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Short Communication

# A review of the mechanism of action and clinical applications of sorafenib in advanced osteosarcoma

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ABSTRACT

*Objective:* To summarise the contemporary literature regarding sorafenib and its effectiveness as a novel treatment in advanced osteosarcoma.
*Background:* Modern treatment has seen the cure rate of osteosarcoma increase to 65%. However, in patients who do not achieve remission, prognosis is poor, as there are no effective, consensual second line therapies. Sorafenib has emerged as a potentially viable drug to be used in this context.
*Method:* A literature review was conducted evaluating articles pertaining to osteosarcoma and sorafenib.
*Discussion:* Clinical studies were prioritised, but preclinical data was also evaluated to elaborate on mechanisms and potential targets for the future. Limitations of the review and data were explored.
*Conclusion:* In isolation, sorafenib was shown to only provide brief clinical benefit due to various described mechanisms. However, when combined with other drugs that addressed its weaknesses or other aspects of the pathogenesis of osteosarcoma, it proved to be effective in reducing disease progression in a variety of advanced cases. Further investigation into the use of sorafenib in combination therapy is needed. Specifically, the combination of sorafenib with denosumab has displayed potential to be an effective future treatment for osteosarcoma.

## 1. Introduction

Osteosarcoma is the most common bone tumour in children, adolescents and young adults [1,2]. Risk factors for osteosarcoma are outlined in Table 1. It is most common between the ages of 10–19, and the incidence rate for the condition ranges between one and five cases per one million people [1,3–6]. It has a variable prognosis, and the main factors affecting disease course have been highlighted in Table 2. Current treatment for osteosarcoma has achieved a universal cure rate of 65% [7]. When diagnosed, patients commence induction chemotherapy [8,9]. The tumour is surgically resected and analysed, and if 90% or more of the tumour is necrosed, the chemotherapy regime is continued to eliminate micrometastasis [1,10]. However, there is no standardised treatment for osteosarcoma that has failed to respond to the first chemotherapy regime [11]. Thus, researchers have attempted to identify potential drugs to fulfil this role. One such drug is sorafenib, which is sold under the trade name “Nexavar” [9]. This literature review evaluates the mechanism of action and efficacy of sorafenib in the treatment of osteosarcoma refractory to chemotherapy.

## 2. Methodology

The terms “sorafenib OR Nexavar” and “osteosarcoma” were used to search the PUBMED database. The initial search was conducted during March 2016, and was repeated in April 2016. The searches were repeated and the original paper was reviewed in January 2017 to account for new evidence. Both preclinical and clinical data sources were evaluated. The oldest article discussing osteosarcoma and sorafenib was from 2009 [24].

## 3. Discussion

### 3.1. Preclinical data: osteosarcoma pathogenesis and sorafenib mechanism of action

Osteosarcoma is a multifactorial disease with a range of genes and mutations contributing to the pathogenesis [25]. The mitogen activated protein kinase/extracellular regulated kinase (MAPK/ERK) pathway is involved in tumour cell proliferation and metastasis [24]. Sorafenib is an inhibitor of a variety of tyrosine kinase receptors and is used to treat chemorefractory tumours of the thyroid, liver and kidney [26–29]. It is

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**Table 1**
Risk factors for osteosarcoma [3,6,12–16].

| Other diseases as risk factors | Other risk factors |
|---|---|
| Previous osteomyelitis | Hispanic and African heritage |
| Paget's bone disease (elderly populations) | Tall stature/large growth spurts |
| Hereditary Multiple Osteochondromas | Previous localised radiation treatment |
| Familial gene mutations, including: | Being aged between 10 and 19, or older than 65. |
| – RB1 (Retinoblastoma) | |
| – REQL4 (Rothmund-Thomson) | |
| – BLM (Bloom) | |
| – WRN (Werner) | |
| – p53 (Li-Fraumeni Syndrome) | |
| – Diamond-Blackfan Anaemia | |
| | Being female (in elderly populations) |
| | Being male (in young populations) |

**Table 2**
Factors affecting osteosarcoma prognosis [1,3,4,12,17–23].

| Factors supporting a positive outcome for the patient | Factors supporting a negative outcome for the patient |
|---|---|
| > 90% necrosis in response to neoadjuvant (induction) chemotherapy | < 90% necrosis in response to neoadjuvant chemotherapy |
| Wide surgical margin upon resection | Age > 40 years |
| Early diagnosis | Tumour located in the axial skeleton |
| Diagnosis before 12 years of age | Metastases at diagnosis |
| | Osteoblastic subtype |
| | Unresectable tumour |
| | Pathological fractures |
| | High serum concentration of vascular endothelial growth factor (VEGF) |

a direct inhibitor of this MAPK/ERK pathway, and acts by binding to rapidly accelerated fibrosarcoma protein kinase (RAF), stem cell growth factor receptor (c-kit), fibroblast-like growth factor receptor (FGFR) and platelet derived growth factor receptor (PDGFR) [30–34]. These actions prevent the activation of the MAPK/ERK pathway, mitigating cell growth and proliferation and depleting the tumour's cell population [30]. Furthermore, sorafenib has been shown to inhibit a variety of other proteins associated with osteosarcoma. [24,35–37]. 63% of osteosarcoma cell lines have upregulated VEGFR and it is associated with angiogenesis and metastasis [37]. Sorafenib also promotes apoptosis in a variety of cancer types by downregulating anti-apoptotic protein MCL-1 [38]. 84% of osteosarcoma cell lines evaluated in a laboratory were found to have elevated expression of MCL-1, making it an important drug target to promote tumour cell death [24].

### 3.2. Clinical efficacy of sorafenib as a standalone therapy

Two studies have evaluated the use of sorafenib alone as a treatment for osteosarcoma. The first was a phase II clinical trial conducted by the Italian Sarcoma Group in 2012 [39]. It involved 35 patients over the age of 14 with relapsed, unresectable tumours refractory to cisplatin, doxorubicin, ifosfamide and high-dose methotrexate. The response was moderately successful, with 46% of patients having progression-free survival at 4 months. However, only 29% had stable disease at 6 months: the benefits were ultimately transient [39]. The other trial involved 4 patients with relapsed, chemorefractory osteosarcoma being treated with sorafenib [40]. Of these patients, three achieved disease stabilisations. However, the median response duration was 3 months, after which the disease continued to progress. This study tested a number of other drugs such as sunitimab in identical circumstances, and each of these agents stabilised disease progression for a longer duration than sorafenib [40]. Thus, these trials established that chemorefractory osteosarcoma progression can be temporarily inhibited by sorafenib [39,40]. However, the benefit of sorafenib was small, and possible explanations were investigated.

### 3.3. Preclinical data: use of sorafenib in conjunction with other pharmacotherapies

Consulting data from an acute myelogenous leukaemia study, the Italian Sarcoma Group hypothesised that sorafenib was being countered by an interaction with mammalian target of rapamycin complex 2 (mTORC 2) [41,42]. mTORC1 and mTORC2 are protein complexes that stimulate the MAPK/ERK pathway downstream from the primary targets of sorafenib, promoting disease progression and metastatic potential [43]. Sorafenib was shown to inhibit mTORC1, but stimulate mTORC2 [24,44]. Thus, despite inhibiting the MAPK/ERK pathway upstream, sorafenib was also stimulating it downstream, resulting in disease progression by upregulating the expression and activity of mTORC2 [24,44]. Sorafenib was subsequently combined with everolimus, a drug that disassembles mTORC 2 and minimises the stimulatory effect of this protein. [41,42]. In vivo and in vitro investigation demonstrated that the combination of the drugs significantly reduced tumour growth, angiogenesis and metastasis [41]. Additionally, immunohistochemistry identified a significant reduction in the activity of mTORC1 and 2 [41].

Preclinical trials have explored the relevance of Receptor Activator of Nuclear Factor κ B (RANK) [10]. RANK is stimulated by RANK Ligand (RANKL) secreted by osteoblasts, which causes differentiation of osteoclasts and stimulates bone resorption. This has also been shown to cause increase in cell mobility in osteosarcoma models [10]. Additionally, overexpression of RANK and RANKL is associated with increased rates of metastasis and poorer outcomes for patients [45]. Denosumab is a monoclonal antibody against RANKL, preventing it from stimulating RANK [46]. Preclinically, it has demonstrated the ability to reduce proliferation and motility of osteosarcoma cells [47]. Thus, given the reported effectiveness of both everolimus and denosumab, studies were conducted to explore the combination of sorafenib and these two drugs.

### 3.4. Clinical efficacy of sorafenib in combination with other drugs

The Italian Sarcoma Group conducted another phase II clinical trial [9]. It was non randomised, as researchers selectively nominated patients with unresectable tumours refractory to both chemotherapy and radiotherapy. This trial tested sorafenib in combination with everolimus, the aforementioned mTORC 2 disassembler [41]. 38 patients were enrolled in the trial, and 17 (45%) of these were progression free at 6 months. 37% of patients were alive after twelve months, but only 5% were alive after 24 [9]. The goal of the trial was to achieve 50% of patients with progression free survival at 6 months to justify a phase III trial [9]. Thus, sorafenib and everolimus failed to achieve the target. Despite this, the benchmark for an experimental treatment of sarcoma to be considered feasible is 20% of subjects having progression free survival at 6 months [48]. The combination exceeded this threshold and was greater than sorafenib used in isolation and should thus still be considered for future investigation. Further preclinical trials should also be undertaken to identify more agents with which to combine this therapy in order to increase the duration of the response and possibly achieve curative action.

In 2015 a case was published involving a patient who had been given two regimes of chemotherapy, radiotherapy and tumour curettage, but was still experiencing progression in their spinal osteosarcoma [11]. Biopsy showed that the tumour was over-expressing RANK, and the osteoid matrix contained a large amount of RANKL. Thus, the patient was started on sorafenib and denosumab (monoclonal antibodies against RANKL). Despite osteosarcoma being consistently documented as a tumour incurable with pharmacotherapy alone, within eight months, positron emission tomography identified a complete