Protocol

EVA (evaluation of votrient in angiosarcoma) is a single-arm, multicenter, open label phase II trial to evaluate the efficacy of pazopanib in combination with paclitaxel in advanced and relapsed angiosarcoma

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Schedule of study assessments

Event	Baseline	Treatment period		End of treatment / Safety Follow-Up	Follow-Up
Planned visits	Screening - 28 days	6 cycles (á 4 weeks) always day 1, 8 and 15 before application of Paclitaxel	Every 8 weeks (+/- 7 days)	30 days after end of tretament with Pazopanib	every 12 weeks (+/- 14 days)
Informed consent	X				
Medical history	X				
Anamnesis	X	X	X	X	
Physical examination	X	X	X	X	
Vital signs	X	X[10]	X[10]	X	
ECOG-Performance Status	X	X	X	X	
Blood count, Serum-Chemistry[1,2]	X	X[10]	X[10]	X	
Coaggzlation[1,3]	X	X	X	X	
Beta-HCG	X		X	X	
Urine status /UPC	X	X	X	X	
TSH,	X		X	X	
ECG	X	X[4]	X	X	
Echo	X			X[6]	
Documentation of measurable skin lesions (measuring and photo)[9]	X		X	X	X[5]
Tumor assessment[8]	X		X	X	X[5]
Paclitaxel		day 1, 8 and 15			
Pazopanib		daily			
Tumor therapy after end of teatment					X
Concomitant medication	X	X			
Adverse events[7]		X			

(1) All la assessments can be performed 1-2 days before visit
(2) Hb, Hkt, Erys Leukos, Thrombos, Differential blood count, plastine time (PTT)
(4) ECG in the first 12 weeks only at beginning of each cycle, then evey 8 weeks.
(5) Tumor control until progresion of disease
(6) if clinically indicated
(7) if Paclitaxel treatments end based on Polyneuropathy, follow up is done by phone after 4 weeks
(8) CT oder MRI of thorax and abdomen and of all known tumor locations
(9) Skin lesion will be summarized as target and non-target lesions and photografically documented combined with a mm ruler as panoramic shot and as zoomed shot. A lesion defined as target lesion needs to have a minimal size of ≥ 1,0 cm at start. Raised lesions will be measured by a caliber.
(10) Lab parameters and vital signs have to be determined in week 3, 5, 7 and 9 and months 3 and 4 during Panzopanib application. If clinically indicated, these determinations should be stricter (at least every 4 weeks).

ABBREVIATIONS

AMG	Deutsches Arzneimittelgesetz (=German Pharmaceuticals Act)
AS	Angiosarcoma(s)
AE	Adverse Event
BET	Brust erhaltende Therapie (=Breast-conserving therapy)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CA	Competent Authority
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CVA	Cerebrovascular Accident
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (=German Society of hematology and medical oncology)
DLT	Dose limiting Toxcity
DMC	Data Monitoring Committee
DVT	Deep venous thrombosis
ECOG	Eastern Cooperative Oncology Group
EC	Ethic Committee
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
IB	Investigator´s Brochure (Prüferinformation)
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMBI	Institut für Medizinische Biometrie und Informatik (=Institute of Biometry and informatics)
INN	International Nonproprietary Name (generic name)
INR	International normalized ratio (coagulation test)
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number
KKS HD	Koordinationszentrum für Klinische Studien Heidelberg
LKP	Leiter der Klinischen Prüfung (gem. AMG §40) (=National Coordinator)
OS	Overall survival
PDGF	Platelet Derived Growth Factor
PDGFR	Platelet Derived Growth Factor Receptor
PE	Pulmonary embolism
PFS-R	Rate of progression-free survival

PID	Patient identificator
PPE	Palmar-plantar Erythrodysesthesia Syndrom
PSN	Pseudonym
R	Response
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAR	Serios Drug Reaction
STS	Soft Ttissue Sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transitory Ischemic Attack
TMF	Trial Master File
AE	Adverse Event
ULN	Upper Level of Normality
VEGF	Vascular Endothelial Growth Factor

1 Introduction and Study's rationale

1.1 Angiosarcomas: Introduction and systemic therapy

Angiosarcomas (AS) are very rare tumor diseases, accounting for approximately 2-3% of all soft tissue sarcomas; thus, approximately 60 to 90 new cases per year can be assumed in Germany [18]. In principle, angiosarcomas can occur anywhere in the body, with approximately 60% arising cutaneously (especially head/neck) and the remainder in the soft tissues or internal organs. The three most common localizations are the skin of the head and neck, the chest, and the extremities. The median age at initial diagnosis was 52-65 years in different case series. AS of the head/neck and chest are more common in women; both sexes are equally affected in the other localizations [19, 20, 21, 22].

Some AS occur secondary to radiation or in chronic lymphedema (the latter: lymphangiosarcoma; Stewart-Treves syndrome) - e.g., in a case series [1], 59% of angiosarcomas of the breast were secondary angiosarcomas after BET and radiation therapy of a breast carcinoma.

The treatment of choice for localized AS, as for other AS, is complete resection possibly followed by postradiation. After 5 years, 31-41% of patients with non-metastatic angiosarcomas are still alive [18, 19, 20, 21, 22].

Approximately 15% of patients with AS are already metastasized at initial diagnosis; a relevant proportion of other patients develop metastases in the course of their disease. Metastatic AS are not curable in the vast majority of cases; thus, patients are usually in a basic palliative situation in which systemic drug therapy is the primary treatment. The median overall survival of patients with metastatic AS is 8-12 months [18, 19, 20, 21, 22].

Case reports and smaller retrospective analyses exist suggesting efficacy of various chemotherapeutic agents such as anthracyclines, ifosfamide, liposomal doxorubicin, vinorelbine, trosfosfamide, or of "molecular targeted agents" such as thalidomide, sunitinib, sorafenib, pazopanib, and bevacizumab. Some larger studies that have evaluated the efficacy of doxorubicin-based chemotherapy regimens (e.g., doxorubicin+ifosfamide) in patients with various soft tissue sarcomas have also included patients with AS; however, in most cases, they have not been specifically evaluated [18].

Overall, as with systemic treatment of patients with other soft tissue sarcomas, doxorubicin or the doxorubicin+ifosfamide combination is believed to be standard therapy in patients with advanced or metastatic AS [18].

In advanced or metastatic AS, unlike other soft tissue sarcomas, therapy with paclitaxel is also effective both in the first line and in pretreated patients. It is administered both tri-weekly at a dose of 175mg/m2 and weekly at 60-80mg/m2. The efficacy of paclitaxel in patients with AS was initially reported in the form of case reports and retrospective analyses; but was later confirmed by a prospective phase II study ("AngioTax" study) [2]. In this study, 30 patients were treated weekly with paclitaxel 80mg/m2. The objective response rate in this study was 19%. After 3 months, 75% of patients were progression-free; after 6 months, 24% of patients were still progression-free. The efficacy of paclitaxel in this study appeared to be comparable in pretreated and chemonaive patients; although the case number was certainly too small for more extensive analyses.
Overall, chemotherapy with paclitaxel is a standard guideline-based treatment option for patients with advanced and metastatic angiosarcoma [37].

In two other prospective phase II trials of new agents in patients with different soft tissue sarcoma subtypes, patients with AS were evaluated in a subgroup-specific manner. One of the two studies evaluated the efficacy of imatinib, which was summarily found to be unconvincingly effective in AS [3].
In the other study, in which a total of 145 patients with advanced and metastatic soft tissue sarcomas were treated with the RAF kinase and VEGF-R inhibitor sorafenib 800mg daily, 37 patients with AS were also included and evaluated as planned stratum. Of these 37 patients, 5 had a true response to therapy (response rate 14%); 65% of patients were progression-free at 3 months and 31% at 6 months [4]

Case reports or initial results of prospective studies have also been published or presented at congresses for other substances that, like sorafenib, inhibit the VEGF receptor (e.g., sunitinib, pazopanib [6, 7]) or bind to VEGF and thus suppress its effect (bevacizumab [8]), suggesting that these drugs may also be effective in the treatment of patients with AS.
This clinical observation is in good agreement with various in vitro or preclinical studies that have shown that VEGF receptors are mutated and/or overexpressed in a high proportion of AS, that the downstream signaling cascade of these receptors is also often strongly activated in AS, and that these alterations are often detectable even in early AS; thus, in the pathogenesis of AS they probably play a major role (review e.g. [5]).

In summary, although several effective systemic therapy options exist for the treatment of patients with advanced and metastatic AS, such that patients with AS now live longer with optimal therapy than they did a decade ago; nevertheless, most patients continue to die from their disease, e.g., due to secondary resistance. Thus, there is an urgent need to improve systemic therapy.
One approach is the search for additional effective substances that are also effective in AS resistant to other drugs; another approach is the combination of already existing substances with as few side effects as possible, such as paclitaxel applied weekly with a VEGF inhibitor.

1.2 Pazopanib

Pazopanib is a multi-tyrosine kinase inhibitor approved in Europe for the treatment of advanced and/or metastatic renal cell carcinoma and for the treatment of certain subtypes of soft tissue sarcoma. Pazopanib is taken orally at a dose of 800 mg 1x daily as continuous therapy.

Pazopanib inhibits the tyrosine kinase-mediated action of the receptors of VEGFR 1, 2, and 3, as well as PDGFR-α, PDGFR-β, and c-kit. This results in simultaneous antiproliferative and antiangiogenic effects. The most common adverse effects include decreased appetite, disturbances in taste perception, hypertension, diarrhea, nausea, vomiting, abdominal pain, change in hair color, fatigue, and elevated liver enzymes; although pazopanib appears to have a particularly favorable side effect profile compared with other multi-tyrosine kinase inhibitors that inhibit VEGF-R, among others.
Clinical efficacy and tolerability were evaluated in a phase II and a phase III trial for patients with advanced soft tissue sarcoma (STS).
In the randomized, placebo-controlled phase III trial in STS, pazopanib significantly prolonged progression-free survival compared with placebo [9]. This study did not specifically evaluate the efficacy of pazopanib in patients with AS, so no further experience is available to date in this regard. Few published single case reports or unpublished anecdotal experience from large sarcoma centers exist that pazopanib can result in a longer lasting treatment response in patients with advanced AS [6].

1.3 Combination of antiangiogenic substances and chemotherapy of sarcomas

The combination of antiangiogenic agents with chemotherapy is a common therapeutic approach in many solid tumors. In recent years, several of these combination therapies have been approved in Europe for the treatment of patients with solid tumors in specific settings (e.g., bevazicumab and chemotherapy for metastatic colorectal carcinoma, lung carcinoma, breast carcinoma).
It is suggested that weekly low-dose paclitaxel may also have antiangiogenic effects [10]; thus, in particular, the combination of this compound with antiangiogenic drugs is also of interest and has been investigated, leading, for example, to the approval of the combination of bevazicumab with paclitaxel in the first-line treatment of patients with metastatic breast carcinomas (in the pivotal trial, patients had received weekly paclitaxel).

To review the combination of antiangiogenic agents with chemotherapy in patients with soft tissue sarcomas, there are only sporadic published prospective studies [12, 16] and few other published experiences in the form of single case reports or case collections [11, 13, 14]; especially for the use of such combinations in patients with advanced or metastatic AS, there are only single case reports without major significance [15].

1.4 Experience with combination of Paclitaxel and Pazopanib

A phase I study was conducted to evaluate the combination of pazopanib with weekly paclitaxel in patients with various advanced solid tumors to evaluate the maximum tolerated regimen (MTR) and dose-limiting side effects and pharmacokinetics of pazopanib in this combination [17]. In this study, paclitaxel was given weekly on days 1, 8, and 15 every 28 days in combination with daily oral pazopanib.
There were 26 patients enrolled in the study and 17 of these patients were treated with the MTR of pazopanib 800mg/day combined with paclitaxel 80mg/m2 on day 1, 8 and 15 every 28 days. The pazopanib at this dose resulted in 14% lower paclitaxel clearance and 31% higher maximum paclitaxel concentration than when paclitaxel was given alone. When the combination was given in the MTR, the paclitaxel AUC was 26% higher than when paclitaxel mono was given at the same dose. These changes were explained by the fact that pazopanib is a weak inhibitor of CYP3A4 and CYP2C8.

The most common side effects of the combination were fatigue (69%), nausea (58%), diarrhea (54%), alopecia (35%), vomiting (35%), and rash (31%). Most adverse events (92%) were classified as grade 1/2 adverse events.
Transaminase elevations were observed, leading to dose reductions of pazopanib in 4 of 10 patients (at all dose levels).
Arterial hypertension was the most common cardiovascular adverse event, with arterial hypertension already present in some patients before study inclusion. Dose modifications of antihypertensives were necessary in a proportion of patients.

Dose limiting side effects (DLT) were grade-3 abscess and grade-2 hyperbilirubinemia at the MTR dose level; no DLT occurred at the other dose levels.
In summary, the authors concluded that pazopanib at a dose of 800mg/day can be safely combined with paclitaxel at therapeutic doses of 80mg/m² when applied every 28 days on days 1, 8, and 15.
There is no published experience on combination therapy of paclitaxel with pazopanib in angiosarcoma.

1.5 Study rationale

Due to the very limited prognosis of patients with advanced and metastatic AS, there is a great need for more effective therapeutic options, as described in 1.1, which lead to a longer response to therapy, especially if they are well tolerated.
Since both paclitaxel and VEGF inhibitors appear to be effective and tolerable systemic therapy options in patients with AS as outlined above, and since pazopanib is the only VEGF-R inhibitor with a proven efficacy that has a marketing authorization for the treatment of patients with advanced soft tissue sarcomas, the combination of paclitaxel and pazopanib appears to be a particularly interesting combination therapy to investigate for patients with advanced or metastatic AS.
The combination of paclitaxel with pazopanib is a safe therapy with few side effects in the MTR established in the cited phase I study.
In the Angiotax study [2], patients were treated with paclitaxel 80mg/m² weekly, and due to dose reductions and treatment delays, the mean applied paclitaxel dose was 53.4 mg/m²/week in all patients who received at least two cycles of chemotherapy.
Due to the above described increases in maximum paclitaxel concentration and paclitaxel AUC in combination with pazopanib, and because the risk of e.g. peripheral nerve damage during therapy with paclitaxel increases with longer therapy and increasing dose, it was decided to

use the paclitaxel in the EVA study at a slightly reduced dose of 70mg/m² (not 80mg/m² as in the MTR of the phase I study), despite the low side effect rate of the MTR in the phase I study.

2 Objectives ad Endpoints

2.1 Objectives

The objective of this phase II study is to evaluate the efficacy of pazopanib in combination with paclitaxel in the treatment of patients with advanced or metastatic angiosarcoma. Secondary objective is to evaluate the tolerability of the combination.

2.2 Primary endpoint

The primary endpoint is progression-free survival at 6 months (PFS).

2.3 Secondary endpoints

The secondary endpoints are overall survival (OS), response (R), (according to RECIST version 1.1), and severity of incident adverse events or toxicities (according to CTCAE, version 4.0).

2.4 Subgoupanalyses

The following subgroup analyses are planned:
1. cutaneous AS vs. visceral AS (PFS, OS, R).
2. primary AS vs. secondary AS (PFS, OS, R)

3 Study concept und Design

This is a multicenter, open-label, prospective, single-arm phase II study designed to evaluate the clinical efficacy and safety of the experimental combination of pazopanib with paclitaxel in the treatment of patients with advanced or metastatic angiosarcomas.
Angiosarcomas are rare serious diseases for which new therapeutic approaches are needed on the one hand, but on the other hand only a very limited number of patients are likely to be available for study participation even in large centers. For this reason, a multi-arm study design and randomization were deliberately avoided in order to allow the study to be conducted in a manageable period of time and thus to generate usable results.

Paclitaxel is given weekly on days 1, 8 and 15 every 28 days as a 2 hour intravenous infusion at a dose of 70mg/m² for 6 cycles in combination with pazopanib at a daily oral dose of 800mg. If progression is not observed after 6 cycles of combination therapy, pazopanib is taken alone until progression.

Safety assessments (physical examination, laboratory controls, toxicity determination/side effect profile according to CTCAE version 4.0) will be performed in each therapy cycle on day 1, 8, 15 and 29 (= day 1 of the next therapy cycle).
Response will be documented clinically by photography for measurable skin lesions and determined radiologically by CT/MRI according to RECIST version 1.1 for the other target lesions every 8 weeks.

4 Study Subjects

4.1 Subject Number

A maximum of 44 participants are to be enrolled in the clinical trial. Enrollment and treatment of participants will be conducted in 10 study centers in Germany and Austria. Patients who have taken pazopanib at least once will not be replaced even if they withdraw from the study early. Otherwise, patient replacement is planned.

4.2 Inclusion criteria

Inclusion criteria

1. Subjects must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up .Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies) and obtained prior to signing informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol
2. Patient is able to give informed consent and able to understand the nature and scope of the clinical trial
3. Age ≥ 18 years
4. Life expectancy > 3 months
5. Ability to swallow tablets

6. Histologically confirmed angiosarcoma, primary and secondary angiosarcoma (e.g. radiation-induced or angiosarcoma in chronical lymphedema) are eligible Patienten mit histologisch gesichertem Angiosarkom. Es können Patienten mit primären oder sekundären Angiosarkomen (z.B. strahleninduziert bzw. AS in chronischem Lymphödem) eingeschlossen werden.
7. Tumor must be locally advanced (unresectable) or metastatic. A progression must be documented within a 6-month period prior to screening.
8. ECOG performance status ≤ 1
9. At least one measurable skin lesion or one measurable radiological (CT or MRI) target lesion (RECIST 1.1)
10. Adequate organ system function as described in table 1

Table 1: Definitions for adequate organ functions

Blood count	
Absolute Neutrophile number (ANC)	≥1.5 X 10^9/L
Hemoglobine	≥9 g/dL (5.6 mmol/L)
Thrombocytes	≥100 X 10^9/L
Coaggulation	
Prothrombin time (PT) or INR	≤1.2 X upper normal limit (ULN)
partial Thromboplastinzeit (PTT)	≤1.2 X ULN
Liver	
Total bilirubine	≤1.5 X ULN
ASAT and ALAT	≤2.5 X ULN
Kindney	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
if Serum creatinine >1.5 mg/dL, then	
calculated glomerular filtration rate (GFR)	≥50 mL/min
Protein/creatinine ratio (UPC)	<1
if UPC ≥1, then 24h-Urine protein	<1g

11. Women can participate in the study if they are unable to give birth (i.e. there is a physiological inability to become pregnant). This includes all women
    - after a hysterectomy,
    - after a bilateral ovariectomy,
    - after bilateral tubal ligation,

- postmenopausal women whose last menstrual bleeding was more than 1 year ago.

Women of childbearing potential must agree to adequate contraception and have a negative serum pregnancy test within two weeks prior to the first dose of study drug.

The pregnancy test should be as close as possible to the first dose application of study drug. Contraceptive measures must be continued for 6 months after the end of therapy. Appropriate contraceptive methods are as follows if used continuously and according to the package insert and as directed by the physician:

- An intrauterine device with a documented failure rate (Pearl index) less than 1% per year.
- A partner who was vasectomized prior to the patient's study entry, who is also the only sexual partner of this woman.
- Absolute sexual abstinence from 14 days prior to study drug intake, during intake until at least 6 months after last study drug intake.
- Double barrier contraception (condom with spermicidal creams or contraceptive foam; diaphragm with spermicides; or condom and diaphragm with spermicides).
- Breastfeeding women should discontinue this before starting study medication and should refrain from breastfeeding for the duration of treatment and until 14 days after the last dose of study medication.

Note: Oral contraceptives do not provide adequate protection due to potential drug interactions**.**

4.3 Exclusion criteria

1. patients requiring active therapy for a malignancy other than angiosarcoma.
2. treatment with a taxane within the last 12 months before study inclusion.
3.Presence of CNS or leptomeningeal sarcomatosis. Screening with head imaging (cranial CT or MRI) is necessary only if clinical abnormalities are present.
4. clinically significant gastrointestinal disorders/ abnormalities that could increase the risk for gastrointestinal bleeding.

a. Florid gastric/duodenal ulcer

b. Known intraluminal metastasis/metastases at risk for bleeding

c. Chronic inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other gastrointestinal findings with increased risk of perforation

d. Patient history of abdominal fistulae, gastrointestinal perforations, or intra-abdominal abscesses within 28 days prior to initiation of study treatment

5. clinically significant gastrointestinal disorders/ abnormalities that could affect absorption of the study drug

a. Malabsorption syndrome

b. Gastrectomy or major surgical resection of the small intestine

6. presence of uncontrolled infections

7. QT prolongation on ECG, QTc > 480 ms.

8. clinically significant cardiovascular disease within the last 6 months prior to study inclusion, e.g., apoplexy (CVA) including transient ischemic attacks (TIA), myocardial infarction, unstable angina, NYHA III or IV heart failure, pulmonary artery embolism, untreated deep vein thrombosis (DVT) (patients with deep vein thrombosis who have been fully anticoagulated for at least 6 weeks may be included)

9. "Major" surgical procedure within the last 28 days, non-healing wound or fracture

10. poorly controlled hypertension (defined as systolic blood pressure of ≥150 mmHg or diastolic blood pressure of ≥100 mmHg). Note: Initiation or adjustment of antihypertensive medication is permitted prior to study entry.

11. hemoptysis (≥½ teaspoon of fresh blood within 8 weeks before first administration of study medication).

12.Presence of massive bleeding or bleeding tendency.

13. presence of endobronchial lesions and/or lesions in the pulmonary vasculature

14. uncontrolled cerebral seizures, CNS or psychiatric disease that jeopardizes patient safety or impairs compliance for medication use

15. pregnant women and nursing mothers

16. patient is unable or unwilling to discontinue taking medications not allowed by the protocol for at least 14 days prior to administration of the first study medication and for the duration of the study.

17. chemotherapy or radiotherapy 14 days prior to the first dose of study medication.

18. any persistent toxicity from previous anti-cancer therapies that is >Grade 1 and/or progressive in severity, except alopecia.
19. concurrent participation in another interventional clinical trial or
    Participation in a clinical trial, 4 weeks prior to study initiation.

Note: Any treatment with pazopanib prior to study inclusion is NOT allowed.

5 Combination therapy

5.1 Medication

5.1.1 Study drug Pazopanib (GW786034, Votrient ®)

The "small molecule" VEGF receptor inhibitor, pazopanib (GW786034) is in clinical development for the treatment of a variety of human cancers.
Pazopanib has been approved by the EMA for the first-line treatment of adult patients with advanced renal cell carcinoma and for the treatment of patients who had received prior cytokine therapy for their advanced disease, as well as for the treatment of adult patients with selected subtypes of advanced soft tissue sarcoma who had received prior chemotherapy for their metastatic disease or who had progressed within 12 months of (neo-)adjuvant therapy.
Pazopanib is a potent and highly selective inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 tyrosine kinases. In preclinical angiogenesis studies, pazopanib inhibited VEGF-dependent angiogenesis in a dose-dependent manner. Twice-daily application of pazopanib in xenograft tumor models significantly inhibited tumor growth in mice implanted with various human tumor cells.

5.1.1.1 Non-clinical studies

A number of non-clinical pharmacological, pharmacokinetic and toxicological studies have been performed with pazopanib. These are described in the current investigator brochure

5.1.1.2 Effects on human beings

More than 1400 tumor patients have been enrolled in completed or ongoing clinical trials with pazopanib. The data collected to date show that pazopanib is orally absorbed after

administration, has an adequate safety profile and is promisingly effective in the treatment of various oncological situations.

5.1.1.3 Summary of pharmacokinetic and pharmacodynamic data

The results of pharmacokinetic and pharmacodynamic analyses show that pazopanib is absorbed after oral administration. A plateau level is achieved with continuous administration of 800 mg daily. Pazopanib has been tested at doses up to 2,000 mg in clinical trials without dose-limiting toxicity.

5.1.1.4 Drug interactions

In vitro data indicate that pazopanib is a potential inhibitor of CYP2C9, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Under high concentrations, pazopanib may lead to induction of human CYP3A4. Simultaneous administration of pazopanib and drugs that are substrates for CYP450 enzymes and that have the potential to cause serious and life-threatening side effects is prohibited.

5.1.1.5 Summary of adverse events (AE) and serious adverse reactions

The most common documented adverse reactions are diarrhea, fatigue, nausea, hypertension, hair color changes (depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, increase in ASAT and ALAT, constipation, cough, and arthralgias.
Most of these adverse events were classified as Grade 1 or 2 according to CTCAE version 4.0.
The most common Grade 3 or 4 events are hypertension, fatigue, diarrhea, and increase in transaminases ALAT and ASAT.
Less common adverse events include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombosis, and bleeding.
Uncommon was the occurrence of intestinal perforation and arterial thrombosis.
Serious adverse events that occurred in patients enrolled in pazopanib trials (regardless of treatment assignment) were vomiting, diarrhea, abdominal pain, hypertension, hypertensive crisis, dyspnea, pleural effusions, fever, anemia, dehydration, and pulmonary artery embolism.

Within one study, nephrotic syndrome due to thrombotic microangiopathy occurred with pazopanib. An association with pazopanib cannot be ruled out. The event was resolved.
A single fatal liver failure occurred with the combination of gemcitabine and pazopanib. Although liver failures including fatal outcomes have been reported for both agents, this SAR was considered unexpected.
There is no clinical evidence that pazopanib affects QTc time. Nevertheless, within clinical trials with pazopanib, severe adverse events due to QT-time prolongation or the occurrence of torsade de pointes arrhythmia occurred twice. One patient received amiodarone as part of the event and another patient discontinued pazopanib due to spinal hemorrhage caused by hemangioblastoma. Seven days after the event, the patient developed polymorphic ventricular tachycardia. Both SARs could be resolved

5.1.1.6 EORTC Phase II Study (EORTC62043/ EVG20002)

Pazopanib was evaluated in patients with relapsed and refractory soft tissue sarcomas in a single-arm phase II EORTC study. This study was stratified according to histology (liposarcomas vs. leiomyosarcomas vs. synovial sarcomas vs. other soft tissue sarcomas).
The drug was well tolerated: of 142 study participants, 6 patients were documented with grade 3-4 neutropenia, 2 patients with grade 3-4 thrombocytopenia, 9 patients with grade 3-4 bilirubinemia, 5 patients with ASAT elevation, 7 patients with ALAT elevation, and 4 patients with creatinine elevation.
Other main toxicities encountered were (all grades; grades 3-4) fatigue (36.6%; 7.7%), hypertension (40.1%; 7.7%), nausea (35.9%; 0.7%), diarrhea (30.3%; 3.5%), and hypopigmentation (36.6%; 0%).

5.1.1.7 Summary of laboratory abnormalities under pazopanib treatment

Pazopanib studies conducted to date indicate that the following therapy-induced laboratory abnormalities (all grades) commonly occur in patients treated with pazopanib: ASAT and ALAT elevation; hyperbilirubinemia; elevation of alkaline phosphatase, amylase, lipase, and creatinine; hyponatremia; hyperkalemia; lymphopenia; leukopenia; thrombocytopenia; neutropenia and anemia; hyperglycemia; and TSH elevation.
There was rarely a simultaneous increase in transaminases and bilirubin. For example, only 2 (<1%) patients were noted in the VEG102616 study.
Elevations of lipase and amylase were primarily grade 1 and 2, and most were asymptomatic, i.e., the appearance of clinical symptoms of pancreatitis was uncommon. Hyponatremia and

hyperkalemia did not occur simultaneously in the same patient, so there was no evidence of adrenocortical insufficiency.

5.1.1.8 Summary of data on efficacy in STS

The efficacy and safety of pazopanib in soft tissue sarcoma was evaluated in a randomized double-blind placebo-controlled multicenter phase III study (VEG110727). A total of 369 patients with advanced soft tissue sarcoma were randomized to receive 800 mg of pazopanib once daily or placebo. Essentially, only patients with selected histologic soft tissue sarcoma subtypes were allowed to participate in the study; therefore, the efficacy and safety of pazopanib can be considered proven only for these soft tissue sarcoma subtypes.

Patients with the following tumor types were included:

Fibroplastic sarcomas (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumors); so-called fibrohistocytic sarcomas (pleomorphic malignant fibrous histiocytoma[MFH], giant cell MFH, inflammatory MFH); Leiomyosarcoma; malignant glomus tumors; skeletal muscle sarcomas (pleomorphic and alveolar rhabdomyosarcomas); **vascular sarcomas (epithelial hemangioendothelioma, angiosarcoma);** Sarcomas of uncertain differentiation (synovial sarcoma, epithelioid sarcoma, alveolar soft tissue sarcoma, clear cell sarcoma, desmoplastic small and round cell tumors, extrarenal rhabdoid tumor, malignant mesenchymoma, perivascular epithelioid cell tumors, intimal sarcoma) excluding chondrosarcoma, Ewing tumor/primitive neuroectodermal tumors (PNET); malignant peripheral nerve sheath tumors; undifferentiated soft tissue sarcomas not otherwise specified (NOS); and other sarcoma types (unless listed as excluded).

Patients with the following tumor types were excluded:

Adipocytic sarcoma (all subtypes); all rhabdomyosarcomas that are not alveolar or pleomorphic; chondrosarcoma; osteosarcoma; Ewing tumor/PNET, GIST; dermatofibrosarcoma protuberans; inflammatory myofibroblastic sarcoma; malignant mesothelioma; and mixed mesodermal tumors of the uterus. Note that patients with adipocytic sarcoma were excluded from the pivotal phase III study because in the previous phase II study (VEG20002), the observed effect of pazopanib (PFS at week 12) in adipocytic sarcoma did not reach the required response rate to allow further clinical review. Other main inclusion criteria for the VEG110727 trial were: histologically proven high- or intermediate-grade soft tissue

sarcoma with disease progression within 6 months of metastatic disease therapy or recurrence within 12 months of (neo-)adjuvant therapy.
Ninety-eight percent (98%) of study participants had received doxorubicin, 70% ifosfamide, and 65% at least three or more chemotherapeutic agents before enrollment.
Patients were stratified by baseline WHO general status (WHO Performance Status [PS] 0 or 1) and number of prior lines of systemic therapy for advanced disease (0 or 1 versus 2+). In each treatment group, there was a slightly higher percentage of patients with more than 2 prior lines of systemic therapy for advanced disease (58% and 55% in the placebo and pazopanib treatment arms, respectively) compared with no or 1 prior line of systemic therapy (42% and 45% in the placebo and pazopanib treatment arms, respectively).
The median duration of follow-up of study participants (defined as day of randomization to day of last contact or death) was comparable in both study arms; 9.36 months [range, 0.69 to 23.0 months] in the placebo arm and 10.04 months [range, 0.2 to 24.3 months] in the pazopanib arm.
The primary objective of this study was progression-free survival (PFS by independent radiologic assessment); secondary end points included overall survival (OS), overall response rate, and duration of response.
Investigator assessment showed a similar prolongation of PFS in the pazopanib arm compared to the placebo arm (HR in the overall ITT population: 0.39; 95% CI, 0.30 to 0.52, p<0.001).
No significant difference in OS was observed between the two treatment arms at the time of final analysis after 76% (280/369) of events occurred (HR: 0.87; 95% CI, 0.67; 1.12; p<0.256).

5.1.2 Paclitaxel

Paclitaxel is a widely used cytotoxic drug. It is indicated as monotherapy or combination therapy for advanced or metastatic non-small cell lung cancer, ovarian cancer, and breast cancer, among others. Chemotherapy with paclitaxel is a guideline-based treatment option for patients with advanced and metastatic angiosarcoma.

5.2 Therapy

In this study, an interval of 4 weeks (28 days) of drug use is referred to as a "treatment period" or "treatment cycle."

The investigational drug pazopanib is used as an add-on to guideline-compliant chemotherapy with paclitaxel.

5.2.1 Paclitaxel

Paclitaxel will be purchased through the participating center. Paclitaxel will be given every 28 days on days 1, 8, and 15 as a 2-h intravenous infusion at a dose of 70 mg/m² in combination with pazopanib at a daily oral dose of 800 mg.

Paclitaxel will be provided as a guideline-compliant routine chemotherapy by the responsible pharmacy at the study sites as a commercial product. There is no separate labeling or additional study-related documentation.

5.2.2 Pazopanib

Pazopanib is available as 200 mg and 400 mg white tablets, each containing pazopanib monohydrochloride salt corresponding to the free base of 200 and 400 mg.

We recommend the application of two 400 mg tablets to reach the initial dose of 800 mg. The 200 mg tablets should be used only in case of dose de-escalation.

All patients will receive pazopanib 800 mg orally once daily during study treatment.
- Pazopanib should be taken at least one hour before and two hours after meals. Care must be taken not to crush or divide the tablets, as this will alter bioavailability. The tablets must be taken undivided.
- The time of day when the study medication is taken should be relatively constant.
- If a dose is forgotten, the dose must be taken as soon as possible but at least 12 hours before taking the next dose.
- If the next dose is less than 12 hours away, the patient should skip the missed dose and take the next dose as scheduled.
- If the patient vomits after taking pazopanib, the next dose should be taken as scheduled. The tablet that may have been vomited will not be replaced.

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5.2.3 Storage, issue and return of study drug Pazopanib

The study drug Pazopanib is provided by the company Novartis Pharma GmbH. The study drug is delivered in doses of 68 tablets 400mg each and 34 tablets 200mg each. Pazopanib should not be stored above 25°C for an extended period of time. The investigator will dispense the study medication to the study participants. Study participants will be instructed to bring the study medication and empty doses to each study visit. Continuous intake of study medication will be verified and documented at regularly scheduled study visits. Empty or opened tablet doses will be stored at the center until monitoring. The destruction of the empty or opened tablet doses will be carried out by the responsible monitor directly at the study center after monitoring has been completed.

5.2.4 Duration of treatment

Treatment with paclitaxel is administered over 6 cycles. Premature discontinuation of paclitaxel therapy is necessary in the event of disease progression or intolerable side effects (see section 5.3.2). In particular, in the presence of peripheral polyneuropathy CTC AE grade 2 (or higher), therapy with paclitaxel should be discontinued. Pazopanib therapy is continued if paclitaxel is discontinued after the 6th treatment cycle without progression. Pazopanib therapy is continued until progression or the occurrence of limiting side effects. If intolerable pazopanib-related adverse events occur during combination therapy, paclitaxel therapy will be continued as monotherapy up to and including cycle 6 if no disease progression or intolerable adverse events occur.

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5.2.5 Concomitant medication

All concomitant medications taken during the study must be documented in the patient record. Patients should receive any necessary supportive treatment while on therapy in the study. This includes transfusion of blood and blood products, treatment with antibiotics, erythropoietin, bisphosphonates and adequate pain therapy if indicated.

5.2.5.1 Prophylaxis of hypersensitivity reactions

Paclitaxel contains macrogolglycerol ricinoleate 35 (Ph.Eur.), which may cause allergic reactions. Paclitaxel should be used only under the supervision of a physician experienced in cytostatic therapy. Because severe hypersensitivity reactions may occur, appropriate

equipment must be available for emergency treatment. Patients must have been pretreated with corticosteroids, antihistamines, and H2 antagonists:
-Dexamethasone 4 mg orally approximately 12 hours prior to paclitaxel
-Dexamethasone 12 mg i.v. 30 to 60 minutes before paclitaxel,
-Diphenhydramine 50 mg i.v. or comparable antihistamine 30 to 60 minutes before paclitaxel.
-Cimetidine 300 mg i.v. or ranitidine 50 mg i.v. 30 to 60 minutes before paclitaxel

5.2.5.2 Antiemesis

Antiemetic prophylaxis with granisetron 1 mg i.v. or ondansetron 8 mg i.v. is recommended before any administration of paclitaxel. In case of emesis, proceed according to local institutional guidelines.

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5.2.5.3 Antibiotics

In patients with diarrhea and neutropenia, even in the afebrile situation, empiric use of antibiotics as prophylaxis for sepsis should be strongly considered. The approach should be based on local institutional guidelines or on DGHO guidelines. Of importance, quinolone antibiotics are not recommended because of potential QT time prolongation.

5.2.5.4 Growth factors

Hematopoietic growth factors (e.g., G- or GM-CSF) should be used according to local institutional guidelines for therapy of febrile neutropenia or as primary or secondary prophylaxis for delayed hematologic reconstitution in the previous treatment cycle. Growth factor therapy must be completed at least 48 hours prior to initiation of re-chemotherapy.

5.2.6 Non-permitted medication

Patients must not receive any other antitumor drug therapy during the study treatment. This excludes the administration of biphosphonates mentioned under the conditions of chapter 5.2.5.
Concurrent treatment with potent CYP3A4 (see Appendix B), P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors should be avoided due to the risk of increased exposure to pazopanib. Consideration should be given to switching to other drugs that do not

inhibit CYP3A4, P-gp, or BCRP, or inhibit them only slightly.
Concurrent treatment with CYP3A4 inducers should be avoided because of the risk of decreased pazopanib exposure.
Cases of hyperglycemia have been observed with concomitant treatment with ketoconazole.
Grapefruit juice should be avoided during treatment with pazopanib.

5.2.6.1 CYP3A4-, P-gp-, BCRP-Inhibitors

In vitro studies suggest that oxidative metabolism of pazopanib in human liver microsomes occurs primarily via CYP3A4, and to a lesser extent via CYP1A2 and CYP2C8. Therefore, CYP3A4 inhibitors and inducers may alter the metabolism of pazopanib.

Pazopanib is a substrate for CYP3A4, P-gp, and BCRP. Co-administration of pazopanib (400 mg once daily) with the potent CYP3A4 and P-gp inhibitor ketoconazole (400 mg once daily) for 5 consecutive days resulted in mean increases in AUC(0 - 24) and Cmax of pazopanib of 66% and 45%, respectively, relative to pazopanib alone (400 mg once daily for 7 days). A comparison of the pharmacokinetic parameters Cmax (range of mean values 27.5 to 58.1 µg/ml) and AUC(0 - 24) (range of mean values 48.7 to 1040 µg*h/ml) after administration of 800 mg pazopanib alone and after administration of 400 mg pazopanib with 400 mg ketoconazole (mean Cmax 59.2 µg/ml, mean AUC(0 - 24) 1300 µg*h/ml) indicates that in the presence of a strong CYP3A4 and P-gp inhibitor, dose reduction of pazopanib to 400 mg once daily results in systemic exposure similar to that after administration of 800 mg pazopanib once daily alone in the majority of patients. However, systemic exposure to pazopanib may be higher in some patients than after 800 mg of pazopanib alone. Co-administration of pazopanib with other potent CYP3A4 family inhibitors (e.g., itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice contains a CYP-3A4 inhibitor and may likewise increase plasma pazopanib concentrations.
Administration of 1,500 mg lapatinib (a substrate and weak inhibitor of CYP3A4and P-gp and a strong inhibitor of BCRP) with 800 mg pazopanib resulted in an increase in mean AUC(0-24) and Cmax values of approximately 50% to 60% compared with 800 mg pazopanib alone. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased pazopanib exposure. Concomitant administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor such as lapatinib may increase plasma pazopanib concentrations. Similarly, concomitant administration of pazopanib with potent P-gp or BCRP inhibitors may alter pazopanib exposure and distribution, including distribution to the central nervous system (CNS). Combinations with

potent P-gp or BCRP inhibitors should be avoided; alternatively, the choice of a concomitant medication with little or no P-gp or BCRP inhibitory potential is recommended.

Drugs that inhibit CYP3A4 may result in increased pazopanib plasma concentrations. **Concomitant use of potent CYP3A4 inhibitors is prohibited from 14 days prior to initiation of study medication until the end of study treatment**, so selection of alternative concomitant medications with only low or no inhibition of CYP3A4 is recommended. If no medically acceptable alternative to a potent CYP3A4 inhibitor is available, the pazopanib dose should be reduced to 400 mg daily when administered concomitantly. In such cases, special attention should be paid to side effects. If potentially drug-related adverse events occur, further dose reduction should be considered.

Strong CYP3A4 inhibitors are besides others:

- Antibiotics: Clarithromycin, telithromycin, troleandomycin.
- HIV protease inhibitors: ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir
- Antifungals: Itraconazole, ketoconazole, vorikonazole, fluconazole
- antidepressants: nefazodone
- Third-generation antihistamines: Terfenadine
- Food: grapefruit juice

5.2.6.2 CYP3A4-, P-gp-, BCRP-Inducers

CYP3A4 inducers may decrease plasma pazopanib concentrations. It is recommended to choose alternative concomitant drugs with only little or no induction of CYP3A4, explicitly excluding from this recommendation the prophylactic administration of steroids prior to the application of paclitaxel mentioned in the protocol under "Prophylaxis of Hypersensitivity Reactions".

CYP3A4-Inducers are bisides others:

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40mg), prednisone (>10mg), methylprednisolone (>8mg), dexamethasone (>1.5mg).
- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, oxcarbazepine.
- HIV virustatics: Efavirenz, Nevirapine
- Others: modafinil, pioglitazone, troglitazone

- Medicinal plants/natural products: Amber

CYP3A4 inducers such as rifampicin may lead to a decrease in plasma pazopanib concentrations. Concomitant administration of pazopanib with potent P-gp or BCRP inducers may alter pazopanib exposure and distribution, including distribution to the CNS. The choice of an alternative concomitant medication with little or no enzyme- or transporter-inducing potential is recommended

5.2.6.3 Effect of Pazoplanib on other medication

In vitro human liver microsome studies demonstrated that pazopanib inhibits CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 enzymes was demonstrated in a PXR assay in human cells in vitro. Clinical pharmacology studies with once-daily administration of 800 mg pazopanib demonstrate that pazopanib has no clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 model substrate), warfarin (CYP2C9 model substrate), or omeprazole (CYP2C19 model substrate) in cancer patients.

Pazopanib administration resulted in an increase in mean AUC and Cmax values of midazolam (CYP3A4 model substrate) of approximately 30% and an increase in the dextromethorphan/dextrophan ratio of 33% to 64% in urine after oral administration of dextromethorphan (CYP2D6 model substrate). Concomitant administration of 800 mg pazopanib once daily and 80mg/m² paclitaxel (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase in AUC and Cmax values of paclitaxel of 25% and 31%, respectively.

Based on IC50 values in vitro and Cmax values in plasma in vivo, the pazopanib metabolites GSK1268992 and GSK1268997 could contribute to the net inhibitory effect of pazopanib on BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Caution is required when pazopanib is co-administered with other oral BCRP and P-gp substrates. In vitro, pazopanib inhibited the human organic anion transport polypeptide (OATP1B1). An influence of pazopanib on the pharmacokinetics of OATP1B1 substrates (e.g., statins) cannot be excluded.

Pazopanib is an inhibitor of uridine diphospho-glucuronosyl transferase enzyme 1A1 (UGT1A1) in vitro. The active metabolite of irinotecan, SN-38, is a substrate for OATP1B1 and UGT1A1. Co-administration of 400 mg pazopanib once daily with 250 mg/m² cetuximab and 150 mg/m² irinotecan resulted in an approximately 20% increase in the systemic exposure of SN-38. Pazopanib may have a greater effect on the disposition of SN-38 relative to subjects

with the wild-type allele in subjects with the UGT1A1*28 polymorphism. However, the UGT1A1 genotype is not always predictive of the effect of pazopanib on SN-38 disposition. Caution should be exercised when pazopanib is coadministered with UGT1A1 substrates.

Simultaneous use of pazopanib and certain drugs (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with CAUTION because of the potential for alteration of the pharmacologic effects of these drugs or the increased risk for serious or life-threatening adverse reactions associated with these drugs (see below) due to secondary inhibition of CYP enzymes by pazopanib.
It should be added that although the potential for drug-drug interaction with such drugs decreases after pazopanib is discontinued, a fundamental potential for such interactions initially remains because of the long half-life of pazopanib (mean 30.9 hours). Therefore, CAUTION should be exercised for at least 7 days up to 15 days after the last dose of pazopanib when such drugs are used.

These drugs include besides others:
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potentially increased risk of developing ergot toxicity, which includes severe vasospasm and can lead to peripheral but also cerebral ischemia).
- Neuroleptics: Pimozide (increased risk of QT time prolongation, ventricular arrhythmia, and sudden cardiac death)
- Antiarrhythmics and other drugs that cause QT time prolongation: Bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidines, propafenone
- Immunomodulators: cyclosporine, tacrolimus, sirolimus (potentially increased risk of nephro- and neurotoxicity)
- Others: quetiapine, risperidone, clozapine, atomoxetine

5.2.6.4 Effect of concomitant use of Pazopanib and Simvastatin

Concomitant use of pazopanib and simvastatin increases the incidence of ALAT (GPT) elevations. Results of a meta-analysis of pooled data from clinical trials with pazopanib showed that ALAT (GPT) levels >3 × ULN were reported in 126/895 (14%) of patients not taking statins compared to 11/41 (27%) of patients taking concomitant simvastatin (p=0.038). If a patient receiving concomitant simvastatin develops ALAT (GPT) elevations, pazopanib dosing guidelines should be followed and simvastatin should be discontinued. In addition, concomitant

use of pazopanib and other statins should be used with caution, as insufficient data are currently available to estimate their impact on ALAT (GPT) levels. It cannot be excluded that pazopanib affects the pharmacokinetics of other statins (e.g., atorvastatin, fluvastatin, pravastatin, rosuvastatin).

5.2.6.5 Influence of food on the pharmacokinetics of Pazopanib

Administration of pazopanib with high or low fat meals resulted in an approximately 2-fold increase in AUC and Cmax values. Therefore, pazopanib should be taken either at least 1 hour before or 2 hours after a meal

5.2.6.6 Drugs that raise the pH of the stomach

Co-administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and Cmax). Co-administration of pazopanib with drugs that raise gastric pH should be avoided. If concomitant use of a proton pump inhibitor (PPI) is medically necessary, it is recommended that the pazopanib dose be taken on an empty stomach once daily in the evening along with the PPI.
If, in addition to the prophylactic administration of antihistamines prior to paclitaxel mentioned in the protocol under "Prophylaxis of Hypersensitivity Reactions," concomitant use of an H2 receptor antagonist is medically necessary, it is recommended that the pazopanib dose be taken on an empty stomach once daily at least 2 hours before or 10 hours after the H2 receptor antagonist. Pazopanib should be taken at least 1 hour before or 2 hours after the administration of short-acting antacids

5.2.7 Special recommendations regarding anticoagulation

Drug interaction studies in cancer patients showed that pazopanib has no effect on the metabolism of s-warfarin. Nevertheless, hemorrhagic events have been documented in clinical trials with pazopanib. Therefore, caution should be exercised when prescribing pazopanib in patients at increased risk of bleeding or patients receiving concurrent anticoagulation (e.g., warfarin or its derivatives, low-molecular-weight heparin, unfractionated heparin). Patients receiving simultaneous anticoagulation should be monitored regularly for relevant coagulation parameters and for clinical indications of bleeding.

5.2.8 Special recommendations regarding potentially hypoglycemia-inducing therapies including insulin

Drug interaction studies in cancer patients found that there are no clinically relevant pharmacokinetic interactions between pazopanib and blood glucose-lowering therapies. A transient decrease in serum glucose levels (mainly grade 1 and 2, rarely grade 3) was observed within clinical trials with pazopanib. In addition, a decrease in blood glucose was recently reported in patients treated with the tyrosine kinase inhibitor sunitinib ([38] British Journal of Cancer 2008: 99,1380). Such developments may require dose adjustment of antihyperglycemic and/or insulin therapy. Patients should be instructed to document their symptoms of hypoglycemia (e.g., dizziness, visual disturbances, palpitations, sweating). Serum glucose monitoring will be performed during treatment with pazopanib according to protocol and clinical indication.

5.3 Dose- and application modifications

Missed drug doses will not be made up. To allow for practical ease of administration, upward or downward rounding of the paclitaxel dose is acceptable (±10%).
Application of premedication before paclitaxel occurs at least 2 h after or 10 h before pazopanib due to drug interactions.
Adverse reactions are graded according to CTCAE, version 4.0.
If side effects occur that, in the judgment of the treating investigator, are unlikely to result in serious or life-threatening events or delay or interrupt therapy (e.g., alopecia, taste changes, etc.), treatment will be continued at the same dose without reduction or interruption

Dose adjustments of the drugs or discontinuation of treatment will occur depending on the observed side effects as indicated below.
Therapy interruptions or dose reductions of investigational drugs may be necessary due to the following potential drug-associated adverse events: Bone marrow suppression, arterial hypertension, proteinuria, hepatotoxicity, bleeding, vascular thrombosis, thrombocytopenia/neutropenia, prolongation of QTc time, and other adverse reactions reported in response to treatment with pazopanib and/or paclitaxel.

At each visit to the study site during treatment, patients should first be questioned, examined, and evaluated for the occurrence of adverse events and laboratory value changes.
Specific recommendations for the management of these potential adverse events, as well as guidelines for therapy interruptions, dose adjustments, or discontinuation of study treatment, are provided below.
If therapy with pazopanib must be interrupted due to adverse events according to guidelines below, therapy with paclitaxel must also be interrupted during this time.
If a patient's treatment is interrupted for more than 14 days due to side effects or for other reasons (unplanned travel or vacation, lack of transportation, etc.), the investigator must contact the medical coordinator to discuss and have the specific patient circumstances reviewed prior to resuming treatment. Interruption of therapy for > 28 days will result in discontinuation of therapy and the pat. will enter the follow-up phase.
If the dose of pazopanib or paclitaxel has been reduced due to side effects, re-escalation is possible if the patient's condition is stable and he/she has fully recovered from the side effects at the reduced dose.

5.3.1 Dose- and application modification of Pazopanib

Permitted dose reduction of Pazopanib:

-If certain side effects occur (see below), two dose reductions are permitted in stages: Initial reduction to 600 mg and then to 400 mg as needed. If the side effects persist with the application of 400 mg, further titration to 200 mg may be considered. However, the investigator should discuss titration to 200 mg with the medical coordinator prior to dose adjustment.
- After toxicity subsides, stepwise re-escalation can be made under monitoring every 10-14 days by 200 mg each up to 800 mg provided toxicity does not recur or increase.

Pazopanib dose reduction should be discussed with the medical coordinator if the patient is benefiting from therapy and recurrent adverse events occur with paclitaxel despite dose reduction to 40mg/m² per week at last and secondary prophylaxis with G-CSF (see below).

If you need further advice or clarification, please contact the medical coordinator via e-mail: studien@gisg.de

Table 2: Adverse reactions and resulting dose modifications of Pazopannib

Adverse reaction and description	**Dose modification**
Hypertonus	
(A) Asymptomatic and persistant blood pressure: - Systolic ≥ 140 und <170 mmHg, - Diastolic ≥ 90 und ≤ 110 mmHg, - Or if there is a clinically significant increase in diastolic blood pressure of 20 mmHg (but still below 110 mmHg overall).	1. continuation of the study treatment at the current dose 2. adjustment of existing or application of new antihypertensive medication. 3. discontinuation of antihypertensive medication for two weeks to regulate blood pressure. If blood pressure is not adjustable within two weeks, this will result in the procedure as in (B).
(B) Asymptomatic systolic blood pressure ≥ 170 mmHg - or diastolic blood pressure ≥ 110 mmHg - or failure of blood pressure control within two weeks as in (A).	1. consideration of dose reduction or interruption of study treatment 2. adjustment of existing or application of new antihypertensive medication 3. discontinuation of antihypertensive medication for two weeks for blood pressure regulation 4. resumption of study treatment with lower dose after blood pressure adjustment
(C) Symptomatic hypertension or recurrent systolic blood pressure > 170 mmHg, or diastolic blood pressure > 110 mmHg, despite modification of antihypertensive medication.	1. interruption of pazopanib intake 2. adjustment of existing antihypertensive medication or application of new antihypertensive medication 3. discontinuation of antihypertensive medication for two weeks for blood pressure control. Recommend referral to specialist for evaluation and further treatment. 4. once blood pressure is well controlled, resume pazopanib intake reduced by 200 mg dose.

(D) Refractory arterial hypertension without response to above interventions.	Discontinuation of pazopanib intake and follow-up as per protocol.
Proteinurie	
UPC< 3	Fortsetzung der Studienbehandlung in der derzeitigen Dosis; Überwachung nach klinischer Indikation
UPC ≥ 3 rep. 24h-Urin Protein ≥ 3g	1. interruption of pazopanib administration. 2. weekly UPC or 24h urine protein measurement: 3. UPC < 3 or 24h urine protein measurement < 3g Restart treatment with dose reduced by 200 mg. Recurrence of UPC ≥ 3 or 24h urine protein measurement ≥ 3g. ➔ repetition of 1. and 2, 4.Recurrence of UPC ≥ 3 or 24h urine protein ≥ 3g despite repeated dose reduction. ➔Discontinuation of Pazopanib intake and „Follow-Up“) as per protocol.
Hemmorhage/ bleedings/ Coaggulopathy	
Grade 1	If hemoptysis occurs, discontinue pazopanib and consider whether continued therapy with pazopanib is appropriate. If other grade 1 bleeding occurs, continue study treatment at current dose; monitor patient as clinically indicated.
Grade 2	1. If pulmonary or gastrointestinal bleeding (excluding hemorrhoidal bleeding) occurs, pazopanib use

	should be discontinued and follow-up ("follow up") should follow protocol. Otherwise, discontinue pazopanib until bleeding reaches < grade 1. 2. resumption of study medication at reduced dose if necessary with appropriate monitoring as clinically indicated.
Grade 3 or 4, or recurrent Grade 2 after dose reduction or pause of study medication oder	1. discontinuation of pazopanib and follow-up according to protocol. If the adverse event is not clearly a clinical consequence associated with the study medication, the medical coordinator may be contacted for discussion of possible continuation of the study medication. If agreement is reached, the patient should be treated at a reduced dose.
Venous Thrombosis (DVT, PE)	
Grade 2	Continuation of study treatment at current dose; monitoring as clinically indicated.
Grade 3	1. interruption of the study medication 2. therapy of the patient with low molecular weight heparin Note: Warfarin is allowed under INR control. 3. continuation of study medication at the current dose during the period of full-dose anticoagulation if the following criteria are met:

	- Patient must have been treated with low molecular weight heparin for at least one week. - Neither Grade 3 nor Grade 4 bleeding has occurred while on anticoagulation. - The patient is monitored during anticoagulation and after continuation of study medication according to clinical indication.
Grade 4	Discontinuation of pazopanib use and follow-up as per protocol.
Arterielle Thrombose/ Ischämie	
Every grade	Discontinuation of pazopanib use and follow-up as per protocol.
Thrombocytopenia/ Neutropenia	
Grade 1 or 2	Continuation of study treatment at current dose; monitoring as clinically indicated
Grade 3 or 4	1. Discontinuation of therapy until reduction to Grade 2 toxicity. 2. resumption of study medication at 200 mg reduced dose with appropriate monitoring as clinically indicated. 3. if there is no improvement to at least one grade 2 toxicity or recurrent grade 3 and 4 neutropenia/thrombocytopenia occurs, this will result in discontinuation of pazopanib and follow-up ("follow up") according to protocol
Prolonged QTc Intervall	

QTc * 480 - <500 msec	Continuation of study treatment at current dose; monitoring as clinically indicated
QTc * ≥500 msec	Discontinuation of study medication and follow-up according to protocol
* Adjustment by using Bazett's formula	
Hepatotoxicity	
In general, many patients take multiple medications simultaneously. It is critical that a careful evaluation of all of the patient's medications be performed. Potentially hepatotoxic medications should be paused if necessary and replaced with non-hepatotoxic equivalents if appropriate	
ALT/ AST ≤3x ULN	Continuation of study treatment at current dose; monitoring as clinically indicated by liver function tests (LFTs*).
ALT >3x ULN to ≤8x ULN **without** bilirubin elevation (defined as total bilirubin <2x ULN or direct bilirubin of 35%) and without occurrence of allergic symptoms (e.g., fever, rash).	1. continuation of study medication at the current dose. 2. monitor patient closely for any clinical signs and symptoms; perform weekly or more frequent liver function tests if clinically indicated until ALT/ AST have dropped to Grade 1
ALT >8x ULN w**ithout** a bilirubin elevation (defined as total bilirubin <2x ULN or direct bilirubin 35%) and **without** the occurrence of allergic symptoms (e.g., fever, rash)	1. discontinuation of study medication and follow-up according to study protocol. 2. report the event as SAE to the KKS Heidelberg within 24 hours after the values become known Every reasonable attempt should be made to have the patient present to the clinic within 24 to 72 hours to check the liver values. - Imaging of the liver and possibly further clinically necessary examinations.

	3. closely monitor the patient for any clinical signs and symptoms; perform weekly or more frequently if clinically indicated. Liver function tests until ALT/ AST have dropped to grade 1.
ALT >3x ULN w**ith** concomitant elevation of bilirubin (defined as total bilirubin ≥2x ULN or direct bilirubin >35%) or **with** presence of allergic symptoms (e.g., fever, rash	1. Immediate discontinuation of study medication. Report the event as an SAE to the Heidelberg PPS within 24 hours of becoming aware of the values Every reasonable attempt should be made to have the patient present to the clinic within 24 hours to check the liver values and to perform any other necessary investigations. Consultation of a gastroenterologist/hepatologist, performance of the following investigations to exclude possible factors involved: - Determination of eosinophils in the differential BB. - Viral serology for hepatitis A, B, C and E, CMV, EBV - Antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti-smooth muscle antibodies - Serum creatinine phosphokinase to rule out possible muscle injury Liver imaging Possibly toxicological blood tests to exclude drug or chemical causes 2. close monitoring of the patient for clinical signs and symptoms. Documenting the onset or worsening of clinical symptoms of hepatitis or allergic reaction, such as fatigue,

	nausea, vomiting, right upper abdominal quadrant pain or tenderness, febrile exanthema, or eosinophilia. Perform weekly or if clinically indicated even more frequent LFTs until a drop to grade 1.
Isolated total bilirubin elevation without concomitant increase in ALT (defined as ALT <3x ULN).	1. isolated hyperbilirubinemia (without increase in ALT or other signs/symptoms of liver injury) does not require dose modification. Study drug inhibits UGT1A1 and OATP1B1, so this may result in an increase in indirect (unconjugated) bilirubin without liver injury. 2. If bilirubin is >1.5x ULN without ALT elevation, fractionation of bilirubin is recommended. Study medication can be continued at the same dosage if bilirubin is predominantly unconjugated. If the direct bilirubin is >35%, further investigation should be done regarding the cause of the cholestasis.
* LFTs include AST, ALT, AP, GGT, total bilirubin.	

Hand-Fuß Syndrom (PPE)	
Grade 1 Minimal skin changes or painless dermatitis (erythema, edema, hyper-keratosis)	Continuation of study treatment at the current dose
Grade 2 Painful skin changes that limit daily activity (ADL's) (skin detachment, blisters, edema, bleeding, hyperkeratosis)	1. interruption of pazopanib intake 2. clinically necessary symptomatic therapy 3. if regression occurs to ≤Grade 1, ➔ resume study medication at reduced dose of 400mg daily. 4. if regression occurs, dose reduction to 200mg daily should be considered
Grade 3, severe painful skin lesions with patient's limitations in daily self-care (ADL's)	Discontinuation of pazopanib intake and follow-up ("follow up") as per protocol.

Other clinically relevant adverse reactions	
Grade 1	Fortsetzung der Studienbehandlung in der aktuellen Dosis. Weitere Kontrollen nach klinischer Notwendigkeit.
Grade 2 or Grade 3, if the adverse reaction is considered clinically relevant and there is a probable association with pazopanbib use	1. Discontinuation of pazopanib until the adverse event has resolved to grade 1. 2. resumption of study medication at 200mg reduced dose with appropriate monitoring as clinically indicated

Recurrence of grade 2 or grade 3 if the adverse reaction is considered clinically relevant	Discontinuation of pazopanib use and follow-up as per protocol.
Grade 4	Discontinuation of pazopanib use and follow-up as per protocol.

5.3.2 Dosis- und Applikationsmodifikation von Paclitaxel

Occurrence of polyneuropathy:

If grade 1 polyneuropathy newly occurs or worsens during paclitaxel therapy, the paclitaxel dose should be reduced to 60mg/m². Otherwise, therapy is continued unchanged.

If polyneuropathy ≥ Grade 2 occurs, therapy with paclitaxel will be discontinued and will not be resumed even if the polyneuropathy resolves. In this case, therapy with pazopanib may be continued at an unchanged dose as part of the study.

At 4 weeks after discontinuation of therapy with paclitaxel due to polyneuropathy, a telephone follow-up will be conducted to follow up the AE.Wenn im Rahmen der Paclitaxeltherapie eine Polyneuropathie Grad 1 neu auftritt oder sich verschlechtert, soll die Paclitaxel-Dosis auf 60mg/m² reduziert werden. Ansonsten wird die Therapie unverändert fortgeführt.

Permitted dose reductions of paclitaxel for other adverse reactions:

For other adverse reactions (not listed below), three dose reductions are allowed in a stepwise manner: Initial reduction to paclitaxel 60mg/m² and then as needed to initially paclitaxel 50mg/m² or finally 40mg/m².

No further reduction in medication dose is permitted in the event of persistent toxicity despite a dose reduction to paclitaxel 40mg/m². The medical coordinator should be contacted in such a case for further discussion of the procedure. If the patient benefits from the therapy, a dose reduction of pazopanib can be discussed. Otherwise, termination of study medication and follow-up is recommended according to protocol

Table 3: Adverse reactions and resulting dose reductions of Paclitaxel

Thrombocytopenia/ Neutropenia	
Grade 1	Continuation of study treatment at current dose; monitoring as clinically indicated

Grade 2	Continuation of study treatment at current dose; monitor as clinically indicated. For primary prophylaxis of neutropenia, consider the use of G-CSF
Grade 3 or 4	1. pause study medication until decline to Grade 2 toxicity. (If the period of pause exceeds two weeks, contact the medical coordinator to arrange further action). 2. resumption of study medication at reduced dose. 3. in case of neutropenia: primary prophylaxis using G-CSF.
Recurrent grade 3/4 events despite dose reduction to most recently paclitaxel 40mg/m² per week and secondary prophylaxis with G-CSF.	Discontinuation of study medication and follow-up according to protocol.

Note: No dose reduction is indicated in the presence of anemia unless the anemia is due to bleeding.

6 Assessments and follow-up

6.1 Assessments before study enrollment

For patients who have been informed about the study and have signed the informed consent form, the following examinations should be performed as part of the screening process or before the start of study therapy:

- Taking a detailed medical history, which includes the complete oncological history. In addition, all relevant medications taken up to 2 weeks prior to study inclusion will be recorded.

- Clinical examination including weight, height, check of vital signs (blood pressure, heart rate, body temperature) and ECOG performance status.

- Medical history (complaints or remaining side effects of previous therapies, signs and symptoms of cancer).

- Blood count and differential, clinical chemistry, thyroid levels, and coagulation (see Table 4).

Tabelle 4: Laboruntersuchungen zum Screening

Hematological assessments	**Clinical chemistry**
Hemoglobin, hematocrit, erythrocytes, leukocytes, platelets, differential BB incl. lymphocytes and neutrophils	Sodium, potassium, calcium, ALAT, ASAT, total bilirubin, alkaline phosphatase, creatinine, glucose, LDH
Coaggulation	**Thyroid values**
Prothrombin time (PT) or INR, partial thromboplastin time (PTT)	TSH

Note: When pazopanib and warfarin (or its derivatives) are administered simultaneously, INR should be monitored within the first three to five days after initiation of therapy, when the dose is escalated or de-escalated, when pazopanib administration is interrupted, and then at least weekly until INR is stable. Adjustment of the dose of warfarin (or its derivatives) may be needed to ensure adequate anticoagulation.

- Urinalysis, protein/creatinine ratio (UPC)
- Serum pregnancy test (for women of childbearing potential).
- Cardiac function tests:
LVEF (echocardiography),
12-lead ECG, QTc time measurement
- Radiological examinations **not older than 28 days** before the start of study medication:
All localizations/lesions of tumor disease must be detected by MRI or CT and documented as a basis for measurement. A CT or MRI examination of the thorax and abdomen is mandatory.

At least one measurable lesion must be identified as a target lesion and measured. These examinations must be performed within 28 days prior to initiation of study therapy.

- If skin manifestations of angiosarcoma are detectable and measurable, these may be used as target lesions. Should multiple skin manifestations be measurable, a maximum of five should be classified as target lesions. Skin lesions can be documented photographically as target or non-target lesions, making sure that the same camera is always used. The photographic documentation is carried out by means of a panoramic image and close-up images corresponding to the number of target lesions; in this case, the size (largest diameter in each case) is recorded by means of a millimeter ruler that is also imaged. The baseline measurement of a target lesion must be ≥ 1cm. For raised skin lesions, the size may need to be measured using a caliper. Optional measurement of skin lesions is also available in the dermatology department. The photographic documentation must be printed out and included in the patient's file with the date of recording and the patient's name.

6.2 Assessments during treatment

In this study, a treatment period or cycle is defined as 28 days.

- Controls that occur every 7 days or less have a control window of +/-3 days.
- Controls that occur every 3 to 8 weeks have a control window of +/-7 days.
- Controls that are performed every 12 weeks have a control window of +/-14 days.

6.2.1 During treamtenmt with Paclitaxel on day 1, day 8 und day 15 in every cycle

The following parameters should be determined or examinations should be performed:

- ECOG performance status, temperature, blood pressure, heart rate and body weight.
- Physical examination
- Symptoms of the cancer, therapy side effects, adverse events
- Concomitant medication
- Complete hematology and clinical chemistry (see Table 4).
- INR/ PTT
- Urine status
- Beta-HCG every 8 weeks in childbearing women

6.2.2 Additonal aassessments at beginnung of every cycle in the first 12 weeks

- 12-lead ECG, QTc time measurement, then every 8 weeks

6.2.3 Every 8 weeks or when clinically indicated every 4 weeks, especially during monotherapy with pazopanib.

.The following parameters should be determined or examinations should be performed:

- ECOG performance status, temperature, blood pressure, heart rate and body weight.
- Physical examination
- Symptoms of the cancer, therapy side effects, adverse events
- Concomitant medication
- Complete hematology and clinical chemistry (see Table 4).
- INR/ PTT
- TSH
- Urine status
- Beta-HCG in childbearing women
- 12-lead ECG and QTc time measurement
- Radiological examinations of thorax, abdomen and all tumor localizations (at least CT or MRI of thorax and abdomen).
- For measurable skin manifestations classified as target lesions: Photographic documentation via a panoramic image and close-up images corresponding to the number of target lesions, here the size (largest diameter in each case) is recorded using a co-imaged millimeter ruler. In the case of raised skin lesions, the size may have to be measured with a caliper. Optionally, the measurement of the skin lesions is also possible in the dermatology department. The photographic documentation must be printed out and included in the patient's file with the date the image was taken and the patient's name.

6.3 Behandlungsende/ Sicherheitsnachbeobachtung („Safety Follow-Up“)

he end-of-treatment examination appointment will take place 30 days after the last study medication.

The following parameters should be determined or examinations should be performed:

- ECOG- performance status, blood pressure, heart rate and body weight.
- Physical examination
- Symptoms of cancer, side effects of therapy, adverse events
- Concomitant medication
- Complete hematology and clinical chemistry (see table)
- INR/ PTT
- TSH
- Urine status
- Beta-HCG, if indicated at inclusion

- 12-lead ECG and QTc time measurement
- LVEF, if clinically indicated

Documentation of disease status if these examinations were not performed within four weeks prior to end of treatment:

- Radiological examinations of thorax, abdomen, and all tumor locations (at least CT or MRI of thorax and abdomen).
- For measurable skin manifestations classified as target lesions: Photographic documentation via a panoramic image and close-up images corresponding to the number of target lesions, here the size (largest diameter in each case) is recorded using a co-imaged millimeter ruler. In the case of raised skin lesions, the size may have to be measured with a caliper. Optionally, the measurement of the skin lesions is also possible in the dermatology department. The photographic documentation must be printed out and included in the patient's file together with the date of recording and the patient's name.

6.4 Follow-Up

After the end of treatment, all the patients are followed up every 12 weeks (+/-14 days) regardless of the reason for the end of treatment, i.e. also in case of premature of treatment, e.g. due to progression or at the patient's request, until the last patient has also reached a follow-up period of 24 weeks.

Documentation of disease status is done every 12 weeks (+/- 14 days) until progression:

- By radiological examinations of thorax, abdomen and all tumor loci¬sations (at least CT or MRI of thorax and abdomen).
- For measurable skin manifestations classified as target lesions: Photographic documentation via a panoramic image and close-up images corresponding to the number of target lesions; the size (largest diameter in each case) is recorded using a millimeter ruler that is also imaged. In the case of raised skin lesions, the size may have to be measured with a caliper. Optionally, the measurement of the skin lesions is also possible in the dermatology department. The photographic documentation must be printed out and included in the patient's file together with the date of recording and the patient's name.

In addition, further tumor therapies performed after the end of treatment are documented.

6.5 Exclusion of patients from the study or termination of study participation

Patients may be excluded from the study by the investigator or may terminate their study participation prematurely due to, for example, the following:

- Withdrawal of informed consent for study participation by the patient. All data collected up to this point will be included in the analysis.
- Termination of the study at the study site
- Termination of the overall study by the sponsor or a regulatory authority

Patients who withdraw consent to the study prior to receiving study medication will be withdrawn from the study and will not require further safety monitoring. These patients will be replaced.

Patients who withdraw consent to study participation after they have already received study medication will be followed up for at least 30 days. The aim of this follow-up is to record the adverse events

6.6 Premature termination of clinical study

The clinical trial may be terminated at any time by the sponsor for medical/safety reasons, e.g. changes in the benefit-risk assessment due to new findings, or administrative reasons, e.g. lack of recruitment. The sponsor may also declare the clinical trial at a participating trial site terminated, e.g. in case of insufficient recruitment or insufficient quality of the data. Furthermore, the clinical trial at an investigational site may also be terminated prematurely due to a decision by the investigator

7 Adverse events

7.1 Definitions

7.1.1 Adverse events

According to GCP, an Adverse Event (AE) is defined as follows: Any adverse medical event that occurs in a patient or participant in a clinical trial after administration of a drug and that is not necessarily causally related to that treatment. An AE may therefore be any adverse and unintended reaction (including an abnormal laboratory finding), symptom, or condition transiently associated with the administration of an investigational drug, whether or not related to the investigational drug.

An AE may involve the following:

- New symptoms/complaints/sensitivity disorders,

- new concomitant diagnosis,
- change in laboratory parameters,
- intercurrent illnesses and accidents of any kind,
- Worsening of symptoms/diseases already existing before the start of the clinical trial,
- Recurrence of disease,
- Increase in frequency or intensity of episodic illness.

A pre-existing disease/symptom does not constitute a UE unless there has been an unfavorable change in its intensity, frequency, or quality. Such a change must be documented by the responsible investigator.

In the context of surgical procedures, the circumstance necessitating the surgery must be documented as a UE and not the surgical procedure itself. Surgical interventions already planned before the start of the study and their cause do not constitute a UE.

Adverse events are classified as "serious" and "non-serious"

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7.1.2 Serious adverse events

A serious adverse event (SAE) is an AE that occurs regardless of the dosage of the investigational product according to the following criteria:

- Leads to death,
- Is acutely life-threatening (i.e., the study participant is in acute danger of death at the time of the UE),
- necessitates or prolongs hospitalization,
- results in permanent or significant disability,
- Is associated with a congenital anomaly/birth defect; or
- is otherwise medically relevant.

7.1.3 Schwangerschaft

If a patient becomes pregnant or suspected of becoming pregnant during the clinical trial, or if the partner of a patient participating in the clinical trial becomes pregnant, the pregnancy must be reported to the sponsor immediately, within 24 hours, as if it was an SAE.

7.1.4 Expected and unexpected events

An unexpected adverse event is an event that is inconsistent in nature or severity with current information (protocol or SmPC) about the investigational product.

Reports that provide significant information regarding the specificity or severity of a known adverse reaction (protocol or SmPC) are to be classified as `expected

7.1.5 suspected unexpected serious adverse reaction (SUSAR)

A serious adverse event for which the investigational product cannot be excluded as the causative agent (serious adverse drug reaction) and which, in addition, is inconsistent in nature or severity with the current information on the investigational product (i.e., is unexpected) is termed an "unexpected serious adverse drug reaction" or SUSAR ("suspected unexpected serious adverse reaction").
If either the investigator who first reported the SAE or the second evaluator identifies the SAE as possibly related and the SAE is unexpected, it is considered a SUSAR.

7.1.6 Study specific SAEs

The following events are also considered serious adverse events (SUE) for the purposes of this study:
- ALT >3.0x ULN with concomitant elevation of bilirubin (defined as total bilirubin ≥2.0x ULN, with direct bilirubin >35%) or with symptoms of a hypersensitivity reaction (e.g., fever, rash), in this case, fractionation of bilirubin should be performed if a test is available.
- ALT >8.0x ULN without elevation of bilirubin (defined as total bilirubin <2.0x ULN or direct bilirubin ≤35%) and without symptoms of a hypersensitivity reaction (e.g., fever, rash), again, fractionation of bilirubin should be performed if a test is available.

7.1.7 Exceptions for SAE reporting

The following events do not require SUE reporting:
- Hospitalizations that were planned prior to informed consent for study participation and do not last longer than expected.
- Hospitalizations that are solely due to progression of the tumor disease (progressive disease).

7.2 Observation period and documentation

All AEs reported by the study participant or observed by the investigator are recorded during the clinical trial and must be documented on the designated pages in the CRF. AEs must also be recorded in the patient's medical record. In the present clinical trial, all UEs occurring from the time the study participant provides informed consent until 30 days after completion of study therapy (visit: end of treatment, safety follow-up) will be documented in the CRF. Regardless of whether a relationship with the study medication is suspected or not, all participants with UEs will be observed until the UEs resolve or until normalization of altered laboratory parameters or until a stable condition is reached.

The assessment of the intensity of a UE is based on a 5-level scale defined in the CTCAE version 4.0:

Grade 1: mild
Grade 2: moderate
Grade 3: severe
Grade 4: life-threatening or with permanent damage
Grade 5: fatal

All AEs not listed in the CTCAE Version 4.0 are classified in terms of intensity using the definitions presented below.

Mild: An event that results in mild impairment, i.e., activities of daily living can be performed without restriction.

Moderate/medium: An event that leads to a moderate impairment, i.e. the activities of daily living are impaired.

Severe: An event that leads to a significant impairment, i.e. the performance of the activities of daily living is not possible.

The investigator will assess the possible relationship to the investigational drug for each AE:

Certain: There is a reasonable assumption that the event is due to the investigational drug. There is a plausible temporal relationship and an alternative cause is unlikely.

Probable: There is a reasonable belief that the event is due to the investigational product. There is a temporal relationship, and a known response pattern occurs, but a possible alternative cause is present.

Possible: There is only a remote possibility that the adverse event and the investigational drug are related. Other conditions including concomitant disease, progression or disease expression, or response to concomitant medication are likely to explain the reported adverse event.

Unlikely: There is little evidence of a causal relationship. A reasonable temporal relationship is lacking. The adverse event can be adequately explained by other factors (e.g., patient's clinical condition; underlying disease; concomitant therapy).

No relationship: there is no temporal relationship to the investigational product and the participant's clinical condition, other therapeutic modalities, or another etiology is a likely explanation for the AE.

Unable to Assess: An assessment of the association is not possible based on the available information.

The outcome of an adverse event at the time of the last contact is classified as follows:

'Recovered': all signs and symptoms of the UE have disappeared without consequence at the time of the last interview.

'Improved': the intensity of signs and symptoms has decreased since the last interview and/ or the clinical pattern has changed as is typical of improvement.

'Not recovered': signs and symptoms of UE are more or less unchanged at the time of interview.

'Recovered with consequences': Acute signs and symptoms of the UE have disappeared, but consequences remain that have their origin in the UE.

'Fatal': has resulted in death. If there are multiple UEs, only the UE that resulted in death (possibly investigational drug related) is classified as 'fatal'.

'Unknown': The outcome is not known or not plausible and the information cannot be completed or verified.

Measures related to the investigational drug are categorized as follows:
'Dose unchanged': no change in the dosage of the investigational drug.

'Dose reduced': the dosage of the investigational medication was reduced

'Drug discontinued': the investigational drug was discontinued

'Unknown': the information is not known or not plausible and the information cannot be completed or verified

'Not applicable': the question is not plausible (e.g., because the participant is dead)

The term 'Countermeasures' refers to specific actions taken to treat or alleviate a UE or to prevent consequential harm.

Countermeasures of a UE are classified as follows:
'None': no countermeasures were taken.

'Drug': a new drug was prescribed or the dosage of a drug was changed

'Other': Other countermeasures were taken, e.g. surgery.

7.3 Meldung schwerwiegender unerwünschter Ereignisse durch den Prüfer

SAEs must be reported to the responsible Safety Officer at KKS Heidelberg on the SAE sheet within 24 hours of becoming known or no later than the following working day.

Fax number 06221/56-33725

The initial report should be as complete as possible and include accurate information on the current illness and SUE, as well as an assessment of the causal relationship between the UE and the investigational product.

After processing and recording the SAEs, the KKS Heidelberg will forward all SAEs on behalf of the sponsor to Novartis, for drug safety data collection, within 24 h of becoming aware of them.

Second assessment
For all SAEs, a second evaluation is performed by a previously designated person who is independent of the reporting investigator. The second evaluator completes a second evaluation form for each SUE and faxes it to the responsible person at KKS Heidelberg within 48 hours.
The secondary evaluation form contains the following information:
I) Assessment of the relationship between SAE and investigational product (causality).
II) Assessment of whether the SAE is "expected" (i.e. described in the SmPC) or not.
III) Opinion on whether the benefit-risk assessment of the clinical trial has changed due to the SUE.
If either the investigator who first reported the SAE or the second evaluator identifies the SUE as possibly related to the investigational product and the SAE is unexpected, then it is a "suspected case of unexpected serious adverse drug reaction" (SUSAR).

7.4 Expedited reporting by the sponsor: reporting of adverse events to the ethics committee, competent authority and all investigators

Suspected cases of unexpected serious adverse drug reactions (SUSARs) must be reported by the sponsor to the lead ethics committee, the competent authority (i.e. BfArM) and all investigators within the legally specified deadlines. Novartis Pharma GmbH also receives all SUSAR notifications in the form of the CIOMS-II sheet sent out.

The reporting (to BOB, ethics committee(s), and investigators) according to the legal requirements and to the company Novartis Pharma GmbH is performed by the responsible Safety Officer/Safety Data Manager at KKS Heidelberg. Only events that occurred after administration of the investigational product are subject to expedited reporting.

7.5 Ermergency treatment

Emergency treatment of AEs is guaranteed by the outpatient and inpatient capacities of the study centers, which also include an intensive care unit, if necessary in cooperation with other clinics of the study centers. The investigator will inform the study participants by telephone or,

if necessary, in writing if an identified intercurrent illness requires medical treatment. Possible scenarios would be, for example, inpatient admission for drug therapy and monitoring in the case of derailed arterial hypertension or outpatient or, if necessary, inpatient infusion therapy in the case of diarrhea refractory to therapy with high fluid losses.

8 Statistical methods

8.1 Statistical analysis and justification for subject number

The primary endpoint of the study is progression-free survival at 6 months.

The null hypothesis to be tested, H0, states that the proportion of patients p who are progression-free and alive at 6 months (PFS rate) is less than or equal to a predefined level p0.

H0: p≤ p0 vs H1: p> p0.

The p0 as PFS rate at 6 months is not considered promising for the combination therapy (paclitaxel and pazopanib) under review. Based on the recently published AngioTax trial (Penel et al. 2008; [2]), p0=0.35 is assumed here. This corresponds to a median time to progression of 4 months

Since monotherapy with paclitaxel results in a median progression-free survival of 4 months in patients with angiosarcoma, a clinically relevant improvement with combination therapy, i.e. simultaneous administration of paclitaxel and pazopanib (instead of the sequential therapy possible outside the study), was assumed for this study if a median progression-free survival of 7 months would be achieved with the combination. This corresponds to a minimally clinically relevant PFS rate at 6 months, of p1=0.55.

A Simon's two stage optimal design is used to test the null hypothesis, which minimizes the expected number of cases assuming the null hypothesis. The one-sided significance level is 5

The maximum recruited number of cases is 44 patients. After inclusion and 6 months follow-up of the first 14 patients, an interim evaluation will be performed. Recruitment will not be stopped for feasibility reasons. If additional patients are recruited during the follow-up period of the first 14 patients, the data of these patients will not be included in the interim analysis.

If, of the first 14 patients, 5 or fewer are progression-free and alive at 6 months, then the study is stopped, the null hypothesis is maintained, and the therapy is declared ineffective.

If of the first 14 patients, 6 or more are progression-free and alive at 6 months, then the study will continue and an additional 30 patients will be recruited.
If of the 44 patients, a total of 20 or fewer are progression-free and alive at 6 months, then the null hypothesis is maintained and therapy is declared ineffective.
If of the 44 patients, a total of 21 or more are progression-free and alive at 6 months, then the null hypothesis is rejected and the therapy is declared effective.
Wenn von den 44 Patienten insgesamt 21 oder mehr progressionsfrei und lebend nach 6 Monaten sind, dann wird die Nullhypothese verworfen und die Therapie wird als wirksam erklärt.

This design has a power of 80%.

In addition, the PFS rate is calculated and the corresponding 95% confidence interval.
Since all patients who are not evaluable for disease response at 6 months or whose follow-up is not available (lost to follow-up) are counted as progressive patients for the analysis of the primary endpoint, there are no missing values for the primary analysis. Patients who withdraw consent to the study before receiving study medication will be replaced.
The primary analysis will be based on the ITT population.

In addition to the primary analysis, PFS rates will be estimated as described in Jung (2004) to obtain unbiased estimators. OS rates can then be derived directly from these rates.
To test for the influence of protocol violations, the analysis described above is repeated based on the PP population.

All analyses described above will also be examined for the above subgroups.
To examine response rates and toxicity rates (AEs/SAEs) absolute and relative frequencies and associated 95% confidence intervals will be calculated. All analyses will be repeated for the above subgroups. Comparison of patients with cutaneous AS vs visceral AS, or with primary AS vs secondary AS in terms of PFS, OS, RR is performed by log rank test and chiquadrat test or by graphical representation, depending on the underlying number of cases. All analyses will be performed in SAS version 9.1 or higher. A detailed statistical analysis strategy will be defined in the Statistical Analysis Plan, which must be completed before the start of the analysis

8.2 Analysis populations

The intention-to-treat (ITT) population includes all patients in the study who have taken the study medication at least once. The per protocol (PP) population is the group of patients who received treatment with pazopanib or paclitaxel for at least 6 weeks and who had the required assessments performed at relevant and pre-specified time points. Patients with serious protocol violations or who have received study therapy not in accordance with the protocol must be excluded from the PP population. The safety population is the same as the ITT population.

All patients who are not evaluable for disease response after 6 months or whose follow-up is not available (lost to follow-up) are counted as progressive patients for the analysis of the primary endpoint.

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9 Data management

9.1 Data collection

All entries in the CRF must be verifiable by source documents. Regardless of this, there must be minimal documentation in the patient file that provides information about study participation and contains all medical information necessary for adequate medical care outside of the clinical trial. The investigator is responsible for accurate, timely, and continuous documentation.

Erroneous entries in the CRF must be crossed out with a single line so that the original entry remains legible. The correction will be made next to the data field and will include the signature of the investigator or authorized member of the study team, date, and reason for the change, if applicable. For self-explanatory corrections (e.g., numerical error in date), the reason may be omitted. Each final CRF page of a visit must be signed and dated once by the investigator to confirm the accuracy of the data

9.2 Data handling

In order to achieve a correct transfer of the documentation on the CRFs into the study database, double data entry is performed in IMBI by two independent persons. Data management is done in the statistical program SAS. Missing and implausible data are queried by the data management in writing to the study center using a prepared data validation plan via queries. The queries must be answered by the test center, if necessary with the support of

the monitor. The resulting additions and corrections are entered into the SAS files and logged in audit files. The processed queries are kept together with the CRFs. At the end of the study, after verification that all CRFs are present and the query process is complete, the database is closed for analysis. All data management processes are performed according to the valid SOPs (Standard Operating Procedures) of the IMBI.

9.3 Storage and archiving of data

The investigator shall retain all study documents including patient identification list and relevant correspondence in the Investigator Site File (ISF). The ISF, all source documents, and all other documents listed in Section 8 of the ICH Consolidated Guideline on GCP shall be archived by the investigator after regular or early termination of the trial in accordance with regulatory requirements

10 Ethical and legal aspects

10.1 Good clinical practise

The described procedures for the conduct, evaluation, and documentation of this clinical trial are intended to ensure that all participants adhere to the principles of Good Clinical Practice (GCP) and the ethical principles set forth in the Declaration of Helsinki. The conduct of the trial will be in accordance with local regulatory and enforcement requirements

10.2 Practice of Informing and Consenting Study Subjects

Before a study subject can be included in the clinical trial, he or she must be informed orally and in writing about the nature, significance and scope of the clinical trial in an understandable form and must subsequently consent in writing to participation.
No non-consenting subjects will be included in this study.
The study participant will receive a copy of the Patient Information and Consent Form for the clinical trial. The original will be retained by the investigator.
These documents must be written in a language understandable to the study participant. They must state who provided the study participant with the information.
Study participants shall be informed of any new information that could affect their decision to participate in the study. The communication of this information is documented

10.3 Data protection

The data collected in the course of the clinical trial will be handled in accordance with the provisions of statutory data protection. During the clinical trial, participants are identified solely by means of an individual identification number (patient number). When study data are stored on a computer, the regulations of the Federal Data Protection Act are observed; the data are treated as strictly confidential. Organizational measures are in place to protect this data and prevent it from being disclosed to unauthorized third parties. The relevant provisions of country-specific data legislation are complied with in full.

With the written consent to participate in the clinical trial, the participant releases the investigator from his duty of confidentiality vis-à-vis representatives of the responsible authorities (inspectors) and the sponsor (monitors) to the extent that these persons may inspect the personal data in order to verify the correct transmission of data and to check the proper conduct of the clinical trial.

The investigator is responsible for keeping an identification list of the study participants (identification number and name of the study participant) to enable any necessary identification.

Patients who do not consent to the sharing of their data in pseudonymized form will not be included in this clinical trial

10.4 Responsibilities of the investigator

The investigator shall ensure that all personnel involved in the clinical trial at the trial site are adequately informed of the protocol, any amendments to the protocol, trial treatments, and trial-related duties and tasks. The investigator shall maintain a list of the members of the study team to whom the investigator has delegated important study-related duties.

10.5 Approval of protocol and protocol amendments

Prior to the start of the clinical trial, the protocol, patient information and consent form, as well as all other required documents, are submitted to the responsible ethics committee and the responsible competent authority for approval.

The approving assessment of the ethics committee and the approval by the competent authority are prerequisites for the start of the clinical trial. The opinion of the EC should include the title of the clinical trial, the short title if applicable, the trial sites and all other reviewed documents. The date on which the decision was made must be mentioned and the opinion must be signed by a member of the Ethics Committee. Complete the affirmative evaluation documentation with a list of the ethics committee members who participated in the

deliberation and a confirmation that the EC operates in accordance with GCP principles (if applicable, the EC's bylaws may be filed with the vote instead).
All correspondence (written and verbal) with the relevant Ethics Committee and the relevant BOB must be documented and retained by the sponsor.
All ethical and legal requirements must be met before the first study participant is enrolled in the clinical trial.
Trial protocol amendments are made in writing and require the approval of all protocol signatories. Subsequent substantial amendments to the protocol also require the consenting evaluation by the responsible ethics committee and the approval of the competent authority.

10.6 Ongoing information from the Ethics Committee and the Competent Autority

The responsible ethics committee and the responsible competent authority must be informed of any suspected case of an unexpected serious adverse reaction (SUSAR; see also item 9.4) that has become known, as well as of any circumstance that requires a renewed review of the benefit-risk assessment of the investigational product. Both institutions will be informed if the benefit-risk assessment changes or other new and significant threats to patient safety and well-being arise.
During the duration of the trial, a list of all suspected serious adverse events occurring during the trial and a report on the safety of the persons concerned (so-called Development Safety Update Report (DSUR)) is submitted once a year - or upon request - to the responsible ethics committee and the competent authority.
The termination of the clinical trial must be reported to the responsible ethics committee, the competent authority and the responsible state authorities. Within one year after the end of the clinical phase (last subject out, LSO) of the trial, a summary of the study results is submitted to the responsible ethics committee and the competent authority.

10.7 Notification of German local authorities

In accordance with AMG §67, the clinical trial must not only be approved by the competent authority (CA), but it must also be notified there prior to enrollment of the first study participant. Likewise, prior to the start of the trial, notification must be made to the state authorities responsible for the investigators. Notification to the CA is the responsibility of the sponsor,

whereas notification to the state authorities is the responsibility of the individual investigators. Subsequent changes, termination or, if applicable, discontinuation of the clinical trial must also be reported.
All correspondence (written and verbal) with the authorities must be documented by the sponsor or investigator and retained by the sponsor or investigator after completion of the clinical trial

10.8 Registration of Clinical trial

The sponsor will ensure that the present study is registered at http://www.clinicaltrials.gov prior to the start of the clinical phase (first subject in, FSI). The study will be assigned a specific number (International Standard Randomised Controlled Trial Number, ISRCTN), a prerequisite for publication in a reputable scientific journal

10.9 Insurance

For the study participants, a proband insurance policy (maximum € 500,000 per study participant) has been taken out with HDI-Gerling Versicherung AG, Am Schönenkamp 45, 40599 Düsseldorf, Germany, in accordance with the legal requirements. In order not to jeopardize the insurance coverage, any damage to health that may have occurred as a result of participation in the clinical trial must be reported immediately to the above address. The obligation to report lies with the trial participant. The insured person must agree to all measures that are suitable to determine the cause and extent of the damage that has occurred and to mitigate the damage.
During the duration of the clinical trial, the study participant may undergo other clinical treatment - except in an emergency - only in agreement with his investigator. Furthermore, there is an obligation to immediately inform the investigator of all adverse events and also of any additional medication taken. The insurance conditions will be handed over to the study participant upon request.
The insurance company must be informed of any subsequent changes that could affect the safety of the participants.

11 Translationale Research

11.1 Rationale

Due to the rarity of AS, relatively few studies on genetic alterations in these tumors exist to date. After gene amplification analyses, mutation analyses and chromosome analyses were initially performed in individual cases [29, 30, 31, 32, 34], several larger series have now also

been published, in which material from up to 61 patients with primary and secondary AS [35] was in part examined with regard to genetic alterations.

In addition to the aforementioned VEGF-R mutations and alterations in amplification of VEGF-R genes in AS, alterations in tumor protein 53 (p53) expression [28, 33, 36], the PIK3CA/AKT/mTOR signaling cascade [36], and expression of protooncogenes such as MYC [35] have now been detected in these tumors. Interestingly, although MYC expression was found to be increased in over 50% of secondary AS samples examined in one study; it was not detectable in any primary AS and thus appears to be a specific feature of secondary AS [35].

Despite these already known alterations, the pathogenesis of AS remains largely unknown, especially to what extent different genetic alterations or other mechanisms contribute to disease development in primary and secondary AS. An above-average proportion of secondary AS develops after breast-preserving therapy including radiation of breast carcinomas. It is unclear whether (genetic) risk factors exist that increase the risk of developing secondary AS for a patient with breast carcinoma who is scheduled to receive BET/radiotherapy.

Should further mutations be discovered in the course of genetic analyses of AS that lead to altered expression or activity of functionally active proteins and thus to pathogenetically relevant changes (e.g., altered signal transduction), additional targets would potentially be available for therapeutic interventions, which are urgently needed to improve treatment options for patients with AS.

The optional translational research project aims to answer the following scientific questions in the context of this clinical trial in angiosarcomas by collecting fresh tissue, kerosene fixed tissue and blood samples after genome-wide sequencing and RNA expression analysis.

1, Are potentially oncogenetically relevant mutations found in AS that are reproducible in a relevant proportion of the cases studied?

2. do these mutations lead to detectable changes at the RNA and protein level?

3. are there differences in points 1 and 2 between primary and secondary AS?

4) Is it possible to detect genetic alterations (see points 1. and 2.) in nucleated blood cells of patients with secondary AS that are not present in patients with primary AS?

5. If genetic alterations can be detected in a relevant subgroup of patients, these subgroups should be evaluated in comparison to the patients with wild-type AS regarding the outcome in the study (primary and secondary study objectives: PFS, R, OS).

11.2 Patient informatioj and informed consent to translational research

In the screening phase of the clinical trial, tissue samples (FFPE blocks and, if available, freshly frozen tumor material) and one 10 ml blood sample each, which serves as a control and as so-called healthy tissue, respectively, can be collected after a detailed educational discussion including the patient information and after receipt of the signed consent form for translational research.

Patients can only participate in the translational research project if they have consented to participate in the clinical trial. Participation in translational research remains optional for patients. Consent may be withdrawn at any time. This does not affect participation in the clinical trial

11.3 Collection, storage and pseudonymization of samples

In the context of this study protocol, existing tumor material should be used whenever possible. If no suitable material is available, a new sample may be taken in individual cases within the framework of this research project after careful consideration of the risks involved in a biopsy for purely scientific purposes and detailed information of the patient as well as obtaining the patient's consent.

From the obtained blood sample, nucleated blood cells will be isolated, cryopreserved and stored according to the locally established Ficoll standard procedure.

Storage of the samples may occur at the study site responsible for the study patient until the assigned collection by the sponsor. The requirement for this is that the study center meets the requirements for storage of blood and tissue samples, according to the state of the art in science and technology. If an investigational center does not meet the requirement for sample storage, participation in the translational research project is not possible. A review of the requirement will be performed during study initiation via a separate checklist or by an inspection of the study site. The storage of the samples at the study center is done via a study-specific patient identifier (PID).

After collection of the samples from the test center, the samples receive a pseudonym (PSN). This pseudonym is a randomly generated letter-number combination. The pseudonymized samples are stored in the central tumor bank of the study group (Prof. Dr. med. Hohenberger,

Section of Special Surgical Oncology and Thoracic Surgery, Department of Surgery, University Medical Center Mannheim, Theodor-Kutzer-Ufer 1-3, 68135 Mannheim, Germany).
The collected specimen and data material will only be shared with PSN coding.
At a later stage, the pseudonymized samples will be forwarded for genome-wide analysis to Prof. Dr. med. C. A. Schmidt, acting director of the Clinic and Polyclinic for Internal Medicine C; Hematology and Oncology - Transplant Center, University Medicine Greifswald, Sauerbruchstraße, Diagnostic Center, 17475 Greifswald.

11.4 Processing of the obtained samples

It is planned that freshly frozen tumor material and the ficollated nucleated blood cells of primary and secondary AS will be sequenced using the "next generation sequencing" technology and, if necessary, checked for mutated genes and altered proteins with regard to RNA expression. From the collected tumor material, 5 participants will initially be brought into the translational research project. If the results of the 5 tissue samples submitted appear to be meaningful for further investigation or confirmation in the context of the questions of this research project (see above), further tumor samples and nucleated blood cells from study participants who have agreed to the transnational research part will be sequenced. For these confirmatory studies and for all further studies, paraffin-embedded material may be sufficient.

11.5 Data protection and traceability of results

The genetic patient data are stored separately and encrypted in different databases, each with controlled access, to protect you. The data can be stored indefinitely until revoked. All genetic data is collected, examined and stored only in encrypted form. Only authorized personnel have access to this encrypted data. Traceability of the data is only possible via a patient identifier (PID) assigned by the study center and via a pseudonym (PSN) assigned by the tumor bank. Inference to patient data for unintended purposes should thus be excluded.

12 Quality assurance

12.1 Monitoring

Center-specific quality control is performed through regular monitoring visits. Monitoring is only performed by clinical monitors who are sufficiently qualified.

Prior to enrollment of the first study participant, an initiation visit is conducted at each study center. A face-to-face initiation visit may be waived if the principal investigator at the study site and the study team have extensive study experience. It is up to the study director to decide if an initiation visit can be replaced by a telephone initiation at the center. During the study initiation, the availability of all essential documents and the requirements for proper study conduct are verified. During the regular monitoring visits (including after inclusion of the first patients at the study center, during the study, and after the end of the study), the responsible monitor checks the entries in the CRFs against the source documents as well as the correct dispensing and use of the study medication The investigator must ensure the monitor free access to all required documents and the study medication. The investigator must support the monitor's work at all times.

Through frequent contact (letter, telephone, email) between visits, the monitor shall verify that the study is being conducted in accordance with the study plan and regulatory requirements.

Details of the scope of monitoring are described in the Monitoring Manual.

12.2 Audits and Inspections

To maintain and enhance quality, the German Interdisciplinary Sarcoma Group reserves the right to conduct study-specific ICH GCP audits at the respective study sites.

The competent authorities may request access to all source documents, CRF and other study documents for the purpose of an on-site inspection. The investigator must ensure free access to these documents and support the work at all times.

By signing the protocol, the investigator gives consent to study participation and allows inspection of all study specific documents by a person designated by GISG or by a competent authority.

In case of an official inspection, please forward the information to the German Interdisciplinary Sarcoma Group at studien@gisg.de.

13 Agreements

13.1 Financing of the clinical trial

The clinical trial is funded by the company Novartis Europharm Ltd. The pazopanib is provided by the company Novartis Europharm Ltd.

13.2 Financial disclosure

Prior to the initiation of this clinical trial, each investigator will disclose any commercial interests related to the sponsoring company, the investigational product, or other commercial organizations involved in the trial. The investigators undertake to update this information in the event of significant changes

13.3 Reports

The study center of the Section of Special Surgical Oncology and Thoracic Surgery and the IMBI Heidelberg are preparing the final study report together with the scientific coordinator. The preparation of the report will be completed 3 months after database closure.

13.4 Publication

All data collected in connection with the clinical trial must be treated confidentially until publication. Publication of the study results will be independent of the results. First author of a publication of the primary and secondary endpoints and the protocol will be the author of the protocol, and senior author of the LKP. The participating biometrician of IMBI will be included as an author.

14 SIGNATURES

This protocol has been critically reviewed by all signatories and approved as presented. The data contained therein are consistent with:

- The current status of the benefit-risk assessment of the investigational product.
- The moral, ethical and scientific principles of clinical research in accordance with the Declaration of Helsinki and in accordance with the principles of GCP.

Each investigator will be fully informed of any important or new findings, including investigational product-related AEs.

Date: _____ Signature: _____

Name (Print letters): Dr. Angela Kalous

Function: Chancellor of University Sponsor

Date: _____ Signature: _____

Name (Print letters): Prof. Dr. P. Hohenberger

Function: Member of Medical Faculty Mannheim, Heidelberg University and National Coordinator as well as Representative of GISG

Date: _____ Signature: _____

Name (Print letters): Dr. Daniel Pink

Function: Investigator, Medical Coordinator (Author)

Date: _____ Signature: _____

Name (Print letters): Dr. Geraldine Rauch

Function: Biometrician (Institut für Medizinische Biometrie und Informatik Heidelberg)

Date: _____ Signature: _____

Name (Print letters): Prof. Dr. Thomas Brodowicz

Function: National Coordinator for Austria

15 INVESTIGATOR's DECLARATION

I have read this protocol and confirm that it contains all the information necessary for the proper conduct of the trial. I agree to conduct the clinical trial as specified in this protocol.

I will not enroll the first study participant in the study until all ethical and legal requirements to begin a clinical trial have been met. I agree to obtain written informed consent from all study participants to participate in the clinical trial.

I understand the requirements for proper reporting of serious adverse events and agree to document and report such events as required.

I agree to retain all trial-related documents and source documents as described. I will submit a curriculum vitae prior to the start of the clinical trial, which may be submitted to the appropriate authorities.

Date: _____ Signature: _____

Name (Print letter): _____

Function: Investigator

Site (Adress): _____

_____

_____

16 Appendix A – Bibliographie

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17 Appendix B: CYP3A3/4 influencers of Plasma-Pazopanib-concentrations

CYP3A3/4 Substrates	
Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine
Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem	Propoxyphene
Dirithromycin	Quinidine
Disulfiram	Quinine
Entacapone (high dose)	Quinupristin and dalfopristin
Erythromycin	Ranitidine
Ethinyl estradiol	Ritonavir
Fluconazole (weak)	Saquinavir
Fluoxetine	Sertindole
Fluvoxamine	Sertraline
Gestodene	Troglitazone
Grapefruit juice	Troleandomycin
Indinavir	Valproic acid (weak)
Isoniazid	Verapamil
Itraconazole	Zafirlukast
	Zileuton