Investigational Plan & Clinical Study Protocol

Phase II randomized clinical trial of Pazopanib alone and Pazopanib plus Gemcitabine in relapsed or metastatic soft tissue sarcoma.

The PAPAGEMO trial

Sponsor: Martin Luther University Halle-Wittenberg

EudraCT Nr: 2009-017261-32

Protocol identification number: KKSH 077

AIO

An AIO joint study AIO-STS-009

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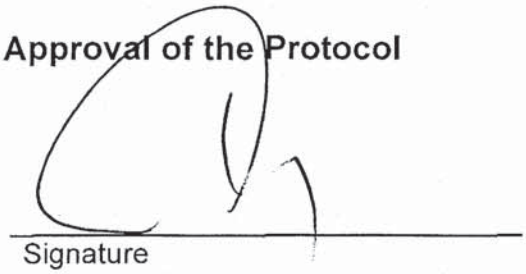
Approval of the Protocol



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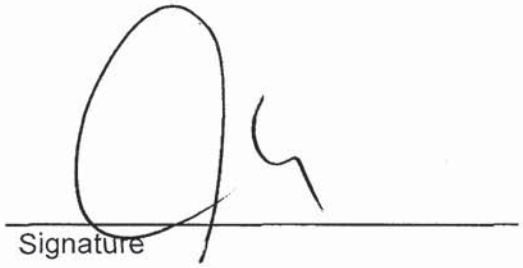

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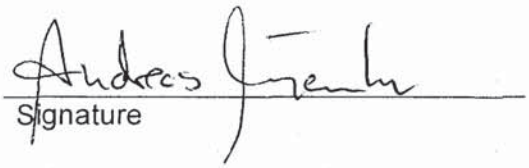

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Investigator's Agreement

I have read the attached protocol entitled:
"Phase II randomized clinical trial of Pazopanib alone and Pazopanib plus Gemcitabine in relapsed or metastatic soft tissue sarcoma." dated 06/2011 (version Final 2.0) and agree to abide by all provisions set forth therein.
I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

Signature

Name of Principle Investigator

Location / Date

Investigator's Institution

Glossary

Abbreviation/Acronym	Definition
ACE	Angiotensin Converting Enzyme
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AJCC	American Joint Committee on Cancer
ANC	Absolute neutrophil count
ALT (SGPT)	alanine aminotransferase (serum glutamic-pyruvic transaminase)
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BP	blood pressure
BUN	blood urea nitrogen
CAF	cytokines and angiogenic factors
CBC	complete blood count
CHF	Congestive heart failure
CI	confidence interval
CNS	central nervous system
CR	Complete response
CrCl	creatinine clearance
CRF	Case Report Form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Chemotherapy
CXR	chest x-ray
DBP	diastolic blood preasure
DCR	Disease control rate
DSUR	Development Safety Update Report
DVT	deep venous thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
FDA	Food and Drug Administration (U.S. government agency)
GCP	Good Clinical Practice
GCP-V	Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen
GGT	

Abbreviation/Acronym	Definition
	gamma-Glutamyl-Transferase
GIST	gastrointestinal stromal tumor
GSK	GlaxoSmithKline
HRT	hormone replacement therapy
γ-GT	γ-glutamyltransferase
IEC	Independent ethics committee
IMP	investigational medicinal product
INR	International Normalized Ratio
ITT	Intention-to-treat
i.v.	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
LKP	Leiter der klinischen Prüfung
LMWH	Low Molecular Weight Heparin
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	Multi Gated Acquisition
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	Objective response rate
OS	overall survival
PD	progressive disease
PDGF	platelet derived growth factor
PFSR	progression free survival rate
PK	pharmacokinetic
PP	per-protokoll
PR	partial response
PT	Prothrombin time
PTT	Partial Thromboplastin Time
QoL	Quality of life
RCC	Renal Cell Carcinoma
RDE	Remote data entry
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SBP	systolic blood preasure
SD	stable disease
SPC	Summary of Product Characteristics
STS	soft tissue sarcoma

Abbreviation/Acronym	Definition
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitors
TSH	thyroid-stimulating hormone
TTP	time to progression
UICC	Union internationale contre le cancer
ULN	Upper limit of normal
UPC	Urine Protein to Creatinine Ratio
VEGF	vascular endothelial growth factor
WBC	white blood cells

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Protocol summary

Title	Phase II randomized clinical trial of Pazopanib alone and Pazopanib plus Gemcitabine in relapsed or metastatic soft tissue sarcoma.
Objective	The objective of this phase II trial is to assess the efficacy and toxicity of pazopanib alone or pazopanib plus gemcitabine in patients with refractory or relapsed metastatic soft tissue sarcoma (STS).
Study Sponsor	Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
Protocol number	KKSH-077
EudraCT number	2009-017261-32
Study Device	Pazopanib
Primary Endpoint	Progression-free survival Rate (PFSR) after 12 weeks
Secondary Endpoints	• Overall survival (OS) • Time to Progression (TTP) • Response Rate (CR+PR+SD) • Toxicity (CTCAE, version 4.0) • Quality of live (EORTC)
Study Design	This is a multicentre, open labeled, prospective, randomized parallel-group phase II study designed to assess the clinical performance of pazopanib with or without gemcitabine in patients with refractory soft tissue sarcoma (STS). Patients will randomly be assigned to one of the treatment arms according to following stratification criteria: liposarcoma vs. non liposarcoma **Arm A** Pazopanib 800mg will be administered orally once a day. Gemcitabin will be administered intravenously at a dose of (1000) mg/m^2 d1, 8 qd 21. **Arm B** Pazopanib 800mg will be administered orally once a day Toxicity will be evaluated at every visit whereas efficacy will be assessed by CT/MRI scan according to RECIST v1.1 initially after 6 and 12 weeks, afterwards every 8 weeks until progression.
Number of patients	90
Duration of study	I. Enrolment period: 18 months II. Study duration: max. 24 months III. Duration of individual patient participation: Until

	progression, unacceptable toxicity, investigator's decision, withdrawal of consent. IV. Subsequent follow-up for the purposes of this study will require access to patient notes to determine disease status and patient survival.
Inclusion criteria	• Histologically or cytological confirmed malignant soft tissue sarcoma including any subtypes except: o Chondrosarcoma o Osteosarcoma o Ewing tumors and primitive neuroectodermal tumors o Gastrointestinal stromal tumors o Dermofibromatosis sarcoma protuberans o Inflammatory myofibroblastic sarcoma o Malignant mesothelioma o Mixed mesodermal tumors of the uterus • Relapse or progress after one or two prior chemotherapies including either an antrazyclin or ifosfamid or both. Patients with relapse or progress with liposarcoma or leiomyosarcoma must be offered a treatment with Trabectedin. • ECOG performance status 0-2 • At least 18 years old • Life expectancy > 3 months • Patients with at least one measurable lesion according to RECIST criteria (v1.1) • Able to swallow and retain oral medication • Adequate organ function as defined in protocol • A female is eligible to enter and participate in this study if she is either of non childbearing potential (defined in protocol) or childbearing potential with negativ pregnancy test within 2 weeks prior to the first dose of study and agrees to use adequate contraception (as defined in protocol) • 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 study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.
Exclusion criteria	• Patient has received prior treatment with any anti angiogenic drug (including bevacizumab and tyrosine kinase inhibitors) • Active malignancy or any malignancy in the last 5 years prior to first dose of study drug other than STS. • History of clinical evidence of CNS metastases or

	leptomeningeal carcinomatosis (more information see protocol) • Clinically significant gastrointestinal disorders/ abnormalities (defined in protocol) • Poorly controlled hypertension (defined in protocol) • Prolongation of corrected QT interval (QTc) > 480msec • Clinically significant cardiovascular disease, for example Cerebrovascular accident, myocardial infarction (≤ 6 months before treatment start), unstable angina, NYHA Class < II CHF, arrhythmia requiring medication • Major surgery or trauma within 28 days or any non-healing wound, fracture or ulcer • Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Pazopanib or Gemcitabine • Presence of uncontrolled infection • Women who are pregnant or breast feeding • Treatment with any other cancer therapies within 14 days prior to the first dose of study drug (defined in protocol) • Evidence of active bleeding or bleeding diathesis • Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug. • Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels • Evidence of active bleeding or bleeding diathesis • Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures • History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months • Unable or unwilling to discontinue use of prohibited medications listed in Section 6.4.4 for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study • Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity, except alopecia. • Existing medication with prohibited and interactional drugs with the study drug must be asked in detail. Indispensable use of long term medication with CYP-inhibitors or inductors,explicitly (changes in long term medication is possible; refer to sections 6.4.4 and 6.4.8) is prohibited. • Insufficient liver function (refer to section 7.1.1: liver toxicity (C and D))

	• Autoimmune disease • uncontrolled hypothyroidism • Diarrhia Grad 3 and 4
Study procedures - baseline	All patients with refractory STS of the above mentioned histological subtypes will be reviewed for study eligibility. After checking suitability to enter the study, patients who agree to participate must sign the informed consent form before undergoing any study related procedures or treatment. Consenting patients will have the following screening/baseline assessments performed within 4 weeks prior to the first treatment: • Detailed medical history including previous cancer history and cancer treatment. Any additional relevant medication taken one year prior to study start will also be recorded • Physical examination including weight, height and vital signs (blood pressure, heart rate, respiratory rate, body temperature) • Laboratory tests (red blood cells, WBC with neutrophils, lymphocytes, monocytes, eosinophils, and basophils, hemoglobin, platelets, hematocrit; blood chemistries: sodium, potassium, calcium, magnesium serum creatinine, urea BUN, glucose, alkaline phosphatase AST, ALT, GGT, total protein, albumin and total bilirubin, TSH, free T4; LDH, and coagulation (baseline and as clinically indicated): INR, PTT, PT) • Urine dipstick • Adverse events • Demographics • Performance Status (ECOG) • 12 lead ECG • MUGA or Echo scan for LVEF • Serum pregnancy test (for women of child bearing potential) • Documentation of disease status (CT/ MRI) within 2 weeks before starting study specific treatment • Quality of live documentation (QLQ-C30) within two weeks prior to randomization
Study procedures –treatment period	- Safety evaluation using NCI Common Terminology Criteria for Adverse Events version 4.0 - Physical examination, including vital signs (blood pressure, heart rate, respiratory rate, body temperature) - Performance Status (ECOG) (Appendix B) - Laboratory determinations (CBC, blood chemistries, Thyroid function test (TSH, fT4) prior to each treatment period) - ECG (week 6, 12 and every 8 weeks afterwards) - Disease status assessment: follow up scan of same lesions

	and method as at study entry at week 6, 12 and every 8 weeks afterwards
Study procedures – follow-up (every 12 weeks)	- Safety evaluation using NCI CTCAE - Physical examination, including vital signs (blood pressure, heart rate, respiratory rate, body temperature) - Laboratory determinations (CBC, blood chemistries) - After progression, patients will be followed every 3 months. The Investigator will record disease status, protracted toxicities, further treatment and patient survival.
Evaluation procedures	*Safety:* Safety assessments will include physical examinations, vital signs, clinical laboratory profile and adverse events. *Adverse Events:* All observed toxicities and side effects will be graded according to NCI-CTCAE v.4.0 for all patients and the degree of association of each with the procedure assessed and summarized. Treatment related Serious Adverse Events (SAE), defined as SAEs considered possibly, probably or certainly related to treatment, will be determined. *Tumour response:* Recent version 1.1 of RECIST will be used within this trial. At least one measurable lesion (size > 1 cm according to RECIST) must be identified as target lesion and measured. This baseline scan must be performed within 2 weeks prior to first treatment. The same measurement technique (CT/MRI) must be used at baseline and follow up.

Statistical considerations	A 1:1 randomisation scheme will be used. Sample size calculation is based on a one-sided chi-square test for two independent groups. PFSR@12 weeks =40% is supposed to be reached by the monotherapy arm. In the drug combination arm treatment should reach a PFSR@12 weeks of >=60% to prove superior drug activity. The study will have 60% power at a 5% significance level to test this hypothesis. 45 evaluable subjects are required per treatment group. *Populations for analysis:* All patients receiving at least one treatment (pazopanib and/or gemcitabine) will be evaluable for safety. The Intention-to-treat (ITT) population will include all patients in the study (signed ICF and confirmation of eligibility). All patients will be grouped according to their randomization regardless of treatment received. The Per-protocol (PP) population will include all patients who receive at least 6 weeks of treatment with pazopanib with or without gemcitabine and who were treated according to their randomization schedule. Patients with major protocol deviations or who did not receive treatment according to their randomization schedule will be excluded from the PP population.

Flow chart

Study Schedule Visit	**Inclusion**	**Maintenance treatment Each cycle (1-open)**		**Before starting 3th cycle**	**End of treatment**	**Follow up Period**
Study Week (W)	Baseline	d1	d8	week 6	after progression	every 3months, after progression
Informed Consent	X					
Medical History/ Demographics	X					
Serum pregnancy test	X					
ECOG Performance Status	X	X	X		X	X
Vital signs and physical examination	X	X	X		X	X
Quality of life assessment	X	X			X	X
Laboratory determinations	X	X	X		X	X
Urine dipstick	X	X			X	
Echo scan or MUGA	X	when clinicly indicated			when clinicly indicated	when clinicly indicated
Radiological assessment	X			X	X	X
12 lead ECG	X	X			when clinicly indicated	when clinicly indicated
Concomitant medication	X	X	X		X	
AE Monitoring	X	X	X		X	X
Survival		X	X		X	X
Paraffine embedded tumor tissue	X					
Blood samples translational research	X			X	X	
Thyroid function test	X	X			X	X

Radiological assessment will be repeated after 12 weeks and afterwards every 8 weeks until progression.

1. Introduction and Rationale of the trial

1.1 Disease background

Soft tissue sarcomas (STS) are malignant tumors of connective tissue (mesenchyme). There are multiple histological subtypes that comprise nonepithelial, extraskeletal tissue, including muscles, fat and fibrous supporting structures, arising mainly from embryonic mesoderm with some neuroectodermal contribution. At present most subtypes are grouped under the heading of STS for the purpose of treatment. Notable are an increasing number of new treatment options that are expected to be directed more specific at individual histological subtypes.
The annual incidence of STS is around 2-3/100000. Overall STS account for approximately 1% of all malignancies.
STS have traditionally been managed by wide excision surgery and radiotherapy, being the only curative approach. However, in many patients even optimal local treatment does often not prevent the occurrence of distant metastasis, especially those with high-grade tumors. Primary sites of metastasizes are the lungs but also bone, liver and other organs, depending on the subtype. The use of chemotherapy has been reserved for advanced disease for systemic control. It may prolong overall survival and maintain quality of life, because most initially chemotherapy-sensitive patients will ultimately relapse and present at that point a chemotherapy-resistant disease.
Five- year survival for all STS patients is approximate 50% depending on tumour size, grade, histology, location of the tumour and response to therapy[1]. Stage III and Stage IV STS (according to AJCC) possess a 5 year survival of 45% and 10%[2]. These advanced STS are stable at a median of 12 months over the last 20 years[3]. Doxorubicin and ifosfamide used as single agents or in combinational schedules are considered to be the standard first line therapy in most of the patients[4,5]. Randomized studies have shown that combination chemotherapy adding additional drugs to antrazycline and/or ifosfamide, can sometimes provide higher response rates than single agent doxorubicine. However, even if present, this higher objective response rate did not translate into improved overall survival. The involved trials compared various combinations such as CYVADIC (cyclophosphamide, vincristin, doxorubicin, DITC), MAID (mesna, adriamycin, ifosfamide and DITC) or MAP (mitomycin C, doxorubicin and cisplatin) with single agent doxorubicine. In all trials single agent doxorubicin yielded to be less toxic than the combination studied. Thus single agent doxorubicin is currently still regarded as standard treatment of the majority of adult patients with metastatic and inresectable STS with exception of certain well-defined subtypes of sarcoma, such as GIST. All in all the use of chemotherapy in STS is limited by relatively poor efficacy, toxicity, expense, and marked chemotherapy resistence.
In refractory patients, only few cytostatic drugs have been proven to be active in STS patients for second and third line therapy. Trabectedin is the only approved drug in Europe for patients' refractory to ifosfamid and antrazycline-based chemotherapy. Nevertheless these patients are candidates for clinical trials of new drugs because treatment outcomes remain unsatisfactory and are limited to palliation in the vast majority of cases.
It has been reported that circulating angiogenetic factor levels correlate with extent of disease and risk of recurrence in patients with STS[6]. Mean levels of VEGF and bFGF were significantly higher in patients compared with controls[7-9]. STS therefore appear to be good targeted tumor type for evaluation of angiogenesis inhibitors.

1.2 The role of growth factors in STS

Solid tumors require the development and expression of a vascular network for nourishment and waste disposal to support their growth. Angiogenesis itself is defined as the development of new blood vessels from a pre-existing vascular bell[10] and is regulated by a complex series of interrelated events, controlled by specific angiogenic growth factors and cytokines, endothelial cells and the extracellular stroma[11]. Platelet- derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and its receptors (VEGFR1-3) have been elucidated as key player in this process[12]. The VEGF family, consisting of VEGF-A (often referred to as VEGF), VEGF-B, VEGF-C, and VEGF-D are dimeric glycoproteins belonging to the so-called cysteine- knot superfamily of growth factors. Although VEGF has a higher affinity to VEGFR-1 than to VEGFR-2, the latter receptor is generally considered to be the main transducer of the VEGF- dependent angiogenic signals. This information is based on in vitro data. Indeed VEGFR-2 has been shown to signal VEGF- mediated mitogenic, chemotactic and survival effects in cultured endothelial cell[13,14]. VEGF expression in tumor tissue of STS is significantly elevated in vitro[15-18]. Furthermore STS patients appeared to have elevated VEGF blood levels, compared to healthy controls[6,16,19,20]. An experimental study shows that the overexpression of VEGF in soft tissue sarcoma is associated with significant accelerated tumor growth, angiogenesis and the occurrence of metastasis[21]. Furthermore, inhibitors of angiogenesis have demonstrated anti tumor activity in appropriate animal models of STS[22,23].

Pazopanib (GW786034) is an orally available, second- generation, multi-targeted tyrosine kinase inhibitor (TKI), which is currently tested in several clinical trials and diverse tumor types. Targets of this drug are VEGFR, PDGF and c-kit. Pazopanib is approved for first line treatment in metastatic renal cancer in europe. Therefore pazopanib represents an attractive therapeutic agent in combination with conventional chemotherapies in relapsed STS.

1.3 Rationale for Trial

In the phase II EORTC study 62043 patients with advanced STS and progression after no more than two prior cytotoxic agents were included. These patients received 800mg Pazopanib orally daily. Four different patient cohorts were recruited: adipocytic sarcomas, leiomyosarcomas, synovialsarcomas and a group of patients with other eligible STS entities. A two stage testing was applied to each of the four cohorts seperately. In the first stage a total of 17 patients per cohort were accrued. The groups with leiomyosarcomas, synovialsarcomas and the “other STS” reached the statisic significants of the first stage and recruitment was completed to the total of 37 patients. 43,9% (leiomyosarcomas), 48,6% (synovialsarcomas) and 39% (other STS) were progression free after 12 weeks. In the authors conclusion pazopanib is well tolerated (not discussed here in) in advanced STS and demonstrates interesting antitumor activity in pretreated patients with leiomyosarcomas, synovial sarcomas and other eligible STS entities.

In the cohort of adipocytic sarcomas the predefined criteria for antitumor activity in the first step were not met and recruiting was stopped. After central histopathologic review two other patients who were initially categorized into the “other STS” cohorts were added to the adipocytic sarcomas stratum. Both of these cases reached the primary end point. Thus statistical significance was reached and the cohort

retrospectively could have continued recruiting[24]. Because of this clincher adipocytic sarcomas will be included in the present study.
Grounding on the efficacy of pazopanib shown in this study a double blind, placebo-controlled, phase III trial of pazopanib versus placebo was initiated by the EORTC. The trial was named PALETTE-study, and results were puplished at ASCO 2011. All included patients must have been pretreated with an anthracycline. A total of 369 patients were recruited in a 2:1 design. PFS as primary endpoint reached statistically significance assessed per independent review (20 vs 7 weeks; HR=0.31). In an interim analysis, overall survival shows non-significant improvement of pazopanib vs. placebo (11,9 vs 10,4 months; HR=0.83). Toxicity was not higher than expected and acceptable in the experimental arm. The authors conclude that Pazopanib is an active drug in anthracycline pretreated metastatic STS patients[25].

TKI are in commen use in diverse tumor entities. In majority of cases single agent TKI is far less active as combining with conventionell chemotherapy. Therefore several clinical studies with potentiell partner drugs for pazopanib are under investigation. Hartmann et al. reviewed the single agent activity of several drugs in salvage treatment of STS[26]. These data suggest some kind of activity for paclitaxel (mostly in angiosarcoma), docetaxel and gemcitabine. Gemcitabine could achieve RR up to 20% and attractive TTP data in the trials published so far[27-40]. Therefore Gemcitabine seems to be a promising partner drug with pazopanib in STS.
Lately the combination of gemcitabine and pazopanib was evaluated and published on a poster at the 22nd EORTC-NCI-AACR symposium on “Molecular targets and Cancer Therapeutics”. 22 patients were enrolled in this study. Eligible patients had progressed on standard therapy, had adequate organ function, and received no prior anti-VEGF(R) therapy. A dose escalation design was followed by an expansion phase. Gemcitabine was administered as a 30min infusion on days 1 and 8 of each 21-day cycle at escalating dose levels. Pazopanib was administered orally once-daily at escalating dose levels. In conclusion of all dose levels administered the most frequent drug-related AEs (as a % of all patients) were fatigue 68%, neutropenia 59%, nausea 55%, anorexia 50%, and thrombocytopenia 41%. Most common Gr 3/4 AEs (as a % of all patients) were neutropenia 45% and thrombocytopenia 18%. Gr 3 (without Gr 4 observed) AEs were ALT increase 18%, and 9 % each for: lymphopenia, fatigue, diarrhea, abdominal pain, hyperbilirubenia. By analysing the different dose levels admitted the authors of the study conclude that the combination of Pazopanib and Gemcitabine appears clinically active and tolerable for extended periods. Based upon analysis of tolerability as a function of dose levels, Pazopanib 800mg daily plus Gemcitabine at 1000 mg/m^2 on days 1 and 8 every 21 days is a feasable combination to be tested in phase II studies[41].

Risk-benefit assessment
Patients included in this clinical trial will ultimately die of the disease. Live expectance in mean is short. An evidence based therapy regime cannot be recommended. New therapy options are awaited eagerly. Therefore in this situation all patients should be offered a clinical trial. Patients’ in general benefit of the close disease control. Future generations profit from the information of new drugs and drug combinations. Pazopanib is an oral drug. Gemcitabin will be admitted once a week for 30 minutes. Therefore patients gain a high level of quality of live by not being hospitalized for treatment compared to possible therapeutic alternatives.
The superior activity of Pazopanib monotherapy, in the patients collective included in this trial, compared to placebo has currently been proven. Compared to historical

data patients profit remarkable good by a Pazopanib monotherpy. Erlotinib (member of the TKI-family) plus gemcitabine is approved in patients with pancreatic cancer because of its synergistic effect.
In the above-mentioned clinical phase I-III trials (1.1-1.3) adverse site effects in the monotherapy- as well in the combination arm are expected to be acceptable and manageable. If the primary endpoint will reach statistic significance, as consequence a randomized phase III trial with the aim to approve the combination therapy of gemcitabine plus pazopanib in second line chemotherapy will be conducted.

1.4 Rationale for the translational research

In STS it is not yet established which CAFs in serum play a key role in vivo, and whether these may predict response to chemotherapy/ small molecules and tumor progression. Preclinical work has suggested that alternate proangiogenic factors may modulate sensitivity to anti-VEGF therapy and allow regrowth of tumor-associated vasculature. No publications are available on how CAFs serum level in STS patients change during the treatment with antiangiogenetic agents compared to a treatment in combination with conventional chemotherapy. To investigate this, patients serum will be screened for relevant, i.g. elevated levels of CAFs using multiplex-bead assays for measurement of cytokine- and immunoassays for VEGF and PIGF levels.

2 Objectives

The objective of this phase II trial is to assess the efficacy and toxicity of pazopanib alone or pazopanib plus gemcitabine in patients with relapsed or metastatic soft tissue sarcoma.

2.1 End points

The primary end-point: progression free survival rate (CR+PR+SD) after 12 weeks

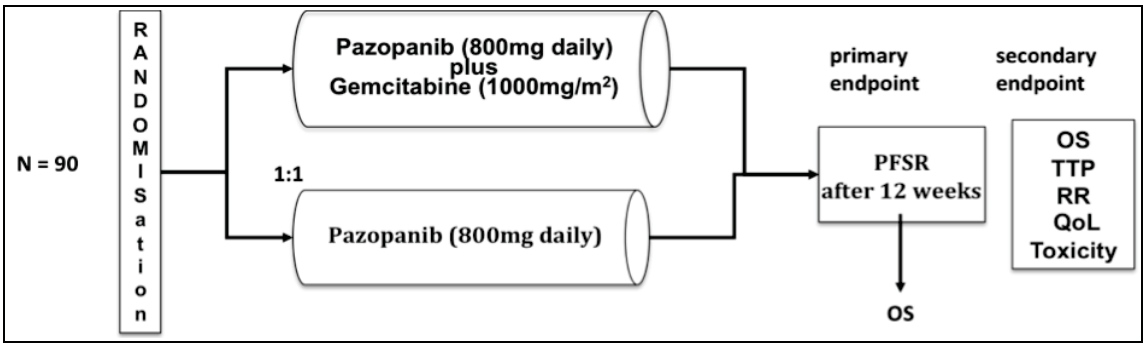
Secondary end-points: Overall survival (OS)
Time to Progression (TTP)
Response Rate (CR+PR)
Toxicity (CTCAE, version 4.0)
Quality of live (EORTC)

3. General design

This study will be a Phase II, national, multicenter, open labelled, prospective, parallel-group randomized study.

Patients will randomly be assigned to one of the treatment arms according to following stratification criteria: liposarcoma versus non liposarcoma.
After Verification of the eligibility criteria patients will be randomized to receive oral pazopanib 800mg once daily or pazopanib 800mg once daily in combination with gemcitabine 1000mg/m^2 d1, 8 qd21 until disease progression, death, unacceptable toxicity or withdrawel of consent for any reason.

Figure1: Trial design overview



4. Study population

4.1 Number of patients

90 patients will be enrolled in this study. Patients withdrawn from the trial will not be replaced.

4.2 Criteria for subject eligibility

4.2.1 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 study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

2. Age ≥ 18 years or legal age of consent if greater than 18 years

3. Histologically or cytological confirmed malignant soft tissue sarcoma including any subtypes except:
   - Gastrointestinal stromal tumors
   - Chondrosarcoma
   - Osteosarcoma
   - Ewing tumors and primitive neurectodermal tumors
   - Dermofibromatosis sarcoma protuberans
   - Inflammatory myofibroblastic sarcoma
   - Malignant mesothelioma
   - Mixed mesodermal tumors of the uterus

4. Patient must have relapsed or progressed after one or two prior chemotherapies including either an antrazyclin or ifosfamid or both. Patients with relapse or progress with liposarcoma or leiomyosarcoma must be offered a treatment with Trabectedin.

5. A female is eligible to enter and participate in this study if she is of:
   Non-childbearing potential (i.e. physiologically incapable of becoming pregnant), including any female who has had:
   - A hysterectomy
   - A bilateral oophorectomy (ovariectomy)
   - A bilateral tubal ligation
   - Is post-menopausal

   Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be g reater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).
   Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT
   Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and

in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).
- Oral contraceptives.
- Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

6. Adequate organ system function as defined in Table1 below:

Table 1: Definitions for Adequate Organ Function

System	**Laboratory Values**
Hematologic	
Absolute neutrophil count (ANC) Hemoglobin[1] Platelets	$\geq 1.5 \times 10^9$/L $\geq$ 9 g/dL (5.6 mmol/L) $\geq 100 \times 10^9$/L
Prothrombin time (PT) or international normalized ratio (INR)	$\leq$ 1.2 X upper limit of normal (ULN)
Partial thromboplastin time (PTT)	$\leq$ 1.2 X ULN
Hepatic[2]	
Total bilirubin AST and ALT	$\leq$ 1.5 X ULN $\leq$ 2.5 X ULN
Renal	
Serum creatinine Or, if greater than 1.5 mg/dL: Calculated creatinine clearance	$\leq$ 1.5 mg/dL (133 µmol/L) $\geq$ 50 mL/min
Urine Protein to Creatinine Ratio (UPC)[3]	< 1

1	Subjects may not have had a transfusion within 7 days of screening assessment.
2	Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN are not permitted
3	If UPC $\geq$ 1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1g to be eligible.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

8. Able to swallow and retain oral medication.

9. Patients with at least one measurable lesion according to RECIST (v1.1)

10. Life expectance > 3 months

4.2.2 Exclusion criteria

1. Presence of another concurrent malignancy. Prior malignancy in the last 5 years except adequately treated basal or squamous cell skin cancer or carcinoma in situ of the cervix

2. History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.

3. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:
   - Active peptic ulcer disease.
   - Known intraluminal metastatic lesion/s with risk of bleeding.
   - Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation.
   - History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.

4. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:
   - Malabsorption syndrome.
   - Major resection of the stomach or small bowel.

5. Presence of uncontrolled infection.

6. Corrected QT interval (QTc) > 450 msecs using Bazett's formula and/or family history of Long QT-Syndrome.

7. History of any one or more of the following cardiovascular conditions within the past 6 months:
   - Cardiac angioplasty or stenting.
   - Myocardial infarction.
   - Unstable angina.
   - Coronary artery bypass graft surgery.
   - Symptomatic peripheral vascular disease.
   - Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (see Appendix F for description).

8. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].
   Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <140/90 mmHg in order for a subject to be eligible for the study.

9. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
   Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible

10. Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).

11. Evidence of active bleeding or bleeding diathesis.

12. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.

13. Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug.

14. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.

15. Treatment with any of the following anti-cancer therapies:
   - Radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR.
   - Chemotherapy , immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib

16. Women who are pregnant or breast feeding

17. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Pazopanib or Gemcitabine

18. Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity, except alopecia.

19. Diarrhia Grad 3 and 4

20. A scrupulous medical history is required. Existing medication with prohibited and interactional medication must be asked in detail. Indispensable use of long term medication with CYP-inhibitors or inductors, explicitely (changes in long term medication is possible; refer to sections 6.4.4 and 6.4.8) is prohibited.

21. Insufficient liver function (refer to section 7.1.1: liver toxicity (C and D))

22. Autoimmune disease

23. Uncontrolled hypothyroidism

5. Medication
5.1 Pazopanib (GW786034, Votrient®)

The small molecule VEGFR inhibitor, pazopanib (GW786034), is in clinical development in the treatment of a variety of human cancers. Currently the EMEA approved Pazopanib for first line therapy in renal cell carcinoma (RCC) . Pazopanib is a potent and highly selective inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 tyrosine kinases. In pre-clinical angiogenesis models, pazopanib inhibited VEGF-dependent angiogenesis in a dose-dependent manner. In xenograft tumor models, twice-daily administration of pazopanib significantly inhibited tumor growth in mice implanted with various human tumor cells.

5.1.1 NonClinical studies

A range of nonclinical pharmacology, pharmacokinetic and toxicology studies have been performed of pazopanib. And are described in the investigator's brochure version 7.0 (19-February- 2010) and in the summery of product characteristics (version June 2010) and in all subsequent appearances.

5.1.2 Effects in humans

More than 1400 cancer patients have been enrolled in completed or ongoing clinical studies of pazopanib. Data collected to date show that oral pazopanib is absorbed after oral administration, has a reasonable safety profile, and encouraging efficacy in various oncology settings. The sections 5 and 6 of the investigator's brochure describe in details the results of clinical studies.

5.1.2.1 Summary of Pharmacokinetic and Pharmacodynamic Data

Results of pharmacokinetic and pharmacodynamic analyses demonstrate that pazopanib is absorbed after oral administration; a plateau is reached in steady-state systemic exposure at a dose of 800 mg daily; a maximum tolerated dose has not been reached at pazopanib doses up to 2000 mg daily; and doses of pazopanib that maintain plasma pazopanib concentrations above 15 g/mL - 20 g/mL (i.e., 800 mg daily and 300 mg twice daily) are associated with pharmacodynamic and clinical effects.

5.1.2.2 Drug-Drug Interactions

In vitro data indicate that pazopanib is a potential inhibitor for CYP2C9, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Coadministration of pazopanib and medications which are substrates for the CYP450 enzymes and which have the potential to cause serious and/or life-threatening adverse events is **PROHIBITED**.

5.1.2.3 Summary of Adverse Reactions (ARs) and Serious Adverse Reactions (SARs)

The most common AEs reported to date include diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) increase, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon. The most common SARs occurring in patients enrolled in pazopanib studies regardless of treatment assignment include vomiting, diarrhoea, abdominal pain, hypertension / hypertensive crisis, dyspnea, pleural effusion, pyrexia, anemia, dehydration, and pulmonary embolism. There is no preclinical evidence of an effect on QTc with pazopanib, however in clinical studies with pazopanib, two SARs of QT prolongation or Torsade de Pointes have occurred. One patient received amiodarone proximal to the event and the other patient discontinued pazopanib due to spinal hemorrhage from a hemangioblastoma. Seven days later the patient developed polymorphic ventricular tachycardia. Both SARs were resolved.

5.1.3 EORTC phase II trial (EORTC62043 / VEG20002)

Pazopanib was explored in relapsed and refractory STS in an EORTC single arm phase II study[24]. This study was stratified by histology (liposarcoma vs leiomyosarcoma vs synovial sarcoma vs other soft tissue sarcoma subtypes). The drug was well tolerated: amongst 142 documented cases, grade 3-4 neutropenia, and thrombopenia were seen in 6 and 2 pts, respectively, grade 3-4 bilirubin, AST, ALT, and creatinine elevations in 9, 5, 7, and 4 pts, respectively. Main other toxicities (all grades; grade 3-4) were 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%).

5.1.4. Summary of Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are available for two Phase II studies (VEG20002 and VEG102616); a review of the data from these 2 studies suggest that treatment-emergent laboratory abnormalities of all grades occurring commonly in patients receiving pazopanib include AST and ALT elevations, hyperbilirubinemia, alkaline phosphatasemia, amylase and lipase elevations, elevations in creatinine, hyponatremia, hyperkalemia, lymphopenia, leukopenia, thrombocytopenia, neutropenia and anemia, hyperglycemia, and increased thyroid-stimulating hormone (TSH). Concomitant elevations in transaminases and bilirubin have been rare; for example, in Study VEG102616 they were observed in 2 (<1%) patients. Elevations in amylase and lipase have been primarily Grade 1 or 2. Most have been asymptomatic; clinical signs and symptoms of pancreatitis have been uncommon. Hyponatremia and hyperkalemia have not been reported concomitantly in the same patients in a manner that would suggest adrenal insufficiency.

5.1.5 Summary of Efficacy Data in STS

Pazopanib 800 mg once daily showed encouraging efficacy signals as monotherapy in the following settings:
Advanced or metastatic soft tissue sarcoma (EORTC phase II study): rate of progression-free survival (PFSR) at 12 weeks, based on investigator assessment, was 16 of 42 patients (38.1%) for leiomyosarcoma; 18 of 37 patients (48.6%) for synovial sarcoma; 16 of 44 patients (36.4%) for other types of sarcoma, but only 4 of 19 patients (21.1%) in liposarcoma. For all histology subtypes except liposarcoma, the PFS at one year was 14 % and the overall survival 34% (not published).

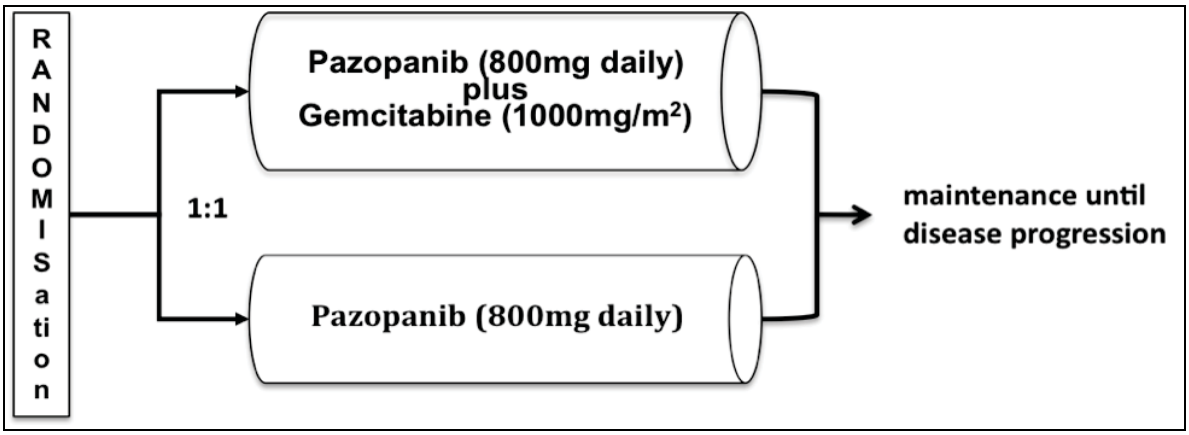
5.2 Gemcitabine

Gemcitabine is a widely used cytotoxic drug. It is indicated as single agent or in combination schedules in advanced or metastatic non-small lung cell cancer, pancreatic cancer, bladder cancer, ovarian cancer, breast cancer and head and neck cancer.
Gemcitabine (2´,2´-difluorodeoxycytidine, dFdC) is a fluorinated analog of deoxycytidine (dCTP). It is an S-phase specific drug that requires intracellular transport and activation to its di- and triphosphate forms to exert its cytotoxic effects. The active di- and triphosphate form is a potent inhibitor of ribonucleotide pools. In contrast, the active triphosphate form is incorporated into DNA, resulting in interference with DNA chain elongation and disruption of cell growth. Once the gemcitabine triphosphate metabolite is incorporated into DNA, one additional nucleoside is incorporated, after which DNA chain synthesis is terminated[43,44].
The ability of cells to accumulate gemcitabine triphosphate was found to be saturable at gemcitabine dose ratest that produced plasma levels of 10-25µM. For using Gemcitabine as effective as possible it was postulated, that a longer exposure to the drug may result in a greater antitumor effect. The proposition that prolonged infusion gemcitabine (10mg/m^2/min) results in higher clinical response rates than with bolus infusion was addressed in a randomized phase II trial in pancreatic cancer[45]. In summary RR and median survival were superior in the group of patients receiving a fixed-dose-rate infusion (1500mg/m^2 at 10mg/ m^2 per minute), compared with the group of patients who received gemcitabine as a 30min bolus infusion (2200 mg/m^2 over 30min). Antitumorefficacy of Gemcitabine in general is therefore postulated to be schedule related. By reviewing the published trials using gemcitabine monotherapy in soft tissue sarcoma no correlation on RR or OS for different schedules are documented (see 1.3 Rationale for Trial).
No randomized trial comparing fixed dose rate and bolus infusion are published.
The main documented side effects of gemcitabine are the supression of bone marrow function, nausea and vomiting, raising liver enzymes, headache, distress, haematurie and proteinuria. Please refer to summary of product characteristics GEMZAR Version May 2010.

6. Study Procedures and Methodology

6.1 Study Schedule Overview

Figure 2: Study Schedule Overview



6.2 Treatment

For administrative reasons (gain of further information for the authorized form, according to § 3 (3) GCP-V) Gemcitabine and Pazopanib will be defined as investigational medicinal products (IMP).
Gemcitabine will be purchased by the participating center.
Pazopanib will be labeled and provided on demand by the Aspen Bad Oldesloe GmbH. Pazopanib tablets are provided as 200 mg and 400 mg tablets, which contain pazopanib monohydrochloride salt equivalent to 200 mg and 400 mg of the free base, respectively. We suggest to applicate 2x400 mg tablets to approach the initial dose level of 800 mg. 200 mg tablets should only be used in case of dose deescalation.

All patients will receive pazopanib orally, 800 mg once daily for the duration of the study. In this study, a 3 week interval of dosing will be considered as a “treatment period” or “cycle of therapy”.

- Pazopanib should be taken at least one hour before or at least two hours after meal.
- The time of day for administration of study medications should be relatively constant.
- If a patient misses a dose, the patient should take the dose as soon as possible, but not less than 12 houres before the next dose is due.
- If the next dose is due in less than 12 houres, the patient should skip the missed dose and take the next dose as scheduled.
- In the event of vomiting at any time after taking a dose of pazopanib, patient should wait until the treatment of the next scheduled dose to take study medication.

6.2.1 Arm A (Pazopanib + Gemcitabine)

Pazopanib at a fixed dose of 800 mg oraly daily, until disease progression.
Gemcitabine at a dose of 1000 mg/m^2 i.v. over 30min (day 1, 8, repeated after 21days), until disease progression.

6.2.2 Arm B (Pazopanib)

Pazopanib at a fixed dose of 800 mg oraly daily (until disease progression).

6.3 Treatment duration

Treatment in both arms will be administered until progression or intolerable toxicity.

6.4 Concomitant medication

All concomitant medications taken during the study will be recorded with dose information, and dates of administration.
Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

6.4.1 Antiemetics

Due to the low emetogen potential of either Pazopanib and gemcitabine no standard antiemetic medication is recommended. In case of vomiting or emesis procedures according to institutional guidelines should be used.

6.4.2 Antibiotics

In patients with diarrhoea and neutropenia, even in the absence of fever, empiric use of antibiotics as prophylaxis against bowel sepsis should be strongly considered. Procedures according to institutional guidelines and or the DGHO guidelines should be used. Of note: the use of a quinolone can not be recommended in this setting due to the potential for QT prolongation (refer to 6.4.4).

6.4.3 Growth factors

Haematopoietic growth factors (i.e., G- or GM-CSF) may be used according to institutional guidelines to treat febrile neutropenia, and as primary or secondary prophylaxis in case of delayed haematologic recovery during the priory cycle of treatment in Arm A. Growth factors must be discontinued at least 48 hours prior to initiation of the next treatment of chemotherapy.

6.4.4 Prohibited medication

Subjects should not receive other anti-cancer therapy while on treatment in this study (see 4.2.2).
CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X recepto transfection assay suggested some potential for human CYP3A4 induction at high concentration results from drug-drug interaction studies conducted in patients with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with CAUTION due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medicant although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise CAUTION for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics and other drugs with the potential for QT prolongation: bepridil, flecainide, lidocaine, mexiletine, amiodarone,
  quinidine, propaf
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine

6.4.5 Specific recommendations regarding radiation during study

Gemcitabine is a potent radiosensitizer. If possible, radiotherapy shoud be avoided during the study. In case of inevitable need of radiatio the LKP should be contacted.

6.4.6 Specific recommendations regarding anticoagulants

Results from drug-drug interaction studies conducted in patients with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in patients with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g. warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Patients taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

6.4.7 Specific recommendations regarding hypoglycemic therapy including insulin

Results drug-drug interaction studies conducted in patients with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in patients treated with another small molecule tyrosine kinase inhibitor, sunitinib (British Journal of Cancer 2008: 99, 1380). Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Patients should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

6.4.8 Potential Impact of Other Medications on Pazopanib

Results *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with CAUTION.
Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Coadministration of strong CYP3A4 inhibitors is **prohibited beginning 14 day prior to the first dose of study drug until discontinuation from the study,** therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

Strong CYP3A4 inhibitors include (but are not limited to)

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone
- 3rd generation antihistamines: terfenadine
- Foodstuff: grapefruit juice

CYP3A4 inducers

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to):

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg),
- methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: modafinil, pioglitazone, troglitazone
- Medicinal plants and natural products: amber

6.5 Assessments and Guidelines for Visits

6.5.1 Baseline Assessment

Consenting patients will have the following screening/baseline assessments performed prior to the first treatment.

- Detailed medical history including previous cancer history and cancer treatment. Any additional relevant medication taken one year prior to study start will also be recorded.
- Physical examination including weight, height and vital signs (blood pressure, heart rate, respiratory rate, body temperature)

  As hypertension is a common drug-related AE observed from other pazopanib studies, blood pressure monitoring is mandatory. The following instructions should be followed for cuff measurement of blood pressure:
  Sitting blood pressure should be measured after the subject has been sitting quietly for at least 10 minutes. The same cuff method should be used to measure blood pressure throughout the study. All measurements will be made on the same arm using the same cuff size and the same equipment. Diastolic blood pressure will be measured at the disappearance of Korotkoff sounds - phase V. If possible, measurements will be taken by the same staff member at each visit. At the baseline visit, blood pressure should be measured three times at approximately 2-minute intervals. All three blood pressure values should be recorded. These three values should be averaged to obtain mean diastolic blood pressure, and mean systolic blood pressure. The mean diastolic and the mean systolic blood pressures are to be used to determine if the subject's blood pressure is within the well-controlled range; or if the subject needs medical attention. At all later visits, a single blood pressure is measured. If both the systolic and the diastolic blood pressure is within the well- controlled range (defined as blood pressure below 140/90 mmHg) this value is recorded on the CRF. If either the systolic or the diastolic pressure is outside the well-controlled range, three blood pressures are measured as described for the baseline visit and the mean blood pressure values are entered on the eCRF and used to determine if the subject needs medical attention. Refer to Section 7.1 for the algorithm of dose modification of study medication in the event that hypertension occurs.

- Adverse events

- Cancer signs and symptoms

- Complete blood counts (including hemoglobin, white blood cells, neutrophils, lymphocytes, and platelets) and serum chemistry including sodium, magnesium potassium, phosphate, creatinine, urea bilirubin, alkaline phosphatase, γ-GT, AST, ALT, glucose, albumin, PT/INR, PTT , LDH
  Note: In case of co-administration of pazopanib with the anticoagulant

warfarin (or its derivatives): International normalized ratio (INR) should be monitored within three to five days after initiating, escalating/de-escalating or discontinuing pazopanib therapy, and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.

Table 2: Hematology and Clinical Chemistry

Hematology	**Clinical Chemistry**		
Hematocrit	Calcium	***Renal Function***	***Liver Function***
Hemoglobin	Magnesium	Albumin	ALT
Red blood cell count	Potassium	Urea	AST
White blood cell count	Sodium	Creatinine	Alkaline phosphatase
Lymphocytes	Inorganic Phosphate		γ-GT
Neutrophils (total)	Glucose		Total bilirubin
Platelet count	Lactate dehydrogenase		

- Thyroid function: TSH and free T4
- Urine dipstick
- Serum pregnancy test (for women of childbearing potential).
- Cardiac function:
  LVEF (MUGA or cardiac ECHO scan)
  12-lead ECG (after at least 10 min rest) and QTc measurement will be recorded.

  In clinical studies with pazopanib, events of QT prolongation have occurred. A 12-lead ECG will be obtained at Baseline and than on day 1 of each cycle during study treatment. Prior to each ECG test, the patient should be at rest for approximately 10 minutes. The patient should be in the semi-recumbent or supine position; the same position must be used for all subsequent ECG tests. All ECGs must include QTc measurements either manually or machine calculated using Bazett's formula, and recorded in the CRF. The Bazett's formula is:

  $$QTcB = QT / RR1/2$$

  At baseline, if QTc interval is > 480 msecs, subject will be excluded from the study.
  If a QTc≥ 500 msec is noted on a scheduled or unscheduled ECG, then 2 additional ECGs should be obtained within 5 minutes to confirm the abnormality. The average QTc will be determined from the 3 ECG tracings by manual evaluation and will be used to determine continued eligibility. If the average QTc is less <500 msec, the subject may continue therapy. If the average QTc is ≥500 msec, the study treatment should be discontinued immediately.

The patient should be treated appropriately for QTc prolongation and monitored until resolution is documented by a repeat ECG with QTc intervals returning to < 480 msec.

- Radiological assessment **within 2 weeks** prior to start of treatment:
  All sites of disease should be identified by MRI or CT and recorded at baseline. At least one measurable lesion must be identified as target lesion and measured. This scan must be performed within 2 weeks prior to first treatment. Radiological imaging of the chest, abdomen and all other sites of disease has to be performed (CT/MRI-scan of the thoracic and abdominal region).

- Quality of life assessment (QLQ-C30) will be performed within two weeks prior to randomization

- Obtain paraffin embedded tumor tissue

- Tumor tissue: formalin fixed paraffin embedded tumor blocks and/or representative H/E (haematoxylin/eosin) slides (preferably both) must be sent for histological central review. Refer to section: 15

- When participating the translational research programm: blood sample 30ml will be drawn before the start of treatment. Refer to Appendix H and section 16

The investigator will confirm the patient's eligibility after all baseline scans and laboratory results have been reviewed.

6.5.2 Randomisation

After checking suitability to enter the study, patients who agree to participate must sign the informed consent form before undergoing any study related procedures or treatment. Patients will afterwards be randomized to Arm A or B and stratified according Liposarcoma and Non-Liposarcoma. Stratification will be done using the result of primary histological examination, not using the results of reference histological review.

6.5.3 Assessments during treatment period

- In this trial, a "treatment period" will be defined as 21 days.
- Quality of life assessment: QLQ-C30 will be performed on day 1 of each cycle (during maintenance).
- Visits with a frequency of 3 to 8 weeks will have a visit window of +/- 7 days.
- Visits with a frequency of 12 weeks will have a visit window of +/- 14 days.

6.5.3.1 The treatment periods (cycle 1 and further cycles)

6.5.3.2 Day 1

The examination should include:

- WHO performance status, blood pressure, pulse rate and body weight
- Adverse events
- Cancer signs and symptoms
- Complete haematologic and serum chemistry (see Table 2)
- PT/INR, PTT
- Urine dipstick
- 12-lead ECG with QTc measurement (refer to 6.5.3.1)
- Quality of life assessment: QLQ-C30

6.5.3.3 Day 8

Visit with a frequency of 7 days of less will have a visit window of +/- 3 days.
This examination should include:

- WHO performance status, blood pressure, pulse rate and body weight
- Adverse events
- Cancer signs and symptoms
- Complete haematologic and serum chemistry (see Table 2)

6.5.3.4 Subsequent treatment periods

When participating the translational research programm: blood sample 30ml will be drawn after 6 weeks of treatment.

After 6 weeks, accordingly after 2 admitted cycles, and before starting third cycle patients will have documentation of disease status (CT/MRI).
CT or MRI will be repeated after 12 weeks and afterwards every 8 weeks until progression. (And any other time during the conduct of the study that there is an indication of a change in disease status: same lesions and method as at study entry.)

Examinations on d1 and d8 of each cycle repeat as presented in 6.5.3.2 and 6.5.3.3 until end of study.

6.5.4 End of treatment

This visit will have a visit window of +/-14 days.
This examination should include

- WHO performance status, pulse rate and body weight
- All adverse events.
- If applicable: documentation of disease status (CT/MRI)
- Complete blood counts (see Table 2)
- Serum chemistry (see Table 2)

- PT/INR, PTT
- TSH, fT4
- Urine dipstick
- 12-lead ECG with QTc measurement (refer to 6.5.3.1)
- Blood pressure (refer to 6.5.3.1)
- LVEF if clinically indicated
- Quality of life assessment: QLQ-C30
- 30ml blood when participating the translational research programm

6.5.5 Follow-up Period

After progression, patients will be followed every 3 months ± 28 days until death. The investigator will record disease status, protracted toxicities, further treatment and patient survival.

This examination should include

- WHO performance status, pulse rate and body weight
- All adverse events.
- Quality of life assessment: QLQ-C30
- TSH, fT4
- MUGA or cardiac ECHO scan, 12-lead ECG if clinically indicated

6.5.6 Study Completion

The study will be considered complete when:

- all patients have exited the study following progression, or
- all patients have discontinued (maintenance-) treatment.

Overall survival post study completion will be assessed by clinical visits for a maximum of two years after last patient out.

6.5.7 Patient Withdrawal

Patients may be withdrawn from the study by the investigator or terminate their participation prematurely based on the following:

- Post-consent determination of ineligibility based on safety or eligibility criteria
- Lack of therapeutic efficacy, as evidenced by progression
- Physician’s judgment following an adverse event
- Termination by the Sponsor, or a regulatory authority
- Any other reason for withdrawal that the study physician or patient indicates is in the overall best interest of the patient

All patients will be followed by clinical visitations or telephone contact post withdrawal for assessment of overall survival.
Patients who withdraw consent prior to receiving any therapy will be withdrawn from the study and no follow-up safety surveillance is required.
Patients who voluntarily withdraw consent or who are withdrawn by the study physician for any reason after receiving therapy will be followed-up for at least 7 days. The purpose of this follow-up is to capture all adverse events and document any serious, procedure related adverse events.
If a patient dies prior to the last scheduled study visit**,** the date and cause of death will be recorded.

7. Dose and schedule modifications

7.1 General notes regarding dose modifications for therapy- related toxicity

Toxicity will be graded according to CTCAE, Version 4.0 (Appendix C).
For adverse events which are considered by the Investigator unlikely to develop into serious or life-threatening events and which do not result in a delay or interruption of therapy (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption.
No dose reduction of either pazopanib or gemcitabine is foreseen for an individual patient. Skipped doses or termination of treatment will be based on the observed toxicities as specified below. No dose adjustments are allowed except for body weight changes of more than 10%. Missed doses will not be made up for. A rounding up or down of the dose is acceptable to allow practical ease of administration (±10%).
Dose interruptions or reductions may be required following potential drug-related toxicities: bone marrow suppression, hypertension, proteinuria, hepatotoxicity, bleeding events, vascular thrombosis, thrombocytopenia/neutropenia, prolongation of QTc and other adverse events that have been reported in response to treatment with pazopanib and or gemcitabine.
At each visit during the treatment period, patients should first be evaluated for the occurrence of adverse events and laboratory abnormalities. Specific recommendations for management of these possible adverse events along with guidelines for dose delay/ modification or discontinuation of study treatment are provided below.
If a patient's treatment has been interrupted for more than 14 days due to toxicity or to reasons other than toxicity (unplanned travel or vacation, or lack of transportation to the site), the investigator must contact PAPAGEMO study commitee to review the patient's condition in order to resume the treatment. In case of toxicity, the re-challenge is possible if the patient's condition has been stable and patient must have recovered from toxicity at reduced dose level.

Table 3: Other Clinical Significant Adverse Events

Other Clinically Significant Adverse Events	
Grade 1	Continue study treatment at the current dose; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	1. Interrupt study treatment until toxicity resolves to Grade 1. 2. Restart study treatment at a lower dose; monitor as clinically indicated.
Recurrent Grade 2/3, if clinically significant	Discontinuation of study treatment and follow-up per protocol.
Grade 4	Discontinuation of study treatment and follow-up per protocol. Note: If the patient is benefiting from therapy contact the medical monitors to discuss course of action.

7.1.1 Dose and schedule modifications of Pazopanib

If dose reduction is necessary:
- Two dose reductions are permitted in a stepwise fashion: initially to 600 mg and subsequently to 400 mg if necessary. However if toxicity is not resolved at 400 mg a further down titration to 200 mg may be considered, the investigator should discuss the down titration to 200 mg with the PAPAGEMO study commitee before this dose adjustment.
- Dose can then be increased step-wise back up to 800 mg in 200 mg steps after monitoring for 10-14 days at each step if toxicity does not recur or worsen.

If you need further guidance or clarification, please contact the medical monitors via the mailbox address (front page).

Table 4: Adverse Event and Resulting Dose Modifiation Pazopanib

Adverse events and descriptions	**Dose modification**
Hypertension	
(A). Asymptomatic and persistent SBP: - ≥140 < SBP < 170 mmHg, - or DBP ≥ 90 and ≤ 110 mmHg, - or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHG)	1. Continue study treatment at the current dose. 2. Adjust current or initiate new antihypertensive medication(s). 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled blood pressure (BP). If BP is not well controlled within 2 weeks, interrupt study treatment.
(B). Asymptomatic SBS, ≥170 mmHg, - or DBP ≥110 mmHg, - or failure to achieve well-controlled BP within 2 weeks in scenario (A).	1. Consider reducing or interrupting study treatment. 2. Adjust current or initiate new antihypertensive medication(s). 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. 4. Restart study treatment at lower dose once BP is well-controlled.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication	Step 1. Interrupt Pazopanib. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also

	recommended. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions	Discontinue Pazopanib and continue follow-up per protocol
Proteinuria	
UPC < 3	Continue study treatment at current dose; monitor as clinically indicated
UPC 3	1. Obtain a 24-hour urine protein. 2. If 24-hour urine protein is < 3g, patient may continue treatment at the current dose. OR If 24-hour urine protein is 3g, interrupt treatment until UPC returns to < 3. Restart therapy at lower dose. Monitor UPC for the remainder of the overall treatment period. If UPC 3 obtain a 24-hour urine protein. 3. If 24-hour urine protein is 3g following repeat dose reductions, discontinue treatment and follow-up per protocol.
Hemorrhage/Bleeding/Coagulopathy	
Grade 1	For hemoptysis, interrupt Pazopanib and consider whether further treatment with Pazopanib is appropriate For other grade 1 hemorrhage/bleeding events continue study treatment at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue Pazopanib and continue follow-up per protocol. Otherwise, interrupt Pazopanib until the AE resolved to ≤ Grade 1. Step 2. Restart Pazopanib; consider reducing dose and monitor as clinically indicated. .
Grade 3 or 4, or Recurrent Grade 2 event after dose Interruption /reduction.	1. Discontinuation of study treatment and follow-up per protocol. <u>Note:</u> If abnormality is not clearly associated with clinical consequences, 2. contact PAPAGEMO monitors to discuss the potential for continuation of study treatment. If agreed, patient may restart treatment at lower dose.

Vascular Thrombosis	
Grade 2	Continue study treatment at the current dose; monitor as clinically indicated.
Grade 3	1. Interrupt study treatment. 2. Start to treat the patient with Low Molecular Weight Heparin (LMWH). <u>Note</u>: Warfarin is allowed but INR has to be monitored (refer to 6.4.6) 3. Resume study treatment at the current dose during the period of full-dose anticoagulation if all of the following criteria are met: - The patient must have been treated with LMWH for at least one week. - No Grade 3 or 4 hemorrhagic events have occurred while on anticoagulation treatment. - Patient should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment.
Grade 4	Discontinuation of study treatment and follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue Pazopanib and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue Pazopanib with current dose; monitor as clinically indicated
Grade 3 or 4	Step 1. Interrupt Pazopanib until toxicity resolves to ≤ Grade 2. Step 2. Restart Pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue Pazopanib and follow-up protocol.
Prolongation of QTc interval	
QTc* 480 < 500 msec	Continue study treatment; monitor as clinically indicated.
QTc* 500 msec	Discontinue study treatment and continue follow-up per protocol.
* Adjustment by using Bazett's formula (ECG machine or manually)	

Liver toxicity	
As a general rule, since many subjects are taking multiple concurrent medications, it is critical to do a thorough evaluation of the patients concurrent medications (and ensure all are recorded in the CRF), and identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Record alcohol use on the liver event alcohol intake form in the CRF. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document progression of malignancy.	
(A): ALT/AST 3.0 x ULN	Continue study treatment at current dose with full panel liver function tests (LFTs)[1] monitored as per protocol.
(B): ALT > 3.0 x ULN to 8.0 x ULN without bilirubin elevation (defined as total bilirubin[2] < 2.0 x ULN or direct bilirubin 35%) and without hypersensitivity symptoms (e.g., fever, rash)	<u>Liver Event Monitoring Criteria:</u> 1. Continue study treatment at current dose level. 2. Perform the following assessments for excluding hypersensitivity and other contributing factors: - Eosinophil count - Viral serology[4] for hepatitis A, B and C - Liver imaging 3. Monitor patient closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST reduced to Grade 1.
(C): ALT > 8.0 x ULN without bilirubin elevation (defined as total bilirubin[2] < 2.0 x ULN or direct bilirubin 35%) and without hypersensitivity symptoms (e.g., fever, rash).	<u>[1]st occurrence – Liver Event Interruption Criteria[3]:</u> 1. Interrupt study treatment until toxicity resolves to Grade 1 or baseline. Report the event to KKS-Halle as an SAE within 24 hours of learning of its occurrence and complete the CRF liver event forms. Make every reasonable attempt to have patients return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. 2. Collect PK sample (see SPM) and perform the following assessments for exclusion of hypersensitivity and other contributing factors: - Eosinophil count - Viral serology[4] for hepatitis A,B,C and E, cytomegalovirus[4], Epstein Barr

	virus[4] (IgM antibody, heterophile antibody, or monospot testing) - Liver imaging 3. Monitor patient closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until LFTs reduced to Grade1. 4. If the patient is benefiting from the study treatment, contact medical monitors for possible re-challenge. Re-treatment may be considered at the same dose if <u>all</u> of following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin < 1.5 x ULN or direct bilirubin 35% - No hypersensitivity signs or symptoms - Patient is benefiting from therapy. If approval for re-treatment is granted, the patient must be re consented (with a separate informed consent specific to hepatotoxicity). <u>Recurrence – Liver Event Stopping Criteria[3]:</u> Discontinue study treatment permanently and monitor patient closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. At the time of the recurrence, collect PK sample and complete the CRF liver event forms.
(D). ALT > 3.0 x ULN with concomitant elevation in bilirubin[2] (defined as total bilirubin 2.0 x ULN; with direct bilirubin > 35%) or with hypersensitivity symptoms (e.g., fever, rash).	Liver Event Stopping Criteria[3] 1. Discontinue study treatment immediately, report the event to KKS-Halle as an SAE within 24 hours of learning of its occurrence and complete the CRF liver event forms. Make every reasonable attempt to have patients return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments.

	2. Consult a gastroenterologist/ hepatologist collect PK sample, and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology[4] for hepatitis A, B, C and E, cytomegalovirus[4], Epstein-Barr virus4 (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody[4], anti-smooth muscle antibody4, anti-mitochondrial antibody[4] - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging 3. Monitor patient closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin[2] elevation without concurrent ALT increases (defined as ALT < 3 X ULN).	1. Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Study treatment inhibits UGT and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. 2. If bilirubin is > 2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue study treatment at the same dose. If bilirubin is >35% direct (conjugated), further evaluation for underlyin cause of cholestasis should be performed.

7.1.2 Dose and schedule modifications of Gemcitabine

If dose reduction is necessary:
Two dose reductions are permitted in a stepwise fashion: initially to 75% and subsequently to 50% if necessary. However if toxicity is not resolved at 50% a further down titration is not permitted. In this case please contact the medical monitors to discuss further procedere. If patient profits of therapy, dose reduction of pazopanib can be discussed. Otherwise discontinue study treatment and follow-up per protocol.

Table 5: Adverse Event and Resulting Dose Modifiation Gemcitabine

Thrombocytopenia /Neutropenia	
Grade 1	Continue study treatment at the current dose; monitor as clinically indicated.
Grade 2	Continue study treatment at the current dose; monitor as clinically indicated. Consider G-CSF for primary prophylaxis (refer to 6.4.3)
Grade 3 or 4	1. Interrupt study treatment until toxicity reduced to Grade 2. (If interruption lasting longer than 2 weeks contact the medical monitors to discuss course of action.) 2. Restart study treatment with lower dose 3. Applicate G-CSF for primary (refer to 6.4.3) prophylaxis.
Recurrent Grade 3/4 event after dose reduction for 50% and secondary prophylaxis with G-CSF	Discontinuation of study treatment and follow-up per protocol. Note: If patient is benefiting from study treatment, contact the medical monitors to discuss course of action.

Note: In case of anemia no dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above (see 7.1.1)

7.2 Patient Monitoring and Management Guidelines for Certain Treatment

7.2.1 Fatigue and asthenia

Fatigue and asthenia are commonly reported symptoms in patients with cancer. Both fatigue and asthenia have been reported with pazopanib and other angiogenesis inhibitors in this class.
To avoid any delay in the treatment of easily manageable conditions such as electrolyte disorders and to quickly recognize possible serious conditions such as cardiac dysfunction, the following steps when caring for patients with fatigue and asthenia are recommended. Patients complaining of grade 2, 3, or 4 fatigue and/or asthenia should be investigated as appropriate including at a minimum the items outlined below.

- Patients with grade 3 or more fatigue and/or asthenia should be seen immediately.
- A workup should include a detailed history and physical examination, measurement electrolytes, liver function tests, an electrocardiogram, chest x-ray, thyroid function tests, and a early morning cortisol.
- Electrolyte abnormality should be treated with replacement therapy.
- An ACTH stimulation test should be performed if the cortisol concentration is < 10mcg/dL (280nmol/L).
- If the patient's history or physical examination point towards symptoms or signs of congestive heart failure, the appropriate investigations should be performed including an echocardiogram.
- Patients should be closely monitored on a weekly basis or more frequently if clinically indicated for duration of severe fatigue and asthenia.

7.2.2 Abdominal pain

Abdominal pain is not an uncommon symptom with vascular endothelial growth factor (VEGF) receptor antagonists, of which pazopanib is one. Bowel perforations have been reported in clinical trials of pazopanib and with other agents in this class. Bowel perforations have been associated in some patients with tumor in the bowel wall, or diverticulitis, while in others there has been no clear explanation. Although bowel perforation is a rare event, investigators and study staff at the site are adviced to be vigilant of this potential complication in patients receiving pazopanib.

7.2.3 Nausea and Vomiting

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are unable to retain pazopanib and Gemcitabine.
Routine pre-medication for nausea is not necessary, but symptomatic subjects should be treated with standard anti-nausea/anti-emetic therapy as necessary.
If a subject vomits after taking study medication, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking pazopanib at the next scheduled dose on the following day.

If vomiting persists then the subject should contact their physician.

To prevent or treat nausea and vomiting standard medications are recommended. Depending upon approved medications in your region, these may include: 5-HT_3 receptor antagonist (granisetron, ondansetron, dolasetron mesylate); NK-1 receptor antagonists such as aprepitant, metoclopramide, phenothiazines (prochlorperazine); corticosteroids, (dexamethasones, prednisone); and cannabinoids (dronabinol).

7.2.4 Surgical procedures / wound healing complications

Pazopanib therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during pazopanib treatment, pazopanib should be withheld until the wound is fully healed.

Pazopanib should be withheld for at least 5 weeks before conducting elective surgery. Emergency surgery should be performed as appropriate without delay.

7.2.5 Congestive heart failure

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating pazopanib therapy in patients with these risk factors. No significant increased incidence of CHF in patients treated with pazopanib was observed in NSCLC or CRC trials. Pazopanib should be permanently discontinued in Grade ≥3 left ventricular systolic dysfunction.

7.2.6 Diarrhea

In cancer patients, diarrhea can be debilitating and potentially life threatening, with dehydration, renal insufficiency, and electrolyte imbalances. Pazopanib as a monotherapy has been associated with an increased incidence of diarrhea, which is grade 1 or 2 in the majority with grade 3/4 diarrhea occurring in approximately 4% of subjects. The incidence and severity may increase when administered with Gemcitabine. Early identification and intervention is critical for the optimal management of diarrhea.

Uncomplicated diarrhea is considered mild to moderate and defined as CTCAE Grade 1 to 2 with no complicating signs or symptoms.
Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with 1 or more of the following signs or symptoms; cramping, nausea/vomiting, Grade
2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, and/or dehydration. If complicated diarrhea goes unrecognized or untreated, it may lead to death.

Experience thus far suggests that, when pazopanib is used as monotherapy, uncomplicated CTCAE Grade 1 or 2 diarrhea may ensue. In rare cases, subjects treated with monotherapy pazopanib may develop debilitating and potentially life-threatening diarrhea with dehydration, renal insufficiency, and electrolyte imbalances. The pathophysiologic mechanism of diarrhea with pazopanib is not known.
The following broad general management principles are recommended as means by which a subject with diarrhea may avoid more serious complications. Guidelines such as these should never replace sound clinical judgment. Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea. The guidance provided here is a modification of the ASCO guidelines.
Early identification and intervention is critical for the optimal management of diarrhea.

- A subject's baseline bowel pattern should be established so that changes in that pattern can be identified.

- Subjects should be educated on the signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

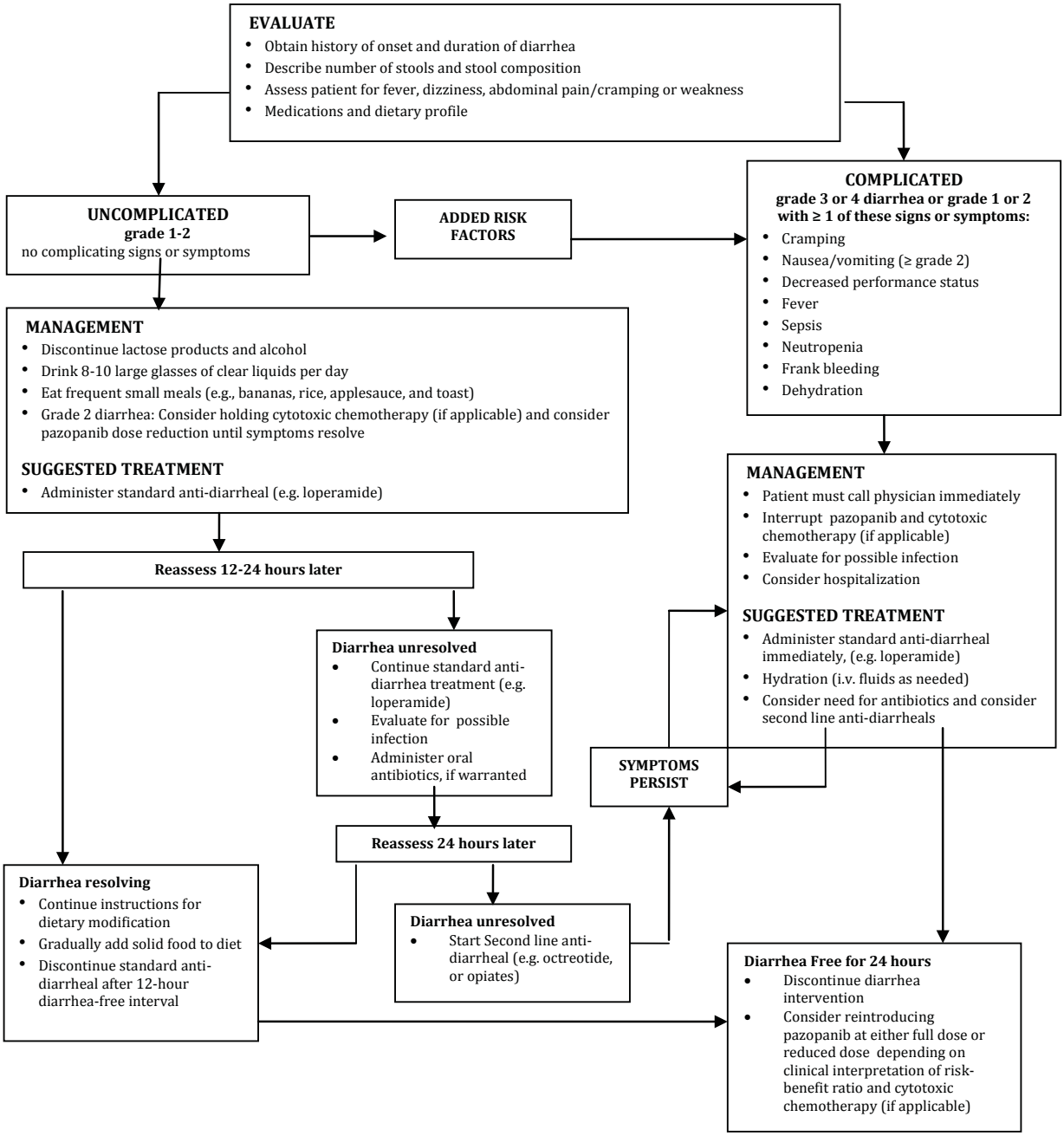
- At the initiation of diarrhea, an assessment of frequency, consistency, duration and other symptoms such as fever, cramping pain, nausea, vomiting, dizziness and thirst should be taken to identify subjects at high risk of complications.

Several treatments have demonstrated efficacy in diarrhea management:

- Loperamide, administered as an initial 4-mg dose, followed by 2-mg doses after every unformed stool with a maximum of 16mg per day. This dose and regimen are moderately effective. Continuation of loperamide is suggested until the subject is diarrhea-free for 12 hours. Dose should not exceed a maximum of 8 tablets (16 mg) per day.

- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. In the treatment of chemotherapy-induced diarrhea, octreotide can be administered at doses ranging from 100μg twice daily to 500μg 3 times daily, with a maximum-tolerated dose of 2000μg 3 times daily in a 5-day regimen. However, the effect of octreotide on diarrhea associated with use of pazopanib is unknown.

Figure 3: Flowchart Diarrhea



7.2.7 Treatment of Investigational Product Overdose

7.2.7.1 Pazopanib

No maximum tolerated dose (MTD) was reached in dose escalation studies of pazopanib administered as a single agent at doses of up to 2000mg/day. Peak pazopanib exposures occurred at 1000mg/day; similar or lower exposures were seen at doses between 1000-2000mg/day.
In the event of overdose (defined as administration of more than the protocol-specified dose), the investigator should contact the PAPAGEMO medical monitors and additional monitoring of the patient for AEs/SAEs and laboratory abnormalities should be considered. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitors based on the clinical evaluation of the patient. A plasma sample for pharmacokinetic analysis may be requested on a case-by-case basis. Information regarding the quantity of the excess dose should be documented in the CRF.

7.2.7.2 Gemcitabine

No specific antidot is known. On spec of overdosing repeated full blood count controlls are recommended. When indicated symptomatic therapy is mandatory. For further information please refer to SPS.

7.2.8 Recommendations for Management of Hypertension

Based on consultation with experts in the field, we recommend the use of calcium channel blockers and ACE inhibitors as the first line and second line therapy respectively, for treatment related hypertension. However it is allowed to follow local practices and guidelines at the discretion of investigator.

8. Criteria of Evaluation

8.1 Progression Free Survival

Time from randomization to date of first observed progression or death. The Progression Free Survival Rate at 12 weeks will be determined by the proportion of patients being alive without progressive disease 12 weeks after randomization.

8.2 Overall Response Rate (CR and PR)

Prior to 1994 the assessment of anti-tumor effect of a treatment was generally determined in accordance with the World Health Organization (WHO) criteria established in the late 1970s. The WHO criteria assess the change in tumor size using two perpendicular measurements of lesions.
The WHO criteria were reviewed in the 1990s leading to the development of a new set of criteria called Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse et al. 2000). Recent version v1.1 of RECIST (Eisenhauer et al. 2009) considers the change in tumor size using the sum of unidimensional measurements of the longest diameter in up to two target lesions per organ (or five in total, representing all involved organs) and also accounts for non measurable lesions.

8.3 RECIST Criteria

RECIST is currently accepted as the basis for assessing antitumor activity in all solid tumor types and is endorsed by regulatory authorities.
Measurement and identification of target lesions
Patients must have at least one measurable lesion, defined as > 10 mm using spiral CT or MRI. Where disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology/histology. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Baseline measurements must be taken no more than 2 weeks prior to commencement of treatment. The same measurement technique (CT/MRI) must be used at baseline and follow up. No more than 2 target lesions in the liver and 5 lesions in total, representative of all sites involved will be identified. Those with the largest diameters should be included. All other (non-target) lesions should be reported but not measured, in order that their presence of lack thereof may be tracked at follow up.

Criteria for target lesions
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30 % decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20 % increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20 %, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Criteria for non-target lesions
Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Response evaluation and reporting
Tumor response will be evaluated after 6 weeks and every 12 weeks thereafter by CT/MRI following the first treatment. During treatment tumor response will be assessed by the investigator. CT and/or MRI scans will be independently reviewed e.g. for resectability and allocation to the clinical groups.
At each follow up visit, response in target and non-target lesions and presence of any new lesions will be reported in the CRF. Overall response will be assigned by combining the response in target lesions, non-target lesions, and the appearance or lack of new lesions as outlined in the table below.

Table 6: Response Evaluation According to RECIST

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Evaluation of best overall response
The best overall response is defined as the best response from start of treatment over all follow up visits or until disease progression/recurrence whichever comes first.

8.4 Overall Survival

Overall survival will be determined as time from randomization to date of death.

8.5 Safety Endpoints

Safety assessments will include physical examinations including vital signs (blood pressure, heart rate, respiratory rate), ECOG, clinical laboratory profile and adverse events.
All observed adverse events, toxicities and side effects will be graded according to NCI Common Terminology Criteria for Adverse Events: NCI CTCAE v4.0 (NCI 2009) for all patients and the degree of association of each with the procedure assessed and summarised.
Treatment related Serious Adverse Events rate (Serious Adverse Reactions), defined as SAEs considered possibly, probably or definitely related to treatment, will be determined.

8.5.1 Quality of life (QoL)

Quality of life will be assessed using the EORTC QLQ C30 questionnaire at baseline, during treatment at the beginning of each cycle and at the end of treatment.

8.6 Assessment of Adverse Events

8.6.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence or experience in a subject or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment.
Disease progression itself is not considered an adverse event. However, signs and symptoms of disease progression may be recorded as adverse events or serious adverse events. Death due to progressive disease during the study should be reported on the applicable study termination case report form with ‘death’ as reason for study termination and ‘disease progression’ as reason for death.
Worsening of a pre-existing medical condition (e.g. diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.
Interventions for pre-treatment conditions (e.g. elective cosmetic surgery) or medical procedures that were planned before study enrolment are not considered adverse events.
The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from

values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.
An **Adverse Drug Reaction (ADR)** is defined as any response to a medical product, that is noxious and unrelated to any dose (ICH-GCP). Response to a medicinal product (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
An **Unexpected Adverse Drug Reaction** is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Summary of product characteristics) (ICH-GCP).
A **Serious Adverse Event (SAE)** is defined as any undesirable experience occurring to a subject, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Drug Reaction (SADR)**.
Adverse events and adverse drug reactions which are considered as **serious** are those which result in:

- death
- a life threatening event (i.e. the subject was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above)
- ALT >3x ULN with simultaneous elevation of bilirubin (defined as total bilirubin >2x ULN, with direct bilirubin >35%) or with hypersensitivity symptoms (e.g., fever, rash) – bilirubin fractionation should be performed if testing is available
- ALT >8x ULN without bilirubin elevation (defined as total bilirubin <2x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)- bilirubin fractionation should be performed if testing is available

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (e.g. emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasia.
Hospitalization for the performing of protocol-required procedures for elective procedures that have been booked in advance of enrolment that are not reasons for exclusion, or administration of study treatment is not classified as an SAE.

SUSAR: Suspected Unexpected Serious Adverse Reactions (the reference documents to assess expectedness are the summery of product characteristics).

8.6.2 Reporting Procedure for All Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the subjects medical records.
In addition, the investigator is responsible for ensuring that all adverse events captured in the subjects medical records (as specified above) are reported on the CRF.
Adverse events will be collected for those subjects who have provided informed consent and entered the study and will be recorded throughout the study period, beginning after the informed consent has been obtained until 28 days after the last administration of treatment in this trial.
Additionally all serious adverse events related to study medication (= serious adverse drug reactions) must be recorded through the entire follow-up period, 18 months after the date of last study drug administration.
The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known), event description (with detail appropriate to the event), dates of onset and resolution, severity, assessment of relatedness to study treatment, and action taken. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRFs and for serious adverse events on the serious adverse event report form.

8.6.3 Assessment of Causality of Adverse Events

An adverse event will not be considered possibly related to study treatment if it

- may be judged to be due to extraneous causes such as disease or environment or toxic factors.
- may be judged to be due to the subject's clinical state or other therapy being administered.
- is not biologically plausible that the event is related to study medication.
- does not reappear or worsen when study treatment is re-administered.
- does not follow a temporal sequence from administration of study treatment.

An adverse event will be considered possibly related to study treatment if it:

- follows a temporal sequence from administration of study treatment.
- is a known response to the investigational product based on clinical or preclinical data.
- could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject.

- disappears or decreases upon cessation or reduction of dose of study treatment.
- reappears or worsens when study treatment is re-administered.

Medically significant adverse events considered related to the study treatment by the investigator or the sponsor will be followed until resolved or considered stable.
It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo a safety follow-up assessment and be under medical supervision until symptoms cease or the condition becomes stable.

8.6.4 Assessment of Severity of Adverse Events

The severity of adverse events will be graded according to the CTCAE version 4.0.

8.6.5 Serious Adverse Events Reporting

Serious adverse events (SAEs) will be collected and recorded throughout the study period, beginning after informed consent until 28 days after the last administration of treatment in this trial.

Additionally all serious adverse events related to study medication (= adverse drug reactions (SADR)) must be recorded through the follow-up visits which occur 18 months after last study drug administration.
The investigator must **unhesitatingly** (within 24 hours) report all serious adverse events on a separate SAE report form to the Koordinierungszentrum für Klinische Studien (KKS) Halle.
Please fax the SAE report form to:

FAX:

Koordinierungszentrum für Klinische Studien
Medizinische Fakultät
Martin-Luther-Universität Halle-Wittenberg
06097 Halle (Saale)
Fax: 0345 557-5210

The sponsor will medically review all SAEs. The sponsor is responsible for ensuring that all reporting requirements to all concerned investigators, to the Central Ethics Committee, and to Regulatory Authorities are fulfilled. In accordance with the legal requirements (Directives 2005/28/EC and 2001/20/EC, GCP-V and the German Drug Law) all Adverse Drug Reactions that are both serious and unexpected (SUSAR) are subject to expedited reporting. Development Safety Update Reports (DSUR) will be sent to the Central Ethics Committee and the competent authority *Bundesoberbehörde* (BfArM).
The sponsor will notify all serious adverse events in patients receiving gemcitabine or pazopanib within one working day to GlaxoSmithKline for internal tracking of product safety.
Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to KKS Halle within the same timelines as a serious adverse event. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. The sponsor will notify GSK of any pregnancies occurring in patients receiving pazopanib.

9. Data Analysis and Statistical Considerations

9.1 Sample size calculation

The primary end-point of the study is progression free survival rate (CR+PR) after 12 weeks. Secondary end-points are Overall survival (OS), Time to Progression (TTP), Response Rate (CR+PR+SD), Toxicity (CTCAE, version 4.0), and Quality of live (EORTC).

In 2002 the EORTC Soft Tissue And Bone Sarcoma Group reviewed the EORTC clinical data base to provide reference values for conducting phase II studies with PFSR as the principal end-point in soft tissue sarcomas[47]. Refering to this publication PFSR@12 weeks =40% is supposed to show drug activity and should be reached by the reference (monotherapy) arm. Both treatment arms will be directly compared. Sample size calculation is based on a one-sided chi-square test for two independent groups. In the drug combination arm treatment should produce a PFSR@12 weeks of >=60% to prove superior drug activity. The study will have 60% power at the 5% significance level to test this hypothesis. 45 evaluable subjects are required per treatment group.
Because of the stratified randomization the Cochran-Mantel-Haenszel test (with control for the two strata - liposarcoma yes or no) will be used to analyze the primary endpoint. This test yields higher power compared to the chi-square test used for sample size calculation. OS and TTP will be analyzed by means of Cox regression adjusted for the strata variable liposarcoma. Response rate will also be analyzed by means of the Cochran-Mantel-Haenszel test (with control for the two strata - liposarcoma yes or no). Toxicity and Quality of life will be compared in a descriptive way.

9.2 Populations of analysis

Patient with major deviation of selection criteria will be excluded from statistical analysis. These cases will be reported anecdotical.
All patients receiving at least one treatment will be evaluable for safety.
The Intention-to-treat (ITT) population will include all patients in the study (signed ICF and confirmation of eligibility). All patients will be grouped according to their randomization regardless of treatment received. The ITT analysis will be used to evaluate the main hypothesis of the trial.

The Per-protocol (PP) population will include all patients who receive at least one treatment cycle and who were treated according to their randomization schedule. Patients with major protocol deviations or who did not receive treatment according to their randomization schedule will be excluded from the PP population. The PP analysis will be used as an additional analysis.

9.3 Patient demographics/ other baseline characteristics

The following demographic and baseline characteristics will be summarized descriptively by treatment group:

- Gender and age
- ECOG performance status
- Disease status/ location
- Other characteristics (e.g liver chemistry)

Medical history will be summarized by primary body system organ class and preferred term.

9.4 Treatments (study treatments and concomitant medications)

The number and dose of treatment cycles will be summarized by treatment group. The previous and concomitant medications will be summarized.

9.5 Stratification

Patients will be stratified in liposarcoma and non- liposarcoma.

10. Data management

10.1 Randomisation Procedure

For randomisation the following data are needed:

- histological type of STS (Liposarcoma vs. Non Liposarcoma)

Please fax the randomisation form to:

KKS-Halle
0345-5575210

Randomisation to study treatment should occur within seven days after eligibility criteria have been met. Upon confirmation of eligibility, study subjects will be randomised to one of two treatment arms in 1:1 ratio, according to the above mentioned stratification factors.

Arm A (Pazopanib plus Gemcitabine)

Arm B (Pazopanib)

10.2 Patient identification list

All randomized patients have to be documented in a confidential patient identification list (subject enrollment log). This list contains the patient specific numbers (patient- and randomization-number) together with date of birth and the full name of the patient. Patient related data will be just transmitted in pseudonymized form. The identification list will stay at the center.

10.3 Data capture

All data will be entered directly at the center by the site staff with remote data entry (RDE). The study-management software eResearchNetwork (eResNet, eResearch Technology Inc., Philadelphia, USA) will be used for data capture and query management. Data will be evaluated for consistency, accuracy and completeness regularly. After completion of data capture data base will be closed and the data will be transferred into the statistic software (SAS).

11 Quality assurance

11.1 Standardization

Criteria for assessing efficacy and safety endpoints will be standardized by using NCI-CTCAE version 4.0 for safety issues and RECIST version 1.1 for efficacy

parameters. Every center has to reveal their laboratory norm values and their validation through certification.

11.2 Data access

All source data have to be in the patients file under the responsibility of the investigator. Documentation in the eCRF must correspond to source data in the patient file. For this trial source data are defined as:

- medical and demographical data
- results of laboratory and imaging data
- selection criteria
- signed informed consent form (original)

11.3 Monitoring/ Source Data Verification (SDV)

The monitoring will be conducted by the KKS Halle. There will be central monitoring by reviewing the data being entered into the trial-software eResNet as well as on-site monitoring. The frequency of on-site visits will depend on the number of recruited patients. The access to trial specific data for the monitor will be ensured through the cooperation treaty between the sponsor and the KKS Halle. The monitor must be given access to subject medical records and other study-related records needed to verify the entries on the case report forms. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved. The investigator has to ensure that all data required according to this protocol will be entered promptly in the eCRF. Data collected on each subject will be recorded in the subjects' medical records and the eCRF.
Quality control of data will be done by reviewing the data entered into the trial software for consistency, accuracy and completeness. During on-site visits the correct transmission of data into the eCRF (source data verification) as well as informed consent forms, selection criteria, efficacy and safety parameters will be reviewed. The complete scale of the monitoring will be defined by the trial specific monitoring plan.

11.4 Audits and Inspections

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating to protocols.
The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital subject charts and other study files) to these authorized individuals.
The investigator must inform the sponsor immediately in case a regulatory authority inspection will be scheduled.

12 Regulatory and Legal Obligations

12.1 General provisions/Declaration of Helsinki

This study is conducted in agreement with the German Drug Law (AMG 1976 in Novelles) the German Medical Device Law (MPG), ICH Harmonized Tripartite Guideline on Good Clinical Practice, valid since 17.01.1997 (Appendix 11) the „Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen“ from August 9th 2004 and the Declaration of Helsinki (from June 1964, Tokyo October 1975, Venice, Hong Kong September 1989, Somerset West October 1996 and Edinburgh amendments from 2000). The Principle Investigator has more than two years of experience in the conduction of clinical drug trials.

12.2 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (from June 1964, Tokyo October 1975, Venice October 1983, Hong Kong September 1989, Somerset West October 1996 and Edinburgh amendments from 2000) or the laws and regulations.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (reference: http://www.ifpma.org/pdfifpma/e6.pdf).

The protocol will be approved by Independent Ethics Committees.

12.3 Competent authority

Prior to the start of the trial an application for authorisation by the competent Higher Federal Authority is submitted by the sponsor including a copy of the protocol and other information and documents required by the competent Higher Federal Authority. If requested, modifications must be incorporated.

12.4 Independent Ethics Committee (IEC)

Prior to the start of the trial an application for the favourable opinion is submitted by the sponsor to the central independent, interdisciplinary ethics committee responsible under Land law for the principle investigator and to the local ethics committees responsible for the other participating institutions including a copy of the protocol, proposed informed consent form and other information and documents required by the ethics committees for their opinion. A copy of the written approval of the protocol and informed consent form must be available before the start of recruitment of subjects into the study. All changes of the study protocol as well as all presumable unexpected heavy events linked to the study medication, will be announced to the IEC, according to §13, Abs. 2 und 3 GCP-V. Once a year or whenever it is questioned the IEC will get information about all SAR and about the security of the

affected subjects, according to §13, Abs. 6 GCP-V. Recommendations and tips of the IEC will be taken up into the study protocol. The sponsor will inform the IEC about the course of the Investigation in security aspects (according §13 GCP-V, Abs. 1 till 6) and also about the end and the results of the investigation (according to §13 GCP-V, Abs. 8 and 9).
The investigator can not influence the decisions of the IEC. A list of the IEC members and the IEC rules will be ordered.

12.5 Amendments

The appendices, attached to this protocol and referred to in the protocol, form an integral part of the protocol. No changes or amendments to this protocol may be made by the Investigator. The sponsor must submit and obtain approval from the IEC and competent Higher Federal Authority for all subsequent protocol amendments. For changes to the informed consent form approval from the IEC has to be obtained.

12.6 Study Reports

A clinical trial report will be written and provided to the IEC and competent Higher Federal Authority independent of the completion or a premature closure of the trial.

12.7 Informed Consent

The informed consent form will be submitted together with the study protocol to the independent ethics committees for review and approval. If requested, modifications must be incorporated. A copy of the written approval of the IEC must be available before starting the trial and dispensing any trial medication to trial subjects. The informed consent form must not be altered by the investigator except for contact data of the investigators. Changes to the informed consent form also have to be approved by the IEC. The revised form will be sent to all sites to replace the preceding version.
Before a subject's participation in the clinical study, the investigator must obtain written informed consent from the subject. All subjects will be informed of the aims of the study, the possible adverse events, the anticipated benefits, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation the subjects also will be informed about alternative treatments. Subjects will be informed of their insurance protection and the Obligations which are linked to insurance. They will be informed as to the strict confidentiality of their subject data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the subject's subsequent care. The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice.
The informed consent consists of three parts: consent to the diagnostic and therapeutic procedures of the trial, consent to the collection and storage of biological material, and consent to the processing and storage of data. The latter one includes consent to inspections where records may be reviewed by authorized individuals (other than their treating physician) of the sponsor or surveillance authorities / ethics

committees. If the subject does not consent to the collection, processing and storage of his data, inclusion in the study is not possible and the subject's refusal should be documented in the medical notes. The subject must be informed about the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study treatment are administered. The collection and storage of biological material in this clinical trial is optional; consent to this part of the trial is not necessary for the participation in this clinical trial.
The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.
If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.
Adequate explanations of the aims, methods, anticipated benefits, and potential hazards of the study, the mechanism of treatment allocation must be given. The subject will have enough time to decide to participate at the study or not.
The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician must be documented in the subject's medical records, and the informed consent form must be signed and personally dated by the subject and by the investigator. One signed original of the informed consent form must be retained in accordance with institutional policy and another original must be provided to the subject. Treatment cannot start before the subject has signed the informed consent, meets all inclusion and no exclusion criteria and is registered.
With signing the informed consent form the investigator confirms that an individual clarification conversation has taken place and that the subject has signed the informed consent form.

12.8 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms, subjects should be identified by their subject study number and only on the SAE report form additionally with date of birth.
In compliance with ICH-GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the sponsor, of regulatory agencies, and the IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject. The investigator must keep a list for the identification of the subjects (including name, birthday, gender, date of informed consent, date of randomization / registration).

12.9 Study Documentation and Archive

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties, including all those authorized to make entries and/or corrections on case report forms.
Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may only be considered source data if the case report form is the site of the original recording (i.e. there is no other written or electronic record of data).
The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the study sponsor and/or applicable regulatory authorities. Elements include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list.
- Study files containing the protocol with all amendments, the summary of product characteristics, copies of pre-study documentation, and all correspondence to and from the IEC.
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.
All study documents and source documents must be kept for at least 10 years from submission of the final study report. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

12.10 Obligation of Application and Registration

The sponsor sends an application to the responsible ethics committee according §7, Abs. 1, 2, 3, 5 till 6 GCP-V, as well as to any ethics committee, which is formed by *Landesrecht* for each single center of the study, according to §7, Abs. 1 GCP-V. On behalf the sponsor announces the single investigators to the responsible regional Authorities, according to § 67 Arzneimittelgesetz and § 12, Abs. 1 GCP-V.
The sponsor will inform the responsible Bundesoberbehörde (parallel to IEC) about the course of the Investigation in security aspects (according §13 GCP-V, Abs. 1 till 6) and also about the end and the results of the investigation (according to §13 GCP-V, Abs. 8 and 9).

12.11 Compensation

Subjects will not be paid for participating in this clinical trial.

13 Trial Insurance

For all subjects participating in the trial the sponsor has taken out a liability insurance policy (mentioned below) according § 40 Abs. 1 Nr. 8 und Abs. 3 German drug law (AMG) which covers the sonsor, the investigator and his co-workers against liability in the event that a subject's health is injured during the course of the clinical trial. The insurance policy provides benefits, even when no one else is liable for the damage death of or injury to any subject during the trial.

A certificate of insurance will be provided to the investigators and the subjects.

Allianz Versicherung AG
Insurance No.: AS-0184421969
Application-No.: 10093/01/2011

14 Publication Policy

After receiving the biometrical results a final report will be published and further publications (abstracts etc.) will be done. First author of the final publication will be the LKP of the study. All participating sites recruiting at least 10% of the patients will become a co-authorship if possible according to the publication policy of the journal. Persons involved in planning, conducting and evaluating the trial will be offered co-authorships. All co-authors will get the option to comment on the manuscript before publication.

15 External review of histology

Pathology will be reviewed for all patients included in this trial, according to the standard procedure of the group. Formalin fixed paraffin embedded tumor blocks and/or representative H/E (haematoxylin/eosin) slides (preferably both) must be sent to the reference pathologist within a reasonable timeframe.

Reference pathologists:

Prof. Dr. D. Katenkamp
Universitätsklinikum Jena
Institut für Pathologie
Ziegelmühlweg 1
07743 Jena

16 Translational research

Participance on the translational research for patients participating this study is optional and voluntarily.
Blood samples (30ml) before starting study medication, at week 6 and after end of treatment will be stored for further examination.
These samples will be used to determine profiles of plasma cytokines and angiogenic factors (CAFs) before starting, during treatment and after progression. In STS it is not yet established which CAFs in plasma play a key role in vivo, and whether these may predict response to chemotherapy/ small molecules and tumor progression. Preclinical work has suggested that alternate proangiogenic factors may modulate sensitivity to anti-VEGF therapy and allow regrowth of tumor-associated vasculature. No publications are available on how CAFs plasma level in STS patients change during the treatment with antiangiogenetic agents compared to a treatment in combination with conventional chemotherapy. To investigate this, patients plasma will be screened for relevant, i.g. elevated levels of CAFs using multiplex-bead assays for measurement of cytokine- and Immunoassays for VEGF and PIGF levels. Significant decrease or increase of CAFs will then be correlated with PFS, RR, and histology of primary tumor.
The following procedure is recomended: refer to Appendix H

17. Trial sponsorship and financing

GlaxoSmithKline (GSK) is the main financial Sponsor of this trial.

GlaxoSmithKline GmbH & Co.KG
Theresienhöhe 11
80339 München

The Martin Luther Universität Halle does support the trial within the „Wilhelm-Roux-Programm“.

Appendix A: Bibliography

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

Another option is via the EORTC Headquarters web site www.eortc.be, which provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix D: RECIST v1.1

In this trial the 2009 updates version of the RECIST (v1.1) will be used. The version was published in European Journal of Cancer 2009

E.A. Eisenhauer, P Therasse
New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)
Europ. J Cancer 45 (2009) 228–247

Access to the guidelines is possible via the EORTC Headquarters web site www.eortc.be, which provides a link to the appropriate RECIST web site. This link will be updated if the RECIST address is changed.

Appendix E: EORTC QLQ C30

GERMAN

EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Patienten ID: _____

Das heutige Datum (Tag, Monat, Jahr): _____

	Überhaupt nicht	Wenig	Mäßig	Sehr
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	1	2	3	4
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:

	Überhaupt nicht	Wenig	Mäßig	Sehr
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8. Waren Sie kurzatmig?	1	2	3	4
9. Hatten Sie Schmerzen?	1	2	3	4
10. Mussten Sie sich ausruhen?	1	2	3	4
11. Hatten Sie Schlafstörungen?	1	2	3	4
12. Fühlten Sie sich schwach?	1	2	3	4
13. Hatten Sie Appetitmangel?	1	2	3	4
14. War Ihnen übel?	1	2	3	4
15. Haben Sie erbrochen?	1	2	3	4

Bitte wenden

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

Appendix F:
New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix G:
Calculation of the glomerular filtration rate (GFR)

COCKCROFT AND GAULT FORMULA:

For the calculation of GFR age is measured in years and weight is measured in kilograms.

If serum creatinine is measured in µmol/l, the following formula applies:

$$\textbf{In males:}\quad \mathrm{GFR[ml/min]} = \frac{1.23 \times (140 - age) \times weight}{serum\ creatinine}$$

$$\textbf{In females:}\quad \mathrm{GFR[ml/min]} = \frac{1.05 \times (140 - age) \times weight}{serum\ creatinine}$$

If serum creatinine is measured in mg/dl, the following formula applies:

$$\textbf{In males:}\quad \mathrm{GFR[ml/min]} = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$$

$$\textbf{In females:}\quad \mathrm{GFR[ml/min]} = \frac{0.85 \times (140 - age) \times weight}{72 \times serum\ creatinine}$$

Appendix H:
Translational research

The following procedure is recomended:

1. take venous blood samples (3x10ml) in EDTA monovettes
2. immediately process for plasma (centrifugation 5min at 1200U/min)
3. sign with patient code, protocol identification number and: „baseline“ or „3thcycle“ or „end of treatment“
3. store at -80°C
4. at the end of the study sent all collected samples in one packet on froozen ice (monday-thursday 07.00-16.00) to:

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