CLINICAL
INVESTIGATION

Rechallenge with imatinib in advanced gastrointestinal stromal tumors: clinical implications of the RIGHT trial

Tyrosine kinase inhibitors (TKIs) are the mainstay of the management of advanced gastrointestinal stromal tumors (GISTs). Currently, imatinib, sunitinib and regorafenib are approved treatments for advanced GISTs. However, most standard therapies eventually stop working due to polyclonal evolution of the disease, which results in TKI resistance and overall disease progression. For patients with refractory GISTs after progression on all approved TKIs, resumption of previously effective TKIs may have clinical benefit. However, no randomized trial had been performed to support TKI reuse in patients with advanced GISTs. Recently, a placebo-controlled randomized Phase III trial (RIGHT) found that imatinib resumption significantly prolonged progression-free survival in patients with TKI-refractory GISTs versus placebo. The details of the RIGHT trial and its clinical implications are reviewed here.

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Rechallenge with imatinib against tyrosine kinase inhibitor-refractory gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GISTs) arise from the mesenchymal tissue of the gastrointestinal tract or other intra-abdominal soft tissues and originate from the interstitial cells of Cajal [1]. GISTs are the most common mesenchymal tumors of the digestive tract and commonly occur in the stomach and small intestine, although they can occur anywhere along the gastrointestinal tract. Representative molecular characteristics of GISTs are that driver mutations in the *KIT* or *PDGFRA* are detectable in >90% of cases. *KIT* exon 11 mutations located in the juxtamembrane domain are the most common primary mutation (about 70%), followed by *KIT* exon 9 mutations in the extracellular domain (about 10%).

Localized resectable GISTs can be cured with surgical resection, but no effective therapy had been established for patients with unresectable and/or metastatic GISTs and their prognosis was extremely poor before the advent of imatinib.

Imatinib mesylate is an oral tyrosine kinase inhibitor (TKI) with activity against KIT, PDGFRA, ABL and DDR. The efficacy of imatinib was first shown in the case report by Joensuu *et al.* [2] and demonstrated in the pivotal B2222 and EORTC early-phase trial [3,4]. This was subsequently confirmed in two Phase III trials [5,6]. The standard dose of imatinib was established as a 400 mg once-daily dose; upfront high-dose imatinib treatment with a 800 mg daily dose showed a higher efficacy in terms of progression-free survival (PFS) in patients with GISTs harboring *KIT* exon 9 mutations and also higher toxicity [7]. The median time-to-progression (TTP) with imatinib was about 2 years in the extended follow-up results of the B2222 trial [8]. Imatinib efficacy correlates with primary *KIT* mutations and patients with *KIT* exon 9 mutations had worse survival outcomes than those with *KIT* exon 11 mutations [7].

For patients with progression or intolerance to imatinib, sunitinib is the approved second-line therapy with a median TTP of about 7 months in the pivotal Phase III

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trial [9]. Although many novel agents have been tested in the setting of failure of both imatinib and sunitinib, only regorafenib has been approved as the standard third-line therapy after the success of a randomized Phase III trial (GRID), which showed a median PFS of about 5 months in the regorafenib arm [10].

Despite the advances to date in the management of advanced GISTs, most standard therapies eventually stop working due to polyclonal evolution of the disease, which results in TKI resistance and ultimately disease progression. For patients with refractory GISTs after progression on all approved TKIs, many experts have suggested that resumption of previously effective TKIs may have clinical benefit [11–13]. However, no randomized trial had been performed to support the reuse of TKIs in patients with advanced GISTs. Hence, a randomized placebo-controlled, Phase III trial (RIGHT) was conducted to evaluate the efficacy and safety of the resumption of imatinib in GIST patients after failure of at least imatinib and sunitinib [14]. In our present review, the details of the RIGHT trial and its clinical implications are discussed.

Rationale of the RIGHT trial

Abandonment of treatment with an anticancer drug after disease progression is typical practice in the management of patients with cancer. However, anecdotal reports have suggested that discontinuation of imatinib in patients with imatinib-refractory GISTs may induce abrupt aggravation of the disease and tumor-related symptoms [15]. Furthermore, previous retrospective studies have suggested that imatinib rechallenge might prolong the survival of patients with TKI-refractory GISTs compared with best supportive care alone, although a selection bias may exist [16,17]. Because the discontinuation of all TKIs in advanced-stage patients may be accompanied by a rapid disease flare with increased pain and other symptoms, as well as pace of progression, many experts believe that the continuing inhibition of KIT with imatinib resumption may be justifiable. Furthermore, a number of studies have indicated that resistance to TKI occurs with polyclonal evolution with mutational heterogeneity, which paradoxically suggests that imatinib-sensitive tumor clones might remain even after disease progression on several TKIs. On the basis of these findings, many international clinical practice guidelines for the treatment of GISTs indicate that the re-introduction of previously tolerated and effective TKI therapy can be considered for palliation of symptoms. Because there are no data from prospective randomized trials; however, the magnitude of the clinical benefit with imatinib rechallenge has been unclear. The RIGHT trial was designed to measure the magnitude of the efficacy and safety of

imatinib in patients who previously benefited from imatinib.

Design of the RIGHT trial

The RIGHT trial was an investigator-initiated, randomized, placebo-controlled, Phase III trial (Figure 1). Patients with histologically proven metastatic or unresectable GISTs were enrolled, if their tumors had progressed during previous active treatment with at least imatinib and sunitinib sequentially in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST), version 1.0 [18]. Because the major rationale for an imatinib rechallenge of TKI-refractory GISTs is that imatinib-sensitive tumor clones may remain, even in cases of progression from multiple lines of TKI therapies, patients included in the trial had to have had documented clinical benefit (i.e., lack of primary resistance) with previous first-line imatinib treatment. This benefit was defined by a complete response, partial response or stable disease for at least 6 months. Other eligibility criteria included an age ≥18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, at least one measurable lesion and adequate hematological, hepatic and renal functions.

Eligible patients were randomly assigned (1:1) to receive once-daily imatinib 400 mg or matched placebo (four capsules once-daily) by use of a random permuted block method. Randomization was done centrally in a double-blind manner, so that the allocated treatment was masked to the investigators and patients. Stratification factors were the ECOG performance status (0–1 vs 2–3) and the number of previous lines of TKI therapy (2 vs ≥3). Study drug doses were modified or interrupted for grade 3–4 hematological toxicities (excluding anemia) and grade 2–4 nonhematological toxicities. Other anticancer treatments, such as chemotherapy, radiotherapy, other targeted therapies and surgical resections, were not allowed during the period in which the study treatments were investigated in a blind manner. Best supportive care was given to all patients in both trial arms. Masked study treatments continued until patients showed disease progression according to a local investigator assessment, unacceptable toxicity or withdrew consent. At the time of progression, as assessed by the local investigators, the treatment group was unmasked. Patients were then allowed to crossover to receive unmasked imatinib therapy at a 400 mg once-daily dose, if they had been assigned to the placebo group. In patients who had been assigned to the imatinib group, patients were allowed to continue imatinib as an open-label treatment. Open-label imatinib therapy was allowed to be continued even after multiple disease progressions at the discretion of the investigator in shared decision making with the patient.
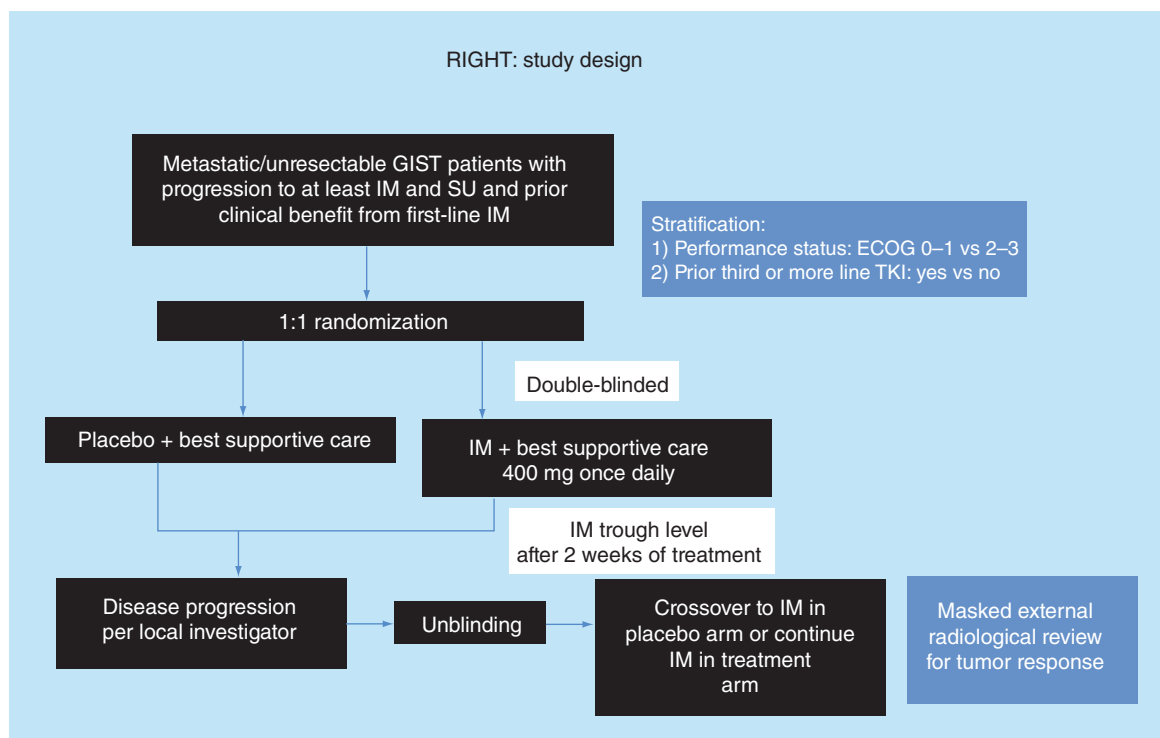
Figure 1. Study design.
ECOG: Eastern cooperative oncology group; GIST: Gastrointestinal stromal tumor; IM: Imatinib; SU: Sunitinib; TKI: Tyrosine kinase inhibitor.

For response assessments of study treatments, CT scans were performed every 4 weeks for the first 4 months of the trial and every 8 weeks thereafter. Additional imaging studies were done whenever disease progression was clinically indicated. Tumor responses were initially determined by the local onsite radiological review in accordance with RECIST 1.0 [18] and the treatment decision was based on this. All imaging data were subsequently collected, anonymized and reviewed centrally in a double-blind manner by two external academic radiology reviewers. In this masked central review, response assessment was determined by use of RECIST 1.1 [19]. Because compliance with the study medications may have critically impacted the results of this trial, the plasma imatinib trough concentration was measured after 2 weeks on study drug in all patients of both arms, and the results were masked from investigators and patients. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

The primary end point of the trial was PFS (defined as the time from randomization to documentation of disease progression or death), according to a masked external radiology central review. Secondary end points included the disease-control rate (defined as the proportion of complete response, partial response and stable disease for at least 12 weeks), overall survival (OS), TTP and safety profile.

With regards to the sample size, 80 patients were required to achieve a power of 85% and two-sided overall alpha of 0.05 to detect a hazard ratio (HR) of 0.5 in PFS at 12 weeks. Two sets of interim analyses were planned when 26 events (progression or death) and 55 events occurred, by use of the O'Brien–Fleming stopping boundaries with a two-sided alpha of 0.001 for the first interim analysis and 0.017 for the second interim analysis. A final analysis for the comparison of PFS between the imatinib and placebo groups was scheduled to take place after 76 events or at 9 weeks after the accrual of the last patient, whichever occurred first, and was performed with a two-sided alpha of 0.044 after adjustment for the two interim analyses. All analyses for efficacy parameters were done based on the full analysis set, which included those patients who received at least one dose of the study drug.

Patient enrollment & data analysis

A total of 81 patients were enrolled in the trial and randomly assigned to the imatinib (n = 41) and placebo (n = 40) arms between 20 July 2010 and 17 January 2013. Patient characteristics were well balanced between the two arms. There were no significant differences in the treatment duration with first-line imatinib (imatinib vs placebo arm; median 30.3 vs 36.0 months for imatinib [p = 0.07]) and sunitinib (9.6 vs 7.7 months for sunitinib [p = 0.27]). About 40% of

patients in each arm had received three or more lines of previous therapy with TKIs. In addition to imatinib and sunitinib, nilotinib (17% in the imatinib arm vs 23% in the placebo arm), regorafenib or sorafenib (12 vs 25%), and dovitinib (17 vs 8%) were given prior to enrollment. About 60% of patients in each arm had received first-line imatinib 400 mg once-daily for at least 2 years. After progression on a standard dose of imatinib, an escalated dose of imatinib (600 or 800 mg daily) was administered to all patients in the imatinib arm and 88% of patients in the placebo arm. As a primary genotype, *KIT* exon 11 mutations were the most common (82% in the imatinib arm vs 77% in the placebo arm), followed by *KIT* exon 9 mutations (11 vs 13%).

An independent data monitoring committee reviewed the two preplanned sets of interim analyses and recommended continuation of the study at both time points. The trial database was locked for the final analysis on 13 March 2013, according to predetermined criteria (9 weeks after enrollment of the last patient). At the time of analysis, 72 events were determined by local investigator review, and 64 events by subsequent masked central review. The median follow-up duration was 5.2 months (interquartile range: 3.4–9.4 months) in surviving patients. A median of three imaging time points per patient were available (range: 2–8). According to a central review, 73% of the imatinib group and 85% of the placebo group patients showed disease progression or had died.

Pharmacokinetic analyses, which measured the plasma imatinib trough concentration after 2 weeks of study treatment, showed that patients in the imatinib arm had an acceptable range of imatinib plasma levels, whereas no plasma imatinib was detectable in most patients in the placebo arm. These results suggested an acceptable adherence to the study treatment regimens in enrolled patients.

Efficacy results

According to the masked external central radiological assessment, the median PFS was 1.8 months (95% CI: 1.7–3.6) in the imatinib group and 0.9 months (0.9–1.7) in the placebo group (Figure 2 & Table 1). Resumption of imatinib was associated with a 54% risk reduction for PFS compared with placebo (HR: 0.46 [95% CI: 0.27–0.78]; p = 0.005). The disease-control rates were significantly higher in the imatinib arm than in the placebo arm at each time point (73 vs 43% at 4 weeks; p = 0.005; 42 vs 15% at 8 weeks; p = 0.008; 32 vs 5% at 12 weeks; p = 0.003). The superiority of imatinib rechallenge in PFS was consistent with the results based on the local investigator assessment (median: 1.8 months [95% CI:

1.7–2.7] vs 1.7 months [0.9–1.8]) with a HR of 0.56 (95% CI: 0.35–0.93; p = 0.019; Figure 3). There was no difference in OS, with a median of 8.2 months (95% CI: 5.5–12.8) in the imatinib arm and 7.5 months (4.4–12.4) in the placebo arm (HR: 1.00 [95% CI: 0.58–1.83]; p = 0.92; Figure 4).

In the placebo arm, 93% of patients crossed over to open-label imatinib after progression on placebo. The median PFS after crossover to open-label imatinib was 1.7 months (95% CI: 1.5–2.0). Furthermore, TKI therapy was given in 20% of patients in the placebo arm after open-label imatinib. In the imatinib arm, 41% of patients continued open-label imatinib after failure of imatinib, resulting in a median second PFS of 1.1 months (95% CI: 0.1–2.1). Otherwise, 22% received other TKIs and 27% did not receive additional anticancer therapies.

Safety results

The study treatments were well tolerated in both arms and there was no treatment-related death. The most common adverse events of any grades in the imatinib arm were anemia (66%) and edema (44%). Although there was no significant difference in the overall incidence of adverse events between the two groups (100% vs 98%; p = 0.49), imatinib rechallenge was significantly associated with more frequent edema (44 vs 13%; p = 0.0027), fatigue (37 vs 13%; p = 0.019), nausea (32 vs 3%; p = 0.0007) and vomiting (32 vs 5%; p = 0.0032). Although severe adverse events were rare overall, imatinib rechallenge was associated with increased incidence of grade 3–4 adverse events compared with placebo (49 vs 18%; p = 0.0043). However, 12 of the 20 cases of grade 3–4 toxicity in the imatinib rechallenge group involved anemia. Except for anemia (29 vs 8%, respectively; p = 0.02), there was no significant association between imatinib rechallenge and each case of grade 3–4 toxicity.

Interpretation & future perspective

The discarding of a particular anticancer agent following disease progression has been the traditional paradigm in the management of cancer patients. In the era of targeted therapy, however, continued treatment with targeted agents beyond disease progression has shown some clinical benefit in patients with other types of cancers [20-24]. This benefit might be due to the different mode of activity of targeted agents compared with conventional cytotoxic chemotherapy.

The RIGHT study is the first randomized trial to show that the resumption of imatinib significantly improves PFS in patients with TKI-refractory GISTs, if there had been no evidence of primary resistance (i.e., progression within 6 months) to initial first-line
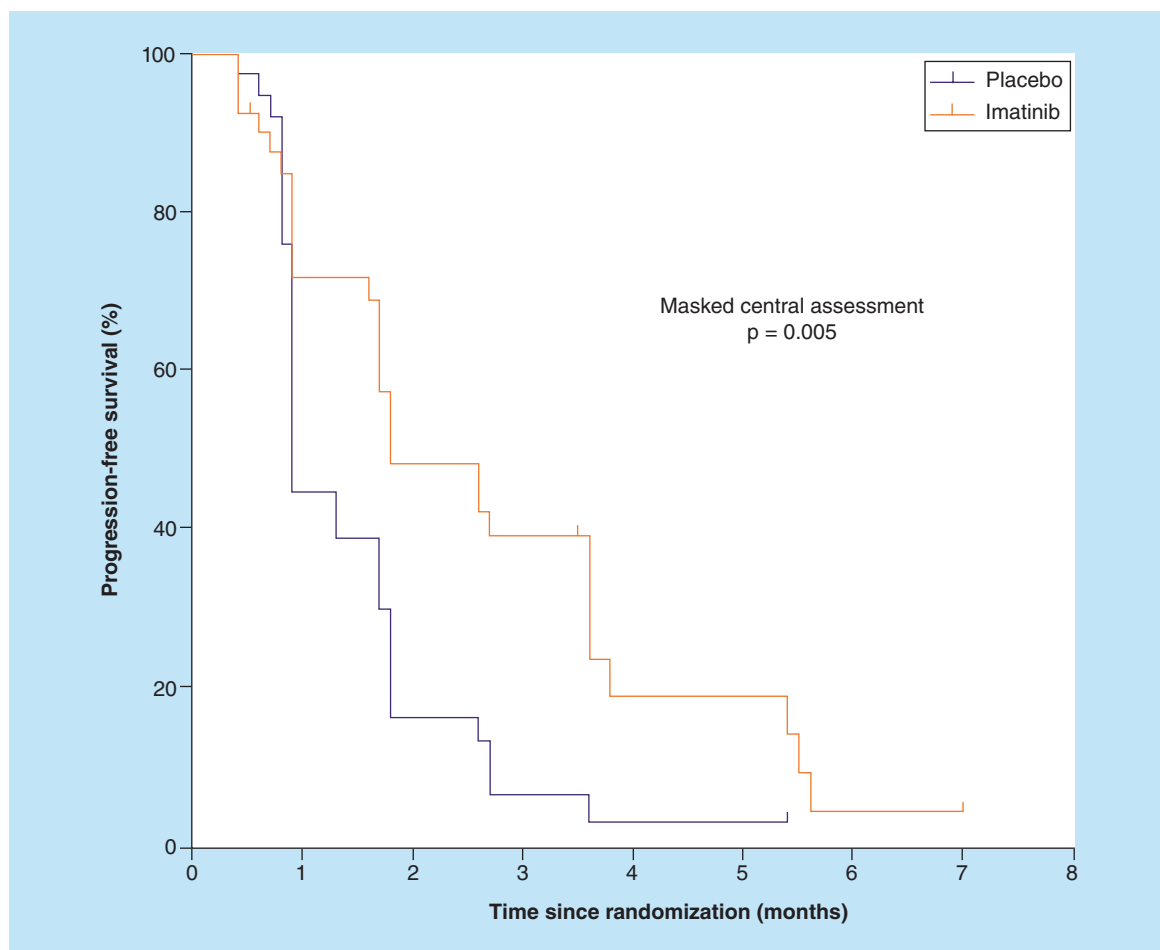
Figure 2. Progression-free survival by masked external review.

imatinib therapy. The results of this trial support the previously recognized concept that the reuse of imatinib can delay disease progression in patients with GIST even after prior failure of the same TKI. Imatinib rechallenge in this trial showed relative risk reduction for PFS (HR of 0.46) with a doubled median PFS compared with a placebo arm (1.8 vs 0.9 months). This impact must be due to the preponderance of imatinib-sensitive tumor clones, which are likely to be more 'fit' in an evolutionary sense. This finding also demonstrated that continuous kinase inhibition after disease progression according to the RECIST may be the alternative treatment for patients not eligible in clinical trials. Although there is no prospective data for the reuse or continuation after progression of other TKIs except imatinib in GIST patients, this strategy might be effective when other TKIs currently available for the treatment of GISTs are used. This is supported by the post hoc analysis of a worldwide treatment-use study of sunitinib, which showed that patients with GISTs who continued on sunitinib after disease progression exhibited a longer OS than those who stopped sunitinib after progression [25]. However, it should be interpreted with

caution because this was based on single-arm study and the influences of different patient or tumor characteristics and selection bias cannot be excluded due to the nature of retrospective analysis. These might indicate that all approved TKIs for GISTs can be resumed or continued for the treatment of refractory GISTs, but the drug tolerability or safety is one of major concerns in salvage therapy, imatinib might have an advantage over sunitinib or regorafenib as a rechallenge therapy.

However, since the entire study population in the RIGHT trial had failed to have continuing disease control despite receiving multiple TKI regimens, including imatinib and sunitinib at a minimum, imatinib rechallenge resulted in a relatively small benefit in terms of the median PFS (about 0.9 months) and a lack of an objective response when evaluated using the conventional response assessment system based on tumor size. Because it is clear that imatinib-resistant clones will progress regardless of the imatinib rechallenge, continued kinase suppression with imatinib may only slow overall disease progression. Thus, the clinical outcomes of imatinib rechallenge might largely depend on the proportion of imatinib-sensitive clones

within the entire tumor or the aggressiveness of the imatinib-resistant clones. However, it is unlikely that these features can be predicted prior to a rechallenge treatment approach. Although imatinib continuation may be a suitable option, if it is well tolerated because the price of imatinib will drop dramatically when its patent expires, we believe that a more flexible approach in patients with far-advanced GISTs may be useful. This, for example, could involve a 'stop or go strategy' involving interim monitoring of drug activity, perhaps using functional imaging modalities or more specific measures of patient-reported outcomes. Although the absolute benefit of prolonged PFS in the overall patient population may be insufficient to be uniformly classified as 'clinically meaningful,' we believe that greater clinical benefit for individuals who differ across the clinical spectrum that comprises 'TKI-resistant GISTs' can be achieved with a more nuanced, individualized approach.

Another consideration is appropriate to take into account for patients with far-advanced disease with no remaining effective treatment options. Not all patients with multiple TKI-refractory disease are hopeless and new investigational drugs may not be available where they live. Novel targeted therapies and combinations are rapidly being developed, such that delaying progression could be meaningful for many medically fit patients without further options by providing sufficient time for novel therapies to become available to them. However, the decision for the imatinib resumption should be done with consideration of patient performance status and life expectancy. Because of short PFS benefit and lack of objective response with imatinib rechallenge, this may not result in clinical benefit,

particularly in patients who have poor performance status and need end-of-life terminal care.

Despite the prolonged PFS, there was no improvement in OS upon imatinib rechallenge in the trial. The lack of a survival benefit in the RIGHT study was likely due to its crossover design, which allowed most patients in the placebo arm to receive imatinib immediately after progression. Similarly, pivotal drug approval trials of sunitinib and regorafenib in GIST patients have also shown that such a crossover study design will have the expected confounding effects on survival [10,26]. For example, the randomized Phase III trial of sunitinib, in which 89% of patients in the placebo arm received sunitinib after progression, found a significant difference in survival after interim analysis of TTP (the primary end point of the study), whereas the final analysis failed to show a significant survival benefit for sunitinib [26]. However, an exploratory analysis using the rank-preserving structural failure time (RPSFT) method found a significant difference in estimated survival between the sunitinib and placebo arms, if the patient outcomes were modeled so as to assume no crossover had been possible [26]. Similarly, in the RIGHT study (in which 93% of patients in the placebo group crossed over to imatinib), it may not be possible to measure the potential survival benefit of imatinib rechallenge within the trial, although we accept that any such impact on OS is likely to be relatively small compared with sunitinib or regorafenib, which have a reportedly longer PFS benefit than imatinib rechallenge.

The lack of an OS benefit with imatinib rechallenge in the RIGHT trial might also be partly

| Table 1. Efficacy outcomes.				
Efficacy variables	Imatinib arm (n = 41), n (%)	Placebo arm (n = 40), n (%)	p-value	Hazard ratio (95% CI)
Progression-free survival (median), months	1.8 (95% CI: 1.7–3.6)	0.9 (95% CI: 0.9–1.7)	0.005	0.46 (95% CI: 0.27–0.78)
Response			0.03	
Complete response/partial response	0	0		
Stable disease	17 (42)	6 (15)		
Progressive disease	19 (46)	29 (73)		
Not evaluable	5 (12)	5 (13)		
Disease control ≥12 weeks†	13 (32)	2 (5)	0.003	
Time-to-progression (median), months	1.8 (95% CI: 1.7–3.6)	0.9 (95% CI: 0.9–1.7)	0.002	0.48 (95% CI: 0.28–0.82)
Overall survival (median), months	8.2 (95% CI: 5.5–12.8)	7.5 (95% CI: 4.4–12.4)	0.92	1.00 (95% CI: 0.58–1.83)
†Complete response or partial response plus stable disease lasting for at least 12 weeks.				
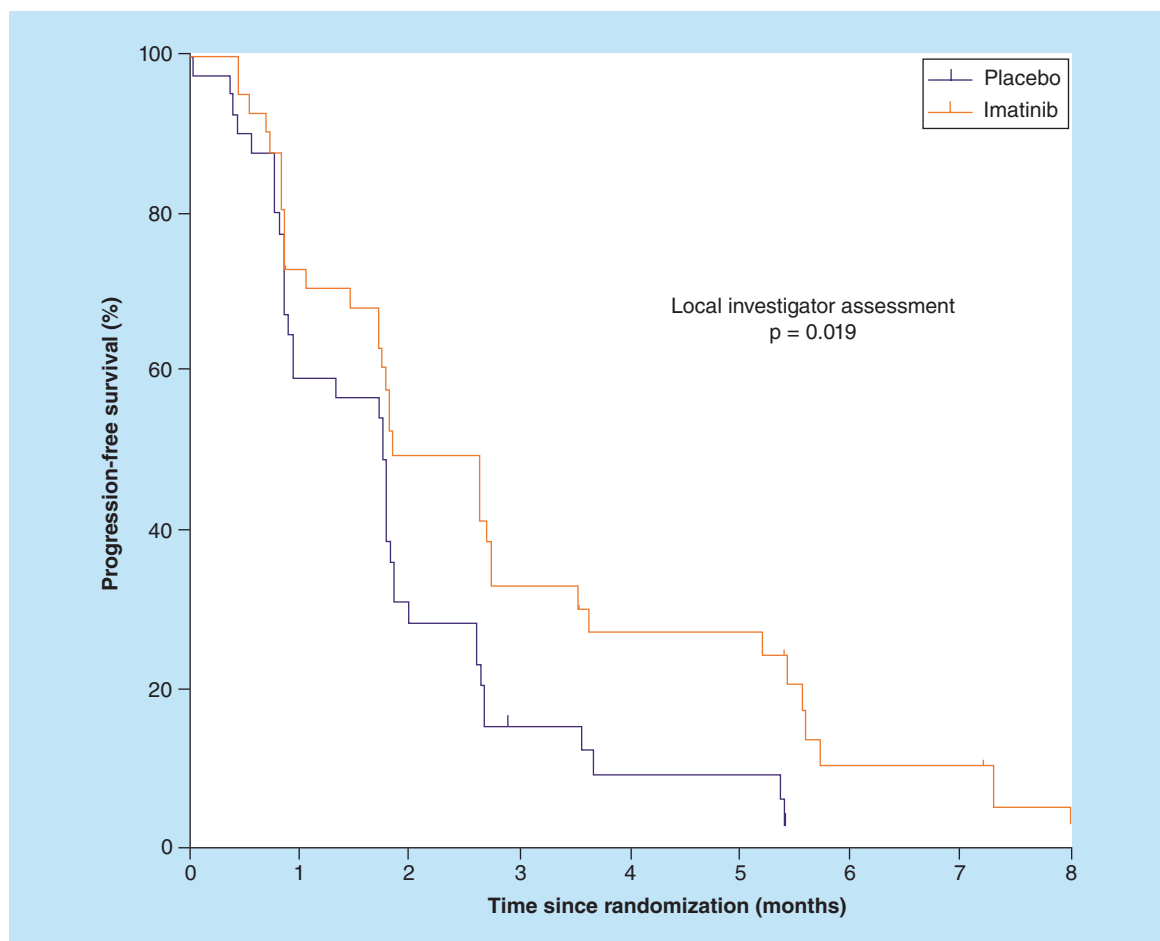
Figure 3. Progression-free survival by the local investigator assessment.

because patients in both the imatinib rechallenge and placebo groups were allowed to continue even after multiple RECIST-defined disease progressions. Considering the registration trials of sunitinib and regorafenib, which allowed study medication continuation until second progression, this difference in trial design might make it more difficult to see any difference in OS. Indeed, most patients continued on imatinib unless they were medically unfit or were able to enroll in clinical trials of other investigational drugs because no other therapeutic option remained. This approach resulted in a longer duration of imatinib exposure in an open-labeled setting (i.e., after first progression on trial) than that of the study medication in a double-blind setting. As a result, there was no significant difference in the total duration of imatinib rechallenge between the imatinib (median: 3.1 months [range: 0.4–16.8 months]) and placebo (median: 2.1 months [range: 0.4–17.0 months]; p = 0.40) arms of the RIGHT study, although patients in the imatinib arm received imatinib earlier than those in the placebo arm. This finding also suggests that frequent CT evaluation

performed in the RIGHT trial may not be feasible or necessary for clinical practice considering its inconvenience and costs. Decision on the continuation of imatinib resumption may be taken based on the possible clinical benefit and imaging studies may be conducted when clinically indicated, not just for regular response evaluation.

The relatively long postprogression survival (median PFS vs OS: 0.9 vs 7.5 months in the placebo arm and 1.8 vs 8.2 months in the imatinib arm) in both arms of the RIGHT study may be attributable to the accumulation of small benefits resulting from continued KIT inhibition by salvage treatment with imatinib, as open-label imatinib resulted in a median second PFS of 1.1 months (95% CI: 0.1–2.1 months) after progression on initial imatinib rechallenge in the imatinib group. Therefore, continuing KIT inhibition with a TKI rechallenge might lead to prolonged survival compared with best supportive care alone in patients with no remaining effective therapeutic option. Previous retrospective studies investigating the impact of imatinib rechallenge on OS showed significant differences in OS between patients
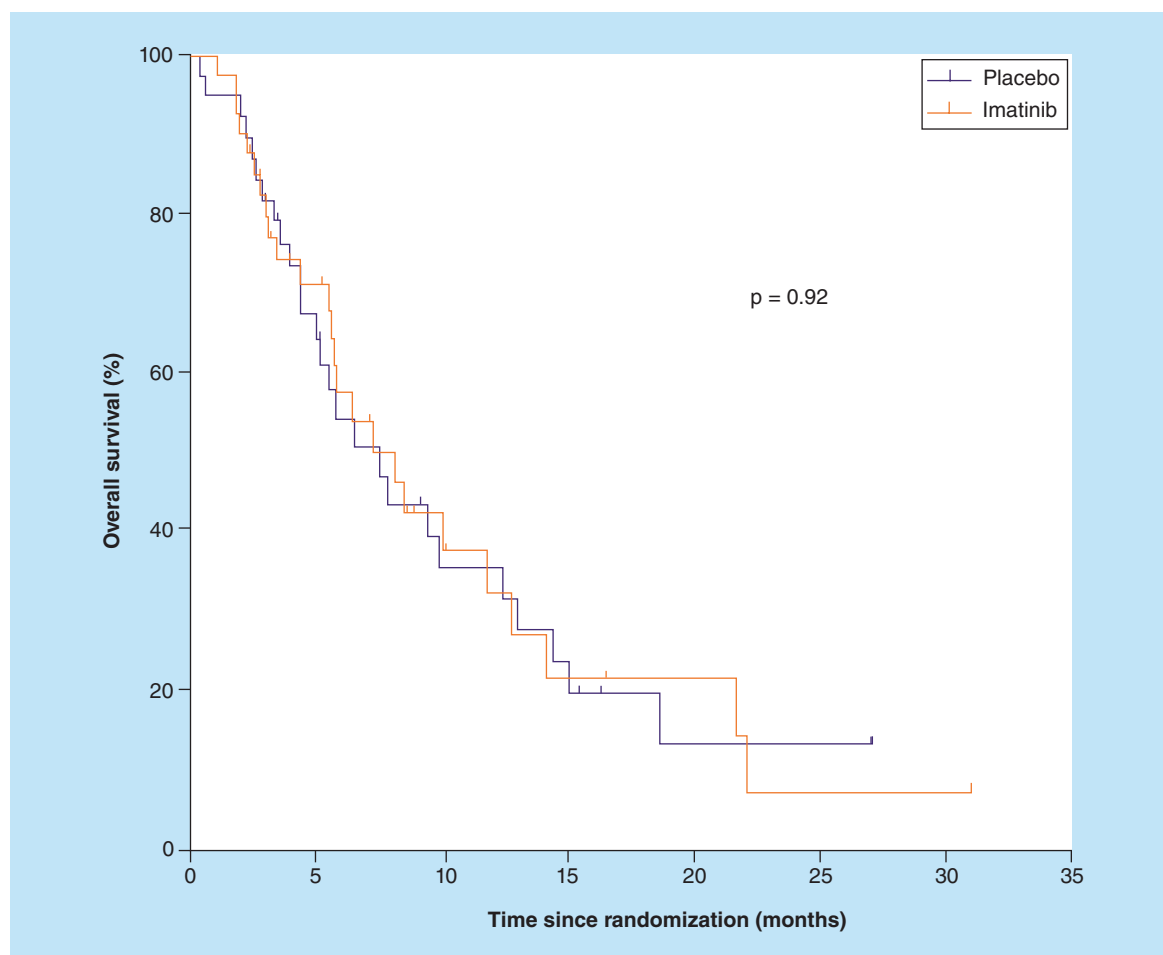
Figure 4. Overall survival.

who received imatinib and those who received best supportive care only [16–17,27].

One may argue that OS is an optimal end point to show the overall impact of imatinib rechallenge by not allowing crossover to imatinib in the placebo group. However, the prospective comparison of imatinib rechallenge versus placebo to detect any impact on OS can be regarded unethical considering that retrospective studies have suggested the clinical benefit of imatinib rechallenge, and it is also highly questionable from the standpoint of patient acceptability. In addition, although RECIST is widely considered a standard indicator in clinical trials of novel anticancer agents, in heavily pretreated GIST patients with high tumor burden, RECIST may have potential pitfalls to measure the real efficacy of agents due to the considerable heterogeneity among the tumors. Based on this, assessment of metabolic activity by ^{18}F-fluorodeoxyglucose (FDG)-PET has been investigated to predict the treatment outcomes in patients with GISTs [28,29]. But, it still needs further validation to be used as a primary end point of clinical trials for

refractory GISTs [29]. Further investigations for optimal end points in refractory GISTs may be helpful to enhance the feasibility and efficiency of trials.

One of the arguments is that imatinib rechallenge can really improve quality of life (QoL) because the relief of tumor-associated symptoms may address other aspects of clinical benefit with imatinib rechallenge. Furthermore, because of significantly increased toxicities in the imatinib arm, the impact of imatinib rechallenge on health-related QoL needs to be defined to assess whether its PFS benefit is accompanied with symptom palliation or counterbalanced by imatinib-induced toxicities. The results of the QoL analysis in the RIGHT trial have not been reported yet and will be presented elsewhere. However, it is unclear whether this subanalysis can show that imatinib rechallenge has potential benefits in terms of QoL because the RIGHT trial was not primarily designed to examine this outcome. Furthermore, QoL status was assessed only during the double-blind phases of the trial, potentially limiting the power of the analysis since the double-blind phase was of short duration

only in both study arms. In studies of patients with far-advanced disease, such as the RIGHT trial, the exclusion of patients who refused to complete QoL questionnaires because of poor general condition may result in an under- and overestimation of the impact of investigational drugs and placebo, respectively, on QoL. Due to these limitations, subanalysis in the earlier GRID trial could not demonstrate the QoL benefits of regorafenib [30].

Resumption of imatinib was well tolerated in the RIGHT trial but associated with a significant increase in grade 3–4 toxicity compared with placebo as a cost of PFS benefit. However, most grade 3–4 toxicities in the imatinib rechallenge group were anemia [14], which may not directly reduce QoL, if supportive care is appropriately provided. Except for anemia, there was no significant difference in the incidence of grade 3–4 toxicity between the two arms. Although the relatively high rate (10%) of grade 3–4 fatigue in the imatinib rechallenge group was a concern [31], there was a lack of statistical significance and no patient experienced disabling grade 4 fatigue. Furthermore, grade 3 fatigue in the imatinib rechallenge group may not be attributable to imatinib *per se*, since patients in the RIGHT trial were heavily pretreated and had large tumor burdens, with 30% having an ECOG performance status of 2–3 at baseline [14].

The assessment of the clinical benefit of a novel strategy should also consider its economic and social burden, as drug costs vary by country in accordance with various payer systems. Unfortunately, the cost-effectiveness of imatinib rechallenge was not evaluated in the RIGHT trial. Some clinicians may consider that imatinib rechallenge has a limited cost-effectiveness

at the current high price of imatinib. However, the price will drop dramatically once the patent expires and generic imatinib is available on the market (as has already happened in certain countries), resulting in a reduced financial burden to society and patients.

The results of the RIGHT trial may have implications for the design of future randomized trials for patients with TKI-refractory GISTs. Placebo-controlled trials can surely give the most accurate information on the safety and efficacy of a new intervention. However, there may be other reasons to use imatinib as the control intervention in future clinical trials. Use of imatinib could rule out the possibility that the effect of any new kinase inhibitor is simply on preexisting imatinib-sensitive clones; this will be important to rule out, since generic imatinib will be far less expensive than any newly developed proprietary agent from future trials. In randomized clinical trials, participants assigned to the control arm have the right to receive the best available standard treatment, even if the benefits are not large. In future randomized trials of investigational drugs for TKI-refractory GISTs, using some 'active' treatment such as imatinib rechallenge as the control arm may also help patients and investigators to accept the use of a noncrossover study design, allowing adequately powered statistical analysis of OS.

As mentioned in the original paper [14], GIST patients who have experienced failure of all proven standard treatments, including imatinib, sunitinib and regorafenib, should be considered for participation in appropriate clinical trials of novel agents rather than being put back on imatinib. If these patients are ineligible for these trials; however, ima-

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Executive summary

- Despite the advances in the management of advanced gastrointestinal stromal tumors (GISTs), most standard therapies eventually stop working due to a polyclonal evolution of the disease that results in resistance to tyrosine kinase inhibitors (TKIs).
- The RIGHT trial was an investigator-initiated, randomized, placebo-controlled, Phase III trial designed to measure the efficacy and safety of imatinib rechallenge in GIST patients who previously benefited from imatinib but subsequently progressed on at least imatinib and sunitinib.
- In the RIGHT trial, imatinib rechallenge was well tolerated and showed impressive relative risk reduction for progression-free survival (hazard ratio of 0.46) with a doubled median progression-free survival compared with placebo (1.8 vs 0.9 months).
- Although there was no survival benefit with imatinib rechallenge in the RIGHT study, this finding was likely due to its crossover design, which allowed most patients in the placebo arm to receive imatinib immediately after progression.

Future perspective

- The results of the RIGHT trial suggest that continuing KIT inhibition with TKI rechallenge might lead to prolonged survival compared with best supportive care alone in patients with no remaining effective therapeutic option.
- In future randomized trials of investigational drugs for TKI-refractory GISTs, the use of some 'active' treatment such as imatinib rechallenge as the control arm may help to exclude the possibility that the effect of any new kinase inhibitor is simply on the preexisting imatinib-sensitive clones.

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tinib rechallenge is still a clinically relevant option, as the PFS is doubled compared with no treatment (1.8 vs 0.9 months). Because of its relatively small benefit, we admit that salvage treatment with imatinib rechallenge may not become a uniform standard. However, it should remain an option accessible for patients with no effective or investigational treatment options.

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