SYSTEMATIC REVIEW

A Systematic Review and Meta-Analysis of Regorafenib's Effectiveness and Safety in the Treatment of Bone Sarcoma

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Abstract

Objectives: Bone sarcomas are rare, aggressive tumors with poor outcomes and limited systemic options in advanced stages. This systematic review and meta-analysis evaluated its efficacy and safety in bone sarcomas using randomized controlled trials (RCTs).

Methods: We searched PubMed, Scopus, and Web of Science for RCTs published from September 27, 2012, to October 14, 2024. After removing duplicates, 350 records were screened, and five RCTs met the inclusion criteria. Primary outcomes were progression-free survival (PFS), overall survival (OS), and adverse events (AEs). Study quality was assessed using the Cochrane Risk of Bias 2 (RoB2) tool. Meta-analyses were performed with a random-effects model, and heterogeneity was evaluated using I^2 statistics. All analyses were conducted using R version 4.3.1.

Results: A total of 350 records were screened after duplicate removal, of which 339 were excluded based on title and abstract. Eleven full-text articles were assessed for eligibility, and six were excluded for not meeting RCT criteria, resulting in five RCTs being included. Most had metastatic disease at baseline. Regorafenib significantly improved PFS (MD = 9.69 weeks; 95% CI: 4.54–14.84; I^2 = 0%), with no statistically significant overall survival (OS) benefit (MD = 0.85 weeks; 95% CI: –36.33 to 38.02; I^2 = 0%). These findings were consistent across studies and histological subtypes. All pooled analyses demonstrated zero or near-zero heterogeneity (I^2 = 0%), indicating highly consistent treatment effects among trials. No significant between-group heterogeneity was observed in subgroup analyses, confirming that regorafenib's benefit on progression-free survival was stable across different bone sarcoma types. Common regorafenib-related AEs included hand–foot skin reaction, hypertension, fatigue, and diarrhea. Grade 3–5 events were mostly hypertension and pain, generally manageable with dose modifications. Safety results were also consistent across studies, showing zero or near-zero heterogeneity (I^2 = 0%) and no significant subgroup differences, indicating a homogeneous safety profile across sarcoma subtypes.

Conclusion: Regorafenib significantly improves progression-free survival in bone sarcomas across multiple subtypes, with a manageable toxicity profile. These results support its use as a novel therapy and highlight the need for future trials focused on optimizing dosing and patient selection.

Level of evidence: I

Keywords: Bone sarcoma, Meta-analysis, Oncology, PFS, RCT, Regorafenib, Tyrosine kinase inhibitor

Introduction

Sarcomas are malignancies originating from mesenchymal cells and constitute roughly 1% of all adult cancers, with bone sarcomas accounting for approximately 0.2% of these cases.[1] Major subtypes of one sarcoma include chondrosarcoma, osteosarcoma, and Ewing sarcoma; uncommon subtypes include chordoma

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and adamantinoma.[2] Various clinical and pathological aspects determine the overall therapeutic method.[3]
Survival, preservation of limbs, functional outcomes, equality of limb length, and cosmesis are essential goals in the management of bone sarcomas. When it comes to some types of cancer, surgical resection is excellent for local control, but chemotherapy is great for systemic control. To preserve function without sacrificing survival, limb salvage surgery is progressively being chosen over amputation.[4] Functional outcomes following these procedures are commonly assessed using validated tools such as the Toronto Extremity Salvage Score (TESS).[5] Nevertheless, amputation remains a lifesaving and definitive option when all attempts at limb salvage have been exhausted, despite being considered a last resort.[6]

Chemotherapy for adult bone sarcoma is still tricky because patients react differently to different treatments. While some subtypes of chondrosarcoma, such as mesenchymal and dedifferentiated, may respond better to specific chemotherapy regimens, conventional chondrosarcoma shows very little chemosensitivity.[7] Chemotherapy has a limited success rate when used to treat metastatic bone sarcoma.[8] Treatment outcomes are worse for older patients as well.[6] Cancer patients already face several difficulties, and the side effects of chemotherapy, such as nausea, vomiting, alopecia, exhaustion, and an increased risk of infection, can make matters worse.[9]

In response to the shortcomings of traditional cancer treatments, a plethora of novel therapeutic approaches have emerged in the field. Bone sarcoma is one of several cancers for which tyrosine kinase inhibitors are currently under active investigation in clinical trials.[10,11] Multiple kinase inhibitor regorafenib inhibits the signaling of angiogenic, stromal, and oncogenic receptor tyrosine kinases.12-15 Regorafenib is a promising new drug for the treatment of bone sarcoma, and this study aims to determine its effectiveness in this challenging condition.

Materials and Methods

Search Strategy

The protocol for this review has been entered into the PROSPERO database with the reference number CRD42024526345. We searched PubMed, Web of Science, and Scopus extensively to find relevant randomized clinical trials (RCTs) published between September 27, 2012, and October 14, 2024. The primary search keywords were: ((bone sarcoma) OR (chondrosarcoma) OR (chondroblastoma) OR (chordoma) OR (ewing sarcoma) OR (osteosarcoma) OR (bone fibrosarcoma) OR (bone leiomyosarcoma) OR (adamantinoma) OR (hemangioendothelioma) OR (hemangiopericytoma) OR (low-grade fibrosarcoma) OR (malignant fibrous histiocytoma)) AND (Stivarga OR regorafenib).

This study followed the PMSHA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards for 2020. The decision to include citations was made after an initial screening of abstracts and titles; full-text articles were then evaluated in depth. Figure 1 shows the PRISMA flowchart depicting the study selection process [Figure 1].

Several supplementary methods were used to enhance the sensitivity of the search strategy. To recover variations of relevant terms and widen search combinations, truncation symbols and Boolean operators were used. Synonyms, alternate spellings, and plural forms were incorporated to capture a broader range of potentially eligible literature. We made sure everyone could participate, regardless of language or location. Also, to ensure no essential entries were missed due to variations in database-specific indexing, the databases were searched separately.

Eligibility Criteria

This review only included RCTs that assessed regorafenib's efficacy in treating bone sarcoma. We only included research with publicly available full-text publications. In addition, to evaluate regorafenib's safety and effectiveness in treating bone sarcoma, all relevant trials had to compare it to a placebo.

One author (M.R.) reviewed the abstracts and titles of all records identified in the literature search during the screening phase. Two separate reviewers, M.R. and S.K., checked the articles for eligibility for full-text evaluation. The authors resolved any differences through frank discussions. A third reviewer (A.T.) served as an arbitrator to resolve disagreements and maintain the validity of the review process when agreement could not be reached.

From the date of regorafenib's FDA clearance on September 27, 2012, to the date of the final literature search, the inclusion date criteria were in effect. To provide a thorough review of the field's progress and evidence since regorafenib's entry into clinical practice, this timeline was chosen.

The following types of research were not considered: case reports, abstracts, guidelines, ongoing or unpublished clinical trials, trial protocols, systematic reviews, literature reviews, gray literature sources, animal studies, and letters to the editor. Inadequate data for evaluating primary and secondary outcomes or studies with partial full-text availability were other grounds for exclusion.

Data Extraction

Two writers (M.R. and S.K.) created standardized data extraction forms to obtain information and findings from the chosen research. When two writers could not agree, a third author (S.H.) stepped in as an arbitrator. Study population, type of clinical trial, baseline participant characteristics, authors' names, year of publication, country of origin, detailed histopathological sarcoma subtype, recruitment period, progression-free survival (PFS), progression-free rate (PFR), response rate (RR), and overall survival (OS) were among the data extracted. Age, sex distribution, and other pertinent baseline data were also gathered from the participants. Along with the outcome data, treatment-related adverse events (AEs) were also retrieved. We contacted the corresponding authors to request clarification when specific data points for important outcomes (PFS, OS, AEs) were not fully disclosed. The trial was excluded from the analysis for that particular outcome if no answer was obtained.

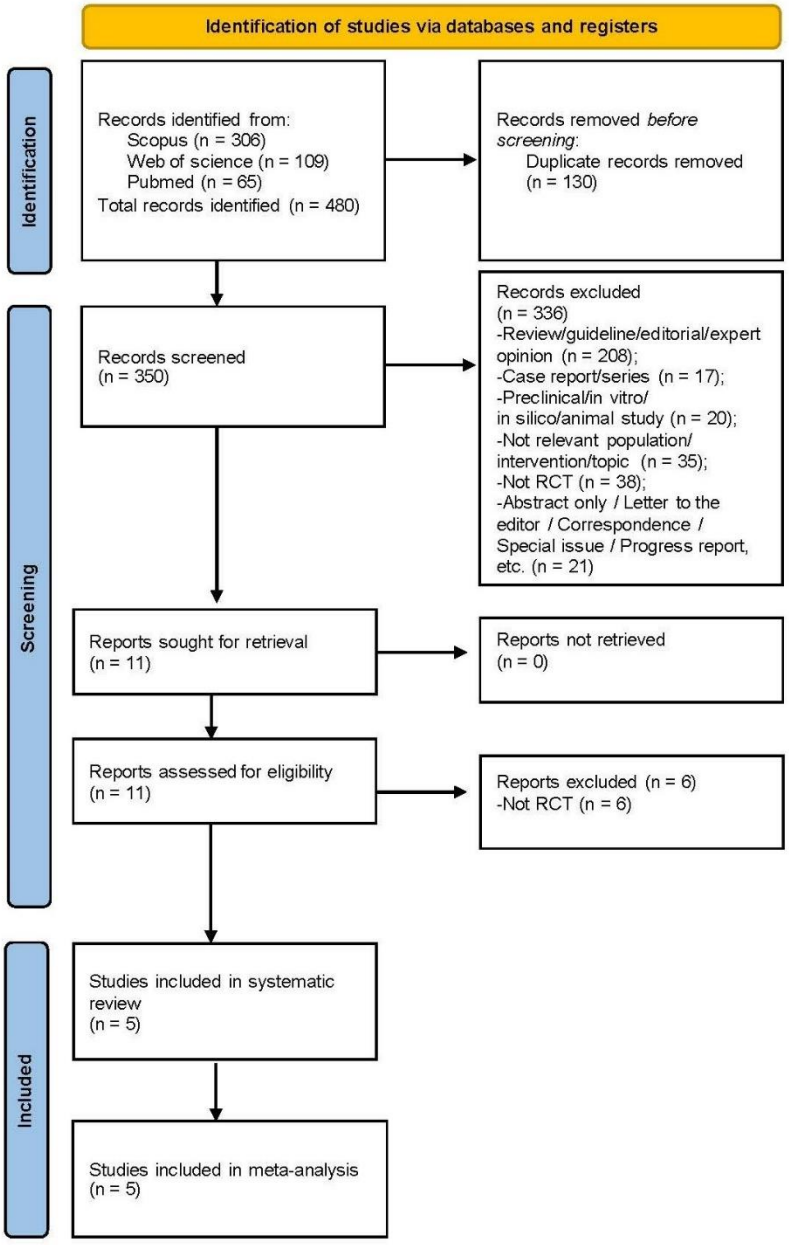

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only

Risk of Bias Assessment

All included randomized controlled trials were evaluated for methodological quality and bias using the revised Cochrane Risk of Bias 2 (RoB 2) approach, in accordance with the recommendations made by Higgins et al. (2019). sixteen[16] It assesses five types of bias at the level of the study: (1) bias in randomization, (2) bias in intervention variation, (3) bias in missing outcome data, (4) bias in measurement, and (5) bias in reported result selection. Reviewers used a predetermined series of signaling questions to assign a hazard rating of "low," "some concerns," or "high" to each subject. Two reviewers (M.R. and S.H.) independently assessed each paper, and a third reviewer (A.T.) either resolved disagreements or discussed them further. With a "low" rating for all domains considered low risk, a "high" rating for at least one domain regarded as high risk, or when

several domains showed some concerns, and a "some concerns" rating for all other situations, the total risk of bias in the RoB 2 decision algorithm was calculated. The risk of bias assessment results for each included study are presented in summary tables and color-coded visual plots, providing a clear picture of judgments across all five areas [Table 1]. There is little danger in the green circles, but some in the yellow ones.

Synthesis methods and Statistical analysis

Only studies with adequate data for PFS, OS, and AEs were included in this pooled analysis. The inverse-variance weighting method was employed, with the week's mean difference (MD) for PFS and OS, and odds ratios (ORs) for adverse events (AEs). All trials used the same outcome measures before pooling. Heterogeneity was scored as high (>75%), moderate (50-75%), or low (25-50%) according to predefined methods and assessed using the I^2 statistic.[17] We used the DerSimonian-Laird method to account for between-study variation in a random-effects meta-analysis, as anticipated clinical heterogeneity across studies necessitated this approach. We did not conduct sensitivity analyses because our sample size was too small to yield reliable findings with subgroup or leave-one-out methods.

Bone sarcoma subtypes were used to conduct subgroup analyses, and we also examined differences between subgroups. The definition of statistical significance was a P value less than 0.05. R version 4.3.1 was used for all statistical analyses.

Table 1. Risk of bias assessment for included studies.

Study	D1: Randomization	D2: Intervention Deviation	D3: Missing Data	D4: Outcome Measurement	D5: Reported Result	Overall Risk
Davis et al. 2019	Some concerns	Low	Low	Low	Low	Some concerns
Duffaud et al. 2019	Low	Low	Low	Low	Low	Low
Duffaud et al. 2021	Low	Low	Low	Low	Low	Low
Le Cesne et al. 2023	Some concerns	Low	Low	Low	Low	Some concerns
Duffaud et al. 2024	Low	Low	Low	Low	Low	Low

Domain Definitions
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended interventions.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement Key:
"Low" → Low risk of bias
"Some concerns" → Potential bias requiring caution

Results

Study Selection

After duplicates were removed, 350 records were screened. Title and abstract screening eliminated 339 articles due to their nature as reviews, case reports, non-RCTs, or studies involving populations or interventions unrelated to the main topic. After reviewing all eleven full-text papers, six were deemed ineligible because they did not meet the criteria for randomized controlled trials. The final analysis ultimately included five randomized controlled trials. A PRISMA flow diagram depicting the study selection process is shown in [Figure 1].[18-22]

Study Characteristics

Phase II trials conducted from 2019 to 2024 comprised all five studies considered for this meta-analysis. Table 2 summarizes the key features of these trials [Table 2].

Study Quality

Across all five trials, the overall risk of bias was assessed to be low. Due to insufficient reporting of sequence generation and allocation concealment approaches, Davis et al. (2019) and Le Cesne et al. (2023) were classified as having "some concerns" in Domain 1, which addresses bias arising from the randomization process. Regardless, in every other category, the two trials were deemed to be of "low risk". The other three studies—Duffaud et al. (2019, 2021, and 2024)—were consistently evaluated as "low risk" across all analyzed domains. It was determined that no study had a "high risk" of bias in any domain. Both Table 1 and Figure 2 offer domain-specific summaries of risk-of-bias judgments [Table 1, Figure 2]. Figure 2 provides a visual overview.

Pooled analysis of PFS comparing regorafenib with the control groups

Response Evaluation Criteria in Solid Tumors (RECIST) was applied to assess progression-free survival (PFS) in three separate trials. After that, the regorafenib and control groups' PFS results were compared using a pooled analysis. Cense et al.'s survey was excluded because there wasn't sufficient data.

To combine PFS results across all recognized histological subtypes, a random-effects meta-analysis was performed

using the inverse-variance approach. There were also tests for subgroup differences and subgroup analyses. There was no indication of heterogeneity among sarcoma subtypes, and the results showed that regorafenib considerably increased PFS in bone sarcoma (MD = 9.69 weeks; 95% CI: 4.54-14.84; I^2 = 0%; P-heterogeneity = 0.87) [Figure 3].

Table 2. Characteristics of the included studies.

Study	Year	Study phase	Design	Condition	Country	Recruitment period	Total Sample Size	Treatment Arm	Placebo Arm	Male	Female	Age	Presence of Metastases (n, %)	Outcomes
Davis *et al.* [18]	2019	Phase 2	Randomized, double-blind, placebo-controlled	Osteosarcoma	USA	September 2014/ May 2018	42	22	20	20	22	Median 37 years	Yes: 100% (Regorafenib: 22/22, Placebo: 20/20)	Median PFS, OS, time to tumor progression, PFS at eight and 16 weeks, OS, Overall response rate,
Duffaud *et al.* [19]	2019 [1]	Phase 2	Non-comparative, randomized, double-blind, placebo-controlled	Osteosarcoma	France	October 2014/ April 2017	43	29	14	24	14	Median 33 years	Yes: 96.2% (Regorafenib: 25/26), 100% (Placebo: 12/12)	Median PSF, OS, PFR at 8, 12, and 24 weeks, Adverse effects.
Duffaud *et al.* [20]	2021	Phase 2	Non-comparative, randomized, double-blind, placebo-controlled	Chondrosarcoma	France	September 2014/February 2019	41	24	16	25	15	-	Yes: 100% (Regorafenib: 24/24), 88% (Placebo: 14/16)	Median PSF, OS, PFR at 12 and 24 weeks, OS at six and 12 months, Adverse effects
Le Cesne *et al* [21]	2023	Phase 2	Randomized, double-blind, placebo-controlled	Chordoma	France	March 2016 /February 2020	27	18	8	16	7	Median 66 years	Yes: 37.5% (Regorafenib: 6/16), 14.3% (Placebo: 1/7)	PFR at six months, Median PFS, OS, response rate, objective response rate, duration of overall response, Adverse effects
Duffaud *et al* [22]	2023	Phase 2	Non-comparative, randomized, double-blind, placebo-controlled	Ewing sarcoma	France	September 24, 2014 to November 4, 2019	36	23	13	28	8	32 in the regorafenib arm, 28 in the placebo arm	Yes: 100% (Regorafenib: 23/23), 92% (Placebo: 12/13)	PFR at eight weeks, PFS Objective response rate (ORR), OS. Duration of response (DoR) Adverse effects

[1] This article was published online on November 23, 2018, and was subsequently included in the January 2019 issue of the journal

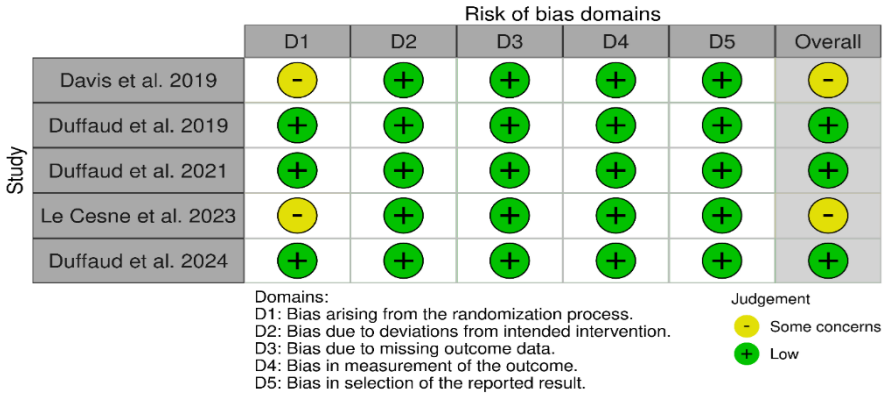

Figure 2. Risk of bias assessment for included randomized controlled trials using the Cochrane Risk of Bias 2.0 tool. Each row represents a study, and each column corresponds to a bias domain:
D1 – Bias arising from the randomization process; D2 – Bias due to deviations from intended interventions;D3 – Bias due to missing outcome data;D4 – Bias in measurement of the outcome;D5 – Bias in the selection of the reported result.
Judgements are categorized as low risk (green) or some concerns (yellow). The final column indicates the overall risk of bias per study.

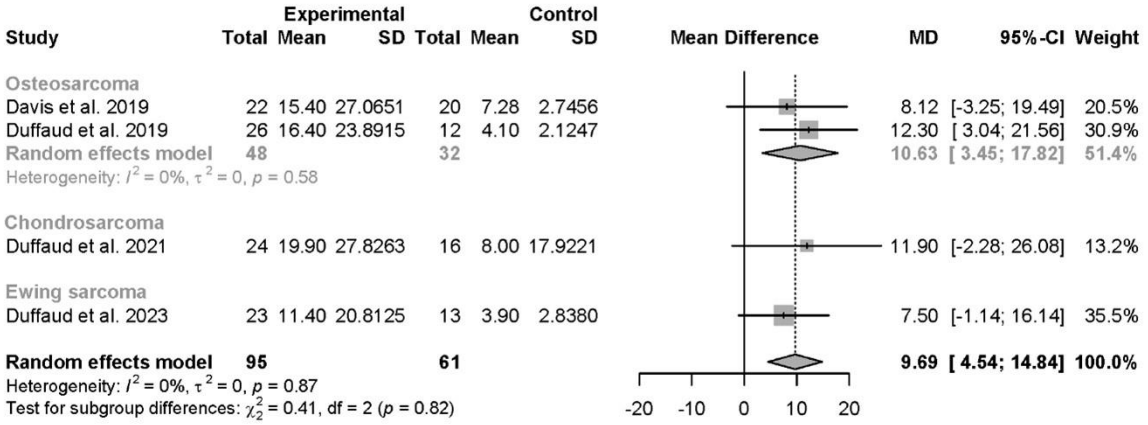

Figure 3. Forest plot of meta-analysis comparing progression-free survival (PFS) between regorafenib and control groups across different bone sarcoma subtypes. Subgroup analyses were conducted for osteosarcoma, chondrosarcoma, and Ewing sarcoma. Each study is represented by its mean difference (MD) in PFS with corresponding 95% confidence intervals (CIs). The pooled effect estimate (MD = 9.69, 95% CI [4.54, 14.84]) favors regorafenib, indicating a statistically significant improvement in PFS compared to control. Heterogeneity was low (I^2 = 0%), and no significant difference was found between subgroups (p = 0.82), suggesting consistent treatment effects across sarcoma types

Pooled analysis of OS comparing regorafenib with the control group

All five randomized controlled trials reported overall survival (OS). The research by Cense et al. and Dauffaud et al. (2023) were not included in the OS analysis due to a lack of data. Cohorts of patients with metastatic or locally advanced chondrosarcoma, metastatic osteosarcoma, or both were analyzed to determine overall survival (OS) between the regorafenib and control groups.

We ran a test for differences across subgroups and analyzed the data using subgroups. The results showed no heterogeneity and no statistically significant difference between the placebo and regorafenib groups. Figure 4 shows that there was no statistically significant difference in variance across bone sarcoma subtypes [Figure 4-6]. The critical interval (CI) ranged from -36.33 to 38.02 weeks, and the likelihood ratio (I^2) was 0%. P-heterogeneity was 0.38.

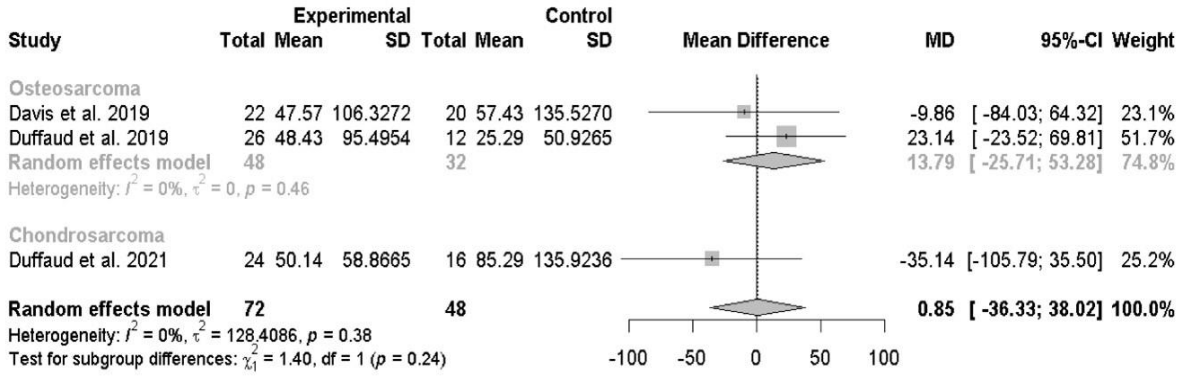

Figure 4. Forest plot of pooled analysis comparing overall survival (OS) between regorafenib and control groups in patients with osteosarcoma and chondrosarcoma. The analysis includes data from three studies and is stratified by sarcoma subtype. The pooled mean difference (MD) in OS was 0.85 week (95% CI: −36.33 to 38.02), indicating no statistically significant improvement in survival with regorafenib compared to control. Heterogeneity was low (I^2 = 0%), and the test for subgroup differences was not significant (p = 0.24), suggesting a consistent treatment effect across the included sarcoma types

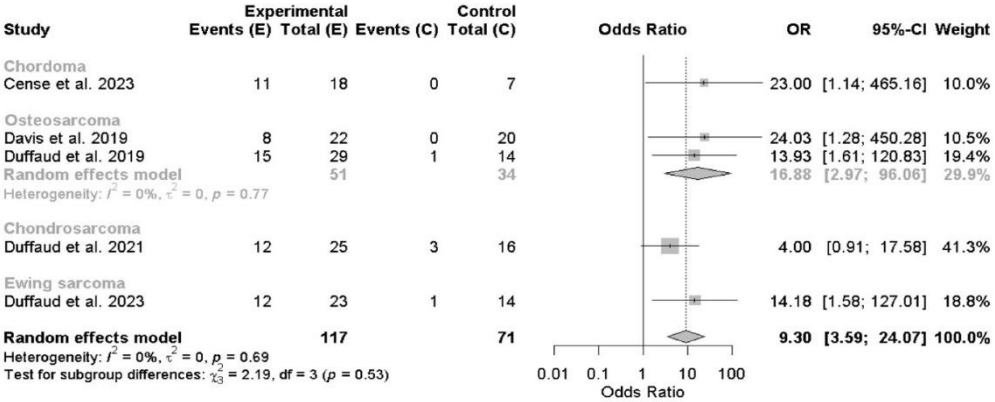

Figure 5. Forest plot of pooled analysis comparing the incidence of hand-foot skin reaction (HFSR) between regorafenib and control groups across various bone and soft tissue sarcoma subtypes, including chordoma, osteosarcoma, chondrosarcoma, and Ewing sarcoma. The pooled odds ratio (OR = 9.30; 95% CI: 3.59 to 24.07) indicates that patients receiving regorafenib had a significantly higher risk of developing HFSR compared to those in the control group. Individual subgroup estimates also suggest elevated risk, particularly in osteosarcoma and Ewing sarcoma. Heterogeneity across studies was low (I^2 = 0%), and no significant difference was observed among subgroups (p = 0.53), supporting consistency in the observed adverse event across sarcoma types

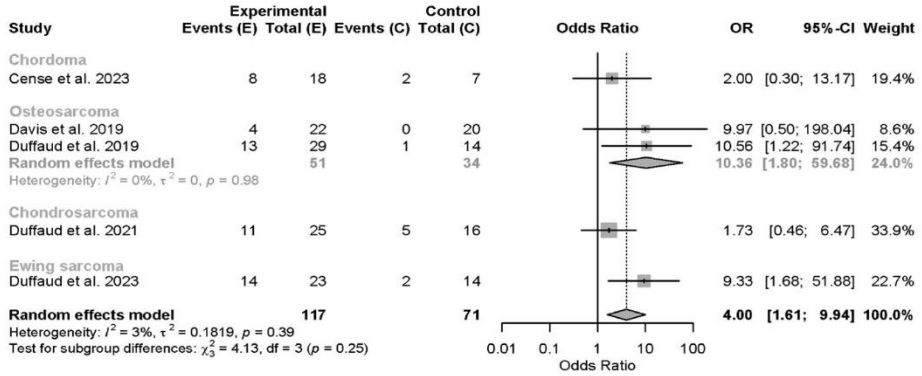

Figure 6. Forest plot of pooled analysis comparing the incidence of diarrhea between regorafenib and control groups across different sarcoma subtypes, including chordoma, osteosarcoma, chondrosarcoma, and Ewing sarcoma. The pooled odds ratio (OR = 4.00; 95% CI: 1.61 to 9.94) indicates a statistically significant increase in the risk of diarrhea in patients receiving regorafenib compared to controls. Although individual study estimates vary in magnitude, most suggest a higher incidence in the regorafenib group. Heterogeneity across studies was low (I^2 = 3%), and the test for subgroup differences was not statistically significant (p = 0.25), suggesting a consistent effect across different sarcoma types

Pooled analysis of the safety profile comparing regorafenib with the control group

For the safety evaluation, we incorporated all pertinent research. The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, produced by the National Cancer Institute, was used to evaluate adverse events [Table 3].

Although it was not noted in the study by Davis et al., fatigue/asthenia was the most commonly reported adverse effect. Figure 7 shows that among the trials that were considered, the most common side effects of the treatment were skin reactions in the hands and feet (OR = 9.30; 95% CI: 3.59-24.07; I^2 = 0%; P-heterogeneity = 0.69), diarrhea (OR = 4.00; 95% CI: 1.61-9.94; I^2 = 0%; P-heterogeneity = 0.39), and high blood pressure (OR = 2.77; 95% CI: 1.28-6.01; I^2 = 0%; P-heterogeneity = 0.82) [Figure 7].

Table 3.Predominant Adverse Effects.

Study		Adverse effects			
Davis et al. 2019	*Any grade*	Hand-foot skin reaction (8/22)	Hypertension (7/22)	Nausea (5/22)	Diarrhea (4/22)
	Grade three–five	Hypertension (3/22)	Maculopapular rash (2/22)	Thrombocytopenia (2/22)	Hypophosphatemia/Extremity pain (2/22)
Duffaud et al. 2019	*Any grade*	Fatigue (26/29)	Hand–foot skin reaction (15/29)	Diarrhea (13/29)	Hypertension (12/29)
	Grade three–five	Hypertension (7/29)	Fatigue (3/29)	Chest pain (3/29)	Hypophosphataemia/Hand-foot skin reaction (3/29)
Duffaud et al. 2021	*Any grade*	Pain (20/25) [1]	Asthenia/fatigue (18/25)	Diarrhea (13/25)	Hand-foot skin reaction (12/25)
	Grade three–five	Pain (5/25)	Hypertension (3/25)	Asthenia/fatigue (3/25)	Neuralgia/Thrombocytopenia/Diarrhoea (2/25)
Le Cesne et al. 2023	*Any grade*	Asthenia (14/18)	Pain (12/18)	Hand-foot skin reaction (11/18)	Hypertension (10/18)
	Grade three–five	Hypertension (4/18)	Hand-foot skin reaction (4/18)	Pain (4/18)	Diarrhea (3/18)
Duffaud et al. 2023	*Any grade*	Pain (17/23)	Asthenia (16/23)	Diarrhea (14/23)	Hand-foot skin reaction (12/23)
	Grade three–five	Pain (5/23)	Asthenia (4/23)	Thrombocytopenia (3/23)	Hand-foot skin reaction / Diarrhea (3/23)

[1]The term "pain" was categorized under general disorders in the studies by Duffaud et al. (2023), Duffaud et al. (2021), and the CENSE study (2023). Additionally, these studies reported instances of skin pain and abdominal pain, which were not included in the overall counts for the term "pain."

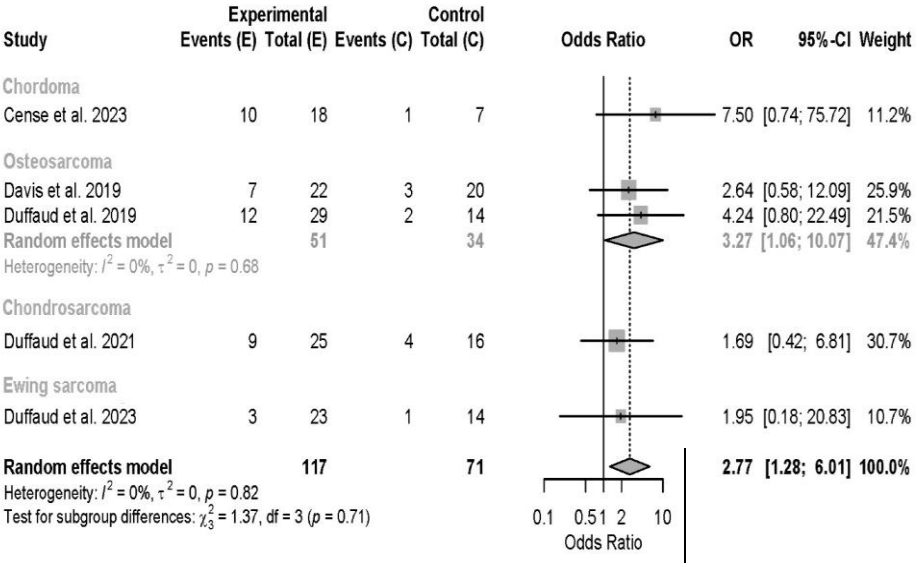

Figure 7. Forest plot of pooled analysis comparing the incidence of hypertension between regorafenib and control groups across different sarcoma subtypes, including chordoma, osteosarcoma, chondrosarcoma, and Ewing sarcoma. The overall pooled odds ratio (OR = 2.77; 95% CI: 1.28 to 6.01) suggests a statistically significant increase in the risk of hypertension among patients treated with regorafenib compared to those receiving control treatments. While individual study estimates varied and some confidence intervals were wide, the direction of effect consistently favored a higher risk with regorafenib. Heterogeneity was low (I^2 = 0%), and the test for subgroup differences was not significant (p = 0.71), indicating a consistent effect across sarcoma types.

Discussion

Efficacy of regorafenib

By inhibiting tumor cell growth in both cell line and patient-derived xenograft models, regorafenib has demonstrated broad antitumor activity in preclinical studies. This activity is mainly observed against Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, and doxorubicin-resistant Ewing sarcoma.[18] Rather than focusing on objective response, this systematic review examined five trials that focused on progression-free survival. According to Duffaud et al., tumor shrinkage in calcified osteosarcoma lesions may not be a reliable indicator of genuine anticancer activity. Additionally, the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to evaluate outcomes across all included studies. The trial conducted by Le Cesne et al. was not included in the efficacy analysis because there was insufficient data for a quantitative evaluation.[19]

The treatment group in the randomized Phase II REGOBONE trial had a median progression-free survival (PFS) of 16.4 weeks, while the control group only managed 4.1 weeks. Duffaud et al. discovered a notable variation in progression-free survival (PFS) by utilizing a modified intention-to-treat technique. While no patients in the placebo group shown any improvement after 8 weeks, 65% of those in the therapy group did. In the study conducted by Davis et al. as part of SARC024, the treatment group demonstrated a median progression-free survival (PFS) of 3.6 months, in contrast to the control group's median PFS of 1.7 months. Compared to 25.0% and 10.0%, the PFS rates at 8 weeks and 16 weeks were 79.0% and 44.4%, respectively. Even though response rates were moderate across trials, regorafenib showed a significant improvement in progression-free survival (PFS).[20,21] The lack of statistical significance in overall survival may be due to the crossover design.

Several tyrosine kinase inhibitors have shown significant activity in osteosarcoma. One partial response (7%) and a median progression-free survival (PFS) of 6 months were observed in a study of 15 patients treated with pazopanib.[22] A Phase II study using sorafenib had a 4-month PFS rate and a 4-month median PFS in a single-arm design. Also, in a single-arm trial of apatinib, 35 patients showed a median progression-free survival (PFS) of 4.5 months and a partial response rate of 57%. There was another group that had an even higher partial response rate of 43% with 16 out of 37 patients.[23]

An investigation of lenvatinib for osteosarcoma yielded promising preliminary results presented at ASCO 2018. The study found that the four-month PFS rate was 33%, with a median PFS of 3.4 months. There was also an 8% partial response (PR) rate, with 2 out of 26 patients obtaining PR.[18] There was a 12% PR rate (5 out of 42 patients) and a six-month PFS rate of 33% in a recent open-label Phase II trial investigating cabozantinib. The median PFS was 6.2 months.[24,25] Combining immune checkpoint inhibitors with multikinase inhibitors, like regorafenib, has shown synergistic activity, especially when it comes to targeting the VEGF pathway. This suggests that there may be a way to improve the therapeutic effects of immune checkpoint inhibitors in metastatic osteosarcoma.[26,27]

Safety of regorafenib

When it came to safety, known side effects of multitarget tyrosine kinase inhibitors were present, although they were tolerable and occurred frequently during therapy.[28-31] Hypertension was the most frequently reported grade ≥3 toxicity related to regorafenib in most studies, even though it was not the most prevalent adverse event overall. One well-known side effect of VEFG pathway-targeting medicines is increased blood pressure, a direct pharmacodynamic effect of VEFG inhibition.[32,33]

As a result of side effects, 68% of patients in the Cense et al. research had to lower their dosage, and 18.7% had to stop treatment altogether. Adverse events of grade ≥3 occurred in 22% of cases, including hand-foot skin response (22%), hypertension (22%), discomfort (22%), and diarrhea (17%). Serious treatment-related events affected 18% of patients.[19]

The frequent need to reduce regorafenib dosage suggests that the full 160 mg/day dose may not be well tolerated. Eleven individuals needed short breaks from therapy, while three had to stop due to toxicity. Out of the three patients who were given regorafenib, a pulmonary problem (n = 1), cholecystitis (n = 2), and acute pancreatitis (n = 1) were the five major adverse events that were ascribed to the treatment. A single case of epilepsy was reported in a placebo group member. No fatalities were reported as a result of the treatment.

The regorafenib group had a higher rate of treatment-related complications, according to the Davis et al. study. At the conclusion of treatment, the median regorafenib dose was 120 mg, and 55% of patients required dose reductions. In the regorafenib group, 13 individuals (59% of the total) experienced dose interruptions. A longer treatment term without a decrease in efficacy may be possible with a lower starting dose, such as 80-120 mg.[20]

Specific side effects, including hypertension, diarrhea, and hand-foot skin reactions, were in line with regorafenib's known toxicity profile. Cases of grade 3 pneumothorax and grade 4 colonic perforation in treated patients highlight the possibility of rare but serious side effects. After just two cycles of treatment at 160 mg, both patients stopped due to these side effects; nevertheless, they were able to resume treatment at lower doses of 120 or 80 mg. Neither treatment-related fatalities nor adverse events of grade 5 were documented.

The recommended starting dose of regorafenib in the Duffaud et al. trial was 160 mg daily. Seven patients (or 24%) experienced serious side effects associated with the medication, such as hypophosphatemia, hand-foot skin response, severe hypertension, and others.[21]

Though there were no fatalities or incidents of grade 5, the number of adverse event calls into question whether the 160 mg/day beginning dose is too high and calls for additional research. Tolerability over the long term could be enhanced with individualised dose changes. For example, studies reported varying degrees of tiredness and soreness as side

effects. While 23 out of 29 individuals in the 2019 research reported feeling weary while using regorafenib, 18 out of 25 patients in the 2021 survey experienced the same thing. In a similar vein, 14 of 18 individuals were reported to have asthenia by Cense et al. (2023).

In the era of targeted therapy, the assumption that greater molecular specificity necessarily translates into superior outcomes has proved overly simplistic.[34,35] Tyrosine kinase inhibitors (TKIs) illustrate this point well, as multitargeted "dirty" TKIs often outperform highly selective agents by inhibiting multiple signaling pathways involved in tumor progression and therapeutic resistance.[36] Conversely, particular agents—including those delivered through advanced nanomedicine-based formulations—may reduce off-target toxicity, offering a different therapeutic advantage. Both approaches, therefore, carry distinct benefits and limitations.[37-41] This dual paradigm may help explain why, in the present analysis, both PFS and OS outcomes were similar across various sarcoma subtypes. Regorafenib's broad inhibition of shared molecular pathways likely contributes to its consistent efficacy and safety profile across histologically diverse bone sarcomas.

Additionally, this research highlights several significant caveats. One limitation is that the patient populations enrolled in the randomized controlled trials included in this study were minimal. This means the results may not apply to larger clinical settings due to limited statistical power. Secondly, it was challenging to detect late adverse events or sustained therapeutic benefit because most trials lacked adequate follow-up to evaluate long-term safety and efficacy. Thirdly, it is challenging to synthesize effect sizes and compare results across trials because most trials reported only point estimates for progression-free survival (PFS) and overall survival (OS), rather than hazard ratios or extensive time-to-event analyses. Another noteworthy limitation is the absence of pediatric patients in all included trials, despite the high prevalence of osteosarcoma among adolescents, underscoring the need for future studies to address pediatric-specific toxicity considerations and optimal dosing strategies. Lastly, deeper subgroup analyses were not possible due to limited access to individual patient data, which may have contributed to the persistence of unnoticed heterogeneity. These caveats, taken together, highlight the urgency of conducting more high-quality studies on regorafenib in bone sarcoma.

Conclusion

Regorafenib has clinically significant efficacy in bone sarcoma, according to this systematic review and meta-analysis, since it significantly improves progression-free survival (PFS) with little variation among trials. Nevertheless, the effect on overall survival (OS) remains unclear, calling for further robust trials with extended follow-up. Small sample sizes, limited long-term outcome data, and limited pediatric participation are significant drawbacks that highlight the need for future studies, especially in adolescent groups.

Overall toxicity was manageable but obvious, with hand-foot skin reaction, hypertension, and diarrhea being the most often reported adverse effects. The typical 160 mg/day dose may be too high for sustained therapy, as seen by the frequent dose decreases. Validating regorafenib's significance across sarcoma subtypes, refining dosing strategies, and establishing its long-term survival advantages will require multi-institutional partnerships due to the rarity of bone sarcomas.

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References

1. Gutowski CJ, Basu-Mallick A, Abraham JA. Management of bone sarcoma. Surg Clin North Am. 2016;96(5):1077-1106. doi:10.1016/j.suc.2016.06.002.
2. Lin PP, Patel S, eds. Bone Sarcoma. New York, NY: Springer; 2013.
3. DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles & Practice of Oncology. Vol 2. Philadelphia, PA: Lippincott; 1985.
4. Gosheger G, Gebert C, Ahrens H, Streitbuerger A, Winkelmann W, Hardes J. Endoprosthetic reconstruction in 250 patients with sarcoma. Clin Orthop Relat Res. 2006;450:164-171. doi:10.1097/01.blo.0000223978.36831.39.
5. Eilber FR, Eckhardt J, Morton DL. Advances in the treatment of sarcomas of the extremity: current status of limb salvage. Cancer. 1984;54(S2):2695-2701. doi: 10.1002/1097-0142(19841201)54:2+<2695::aid-cncr2820541415>3.0.co;2-o.
6. Biermann JS, Adkins DR, Agulnik M, et al. Bone cancer. J Natl Compr Canc Netw. 2013;11(6):688-723. doi:10.6004/jnccn.2013.0088.
7. Wagner MJ, Livingston JA, Patel SR, Benjamin RS. Chemotherapy for bone sarcoma in adults. J Oncol Pract. 2016;12(3):208-216. doi:10.1200/JOP.2015.009944.
8. Harris MA, Hawkins CJ. Recent and ongoing research into metastatic osteosarcoma treatments. Int J Mol Sci. 2022;23(7):3817. doi:10.3390/ijms23073817.
9. Altun I, Sonkaya A. The most common side effects experienced by patients receiving the first cycle of chemotherapy. Iran J Public Health. 2018;47(8):1218-1219. doi:10.15171/ijph.2018.14306.
10. Tian Z, Niu X, Yao W. Receptor tyrosine kinases in osteosarcoma treatment: which is the key target? Front Oncol. 2020;10:1642. doi:10.3389/fonc.2020.01642.
11. Duffaud F. Role of TKI for metastatic osteogenic sarcoma. Curr Treat Options Oncol. 2020;21(8):60. doi:10.1007/s11864-020-00760-w.
12. Skårderud MR, Polk A, Vistisen KK, Larsen FO, Nielsen DL. Efficacy and safety of regorafenib in the treatment of metastatic colorectal cancer: a systematic review. Cancer Treat Rev. 2018;62:61-73. doi:10.1016/j.ctrv.2017.11.010.
13. Khachatryan V, Muazzam A, Hamal C, et al. The role of regorafenib in the management of advanced gastrointestinal stromal tumors: a systematic review. Cureus. 2022;14(9):e28665. doi: 10.7759/cureus.28665.
14. Facciorusso A, Abd El Aziz MA, Sacco R. Efficacy of regorafenib in hepatocellular carcinoma patients: a systematic review and meta-analysis. Cancers (Basel). 2019;12(1):79. doi:10.3390/cancers12010036.
15. Mercier J, Voutsadakis IA. A systematic review and meta-analysis of retrospective series of regorafenib for treatment of metastatic colorectal cancer. Anticancer Res. 2017;37(11):5925-5934. doi:10.21873/anticanres.12039.
16. Cochrane Methods Bias.Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, Siegfried N, Higgins JP. Revised Cochrane risk of bias tool for randomized trials (RoB 2). Available at: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials. Cochrane Handbook for Systematic Reviews of Interventions;2019.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-1558. doi:10.1002/sim.1186.
18. Duffaud F, Mir O, Boudou-Rouquette P, 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):120-133. doi:10.1016/S1470-2045(18)30742-3.
19. 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;150:108-118. doi: 10.1016/j.ejca.2021.03.039.
20. 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):1940-1948. doi: 10.1038/s41416-023-02413-9.
21. 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. doi:10.1016/j.esmoop.2023.101569.
22. Davis L, Bolejack V, Ryan C, et al. Randomized double-blind phase II study of regorafenib in patients with metastatic osteosarcoma. J Clin Oncol. 2019;37(16):1424-1431. doi:10.1200/JCO.18.02374.
23. Blay JY, Duffaud F, George S, Maki RG, Penel N. Regorafenib for the treatment of sarcoma. Curr Treat Options Oncol. 2022;23(11):1477-1502. doi: 10.1007/s11864-022-00990-0.
24. Longhi A, Paioli A, Palmerini E, et al. Pazopanib in relapsed osteosarcoma patients: report on 15 cases. Acta Oncol. 2019;58(1):124-128. doi:10.1080/0284186X.2018.1503714.
25. Xie L, Xu J, Sun X, et al. Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: an open-label phase II clinical trial. Oncologist. 2019;24(7):e542-e550. doi:10.1634/theoncologist.2018-0246.
26. Gaspar N, Casanova M, Sirvent FJ, et al. Single-agent expansion cohort of lenvatinib (LEN) and combination dose-finding cohort of LEN+ etoposide (ETP)+ ifosfamide (IFM) in patients (pts) aged 2 to≤ 25 years with relapsed/refractory osteosarcoma (OS). Lancet Oncol. 2018. doi:10.1016/S1470-2045(21)00387-9.
27. Italiano A, Penel N, Toulmonde M, et al. Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas: a French Sarcoma Group/US National Cancer Institute phase II collaborative study. Ann Oncol. 2018;29(suppl 8):viii753. doi:10.1016/S1470-2045(19)30825-3.
28. Ott PA, Hodi FS, Buchbinder EI. Inhibition of immune checkpoints and vascular endothelial growth factor as combination therapy for metastatic melanoma: an overview of rationale, preclinical evidence, and initial clinical data. Front Oncol. 2015;5:202. doi:10.3389/fonc.2015.00202.
29. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell

cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol. 2018;19(3):405-415. doi:10.1016/S1470-2045(18)30081-0.

30. Kim SY, Kim SM, Chang H, et al. Safety of tyrosine kinase inhibitors in patients with differentiated thyroid cancer: real-world use of lenvatinib and sorafenib in Korea. Front Endocrinol (Lausanne). 2019;10:384. doi:10.3389/fendo.2019.00384.
31. Zhang L, Zhou Q, Ma L, Wu Z, Wang Y. Meta-analysis of dermatological toxicities associated with sorafenib. Clin Exp Dermatol. 2011;36(4):344-350. doi:10.1111/j.1365-2230.2011.04060.x.
32. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer. 2013;49(6):1287-1296. doi:10.1016/j.ejca.2012.12.010.
33. McCormack PL. Pazopanib: a review of its use in the management of advanced renal cell carcinoma. Drugs. 2014;74:1111-1125. doi:10.1007/s40265-014-0243-3.
34. Small HY, Montezano AC, Rios FJ, Savoia C, Touyz RM. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: understanding and managing a new syndrome. Can J Cardiol. 2014;30(5):534-543. doi:10.1016/j.cjca.2014.02.011.
35. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. InSeminars in nephrology 2010 (Vol. 30, No. 6, pp. 591-601). WB Saunders.
36. Fojo T. Commentary: novel therapies for cancer: why dirty might be better. Oncologist. 2008;13(3):277-283. doi:10.1634/theoncologist.2007-0090.
37. Ghazanfary S, Rahmanian M, Vatanchian M, Haghbin A, Shakeri F, Oroojalian F. Characterization and Efficacy Evaluation of mPEG-PLGA/Taraxasterol Acetate Nanoparticles as Nano-Therapeutic Agents in Asthma Management. BioNanoScience. 2025;15(1):124.
38. Rahmanian M, Oroojalian F, Kesharwani P, Sahebkar A. Liposome-mediated anticancer drug delivery strategies for advancing brain tumor therapy. Eur Polym J. 2025;114001. doi:10.1016/j.eurpolymj.2025.114001.
39. Sanna V, Pala N, Sechi M. Targeted therapy using nanotechnology: focus on cancer. Int J Nanomedicine. 2014;9:467-483. doi:10.2147/IJN.S36654.
40. Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct Target Ther. 2022;7(1):93. doi:10.1038/s41392-022-00947-7.
41. Sadek WS, Ahmed AG, Abou Senna WG, Ebeid WA. Does Unplanned Excision of Soft Tissue Sarcomas Affect the Oncological Outcome: A retrospective study. Arch Bone Jt Surg. 2025 Oct 4. In Press