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REVIEW

Receptor tyrosine kinase inhibitors for the treatment of osteosarcoma and Ewing sarcoma

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Abstract

Adjuvant chemotherapy for osteosarcoma and Ewing sarcoma consists of conventional cytotoxic regimens that have changed little over the past decades. There is an urgent need for agents that are more effective and have less long-term toxicity. Receptor tyrosine kinases regulate cell growth and proliferation of these tumors, and small-molecule inhibitors for many of these kinases are now available. In this article, we review published phase II trials for patients with recurrent disease and highlight the pathways targeted by available agents, as well as the toxicity and efficacy results seen to date. We also discuss the difficulties in identifying biomarkers to facilitate rational patient selection, as well as published and proposed strategies for how these inhibitors can be combined with conventional chemotherapy or other targeted agents. It is hoped future trials can capitalize on this growing experience to optimize the use of this exciting class of agents.

KEYWORDS
adolescent and young adult oncology, Ewing sarcoma, osteosarcoma, pediatric oncology, tyrosine kinase inhibitors

1 | INTRODUCTION

Bone sarcomas account for approximately 5% of all pediatric cancers, with osteosarcoma and Ewing sarcoma being the most common types. Because most patients develop fatal metastatic disease if treated only with surgery and/or radiotherapy, adjuvant chemotherapy is routinely administered.[1–3] Chemotherapy regimens consist of conventional agents that have been used for decades. For both diseases, adding additional cytotoxic chemotherapy onto these standard backbones has not proven beneficial.[4,5]

Although current treatments cure 65%-75% of patients with localized osteosarcoma or Ewing sarcoma, fewer than one-third of patients with metastatic or recurrent disease are long-term survivors.[1,6,7] In addition, the acute and late effects of conventional chemotherapy are considerable, leading to hospitalizations, infertility, heart failure, and second malignancies. New treatment approaches are needed to improve outcomes and reduce long-term side effects among survivors.

Although conventional chemotherapy agents kill rapidly dividing cells in a relatively nonspecific manner, targeted therapies selectively exploit vulnerabilities more unique to tumor cells. Inhibitors of receptor tyrosine kinases (RTKs) represent the largest group of approved targeted therapies, and they are actively being investigated for bone sarcoma. RTKs have extracellular domain that connects to an intracellular catalytic kinase domain via a transmembrane linker. Binding of the receptor by ligand generates conformational changes leading to activation, autophosphorylation, and propagation of intracellular signaling pathways through interactions with ATP or other substrates. Most small-molecule RTK inhibitors interfere with this intracellular binding, thereby disrupting downstream catalytic activity. Because intracellular domains of many receptor tyrosine kinases are similar, a single inhibitor may affect the activity of multiple RTKs. In fact, most RTK inhibitors used for bone sarcoma affect several RTKs due to this lack of specificity.

The use of small-molecule RTK inhibitors has been most successful in treating sarcomas that harbor mutations or translocations of RTKs. For example, the use of imatinib to target *KIT* or *PDGFR* mutations has revolutionized treatment of gastrointestinal stromal tumor.[8] Similarly, using larotrectinib to target the translocation of the tyrosine

Abbreviations: PFS, progression-free survival; RTK, receptor tyrosine kinases; VEGF, vascular endothelial growth factor.

TABLE 1 Targeted RTKs of selected agents in osteosarcoma cell lines

Agent	IC_{50} < 10	IC_{50} 10-100	Reference
Osteosarcoma			
Apatinib	RET, VEGFR- 2	VEGFR-1	17, 21
Cabozantinib	KIT, MET, RET, VEGFR-2[a], 3	VEGFR-1	17, 22
Lenvatinib	RET, VEGFR-1, 2, 3	KIT, FGFR-1, PDGFR-α	17
Regorafenib	KIT, RET, VEGFR-2	PDGFR-β, VEGFR-1,3	17
Sorafenib	RET, VEGFR-2	KIT, PDGFR-α, PDGFR-β, VEGFR-3	17

[a]The IC_{50} of VEGFR-2 is 0.035 nM.

kinase *NTRK* found in infantile fibrosarcoma has shown great benefit.[9] Unfortunately, osteosarcoma and Ewing sarcoma rarely have activating mutations or translocations involving RTKs.[10–12] However, there is growing evidence that several RTKs are important for maintaining cell growth and viability, and their expression may be associated with poor outcome.[13–17] These findings have provided a rationale for investigating RTK inhibitors in patients with these diseases, and the modest success seen so far is detailed below. Use of these agents to treat relapsed/refractory bone sarcoma is becoming more common in clinical practice,[18] and RTK inhibitors are now included in guidelines for management of relapsed osteosarcoma from both the European Society of Medical Oncology[19] and the National Comprehensive Cancer Network.[20]

Although preliminary results are encouraging, several fundamental issues must be addressed in order to optimize the use of small-molecule RTK inhibitors for pediatric bone sarcoma. These include the choice of inhibitor, the mechanisms of response and resistance, pharmacokinetic and toxicity considerations, and the best clinical context for drug administration. Using results from recently reported phase II trials, we provide perspective on these issues and a summary for the clinician. We review the clinical experience with several different inhibitors and discuss barriers and possibilities regarding use of these agents for the treatment of pediatric bone sarcoma. Both osteosarcoma and Ewing sarcoma are included in this discussion given the similarities between these diseases and the overlap in patient age and agents tested.

1.1 | Key RTKs in osteosarcoma and Ewing sarcoma

Multiple RTKs appear important for osteosarcoma and Ewing sarcoma growth, including those regulating tumor angiogenesis (VEGFR-1, 2, and 3), oncogenesis (KIT, MET, RET), and the tumor microenvironment (PDGFR, FGFR). Not all RTKs have been studied in both diseases, and uncertainty remains about which may be key drivers. A detailed discussion of these RTKs is available elsewhere.[13–17] In this article, we highlight five drugs (cabozantinib, regorafenib, sorafenib, apatinib, and lenvatinib) that have been the subject of recent phase II trials. The extent to which each agent is suspected to inhibit key RTKs to an IC_{50} of $\leq$ 100 nanomolar is listed in Table 1.[17,21,22]

Vascular endothelial growth factor (VEGF) promotes tumor growth and metastasis through a variety of mechanisms, including vascular permeability and tumor angiogenesis. Of the identified VEGF RTKs, VEGFR2 is the primary mediator of downstream effects,[23] and it is inhibited at low nanomolar levels by all five agents mentioned above. VEGF is one of the most characterized RTK pathways, with a meta-analysis of 12 studies including 559 osteosarcoma patients showing that VEGF expression is linked to outcome.[24] Data also suggest that this pathway is a reasonable target in Ewing sarcoma.[25] Of note, direct inhibition of VEGF signaling with the monoclonal antibody bevacizumab did not improve histologic response or overall outcomes in newly diagnosed osteosarcoma patients also receiving standard chemotherapy,[26] raising the hypothesis that disruption of VEGF signaling alone may be important but not sufficient to achieve meaningful antitumor activity.

Signaling through the RET receptor tyrosine kinase has also been established as a therapeutic target for osteosarcoma,[14] although involvement in Ewing sarcoma is less clear. Like VEGFR2, RET is also inhibited at nanomolar concentrations by all five agents above. In contrast, other potentially relevant RTKs such as KIT, MET, AXL, PDGFR, and FGFR are inhibited by some but not all of the agents shown to be active for pediatric bone sarcoma. Given that a single agent can inhibit multiple targets, it is difficult to determine the significance of disrupting signaling for a specific RTK. Nevertheless, defining the relative importance of specific RTKs to tumor growth is important to help with drug selection. To assess the clinical significance of the relative RTKs in osteosarcoma, Tian and colleagues compared the documented in vitro inhibition of key RTKs with the results from available clinical trials.[17] By considering the reported clinical activity seen for a particular drug and the known RTKs inhibited by that agent, they used an inclusion/exclusion strategy to identify which RTK may be the most clinically relevant. They concluded that while single-target inhibition was not effective, multitargeted agents focusing on VEGFRs (1, 2, and 3) and RET was associated with better outcomes. Although limited by the relatively few clinical trials performed, this strategy provides preliminary information about which targets may be most closely linked to clinical benefit. However, the absence of direct comparison studies makes it hard to know whether one RTK inhibitor is truly better than another with an overlapping targeting profile. In addition, it is unclear whether there is differential activity between the two bone sarcoma types.

1.2 | Key clinical trials of RTK inhibitors for relapsed or refractory bone sarcoma

Context for interpreting studies of RTKs in bone sarcomas is provided by the experience with pazopanib in non-GIST adult soft-tissue sarcoma. For that disease, pazopanib demonstrated a low response rate (6%), but the three-month improvement in progression-free survival (PFS) compared with placebo led to its regulatory approval.[27] However, overall survival was not superior. Given that bone sarcomas generally lack activating RTK mutations, it is not surprising that similar results of low response rates and modest improvement in PFS have emerged from phase II studies to date. For pazopanib, retrospective case reports show some activity in bone sarcoma,[28,29] but results from a prospective phase II trial of pazopanib (clinicaltrials.gov identifier number NCT01956669) have not been reported.

For patients with relapsed osteosarcoma, a critical element in study design is to define a meaningful response criterion. Some osteosarcoma tumors will calcify and not shrink in response to treatment, which has led to PFS rather than response rate being widely adopted as the primary clinical endpoint. Patients with relapsed osteosarcoma and measurable disease who receive placebo have a median PFS of one month,[30] and those receiving ineffective agents have a four-month PFS of 12%.[31] Table 2 lists results from six phase II trials in which more than 10 patients with relapsed osteosarcoma were included.[21,30,32–35] Treatment with either sorafenib, apatinib, cabozantinib, lenvatinib, or regorafenib resulted in four-month PFS ranging from 33% (lenvatinib) to 71% (cabozantinib). Response rates ranged from 7% (lenvatinib) to 43% (apatinib), with all being partial responses. Although these studies are relatively small and outcomes have large confidence intervals, collectively these data show a consistent activity signal for this class of agents in relapsed osteosarcoma.

For Ewing sarcoma, only three phase II trials of more than 10 patients treated with small-molecule RTK inhibitors have been reported (Table 2).[32,36,37] Response rates were 10%-22% with regorafenib[36,37] and 26% with cabozantinib.[32] Previous estimates of futility include a six-month PFS of 12%,[38] with placebo resulting in PFS of one month.[37] The median PFS for these two agents was three to four months, with reported six-month PFS of 26% with cabozantinib. Therefore, regorafenib and cabozantinib can produce partial responses in some patients with relapsed Ewing sarcoma, and in both diseases PFS may be better than historical controls or placebo. However, dramatic improvements in outcome for patients with recurrent osteosarcoma or Ewing sarcoma have not been realized.

1.3 | Response and resistance to RTK inhibitors

As noted above, use of RTK inhibitors is substantially limited by incomplete knowledge of the precise mechanisms of response and resistance. At present, there is not yet certainty about which RTKs must be inhibited for treatment to be successful, and whether these markers must be present on tumor cells and/or in tumor-associated vasculature. For example, it is unclear whether the activity of sorafenib is related to its inhibition of the MAPK/ERK pathway, its effects on VEGFR and RET, or the combination of multiple pathways being inhibited.[39] Given the low likelihood of activating mutations of RTKs in pediatric bone sarcoma, perhaps it is helpful for inhibitors to be "dirty" and have several potential targets. Nevertheless, uncertainty about the precise mechanism of action has substantially limited the identification of predictive biomarkers, likely diluting out the effectiveness of these agents in clinical trials in which all patients are included instead of those more likely to benefit. Because phase II trials have shown at best partial responses and/or stable disease for a few months, it follows that most sarcomas demonstrate either primary resistance or the capacity to develop acquired resistance to RTK inhibitors. The mechanisms of resistance are complicated and often multiple, and may include absent expression or mutation of the target RTK, altered downstream effector pathways, or compensatory signaling through alternative pathways, rendering inhibition of the originally targeted RTK meaningless.[15,40,41] For example, treatment of osteosarcoma cells with sorafenib results in upregulation of mTORC2 as an escape mechanism, which is abrogated by the addition of everolimus.[42]

Potential strategies for identifying sensitive or resistant patients include assessment for presence of target by either protein expression or copy number.[43,44] Issues such as access to tissue, intratumoral heterogeneity, possible differences between primary and metastatic sites, and technical processing complexities have made routine use of this approach challenging. Another strategy is measurement of serum proteins related to the target of inhibition. For example, patients with recurrent osteosarcoma and high levels of soluble MET or low levels of VEGFA were found to have a better response to cabozantinib.[32] However, this relationship was not seen in similarly treated patients with recurrent Ewing sarcoma.

It will be important to validate findings like this and to determine whether these are general prognostic factors of outcome versus predictive factors truly dependent on the specific treatment. In that same study, assessment of metabolic response by ^{18}F-FDG PET-CT one month after starting treatment was correlated with PFS for both osteosarcoma and Ewing sarcoma patients. Although this approach cannot be used for patient assignment to therapy, early imaging could perhaps identify nonresponders to pull off treatment, provided these results are validated in subsequent studies.

1.4 | Pharmacokinetic considerations

Another factor complicating use of RTK inhibitors is significant interpatient variability in pharmacokinetics, causing up to a 10-fold difference in trough levels.[45] These differences may be due in part to variations in metabolizing enzymes such as CYP3A4.[46] In addition, careful attention for drug interactions is warranted, as many pediatric bone sarcoma patients are on multiple medications metabolized by similar pathways. Long-acting antacids such as proton pump inhibitors or H2-receptor antagonists may also affect drug absorption of these oral RTK inhibitors.[47] Given these issues, investigators have explored therapeutic drug monitoring for patients treated with RTK inhibitors.[48]

TABLE 2 Summary of key phase II trials of RTK inhibitors in patients with bone sarcoma[a]

Agent[ref.]	US FDA-approved indication	Phase II MTD			N	RR (%)[b]	4-Month PFS (%) (95% CI)	Median PFS (m) (95% CI)
		Bone sarcoma		Other diseases				
		Pediatric	Adult	Adult				
Osteosarcoma								
Apatinib[35]	Not approved in the USA[c]	500 mg/d[d]	750 mg/d[d]	500-850 mg/d	37	43	57 (39-71)	4.5 (3.5-6.3)
Cabozantinib[33]	RCC, HCC, TC	40 mg/m^2/d	60 mg/d	60-140 mg/d	42	12	71 (55-83)	6.7 (5.4-7.9)
Lenvatinib[e,36]	RCC, HCC, TC, EC	14 mg/m^2/d	14 mg/m^2/d	8-24 mg/d	16	7	33 (NR)	3.4 (NR)
Regorafenib	CRC, GIST, RCC	160 mg/d[f]	160 mg/d[f]	160 mg/d[f]				
REGOBONE[34]					43	8	62[g] (40-77)	16.4 weeks (8.0-27.3)
SARC024[31]					42	14	44 (NR)	3.6 (2.0-7.6)
Sorafenib[37]	RCC, HCC, TC	400 mg b.i.d.	400 mg b.i.d.	400 mg b.i.d.	35	14	46 (28-63)	4.0 (2.0-5.0)
Ewing sarcoma								
Cabozantinib[33]	RCC, HCC, TC	40 mg/m^2/d	60 mg/d	60 -140 mg/d	39	26		4.4 (3.7-5.6)
Regorafenib	CRC, GIST, RCC	160 mg/d[f]	160 mg/d[f]	160 mg/d[f]				
REGOBONE[39]					41	22		11.4 weeks (4.6-22.9)
SARC024[38]					30	10		3.6 (2.8-3.8)

Abbreviations: CI, confidence interval; CRC, colorectal cancer; EC, endometrial cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; m, months; *N*, number of patients enrolled; NR, not reported; PFS, progression-free survival; RCC, renal cell carcinoma; RR, response rate; TC, thyroid cancer.

[a] Trials are listed if they were prospective and enrolled > 10 patients.

[b] Response rate (RR) = complete + partial responses.

[c] Apatinib is approved for gastric cancer in China.

[d] Dose for patients with BSA < 1.5 = 500 mg/d and for BSA > 1.5 = 750 mg/d.

[e] Study ongoing—full results not yet reported.

[f] Drug is given daily for 21 days in 28-day cycles.

[g] Study reports a 12-week progression-free survival.

Although dose-response relationships with RTK inhibitors may not be as tightly linked as with conventional cytotoxic chemotherapy, there is a general relationship between dose, efficacy, and toxicity that remains for many of these agents.[49–54] Overall, these studies suggest sarcoma patients treated with RTK inhibitors remain at risk for toxicity if levels are inappropriately high, and treatment failure if levels are too low. To date, therapeutic drug monitoring has been best characterized with pazopanib, a drug in which 20% of adults receiving the recommended daily dose of 800 mg do not achieve drug levels associated with response.[55] Although interpatient variability and drug interactions are possible with any chemotherapy agent, particular attention should be given to RTK inhibitors. Given these issues, therapeutic drug monitoring is intuitively attractive, but the feasibility and degree of meaningful impact on patient care need to be confirmed. Table 3 provides information on grade 3-4 toxicities and the frequency of dose modification or discontinuation of RTK inhibitors reported in several phase II trials. Toxicities for RTK inhibitors differ between agents[56] and are generally related to the specific pathways being inhibited.[57] Typical effects of VEGFR inhibition include hypertension, delayed wound healing, proteinuria, diarrhea, hand-foot skin reaction (palmar-plantar erythrodysesthesia syndrome) and hypothyroidism. In contrast, agents inhibiting ALK or MET may cause nausea and elevated amylase and lipase. These side effects are distinct from the conventional chemotherapy agents commonly used to treat sarcoma patients. However, the incidence of cumulative toxicity that requires dose modification or discontinuation is still considerable for all the agents reviewed, with about one-third or more of patients receiving less than the planned dose over time.

The impact of symptoms on patients receiving chronic administration may be underappreciated by current toxicity grading.[58] For example, grade 2 fatigue is tolerable if occurring for a few days, but may be intolerable if chronic. Some toxicities may result in the need for additional daily medication, such as hypertension, hypothyroidism, or hypophosphatemia. Other toxicities, like pneumothorax, may cause hospitalization and/or the need for invasive procedures to be performed. This particular complication is seen with a variety of RTK inhibitors and can occur in up to 25% of bone sarcoma patients,[51] likely as a result of treatment-related changes occurring within pleural-based and/or cavitating lung nodules.[59] The overall impact of toxicity on quality of life is not clear, although patients with recurrent osteosarcoma receiving apatinib reported worse quality of life throughout treatment despite a 43% response rate.[21] Examining toxicity using patient-reported outcomes may be an avenue of further investigation.

Although higher drug exposures are related to many side effects from RTK inhibitors,[55] the relationship between toxicity and response is less clear. There is some suggestion that developing hypertension, anorexia, pneumothorax, or hypothyroidism may correlate with PFS or clinical benefit in osteosarcoma patients receiving apatinib.[51] However, these side effects often do not occur until 3-4 months into treatment, and patients with primary resistance are likely to have experienced disease progression and stopped therapy by then. Also unknown is whether side effects occurring with one RTK inhibitor will likely recur if changed to another RTK inhibitor. Finally, it must be recognized that

TABLE 3 Toxicity data in phase II trials of select RTK inhibitors in bone sarcoma patients

Agent[Ref]	Type	*N*	Incidence of grade 3-4 toxicity (%)	Pts dose-reduced for toxicity (%)	Pts withdrawing for toxicity (%)	Most common grade 3-4 toxicities
Apatinib[35]	OS	22	14[a]	NR	NR	Pneumothorax, wound dehiscence, HFSR
Cabozantinib[33]	OS/ES	90	68	21	14	Pneumothorax, hypophosphatemia, lipase elevation
Lenvatinib[b,36]	OS	16	NR	NR	7	Back pain, dyspnea
Regorafenib						
REGOBONE[34]	OS	29[c]	24	38	0	Pain, fatigue
SARC024[38]	ES	30	NR	43	7	Hypertension, hypophosphatemia, lipase elevation
SARC024[31]	OS	22[c]	64	55	NR	Hypertension, rash, pain, hypophosphatemia
Sorafenib[37]	OS	35	NR	46	3	Myelosuppression, HSFR, CK elevation

Abbreviations: CK, creatinine kinase; ES, Ewing sarcoma; HFSR, hand, foot, skin reaction; NR, not reported; OS, osteosarcoma; Pts, patients.

[a]Includes all study participants receiving drug ($N = 56$).

[b]Study ongoing—full results not yet reported. Data are representative of the expansion cohort (phase II only).

[c]Only patients who received study drug included in this number.

the presence of chronic toxicities may worsen compliance,[60] particularly in high-risk adolescent/young adult patients who may have an overall poor prognosis.

1.5 | Dosing of RTK inhibitors

As shown in Table 2, doses for RTK inhibitors have varied depending on the tumor type being treated and use of other agents. All agents tested in phase II for bone sarcoma used continuous administration schedules except for regorafenib, in which the drug was given for 21 days followed by a 7-day break. Patients treated with this agent received an average of 75% of planned dose,[30] with 85% mean dose intensity reported for sorafenib.[35] Evaluation of alternative doses or schedules in bone sarcoma has not been reported, although for soft-tissue sarcoma some clinicians prefer starting at lower doses of pazopanib and escalating as tolerated,[53] given the frequency of side effects that cause at least temporary interruptions or dose reductions.

1.6 | Optimizing use of RTK inhibitors

The optimal strategy for how these agents fit into overall treatment remains unknown. Like most chemotherapy agents, RTK inhibitors have first been tested in patients with relapsed bulky disease. Although the studies reviewed above show signals of activity, few of these patients with relapsed disease are actually cured due to the likely development of secondary resistance. Little is known about the success of treating patients with other RTK inhibitors once resistance has developed. Strategies to circumvent resistance include coadministration of RTK inhibitors with conventional chemotherapy, with other targeted drugs, or as a single agent in the setting of minimal residual disease that presumably exists in most high-risk patients in first remission.

The rationale for combining RTK inhibitors with conventional chemotherapy includes the nonoverlapping toxicities and mechanisms of action, and the possibility for synergy/additive effect as seen in some preclinical models.[61] Greater cytotoxicity associated with conventional chemotherapy may also reduce the development of secondary resistance. Although there remains limited experience with this strategy, a recently reported randomized trial combining pazopanib with ifosfamide and doxorubicin for pediatric and adult patients with soft-tissue sarcoma showed a higher rate of near-complete pathologic response compared with chemotherapy alone.[62] Importantly, an initial dose-finding phase identified a tolerable pazopanib dose of 600 mg (350 mg/m^2), which is lower than the standard single-agent dose of 800 mg daily. Although the incidence of wound infections did not seem higher than historical controls, this complication will need to be monitored closely if RTK inhibitors are used in combination with chemotherapy for newly diagnosed bone sarcoma patients. Several other studies have been reported in abstract form, including some showing combination with conventional chemotherapy is reasonably well tolerated,[63,64] some showing only sequential rather than concomitant therapy is tolerable,[65] and some showing the combination did not appear tolerable at all.[66] Careful consideration of overlapping toxicity and pharmacokinetics is important for study design. For example, coadministration of sorafenib may exacerbate cardiotoxicity of anthracyclines,[67] and regorafenib may inhibit UGTA1A and increase irinotecan toxicity if given concurrently.[65] It is clear that each regimen will need to be carefully evaluated for feasibility and safety, and then controlled studies will need to be conducted to determine the true benefit of adding the inhibitor. For promising combinations being studied in larger populations, careful attention will also need to be paid to late effects such as cardiotoxicity.[68]

Combining RTK inhibitors with other targeted agents is intuitively attractive, given that activation of alternative RTKs is an established mechanism of acquired resistance.[40,41] These strategies include targeting downstream pathways (vertical inhibition), or compensatory alternative pathways (horizontal inhibition). For example, Grignani et al. combined sorafenib with the mTOR inhibitor everolimus to treat patients with recurrent osteosarcoma, identifying a 6-month PFS of 45% that exceeded a historical cohort of patients treated with sorafenib alone.[69] Similar to this study, other reports of combination targeted therapy have shown increased but manageable toxicity,[70,71] although no dramatic improvements in activity have been noted with the pairings tested so far. Given the potentially broad effects of RTK inhibitors on the tumor microenvironment,[72,73] combinations with immunotherapies such as immune-checkpoint inhibitors are also being explored.[74,75]

Finally, maintenance therapy after completion of standard chemotherapy in high-risk sarcoma patients allows treatment in the setting of minimal residual disease, and is another possible strategy for using RTK inhibitors. Unfortunately, previous studies using metronomic administration of low-dose chemotherapy,[76] immune adjuvants,[60] or nonreceptor tyrosine kinase inhibitors[77] have not shown convincing benefit as maintenance therapy. However, it is possible that RTK inhibitors may have greater activity than previous agents tested, and future studies are likely to explore this treatment paradigm. Table 4 provides a summary of ongoing trials of RTK inhibitors for treating osteosarcoma or Ewing sarcoma. Of note, many of these trials are single-arm studies, and assessing benefit will require randomized trials.

2 | CONCLUSIONS

In summary, RTK inhibition is increasingly being used for patients with osteosarcoma and Ewing sarcoma, with early studies showing consistent but modest activity as single agents in patients with bulky relapsed disease. These drugs are reasonable to consider for treatment of relapsed patients if enrollment on a clinical trial is not pursued. However, side effects are common and may lead to dose modifications or reduced quality of life. Further, monotherapy with available agents in this clinical setting often does not substantially affect long-term survival. These drugs can inhibit multiple targets, and we rarely know the presence or significance of targets in a given patient. The absence of established predictive biomarkers or trials directly compar-

TABLE 4 Ongoing studies of RTK inhibitors in bone sarcoma

Clinicaltrials.gov identifier	Population	Country	Additional agent(s)
Apatinib			
NCT03064243	ES	China	
NCT03396211	ES/OS[a]	China	Nivolumab
NCT03711279	ES	China	Camrelizumab
NCT03742193	OS	China	GD
NCT04012827	ES	China	Doxo/ifos
NCT04072042	ES/OS	China	
NCT04074564	ES/OS	China	MASCT-I/PD-1 AB
NCT04126993	ES/OS[a]	China	Camrelizumab
NCT04282278	ES/OS[a]	China	Camrelizumab/sintilimab
NCT04351308	OS	China	MAPI/camrelizumab
Cabozantinib			
NCT01755195	ES/OS[a]	USA	
NCT02243605	ES/OS	France	
NCT02867592	ES/OS	USA	
NCT03611595	ES/OS[a]	USA	13-cis-retinoic acid
NCT04116541	ES/OS[b]	USA	
Lenvatinib			
NCT02432274	OS	USA	Ifos/etop
NCT02720068	ES/OS[a]	USA	Pembrolizumab/MK-4280
NCT03009292	ES/OS[a]	China	
NCT03245151	ES	USA	Everolimus
NCT04154189	ES/OS	USA	Ifos/etop
NCT04447755	ES/OS[a]	USA	
Pazopanib			
NCT01407562	ES/OS[a]	USA	Paclitaxel/carbo
NCT01430572	ES/OS[b]	USA	Everolimus
NCT01552356	ES/OS[a]	USA	
NCT02303028	ES/OS[a,c]	Canada	Topotecan
NCT02638428	ES/OS[a]	USA	Ifos/carbo/etop[d]
NCT03139331	ES/OS	USA	Irinotecan/temozolomide
NCT03628131	ES/OS[a]	Korea	Carbo/etop/ifos
NCT04199026	ES/OS[a]	USA	Implantable microdevice
Regorafenib			
NCT02048371	ES/OS	USA	
NCT02085148	ES/OS[a]	USA	Vincristine/Irinotecan
NCT02389244	ES/OS	France	
NCT04055220	OS	USA	
NCT04200404	ES/OS[a]	Australia	CS1001
Sorafenib			
NCT01946529	ES	USA	See comment[e]

(Continues)

Note to Table 4: Abbreviations: Carbo, carboplatin; Doxo, doxorubicin; etop, etoposide; ES, Ewing sarcoma; GD, gemcitabine/docetaxel; ifos, ifosfamide; MAPI, methotrexate, doxorubicin, cisplatin; OS, osteosarcoma.

[a]Study inclusion states solid tumor or sarcoma and does not exclude ES or OS.

[b]Study includes tumors with certain molecular alterations.

[c]ES/OS only included in phase I of study.

[d]Choice of additional agent based on genomic aberrations of tumor.

[e]Patients receive a standard backbone of vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide (VDC-IE) followed by temsirolimus, temozolomide, and irinotecan with a maintenance phase of bevacizumab, sorafenib, and cyclophosphamide.

ing agents makes it impossible to know which inhibitor is best for these diseases. Currently, use of these drugs for pediatric bone sarcoma represents targeted therapy but not personalized medicine, as our incomplete understanding of mechanisms of response and resistance limits more appropriate assignment of patients. Additional correlative biology studies will be required to improve patient selection, and exploration of novel combinations and trial designs may help us realize the full potential of these drugs.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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