Lestaurtinib Enhances the Antitumor Efficacy of Chemotherapy in Murine Xenograft Models of Neuroblastoma

Radhika Iyer¹, Audrey E. Evans¹,³, Xiaoxue Qi³, Ruth Ho¹, Jane E. Minturn¹,³, Huaqing Zhao², Naomi Balamuth¹, John M. Maris¹,³, and Garrett M. Brodeur¹,³

Abstract

Purpose: Neuroblastoma, a common pediatric tumor of the sympathetic nervous system, is characterized by clinical heterogeneity. The Trk family neurotrophin receptors play an important role in this behavior. Expression of TrkA is associated with favorable clinical features and outcome, whereas TrkB expression is associated with an unfavorable prognosis. We wanted to determine if the Trk-selective inhibitor lestaurtinib had therapeutic efficacy in a preclinical neuroblastoma model.

Experimental Design: We performed intervention trials of lestaurtinib alone or in combination with other agents in TrkB-overexpressing neuroblastoma xenograft models.

Results: Lestaurtinib alone significantly inhibited tumor growth compared to vehicle-treated animals [P = 0.0004 for tumor size and P = 0.011 for event-free survival (EFS)]. Lestaurtinib also enhanced the antitumor efficacy of the combinations of topotecan plus cyclophosphamide (P < 0.0001 for size and P < 0.0001 for EFS) or irinotecan plus temozolomide (P = 0.011 for size and P = 0.012 for EFS). There was no additive benefit of combining either 13-cis-retinoic acid or fenretinide with lestaurtinib compared to lestaurtinib alone. There was dramatic growth inhibition combining lestaurtinib with bevacizumab (P < 0.0001), but this combination had substantial systemic toxicity.

Conclusions: We show that lestaurtinib can inhibit the growth of neuroblastoma both in vitro and in vivo and can substantially enhance the efficacy of conventional chemotherapy, presumably by inhibition of the Trk/brain-derived neurotrophic factor autocrine survival pathway. It may also enhance the efficacy of selected biological agents, but further testing is required to rule out unanticipated toxicities. Our data support the incorporation of Trk inhibitors, such as lestaurtinib, in clinical trials of neuroblastoma or other tumors relying on Trk signaling pathways for survival. Clin Cancer Res; 16(5); 1478–85. ©2010 AACR.

Neurotrophin signaling through the Trk family of receptor tyrosine kinases plays a critical role in the development, maintenance, and function of the nervous system. Activation of these receptors regulates cell survival, proliferation, migration, differentiation, and apoptosis during development. They exert this influence by modulating the responses of neurons to the neurotrophin family of growth factors in a temporally and spatially regulated manner. The neurotrophins nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophin-3 are the cognate ligands for TrkA (NTRK1), TrkB (NTRK2), and TrkC (NTRK3), respectively (1–3).

Neuroblastoma, a common pediatric tumor of the post-ganglionic sympathetic nervous system, provides an ideal model for the study of Trk signaling and inhibition in cancer (4). Neuroblastomas are characterized by clinical heterogeneity, from spontaneous regression in infants to relentless progression in older children. The prognosis for these latter patients remains poor, with 3-year event-free survival (EFS) probabilities of 30% to 40% (5–7). Indeed, neuroblastomas can be classified into distinct subsets based on genetic alterations and biological features (8), and the expression of Trk receptors likely contributes to these distinct behaviors (4, 9–15).

Expression of TrkA in neuroblastoma cell lines has been shown to mediate neuronal differentiation, growth arrest, and inhibition of angiogenesis in response to nerve growth factor (16, 17). In contrast, unfavorable neuroblastomas frequently express TrkB and its ligand BDNF, which together comprise an autocrine or paracrine survival pathway (11, 18, 19). These tumors typically have gross segmental chromosomal aberrations including amplification of the MYCN proto-oncogene. The TrkB/BDNF pathway promotes cell survival, protects cells from injury, and blocks chemotherapy-mediated cell death in vitro (20–22).
Translational Relevance

Trk family receptors play an important role in the behavior of neuroblastomas as well as other pediatric and adult cancers. Activation of these receptors by mutation, translocation, autocrine ligand expression, or other mechanisms can enhance survival and favor malignant behavior. Therefore, biologically targeted agents that inhibit Trk activation could be very effective and nontoxic therapy either alone or in combination with other therapies. Our earlier studies showed the importance of Trk signaling for neuroblastomas, and our results have shown the therapeutic efficacy of Trk inhibition in a mouse xenograft model of neuroblastoma. Indeed, our findings served as the basis for a phase I clinical trial of lestaurtinib for relapsed or refractory neuroblastoma. Given the prevalence of Trk receptor expression in many human cancers, our data support the incorporation of Trk inhibitors, such as lestaurtinib, in clinical trials of neuroblastoma or other cancers relying on Trk signaling pathways for survival.

Although several genes are likely involved in the development and clinical behavior of favorable and unfavorable neuroblastomas, the pattern of Trk gene expression (TrkA versus TrkB) likely plays a role.

Lestaurtinib (CEP-701; Cephalon) is a small-molecule inhibitor of several receptor tyrosine kinases, and it competitively inhibits ATP binding to the Trk kinase domain at nanomolar concentrations. Here, we tested the efficacy of lestaurtinib in a xenograft model of neuroblastoma to determine if it could enhance the antitumor efficacy of conventional chemotherapy as well as selected, biologically targeted agents. We first determined the antitumor efficacy of lestaurtinib alone, and then in combination with cyclophosphamide, as well as two pairs of conventional agents (topotecan plus cyclophosphamide and irinotecan plus temozolomide) that are currently used to treat high-risk neuroblastoma patients. We also tested lestaurtinib in combination with biologically targeted anticancer agents [13-cis-retinoic acid (13-cRA), fenretinide (4-HPR), and bevacizumab] that are currently in use or being developed to treat recurrent or refractory disease.

Materials and Methods

Compounds. Lestaurtinib (CEP-701; Cephalon) is an orally active, small-molecule kinase inhibitor with nanomolar potency against TrkA, TrkB, and TrkC as well as FLT3 and JAK2 (23–26). Lestaurtinib competitively inhibits the ATP-binding site for these kinases, with less potent inhibition of other receptor tyrosine kinases. Lestaurtinib was dissolved in a vehicle consisting of 40% polyethylene glycol 100 (Spectrum), 10% povidone C30 (ISP), and 2% benzyl alcohol (Spectrum) in distilled water and given subcutaneously at 20 mg/kg twice daily (from Monday to Friday) and once daily on Saturday and Sunday. The vehicle alone was used as the control.

Cyclophosphamide was given at dose of 113 mg/kg intraperitoneally once daily on days 4 and 6 of lestaurtinib treatment. When given in combination with topotecan, the cyclophosphamide dose was reduced to 75 mg/kg/d. The topotecan dose was 0.25 mg/kg/d, and both agents were given together intraperitoneally on days 5 and 7 of lestaurtinib treatment. Irinotecan was given at a dose of 0.63 mg/kg/d by oral gavage from Monday to Friday of each week. Temozolomide was given at a dose of 7.5 mg/kg/d by oral gavage from Monday to Friday of each week. The same doses were used when combined with lestaurtinib. Both irinotecan and temozolomide were suspended in saline for the oral gavage. 13-cRA was given at a dose of 10 mg/kg/d intraperitoneally and given daily from Monday to Friday. 4-HPR was given at a dose of 120 mg/kg/d intraperitoneally and given daily 7 days/wk. Bevacizumab was given at a dose of 5 mg/kg intraperitoneally twice weekly. All chemotherapy and biological agents other than lestaurtinib were obtained through the pharmacy at the Children's Hospital of Philadelphia. The doses used in these studies were based on published studies with these drugs and, in some cases, modified based on our own experience with these drugs in our xenograft model system (Table 1; refs. 27–35). Some doses were reduced from those recommended in the literature, mainly so the chemotherapy alone would not cure all the animals; therefore, an effect of combining lestaurtinib with other agents could be assessed.

Cell lines. For most of the xenograft tumor studies, we used SY5Y-TrkB (BR6), a subclone of SY5Y transfected with TrkB that expresses this receptor at high levels (20). This line does not express detectable levels of the TrkAIII isoform at the mRNA or protein level (36). Some studies were confirmed with other neuroblastoma lines expressing endogenous or exogenous TrkB (11, 20). Cells were grown in RPMI 1640 containing 10% fetal bovine serum and 0.3 mg/mL G418 and maintained in 150 cm² Costar culture flasks in a humidified atmosphere of 95% air and 5% CO2. Cells were harvested using 0.2% tetrasodium EDTA in PBS.

Animals. Four-week-old athymic nu/nu mice were obtained from Charles River Laboratories. Mice were maintained at five per cage under humidity- and temperature-controlled conditions in a light/dark cycle that was set at 12 h intervals. The Institutional Animal Care Committee of the Joseph Stokes, Jr., Research Institute at Children’s Hospital of Philadelphia approved the animal studies described herein.

In vitro experiments. To determine the effect of lestaurtinib on TrkB-expressing cells, SY5Y-TrkB were grown in 10 cm² dishes to 70% to 80% confluency in standard culture medium and harvested for protein extraction. We analyzed TrkB expression by Western blot using an anti-phospho-TrkB antibody (phospho-TrkB, Tyr490 antibody; Cell Signaling Technologies) or an anti-pan-TrkB antibody (Santa Cruz Biotechnology). We exposed cells to BDNF for 10 min in the absence or presence of increasing concentrations
the average SY5Y-TrkB tumor size was 0.2 cm³.

nib was started ∼
pound was adjusted accordingly. Treatment with lestaurtinib weights were obtained twice weekly, and the dose of compound was adjusted accordingly. Treatment with lestaurtinib was started ~10 days after tumor inoculation when the average SY5Y-TrkB tumor size was 0.2 cm³.

Statistical analysis. Comparisons of tumor size results were analyzed by two-sample Student's t test. Comparison of tumor size change over time was analyzed by linear mixed models. For EFS life-table analysis, an event was defined as tumor size that exceeded 3 cm³ or any evidence of animal discomfort resulting from the tumor or the treatment. Kaplan-Meier curves were estimated and compared between groups by log-rank test. All analyses were conducted using SAS-9 or Stata-8.

Results

Effect of lestaurtinib on TrkB activation in vitro. We first tested the ability of lestaurtinib to inhibit TrkB phosphorylation induced by exogenous BDNF in the SY5Y-TrkB neuroblastoma line. Virtually no TrkB phosphorylation was seen at steady state in the absence of exogenous BDNF (Fig. 1), although BDNF was expressed in these cells. However, there was intense phosphorylation of TrkB by 10 min after the addition of exogenous BDNF in the absence of lestaurtinib. Increasing concentrations of lestaurtinib progressively inhibited this ligand-induced TrkB phosphorylation. We saw substantial inhibition of phosphorylation at 10 to 25 nmol/L lestaurtinib, with maximal inhibition between 100 and 250 nmol/L. We did not see complete inhibition of TrkB phosphorylation presumably because of very high level of TrkB expression in these cells.

Effect of single-agent lestaurtinib on SY5Y-TrkB neuroblastoma xenografts. We tested the ability of lestaurtinib to inhibit the SY5Y-TrkB cells growing as xenografts in athymic nu/nu mice. We injected 1 × 10⁷ cells subcutaneously in the flank of nude mice. We initiated treatment when the tumor size measured 0.2 cm³, usually 10 to 14 days from inoculation. We treated mice (10 per group) with either lestaurtinib or vehicle twice daily (from Monday to Friday) and once daily on Saturday and Sunday, and tumors were measured twice weekly. Significant tumor growth inhibition was observed with lestaurtinib treatment (P = 0.0004; Fig. 2A). EFS was also significantly prolonged by administration of lestaurtinib (P = 0.011; data not shown), with all tumors in control animals reaching or exceeding 3 cm³ by day 18, compared to only two of the lestaurtinib treated animals. Analysis of tumors from control and lestaurtinib-treated animals showed a modest but consistent decrease in phosphorylation of TrkB and the signaling intermediates mitogen-activated protein kinase and the phosphoinositide 3-kinase p110α subunit (data not shown).

Effect of lestaurtinib in combination with conventional chemotherapy on SY5Y-TrkB xenografts. To determine if lestaurtinib cotreatment enhanced the effect of standard chemotherapy, we treated groups of mice with either vehicle, lestaurtinib, cyclophosphamide, or both. Control tumors grew rapidly, and the growth of lestaurtinib-treated animals was significantly delayed. However, both groups grew more rapidly than tumors in the other two groups, so they were not included to allow us to compare the effect of lestaurtinib on cyclophosphamide-treated tumors. Tumors treated with cyclophosphamide plus lestaurtinib grew significantly more slowly than tumors treated with cyclophosphamide alone (P = 0.0001; Fig. 2B), and there was also a statistically significant difference in EFS (P = 0.0014; data not shown). Next, we tested the combination of toptotecan-cyclophosphamide, a combination currently used for neuroblastoma induction therapy, with or without lestaurtinib. The difference in the slopes of tumor growth was significantly different among the four groups (P < 0.0001; Fig. 3A), and the effect on EFS was also highly significant (P < 0.0001; Fig. 3B).

We also tested the combination of irinotecan-temozolomide with or without lestaurtinib. This combination was recently developed to treat for recurrent neuroblastomas. Tumors treated with the combination of irinotecan-temozolomide

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### Table 1. Drugs and doses used for xenograft studies

<table>
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<tr>
<th>Drug</th>
<th>Route</th>
<th>Solvent</th>
<th>Dose/d this study (literature dose/range)</th>
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<tr>
<td>Lestaurtinib</td>
<td>Subcutaneous</td>
<td>Vehicle</td>
<td>40 mg/kg (40 mg/kg)</td>
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<td>Cyclophosphamide</td>
<td>Intrapertoneal</td>
<td>Saline</td>
<td>113 mg/kg; 75 mg/kg (150 mg/kg)</td>
<td>Shusterman et al. (33); Houghton et al. (28)</td>
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<td>Topotecan</td>
<td>Intrapertoneal</td>
<td>Saline</td>
<td>0.25 mg/kg (0.16-2.0 mg/kg)</td>
<td>Zamboni et al. (35); Thompson et al. (34)</td>
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<tr>
<td>Irinotecan</td>
<td>Oral</td>
<td>Saline</td>
<td>0.63 mg/kg (0.16-2.5 mg/kg)</td>
<td>Houghton et al. (29)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Oral</td>
<td>Saline</td>
<td>7.5 mg/kg (14-66 mg/kg)</td>
<td>Houghton et al. (29)</td>
</tr>
<tr>
<td>13-cRA</td>
<td>Intrapertoneal</td>
<td>Saline</td>
<td>10 mg/kg (10 mg/kg)</td>
<td>Ponther et al. (31)</td>
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<tr>
<td>4-HPR</td>
<td>Intrapertoneal</td>
<td>DMSO</td>
<td>120 mg/kg (120 mg/kg)</td>
<td>Maurer et al. (30)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Intrapertoneal</td>
<td>Saline</td>
<td>5 mg/kg (5 mg/kg)</td>
<td>Segerstrom et al. (32)</td>
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plus lestaurtinib grew significantly more slowly than with either chemotherapy or lestaurtinib alone \((P = 0.011; \text{ Fig} .4A)\). This resulted in a 100% EFS by day 21 in the combination group, which was significantly better than all other groups \((P = 0.012; \text{ Fig} .4B)\). Thus, cotreatment with lestaurtinib significantly enhanced the effect of both single-agent and paired-agent chemotherapy. Furthermore, this was achieved without additional toxicity.

**Effect of lestaurtinib in combination with retinoids on SY5Y-TrkB xenografts.** Next, we tested the effect of lestaurtinib in combination with two different retinoids \((13\text{-cRA and 4-HPR})\) that are currently in clinical use to treat neuroblastoma patients. We saw no effect of 13-cRA compared to vehicle on the SY5Y-TrkB cells and no significant difference when 13-cRA was combined with lestaurtinib compared to lestaurtinib alone \((\text{data not shown})\). 4-HPR did have a therapeutic effect when compared to vehicle. However, the effect of lestaurtinib alone on inhibiting tumor growth was significantly better than vehicle or 4-HPR alone \((P < 0.0001\) for tumor size and \(P = 0.0007\) for EFS), and the combination of lestaurtinib plus 4-HPR was not better than lestaurtinib alone \((\text{Fig} .5A\text{ and }B)\). Thus, lestaurtinib was more effective as a single agent than either retinoid alone, and the addition of either retinoid to lestaurtinib did not provide additional efficacy compared to lestaurtinib treatment alone.

**Effect of lestaurtinib in combination with bevacizumab on SY5Y-TrkB xenografts.** We also tested the efficacy of combined vascular endothelial growth factor and Trk signaling inhibition in our neuroblastoma xenograft model. We performed a four-arm interventional trial \((n = 10\text{ mice per arm})\) using the vascular endothelial growth factor inhibitor bevacizumab and the Trk inhibitor lestaurtinib as single agents or in combination compared to vehicle control. Bevacizumab or lestaurtinib alone each caused subtle growth delay of xenografts compared to vehicle, but the combination of the two showed complete and sustained regression of xenografts \((P < 0.0001\) for tumor size). However, there was substantial systemic toxicity experienced in the mice treated with the combination of drugs that was not seen with either as a single agent, and half the animals had died of toxicity \((\text{anasarca and death within 24 h following a bevacizumab dose})\) by 2 weeks of treatment. Indeed, there was no significant difference in EFS between either bevacizumab or lestaurtinib and the combination arm due to deaths from toxicity \((\text{data not shown})\), raising questions about this particular combination in clinical trials without further preclinical testing.

**Discussion**

Neuroblastomas show clinical heterogeneity, from spontaneous regression to relentless progression. Data from our laboratory and others suggest that Trk receptors play an important role in these disparate clinical behaviors \((4, 9, 11–15, 17, 37)\). TrkA is expressed in favorable tumors, and these tumors are likely to differentiate or regress depending on the presence or absence of nerve growth factor in their microenvironment \((9, 12, 14, 37)\). Conversely, aggressive tumors, especially those with MYCN amplification, express TrkB and its ligand, BDNF \((11)\). The coexpression of TrkB and BDNF comprises an autocrine survival pathway that promotes invasion, metastasis, angiogenesis, and drug resistance \((17, 19–21)\). Therefore, targeted therapy aimed at inhibiting the Trk receptor pathways could be a useful adjunct to conventional therapy in these tumors.

Despite improvements in the overall cure rate of neuroblastomas, the progress in curing patients with high-risk disease \((\text{stage 4 at age >18 months or with MYCN amplification})\) has been modest. Therapy for these patients includes surgery, local radiation therapy, intensive chemotherapy, and one or two autologous stem cell transplantations. These therapies have reached the maximum tolerated intensity, so improvements in the cure rates of these patients will likely require more biologically targeted therapy and/or therapy that enhances the effectiveness of current therapy without substantially increasing side effects.

Given the important role that Trk receptors play in the behavior of favorable and unfavorable neuroblastomas, we wanted to develop an approach that targeted these receptors. CEP-751 \((\text{KT-6587})\) is a Trk-selective inhibitor provided by Cephalon. \((38)\). This compound inhibits Trk family kinases at nanomolar concentrations, whereas most other tyrosine kinases are only inhibited at micromolar concentrations. Lestaurtinib \((\text{CEP-701, KT-5555})\) is an active metabolite of CEP-751 that can be administered orally, making it more suitable for clinical trials \((23, 25)\). Previously, we have tested the efficacy of CEP-751 to inhibit Trk-expressing neuroblastomas in vitro and
in vivo (27, 39). In this report, we examined the efficacy of lestaurtinib alone and in combination with conventional and biologically targeted therapies in a mouse xenograft model.

We showed that lestaurtinib dramatically inhibited the autophosphorylation of TrkB (after BDNF exposure) in SY5Y-TrkB cells. Maximal inhibition was seen at concentrations of 100 to 200 nmol/L (Fig. 1), which is well within the range of what is achievable clinically. These results are also comparable to those we obtained previously with CEP-751 (27, 39). Then, we tested the ability of lestaurtinib to inhibit the growth of SY5Y-TrkB cells growing in vivo as xenografts in athymic nu/nu mice. The biological effect on phosphorylation of TrkB and signaling intermediates in the xenografts was modest probably due to the low level of steady-state activation by the autocrine survival pathway. However, significant inhibition of tumor growth was seen with lestaurtinib treatment compared to a vehicle control (Figs. 2 and 3), and this was achieved without apparent toxicity.

Next, we tested the ability of lestaurtinib to enhance the efficacy of conventional chemotherapy. We tested the ability of cyclophosphamide and/or lestaurtinib to inhibit the growth of SY5Y-TrkB xenografts. We showed significantly greater inhibition of tumor growth in tumors treated with lestaurtinib plus cyclophosphamide compared to either alone (Fig. 2). We also tested the antitumor efficacy of topotecan-cyclophosphamide with or without lestaurtinib. Topotecan-cyclophosphamide has been proven to be an effective combination for recurrent or refractory neuroblastomas (Fig. 3), and it is currently being used in front-line therapy for high-risk neuroblastoma patients. The combination of topotecan-cyclophosphamide plus lestaurtinib inhibited tumor growth more effectively than either topotecan-cyclophosphamide or lestaurtinib alone. Furthermore, we tested the combination of irinotecan-temozolomide with or without lestaurtinib. Irinotecan-temozolomide is an effective combination that is currently in use for high-risk neuroblastoma patients with recurrent or refractory disease. Again, we saw significant inhibition of tumor growth with the combination compared to chemotherapy alone (Fig. 4). Together, these results show...
that lestaurtinib enhanced the efficacy of chemotherapy agents in current clinical use, either alone or in pairwise combinations.

Finally, we tested the combination of lestaurtinib with biologically targeted agents that are in use to treat neuroblastomas. 13-cRA did not have a significant effect on neuroblastoma xenografts in our model system, but 4-HPR did cause a significant inhibition in tumor growth. Nevertheless, lestaurtinib was more effective at inhibiting tumor growth as a single agent than either 13-cRA or 4-HPR in this system, and the combination was no more effective than lestaurtinib alone (Fig. 5). The results with bevacizumab plus lestaurtinib were more striking. Although both were effective at inhibiting tumor growth as single agents, the combination resulted in very significant growth inhibition. However, this combination was also associated with substantial systemic toxicity in the combination group, which raises questions about using this particular therapeutic combination in clinical trials without further testing.

Lestaurtinib can inhibit neuroblastoma xenograft growth, and it substantially enhances the efficacy of single and pairwise combinations of chemotherapy agents, without additional toxicities. Lestaurtinib also enhanced the efficacy of bevacizumab, but no enhancement was seen for the retinoids 13-cRA or 4-HPR. Assuming that the mechanism of lestaurtinib inhibition is by blocking an important autocrine survival pathway, this agent may have a more profound effect on the growth of neuroblastomas treated with conventional chemotherapy because the pathways affected by 13-cRA or 4-HPR are different. The reason for substantial systemic toxicity with the combination of lestaurtinib plus bevacizumab compared to either agent alone is unclear but presumably is a result of a synergistic or off-target effect with the combination.

Brown et al. (40) reported that lestaurtinib combined synergistically with other agents in the treatment of childhood acute lymphoblastic leukemias containing MLL gene rearrangements and FLT3 kinase overexpression. Furthermore, they reported that this synergism was sequence
dependent, with the greatest effect seen when chemotherapy was given first followed by lestaurtinib. We saw significant inhibition when given simultaneously with chemotherapy (e.g., cyclophosphamide), but there was no added benefit when CEP-751, an analogue of lestaurtinib, was given first followed by cyclophosphamide (data not shown). We did not test the schedule of chemotherapy followed by lestaurtinib, but our protocol of continuous administration did continue lestaurtinib for weeks after the chemotherapy was given, essentially mimicking the most effective schedule identified by Brown et al. (40).

Lestaurtinib is currently in phase III clinical trials to treat patients with FLT3-positive acute myelogenous leukemia, in combination with conventional induction therapy, and it is in phase II clinical trials to treat patients with myeloproliferative diseases and myelofibrosis (26, 41–43). Furthermore, lestaurtinib has been tested in phase I clinical trials in neuroblastoma patients. Our preclinical studies would suggest that lestaurtinib will be particularly effective in combination with conventional chemotherapy agents and may be effective when combined with selective biological agents. However, caution should be used in testing lestaurtinib plus bevacinuzumab in clinical trials without further preclinical studies of this combination.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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