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A systematic review and network meta-analysis of post-imatinib therapy in advanced gastrointestinal stromal tumour

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ABSTRACT

Background The standard first-line systemic therapy for advanced gastrointestinal stromal tumour (GIST) is imatinib. However, most GISTs develop imatinib resistance, highlighting the need for new agents in the imatinib-refractory setting. Currently, no randomized studies have directly compared the available post–first-line treatments.

Methods In a systematic review, the MEDLINE, EMBASE, and CENTRAL databases, and American Society of Clinical Oncology abstracts to July 2014 were searched to identify randomized controlled trials that included GIST patients treated with post–first-line therapies. Hazard ratios (HRs) for progression-free (PFS) and overall survival (OS) were extracted. Direct pairwise meta-analyses and indirect comparisons using the Butcher method were performed.

Results Four studies were identified for the systematic review. One study showed that sunitinib in the second-line setting (vs. placebo) was associated with improved PFS, but not improved OS. Three studies examined the third-line setting (imatinib resumption vs. placebo, regorafenib vs. placebo, nilotinib vs. best supportive care). In the third-line settings, the two placebo-controlled and the non-placebo-controlled trials showed significant heterogeneity (I^2 = 98%). Indirect comparisons of imatinib resumption and regorafenib suggested that the HR for PFS was 0.59 (95% confidence interval: 0.31 to 1.12; p = 0.10), trending in favour of regorafenib. Indirect comparisons found that toxicities were higher in the regorafenib group, with a risk difference of 27.8% for any-grade toxicities and 19.5% for grades 3 and 4 toxicities.

Conclusions Because a head-to-head study of imatinib resumption compared with regorafenib is unlikely ever to be conducted, our study suggests that, in terms of PFS, regorafenib might be the preferred treatment. However, given the increased toxicity observed with regorafenib, clinicians should interpret that evidence with caution at an individual patient level.

Key Words Gastrointestinal stromal tumour, second-line therapy, chemotherapy, antineoplastic therapy, molecularly targeted therapy, refractory disease, network meta-analyses, systematic reviews

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INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract[1]. Their unique histologic, immunophenotypic, and molecular genetic features distinguish them from other smooth-muscle gastrointestinal tumours[2]. Gastrointestinal stromal tumours can develop anywhere in the gastrointestinal tract, but more than half arise in the stomach, and 25% originate in the small bowel[1]. Most patients diagnosed with GIST are more than 50 years of age at time of diagnosis, and the incidence of GIST is equal in men and women[3]. Gastrointestinal stromal tumours share many histologic characteristics with the interstitial cells of Cajal, such that those cells have been considered the putative cells of origin[4]. In patients with localized disease, the main treatment is complete surgical resection, ideally without tumour rupture.

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Approximately 50% of patients with GIST present with metastatic disease, and management becomes more complex in those patients[3]. Aggressive GISTs most commonly metastasize to the liver and throughout the abdomen[3]. Even for resectable tumours after adjuvant therapy with imatinib, subsequent relapse is still a risk for many patients—at which time, treatment is generally considered to be palliative.

Extensive research starting in the early 2000s identified activating mutations in the *KIT* oncogene or in *PDGFRA*, as well as a number of other unique mutations. That breakthrough led to the development of imatinib—a powerful and relatively selective and competitive inhibitor of all Abl tyrosine kinases, PDGFR, and c-Kit—for the treatment of advanced GIST. Imatinib selectively binds to the ATP-binding sites of the kinase it is targeting and prevents downstream signalling of the tyrosine kinase, thereby reducing cellular proliferation and increasing apoptosis[5]. Imatinib was the first effective systemic therapy for metastatic or localized unresectable GIST. However, in a pivotal study of imatinib for the treatment of advanced GIST, 5% of patients showed primary resistance to imatinib, and another 14% developed early resistance[6]. Secondary or acquired resistance commonly develops after about 2 years of treatment, usually because of secondary *KIT* mutations. Because of the growing problem of imatinib resistance, other targeted agents were developed as post–first-line treatments.

Although several novel tyrosine kinase inhibitors (TKIs) have been examined in the post–first-line setting, only sunitinib and regorafenib have been approved for patients who progress after initial imatinib therapy or who are imatinib-intolerant. Although some studies to compare treatments for GIST in the post–first-line setting and in the second-line setting have been conducted, no consensus has yet been reached concerning treatments that are effective for GIST after imatinib resistance.

A network meta-analysis (NMA) is able to synthesize evidence from randomized controlled trials (RCTs) using both direct (head-to-head) and indirect (common comparator) comparisons[7]. It is a useful tool in instances in which direct evidence is not available, and it is frequently used by health care decision-makers such as the U.K. National Institute for Health and Care Excellence[8]. Network meta-analyses have been effectively used in making treatment comparisons in pancreatic, colorectal, and breast cancer, among others[9–11].

In the present study, we used a systematic review to identify second- and third-line therapeutic agents for the treatment of GIST and a NMA to compare those agents.

METHODS

Literature Search

For the systematic review, the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases and American Society of Clinical Oncology meeting abstracts were searched up to and including 1 July 2014. Combinations of the following key words and corresponding MESH terms were used for the literature searches: "gastrointestinal stromal tumor," "neoplasm metastasis," "palliative care," and "advanced." Studies were limited to RCTs. Those searches yielded 161 hits in MEDLINE, 952 in EMBASE, and 58 in CENTRAL. Systematic reviews and meta-analyses on the topic were also screened to identify any publications that had not been identified in the literature search. Details of the search strategies for each database can be seen in Table I.

To be eligible for our review, studies had to

- involve advanced, metastatic, or unresectable or inoperable GISTs;
- enrol patients who had previously been treated with a first-line chemotherapy regimen for advanced disease; and
- be phase II or phase III RCTs.

The outcomes of interest included progression-free survival (PFS) and overall survival (OS). Only trials that reported at least one of the outcomes of interest were included in the review. Nonrandomized trials and those not specific to GIST were excluded. Trials with comparators of radiotherapy, hormonal therapy, or gene therapy were excluded. No language restrictions were imposed. We contacted authors directly to request access to publications that were not available to us.

Screening and Data Extraction

Two independent reviewers screened titles and abstracts of the studies identified in the literature search, and full texts of any potentially relevant articles were obtained. The full texts were also independently reviewed by the same two authors, who applied the eligibility criteria that had been decided *a priori*. When studies overlapped or were duplicated, we retained the study reporting the most recent information that could be used in the meta-analysis. Any discrepancies between reviewers were resolved by discussion or consultation with a third author for consensus. The literature review was reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1). The methodologic quality of each included study was assessed using the Cochrane risk of bias tool[12].

Data extraction was also completed independently by two authors using a standardized data extraction form. Any discrepancies were resolved through discussion. The recorded information included first author, study name, publication year, study location, regimens being compared, prior first-line regimens that patients had received, number of patients in each arm, median age of the patients, ratio of male to female patients in the study, inclusion and exclusion criteria for each included trial, and the treatment dose and schedule. Treatments were sorted into categories based on the regimens being compared. The data extracted from each study included median PFS, median OS, number of partial and complete responses, and number of grade 3 or 4 adverse events (diarrhea, fatigue, anorexia, nausea, constipation, vomiting, thrombocytopenia, and anemia) for all treatment arms. If the hazard ratios (HRS) for OS and PFS were available in the publication, they were extracted directly, together with their 95% confidence intervals (CIS). A two-tailed p value less than 0.05 was recorded, whenever available, to determine whether a statistically

TABLE I Search strategy for the literature review

Database	Period	Search steps	Hits
Ovid MEDLINE and Ovid OLDMEDLINE			
	<1946 to July Week 1, 2014		
	1.	Gastrointestinal Stromal Tumors/ or gastrointestinal stromal tumor*.mp.	5,582
	2.	exp Neoplasm Metastasis/	156,625
	3.	Palliative care/	40,507
	4.	(advanced or metastat* or palliative or unresectable or inoperable or refractory or relapse*).mp.	571,908
	5.	1 and (2 or 3 or 4)	1,575
	6.	limit 5 to clinical trial, all	161
	7.	limit 5 to (meta analysis or "review" or systematic reviews)	461
EMBASE Classic and EMBASE			
	<1947 to 2014 Week 28		
	1.	gastrointestinal stromal tumor/ or (gastrointestinal stromal tumor* or gastrointestinal stromal tumour*).mp.	11,463
	2.	advanced cancer/	51,500
	3.	exp metastasis/	424,620
	4.	cancer palliative therapy/	15,528
	5.	(advanced or metastat* or palliative or unresectable or inoperable or refractory or relapse*).mp.	920,243
	6.	1 and (2 or 3 or 4 or 5)	4,446
	7.	limit 6 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)	952
	8.	limit 6 to (meta analysis or "systematic review")	66
	9.	limit 6 to "review"	1,244
	10.	8 or 9	1,270
EBM Reviews—Cochrane Central Register of Controlled Trials			
	<June 2014		
	1.	Gastrointestinal stromal tumors/or (gastrointestinal stromal tumor* or gastrointestinal stromal tumour*).mp.	101
	2.	exp Neoplasm Metastasis/	3,201
	3.	Palliative care/	1,084
	4.	(advanced or metastat* or palliative or unresectable or inoperable or refractory or relapse*).mp.	41,342
	5.	1 and (2 or 3 or 4)	58

significant difference was detected between the regimens being compared.

Statistical Analysis

Pairwise meta-analyses were conducted using the Review Manager software (version 5.2.5: The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Hazard ratios for both OS and PFS were generated in Review Manager using random effects.

The methods of Bucher *et al.*[13] were used for performing indirect comparisons. In meta-analysis, the combined measure of association is calculated by taking the weighted average from each included study, the weights being the inverse of the variance of each study. Degrees of freedom were calculated as the number of pairwise comparisons included in the meta-analysis. The measure of association for the indirect comparisons was found by taking the ratio of the log HRs from each comparison[13].

The primary endpoint was PFS, and the secondary endpoints were OS, response rate, disease control rate, all-grade toxicities, and grades 3 and 4 toxicities. The PFS and OS are summarized as log[HR]; the response rate, disease-control rate, all-grade toxicities, and grades 3 and 4 toxicities are summarized as percentages; and the differences between treatments are represented by risk difference (that is, the difference between the percentages). Between-study heterogeneity was also estimated and reported using the I^2 statistic, which ranges from 0% to 100%, where 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity[13].

RESULTS

Literature Search

The literature search identified 1183 studies, and after duplicates had been removed, 1069 citations were reviewed. Based on the pre-specified eligibility criteria, 1054 studies were excluded, and the remaining 15 studies underwent full-text review. Of those fifteen studies, eleven were excluded: two were abstracts of (included) full studies, three

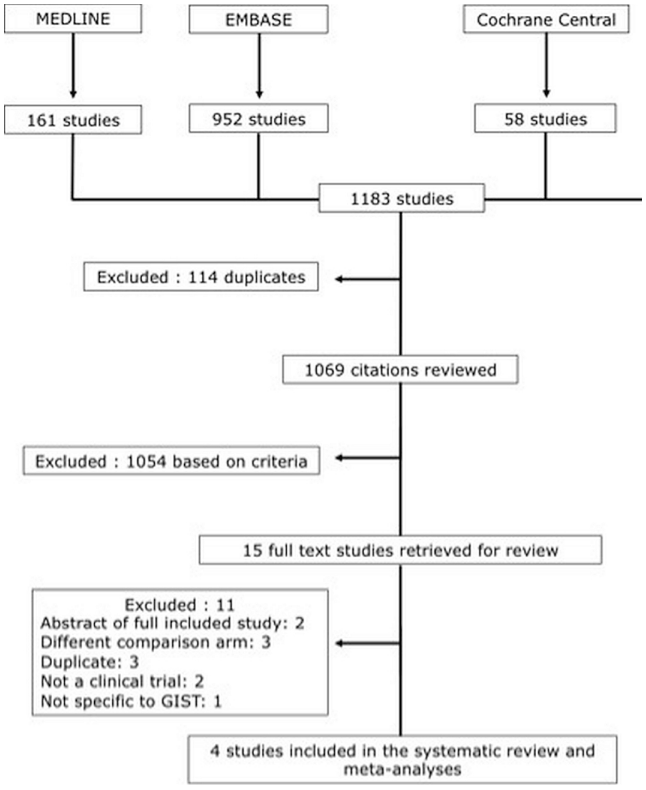

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the literature search.

had a different comparator arm, three were duplicates, two were not clinical trials, and one was not specific to GIST. Of the four studies thus included in the systematic review[14–17], one (the 2006 study by Demetri *et al.*[16]) compared sunitinib with placebo as second-line therapy in imatinib-resistant GIST patients. Of the remaining three studies, two[15–16] compared a third-line chemotherapy regimen with placebo in patients who had become refractory to imatinib and sunitinib therapy. The fourth study was a trial by Reichardt *et al.*[17] that compared nilotinib as a third-line agent with best supportive care (BSC), with or without imatinib or sunitinib. Because the placebo arm in the latter trial was contaminated with sunitinib or imatinib treatment, and because no distinction was made in the reporting of outcomes between patients receiving imatinib or sunitinib in addition to BSC, the Reichardt *et al.*[17] study was not included in the network comparisons. It was, however, included in the quantitative synthesis and in the systematic review. The literature search is summarized in a PRISMA flow diagram (Figure 1).

All included studies were RCTs that included descriptions of the randomization sequence. Allocation concealment was adequately explained in two of the trials[14,15], but was not discussed in the remaining two studies[16,17], which might lead to some selection bias. Blinding of participants and personnel occurred in three of the studies (the exception being the Reichardt *et al.*[17] trial). The risks of attrition and reporting bias are low in all the studies, because all enrolled participants were included in the primary outcome analysis and all planned outcomes were reported. The risk of bias for the included studies is summarized in Figures 2 and 3.

Trial Characteristics

Of the four trials included in the systematic review, three examined treatment for GIST in the third-line setting, and one, in the second-line setting.

Figure 4 presents the treatment strategy network for the third-line treatments being compared. One trial (199 patients) compared regorafenib with placebo in patients previously treated with imatinib and sunitinib[14]. A second trial compared imatinib resumption with placebo in 81 randomized patients who were refractory to imatinib and sunitinib[15]. The third trial (248 patients) compared nilotinib with BSC, with or without imatinib or sunitinib, in patients for whom imatinib and sunitinib therapy had failed. The primary endpoint for all those trials was PFS, but OS, time to progression, objective response rate, disease control rate, and toxicity were also reported.

The fourth study, which looked at second-line treatment with sunitinib compared with placebo in 312 patients previously treated with imatinib[16], was considered separately in the meta-analysis because it was the only second-line trial.

Table II summarizes the characteristics of each included study.

Comparison of Regimens

Third-Line Setting

The third-line studies were compared using direct pairwise comparisons in random effects, which found that the PFS and OS in each study were higher for the treatment arm than for the control arm (Table II). In a subgroup analysis, the two placebo-controlled trials (imatinib resumption and regorafenib) and the non-placebo-controlled trial (nilotinib) were compared (Figures 5 and 6). That analysis found significant heterogeneity (I^2 = 91%) between the placebo-controlled and non-placebo-controlled trials. The two groups were therefore analyzed separately.

Placebo-Controlled Studies: Direct pairwise meta-analysis in random effects of the two placebo-controlled third-line studies (regorafenib vs. placebo and imatinib resumption vs. placebo) showed that the HR for PFS was 0.34 (95% CI: 0.20 to 0.57; Figure 5) and the HR for OS was 0.88 (95% CI: 0.58 to 1.34; Figure 6).

Non-Placebo-Controlled Study: The HR for PFS for the non-placebo-controlled study (nilotinib vs. BSC with or without imatinib or sunitinib) was 0.90 (95% CI: 0.56 to 1.26; p = 0.56), and the HR for OS was 0.79 (95% CI: 0.52 to 1.21)—values that were extracted from the publication by Reichardt *et al.*[17].

Network Meta-analysis: Indirect comparison of imatinib resumption and regorafenib suggested that the PFS HR was 0.59 (95% CI: 0.31 to 1.12; p = 0.10), which favours regorafenib, but not with statistical significance (Figure 5). The OS HR was also not significant for this indirect comparison in the third-line setting.

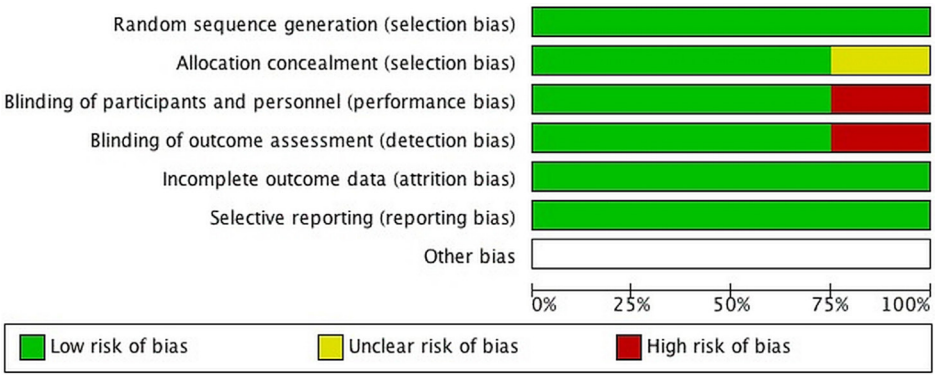

FIGURE 2 Overall risk of bias in the included randomized controlled trials[14–17].

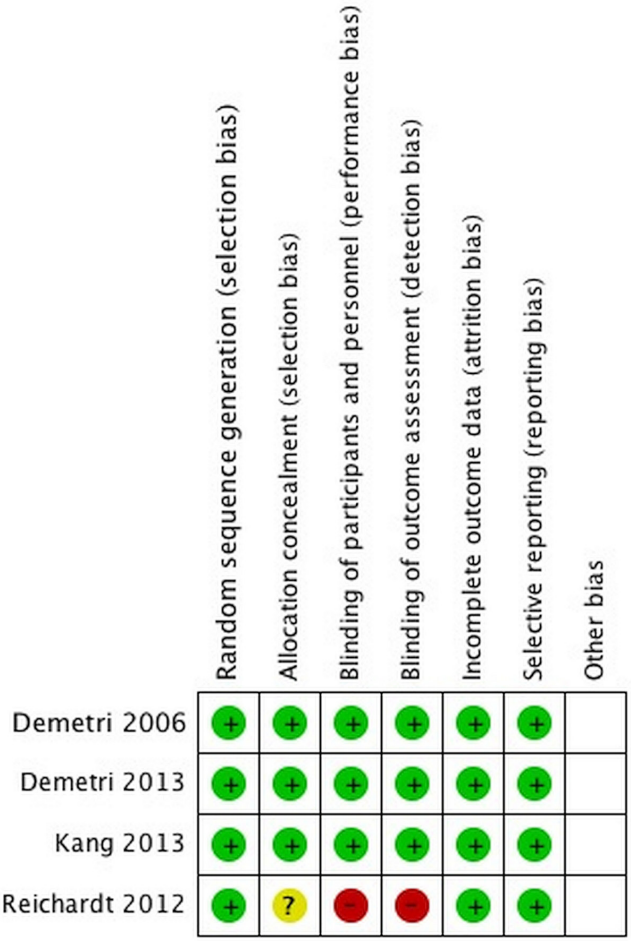

FIGURE 3 Risk of bias by trial design factor and trial[14–17].

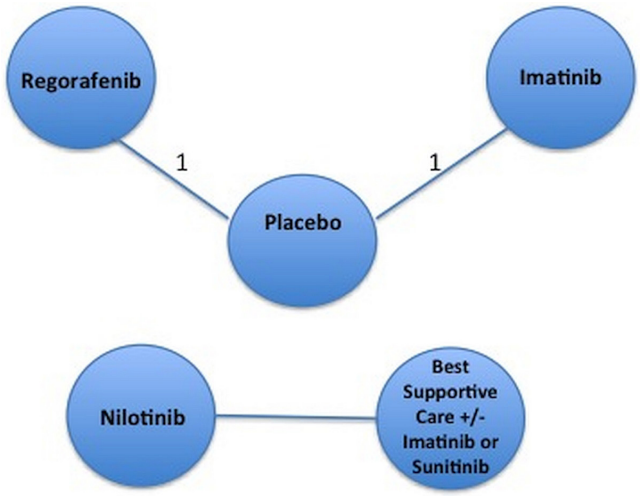

FIGURE 4 Treatment strategy network for third-line treatments.

Indirect comparisons of regorafenib with imatinib resumption found a minimal risk difference of 3% for the response rate (95% CI: –4.8% to 9.7%; $p = 0.38$) favouring regorafenib. The risk difference for the disease control rate was 16.8% in the regorafenib group (95% CI: –2.4% to 36.0%; $p = 0.09$); however, that difference was not statistically significant. Indirect comparisons for toxicities found a statistically significant risk difference of 27.8% (95% CI: 11.3% to 44.3%; $p < 0.001$) for any-grade toxicities and 19.5% (95% CI: –0.4% to 39.4%; $p = 0.05$) for grades 3 and 4 toxicities. Thus, when considering toxicities, imatinib resumption is the more favourable option.

Second-Line Setting

In the second-line setting, only one study in which sunitinib was compared with placebo was identified. The HR for PFS was 0.33 (95% CI: 0.24 to 0.47), and the HR for OS was 0.49 (95% CI: 0.29 to 0.83). Both values are statistically significant compared with placebo.

DISCUSSION

Key Findings and Implications

The current standard first-line therapy for metastatic or unresectable GIST is imatinib, with sunitinib being used in the second-line setting. However, no regimen has been established for use after failure of imatinib and sunitinib, although many clinicians prescribe regorafenib. Our study aims to fill that gap using a systematic review

TABLE II Characteristics of the four trials included in the systematic review

Reference	Regimen	Pts (*n*)	Survival duration						Toxicities [*n* (%)]		ORR (%)	Disease control rate (%)
			Progression-free			Overall			All grades	Grades 3 and 4		
			Median (months)	HR	95% CI	Median (months)	HR	95% CI				
Second-line treatment												
Demetri *et al.*, 2006[16]	Sunitinib	207	5.5	0.33	0.20 to 0.47	Not reported	0.49	0.29 to 0.83	168 (83)	Not reported	27.5	69.5
	Placebo	105	1.4						60 (59)		35.2	69.6
Third-line treatment												
Demetri *et al.*, 2013[14]	Regorafenib	133	4.8	0.27	0.19 to 0.39	Not reported	0.77	0.42 to 1.41	130 (98)	79 (60)	4.5	52.6
	Placebo	66	0.9						45 (68)	6 (9)	1.5	9.1
Kang *et al.*, 2013[15]	Imatinib	41	1.8	0.46	0.27 to 0.78	8.2	1.0	0.58 to 1.83	41 (100)	20 (49)	0.0	31.7
	Placebo	40	0.9			7.5			39 (98)	7 (18)	0.0	5.0
Reichardt *et al.*, 2012[17]	Nilotinib	165	3.58	0.9	0.65 to 1.26	10.6	0.79	0.52 to 1.22	164 (99)	29 (17.6)	0.6	52.7
	BSC with or without imatinib or sunitinib	83	3.61			9.2			78 (94)	10 (12)	0.0	44.6

Pts = patients; HR = hazard ratio; CI = confidence interval; ORR = objective response rate; BSC = best supportive care.

and NMA of studies that trialed treatments of GIST in the post–first-line setting.

In the second-line setting, our analysis found that statistically significant improvements in OS and PFS were associated with sunitinib compared with placebo. Of the three third-line treatments, two were placebo-controlled: regorafenib compared with placebo, and imatinib resumption compared with placebo. Direct pairwise meta-analysis of those two studies found that, compared with placebo, regorafenib and imatinib resumption both provided better PFS, but not OS, in patients who developed imatinib resistance (PFS HR: 0.34; OS HR: 0.88). The non-placebo-controlled study of nilotinib compared with BSC with or without imatinib or sunitinib also showed improved PFS in the nilotinib arm. That study was not included in the indirect comparisons because it had no study arm in common the other studies.

Based on our indirect comparison (Figure 7), regorafenib was found to be the most favourable regimen in terms of PFS for the treatment of GIST in the post-first-line setting. The indirect comparisons of imatinib resumption and regorafenib found a PFS HR of 0.59 favouring regorafenib. Regorafenib is a novel multi-targeted TKI used in the treatment of metastatic colorectal cancer and imatinib- and sunitinib-resistant GISTs. Few studies have examined TKIs in the imatinib- and sunitinib-refractory setting. The GRID trial, which randomized patients with GIST to either placebo or regorafenib, demonstrated a favourable trend in PFS that led to unblinding of the trial and crossover to regorafenib for patients who were receiving placebo[14]. In our indirect comparison, a superior treatment in terms of OS could not be determined, even with an indirect pairwise comparison. The disease control rate was also higher in the regorafenib group, and the response rate showed a minimal risk difference.

When comparing the relative safety of regorafenib and placebo, the GRID trial found that 98% of assessable patients in the regorafenib group and 68% in the placebo group experienced drug-related adverse events. The most common grade 3 or greater regorafenib-related adverse events were hypertension (31 of 132 patients, 23%), hand–foot skin reaction (20%), and diarrhea (5%). Hypertension is likely related to the drug's antiangiogenic effects and can be managed with dose modification or antihypertensive agents. The hand–foot skin reactions are commonly implicated in other multi-targeted TKIs. Adverse events leading to the permanent discontinuation of treatment were similar in the two groups. Most of those adverse events could be managed by dose modification; the safety profile of regorafenib therefore does not appear to outweigh its benefits in terms of efficacy. Our indirect comparisons suggest that regorafenib is associated with more all-grade toxicities and trends toward more all-grade toxicities when compared with imatinib resumption.

Another post–first-line therapy that could be considered is high-dose imatinib after failure of standard-dose imatinib therapy for advanced GIST. Blanke *et al.*[18] published a randomized phase III trial that compared standard-dose imatinib (400 mg once daily) with high-dose imatinib (400 mg twice daily) as first-line systemic therapy in patients with incurable GIST. Their study found

that the standard dose was effective and that no statistically significant difference in PFS, OS, or objective response rate was evident between the two doses. However, after progression on standard-dose imatinib, 33% of patients who crossed over to the high-dose group achieved an objective response and stable disease. No increase in toxicities was observed in the high dose group. Therefore, after failure of imatinib in the first-line setting at the standard dose of 400 mg daily, dose escalation could be considered as a post–first-line therapy. Because the Blanke *et al.* study randomized patients to therapies in the first-line setting, it was not included in our analysis. The trial by Kang *et al.*[15], which compared imatinib resumption at the standard dose with placebo, administered only the standard dose of imatinib, and so a higher dose in the post–first-line setting remains to be studied in a head-to-head trial.

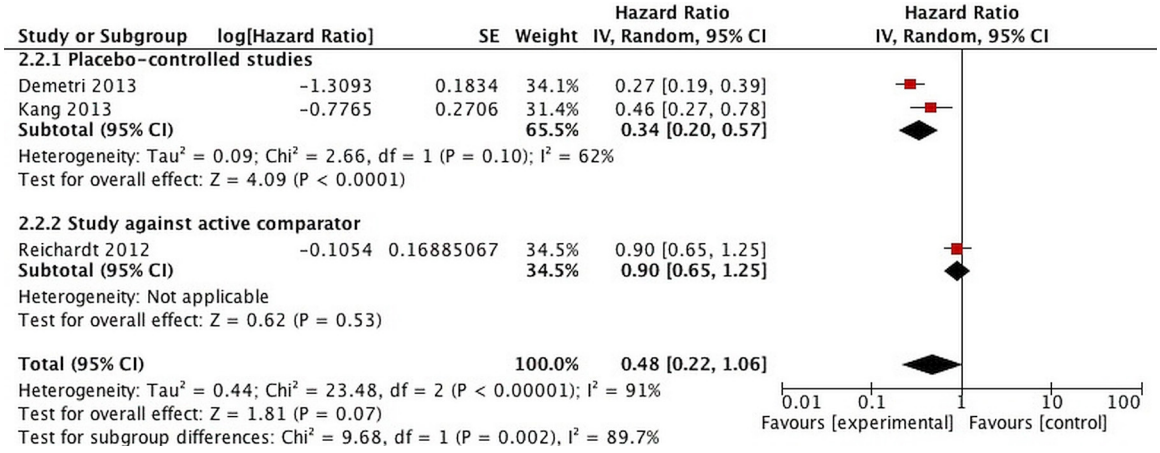

FIGURE 5 Subgroup analysis of progression-free survival in random effects of two placebo-controlled trials. SE = standard error; IV = inverse of variance; CI = confidence interval.

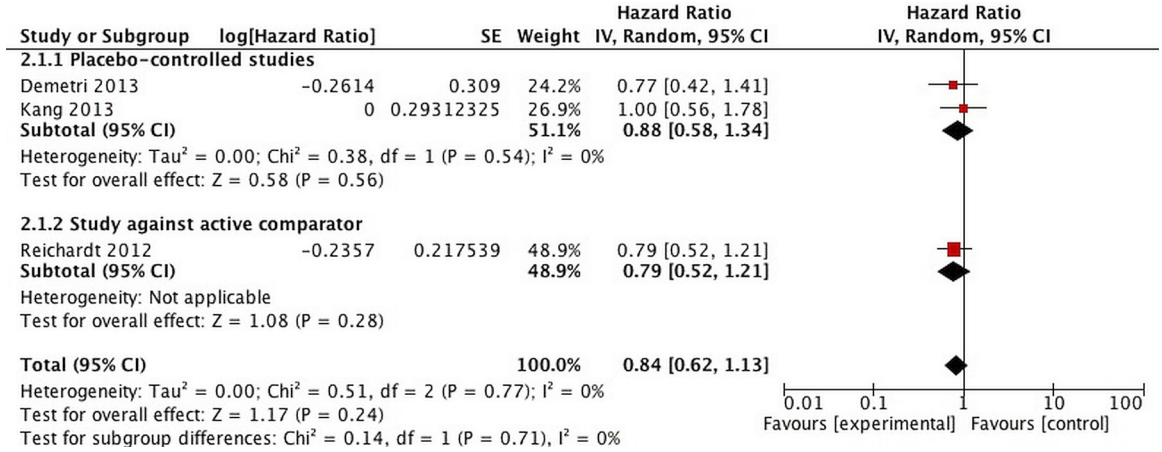

FIGURE 6 Subgroup analysis of overall survival in random effects of two placebo-controlled trials. SE = standard error; IV = inverse of variance; CI = confidence interval.

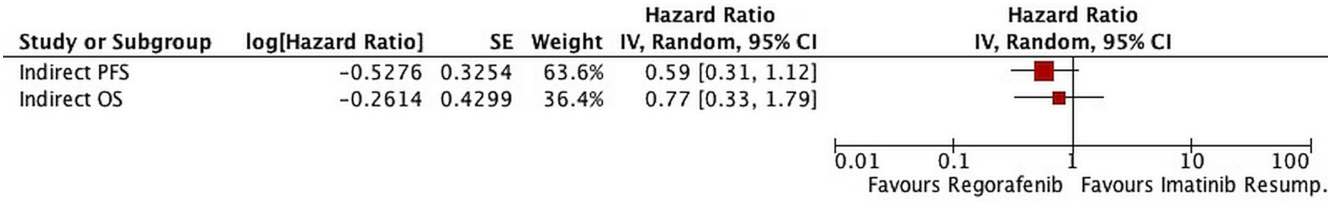

FIGURE 7 Indirect comparison of progression-free survival (PFS) and overall survival (OS) with regorafenib or continuation of imatinib. SE = standard error; IV = inverse of variance; CI = confidence interval.

Strengths and Limitations

Our NMA and systematic review have number of strengths. A thorough and robust literature search strategy was used, and to ensure accuracy, the data were extracted by two independent authors. Although NMA allows for indirect comparisons, ensuring the homogeneity and consistency of the included studies across the treatment network is important. In our NMA, indirect comparisons were made only between the two placebo-controlled studies in the third-line setting (imatinib resumption and regorafenib). One study was analyzed separately because it was the only one to look at a second-line treatment (sunitinib). The heterogeneity between the two placebo-controlled studies and the one non-placebo-controlled study (nilotinib) was significant ($I^2 = 98\%$), and the non-placebo controlled study was therefore not incorporated into the indirect analysis.

However, after controlling for those factors, the treatment strategy network for the NMA included only two studies, allowing for only one indirect comparison to be made. Because the data used for the comparison came from only two studies, any biases or limitations of those studies were more likely to affect the conclusions drawn from the NMA. Our systematic review was also limited because of the presence of heterogeneity and the paucity of studies, making it difficult to draw reliable conclusions. That difficulty is a limitation in our study, but also a reflection of the current landscape of research in the post–first-line treatment of GIST. Another limitation of using a NMA is that the analysis used published group data rather than individual patient data. Identifying any patient characteristics or risk factors that might be associated with the effectiveness of each treatment regimen is therefore difficult; however, making such inferences in a complex treatment network is typically difficult.

Although our NMA provided indirect evidence that regorafenib is the most favourable treatment in the third-line setting, RCTs directly comparing the available treatments would provide more definitive results. But because RCTs directly comparing regorafenib with imatinib resumption or nilotinib in GIST are unlikely to be conducted in the future for both commercial and scientific reasons, indirect evidence such as the present NMA might be the best possible evidence to become available. That evidence will be useful in clinical decision-making and could help to inspire further research on this topic.

CONCLUSIONS

The present systematic review and NMA sought and analyzed high-quality evidence for the post–first-line treatment of metastatic and unresectable GIST. The NMA demonstrated that regorafenib is the regimen with the highest PFS in the setting of progression on imatinib for patients with GIST. Few studies have examined TKIs in the imatinib- and sunitinib-refractory setting. A small randomized trial that compared imatinib resumption with placebo demonstrated better PFS for patients treated with imatinib. Because a head-to-head study of imatinib resumption compared with regorafenib is unlikely to be conducted in future, our study suggests that, in terms of PFS, regorafenib might be the preferred treatment in that setting. However, regorafenib also carries a greater risk of toxicities. Uncertainties about the relative effectiveness and safety of regorafenib in individual patient populations remain, but in the likely event that clinical trials will not be done in the future, indirect comparisons such as ours can help to guide clinical decision-making. Nevertheless, patients should still be reviewed on a case-by-case basis when prescribing.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none. No sponsors were involved in the study design; in data collection, analysis, and interpretation; in the writing of the report; or in the decision to submit the report for publication.

AUTHOR AFFILIATIONS

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