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ORIGINAL ARTICLE – SARCOMA

Preoperative Pazopanib in High-Risk Soft Tissue Sarcoma: Phase II Window-of Opportunity Study of the German Interdisciplinary Sarcoma Group (NOPASS/GISG-04)

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ABSTRACT

Background. Preoperative devascularization might improve local control and thus the outcome of patients with soft tissue sarcoma (STS). The multikinase inhibitor pazopanib has antiangiogenic effects and is approved for treating metastatic STS. We conducted a trial of preoperative pazopanib therapy in high-risk STS.

Methods. This single-arm, phase II trial included patients with resectable, non-metastatic, treatment-naïve, high-risk STS. Patients received pazopanib 800 mg daily while waiting for surgery (21-day 'window of opportunity'). The primary endpoint was metabolic response rate (MRR; proportion of patients with $\geq$ 50% reduction of mean standardized uptake value [SUV_{mean}] in post- vs. pretreatment fluorodeoxyglucose–positron emission tomography/computed tomography [FDG-PET-CT]). Planned sample size was 35 patients (type I error, 5%; type II error, 20%). A translational substudy explored associations between response and concentration of circulating angiogenic factors.

Results. Futility analysis was performed after 21 patients (11 female, mean age 67 years; liposarcoma $n = 15$); 17/21 patients were evaluable for the primary endpoint. The MRR was 1/17 (5.9%, 95% confidence interval < 0.01–0.29). Mean change in SUV_{mean} of post- versus pretreatment PET was a 6% decrease (range 65% decrease to 34% increase); 7/21 (33.3%) patients had 12 grade 3/4 toxicities, and 19/21 (95.2%) patients were resected (all R0). One (4.8%) patient suffered a grade 4 postoperative complication (anastomotic leakage). Circulating endothelial progenitor cells, soluble vascular endothelial growth factor, and angiopoietin-2 concentrations showed no relevant changes during treatment.

Conclusions. Although this study showed that preoperative pazopanib is not effective for unselected high-risk STS patients, relevant treatment effects were observed in a single patient. Future research needs to better define subgroups potentially benefiting from preoperative pazopanib treatment.

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High-risk soft tissue sarcoma (STS) has a poor prognosis, and surgery is the only potentially curative modality.[1,2] To improve outcomes, preoperative treatments have been tested.[3] Preoperative chemotherapy has yielded mixed results, even if it is histotype-tailored.[4–6] Adding regional hyperthermia improves survival,[7] but availability is limited. Isolated limb perfusion can achieve long-term recurrence-free survival for selected patients but does not control micrometastatic disease;[8] thus, there is no consensus regarding preoperative STS therapy.[1,2]

The multikinase inhibitor pazopanib has been approved for metastatic STS based on a phase III trial in patients with non-adipocytic STS,[9] but later studies demonstrated response rates of 20% or more in liposarcoma[10] and angiosarcoma.[11,12] Given this proof of efficacy, its fast and pronounced antiangiogenic effects,[13] and its favorable safety profile,[14] pazopanib seems a good candidate for neoadjuvant STS treatment. We decided to test the drug in a 'window-of-opportunity' study,[15] minimizing the risk that effective treatment is unduly delayed by keeping investigational treatment short.

A crucial precondition for preoperative treatment is valid early response assessment. As volumetric response[16] cannot be expected after short pazopanib treatment, we selected metabolic response, measured by fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT), as the primary endpoint, which has been prospectively validated as a predictor of progression-free survival in STS.[17,18]

Studying neoadjuvant STS treatment can provide information on biomarkers for response prediction. Regarding antiangiogenic therapy, circulating angiogenic factors might serve for this purpose. Circulating endothelial progenitor cells (cEPCs) and soluble vascular endothelial growth factor (sVEGF) correlate with tumor burden in STS[19] and response to kinase inhibition in other entities.[20,21] We evaluated whether these factors predict STS response to pazopanib.

PATIENTS AND METHODS

Details of the study protocol have been previously published.[22] This study was conducted with the following characteristics.

Patients

Patients were $\geq$ 18 years of age, with resectable, non-metastatic, histologically confirmed high-risk (grade 2/3, diameter $\geq$ 5 cm) STS of any location for which upfront resection was planned. Patients had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[16]

Treatment

Treatment consisted of pazopanib 800 mg daily for 21 days, and surgery was scheduled 7–14 days after the end of treatment. Adjuvant radiotherapy was administered at least $>$ 14 days after surgery.

Study Examinations

In the 14 days prior to and 1–7 days after treatment, patients underwent dynamic FDG-PET/CT over the tumor area, followed by whole-body PET/CT. All examinations were performed centrally (Biograph mCT, S128; Siemens, Erlangen, Germany) with an axial field of view of 21.6 cm with TruePoint and TrueV, operated in three-dimensional mode. Low-dose CT (120 kV, 30 mA) was used for attenuation correction and image fusion. An image matrix of 400 $\times$ 400 pixels was used for iterative image reconstruction, based on the ordered subset expectation maximization (OSEM) algorithm with 6 iterations and 12 subsets. Following intravenous application of 250 MBq of FDG, dynamic data acquisition (four-dimensional mode) was performed for 60 min. Whole body PET/CT was then acquired using the 2 min per bed position. Iteratively reconstructed images were evaluated using dedicated software. Semi-quantitative evaluation involved standardized uptake value (SUV) calculations, based on volumes of interest (VOIs) drawn using the pseudo-snake algorithm of the Pmod software (PMOD, Zürich, Switzerland). The mean SUV (SUV_{mean}) of 60 min following FDG injection was used to assess therapeutic effects.

Resection specimens were histopathologically assessed, and the following data were recorded: tumor size in three dimensions, resection status (free margins, microscopic infiltration, macroscopic infiltration), smallest distance between the margin and the vital tumor, histological subtype, grade (1–3),[23] regression grade (percentage, semiquantitative value), most prevalent type of regression (hyaline necrosis, apoptosis, scar tissue, hemorrhagic necrosis).

Endpoints

The primary endpoint of the study was metabolic response rate (MRR). Metabolic response was defined as a $>$ 50% decrease in SUV_{mean} over the tumor area in post-treatment compared with pretreatment FDG-PET/CT. MRR was the proportion of patients achieving metabolic response. Secondary endpoints were resection status, histopathological regression, toxicity (including

perioperative complications according to Common Terminology Criteria for Adverse Events [CTCAE] version 4.0[24]), and delayed resection, categorized as 'treatment-related' or 'not treatment-related'.

Study Design and Sample Size

This was a single-arm trial with MRR as the primary endpoint, using an exact single-stage design based on binomial distribution.[25] The MRR below which treatment was considered ineffective was 0.2, while the MRR above which treatment was considered to warrant further exploration in a phase III trial was 0.4.[17,26–28] With a predefined significance level of 5% and power of 80% in a one-sided test, the sample size was 35 evaluable patients, with a significance level of 0.034 and a power of 0.805, and a critical value of 12 patients at the upper proportion limit (STPLAN 4.5, University of Texas).[25] MRR analysis was performed after all patients had received post-treatment FDG-PET/CT. H0 was rejected if ≥ 12 patients showed metabolic response.[25] If < 35 individuals were evaluable for metabolic response, the border for acceptance of H1 was modified accordingly, with a type I error $\leq 5\%$. MRR was presented as a percentage with 95% confidence interval (CI). In addition, metabolic response was visualized as a waterfall plot with the percentage change in SUV_{mean} on the y-axis. Secondary outcomes are presented as proportions with 95% CIs.

Translational Substudy

We explored associations between response and changes in blood levels of cEPCs, sVEGF, and angiopoietin-2 (Ang-2), which were measured simultaneously with FDG-PET/CT and 14 days after surgery. Blood was processed within 1 h after collection. Peripheral blood mononuclear cells (PBMCs) were prepared by density gradient centrifugation using Ficoll-Hypaque (GE Healthcare Bio-Sciences, Uppsala, Sweden), and cell-surface antigen expression was determined by immunofluorescence staining. 100 µL PBMCs were incubated with 20 µL of Fc receptor blocking reagent (Miltenyi Biotec, Bergisch-Gladbach, Germany) for 10 min to inhibit non-specific bindings. The cells were then incubated at 4–8 °C for 30 min with 10 µL phycoerythrin-conjugated anti-human CD133 monoclonal antibodies (mAb; Miltenyi Biotec), 10 µL peridinin chlorophyll protein complex-conjugated anti-human CD45 mAbs (BD Biosciences Pharmingen, Heidelberg, Germany), 10 µL allophycocyanin-conjugated CD31, and 10 µL fluorescein isothiocyanate-anti-CD34 mAb (BD Biosciences Pharmingen). Isotype-matched immunoglobulin (Ig) G1 and IgG2a antibodies (DakoCytomation, Hamburg, Germany) were used as negative controls. Cells were washed three times to remove unbound antibodies and resuspended in 400 µL CellFix (BD Biosciences). Fluorescence-activated cell sorting (FACS) analysis was performed on a CANTO flow cytometer (BD Biosciences) and data were analyzed using FlowJo® 7.6 (TreeStar, Ashland, OR, USA). At least 500,000 events were collected. cEPC frequency in peripheral blood was determined by a two-dimensional side-scatter fluorescence dot-plot analysis. The non-parametric Wilcoxon rank-sum test was used to compare cEPC, sVEGF, and Ang-2 values before and after pazopanib treatment, and before pazopanib treatment and after surgery. Normal distribution could not be assumed throughout the measures under consideration (d'Agostino–Pearson test). The level of statistical significance was set at $\alpha = 0.05$ and multiple testing was corrected using the Bonferroni–Holms procedure.

Ethical Approval

This study was approved by the Ethics Committee of the Medical Faculty Mannheim, University of Heidelberg (2012-019F-MA) and the German Federal Agency for Radiation Protection (Z5-22463/2-2012-007), and was registered with ClinicalTrials.gov (NCT01543802). Informed consent was obtained from all participants.

RESULTS

Twenty-one patients were enrolled in the study. A futility analysis showed a probability of 4.7% that H0 could be rejected if recruitment had been completed as planned. At the same time, the power to reach the original goal of such a result decreased to 7.2%. Therefore, further enrolment was stopped. The demographic and clinical characteristics of patients are displayed in Table 1. The majority of patients had extremity STS and dedifferentiated liposarcoma. Two patients withdrew consent and discontinued pazopanib prematurely prior to the second FDG-PET/CT. One patient had clinical progression and underwent surgery prior to the second FDG-PET/CT, and, in one patient, FDG-PET/CT showed no evaluable hypermetabolic lesions. Consequently, the analysis of the primary endpoint MRR was performed in 17/21 patients (Fig. 1). A safety analysis was conducted in all 21 patients receiving pazopanib at least once. Secondary endpoints were analyzed in a varying number of patients, according to the availability of respective data.

Efficacy Results

The mean change in SUV_{mean} of post- versus pretreatment PET/CT was a 6% decrease, ranging from a 65%

TABLE 1 Demographic and clinical characteristics of patients included in the study

	N	Percentage
Sex		
Male	10	47.6
Female	11	52.4
Age, years [mean (range)]	67 (46–81)	
ECOG PS		
0	19	90.5
1	2	9.5
Tumor site		
Extremities	9	42.9
Retroperitoneal	7	33.3
Trunk	4	19.0
Neck	1	4.8
Histology		
Dedifferentiated liposarcoma	11	52.4
Pleomorphic liposarcoma	2	9.5
Myxoid liposarcoma	1	4.8
Undifferentiated pleomorphic sarcoma	3	14.3
Fibrohistiocytic sarcoma	1	4.8
Leiomyosarcoma	1	4.8
Malignant peripheral nerve sheath tumor	1	4.8
Synovial sarcoma	1	4.8
Tumor grade		
2	13	61.9
3	8	38.1
Tumor diameter, mm [mean (range)]	126 (28–255)	

ECOG PS Eastern Cooperative Oncology Group performance status

decrease to a 34% increase (Fig. 2). One patient fulfilled the prespecified response criterion of $\geq$ 50% decrease in SUV_{mean}, resulting in an MRR of 5.9% (95% CI $<$ 0.01–0.29). Two other patients had a $\geq$ 25% decrease in SUV_{mean}. H0 could not be rejected. To assume efficacy with 17 evaluable patients, 7 patients should have experienced metabolic response. The power to detect efficacy under these assumptions was 83.4%.

The one patient with metabolic response had grade 2 undifferentiated sarcoma of the lower leg. The tumor showed 70% regression with hyaline necrosis and did not reduce in size during neoadjuvant therapy. The patient is alive and without evidence of tumor recurrence 43 months after R0 surgery.

Nineteen of 21 (90.5%) patients underwent tumor resection. One patient had progressed during therapy with intraoperative detection of liver metastases from a retroperitoneal sarcoma. Palliative right hemicolectomy without tumor resection was performed. In one patient who could not complete pazopanib treatment due to gastric outlet obstruction, peritoneal sarcomatosis was found intraoperatively and gastroenterostomy was performed. Seven of 19 (36.8%) operations were compartment-oriented limb resections, 1/19 (5.3%) was a wide resection in a limb, 3/19 (15.8%) were retroperitoneal compartment resections, 1/19 (5.3%) was a partial cystectomy, 1/19 (5.3%) was a wide cervical resection, and 6/19 (31.6%) were wide resections in the trunk. All margins were tumor-free, and the mean tumor margin distance was 9.8 mm (range 0–100 mm).

Histological response was evaluable in 16/17 patients who completed pazopanib treatment and underwent tumor resection. In the one remaining patient, histopathological work-up showed scar tissue without viable tumor cells. The proportion of regression was $\leq$ 20% in eight evaluable patients and $>$ 20% in a further eight evaluable patients (range 5–90%). The type of regression was hyaline necrosis in 11 patients, scarring in four patients, and hemorrhagic necrosis in one patient. There was no tangible correlation between regression and metabolic response, with 5/8 metabolic responses in patients with $>$ 20% and $\leq$ 20% regression.

Safety Results

During the trial, 7/21 (33%, 95% CI 17.1–54.8%) patients who took pazopanib at least once experienced 12 grade 3/4 toxicities. Two patients had three events and one patient had two events. The most frequent grade 3/4 toxicities were hypertension in four patients and hepatic enzyme elevation in four patients. In 5/21 (24%, 95% CI 10.2–45.5%) patients who took pazopanib at least once and were subsequently operated, eight adverse or serious adverse events occurred up to 30 days postoperatively. One patient experienced three events and another patient experienced two events (Table 2). Surgery was not delayed in any of the patients due to treatment-related causes.

Results of the Translational Substudy

Thirteen patients completed all three blood samples, providing data for analysis of angiogenic markers. cEPCs and Ang-2 slightly decreased during pazopanib treatment and increased again after surgery, whereas sVEGF showed a vague increase from the first to the last sample. None of the changes in the cEPC, sVEGF, and Ang-2 levels reached statistical significance (Table 3).

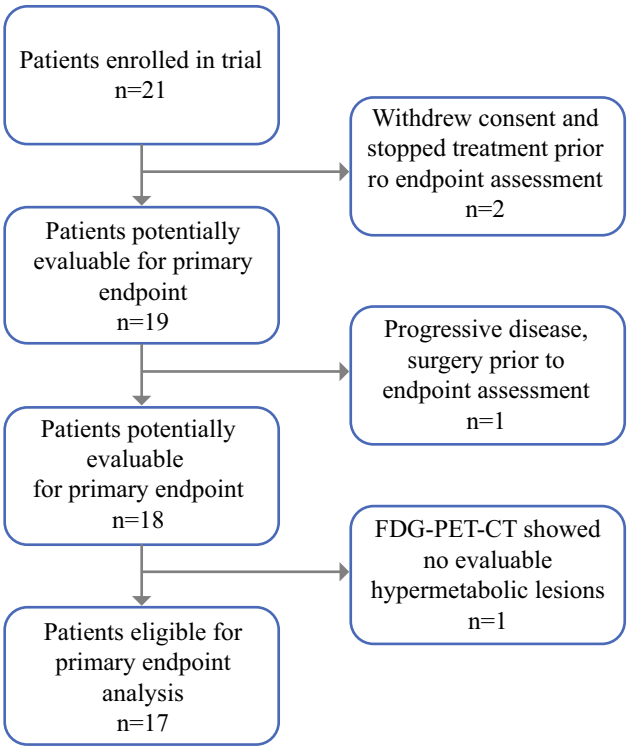

FIG. 1 Flowchart of patients in the study. *FDG-PET/CT* fluorodeoxyglucose–positron emission tomography/computed tomography

DISCUSSION

This trial was the first to assess preoperative pazopanib monotherapy for resectable high-risk STS. The underlying hypothesis was that given the antiangiogenic effects of pazopanib,[13] tumor metabolism would rapidly decrease during therapy. This would facilitate resection and improve oncological results. These assumptions are not supported by the results of the study, with only one metabolic responder.

This result is somewhat unexpected given the proven efficacy of pazopanib in metastatic STS.[9,29] However, there are several differences. First, the trials in metastatic STS did not assess metabolic response. The phase II trial assessed volumetric response,[29] and the primary outcome of the phase III trial was progression-free survival.[9] One would expect metabolic response to be a prerequisite for volumetric response and improved survival, but the exact associations are not fully understood. Although response to kinase inhibitors usually manifests early after treatment onset,[13,30] it cannot be fully excluded that, in the present trial, metabolic response assessment took place too early to capture response. A phase II trial of neoadjuvant pazopanib for renal cell cancer found a high response rate after 12–14 weeks of treatment.[31] Nonetheless, a delayed response pattern, with possible intercurrent tumor progression, would disqualify pazopanib from being a safe neoadjuvant treatment for STS. Second, response patterns might be different between later-line pazopanib therapy in metastatic disease and preoperative first-line pazopanib therapy in locally confined disease. However, there is no simple biological explanation as to why pretreated STS would respond to pazopanib and treatment-naïve tumors would not. Third, the distribution of histological subtypes differs between our trial and previous trials. The phase II trial comprised four separately analyzed histological strata: liposarcoma, leiomyosarcoma, synovial sarcoma, and other STSs. Compared with historical controls, survival was prolonged in the last three cohorts, while efficacy could not

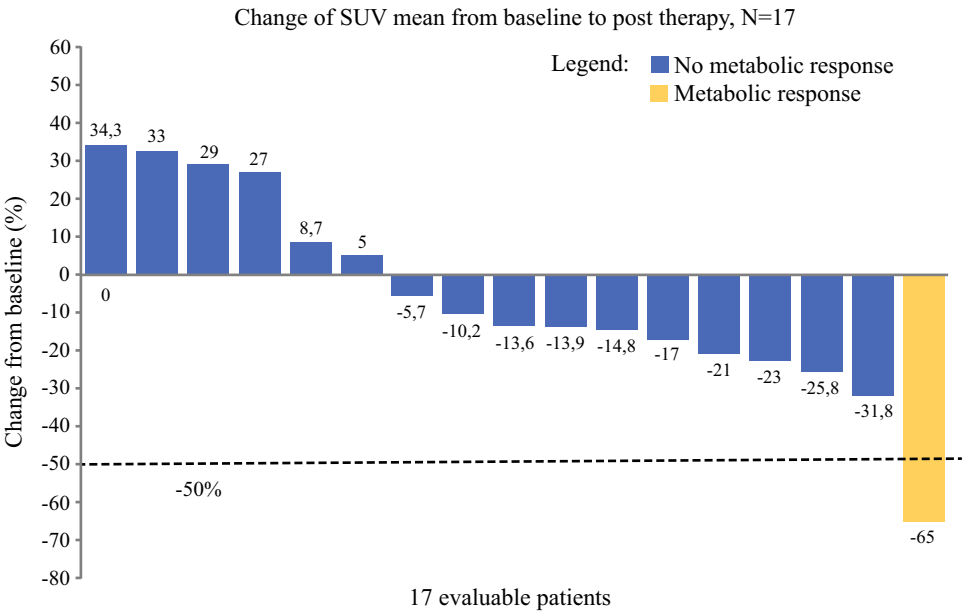

FIG. 2 Waterfall plot of change in SUV_{mean} between pre- and post-therapeutic FDG-PET/CT. *SUV* standardized uptake value, *SUV_{mean}* mean standardized uptake value, *FDG-PET/CT* fluorodeoxyglucose–positron emission tomography/computed tomography

TABLE 2 Postoperative adverse and serious adverse events in 21 patients (multiple events per patient possible)

Event	Grade	*N*	Percentage (95% CI)
Atrial fibrillation	2	1	4.8 (< 0.1–24.4%)
Gastroparesis	2	1	4.8 (< 0.1–24.4%)
Paralytic ileus	2	1	4.8 (< 0.1–24.4%)
Anastomic leak	4	1	4.8 (< 0.1–24.4%)
Hemorrhage	2	1	4.8 (< 0.1–24.4%)
Seroma	2	2	9.5 (1.5–30.1%)
Stoma placement	2	1	4.8 (< 0.1–24.4%)

CI confidence interval

be shown in the liposarcoma cohort.[29] This led to liposarcoma being excluded from the ensuing phase III trial.[9] However, subsequent central pathology review of tumor specimens from phase II trials reclassified two patients with stable disease and 'other sarcoma' as having liposarcoma (internal communication by the trial sponsor). Based on this finding, the liposarcoma stratum of the trial would have been expanded to the full number of 39 patients, and pazopanib activity against liposarcoma seems probable. These findings are supported by a study of 41 patients with liposarcoma treated with pazopanib, which reported a 68.3% progression-free rate at 12 weeks of treatment.[10] Therefore, we chose to include patients with liposarcoma, which is the most common subtype, into our trial. In fact, liposarcoma constituted more than two-thirds of tumors in our trial, and most of the patients with liposarcoma had a dedifferentiated subtype. This difference in histological distribution might explain the lack of response compared with the previous two trials. The heterogeneity of histopathological subtypes in the small group of non-liposarcoma patients in our trial makes it very difficult to draw conclusions regarding the efficacy of neoadjuvant pazopanib treatment in subtypes other than liposarcoma. The fact that approximately 60% of patients in our trial had grade 2 tumors might also explain the low MRR. Better differentiated tumors are supposed to have a lower metabolic activity and could thus be less susceptible to a drug-inducing metabolic response.

The primary endpoint of this study was based on a definition of metabolic response as a $> 50\%$ decrease in SUV_{mean}. A lower threshold would have led to a higher MRR. There is no validated definition of what changes in PET measurements constitute a meaningful response in neoadjuvant STS treatment with kinase inhibitors. Our definition was adapted from the study by Schuetze et al., in which a $> 40\%$ decrease of SUV_{mean} after neoadjuvant cytotoxic treatment of STS was shown to predict recurrence and survival.[17] As pazopanib is not established for neoadjuvant STS treatment, we chose an even higher threshold to avoid overestimating the efficacy of the drug. A reduction of the threshold in our trial to 40% would have yielded the same MRR, and a reduction to 20% would have resulted in an MRR of 29.4%, thus still resulting in a formally negative trial result. An even further reduction would have probably led to a positive trial, but is most likely not to be considered clinically relevant. Nonetheless, the fact that the majority of patients experienced a reduction in SUV_{mean} suggests that pazopanib has at least some activity on tumor metabolism in STS.

As a secondary endpoint, we analyzed histopathological regression. In half of the patients with available results, regression of $> 20\%$ was observed; there was no association with a decrease in tumor metabolism. A phase I trial combining preoperative pazopanib with radiotherapy observed near-complete regression in 4/10 patients with extremity STS, but none of these patients showed volumetric response.[32] Whether histopathological regression after pazopanib therapy has true prognostic value cannot be answered by either trial. The results from a series of STS patients treated with neoadjuvant radiotherapy suggest that the histological appearance of the tumor after treatment, particularly hyalinization, is associated with a favorable

TABLE 3 Mean (±SD)/median concentrations of cEPC, sVEGF and Ang-2 throughout the study period

	Before pazopanib	After pazopanib	Postoperatively	*p* value[a]
cEPC (%PBMCs)	0.0977 ± 0.0555/0.1112	0.0831 ± 0.0604/0.0665	0.1328 ± 0.0834/0.1251	0.2163/0.3012
sVEGF (pg/mL)	527.4 ± 295.5/526.0	602.3 ± 475.0/512.0	680.0 ± 337.8/642.0	0.8926/0.0673
Ang-2 (pg/mL)	3917 ± 3380/2366	3606 ± 3775/2162	4846 ± 3962/3413	0.3804/0.2036

All differences of values before and after pazopanib treatment, and before pazopanib treatment and after surgery, were statistically not significant

SD standard deviation, *cEPC* circulating endothelial progenitor cells, *sVEGF* soluble vascular endothelial growth factor, *Ang-2* angiopoietin-2, *PBMCs* peripheral blood mononuclear cells

[a]Wilcoxon rank-sum test presenting the changes in the measured parameters before pazopanib–after pazopanib/after pazopanib postoperatively

outcome[33]. The majority of patients with evaluable histological response in our study, including the one patient with metabolic response according to our definition, showed hyalinization. The absolute number of patients was too small to perform a valid comparison of this subgroup with the group of patients with other histological appearance; however, histological appearance following antiangiogenetic treatment should be accounted for in future studies.

Notwithstanding the lack of relevant metabolic response, all resections were microscopically complete, and no tumor had progressed during neoadjuvant therapy. However, two patients were not resected due to intraoperative findings of distant or peritoneal metastases, which remained undetected on preoperative FDG-PET/CT. Because the trial used pazopanib perioperatively, perioperative morbidity was a major concern. Participants underwent a variety of procedures, comprising multivisceral and extensive limb resections. There was no sign of elevated perioperative morbidity compared with STS patients undergoing immediate surgery, which is in line with the results of a phase I trial combining preoperative pazopanib with radiotherapy.[32] In our trial, the incidence and nature of toxicities during preoperative pazopanib treatment were similar to previous trials in metastatic disease.[9,29] In contrast to the trial combining radiotherapy with pazopanib, no increased hepatotoxicity was observed.[32] Consequently, perioperative pazopanib monotherapy for STS appears to be safe.

The translational substudy failed to show significant changes of angiogenic markers, which contrasts with our previous results where cEPCs seemed a reliable surrogate marker for progression in patients with soft-tissue tumors.[34] Looking at individual patients, we identified three with a remarkable increase of Ang-2 throughout the study period. One patient developed early metastasis; the second patient developed urinary tract infection and also early tumor recurrence requiring reoperation; and the last patient developed lung metastasis a few months after resection, but also had postoperative urological complications. In the last two cases, it was unclear if the increase in Ang-2 values was caused by urological comorbidities or tumor recurrence. In the patient with metabolic response, cEPC levels remained unchanged during and after treatment, while Ang-2 more than halved during treatment and rose to the pretreatment level after resection. Generally, we expected a decrease in the levels of the angiogenic markers after pazopanib treatment, but there was a tendency towards lower cEPC and Ang-2 values; however, VEGF-A increased during pazopanib treatment.

CONCLUSIONS

This phase II trial did not show metabolic efficacy of neoadjuvant pazopanib treatment in unselected patients with high-risk STS, the majority of whom had liposarcoma. However, there was a meaningful response in a specific patient. Future research is warranted and needs to better define potential responders. To this end, biomarkers might be of additional use. Future trials should recruit a sufficient number of patients with specific STS subtypes in order to draw valid conclusions about the efficacy of pazopanib in these subtypes. Whether adding radiotherapy to preoperative pazopanib leads to a higher probability of response, as suggested by a phase I trial in patients with extremity STS,[32] also remains to be studied.

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REFERENCES

1. Casali P, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29 (Suppl 4):iv268–iv269.
2. National Comprehensive Cancer Network Clinical Practice Guidelines. Soft Tissue Sarcoma. Version 2.2018.
3. Hohenberger P, Wysocki WM. Neoadjuvant treatment of locally advanced soft tissue sarcoma of the limbs: which treatment to choose? *Oncologist* 2008; 13:175–186.
4. Saponara M, Stacchiotti S, Casali PG, Gronchi A. (Neo)adjuvant treatment in localised soft tissue sarcoma: the unsolved affair. *Eur J Cancer* 2017; 70:1–11.
5. Gronchi A, Jones RL. The value of neoadjuvant chemotherapy in localized high-risk soft-tissue sarcoma of the extremities and trunk. *JAMA Oncol* 2018;4(9):1167–1168.
6. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol* 2017; 18:812–822.
7. Issels RD, Lindner LH, Verweij J, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 randomized clinical trial. *JAMA Oncol* 2018; 4:483–492.
8. Jakob J, Hohenberger P. Role of isolated limb perfusion with recombinant human tumor necrosis factor α and melphalan in locally advanced extremity soft tissue sarcoma. *Cancer* 2016; 122:2624–2632.
9. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012; 379:1879–1886.
10. Samuels BL, Chawla SP, Somaiah N, et al. Results of a prospective phase 2 study of pazopanib in patients with advanced

intermediate-grade or high-grade liposarcoma. *Cancer* 2017; 123:4640–4647.
11. Kasper B, Sleijfer S, Litière S, et al. Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072. *Ann Oncol* 2014; 25:719–724.
12. Kollár A, Jones RL, Stacchiotti S, et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. *Acta Oncol* 2017; 56:88–92.
13. Gotink KJ, Verheul HM. Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action? *Angiogenesis* 2010; 13:1–14.
14. Hamberg P, Verweij J, Sleijfer S. (Pre-)clinical pharmacology and activity of pazopanib, a novel multikinase angiogenesis inhibitor. *Oncologist* 2010; 15:539–547.
15. Glimelius B, Lahn M. Window-of-opportunity trials to evaluate clinical activity of new molecular entities in oncology. *Ann Oncol* 2011; 22:1717–1725.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228–247.
17. Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. *Cancer* 2005; 103:339–348.
18. Dimitrakopoulou-Strauss A, Strauss LG, Egerer G, et al. Impact of dynamic 18F-FDG PET on the early prediction of therapy outcome in patients with high-risk soft-tissue sarcomas after neoadjuvant chemotherapy: a feasibility study. *J Nucl Med* 2010;51:551–558.
19. Yoon SS, Segal NH, Olshen AB, Brennan MF, Singer S. Circulating angiogenic factor levels correlate with extent of disease and risk of recurrence in patients with soft tissue sarcoma. *Ann Oncol* 2004; 15:1261–1266.
20. Roodhart JM, Langenberg MH, Daenen LG, Voest EE. Translating preclinical findings of (endothelial) progenitor cell mobilization into the clinic; from bedside to bench and back. *Biochim Biophys Acta* 2009; 1796:41–49.
21. Norden-Zfoni A, Desai J, Manola J, et al. Blood-based biomarkers of SU11248 activity and clinical outcome in patients with metastatic imatinib-resistant gastrointestinal stromal tumor. *Clin Cancer Res* 2007; 13:2643–2650.
22. Ronellenfitsch U, Dimitrakopoulou-Strauss A, Jakob J, et al. Preoperative therapy with pazopanib in high-risk soft tissue sarcoma: a phase II window-of-opportunity study by the German Interdisciplinary Sarcoma Group (GISG-04/NOPASS). *BMJ Open* 2016; 6:e009558.
23. Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med* 2006; 130:1448–1453.
24. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: 28 May 2009 (v4.03: 14 June 2010). https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 12 Oct 2018.
25. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Stat Med* 2001; 20:859–866.
26. Benz MR, Allen-Auerbach MS, Eilber FC, et al. Combined assessment of metabolic and volumetric changes for assessment of tumor response in patients with soft-tissue sarcomas. *J Nucl Med* 2008; 49:1579–1584.
27. Benz MR, Czernin J, Allen-Auerbach MS, et al. FDG-PET/CT imaging predicts histopathologic treatment responses after the initial cycle of neoadjuvant chemotherapy in high-grade soft-tissue sarcomas. *Clin Cancer Res* 2009; 15:2856–2863.
28. Evilevitch V, Weber WA, Tap WD, Allen-Auerbach M, Chow K, Nelson SD, et al. Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. *Clin Cancer Res*. 2008; 14:715–720.
29. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC Study 62043). *J Clin Oncol* 2009; 27:3126–3132.
30. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; 347:472–480.
31. Powles T, Sarwar N, Stockdale A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. *JAMA Oncol* 2016; 2:1303–1309.
32. Haas RL, Gelderblom H, Sleijfer S, et al. A phase I study on the combination of neoadjuvant radiotherapy plus pazopanib in patients with locally advanced soft tissue sarcoma of the extremities. *Acta Oncol* 2015; 54:1195–1201.
33. Schaefer IM, Hornick JL, Barysauskas CM, et al. Histologic appearance after preoperative radiation therapy for soft tissue sarcoma: assessment of the European organization for research and treatment of cancer-soft tissue and bone sarcoma group response score. *Int J Radiat Oncol Biol Phys*. 2017; 98:375–383.
34. Karampinis I, Joas E, Dreyer A, et al. The evaluation of circulating endothelial progenitor cells and related angiogenic markers as prognostic factors in soft-tissue tumors. *Eur J Surg Oncol* 2018; 44:496–501.