Editorial

Micromanagement of drug-resistant advanced gastrointestinal stromal tumors: regorafenib—new ammunition in battling exon 17 mutations

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Gastrointestinal stromal tumors (GIST) are the most common gastrointestinal (GI) mesenchymal tumors originating from pluripotent precursor mesenchymal cells that normally differentiate into the interstitial cells of Cajal. Overall, GISTs account for less than 1% of all reported GI cancers. Most GISTs are incidental findings at endoscopic or radiologic procedures and they can be cured by surgical resection when detected early. The risk of malignant spread depends on size, mitotic count and location in the GI tract. Because of their subepithelial location, GISTs may grow to substantial size before they become symptomatic and therefore more than half of GISTs may be locally advanced or metastatic at first diagnosis (1). A landmark study by Hirota *et al.* initially identified c-KIT (CD 117) as a key proto-oncogene in the pathogenesis of most GISTs (2) and subsequently mutations in platelet derived growth factor alpha (PDGFRA) or B-Rapidly Accelerated Fibrosarcoma (BRAF) were identified in those GISTs lacking c-KIT expression. Activation of c-KIT receptor tyrosine kinase plays a critical role in the pathogenesis and growth of GISTs and therefore this receptor is used for targeted therapy. In another landmark study, Demetri *et al.* showed that the tyrosine kinase inhibitor (TKI) imatinib induced a sustained objective response in unresectable and metastatic GISTs (3) and it is now considered standard first line therapy in this setting. Unfortunately, secondary drug resistances have emerged as a significant problem over the past years. First-line therapy with imatinib has been augmented by second-line treatment with sunitinib and third-line treatment with regorafenib, which were approved by the FDA in 2006 and 2013, respectively. c-KIT mutations, accounting for such drug resistances, mostly occur in exons 11, 9, 13 and 17 in 70%, 10–15%, 1–3% and 1–3% of cases, respectively (4). However, imatinib-resistant GIST may harbor exon 17 mutations in up to 48% of cases (5). Both imatinib and sunitinib have proved ineffective in battling exon 17 mutations in preclinical studies. As exon 17 encodes the activation loop region of cKIT-kinase, mutation of this region renders newer TKIs, such as sorafenib, dasatinib and nilotinib, ineffective. Regorafenib (Stivarga, Bayer HealthCare Pharmaceuticals Inc., Whippany, USA) is a TKI with a broader pharmacodynamic spectrum against multiple targets of tumor angiogenesis, oncogenesis and overall maintenance of the tumor microenvironment, including inhibitory activity against the activating loop kinase mutation, mentioned above. Therefore, it is suitable for targeting GISTs refractory to other TKI (6-8). Thus far it remains unclear, whether regorafenib may fill the therapeutic gap in the subgroup of drug-resistant GIST with exon 17 mutations.

Dr. Yeh and colleagues now published a controlled, open-label, phase II trial in *Oncotarget* assessing the safety and

efficacy of regorafenib in the small, but relevant, subgroup of patients with metastatic and/or unresectable GIST harboring secondary exon 17 mutations. Patients received 160 mg of oral regorafenib daily for 3 weeks followed by 1 week without treatment as part of a 4-week cycle. Response to therapy was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) every 8 weeks. The primary endpoint of the study was the overall clinical benefit rate (OCR) defined as the combination of complete response (CR), partial response (PR) and stable disease (SD). Secondary endpoints were progression-free survival (PFS) and assessment of toxicities. All patients had been previously treated with imatinib as first-line therapy and 55.6% of patients had also received sunitinib prior to enrollment. All patients harbored additional c-KIT mutations, including exon 11 (77.8%), 9 and 13. Although the majority of patients had disease progression at the time of enrollment, 33.3% had SD. Fifteen unmatched patients with similar age, gender and mutational status, who had not received regorafenib, were used as a historical control group. The primary endpoint was reached in 93.3% of the patients included in the final analysis. Although no CR was obtained, 40% had PR, 53% had SD and 1 patient (7%) had disease progression at the end of a 16 months-observation period. The median PFS was 22.1 months in the regorafenib group and 5.5 months in the control group (P=0.0001). Toxicities occurred in all patients receiving regorafenib at a median dose of 120 mg at 24 weeks. Re-escalation of the dose after initial reduction was possible in 3 (16.7%) patients. Two patients were excluded from the final analysis because of complete drug intolerance. Severe (grade 3) toxicities occurred in 61.1% of the 15 patients that entered the final analysis and were treated with regorafenib. These were mostly hand-foot skin reactions (HFSR) in 55.6%, followed by hypertension (27.8%), hepatic toxicity and leukopenia. Overall the authors concluded that regorafenib significantly prolongs PFS in patients harboring exon 17 mutations with a toxicity profile that is comparable to previous studies and suggest that a phase III trial is warranted for this subgroup of patients with refractory GIST.

Although the management of advanced GIST has been revolutionized by the introduction of TKI, drug-resistance in advanced disease remains a major challenge. Mutation analyses now give the opportunity to individualize treatment for different subgroups of patients with such resistances. This evidence adds to previous reports from a subgroup analysis of a large international, multi-center, randomized-controlled phase III trial (GRID trial), which initially established the efficacy of regorafenib in advanced GIST resistant to imatinib and sunitinib (9). In a subgroup analysis of the GRID trial Ben-Ami *et al.* analyzed 7 patients with exon 17 mutations. The median PFS in that study was 22 months and therefore identical to the study under discussion (10). Yeh *et al.* now confirm that regorafenib might be promising armamentarium in the third- and second-line treatment of patients harboring exon 17 mutations. Their main findings are: (I) patients with advanced and/or metastatic GIST with exon 17 mutations receiving regorafenib have favorable PFS as compared to historical controls; (II) regorafenib might be effective second-line treatment in patients with exon 17 mutations; (III) HFSR was a universal adverse event in this subgroup of patients, accounting for 55.6% of severe grade 3 toxicities.

Several limitations of the study must be considered. The authors only included 15 patients with exon 17 mutations in their final analysis. Although this is a substantial number of patients, considering the rarity of refractory disease with this mutation overall, it is accompanied by a suboptimal control group. Despite the fact that the control group had a similar age, gender and mutational status, there are many additional factors that may have affected the outcome, including tumor biology, number of surgical procedures, ablative therapies and the previous use of TKI. Therefore, the observed differences might have been much smaller if the study had been randomized. In addition, 6 (33.3%) patients had SD upon study inclusion under treatment with another TKI. It remains speculative, whether the switch to regorafenib from their initial TKI actually improved PFS in these stable patients. Furthermore, it must be mentioned that none of the treated patients had a CR and PR was only achieved in 40%. In this regard, a recent meta-analysis suggests that overall survival may not be improved by regorafenib, despite improved PFS (11). However, the primary endpoint of disease control (OCR) was reached in 93.3% of patients, which compares favorably to the 52.6% of patients in the GRID-trial, who were not pre-selected by their mutational status, suggesting that regorafenib holds some promise in this setting.

The question might be raised, whether the use of RECIST 1.1 for the assessment of primary and secondary outcomes could have resulted in an under- or over-estimation of the treatment effect, respectively. In 2007, Haesun Choi first voiced the concern that RECIST might not be optimal for response assessment in GIST because cystic or necrotic changes may prevent a decrease in tumor-

size, even in the case of a positive treatment response. The authors used the catchy phrase "*we should desist using RESIST, at least in GIST*" (12,13). In a recent study by Shinagare *et al.* several tumor response criteria, including RECIST 1.1 and Choi criteria, were compared in the assessment of regorafenib activity in advanced GIST after failure of imatinib and sunitinib (14). Although the Choi criteria were far more sensitive than RECIST 1.1 criteria to assess tumor response, the authors found that the clinical benefit is not affected when SD is included in the definition of response (such as in the study under discussion). In addition, they found that the Choi criteria were also more sensitive than RECIST 1.1 in detecting disease progression, which resulted in shorter PFS. Because PFS was not strongly concordant with OS in their study, the authors concluded that RECIST 1.1 should be preferred in this setting to avoid early withdrawal of effective treatment when disease progression is noted.

A novelty of the current study is the inclusion of 8 patients who were refractory to imatinib, but did not receive previous second-line treatment with sunitinib, which suggests that regorafenib should be evaluated as second-line (or even first-line) treatment for patients with exon 17 mutations. An Australian randomised trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced GIST (ALT GIST; NCT02365441) is currently recruiting and another ongoing study is evaluating regorafenib as first-line for metastatic/unresectable KIT/PDGFR wild type GIST (REGISTRI; NCT02638766). However, it is not clear, whether exon 17 mutations will be included in these trials. Further evaluation of regorafenib as primary- or secondary-treatment, especially in patients with exon 17 mutations seems warranted.

The risk of severe grade 3 toxicity from HFSR was 55.6% in the study under discussion as compared with 19.7% in the GRID-trial and 17% in the CORRECT-trial, the latter of which evaluated regorafenib in patients with metastatic colorectal cancer (15). Whether this is due to the selection of patients with exon 17 mutations is unclear. Genetic differences in study populations could account for the observed difference. Another Asian study from Korea, which included mostly patients with exon 9 and 11 mutations, also showed a rather high incidence of severe HFSR in 25% of regorafenib treated patients (15). In contrast, a subgroup analysis in of the GRID trial in Japanese patients only showed an incidence of 17% (16). Certainly patients should be made aware of a possible frequent occurrence of severe HFSR.

In summary, both imatinib and sunitinib have proved mostly ineffective in battling exon 17 mutations and the current study by Yeh *et al.* adds valuable evidence that regorafenib might have efficacy in improving PFR in these patients, despite some limitations. These data raise the question, whether regorafenib should be considered as first- or second-line treatment in this patient population and further studies regarding these questions are warranted. A number of novel treatments, targeting additional mutations and downstream molecular pathways, are currently under investigation, but comparative data are missing (4,6). Further understanding in tumor-biology and early performance of mutational analyses will likely alter the micromanagement of advanced GISTs in the future by individualizing targeted treatments.

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Footnote

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

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