BMC Cancer

SYSTEMATIC REVIEW Open Access

Efficacy and safety of regorafenib in the treatment of bone sarcomas: systematic review and meta-analysis

Yuanhang Han[1†], Jiangtao Xie[1†], Yuyang Wang[1], Xiaoxiao Liang[2*] and Yuanlong Xie[1*]

Abstract

Background Metastatic or recurrent bone sarcomas are often associated with an unfavorable prognosis, posing a formidable challenge in extending patients' survival. Currently, regorafenib has shown promise in treating metastatic and recurrent bone sarcomas. However, there is a lack of consensus on its efficacy and safety. This systematic review and meta-analysis aims to consolidate existing data to assess the efficacy and safety of regorafenib in bone sarcomas.

Methods A comprehensive search strategy utilizing MeSH terms and free-text keywords was employed to systematically search the Embase, PubMed, Web of Science, and Cochrane databases up to May 26, 2024. Randomized controlled trials investigating regorafenib monotherapy for metastatic or recurrent bone sarcomas were included. The primary outcomes of interest were progression-free survival (PFS), overall survival(OS) and adverse events (AEs).

Results We retrieved 335 articles and included 5 of them. Regorafenib significantly extended PFS-3 months and PFS-6 months in patients with metastatic or recurrent bone sarcomas compared to the control group, exhibiting a favorable odds ratio (OR) of 2.04 (95% CI: 1.21–2.86, $P<0.01$) and 1.03 (95% CI: 0.08–1.99, $P<0.05$), respectively. However, regorafenib did not improve OS at any observation point compared with the control group($P>0.05$), and the frequency of AEs was higher, with an odds ratio of 1.35 (95% CI: 0.63–2.07, $P<0.01$).

Conclusion Regorafenib emerges as a promising therapeutic option for metastatic or recurrent bone sarcomas, demonstrating certain clinical benefits alongside manageable adverse reactions. Nevertheless, further research is warranted to refine the efficacy and safety profile of regorafenib, particularly in exploring safe dosage ranges or alternative treatment modalities.

Registration number CRD42024551705.

Keywords Bone sarcomas, Regorafenib, Progression-free survival, Overall survival, Adverse events

[†]Yuanhang Han and Jiangtao Xie co-first authors.

*Correspondence:
Xiaoxiao Liang
xiaoliangwhu@163.com
Yuanlong Xie
yuanlongxie@whu.edu.cn

[1]Department of Spine Surgery and Musculoskeletal Tumor, Zhongnan Hospital of Wuhan University, No.169,Donghu St, Wuhan, Hubei 430071, PR China
[2]Department of Bone and Soft Tissue Oncology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, No.127,Dongming St, Zhengzhou, Henan 450008, PR China

Introduction

Bone sarcomas comprise various types, including osteosarcoma, Ewing's sarcoma, chondrosarcoma, and chordoma, these rare tumors account for less than 1% of annual cancer diagnoses [1]. Chondrosarcoma and chordoma are prevalent among adults around 40, while osteosarcoma and Ewing's sarcoma are more common in children and adolescents, often affecting limb bones and exhibiting high malignancy and metastatic potential [2].

Advancements in treatment modalities have transformed the management of bone sarcomas beyond sole surgical treatment. For osteosarcoma and Ewing's sarcoma, surgery and chemotherapy remain the primary treatment approaches, utilizing drugs like doxorubicin, cisplatin, high-dose methotrexate, vincristine, ifosfamide, doxorubicin and etoposide [3–4]. Radiotherapy is considered for unresectable or non-surgical cases [5]. Conversely, chondrosarcoma and chordoma treatments focus on surgery and radiotherapy, with chemotherapy not being recommended [6]. These multimodality treatments have significantly enhanced the 5-year survival rate of bone sarcomas to over 70% [7]. However, recurrence, metastasis, chemotherapy resistance, or unresectability drastically reduce the prognosis, such as in patients with osteosarcoma metastases, whose 5-year survival rate is even less than 30% [8–9].

The presence of multiple tyrosine kinase receptors (e.g.,VEGFR, RET, PDGFR, FGFR, KIT, MET, IGF-1R, AXL) in bone sarcomas plays a pivotal role in their development, proliferation, and invasion [10]. These receptors offer potential targets for systemic therapy, aiming to improve survival rates in recurrent and metastatic bone sarcomas. Various studies have demonstrated the promising efficacy of tyrosine kinase inhibitors (TKIs) in extending the progression-free survival of bone sarcoma patients [11].

Regorafenib (BAY 73-4506, Stivarga), a small-molecule multi-kinase inhibitor, aims to inhibit angiogenesis and apoptosis, demonstrating its efficacy in the treatment of various malignancies [12]. In past research, it has been primarily employed in managing metastatic colorectal cancer, metastatic gastrointestinal stromal tumors, advanced hepatocellular carcinoma, and soft tissue sarcomas [13–16]. According to Blay et al. [17], regorafenib exhibits significant clinical benefits in diverse sarcoma types beyond non-adipocytic soft tissue sarcomas, offering a promising therapeutic alternative for patients with limited treatment options, such as recurrent and metastatic disease.

In the REGOBONE multi-center trial and the SARC024 trial, regorafenib emerged as a promising treatment option for patients with metastatic, recurrent, and locally advanced bone sarcomas [18–22]. These studies showed that more patients in the regorafenib group achieved progression-free survival (PFS) at 3 and 6 months compared to placebo, while maintaining an acceptable safety profile. However, there were differences in baseline numbers between experimental and control groups, and conclusions on overall survival(OS) varied across studies. Therefore, it is impossible to accurately determine the efficacy of regorafenib in the treatment of recurrent, metastatic and locally advanced bone sarcomas.

The current evidence base for the use of regorafenib in bone sarcoma treatment remains limited. To address this gap, we conducted a comprehensive meta-analysis of randomized clinical controlled trials evaluating the efficacy and safety of regorafenib monotherapy in patients with metastatic, recurrent, and locally advanced bone sarcomas. This review aims to provide a more robust assessment of regorafenib's therapeutic potential in this challenging patient population.

Methods and materials

This systematic review and meta-analysis was conducted following a rigorous experimental plan that was formulated and registered on the PROSPERO platform (https://www.crd.york.ac.uk/PROSPERO/)(Registration number: CRD42024551705,09/07/2024). But we expanded the population in the registration information to bone sarcomas.The work had been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [23–24]. As this was a meta-analysis of published data, there was no need to obtain informed consent or ethical approval.

Inclusion and exclusion criteria

Inclusion criteria for the meta-analysis were established using the PICOS framework, which stands for Population, Intervention, Comparator, Outcomes, and Study design [25]. The following criterias were used to select eligible studies: (a) Population: Patients with recurrent, metastatic, locally advanced bone sarcomas, including osteosarcoma, chondrosarcoma, Ewing's sarcoma, chordoma.(b) Intervention: Treatment with regorafenib monotherapy.(c) Comparator: The control group should receive placebo as the comparator.(d) Outcomes: The primary outcome is efficacy(PFS and OS), while safety outcomes such as AEs will also be considered.(e) Study design: Randomized controlled trials (RCTs).Exclusion criteria: (a) Studies that do not conform to the PICOS criteria mentioned above.(b) Study protocols or ongoing studies without complete results.(c) Inability to obtain the full text of the study for data extraction.

Literature search strategy

A comprehensive literature search was conducted in four major databases: Embase, PubMed, Web of Science, and Cochrane Library. The search covered the period from the inception of the respective databases up to May 26, 2024. A combination of subject headings and free-text terms were used, with MeSH terms such as "Bone sarcomas","Osteosarcoma," "Chordoma", "Sarcoma, Ewing", "Chondrosarcoma" and "Regorafenib" being included in the search strategy. The detailed search strategy is provided in the supplementary file.

Literature screening

Two authors independently use NoteExpress4.0 software to eliminate duplicate literature and screen the titles and abstracts based on the established inclusion and exclusion criteria. The PRISMA flowchart was utilized to report the screening results. All selection processes was conducted independently by the authors, and the full text of the selected studies were retrieved. Data extraction was performed separately by two authors, and any discrepancies were resolved through consultation with a third author to ensure consistency in the results.

Data extraction

Data extraction from the included studies was conducted by two authors independently. To ensure the reliability of the extracted data, a third author was consulted to confirm the extracted information. The fields of data extraction include: author, publication year, country, study type, demographic data of the included analysis population (e.g., total number, number of females, median age of the trial and control groups), information about bone sarcomas (e.g., sites of metastases and previous therapy), intervention details (e.g., name of intervention drug, dose, and duration), and outcomes. For missing data in the literature, we obtained it by contacting the authors and analyzing the charts. In the included literature, several articles only reported the number of specific AEs, so the total number of AEs was replaced by the value of the most frequent AEs.

Risk of bias assessment of studies

The risk of bias in the selected RCTs was assessed using the criteria recommended by The Cochrane Handbook for Systematic Reviews of Interventions(ROB2 tool). Specifically, the following seven domains were evaluated: randomization, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete data, selective reporting, and other biases.For each domain, the risk of bias was categorized as "high," "low," or "unclear."

Statistical analysis

The endpoints of interest in this analysis were PFS, OS and AEs. The odds ratios (OR) for the efficacy and safety of regorafenib in treating bone sarcomas were calculated using a random effects model(The OR value was obtained after logarithmic transformation by Stata17.0). At the same time, due to the small sample size, we also used a one-by-one culling method to verify the robustness of the meta-analysis results. Heterogeneity among studies was assessed using the I^2 statistic. As per convention, I^2 values of $<25\%$ indicated low heterogeneity, 25-49% indicated moderate heterogeneity, 50-74% indicated substantial heterogeneity, and $>75\%$ indicated considerable heterogeneity. Forest plots were used to visually represent the endpoints of the included studies. When the summary plot was centered on the zero axis or the 95% confidence interval (95% CI) included zero, it suggested no significant difference between the experimental and control groups. A p-value of <0.05 was considered statistically significant. To assess publication bias, a funnel plot was visually inspected, and the Egger test was used to determine any potential asymmetry in the plot. The Egger test used regression analysis to detect funnel plot asymmetry, which could indicate publication bias.All data analysis procedures will be performed in stata17.0.

Results

Study screening

The initial search strategy yielded 335 studies. After removing duplicates using NoteExpress4.0 software, 259 studies underwent title and abstract screening based on PICOS criteria. Of these, 239 studies were excluded for not meeting the inclusion criteria: they were not randomized controlled trials (e.g., reviews, case reports, and retrospective studies) ($n=198$), did not involve bone sarcoma patients ($n=29$), or did not include regorafenib as an intervention ($n=12$). Among the remaining studies, 20 met the initial inclusion criteria. However, upon full-text review, 15 were further excluded for reasons such as not being RCTs ($n=1$), lack of relevance to the outcomes ($n=1$), inaccessibility to full texts ($n=5$), and being ongoing studies or study protocols ($n=8$). Ultimately, five RCTs evaluating the treatment of bone sarcomas with regorafenib were included in this study [17–21]. The literature sources and screening process are visually represented in the PRISMA flowchart (Fig. 1).

Study characteristics

A total of 179 subjects were enrolled across the five selected RCTs, with 66 being female (37.5%). Four studies were conducted in France, and one in the United States. The bone sarcoma patients included those with osteosarcoma, Ewing's sarcoma, chondrosarcoma, and chordoma. In all trials, the intervention group received

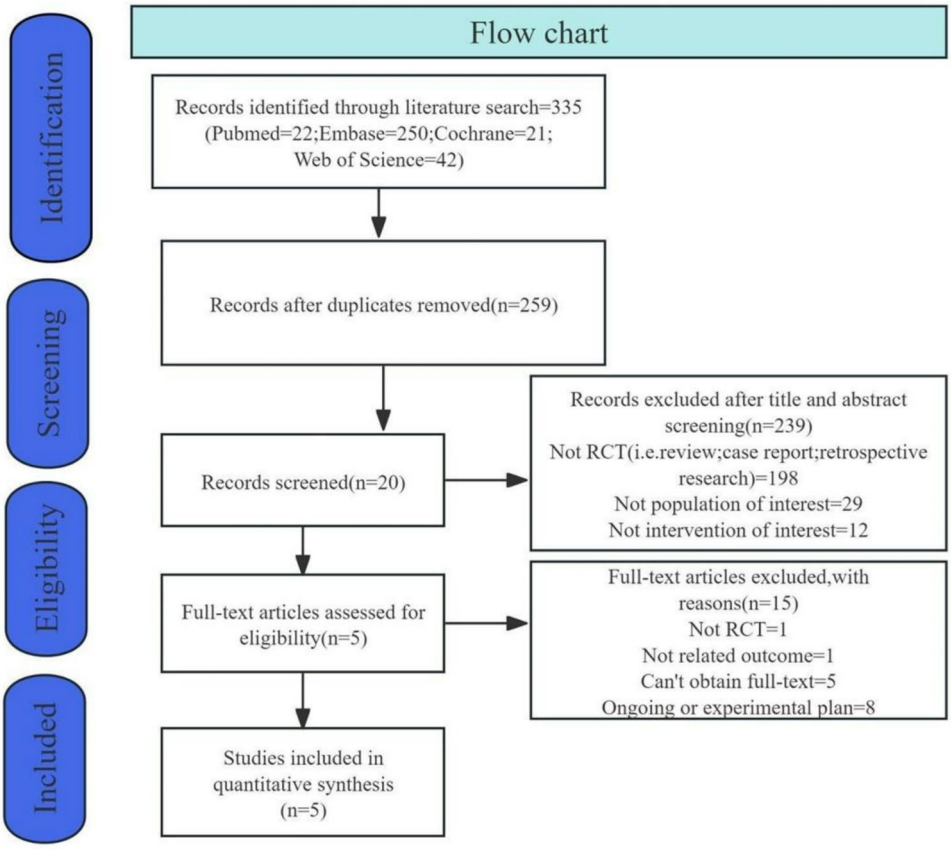

Fig. 1 Flowchart. After literature screening according to PRISMA principles, 5 RCTs are finally included

regorafenib at a dose of 160 mg/day for three weeks. The control group received placebo interventions, typically comprising first-line treatment drugs for bone sarcomas. The primary outcomes reported in all studies were progression-free survival (PFS), overall response rate (ORR), overall survival (OS), duration of response (DoR), and adverse events (AEs). Detailed characteristics of these studies are outlined in Table 1.

Risk of bias in studies

The quality of the five RCTs was assessed using the Cochrane Risk of Bias Assessment Tool. Most studies demonstrated a low risk of bias, except for the study by Davis et al., which had a potential risk of bias due to lack of mention regarding allocation concealment (Table 2). Additionally, there may be a slight risk of bias due to dose adjustments of regorafenib based on varying adverse events experienced by patients.

Efficacy

PFS data from the five studies showed a significantly higher proportion of patients achieving PFS at 3 months (Fig. 2a) and 6 months (Fig. 2b) in the regorafenib group compared to the control group. This difference was statistically significant, with an odds ratio (OR) of 2.04 (95% CI: 1.21–2.86, $P<0.01$) for PFS at 3 months and an OR of 1.03 (95% CI: 0.08–1.99, $P=0.03$) for PFS at 6 months. These results indicate that regorafenib significantly improves PFS in bone sarcoma patients, with no heterogeneity observed between the studies ($I^2=0.00\%$). Furthermore, the Egger test and visual inspection of the funnel plot revealed no significant publication bias (Supplementary Material, Fig. S2). For PFS at 3 months, the combined analysis remained statistically significant after removing any one study (Supplementary Material, Table S1). However, for PFS at 6 months, the combined analysis was only statistically significant after removing the study by Li et al., with an OR of 1.24 (95% CI: 0.14–2.33) (Supplementary Material, Table S1).

From the perspective of OS, a meta-analysis was conducted on the number of patients achieving 6-month, 12-month, 18-month, and 24-month OS across the five studies (Fig. 3a-d). Despite variations in reported efficacy across studies, the meta-analysis showed no significant difference in OS between the regorafenib and placebo groups, with no heterogeneity among the studies ($I^2=0.00\%$). Statistical analysis indicated that these meta-analysis results were not statistically significant ($P>0.05$). Sensitivity analyses for the 12-month and 24-month

Table 1 Summary of included studies

Author/year	Duffaud,2023	Duffaud,2021	Le,2023	Davis,2019	Duffaud,2018
Country	France	France	France	US	France
Study design	RCT	RCT	RCT	RCT	RCT
Sample size	36	40	23	42	38
Female	8	15	7	22	14
Age(median)	32(28)	64(53)	67(54)	33(47)	32(40)
Type of disease	Ewing sarcoma	Chondrosarcoma	Chordoma	Osteosarcoma	Osteosarcoma
Sites of metastases	Lung, bone, lymph nodes	Lung, bone, lymph nodes	Lung, pleura, bone, lymph nodes	NA	Lung, bone, lymph nodes, pleural
Previous therapy	Doxorubicine, ifosfamide, cisplatin, CTX, vinvristin, dactinomycin, temozolomide, irinotecan	Doxorubicine, ifosfamide, cisplatin, oral CTX	Surgery, radiation, imatinib	Systemic therapy in the neoadjuvant, adjuvant, or metastatic setting	Doxorubicine, ifosfamide, cisplatin, high-dose methotrexate, etoposide, gemcitabine, docetaxel, oral CTX
Experimental group	Regorafenib 160 mg/day; 3 weeks	Regorafenib 160 mg/day; 3 weeks	Regorafenib 160 mg/day 3 weeks	Regorafenib 160 mg/day; 3 weeks	Regorafenib 160 mg/day; 3 weeks
Control group	placebo	placebo	placebo	placebo	placebo
Outcome	PFR; PFS; ORR; OS; DoR; safety/tolerability	PFR; PFS; ORR; OS; DoR; safety/tolerability	PFR; PFS; ORR; OS; DoR; safety/tolerability	PFS; AEs; ORR; TTP; OS; DoR	PFS; ORR; OS; DoR; safety/tolerability

Note: cyclophosphamide(CTX); progression-free rate(PFR); progression-free survival(PFS); objective response rate(ORR); overall survival(OS); duration of overall response(DoR); time to tumor progression(TTP); adverse events(AEs)

Table 1.Summary of included studies.Summary of the included countries, study type, Sample size, Female, Age(median), Type of disease, Experimental group, Control group and Outcome

Table 2 Quality assessment of the included studies

Studies	Davis,2019	Le,2023*	Duffaud,2023*	Duffaud,2021*	Duffaud,2018*
Random sequence generation	L	L	L	L	L
Allocation concealment	U	L	L	L	L
Blinding of participants and personnel	L	L	L	L	L
Blinding of outcome assessment	L	L	L	L	L
Incomplete outcome data	L	L	L	L	L
Selective reporting	L	L	L	L	L
Other bias	L	L	L	L	L

Note: L = Low risk of bias, H = High risk of bias and U = Unclear risk of bias

Table 2.The quality evaluation of the included studies shows a high level of literature quality. Each "*" represents that there is no risk of bias in this study

meta-analyses showed stable results upon removal of any one study (Supplementary Material, Table S1).

Safety

Data from the five studies indicated a higher incidence of adverse events in the regorafenib group compared to the control group, with a statistically significant difference (OR = 1.35, 95% CI: 0.63–2.07, $P < 0.01$) and stable results (Fig. 4 and Supplementary Material, Table S1). No heterogeneity was observed among the studies (I^2=0.00%). Leave-one-out sensitivity analysis confirmed the stability and statistical significance of the combined analysis results.

Detailed analysis of specific adverse events revealed that the most commonly reported were hand-foot skin reaction (OR = 2.30, 95% CI: 1.34–3.25, $P < 0.01$) (Fig. 5a), diarrhea (OR = 1.22, 95% CI: 0.54–1.91, $P < 0.01$) (Fig. 5b), weight decrease (OR = 2.35, 95% CI: 1.10–3.59, $P < 0.01$) (Fig. 5c), fatigue or asthenia (OR = 1.68, 95% CI: 0.88–2.48, $P < 0.01$) (Fig. 5d), and hypertension (OR = 1.07, 95% CI: 0.29–1.85, $P < 0.05$) (Fig. 6a). These findings suggest that regorafenib is more likely to induce adverse events affecting the skin, digestive system, cardiovascular system, and general physical condition of bone sarcoma patients. Notably, the I^2 values for these common

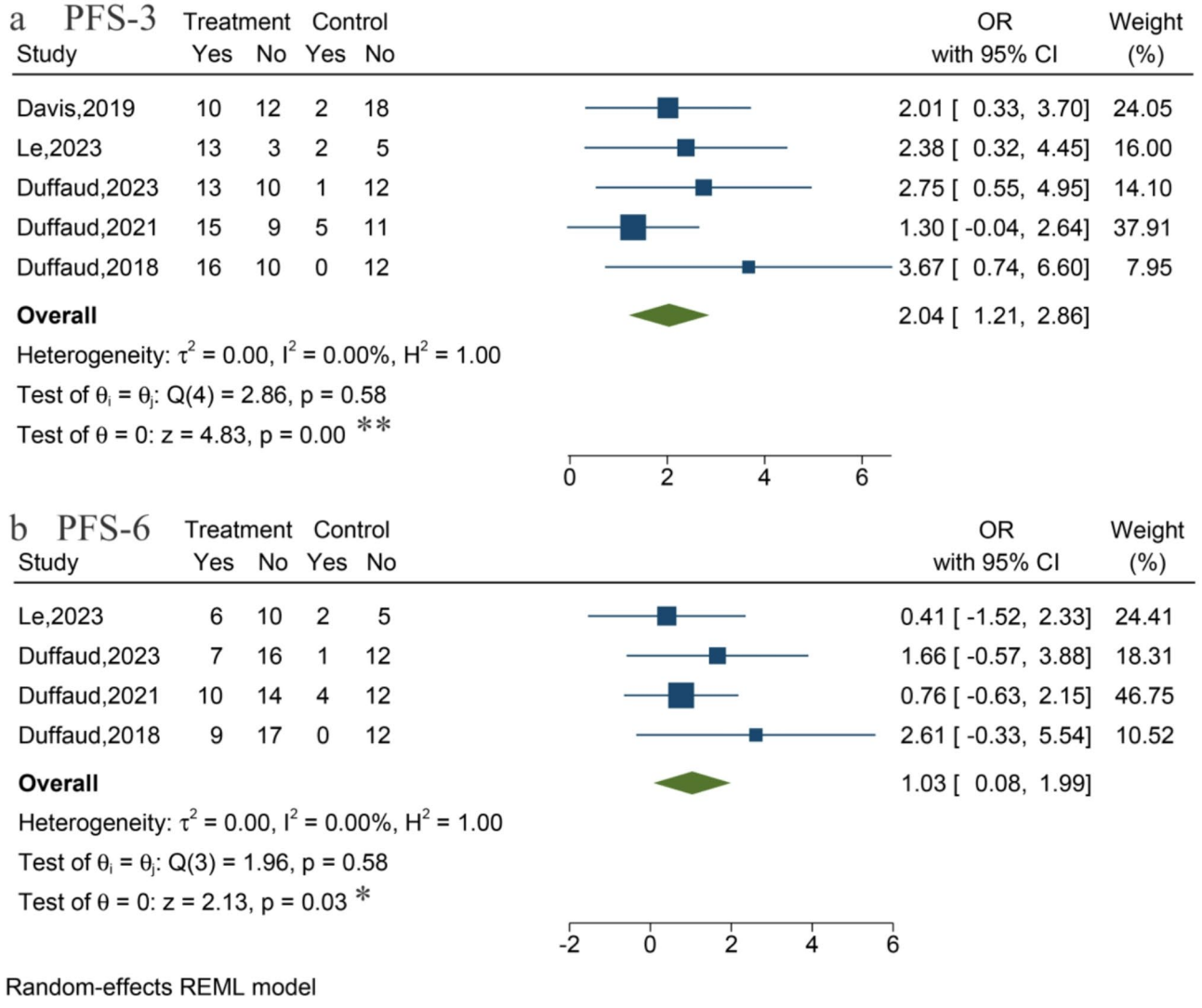

Fig. 2 Forest plot. **a** shows the efficacy of regorafenib in improving 3-month PFS in bone sarcomas patients, and **b** shows the efficacy of regorafenib in improving 6-month PFS in bone sarcomas patients. The results show that regorafenib significantly prolongs PFS in bone sarcomas patients. Each "**" represents that "P < 0.01"

adverse events were all 0.00%, indicating no heterogeneity between the studies.

However, the pooled analysis showed no significant difference in the incidence of thrombocytopenia (OR = 1.28, 95% CI: -0.01 to 2.58, $P \geq 0.05$) (Fig. 6b), anemia (OR = 0.68, 95% CI: -0.49 to 1.85, $P \geq 0.05$) (Fig. 6c), or hypophosphatemia (OR = 1.15, 95% CI: -0.02 to 2.32, $P \geq 0.05$) (Fig. 6d) between the regorafenib and control groups. This suggests that regorafenib does not significantly impact the hematological system of bone sarcoma patients compared to the control group.

Discussion

Regorafenib, a potent oral multi-kinase targeted inhibitor, has garnered significant attention for its emerging role in the treatment of sarcoma patients [26]. Bone sarcomas harbor numerous tyrosine kinase receptors (TKRs), which are vital therapeutic targets for regorafenib. This medication works by binding to these receptors, effectively blocking TKRs implicated in tumor growth (e.g.,RET, PDGFRs, KIT, etc.) and angiogenesis (e.g.,VEGFR, FGFR, etc.) [10, 27]. Specifically, in osteosarcoma, VEGF overexpression is inversely correlated with PFS and OS, and regorafenib's primary mechanism of action involves binding to VEGFR-3 to achieve anti-tumor effects [28]. Similarly, in Ewing's sarcomas, where IGF-1R, PDGER, and FGFR are highly expressed and associated with prognosis, these protein tyrosine kinases emerge as critical targets for regorafenib's therapeutic potential [29–30]. For other bone sarcomas, while the precise mechanism of TKRs remains elusive, studies indicate that PDGER, IGFR1, EGFR, FGER, and MET

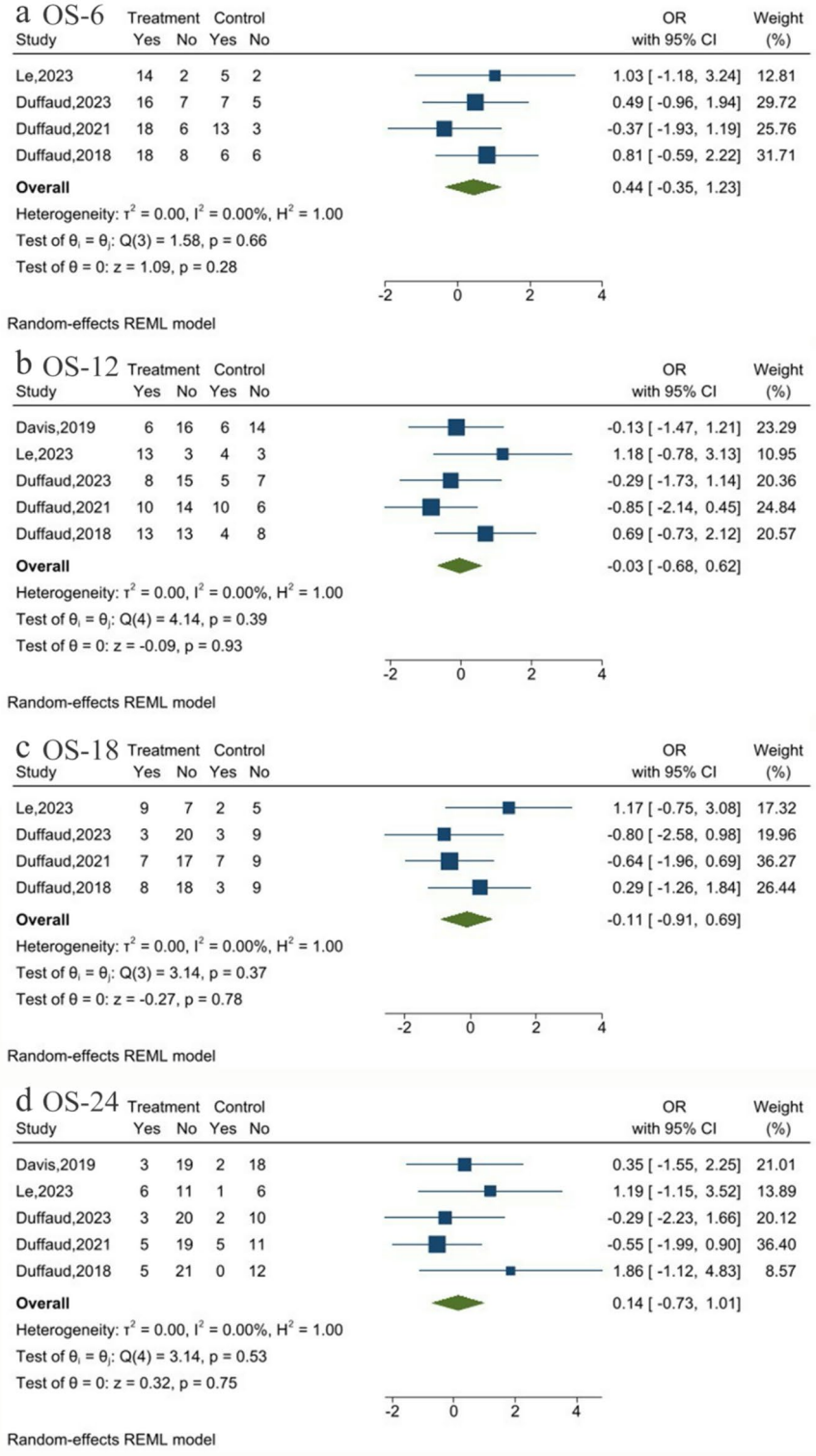

Fig. 3 Forest plot. **a** shows the efficacy of regorafenib in improving 6-month OS in bone sarcomas patients, and **b** shows the efficacy of regorafenib in improving 12-month OS in bone sarcomas patients. **c** shows the efficacy of regorafenib in improving 18-month OS in bone sarcomas patients, and **b** shows the efficacy of regorafenib in improving 24-month OS in bone sarcomas patients

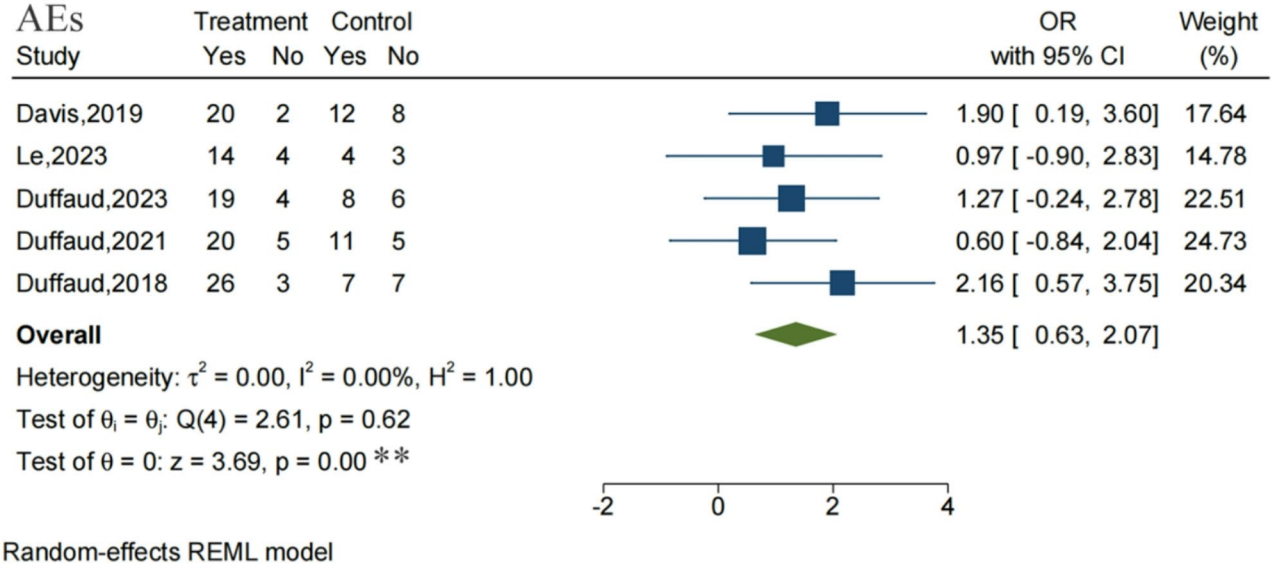

Fig. 4 Forest plot. Safety of regorafenib treatment in bone sarcomas patients. The results show that the regorafenib group is more prone to AEs. Each "**" represents that "P < 0.01"

TKRs are overexpressed and expected to be vital targets for TKI-based bone sarcoma treatments [31–34].

A review by Assi et al. [11] suggested regorafenib as a promising treatment option for advanced recurrent or refractory bone sarcomas, outperforming sorafenib in efficacy. However, this review lacked comprehensive evidence to substantiate its conclusions, particularly regarding regorafenib's application in treating diverse bone sarcoma types in clinical settings. Therefore, to address this gap, we conducted a rigorous statistical analysis of RCTs examining regorafenib's therapeutic efficacy in various bone sarcoma subtypes.

In our comprehensive review, the regorafenib group exhibited a noteworthy PFS benefit, indicating its potential as a novel treatment option for metastatic, recurrent, and locally advanced bone sarcomas. However, the OR value decreased with the duration of treatment, and the results of statistical analysis were unstable. This suggested that the difference between groups was inversely related to time, and that more evidence was needed to support the efficacy of regorafenib. We speculated that this group difference was due to the development of resistance to regorafenib in bone sarcomas. In addition, although all studies reported the median OS in the regorafenib group, there was no statistically significant difference in OS between the regorafenib group and the control group in our meta-analysis. In the studies included in our analysis, patients with bone sarcomas were mainly of advanced, metastatic, and recurrent types, which represent poorer prognoses and thus weaken the efficacy of regorafenib. Furthermore, research had found that differences in drug targets can also affect survival outcomes. High VEGFR2 in bone sarcoma patients was associated with poorer survival rates, VEGF was related to poorer PFS, and high PDGFRA was linked to poorer prognosis [35]. Regorafenib needed to target relevant targets to exert its antitumor effects, but there were differences in the activation levels of drug targets among different types of bone sarcomas and even within the same type of sarcoma, and these differences led to variations in the final efficacy [36]. Based on the above evidence, tyrosine kinase inhibitors (TKIs) might play a certain role in the treatment of bone sarcomas, but there was currently insufficient evidence to demonstrate the efficacy of regorafenib alone in treating recurrent, metastatic, and locally advanced bone sarcomas, and it might need to be used in combination with other treatment modalities in the future.

Regarding safety, the frequency of AEs in the regorafenib group was considerably higher than in the control group. These AEs primarily encompassed hand-foot skin reactions, weight loss, diarrhea, fatigue, and hypertension. However, the incidence of anemia, thrombocytopenia, and hypophosphatemia, though higher in the regorafenib group, did not exhibit a significant difference compared to the control group. It is worth noting that while the regorafenib group was more susceptible to AEs, these were manageable through dose reduction or drug discontinuation.

In the study conducted by Sugiyama et al. [37], regorafenib not only significantly prolonged median PFS but also exhibited comparable safety profiles to other multitarget TKIs when treating metastatic or recurrent bone sarcomas. This underscores the need for further research to determine the optimal dosing of regorafenib that balances efficacy and tolerability.

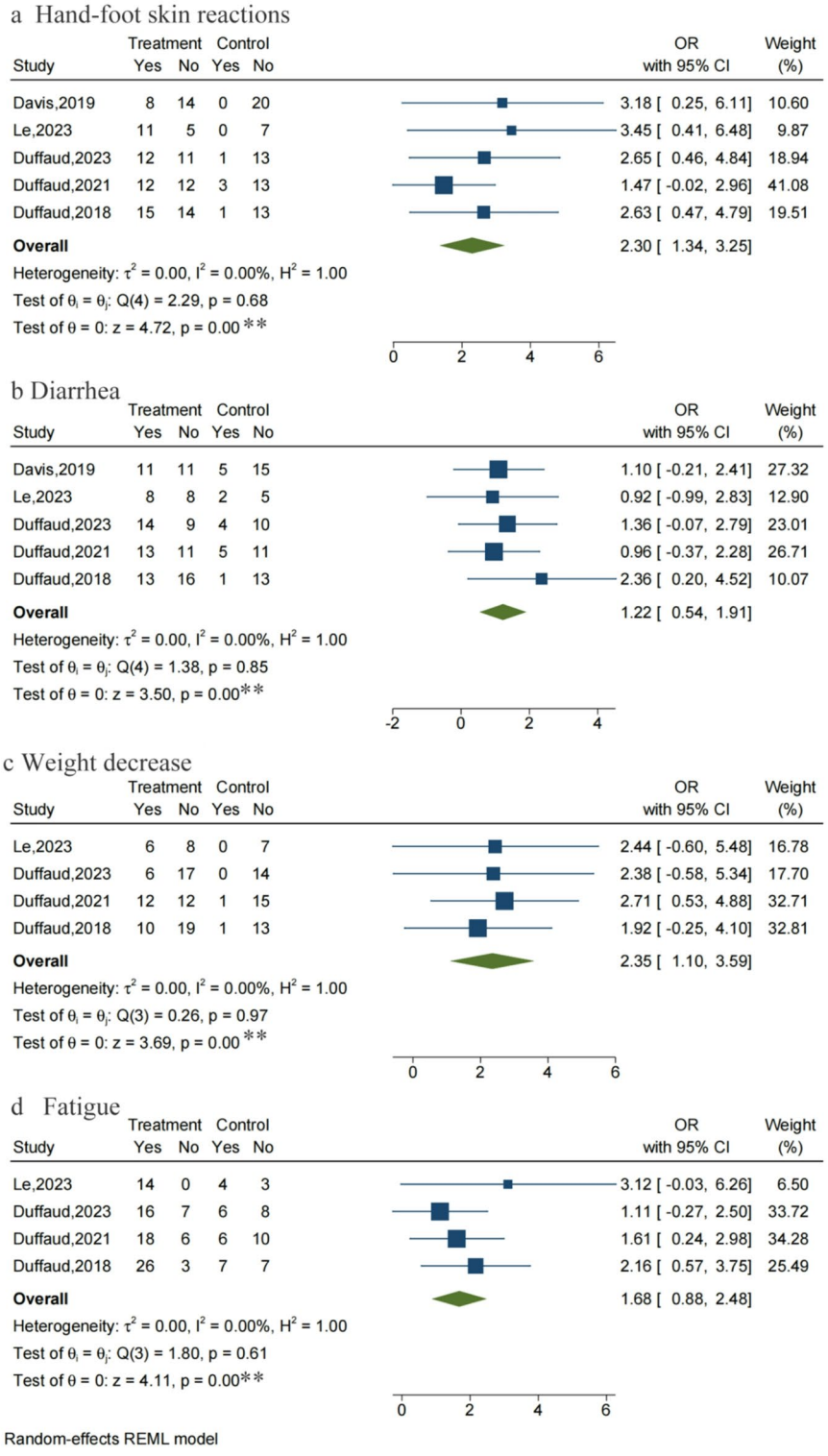

Fig. 5 Forest plot. Risk of AEs in the regorafenib group. **a** represents hand-foot skin reactions, **b** represents diarrhea, **c** represents weight decrease, and **d** represents fatigue. Each "**" represents that "P < 0.01"

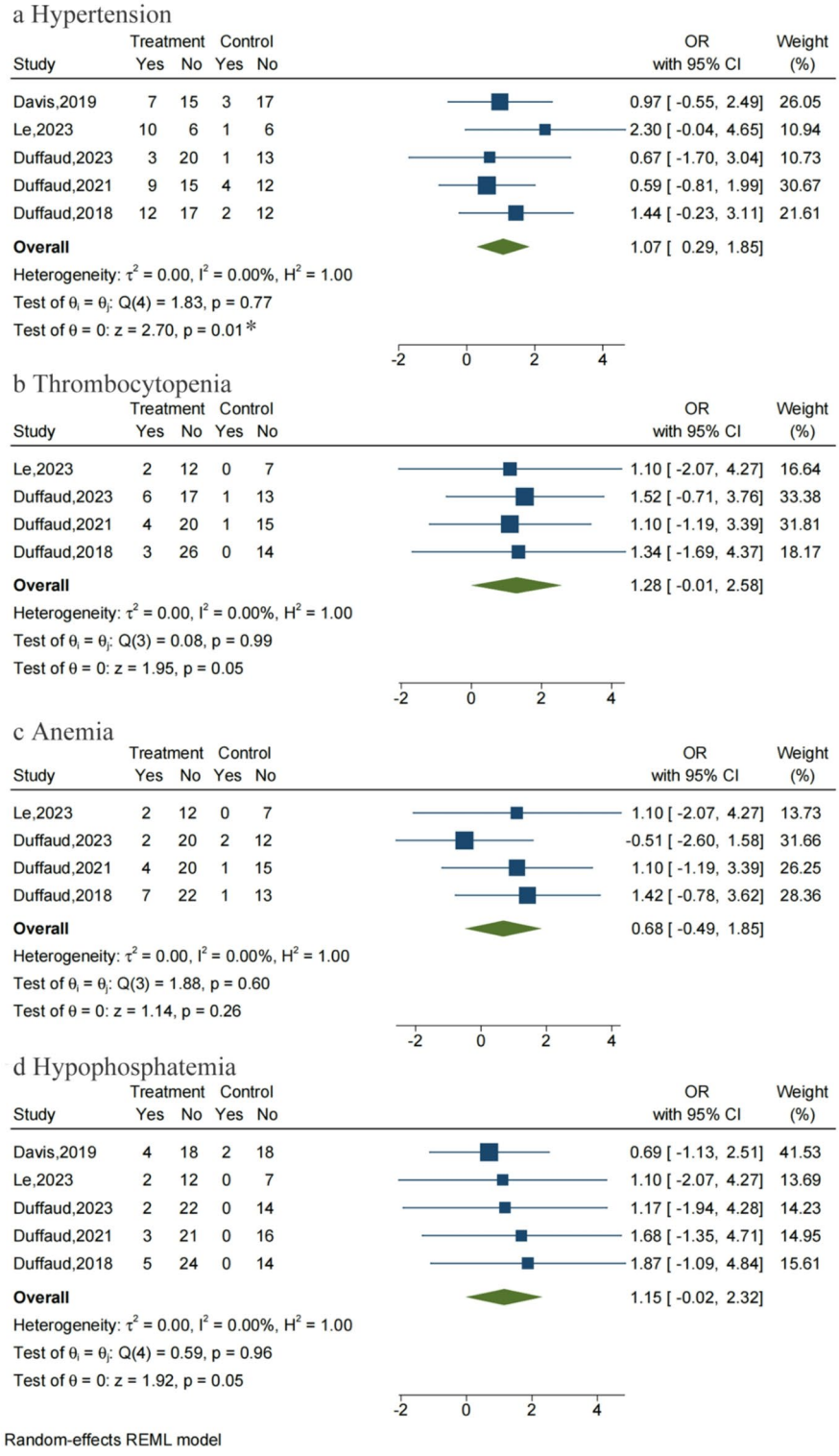

Fig. 6 Forest plot. Risk of AEs in the regorafenib group. **a** represents hypertension, **b** represents thrombocytopenia, **c** represents anemia, and **d** represents hypophosphatemia. Each "*" represents that "$0.01 \leq P < 0.05$"

To my knowledge, this is the first systematic review and meta-analysis introducing the use of regorafenib in the treatment of bone sarcomas.Our statistical analysis indicates that regorafenib holds promise as a novel treatment option for metastatic, recurrent, or locally advanced bone sarcomas. However, several crucial aspects remain to be addressed. Firstly, the relatively small number of bone sarcoma patients included in this review necessitates larger-scale trials for validation. Secondly, the patients in this review were primarily from France and the US, leaving us unaware of the outcomes in other regions. Therefore, clinical trials in diverse geographical areas are imperative for further validation.In addition, the current research primarily focuses on regorafenib monotherapy for bone sarcomas, but its significant adverse effects and the potential for drug resistance present an inevitable challenge that requires extensive further investigation. Lastly, due to the limited number of studies, the number of studies on each type of bone sarcoma is small, preventing us from conducting subgroup analyses. Although our results indicate that regorafenib can improve the PFS of bone sarcoma patients, the inclusion of multiple types of bone sarcomas to some extent reduces the accuracy of the study results. Based on its poor performance in OS and the inability to perform subgroup analyses, we must acknowledge that the current evidence cannot definitively prove that regorafenib is sufficiently effective for bone sarcomas. Therefore, the application of regorafenib in bone sarcomas is still in its early stages, but its efficacy remains worthy of continued research in this field.

For regorafenib, future research should explore the potential of combining it with other treatment modalities, such as radiotherapy, chemotherapy, and immunotherapy, to enhance efficacy while mitigating side effects and drug resistance. In Casanova et al.'s study, regorafenib was combined with drugs like vincristine to treat pediatric solid tumors (such as rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma, etc.), and the feasibility was demonstrated through dose adjustments and combination use [38]. Currently, the application of nanotechnology in addressing cancer drug resistance is becoming increasingly widespread. Among these, lipid-based nanomaterials are favored by researchers due to their biocompatibility and other properties. In the future, improving the formulation and delivery routes of regorafenib may help address issues of drug resistance, enhance drug targeting ability, and improve drug utilization [39–40]. Additionally, due to the differences in target pathways between various types of bone sarcomas and variations in pathway activity within the same type of sarcoma, using pathway activity as a novel biomarker for selecting specific targets holds significant importance [36].

In summary, while regorafenib shows promise in extending survival for patients with metastatic and recurrent bone sarcomas, who have limited treatment options, the frequency of adverse events in the regorafenib group raises safety concerns. Therefore, more research is needed to determine the optimal dosage of regorafenib or to identify alternative therapeutic strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13722-y.

Supplementary Material 1

Acknowledgements
We thank all the team members for their dedication and support, and we also thank the authors of the included studies for their wonderful results.

Author contributions
Yuanhang Han and Jiangtao Xie are co-first authors. Study conception and design by Yuanhang Han and Jiangtao Xie; data extraction by Yuyang Wang; Jiangtao Xie negotiated the differences in the literature screening process, analyzed and explained the data of the article; Yuanhang Han drafted the article; Xiaoxiao Liang and Yuanlong Xie critically revised the important knowledge content and determined the final submitted version, they were corresponding author.

Funding
This review was supported by the Hubei provincial Natural Science Foundation of China (project number: 2023AFB824), the Youth interdisciplinary Special Fund of Zhongnan Hospital of Wuhan University (project number: ZNQNJC2022009), the Wuhan Natural Science Foundation Exploration Program (Chenguang Program)(project number: 2024040801020356).

Data availability
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethical approval
Our study is a systematic review and meta-analysis, and thus does not require ethical approval.

Consent for publication
Not applicable.

Provenance and peer review
Not commissioned, externally peer-reviewed.

Competing interests
The authors declare no competing interests.

Received: 19 November 2024 / Accepted: 12 February 2025
Published online: 19 February 2025

References

1. Ferguson JL, Turner SP. Bone Cancer: diagnosis and treatment principles. Am Fam Physician. 2018;98(4):205–13. PMID: 30215968.
2. Blay JY, Palmerini E, Bollard J et al. SELNET clinical practice guidelines for bone sarcoma. Crit Rev Oncol Hematol. 2022;174:103685. doi: 10.1016/j.critrevonc.2022.103685. Epub 2022 Apr 21. Erratum in: Crit Rev Oncol Hematol. 2022;180:103827. https://doi.org/10.1016/j.critrevonc.2022.103827. PMID: 35460913.

3. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. Lancet Oncol. 2016;17(10):1396–408. Epub 2016 Aug 25. PMID: 27569442; PMCID: PMC5052459.
4. Le Deley MC, Paulussen M, Lewis I, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. J Clin Oncol. 2014;32(23):2440–8. Epub 2014 Jun 30. PMID: 24982464.
5. Locquet MA, Brahmi M, Blay JY, Dutour A. Radiotherapy in bone sarcoma: the quest for better treatment option. BMC Cancer. 2023;23(1):742. https://doi.org/10.1186/s12885-023-11232-3. PMID: 37563551; PMCID: PMC10416357.
6. Strauss SJ, Frezza AM, Abecassis N, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(12):1520–36. Epub 2021 Sep 6. PMID: 34500044.
7. Voskuil R, Evenski AJ, Montgomery C, Emory CL. Malignant bone tumors of the knee: how to identify and treat. J Knee Surg. 2019;32(4):305–14. https://doi.org/10.1055/s-0038-1675828. Epub 2018 Nov 16. PMID: 30449025.
8. Ferrari S, Briccoli A, Mercuri M et al. Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol. 2003;21(4):710-5. https://doi.org/10.1200/JCO.2003.03.141. PMID: 12586810.
9. Shoaib Z, Fan TM, Irudayaraj JMK. Osteosarcoma mechanobiology and therapeutic targets. Br J Pharmacol. 2022;179(2):201–17. https://doi.org/10.1111/bph.15713. Epub 2021 Dec 21. PMID: 34679192; PMCID: PMC9305477.
10. Albarrán V, Villamayor ML, Chamorro J, et al. Receptor tyrosine kinase inhibitors for the treatment of recurrent and Unresectable Bone Sarcomas. Int J Mol Sci. 2022;23(22):13784. https://doi.org/10.3390/ijms232213784. PMID: 36430263; PMCID: PMC9697271.
11. Assi A, Farhat M, Hachem MCR, et al. Tyrosine kinase inhibitors in osteosarcoma: adapting treatment strategiesa. J Bone Oncol. 2023;43:100511. https://doi.org/10.1016/j.jbo.2023.100511. PMID: 38058514; PMCID: PMC10696463.
12. Ettrich TJ, Seufferlein T, Regorafenib. Recent Results Cancer Res. 2018;211:45–56. https://doi.org/10.1007/978-3-319-91442-8_3. PMID: 30069758.
13. Cerrito L, Ponziani FR, Garcovich M, et al. Regorafenib: a promising treatment for hepatocellular carcinoma. Expert Opin Pharmacother. 2018;19(17):1941–8. Epub 2018 Oct 20. PMID: 30345837.
14. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295–302. https://doi.org/10.1016/S0140-6736(12)61857-1. Epub 2012 Nov 22. PMID: 23177515; PMCID: PMC3819942.
15. Mir O, Brodowicz T, Italiano A et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2016;17(12):1732–1742. https://doi.org/10.1016/S1470-2045(16)30507-1. Epub 2016 Oct 14. PMID: 27751846.
16. Xue WS, Men SY, Liu W, Liu RH. A meta-analysis of safety and efficacy of regorafenib for refractory metastatic colorectal cancer. Med (Baltim). 2018;97(40):e12635. https://doi.org/10.1097/MD.0000000000012635. PMID: 30290640; PMCID: PMC6200445.
17. Blay JY, Duffaud F, George S, Maki RG, Penel N. Regorafenib for the treatment of Sarcoma. Curr Treat Options Oncol. 2022;23(11):1477–502. https://doi.org/10.1007/s11864-022-00990-0. Epub 2022 Sep 30. PMID: 36178573.
18. Duffaud F, Blay JY, Le Cesne A, et al. Regorafenib in patients with advanced ewing sarcoma: results of a non-comparative, randomised, double-blind, placebo-controlled, multicentre phase II study. Br J Cancer. 2023;129(12):1940–8. https://doi.org/10.1038/s41416-023-02413-9. Epub 2023 Nov 1. PMID: 37914801; PMCID: PMC10703915.
19. Le Cesne A, Chevreau C, Perrin C, et al. Regorafenib in patients with relapsed advanced or metastatic chordoma: results of a non-comparative, randomised, double-blind, placebo-controlled, multicentre phase II study. ESMO Open. 2023;8(3):101569. https://doi.org/10.1016/j.esmoop.2023.101569. Epub 2023 Jun 6. PMID: 37285716; PMCID: PMC10265601.
20. Duffaud F, Mir O, Boudou-Rouquette P, Piperno-Neumann S, et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol. 2019;20(1):120–33. Epub 2018 Nov 23. PMID: 30477937.
21. Duffaud F, Italiano A, Bompas E, et al. Efficacy and safety of regorafenib in patients with metastatic or locally advanced chondrosarcoma: results of a non-comparative, randomised, double-blind, placebo controlled, multicentre phase II study. Eur J Cancer. 2021;150:108–18. Epub 2021 Apr 22. PMID: 33895682.
22. Davis LE, Bolejack V, Ryan CW, et al. Randomized double-blind phase II study of Regorafenib in patients with metastatic osteosarcoma. J Clin Oncol. 2019;37(16):1424–31. https://doi.org/10.1200/JCO.18.02374. Epub 2019 Apr 23. PMID: 31013172; PMCID: PMC7799443.
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906. https://doi.org/10.1016/j.ijsu.2021.105906. Epub 2021 Mar 29. PMID: 33789826.
24. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. https://doi.org/10.1136/bmj.j4008. PMID: 28935701; PMCID: PMC5833365.
25. Amir-Behghadami M, Janati A, Population. Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J. 2020;37(6):387. https://doi.org/10.1136/emermed-2020-209567. Epub 2020 Apr 5. PMID: 32253195.
26. Agulnik M, Attia S. Growing Role of Regorafenib in the Treatment of Patients with Sarcoma. Target Oncol. 2018;13(4):417–422. https://doi.org/10.1007/s11523-018-0575-0. PMID: 29931504.
27. Neijenhuis LKA, Naumann LL, Ferkel SAM, Rubin SJS, Rogalla S. Exploring the effects of taurolidine on tumor weight and microvessel density in a murine model of osteosarcoma. Oncol Res. 2024;32(7):1163–72. https://doi.org/10.32604/or.2024.050907. PMID: 38948019; PMCID: PMC11209741.
28. Tian Z, Niu X, Yao W. Receptor tyrosine kinases in Osteosarcoma Treatment: which is the key target? Front Oncol. 2020;10:1642. https://doi.org/10.3389/fonc.2020.01642. PMID: 32984034; PMCID: PMC7485562.
29. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer. 2017;17(5):318–32. https://doi.org/10.1038/nrc.2017.8. Epub 2017 Mar 17. PMID: 28303906.
30. Mora J, Rodríguez E, de Torres C, et al. Activated growth signaling pathway expression in ewing sarcoma and clinical outcome. Pediatr Blood Cancer. 2012;58(4):532–8. https://doi.org/10.1002/pbc.23348. Epub 2011 Oct 12. PMID: 21994054.
31. Shalaby A, Presneau N, Ye H, et al. The role of epidermal growth factor receptor in chordoma pathogenesis: a potential therapeutic target. J Pathol. 2011;223(3):336–46. https://doi.org/10.1002/path.2818. Epub 2010 Dec 10. PMID: 21171079.
32. Klenke FM, Abdollahi A, Bertl E, et al. Tyrosine kinase inhibitor SU6668 represses chondrosarcoma growth via antiangiogenesis in vivo. BMC Cancer. 2007;7:49. https://doi.org/10.1186/1471-2407-7-49. PMID: 17367541; PMCID: PMC1832206.
33. Tamborini E, Miselli F, Negri T et al. Molecular and biochemical analyses of platelet-derived growth factor receptor (PDGFR) B, PDGFRA, and KIT receptors in chordomas. Clin Cancer Res. 2006;12(23):6920-8. https://doi.org/10.1158/1078-0432.CCR-06-1584. PMID: 17145809.
34. Weinberger PM, Yu Z, Kowalski D et al. Differential expression of epidermal growth factor receptor, c-Met, and HER2/neu in chordoma compared with 17 other malignancies. Arch Otolaryngol Head Neck Surg. 2005;131(8):707– 11. https://doi.org/10.1001/archotol.131.8.707. PMID: 16103303.
35. Fleuren EDG, Vlenterie M, van der Graaf WTA. Recent advances on anti-angiogenic multi-receptor tyrosine kinase inhibitors in osteosarcoma and Ewing sarcoma. Front Oncol. 2023;13:1013359. https://doi.org/10.3389/fonc.2023.1013359. PMID: 36994209; PMCID: PMC10040783.
36. Fordham AM, Ekert PG, Fleuren EDG. Precision medicine and phosphoproteomics for the identification of novel targeted therapeutic avenues in sarcomas. Biochim Biophys Acta Rev Cancer. 2021;1876(2):188613. https://doi.org/10.1016/j.bbcan.2021.188613. Epub 2021 Aug 11. PMID: 34390800.
37. Sugiyama M, Arakawa A, Shirakawa N, et al. Safety and efficacy of multiple tyrosine kinase inhibitors in pediatric/adolescent and young adult patients with relapsed or refractory osteosarcomas: a single-institution retrospective analysis. Pediatr Blood Cancer. 2023;70(7):e30360. https://doi.org/10.1002/pbc.30360. Epub 2023 Apr 19. PMID: 37073613.
38. Casanova M, Bautista F, Campbell-Hewson Q, Makin G, Marshall LV, Verschuur AC, Cañete Nieto A, Corradini N, Ploeger BA, Brennan BJ, Mueller U, Zebger-Gong H, Chung JW, Geoerger B. Regorafenib plus Vincristine and Irinotecan in Pediatric patients with Recurrent/Refractory solid tumors: an innovative therapy for children with Cancer Study. Clin Cancer Res. 2023;29(21):4341–51. https://doi.org/10.1158/1078-0432.CCR-23-0257. PMID: 37606641; PMCID: PMC10618645.

39. Dechbumroong P, Hu R, Keaswejjareansuk W, Namdee K, Liang X. Recent advanced lipid-based nanomedicines for overcoming cancer resistance. Cancer Drug Resist. 2024-06-21. https://doi.org/10.20517/cdr.2024.19.
40. Li L, Rong G, Gao X, Cheng Y, Sun Z, Cai X, Xiao J. Bone-targeted Fluoropeptide Nanoparticle inhibits NF-κB signaling to treat Osteosarcoma and Tumor-Induced Bone Destruction. Adv Sci (Weinh). 2025;12(1):e2412014. https://doi.org/10.1002/advs.202412014. Epub 2024 Nov 6. PMID: 39501934; PMCID: PMC11714165.

Publisher's note