advanced molecularly unselected GIST in the preceding phase I study (NAVIGATOR) (10). The NAVIGATOR trial was a 2-part, dose escalation and dose expansion phase 1 trial. The dose escalation part 1 included patients with advanced GIST who were refractory to two lines of therapy with a TKI; the dose expansion component involved several cohorts, with one group of patients having tumours that had a PDGFRA D842V mutation, regardless of prior lines of treatment. In patients with advanced PDGFRA D842V–mutant GIST, the results were remarkable. Regardless of the number of prior lines of treatments, the overall response rate was 91% and the median progression free survival (mPFS) was 34 months. The results from the NAVIGATOR trial led to the approval of avapritinib by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment refractory GIST that is characterized by a PDGFRA exon 18 mutation, including D842V mutations.

Kang *et al.* recently reported on the phase III VOYAGER trial. This study compared avapritinib to regorafenib as a third or later-line of treatment in patients with unresectable or metastatic GIST (11). VOYAGER was a randomized, multicentre phase III study that randomised eligible patients 1:1 to receive either avapritinib 300 mg once daily or regorafenib 160 mg once daily, 3 weeks on and 1 week off. Regorafenib as a third line agent had demonstrated activity with improved PFS compared to placebo (4.8 *vs.* 0.9 m) in the prior GRID trial (7). Subsequent exploratory analysis that modelled and corrected for the impact of crossover to regorafenib in the control arm of the GRID trial (given that 85% of randomized to the placebo arm crossed over to regorafenib), demonstrated a hazard ratio for OS favouring regorafenib (12).

In VOYAGER four hundred and seventy-six patients were enrolled. The randomisation was stratified based on the line of treatment (third line versus fourth line), geographical region and PDGFRA D842V mutation status. All patients had received prior imatinib, and the majority had also received prior sunitinib (with both TKIs received in approximately 85% of patients). A small proportion of

patients (14.3%) had received three lines of treatment with a TKI. Based on ctDNA analysis in VOYAGER, 3.8% of patients had a PDGFRA exon 18 mutation, 2.7% of patients had a D842V mutation in the activation loop sequence of PDGFRA exon 18 and 30.7% of patients had mutations other than PDGFRA exon 18 (KIT V654A, KIT T670I, or KIT exon 17). Mutation status in ctDNA was unknown in approximately a third of patients in the study.

The primary endpoint of the study was not met. There was no significant difference in mPFS between avapritinib and regorafenib (HR: 1.25). A pre-planned subgroup analysis failed to identify a subgroup of patients that would benefit from avapritinib. There were thirteen patients in the study that had PDGFRA D842V mutation and the median PFS was not reached in patients with a PDGFRA D842V mutation (n=7) that were treated with avapritinib compared to a median of 4.5 months in the six patients that were treated with regorafenib highlighting the activity of avapritinib in this population. When these thirteen patients were excluded from the ITT analysis the mPFS was significantly better with regorafenib compared to avapritinib (HR, 1.34, mPFS 5.6 *vs.* 3.9 m; P=0.01). As expected, based on the NAVIGATOR study, all seven patients with a PDGFRA D842V mutation treated with avapritinib at the time of analysis had disease control, compared to only a third of the six patients with a PDGFRA D842V mutation treated with regorafenib. Overall survival data were immature at the time of reporting; however; 12-month survival estimates were similar for both groups.

It is interesting to note that in the ITT population, the ORR was significantly higher with avapritinib for all patients including patients with a PDGFRA D842V mutation compared to regorafenib. However, the duration of response was better with regorafenib. In addition, the improved ORR with avapritinib was confined to patients receiving this agent as third-line treatment, with no difference in the ORR amongst patients that received avapritinib versus regorafenib as fourth-line treatment.

With respect to safety, avapritinib appears to have an acceptable tolerance, albeit with some unique considerations. Most patients experienced only grade 1 or 2 adverse effects. Overall, the rate of discontinuation because of adverse effects was 8.3% for avapritinib and 5.6% for regorafenib possibly indicating that avapritinib may be more toxic than regorafenib. Interestingly, approximately 40% of patients experienced cognitive effects with avapritinib in the form of memory impairment, cognitive disorder, confusional state, and rarely encephalopathy, an adverse effect profile not reported to this extent with other TKIs used in GIST. Despite this profile, the discontinuation of treatment with avapritinib due to cognitive side effects alone occurred in only 2 patients.

Potentially the difference in the inhibitory spectrum against various mutations is the reason why avapritinib failed to improve outcomes in the VOYAGER trial. Avapritinib is less potent against KIT mutations in exons 13 and 14 but a potent inhibitor of PDGFRA-D842V mutations (on exon 18) (13,14). It is also a potent inhibitor of several other primary PDGFRA or KIT mutations (on exon 11 and exon 11/17) and secondary activation loop mutations in the KIT domain. Regorafenib on the other hand is an inhibitor of primary mutations in exons 9 and 11 of KIT and secondary mutations in exons 14 and 17 (15). The VOYAGER patient cohort was characterized by considerable mutational heterogeneity and hence the efficacy of avapritinib over regorafenib was not seen presumably due to this underlying mutational landscape differing from patient-to-patient. It is notable that in recent studies, compound mutations of exons 13, 14, and 15 of PDGFRA have been shown to be the likely reason for resistance to TKIs that inhibit PDGFRA mutations (16).

Despite a meaningful improvement in patient outcomes, over time, resistance to each of the TKIs used in the management of advanced or unresectable GIST (including avapritinib) is inevitable representing the major limitation of these early generation TKIs. However, common to each is that they target the inactive conformation of KIT/PDGFRA which makes them unable to inhibit the secondary KIT resistance mutations in the kinase activation loop. However the landscape is changing with the development and recent approval of ripretinib, a first-in-class 'switch control' inhibitor that can target PDGFRA- D842V mutations and D861V resistance mutations on exon 17 and several other KIT mutations (17). Ripretinib was tested in the placebo controlled INVICTUS trial that recruited one hundred and twenty nine patients with advanced GIST refractory to imatinib, sunitinib, and regorafenib. Regardless of mutation status, ripretinib (compared to placebo) was associated with an improved median overall survival (OS 15 *vs.* 6 months, HR =0.36) and PFS (6 *vs.* 1 months, HR =0.15). The mutational profile of patients and response to ripretinib per specific mutation in INVICTUS is currently awaited. There are no head-to-head data comparing avapritinib to ripretinib in patients with tumours that have a PDGFRA mutation—making it difficult to compare these agents in this population. Notwithstanding this hypothetical advantage,

it is important to note that ripretinib failed to improve outcomes when compared to sunitinib in the second line setting in a molecularly unselected population and we await the final publication of the INTRIGUE trial (18) with interest.

As a mutationally heterogeneous disease, GISTs will always pose a challenge in long term disease control due to the development of secondary kinase mutations and subsequent clonal expansion induced through treatment-related selective pressure either on the tumour or on pre-existing, resistant clones in the primary tumour. In addition, tumour heterogeneity is difficult to establish at the outset in newly diagnosed patients in whom mutation analyses are usually confined. It is known that up to 45% of patients with primary GIST mutations can develop multiple secondary kinase mutations and majority will have ≥2 different mutations or mutational heterogeneity in separate metastases—hence TKIs with selective inhibitory efficacy for specific mutations may fail to provide meaningful disease control (19).

Whilst ensuring that all patients with a primary GIST are tested for mutations in KIT or PDGFRA at a minimum has been a challenge world-wide, optimal management in the future may rely on our ability to establish and target dynamic mutational changes at the time of cancer progression on a TKI. The field is moving towards utilisation of next-generation sequencing techniques to monitor the evolution of mutation in circulating GIST cells and circulating (GIST) tumour DNA (ctDNA). Whole genome sequencing has been shown to detect resistant mutations that could potentially mediate TKI resistance by independently activating the KIT downstream signalling intermediates such as NF1/2, PTEN, PIK3CA, AKT, RAS and BRAF (20). Recent studies have demonstrated that next generation sequencing of liquid biopsies from GIST patients is feasible. These preliminary studies have shown concordance between the molecular spectrum in ctDNA and tumour tissue as well as detection of secondary resistant mutation in the ctDNA (21,22). When combined with primary tumour genotyping, ctDNA once validated, may become a potent clinical tool as a decision-guide to determine future selection of appropriate treatment options in resistant GIST. In the meantime, the armamentarium for the management of resistant GIST continues to expand, giving patients, their families and the clinical community continuing hope that further research efforts for this rare disease will deliver ongoing benefits to the many patients and their families with GIST.

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Footnote

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