Final Study Report

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

(multicentre, open-labeled, prospective, randomized parallel-group phase II)

PAPAGEMO

Investigational Medicinal Products:
Pazopanib alone + Pazopanib plus Gemcitabine

Indication: relapsed or metastatic soft tissue sarcoma

Phase of the clinical trial: Phase II

EudraCT-Number: 2009-017261-32

AIO- STS- 009

04.10.
Version Date: ~~07.08.~~2017
Version: V01, final

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Sponsor
Martin-Luther -University Halle-Wittenberg,
represented by the chancellor, represented by the
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Study Start (FPI): 26.09.2011
End of Study (LPO): 11.04.2016

Signatures

I agree with the content of the final study report in its final version. The reported clinical trial was conducted in accordance with the current version of the Declaration of Helsinki, ICHGCP Guideline (International Conference on Harmonization - Good Clinical Practice) and applicable national laws and regulatory requirements.

Sponsor	Prof. Michael Gekle	26.10.2017 Date
Author and Coordinating Investigator	Prof. Hans-Joachim Schmoll	16.10.17 Date
Statistician	Apl. Prof. Andreas Wienke	23.10.17 Date

Table of Contents

List of tables

List of figures

1. Name of the Sponsor

Martin-Luther-University Halle-Wittenberg, represented by the chancellor, represented by the Dean of the Faculty of Medicine

2 Finished Products	3 Active Substances
Votrient®	Pazopanib
Gemzar®	Gemcitabine

4 Individual Study Chart

Not applicable

5 Study Title

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

- Protocol-Version: Final 2.0 (06-2011) was the first version approved by the EC on 18.08.2011 and by the CA on 02.08.2011, Version 1.1 (28.04.2011) was not approved neither by the EC nor by the CA.

- Amendment 01: Submission of four additional trial sites, approved by the EC on 24.11.2011, 07.12.2011, 12.12.2011

- Amendment 02: Submission of a temporary halt of the trial due to a fatal hepatic SAE which occurred in a further clinical study investigating the combination of gemcitabine and pazopanib for the treatment of patients with advanced soft tissue sarcoma, approved by the EC on 15.08.2013, implicit approval by BfArM

- Amendment 03: Submission of the restart of the trial,
  New information regarding the fatal hepatic event in another soft tissue sarcoma study that led to the temporary halt of the trial was available. Further investigations on the combination of gemcitabine and pazopanib were done. According to the new information the informed consent form was updated and submitted along with the restart o the trial, approved by the EC on 19.12.2013, implicit approval by BfArM

- Amendment 04: Protocol Amendment No1 (17.07.2014) to protocol 2.0 (06-2011),submission of changes regarding the time frame of the analysis of the primary end-point. *"The analysis of the primary end-point (progression free survival rate after 12 weeks) will be done after the last subject has obtained the End of Treatment. Secondary end-points (OS, TTP, response rate, toxicity and quality of live) will be analysed if the last subject has finished the follow-up period (last patient, last visit)"*, approved by the EC on 28.08.2014, implicit approval by BfArM

The last valid version of the protocol was version 2.0 (06-2011) including protocol amendment no1 (17.07.2014).

6 Investigators	7 Study Trial Sites
-	01: University Hospital Halle, Department of Oncology and Haematology, Internal Medicine IV, Ernst-Grube-Str. 40, 06097 Halle (Saale)
-	02: University Hospital Leipzig, Department of Internal Medicine, Johannisallee 32A, 04103 Leipzig
-	03: Charité Berlin, Charité Center 14, Tumor Medicine, Augustenburger Platz 1,13353 Berlin
-	04: University Hospital Tuebingen, Medical Clinic II, Otfried-Müller-Str. 10, 72076 Tuebingen
-	05: University Hospital Munich, Campus Großhadern, Medical Clinic 111, Marchioninistr. 15, 81377 Munich
-	06: University Hospital Hamburg-Eppendorf, UCCH, Medical Clinic II, Martinistr. 52, 2046 Hamburg
-	08: Helios Clinic Bad Saarow, Department of Internal Medicine;, Medical Clinic, Department of Internal Medicine III, Pieskower Straße 33, 15526 Bad Saarow
-	09: University Hospital Aachen, Medical Clinic IV, Pauwelsstraße 30, 52074 Aachen
-	10: University Hospital Heidelberg Medical Clinic, Department of Internal Medicine IV, Am Neuenheimer Feld 410, 69120 Heidelberg
-	11: Medical Practice Oncology, Wuerselen
-	12: University Hospital Ulm, Department of Internal Medicine III, Albert-Einstein-Allee 23,89081 Ulm
-	13: Surgical University Hospital Mannheim, Department of Surgical Oncology, Theodor-Kutzer-Ufer 1-3, 68135 Mannheim
-	14: University Hospital Jena, Department of Internal Medicine II, Erlanger Allee 101, 07747 Jena
-	15: University Hospital Muenster, Medical Clinic A, Albert-Schweitzer-Str. 33, 48129 Muenster
The following trial site refused their participation after the approval, the EC and CA were informed about their decision	
-	07: **University Hospital Schleswig-Holstein, Medical Clinic II, Arnold-Heller-Str. 3, 24105 Kiel**

8 Publikationen

Not applicable

9 Study Period (years)

Date of first enrolment: 26.09.2011
Date of last patient last visit: 11.04.2016
Date of last entry eCRF: 30.05.2016 (date of death of last enrolled patient)

Between September 2011 and June 2014, the planned number of 90 patients were recruited at 14 trial sites (Table 1). The last patient completed study treatment in September 2015 and study follow-up in May 2016. In the individual patient, study treatment was scheduled until progression or intolerable toxicity.

Table 1: Recruitment and study duration by trial site

					Duration [months]			
Center	First patient in (date of signed ICF)	Last patient in (date of signed ICF)	Last patient out (EOT)	End of Study	Recruit-ment	Therapy	Study	Number of Patients
001	14SEP2011	02MAY2014	03DEC2014	13DEC2014	31.6	38.1	39.0	7
002	02FEB2012	12DEC2012	08JAN2014	23FEB2014	10.3	23.0	24.7	3
003	26MAR2012	27MAR2012	27JUN2013	27JUN2015	<0.1	14.9	39.1	2
004	26NOV2012	30MAY2014	07SEP2015	11APR2016	18.1	32.8	40.5	10
005	13OCT2011	26JUN2014	28AUG2014	30MAY2016	32.5	33.9	55.6	17
006	25OCT2011	30JUL2012	23OCT2012	29SEP2013	9.2	11.8	23.2	4
008	04JUN2012	12JUN2013	19DEC2013	04JAN2016	12.3	18.3	43.0	12
009	26MAR2012	24APR2014	25JUL2014	04AUG2014	25.0	27.5	28.3	6
010	26APR2012	24JAN2014	27MAR2014	09MAR2016	21.0	22.6	46.5	6
011	13SEP2012	13SEP2012	08NOV2012	10JAN2013	<0.1	1.6	3.9	1
012	21MAR2012	17JUN2014	21OCT2014	19APR2016	26.9	31.0	49.0	8
013	15MAY2012	14MAY2013	21AUG2013	10JUN2015	12.0	15.0	36.9	4
014	15MAY2012	08MAY2013	05JUL2013	29JUL2015	11.8	13.6	38.5	2
015	28FEB2012	05JUL2013	04NOV2013	13APR2014	16.2	19.7	25.5	8
Total	14SEP2011	26JUN2014	07SEP2015	30MAY2016	33.4	47.3	56.5	90

The study was set on a temporary halt from July 23rd, 2013 until December 19th, 2013 due to a fatal hepatic SAE which occurred in a further clinical study investigating the combination of gemcitabine and pazopanib for the treatment of patients with advanced soft tissue sarcoma. The restart of the trial was done as new information regarding the fatal hepatic event was available. The ingestion of crushed tablets may have contributed to this event and an association between this event and pazopanib cannot be ruled out. The pazopanib label states that tablets should not be crushed because exposure may be increased.

GSK recommends the addition of day 8 liver function tests in each study with the aim of Identifying any potential liver dysfunction with this combination as early as possible. GSK also requests that all results of cycle 1 liver function tests are collected and shared with GSK so that they may continue to review and monitor any hepatic events associated with this combination, and relay any concerns that may develop over time.
Patient informed consent language should be updated to reflect this fatal event, existing study subjects re-consented, and IRB approval obtained prior to reopening the study.

All recommendations from GSK were implemented in the corresponding documents and were forwarded to all sites as soon as possible.

10 Phase of Development

Phase II.
The investigational medicinal products used in this trial have a marketing authorization in the member state concerned. At the beginning of the trial pazopanib (small molecule VEGFR inhibitor) was in clinical development in the treatment of a variety of human cancers. During the trial (Aug 2012) pazopanib was approved for advanced (relapsed) soft tissue sarcoma.

Gemcitabine (fluorinated analog of deoxycytidine) 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.
The combination of pazopanib 800mg daily plus gemcitabine at 1000 mg/m^2 on days 1 and 8 every 21 days was tested in this phase II study.

11 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.

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.

The primary endpoint was progression-free survival (PFS) 12 weeks after randomisation. PFS was defined as time from randomisation to date of first observed progression or death.

Secondary endpoints were
- overall survival (OS): time from randomisation to date of death
- time to progression (TTP): time from randomisation to date of first observed progression (or death caused by tumour/PD)
- best overall response (yes:=CR+PR/no:=SD+PD+death): best response from start of treatment over all follow up visits or until disease progression/recurrence whichever comes first
- Toxicity (CTCAE, version 4.0)
- Quality of life assessed using EORTC QLQ-C30 questionnaire, version 3.0, at baseline, during treatment at the beginning of each cycle and during follow-up.

According to protocol amendment no.1 (17.07.2014) to protocol 2.0 (06-2011) the analysis of the primary end-point (progression free survival rate after 12 weeks) was done after the last subject has obtained the end of treatment. Secondary end-points (OS, TTP, response rate, toxicity and quality of live) were analysed when the last subject has finished the follow-up period (last patient, last visit).

12 Methodology

This trial was designed as multicentre, open-labeled, prospective, randomized parallel-group phase II study with stratification criterion liposarcoma vs. non-liposarcoma for patients with relapsed or metastatic soft tissue sarcoma. A sample size of 90 patients was planned to allocate by stratified randomisation to arm A (pazopanib plus gemcitabine) or arm B (pazopanib) in a 1:1 ratio.

Patients were randomly assigned to one of the treatment arms according to following stratification criteria: liposarcoma versus non liposarcoma. After Verification of the eligibility criteria patients were 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 withdrawal of consent for any reason.

Due to the marketing authorization status (not authorized for relapsed STS) of pazopanib at the time, when the study was designed, neither arm A nor arm B could be identified as the standard therapy for relapsed STS.

Randomisation Method
In this randomised parallel-group study, a total of 90 patients were randomised in a 1:1 ratio to arm A (Pazopanib plus Gemcitabine) or arm B (Pazopanib) stratified by liposarcoma (yes or no). For each stratum, a separate block randomisation list was generated with block lengths of 4 and 6 in random order using SAS software version 9.1.3. Central randomisation was carried out via fax.

Both IMPs in this study are authorized drugs with a comprehensive safety data profile. Therefore the establishment of a DMC for this study was assessed as not necessary by the coordinating investigator. The EC was informed about that decision.

13 Number of Patients

See also flow chart appendix 21.1

A total of 90 patients were enrolled in the study. All of them were stratified by liposarcoma (yes or no) and randomised to arm A (44 patients: 9 liposarcoma and 35 non-liposarcoma patients) or arm B (46 patients: 10 liposarcoma and 36 non-liposarcoma patients). Two patients dropped out because of screening failure and another one withdrew on day of randomisation. The remaining 87 patients received at least one study treatment and thus were evaluable for safety, 43 in arm A (Pazopanib+GEM) and 44 in arm B (Pazopanib).

Discontinuation / Drop-out / Protocol Violators
In arm A (Pazopanib+GEM), one patient did not meet the inclusion criterion "adequate organ function"; in arm B (Pazopanib), one patient met the exclusion criterion of an increased risk for gastrointestinal bleeding. Both of them dropped out because of screening failure and did not receive any study treatment. Another patient left study at his own request on the day of having been randomised to arm B (Pazopanib) and before start of study treatment. The inclusion criteria "at least one measurable lesion according to RECIST criteria (v1.1)" and "relapse or progress after one or two prior chemotherapies including either an antrazyclin or ifosfamid or both" were not met by one patient of arm A (Pazopanib+GEM) and one of arm B (Pazopanib), respectively. Violations of selection criteria are listed by patient in table 2 and 3.

Table 2: Inclusion exceptions, randomised n=90

Arm	PATID	Age [yr]	Sex	Inclusion exception
A	004-047	66	F	Adequate organ function
	006-003	23	F	At least one measurable lesion according to RECIST criteria (v1.1)
B	009-044	60	M	Relapse or progress after one or two prior chemotherapies including either an antraz both

Table 3: Exclusion exceptions, randomised n=90

Arm	PATID	Age [yr]	Sex	Exclusion exception
B	004-088	56	M	Clinically significant gastrointestinal abnormalities that may increase the ris bleeding (defined in protocol)

The ITT analysis set included 20 men and 23 women from 23 to 84 years (mean ± standard deviation STD 55.2 ± 14.0 years) in arm A (Pazopanib+GEM) and 23 men and 20 women from 22 to 81 years (55.6 ± 13.2 years) in arm B (Pazopanib), see table 4 and 5. Mean body weight ± STD was 73.3 ± 13.0 kg and 76.4 ± 15.7 kg, height 171.9 ± 9.4 cm and 171.2 ± 8.9 cm, body mass index 24.68 ± 3.99 kg/m² and 26.11 ± 4.87 kg/m² in arm A (Pazopanib+GEM) and arm B (Pazopanib), respectively. ECOG performance status was 0 or 1 in 38 of 43 patients in arm A (Pazopanib+GEM) and 39 of 43 patients in arm B (Pazopanib) and overall not above 2 in accordance with inclusion criteria. Liposarcoma was diagnosed in 9 and 7 patients in arm A (Pazopanib+ GEM) and arm B (Pazopanib), respectively. The histological classification at initial diagnosis is described in table 6.

Table 4: Gender, ITT n=86

Gender	Arm A Pazopanib+GEM n=43		Arm B Pazopanib n=43		Total n=86	
	N	(%)	N	(%)	N	(%)
Male	20	(47)	23	(53)	43	(50)
Female	23	(53)	20	(47)	43	(50)
Total	43	(100)	43	(100)	86	(100)

Table 5: Age, ITT n=86

Age [yr]	Arm A Pazopanib+GEM n=43	Arm B Pazopanib n=43	Total n=86
N	43	43	86
Mean	55.2	55.6	55.4
STD	14.0	13.2	13.5
Min	23	22	22
Q1	43.0	47.0	45.0
Median	57.0	59.0	57.0
Q3	64.0	65.0	65.0
Max	84	81	84

Table 6: WHO histological classification at initial diagnosis, ITT n=86

Histological Classification (WHO)	Arm A Pazopanib+GEM n=43		Arm B Pazopanib n=43		Total n=86	
	N	(%)	N	(%)	N	(%)
Angiosarcoma	2	(5)	2	(5)	4	(5)
Fibrosarcoma	0	(0)	0	(0)	0	(0)
Haemangioendothelioma	0	(0)	0	(0)	0	(0)
Leiomyosarcoma	14	(33)	8	(19)	22	(26)
Liposarcoma	9	(21)	7	(16)	16	(19)
Malignant glomus tumour	0	(0)	0	(0)	0	(0)
Malignant peripheral nerve sheath tumour	1	(2)	3	(7)	4	(5)
Malignant tenosynovial giant cell tumour	0	(0)	0	(0)	0	(0)
Malignant fibrous histiocytoma (MFH)	1	(2)	1	(2)	2	(2)
Malignant haemangiopericytoma	0	(0)	0	(0)	0	(0)

Histological Classification (WHO)	Arm A Pazopanib+GEM n=43		Arm B Pazopanib n=43		Total n=86	
	N	(%)	N	(%)	N	(%)
Malignant mesenchymoma	1	(2)	0	(0)	1	(1)
Malignant paraganglioma	0	(0)	0	(0)	0	(0)
Mesothelioma	0	(0)	0	(0)	0	(0)
Rhabdomyosarcoma	0	(0)	3	(7)	3	(3)
Other	15	(35)	19	(44)	34	(40)
Total	43	(100)	43	(100)	86	(100)

The Per-protocol (PP) analysis set included the 59 patients, 24/35 in arm A (Pazopanib+ GEM)/arm B (Pazopanib), of the ITT population who received at least one treatment cycle without a delay of therapy and without dose modification, interruption or reduction (table 7 +8), and who were treated according to their randomisation schedule.

Table 7: At least one treatment cycle without a delay of therapy and without dose modification, interruption or reduction

Safety n=87

At least one treatment cycle without delay or dose modification/interruption/reduction	Arm A Pazopanib+GEM n=43		Arm B Pazopanib n=44		Total n=87	
	N	(%)	N	(%)	N	(%)
No	19	(44)	8	(18)	27	(31)
Yes	24	(56)	36	(82)	60	(69)
Total	43	(100)	44	(100)	87	(100)

Table 8: At least one treatment cycle without a delay of therapy and without dose modification, interruption or reduction

ITT n=86

At least one treatment cycle without delay or dose modification/interruption/reduction	Arm A Pazopanib+GEM n=43		Arm B Pazopanib n=43		Total n=86	
	N	(%)	N	(%)	N	(%)
No	19	(44)	8	(19)	27	(31)
Yes	24	(56)	35	(81)	59	(69)
Total	43	(100)	43	(100)	86	(100)

14 Diagnosis and main inclusion criteria

Diagnosis: refractory or relapsed metastatic soft tissue sarcoma

Inclusion criteria:

- Written informed consent prior to performance of study-specific procedures or assessments, and willingness to comply with treatment and follow up
- At least 18 years old
- Histologically or cytological confirmed malignant soft tissue sarcoma including any subtypes except:
    - Chondrosarcoma

  - Osteosarcoma
  - Ewing tumors and primitive neuroectodermal tumors
  - Gastrointestinal stromal tumors
  - Dermofibromatosis sarcoma protuberans
  - Inflammatory myofibroblastic sarcoma
  - Malignant mesothelioma
  - Mixed mesodermal tumors of the uterus
- Relapse or progress after one or two prior chemotherapies including either an antrazyclin or ifosfamid or both
- If female either of non childbearing potential or childbearing potential with negativ pregnancy test within 2 weeks prior to the first dose of study and agreed to use adequate contraception
- Adequate organ function as defined in protocol
- ECOG performance status 0-2
- Able to swallow and retain oral medication
- At least one measurable lesion according to RECIST criteria (v1.1)
- Life expectancy > 3 months

Exclusion criteria:

- 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
- Clinically significant gastrointestinal disorders/abnormalities
- Poorly controlled hypertension
- Prolongation of corrected QT interval (QTc) > 450 msec
- 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
- 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
- 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 protocol 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 is prohibited
- Insufficient liver function
- Autoimmune disease
- Uncontrolled hypothyroidism
- Diarrhea Grad 3 and 4

15 Investigational medicinal products, dose, mode of administration, batch number

Votrient® (Pazopanib), provided by Novartis Pharma (formerly GlaxoSmithKline)

Mode of action: tyrosine kinase inhibitor
Dose: 800 mg
Route of administration: p.o.
Formulation: tablet

Pazopanib (Votrient®) (Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01 XE11) is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived grow1h factor (PDGFR)-a and -ß, and stem cell factor receptor (c-KIT), with IC50 values of 10, 30, 47, 71 , 84 and 74 nM, respectively.

Batch No:
200 mg: P11810G (Expiry date 31.05.2014), P11810G2 (Expiry date 31.10.2015)
400 mg: P11810G1 (Expiry date 30.06.2013), P11810G3 (Expiry date 30.11.2016)

Gemcitabine, site dependent brand from each hospitals stock was used

Mode of action: cytotoxic agent
Dose: 1000 mg/m^2
Route of administration: i.v.
Formulation: infusion

Gemcitabine (Pharmacotherapeutic group: pyrimidine analogues, ATC code: L01BC05) is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides.

16 Duration of treatment

The therapy of arm B consisted of receiving pazopanib at a fixed dose of 800 mg oraly daily. All patients in arm A were scheduled to receive gemcitabine at a dose of 1000 mg/m^2 i.v. over 30min (day 1, 8, repeated after 21days), additionally. The treatment in both arms was intendet to be administered until progression or intolerable toxicity.
In this study, a 3 week interval of dosing was considered as a "treatment period" or "cycle of therapy".

After progression or individual end of treatment patients should have been followed every 3 months ± 28 days until death. The study was considered to be completed when all patients had exited the study following progression, or all patients had discontinued (maintenance-) treatment.

Actually, the study was terminated when the response status of the last patient was assessed as progressive disease.

17 Test product, dose, mode of administration, batch number

Not applicable

18 Criteria for evaluation

18.1 Efficiency

Patient with major deviation of selection criteria were excluded from statistical analysis. These cases are being reported anecdotical.

The Intention-to-treat (ITT) population includes all patients in the study (signed ICF and confirmation of eligibility). All patients were grouped according to their randomization regardless of treatment received. The ITT analysis is being used to evaluate the main hypothesis of the trial.

The Per-protocol (PP) population includes all patients who received 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 were excluded from the PP population. The PP analysis was used as an additional analysis.

Progression Free Survival

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

RECIST Criteria

To assess the overall response rate the *Response Evaluation Criteria in Solid Tumors* (RECIST), in it´s recent version v1.1 was used. RECIST v1.1 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.

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 %, th 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 normalization 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 was planned to be evaluated after 6 weeks and every 12 weeks thereafter by CT/MRI following the first treatment. During treatment tumor response was assessed by the investigator. CT and/or MRI scans were 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 were reported in the CRF. Overall response was 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 9: 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.

Overall Survival
Overall survival was determined as time from randomization to date of death.

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.

18.2 Safety

All patients receiving at least one treatment were evaluated for safety.

Safety assessments 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 were 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 summarized.
Treatment related Serious Adverse Events rate (Serious Adverse Reactions), defined as SAEs considered possibly, probably or definitely related to treatment, were determined.

Adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1, and summarized by System Organ Class (SOC), Preferred Term (PT), CTC grade, and relationship to study treatment. In the summary by grade, only the worst case per PT for each patient was counted, if a patient experienced more than one AE within a PT.

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

19 Statistical methods

The primary endpoint PFSR after 12 weeks was compared in the two treatment arms using the one-sided Cochran-Mantel-Haenszel test with control for the two strata liposarcoma yes or no and a significance level of α=0.05. Relative risk was given with corresponding two-sided 90% confidence interval (CI). The main analysis was based on the intention-to-treat (ITT) population, whereas per-protocol (PP) analysis was used as an additional analysis.
The secondary efficacy analyses were done in an exploratory way without adjustment of p-values for multiple testing. OS, TTP and PFS were analyzed by means of Cox regression adjusted for the strata variable liposarcoma. Hazard ratios and their two-sided 95% CIs were estimated. In addition, Kaplan-Meier estimates were presented together with associated median event times. Response rate was analyzed by means of the one-sided Cochran-Mantel-Haenszel test (with control for the two strata - liposarcoma yes or no). Quality of life was compared in a descriptive way.

20 Summary / Conclusions

20.1 Efficiency Results

The main analysis of efficacy was done in the ITT analysis set including 86 patients, 43 in each arm. An additional analysis used the PP analysis set of 59 patients, 24 in arm A (Pazopanib+GEM) and 35 in arm B (Pazopanib).

Analysis of Primary Endpoint

Primary endpoint was progression-free survival (PFS) 12 weeks after randomisation. Because of the stratified randomisation the one-sided Cochran-Mantel-Haenszel (CMH) test (with control for the two strata - liposarcoma yes or no) was applied to compare both treatment arms.
In the ITT analysis set in arm A (Pazopanib+GEM), primary endpoint of one patient was missing and 31 of the remaining 42 patients were progression-free alive at 12 weeks; in arm B (Pazopanib), the latter was the case with 20 of 43 patients (table 10). The difference between treatment arms in PFSR 12 weeks after randomisation adjusted for liposarcoma (no/yes) was statistically significant at the 5% level (one-sided CMH test, p=0.006, ITT n=86, n valid=85, nmiss=1). Adjusted relative risk estimate of being progression-free alive at 12 weeks in arm A (Pazopanib+GEM) compared to arm B (Pazopanib) was 1.60 with two-sided 90% CI [1.15,2.23]; unadjusted relative risk with 90% CI was 1.59 [1.17,2.16].
The additional PP analysis yielded an adjusted relative risk estimate of 1.57 with 90% CI [1.10,2.25] (one-sided CMH test with control for liposarcoma, p=0.015, PP n valid=59), see table 11; unadjusted relative risk with 90% CI was 1.54 [1.12,2.12].

Table 10: PFS 12 weeks after randomisation ITT n=86 (one-sided CMH test with control for liposarcoma, p=0.03, p=0.006; adjusted relative risk with 90% CI 1.60 [1.15,2.23], n valid=85, nmiss=1)

		PFS status after 12 weeks					
		Missing	Alive without PD		PD/dead	Total	
		N	N	(%)	N (%)	N	(%)
Arm	Liposarcoma						
Arm A Pazopanib+GEM	No	1	22	(66.7)	11 (33.3)	33	(100.0)
	Yes	0	9	(100.0)	0 (0.0)	9	(100.0)
	Total	1	31	(73.8)	11 (26.2)	42	(100.0)
Arm B Pazopanib	No	0	19	(52.8)	17 (47.2)	36	(100.0)
	Yes	0	1	(14.3)	6 (85.7)	7	(100.0)
	Total	0	20	(46.5)	23 (53.5)	43	(100.0)
Total	No	1	41	(59.4)	28 (40.6)	69	(100.0)
	Yes	0	10	(62.5)	6 (37.5)	16	(100.0)
	Total	1	51	(60.0)	34 (40.0)	85	(100.0)

Table 11: PFS 12 weeks after randomisation: PP n=59 (one-sided CMH test with control for liposarcoma, p=0.015; adjusted relative risk with 90% CI 1.57 [1.10,2.25], n valid=59)

		PFS status after 12 weeks					
		Alive without PD		PD/dead		Total	
		N	(%)	N	(%)	N	(%)
Arm	Liposarcoma						
Arm A Pazopanib+GEM	No	13	(72.2)	5	(27.8)	18	(100.0)
	Yes	6	(100.0)	0	(0.0)	6	(100.0)
	Total	19	(79.2)	5	(20.8)	24	(100.0)
Arm B Pazopanib	No	17	(58.6)	12	(41.4)	29	(100.0)
	Yes	1	(16.7)	5	(83.3)	6	(100.0)
	Total	18	(51.4)	17	(48.6)	35	(100.0)

		PFS status after 12 weeks					
		Alive without PD		PD/dead		Total	
		N	(%)	N	(%)	N	(%)
Total	No	30	(63.8)	17	(36.2)	47	(100.0)
	Yes	7	(58.3)	5	(41.7)	12	(100.0)
	Total	37	(62.7)	22	(37.3)	59	(100.0)

Analysis of Secondary Endpoints

Secondary efficacy endpoints were

- overall survival (OS) after randomisation
- time to progression (TTP) after randomisation
- best overall response from start of treatment
- quality of life by EORTC QLQ-C30

These secondary endpoints were analyzed in an exploratory manner, thus given p-values were not corrected for multiple testing and have to be interpreted accordingly.
In ITT analysis, median OS times with 95% CI were 13.1 [7.3,17.9] months in arm A (Pazopanib+GEM) and 11.2 [7.2,20.4] months in arm B (Pazopanib); hazard ratio of arm A (Pazopanib+GEM) vs. arm B (Pazopanib) adjusted for liposarcoma was estimated as 0.98 with 95% CI [0.60,1.58], see table 12, table 15a and figure 1. Median TTP were 5.6 [4.1,8.5] months in arm A (Pazopanib+GEM) and 2.0 [1.6,3.2] months in arm B (Pazopanib); adjusted hazard ratio was 0.57 [0.36,0.91], see table 13, table 16a and figure 2. Median PFS times were 5.6 [4.1,8.1] months in arm A (Pazopanib+GEM) and 2.0 [1.6,3.2] months in arm B (Pazopanib); adjusted hazard ratio was 0.58 [0.36,0.92], see table 14 a, table 17 a and figure 3. The results of the additional per-protocol analysis were quite similar as can be seen from table 12 b to table 17 b and figure 4 to figure 6.

Table 12: OS, median event times with two-sided 95% CIs

a ITT n=86

Arm	Median [months]	95% CI	n	n Event	n Censored
Arm A Pazopanib+GEM	13.1	[7.3,17.9]	43	34	9
Arm B Pazopanib	11.2	[7.2,20.4]	43	36	7

b. PP n=59

Arm	Median [months]	95% CI	n	n Event	n Censored
Arm A Pazopanib+GEM	17.3	[8.6,30.7]	24	18	6
Arm B Pazopanib	19.2	[7.3,22.9]	35	28	7

Table 13: TTP, median event times with two-sided 95% CIs

a ITT n=86

Arm	Median [months]	95% CI	n	n Event	n Censored
Arm A Pazopanib+GEM	5.6	[4.1,8.5]	43	39	4
Arm B Pazopanib	2.0	[1.6,3.2]	43	43	0

b. PP n=59

Arm	Median [months]	95% CI	n	n Event	n Censored
Arm A Pazopanib+GEM	5.4	[3.2,10.0]	24	23	1
Arm B Pazopanib	2.9	[1.6,4.4]	35	35	0

Table 14: PFS, median event times with two-sided 95% CIs

a, ITT n=86

Arm	Median [months]	95% CI	n	n Event	n Censored
Arm A Pazopanib+GEM	5.6	[4.1,8.1]	43	40	3
Arm B Pazopanib	2.0	[1.6,3.2]	43	43	0

b, PP n=59

Arm	Median [months]	95% CI	n	n Event	n Censored
Arm A Pazopanib+GEM	5.4	[3.2,10.0]	24	23	1
Arm B Pazopanib	2.9	[1.6,4.4]	35	35	0

Table 15:OS, Cox regression

a, ITT n=86

Characteristic	Regression Coefficient	SE	Chi²	p	Hazard Ratio	95% CI
Arm A vs. B	-0.024	0.25	0.01	0.924	0.98	[0.60,1.58]
Liposarcoma Yes vs. No	0.006	0.32	0.00	0.984	1.01	[0.54,1.87]

b, PP n=59

Characteristic	Regression Coefficient	SE	Chi²	p	Hazard Ratio	95% CI
Arm A vs. B	-0.102	0.31	0.11	0.745	0.90	[0.49,1.67]
Liposarcoma Yes vs. No	0.092	0.39	0.06	0.811	1.10	[0.52,2.33]

Table 16: TTP, Cox regression

a, ITT n=86

Characteristic	Regression Coefficient	SE	Chi²	p	Hazard Ratio	95% CI
Arm A vs. B	-0.562	0.24	5.60	0.018	0.57	[0.36,0.91]
Liposarcoma Yes vs. No	0.146	0.31	0.23	0.632	1.16	[0.64,2.10]

b, PP n=59

Characteristic	Regression Coefficient	SE	Chi²	p	Hazard Ratio	95% CI
Arm A vs. B	-0.639	0.30	4.56	0.033	0.53	[0.29,0.95]
Liposarcoma Yes vs. No	0.413	0.37	1.24	0.266	1.51	[0.73,3.13]

Table 17: PFS, Cox regression

a. ITT n=86

Characteristic	Regression Coefficient	SE	Chi²	p	Hazard Ratio	95% CI
Arm A vs. B	-0.547	0.24	5.40	0.020	0.58	[0.36,0.92]
Liposarcoma Yes vs. No	0.109	0.30	0.13	0.721	1.11	[0.61,2.02]

b. PP n=68

Characteristic	Regression Coefficient	SE	Chi²	p	Hazard Ratio	95% CI
Arm A vs. B	-0.646	0.30	4.63	0.031	0.52	[0.29,0.94]
Liposarcoma Yes vs. No	0.381	0.37	1.05	0.305	1.46	[0.71,3.03]

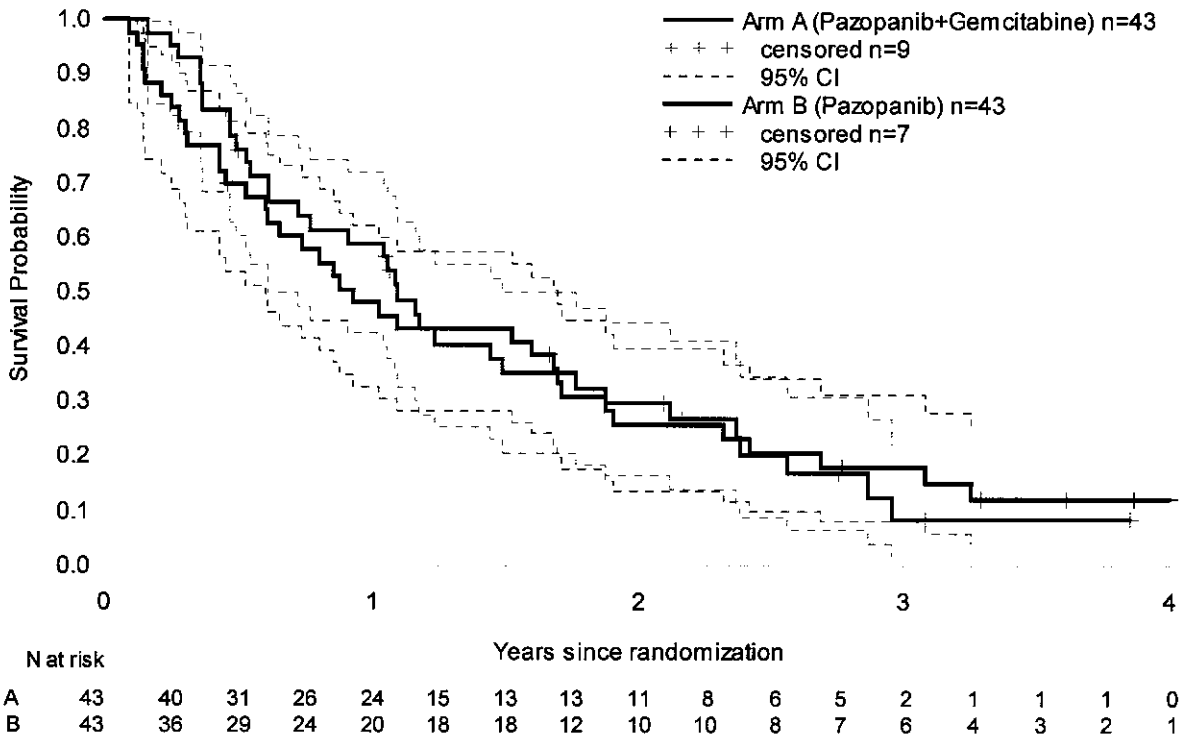

Figure 1: Overall survival (OS), Kaplan-Meier estimate with pointwise 95% CI; stratified log-rank (controlling for the effect of liposarcoma) p=0.831, ITT n=86

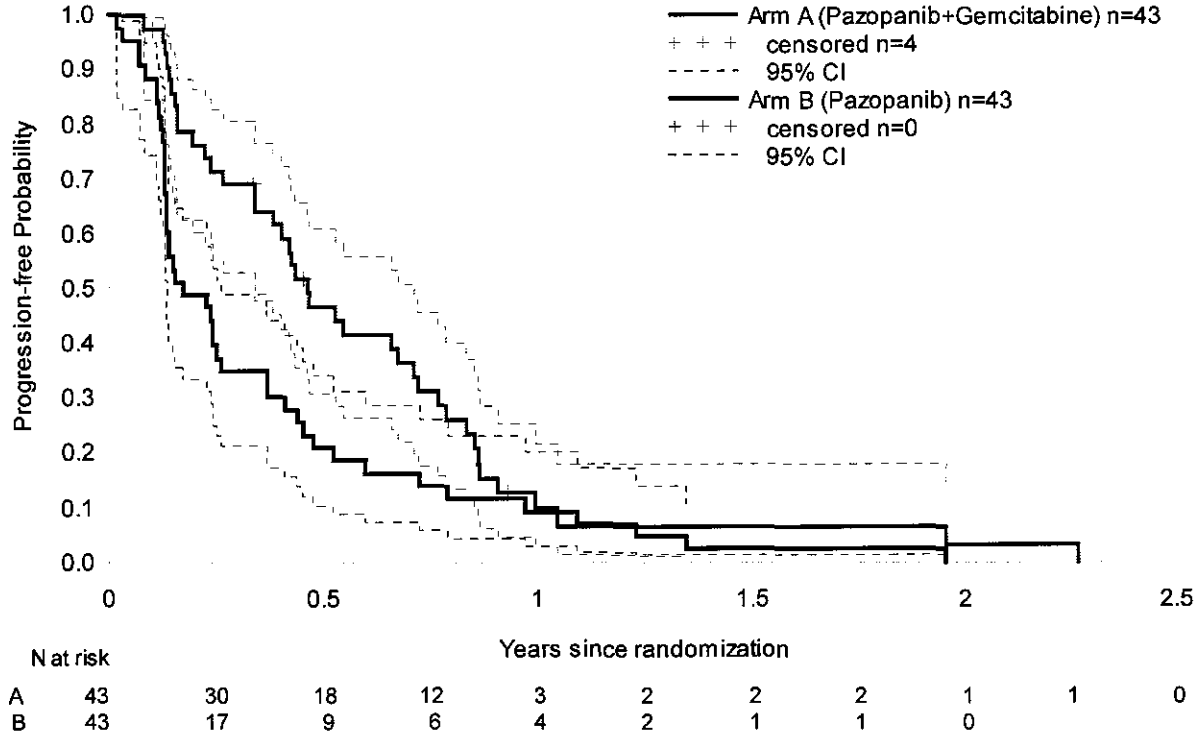

Figure 2: Time to progression (TTP). Kaplan-Meier estimate with 95% pointwise CI; stratified log-rank (controlling for the effect of liposarcoma) p=0.015, ITT n=86

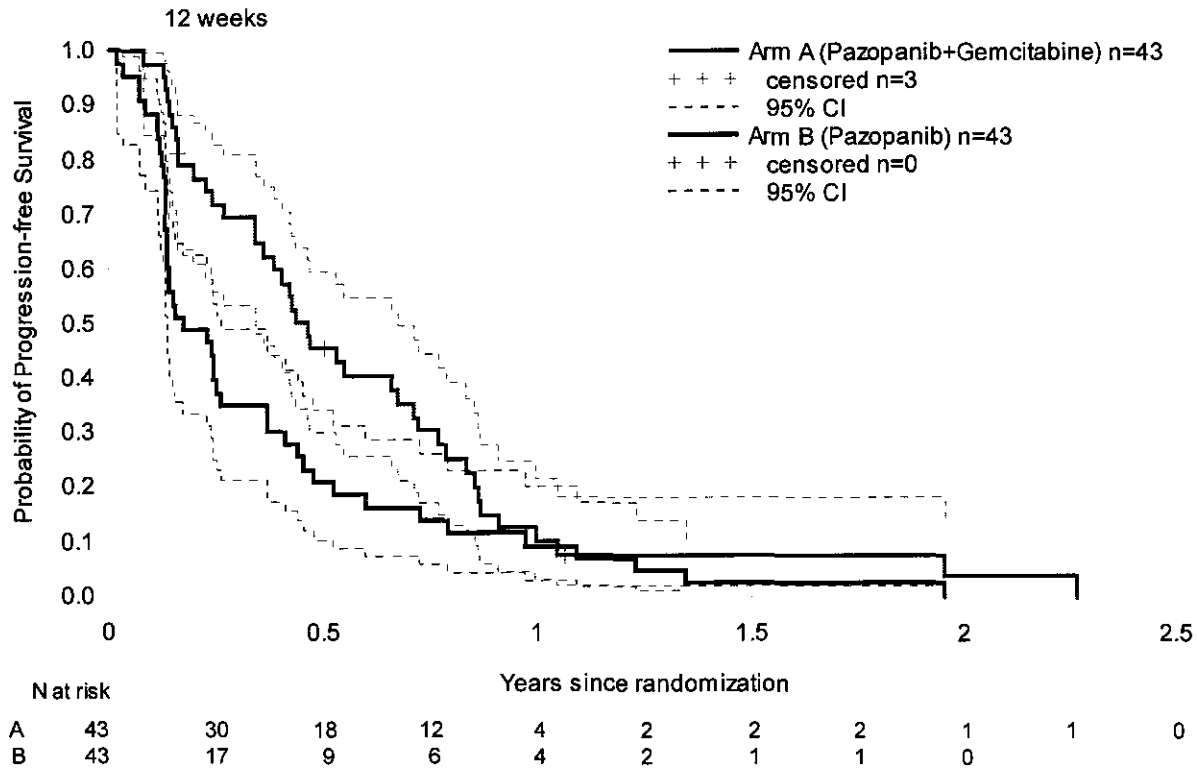

Figure 3: Progression-free survival (PFS). Kaplan-Meier estimate with pointwise 95% CI; stratified log-rank (controlling for the effect of liposarcoma) p=0.019, ITT n=86

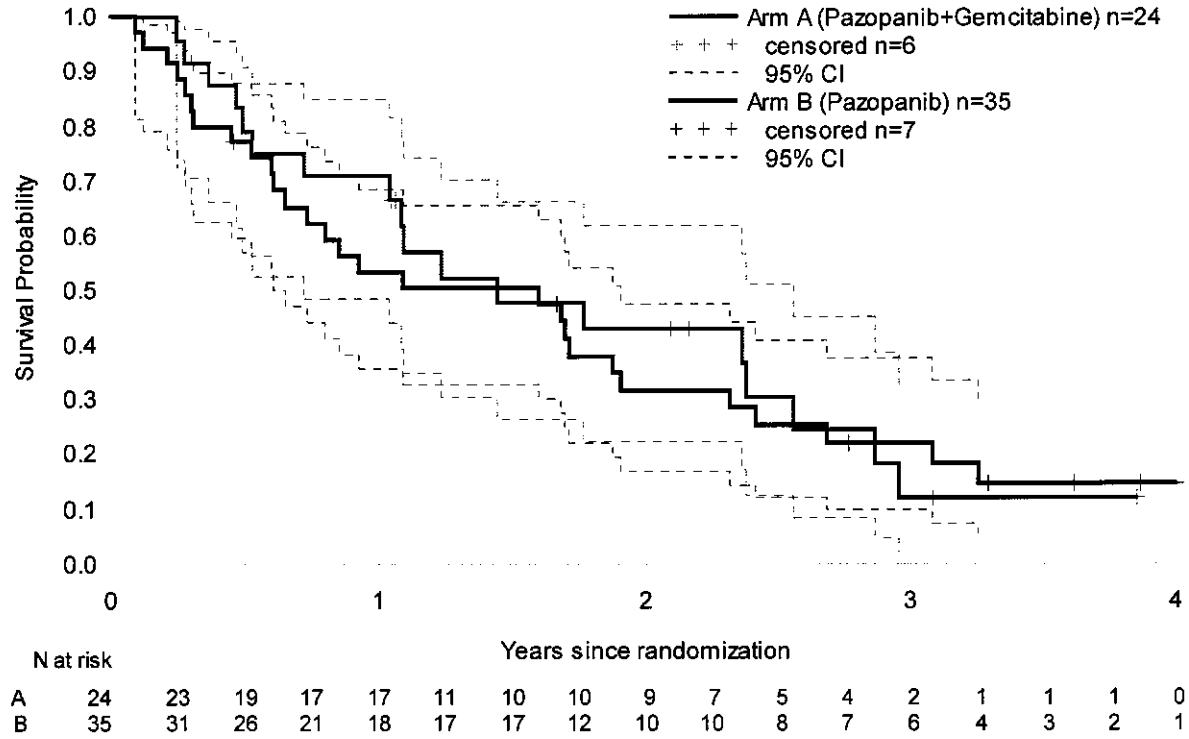

Figure 4: Overall survival (OS). Kaplan-Meier estimate with pointwise 95% CI; stratified log-rank (controlling for the effect of liposarcoma) p=0.652, PP n=59

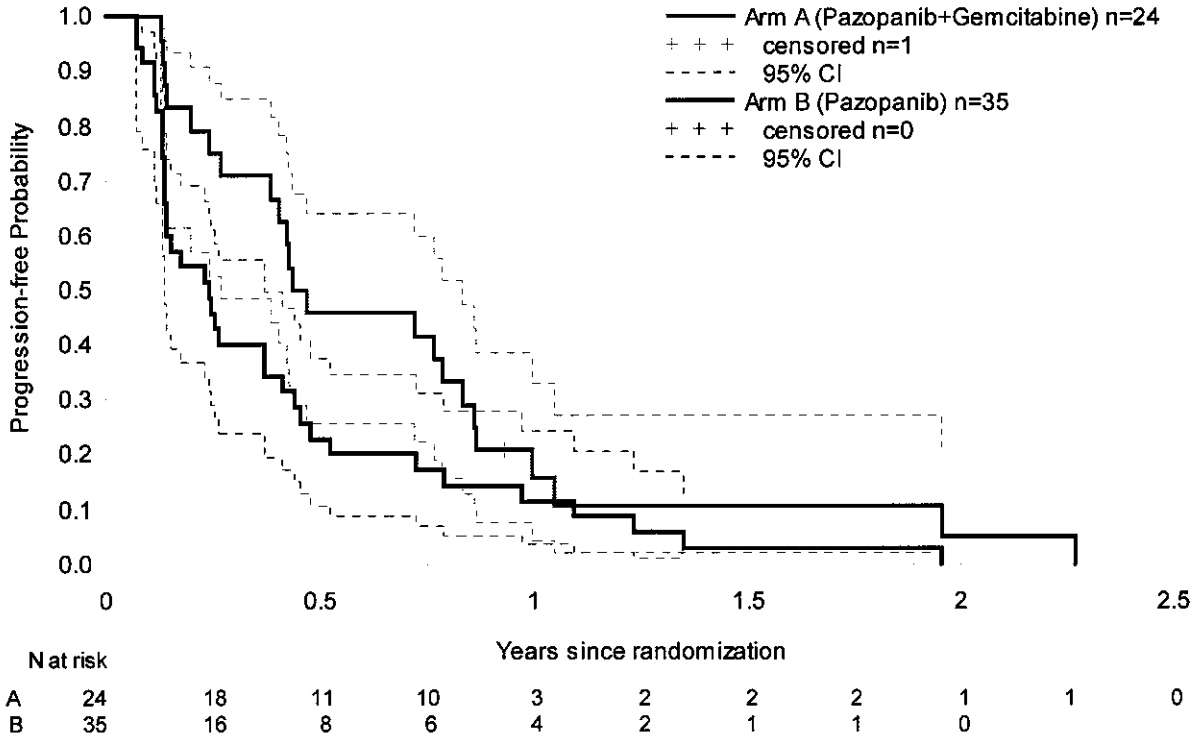

Figure 5: Time to progression (TTP). Kaplan-Meier estimate with 95% pointwise CI; stratified log-rank (controlling for the effect of liposarcoma) p=0.039, PP n=59

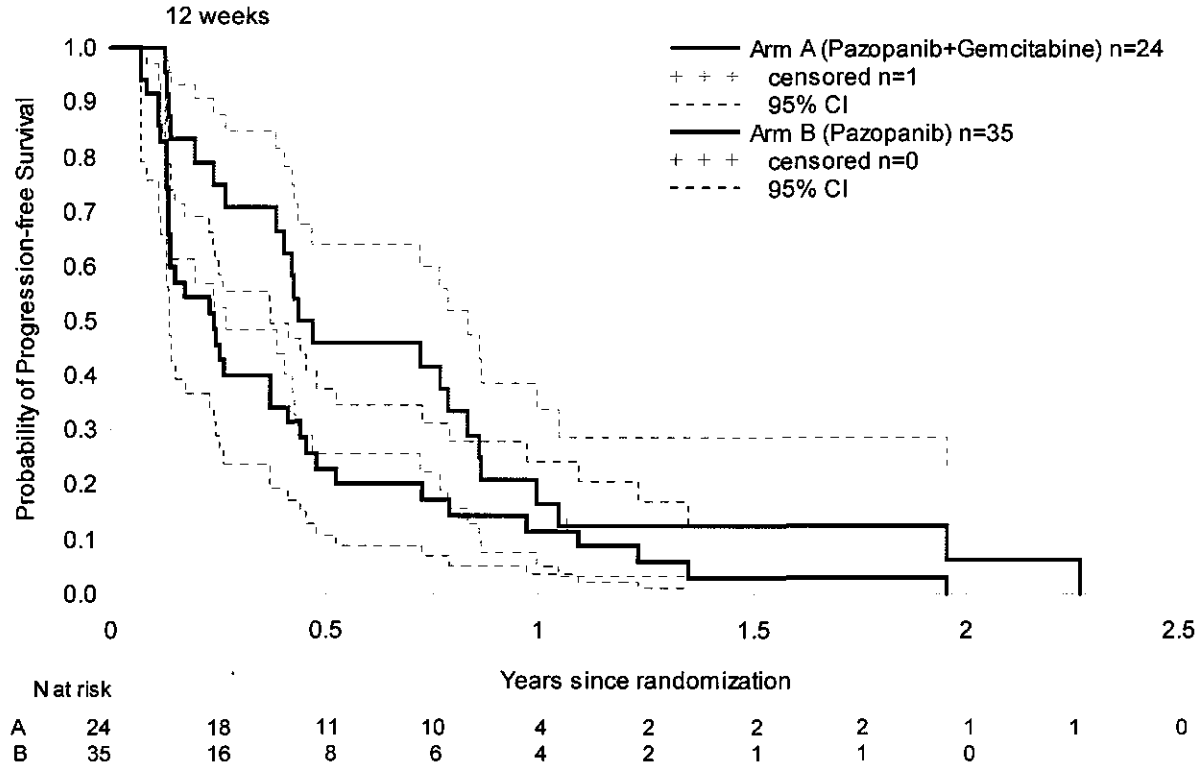

Figure 6: Progression-free survival (PFS), Kaplan-Meier estimate with pointwise 95% CI; stratified log-rank (controlling for the effect of liposarcoma) p=0.039, PP n=59

In ITT population, best overall response was CR or PR in 5 of 43 patients in arm A (Pazopanib+GEM) and 2 of 43 in arm B (Pazopanib). Adjusted relative risk of response in arm A (Pazopanib+GEM) compared to arm B (Pazopanib) was estimated as 2.65 with 90% CI [0.71,9.90] (one-sided CMH test with control for liposarcoma, p=0.103, ITT n valid=86), see table 18 a.
The additional PP analysis resulted in an adjusted relative risk of 3.22 with 90% CI [0.85,12.26] (one-sided CMH test with control for liposarcoma, p=0.065, PP n valid=59), see table 18 b.

Table 18: Best overall response (yes:=CR+PR / no:=SD+PD+death)

a. ITT n=86 (one-sided CMH test with control for liposarcoma, p=0.103; adjusted relative risk with 90% CI 2.65 [0.71,9.90], n valid=86)

		Overall response					
		No		Yes		Total	
		N	(%)	N	(%)	N	(%)
Arm	**Liposarcoma**						
Arm A Pazopanib+GEM	**No**	29	(85.3)	5	(14.7)	34	(100.0)
	Yes	9	(100.0)	0	(0.0)	9	(100.0)
	Total	38	(88.4)	5	(11.6)	43	(100.0)
Arm B Pazopanib	**No**	34	(94.4)	2	(5.6)	36	(100.0)
	Yes	7	(100.0)	0	(0.0)	7	(100.0)
	Total	41	(95.3)	2	(4.7)	43	(100.0)

		Overall response					
		No		Yes		Total	
		N	(%)	N	(%)	N	(%)
Total	No	63	(90.0)	7	(10.0)	70	(100.0)
	Yes	16	(100.0)	0	(0.0)	16	(100.0)
	Total	79	(91.9)	7	(8.1)	86	(100.0)

[illegible] n=59 (one-sided CMH test with control for liposarcoma, p=0.065; adjusted relative risk with 90% CI [illegible] n-valid=59)

		Overall response					
		No		Yes		Total	
		N	(%)	N	(%)	N	(%)
Arm	Liposarcoma						
Arm A Pazopanib+GEM	No	14	(77.8)	4	(22.2)	18	(100.0)
	Yes	6	(100.0)	0	(0.0)	6	(100.0)
	Total	20	(83.3)	4	(16.7)	24	(100.0)
Arm B Pazopanib	No	27	(93.1)	2	(6.9)	29	(100.0)
	Yes	6	(100.0)	0	(0.0)	6	(100.0)
	Total	33	(94.3)	2	(5.7)	35	(100.0)
Total	No	41	(87.2)	6	(12.8)	47	(100.0)
	Yes	12	(100.0)	0	(0.0)	12	(100.0)
	Total	53	(89.8)	6	(10.2)	59	(100.0)

Quality of life scores obtained by means of EORTC QLQ-C30 were descriptively summarized in table 19. "All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems." ([1] p. 6).

Table 19: EORTC QLQ-C30 scores, ITT n=86

a. Global health status/QoL (QL) (0-100: the higher the better)

Global health status/QoL		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	58.3	25.5	8	41.7	58.3	83.3	100
	Cycle 1 d1	30	13	60.8	24.3	17	50.0	66.7	83.3	100
	Cycle 2 d1	32	8	46.9	23.2	0	33.3	50.0	58.3	83
	Cycle 3 d1	21	15	54.0	18.6	33	41.7	50.0	66.7	92
	Cycle 4 d1	24	6	55.2	19.8	17	45.8	58.3	66.7	83
	Cycle 5 d1	17	7	57.4	20.6	17	50.0	50.0	66.7	100
Arm B Pazopanib	Baseline	38	5	59.6	22.4	0	50.0	66.7	75.0	100
	Cycle 1 d1	29	13	56.6	23.8	0	33.3	66.7	75.0	100
	Cycle 2 d1	31	9	56.2	19.0	17	41.7	50.0	75.0	100
	Cycle 3 d1	21	8	58.3	19.5	8	50.0	58.3	75.0	83
	Cycle 4 d1	16	5	50.0	22.6	8	45.8	50.0	58.3	100
	Cycle 5 d1	16	1	51.0	23.7	0	41.7	50.0	66.7	83

Global health status/QoL		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Total	Baseline	73	13	59.0	23.8	0	50.0	66.7	75.0	100
	Cycle 1 d1	59	26	58.8	23.9	0	33.3	66.7	75.0	100
	Cycle 2 d1	63	17	51.5	21.6	0	41.7	50.0	66.7	100
	Cycle 3 d1	42	23	56.2	19.0	8	41.7	50.0	75.0	92
	Cycle 4 d1	40	11	53.1	20.8	8	45.8	50.0	66.7	100
	Cycle 5 d1	33	8	54.3	22.1	0	41.7	50.0	66.7	100

b. Functional scale (0-100: the higher the better): Physical functioning (PF)

Physical functioning		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	63.0	30.4	0	33.3	73.3	86.7	100
	Cycle 1 d1	31	12	68.0	27.8	7	53.3	73.3	86.7	100
	Cycle 2 d1	31	9	57.2	26.4	0	33.3	53.3	73.3	100
	Cycle 3 d1	21	15	60.3	22.4	20	53.3	60.0	73.3	100
	Cycle 4 d1	24	6	57.2	23.3	20	46.7	53.3	70.0	100
	Cycle 5 d1	17	7	65.1	21.7	27	53.3	66.7	80.0	100
Arm B Pazopanib	Baseline	37	6	67.6	22.7	7	53.3	73.3	86.7	100
	Cycle 1 d1	29	13	67.6	23.1	13	60.0	66.7	80.0	100
	Cycle 2 d1	30	10	64.4	24.5	7	53.3	66.7	86.7	100
	Cycle 3 d1	20	9	70.9	24.7	27	52.5	76.7	93.3	100
	Cycle 4 d1	16	5	66.3	20.3	27	50.0	70.0	83.3	93
	Cycle 5 d1	16	1	60.8	31.4	0	33.3	70.0	86.7	100
Total	Baseline	72	14	65.4	26.7	0	50.0	73.3	86.7	100
	Cycle 1 d1	60	25	67.8	25.4	7	56.7	73.3	86.7	100
	Cycle 2 d1	61	19	60.7	25.5	0	40.0	66.7	80.0	100
	Cycle 3 d1	41	24	65.5	23.9	20	53.3	66.7	86.7	100
	Cycle 4 d1	40	11	60.8	22.3	20	46.7	60.0	76.7	100
	Cycle 5 d1	33	8	63.0	26.5	0	46.7	66.7	86.7	100

c. Functional scale (0-100: the higher the better): Role functioning (RF)

Role functioning		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	**Baseline**	35	8	57.6	34.4	0	33.3	66.7	83.3	100
	Cycle 1 d1	31	12	54.3	31.6	0	33.3	66.7	66.7	100
	Cycle 2 d1	31	9	43.0	28.1	0	16.7	50.0	66.7	100
	Cycle 3 d1	21	15	43.7	28.1	0	33.3	33.3	66.7	100
	Cycle 4 d1	24	6	41.0	33.0	0	16.7	33.3	66.7	100
	Cycle 5 d1	17	7	46.1	34.1	0	0.0	66.7	66.7	100
Arm B Pazopanib	**Baseline**	38	5	62.3	29.4	0	33.3	66.7	83.3	100
	Cycle 1 d1	30	12	51.7	34.0	0	33.3	50.0	66.7	100
	Cycle 2 d1	31	9	52.7	28.6	0	33.3	50.0	66.7	100
	Cycle 3 d1	21	8	53.2	34.0	0	33.3	66.7	66.7	100
	Cycle 4 d1	16	5	53.1	26.7	0	33.3	50.0	66.7	100
	Cycle 5 d1	16	1	51.0	26.2	0	33.3	58.3	66.7	100
Total	**Baseline**	73	13	60.0	31.8	0	33.3	66.7	83.3	100
	Cycle 1 d1	61	24	53.0	32.6	0	33.3	66.7	66.7	100
	Cycle 2 d1	62	18	47.8	28.5	0	33.3	50.0	66.7	100
	Cycle 3 d1	42	23	48.4	31.2	0	33.3	50.0	66.7	100
	Cycle 4 d1	40	11	45.8	30.8	0	25.0	41.7	66.7	100
	Cycle 5 d1	33	8	48.5	30.2	0	33.3	66.7	66.7	100

d. Functional scale (0-100: the higher the better): Emotional functioning (EF)

Emotional functioning		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	[illegible]								
	Cycle 1 d1									
	Cycle 2 d1									
	Cycle 3 d1									
	Cycle 4 d1									
	Cycle 5 d1									
Arm B Pazopanib	Baseline									
	Cycle 1 d1									
	Cycle 2 d1									
	Cycle 3 d1									
	Cycle 4 d1									
	Cycle 5 d1									
Total	Baseline									
	Cycle 1 d1									
	Cycle 2 d1									
	Cycle 3 d1									
	Cycle 4 d1									
	Cycle 5 d1									

5. Functional scale (0-100; the higher the better): Cognitive functioning (CF)

Cognitive functioning		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	83.3	25.9	17	66.7	100.0	100.0	100
	Cycle 1 d1	31	12	82.3	27.2	17	66.7	100.0	100.0	100
	Cycle 2 d1	31	9	78.5	23.6	0	66.7	83.3	100.0	100
	Cycle 3 d1	21	15	82.5	17.1	50	66.7	83.3	100.0	100
	Cycle 4 d1	24	6	78.5	20.5	33	66.7	83.3	100.0	100
	Cycle 5 d1	17	7	79.4	22.5	33	66.7	83.3	100.0	100
Arm B Pazopanib	Baseline	38	5	84.2	16.4	50	66.7	83.3	100.0	100
	Cycle 1 d1	30	12	82.2	18.0	50	66.7	83.3	100.0	100
	Cycle 2 d1	31	9	83.3	21.1	33	66.7	100.0	100.0	100
	Cycle 3 d1	21	8	79.4	25.8	0	66.7	83.3	100.0	100
	Cycle 4 d1	16	5	77.1	17.1	50	66.7	75.0	91.7	100
	Cycle 5 d1	16	1	71.9	24.1	17	50.0	75.0	91.7	100
Total	Baseline	73	13	83.8	21.3	17	66.7	100.0	100.0	100
	Cycle 1 d1	61	24	82.2	22.9	17	66.7	100.0	100.0	100
	Cycle 2 d1	62	18	80.9	22.3	0	66.7	83.3	100.0	100
	Cycle 3 d1	42	23	81.0	21.6	0	66.7	83.3	100.0	100
	Cycle 4 d1	40	11	77.9	19.0	33	66.7	83.3	100.0	100
	Cycle 5 d1	33	8	75.8	23.2	17	50.0	83.3	100.0	100

6. Functional scale (0-100; the higher the better): Social functioning (SF)

Social functioning		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	59.5	28.7	0	33.3	66.7	83.3	100
	Cycle 1 d1	31	12	68.3	31.7	0	33.3	83.3	100.0	100
	Cycle 2 d1	32	8	60.4	29.6	0	41.7	66.7	83.3	100
	Cycle 3 d1	21	15	59.5	31.9	0	33.3	66.7	100.0	100
	Cycle 4 d1	24	6	52.8	29.8	0	33.3	50.0	66.7	100
	Cycle 5 d1	17	7	52.0	26.9	0	33.3	66.7	66.7	83
Arm B Pazopanib	Baseline	38	5	58.8	29.4	0	33.3	50.0	83.3	100
	Cycle 1 d1	30	12	52.2	35.2	0	16.7	50.0	83.3	100
	Cycle 2 d1	31	9	64.0	28.3	0	50.0	66.7	83.3	100
	Cycle 3 d1	21	8	65.9	25.0	0	50.0	66.7	83.3	100
	Cycle 4 d1	16	5	51.0	25.4	0	33.3	50.0	66.7	100
	Cycle 5 d1	16	1	57.3	23.5	0	50.0	58.3	66.7	100
Total	Baseline	73	13	59.1	28.9	0	33.3	50.0	83.3	100
	Cycle 1 d1	61	24	60.4	34.2	0	33.3	66.7	83.3	100
	Cycle 2 d1	63	17	62.2	28.7	0	50.0	66.7	83.3	100
	Cycle 3 d1	42	23	62.7	28.5	0	50.0	66.7	83.3	100
	Cycle 4 d1	40	11	52.1	27.8	0	33.3	50.0	66.7	100
	Cycle 5 d1	33	8	54.5	25.1	0	50.0	66.7	66.7	100

g. Symptom scale (0-100: the higher the worse): Fatigue (FA)

Fatigue		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	43.8	29.6	0	22.2	33.3	66.7	100
	Cycle 1 d1	29	14	41.4	29.1	0	22.2	33.3	55.6	100
	Cycle 2 d1	31	9	53.8	28.1	0	33.3	44.4	77.8	100
	Cycle 3 d1	21	15	52.9	23.0	0	33.3	55.6	66.7	89
	Cycle 4 d1	24	6	58.8	23.3	33	33.3	55.6	77.8	100
	Cycle 5 d1	17	7	55.6	25.8	22	33.3	55.6	77.8	100
Arm B Pazopanib	Baseline	38	5	36.5	21.1	0	22.2	33.3	55.6	78
	Cycle 1 d1	30	12	42.8	28.8	0	22.2	38.9	66.7	100
	Cycle 2 d1	31	9	47.7	24.9	11	33.3	33.3	66.7	100
	Cycle 3 d1	21	8	45.0	22.1	11	33.3	33.3	55.6	100
	Cycle 4 d1	16	5	47.9	25.2	11	27.8	44.4	72.2	89
	Cycle 5 d1	16	1	48.6	28.4	22	33.3	33.3	66.7	100
Total	Baseline	73	13	40.0	25.6	0	22.2	33.3	55.6	100
	Cycle 1 d1	59	26	42.1	28.7	0	22.2	33.3	66.7	100
	Cycle 2 d1	62	18	50.7	26.5	0	33.3	44.4	66.7	100
	Cycle 3 d1	42	23	48.9	22.6	0	33.3	44.4	66.7	100
	Cycle 4 d1	40	11	54.4	24.4	11	33.3	50.0	77.8	100
	Cycle 5 d1	33	8	52.2	26.9	22	33.3	33.3	66.7	100

h. Symptom scale (0-100: the higher the worse): Nausea and vomiting (NV)

Nausea and vomiting		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	10.5	18.1	0	0.0	0.0	16.7	67
	Cycle 1 d1	31	12	8.1	16.0	0	0.0	0.0	16.7	67
	Cycle 2 d1	31	9	14.5	19.1	0	0.0	16.7	16.7	83
	Cycle 3 d1	21	15	13.5	20.8	0	0.0	0.0	16.7	67
	Cycle 4 d1	24	6	16.7	20.3	0	0.0	16.7	25.0	67
	Cycle 5 d1	17	7	12.7	18.2	0	0.0	0.0	16.7	50
Arm B Pazopanib	Baseline	38	5	3.5	8.8	0	0.0	0.0	0.0	33
	Cycle 1 d1	30	12	6.1	13.5	0	0.0	0.0	0.0	50
	Cycle 2 d1	31	9	12.4	16.6	0	0.0	0.0	33.3	50
	Cycle 3 d1	21	8	15.9	22.7	0	0.0	0.0	33.3	67
	Cycle 4 d1	16	5	12.5	18.8	0	0.0	0.0	25.0	50
	Cycle 5 d1	16	1	10.4	25.0	0	0.0	0.0	16.7	100
Total	Baseline	73	13	6.8	14.4	0	0.0	0.0	0.0	67
	Cycle 1 d1	61	24	7.1	14.7	0	0.0	0.0	0.0	67
	Cycle 2 d1	62	18	13.4	17.8	0	0.0	0.0	16.7	83
	Cycle 3 d1	42	23	14.7	21.5	0	0.0	0.0	33.3	67
	Cycle 4 d1	40	11	15.0	19.5	0	0.0	0.0	25.0	67
	Cycle 5 d1	33	8	11.6	21.4	0	0.0	0.0	16.7	100

1. Symptom scale (0-100: the higher the worse): Pain (PA)

Pain		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	28.6	30.9	0	0.0	16.7	50.0	100
	Cycle 1 d1	31	12	33.3	32.8	0	0.0	33.3	66.7	100
	Cycle 2 d1	32	8	35.4	28.6	0	16.7	33.3	58.3	100
	Cycle 3 d1	21	15	31.0	33.5	0	0.0	33.3	50.0	100
	Cycle 4 d1	24	6	32.6	30.1	0	0.0	33.3	58.3	83
	Cycle 5 d1	17	7	31.4	34.3	0	0.0	16.7	66.7	100
Arm B Pazopanib	Baseline	38	5	35.5	32.7	0	0.0	33.3	50.0	100
	Cycle 1 d1	30	12	46.1	37.3	0	0.0	50.0	83.3	100
	Cycle 2 d1	31	9	42.5	27.5	0	16.7	50.0	66.7	100
	Cycle 3 d1	21	8	42.1	28.7	0	33.3	33.3	50.0	100
	Cycle 4 d1	16	5	44.8	33.2	0	25.0	33.3	66.7	100
	Cycle 5 d1	16	1	46.9	30.6	0	25.0	33.3	66.7	100
Total	Baseline	73	13	32.2	31.8	0	0.0	16.7	50.0	100
	Cycle 1 d1	61	24	39.6	35.4	0	0.0	33.3	66.7	100
	Cycle 2 d1	63	17	38.9	28.1	0	16.7	33.3	66.7	100
	Cycle 3 d1	42	23	36.5	31.3	0	0.0	33.3	50.0	100
	Cycle 4 d1	40	11	37.5	31.5	0	0.0	33.3	66.7	100
	Cycle 5 d1	33	8	38.9	33.0	0	16.7	33.3	66.7	100

1. Symptom scale (0-100: the higher the worse): Dyspnoea (DY)

Dyspnoea		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	34.3	34.8	0	0.0	33.3	66.7	100
	Cycle 1 d1	31	12	35.5	32.1	0	0.0	33.3	66.7	100
	Cycle 2 d1	32	8	36.5	34.2	0	0.0	33.3	66.7	100
	Cycle 3 d1	21	15	39.7	30.9	0	33.3	33.3	66.7	100
	Cycle 4 d1	24	6	45.8	30.8	0	33.3	33.3	66.7	100
	Cycle 5 d1	17	7	35.3	27.6	0	33.3	33.3	33.3	100
Arm B Pazopanib	Baseline	38	5	23.7	26.7	0	0.0	16.7	33.3	67
	Cycle 1 d1	29	13	25.3	27.7	0	0.0	33.3	33.3	67
	Cycle 2 d1	31	9	28.0	31.1	0	0.0	33.3	33.3	100
	Cycle 3 d1	20	9	16.7	22.9	0	0.0	0.0	33.3	67
	Cycle 4 d1	16	5	25.0	25.8	0	0.0	33.3	33.3	100
	Cycle 5 d1	16	1	25.0	22.8	0	0.0	33.3	33.3	67
Total	Baseline	73	13	28.8	31.1	0	0.0	33.3	33.3	100
	Cycle 1 d1	60	25	30.6	30.2	0	0.0	33.3	66.7	100
	Cycle 2 d1	63	17	32.3	32.8	0	0.0	33.3	33.3	100
	Cycle 3 d1	41	24	28.5	29.4	0	0.0	33.3	33.3	100
	Cycle 4 d1	40	11	37.5	30.4	0	16.7	33.3	66.7	100
	Cycle 5 d1	33	8	30.3	25.5	0	0.0	33.3	33.3	100

1. Symptom scale (0-100: the higher the worse): Insomnia (SL)

Insomnia		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	32.4	29.7	0	0.0	33.3	66.7	100
	Cycle 1 d1	31	12	28.0	31.1	0	0.0	33.3	33.3	100
	Cycle 2 d1	31	9	25.8	25.4	0	0.0	33.3	33.3	100
	Cycle 3 d1	21	15	31.7	34.1	0	0.0	33.3	66.7	100
	Cycle 4 d1	24	6	33.3	34.1	0	0.0	33.3	66.7	100
	Cycle 5 d1	17	7	21.6	26.2	0	0.0	0.0	33.3	67
Arm B Pazopanib	Baseline	38	5	30.7	29.4	0	0.0	33.3	33.3	100
	Cycle 1 d1	29	13	35.6	33.3	0	0.0	33.3	66.7	100
	Cycle 2 d1	30	10	28.9	25.9	0	0.0	33.3	33.3	100
	Cycle 3 d1	21	8	34.9	30.7	0	0.0	33.3	66.7	100
	Cycle 4 d1	16	5	31.3	25.7	0	0.0	33.3	50.0	67
	Cycle 5 d1	16	1	31.3	28.5	0	0.0	33.3	33.3	100
Total	Baseline	73	13	31.5	29.3	0	0.0	33.3	33.3	100
	Cycle 1 d1	60	25	31.7	32.1	0	0.0	33.3	66.7	100
	Cycle 2 d1	61	19	27.3	25.5	0	0.0	33.3	33.3	100
	Cycle 3 d1	42	23	33.3	32.1	0	0.0	33.3	66.7	100
	Cycle 4 d1	40	11	32.5	30.7	0	0.0	33.3	66.7	100
	Cycle 5 d1	33	8	26.3	27.3	0	0.0	33.3	33.3	100

1. Symptom scale (0-100: the higher the worse): Appetite loss (AP)

Appetite loss		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	22.9	32.1	0	0.0	0.0	33.3	100
	Cycle 1 d1	30	13	25.6	31.2	0	0.0	16.7	33.3	100
	Cycle 2 d1	31	9	29.0	30.7	0	0.0	33.3	33.3	100
	Cycle 3 d1	21	15	28.6	30.3	0	0.0	33.3	33.3	100
	Cycle 4 d1	24	6	29.2	30.0	0	0.0	33.3	50.0	100
	Cycle 5 d1	17	7	33.3	33.3	0	0.0	33.3	66.7	100
Arm B Pazopanib	Baseline	38	5	14.9	25.3	0	0.0	0.0	33.3	100
	Cycle 1 d1	30	12	17.8	25.9	0	0.0	0.0	33.3	100
	Cycle 2 d1	31	9	31.2	32.1	0	0.0	33.3	66.7	100
	Cycle 3 d1	21	8	30.2	33.2	0	0.0	33.3	33.3	100
	Cycle 4 d1	16	5	41.7	37.5	0	0.0	33.3	66.7	100
	Cycle 5 d1	16	1	27.1	25.0	0	0.0	33.3	33.3	67
Total	Baseline	73	13	18.7	28.9	0	0.0	0.0	33.3	100
	Cycle 1 d1	60	25	21.7	28.7	0	0.0	0.0	33.3	100
	Cycle 2 d1	62	18	30.1	31.2	0	0.0	33.3	66.7	100
	Cycle 3 d1	42	23	29.4	31.4	0	0.0	33.3	33.3	100
	Cycle 4 d1	40	11	34.2	33.3	0	0.0	33.3	66.7	100
	Cycle 5 d1	33	8	30.3	29.3	0	0.0	33.3	66.7	100

n. Symptom scale (0-100; the higher the worse): Constipation (CO)

Constipation		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	15.2	27.2	0	0.0	0.0	33.3	100
	Cycle 1 d1	31	12	15.1	30.8	0	0.0	0.0	0.0	100
	Cycle 2 d1	31	9	12.9	20.5	0	0.0	0.0	33.3	67
	Cycle 3 d1	21	15	11.1	21.9	0	0.0	0.0	0.0	67
	Cycle 4 d1	24	6	9.7	23.0	0	0.0	0.0	0.0	100
	Cycle 5 d1	17	7	3.9	11.1	0	0.0	0.0	0.0	33
Arm B Pazopanib	Baseline	38	5	14.9	30.7	0	0.0	0.0	0.0	100
	Cycle 1 d1	29	13	18.4	34.0	0	0.0	0.0	33.3	100
	Cycle 2 d1	30	10	5.6	15.4	0	0.0	0.0	0.0	67
	Cycle 3 d1	21	8	4.8	12.0	0	0.0	0.0	0.0	33
	Cycle 4 d1	16	5	6.3	25.0	0	0.0	0.0	0.0	100
	Cycle 5 d1	16	1	0.0	0.0	0	0.0	0.0	0.0	0
Total	Baseline	73	13	15.1	28.9	0	0.0	0.0	33.3	100
	Cycle 1 d1	60	25	16.7	32.2	0	0.0	0.0	16.7	100
	Cycle 2 d1	61	19	9.3	18.4	0	0.0	0.0	0.0	67
	Cycle 3 d1	42	23	7.9	17.7	0	0.0	0.0	0.0	67
	Cycle 4 d1	40	11	8.3	23.6	0	0.0	0.0	0.0	100
	Cycle 5 d1	33	8	2.0	8.1	0	0.0	0.0	0.0	33

n. Symptom scale (0-100; the higher the worse): Diarrhoea (DI)

Diarrhoea		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	8.6	20.4	0	0.0	0.0	0.0	67
	Cycle 1 d1	31	12	6.5	15.9	0	0.0	0.0	0.0	67
	Cycle 2 d1	32	8	14.6	23.9	0	0.0	0.0	33.3	100
	Cycle 3 d1	21	15	31.7	34.1	0	0.0	33.3	66.7	100
	Cycle 4 d1	24	6	22.2	27.2	0	0.0	0.0	33.3	67
	Cycle 5 d1	16	8	31.3	31.0	0	0.0	33.3	66.7	67
Arm B Pazopanib	Baseline	37	6	9.0	24.4	0	0.0	0.0	0.0	100
	Cycle 1 d1	30	12	4.4	14.5	0	0.0	0.0	0.0	67
	Cycle 2 d1	31	9	36.6	36.9	0	0.0	33.3	66.7	100
	Cycle 3 d1	21	8	41.3	34.8	0	0.0	33.3	66.7	100
	Cycle 4 d1	16	5	33.3	29.8	0	0.0	33.3	50.0	100
	Cycle 5 d1	16	1	33.3	32.2	0	0.0	33.3	66.7	100
Total	Baseline	72	14	8.8	22.4	0	0.0	0.0	0.0	100
	Cycle 1 d1	61	24	5.5	15.1	0	0.0	0.0	0.0	67
	Cycle 2 d1	63	17	25.4	32.6	0	0.0	0.0	33.3	100
	Cycle 3 d1	42	23	36.5	34.4	0	0.0	33.3	66.7	100
	Cycle 4 d1	40	11	26.7	28.4	0	0.0	33.3	33.3	100
	Cycle 5 d1	32	9	32.3	31.1	0	0.0	33.3	66.7	100

n. Symptom scale (0-100; the higher the worse): Financial difficulties (FI)

Financial difficulties		N	NMiss	Mean	Std	Min	Q1	Median	Q3	Max
Arm A Pazopanib +GEM	Baseline	35	8	34.3	35.7	0	0.0	33.3	66.7	100
	Cycle 1 d1	31	12	26.9	32.7	0	0.0	0.0	66.7	100
	Cycle 2 d1	31	9	31.2	33.3	0	0.0	33.3	66.7	100
	Cycle 3 d1	21	15	27.0	34.3	0	0.0	0.0	33.3	100
	Cycle 4 d1	24	6	29.2	34.5	0	0.0	16.7	66.7	100
	Cycle 5 d1	17	7	27.5	31.7	0	0.0	33.3	33.3	100
Arm B Pazopanib	Baseline	38	5	29.8	39.4	0	0.0	0.0	66.7	100
	Cycle 1 d1	30	12	34.4	40.6	0	0.0	16.7	66.7	100
	Cycle 2 d1	31	9	26.9	37.9	0	0.0	0.0	66.7	100
	Cycle 3 d1	21	8	30.2	40.7	0	0.0	0.0	66.7	100
	Cycle 4 d1	16	5	31.3	35.4	0	0.0	33.3	50.0	100
	Cycle 5 d1	16	1	33.3	34.4	0	0.0	33.3	50.0	100
Total	Baseline	73	13	32.0	37.4	0	0.0	33.3	66.7	100
	Cycle 1 d1	61	24	30.6	36.7	0	0.0	0.0	66.7	100
	Cycle 2 d1	62	18	29.0	35.4	0	0.0	0.0	66.7	100
	Cycle 3 d1	42	23	28.6	37.2	0	0.0	0.0	66.7	100
	Cycle 4 d1	40	11	30.0	34.4	0	0.0	33.3	66.7	100
	Cycle 5 d1	33	8	30.3	32.7	0	0.0	33.3	33.3	100

20.2 Safety Results

The safety analysis was performed in the safety analysis set including 43 patients in arm A (Pazopanib+GEM) and 44 patients in arm B (Pazopanib).

Adverse Events

Adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1, and summarized by System Organ Class (SOC), Preferred Term (PT), CTC grade, and relationship to study treatment. In the summary by grade, only the worst case per PT for each patient was counted, if a patient experienced more than one AE within a PT; in the summary by relationship to study treatment, all AEs were included; table 20 shows both frequencies (N AE* and N AE, respectively).
All patients, 43 in arm A (Pazopanib+GEM) and 44 in arm B (Pazopanib), experienced adverse events. Overall, 908 and 452 AEs were documented in arm A and B, respectively, see table 20 for details.

Table 20: AEs by SOC, Safety n=87

N: Number of patients with AE, N AE: Number of AEs

Adverse Events by System Organ Class (SOC)	Arm A Pazopanib+GEM n=43				Arm B Pazopanib n=44				Total n=87			
	N	(%)	N AE	N AE*	N	(%)	N AE	N AE*	N	(%)	N AE	N AE*
Any AE	43	(100)	908	637	44	(100)	452	362	87	(100)	1360	999
Infections and infestations	27	(63)	53	44	13	(30)	31	21	40	(46)	84	65

Adverse Events by System Organ Class (SOC)	Arm A Pazopanib+GEM n=43				Arm B Pazopanib n=44				Total n=87			
	N	(%)	N AE	N AE*	N	(%)	N AE	N AE*	N	(%)	N AE	N AE*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(9)	4	4	5	(11)	6	6	9	(10)	10	10
Blood and lymphatic system disorders	36	(84)	199	80	8	(18)	37	15	44	(51)	236	95
Endocrine disorders	7	(16)	7	7	5	(11)	6	5	12	(14)	13	12
Metabolism and nutrition disorders	19	(44)	34	32	11	(25)	12	12	30	(34)	46	44
Psychiatric disorders	7	(16)	9	8	3	(7)	7	6	10	(11)	16	14
Nervous system disorders	30	(70)	57	48	24	(55)	36	34	54	(62)	93	82
Eye disorders	7	(16)	8	8	3	(7)	3	3	10	(11)	11	11
Ear and labyrinth disorders	3	(7)	4	4	0		0	0	3	(3)	4	4
Cardiac disorders	5	(12)	6	6	2	(5)	2	2	7	(8)	8	8
Vascular disorders	13	(30)	20	14	11	(25)	15	12	24	(28)	35	26
Respiratory, thoracic and mediastinal disorders	25	(58)	66	53	19	(43)	41	30	44	(51)	107	83
Gastrointestinal disorders	40	(93)	142	112	32	(73)	97	80	72	(83)	239	192
Hepatobiliary disorders	2	(5)	2	2	3	(7)	3	3	5	(6)	5	5
Skin and subcutaneous tissue disorders	17	(40)	31	27	17	(39)	28	25	34	(39)	59	52
Musculoskeletal and connective tissue disorders	18	(42)	26	23	20	(45)	35	28	38	(44)	61	51
Renal and urinary disorders	9	(21)	13	12	3	(7)	5	4	12	(14)	18	16
Reproductive system and breast disorders	4	(9)	4	4	0		0	0	4	(5)	4	4
Congenital, familial and genetic disorders	1	(2)	1	1	0		0	0	1	(1)	1	1
General disorders and administration site conditions	31	(72)	87	66	28	(64)	44	41	59	(68)	131	107
Investigations	27	(63)	126	73	21	(48)	40	31	48	(55)	166	104
Injury, poisoning and procedural complications	7	(16)	8	8	4	(9)	4	4	11	(13)	12	12
Surgical and medical procedures	1	(2)	1	1	0		0	0	1	(1)	1	1

***worst case on PT level per patient counted only**

In arm A (Pazopanib+GEM), the most common AEs were diarrhea in 26 of 43 patients, thrombocytopenia in 25 patients, nausea in 22 patients, leucopenia in 20 patients, somnolence in 19 patients, anemia in 16 patients, cough in 15 patients, fatigue in 14 patients, constipation, decreased weight and decreased appetite in 12 patients each, neutropenia, vomiting, nasopharyngitis and increased aspartate aminotransferase in 11 patients each, peripheral oedema, pyrexia, infection, increased alanine aminotransferase and increased gamma-glutamyltransferase in 10 patients each and dyspnoea in 9 of 43 patients; and in arm B (Pazopanib) diarrhea in 18 of 44 patients, nausea in 18 patients, fatigue in 17 patients, decreased weight and somnolence in 11 patients each and hypertension in 9 of 44 patients.

The frequencies of patients with AEs by grade 3+4 and 5 are given in table 21. In this table, no multiply occurring AE on PT level was counted more than once per patient. In arm A (Pazopanib+GEM), 1 patient had a grade 5 AE and 34 of 43 patients had grade 3 and/or 4 AEs; in arm B (Pazopanib), 3 patients had grade 5 AEs and 25 patients had grade 3 and/or 4 AEs. Grade 5 AEs were acute respiratory distress syndrome in arm A (Pazopanib+GEM) and multi-organ failure, general physical health deterioration and disease progression in arm B (Pazopanib). In arm A (Pazopanib+GEM), the five most frequently observed grade 3/4 AEs were thrombocytopenia in 17 of 43 patients, leucopenia in 14 patients, neutropenia in 9 patients, hypertension in 5 patients and anemia 4 patients. In arm B (Pazopanib), the six most frequent grade 3/4 AEs occurred in 2 of 44 patients each (table 21).

Table 21: AEs by SOC, PT and CTC grade (3+4|5|All), Safety n=87

N: Number of patients with AE (worst case on PT level per patient)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Any AE		Grade 3+4	34	(79)	25	(57)	59	(68)
		Grade 5	1	(2)	3	(7)	4	(5)
		All AEs	43	(100)	44	(100)	87	(100)
Infections and infestations		Grade 3+4	5	(12)	2	(5)	7	(8)
		All AEs	27	(63)	13	(30)	40	(46)
	Abdominal abscess	All AEs	0		1	(2)	1	(1)
	Bacteriuria	All AEs	0		1	(2)	1	(1)
	Bronchitis	All AEs	2	(5)	2	(5)	4	(5)
	Clostridial infection	All AEs	1	(2)	0		1	(1)
	Cystitis	All AEs	0		1	(2)	1	(1)
	Diarrhoea infectious	All AEs	1	(2)	0		1	(1)
	Diverticulitis	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Febrile infection	All AEs	2	(5)	0		2	(2)
	Gastroenteritis	All AEs	1	(2)	1	(2)	2	(2)
	Infection	Grade 3+4	1	(2)	0		1	(1)
		All AEs	10	(23)	5	(11)	15	(17)
	Nasopharyngitis	All AEs	11	(26)	3	(7)	14	(16)
	Oral candidiasis	All AEs	1	(2)	0		1	(1)
	Oral herpes	All AEs	3	(7)	0		3	(3)
	Pneumonia	Grade 3+4	2	(5)	0		2	(2)
		All AEs	3	(7)	0		3	(3)
	Pneumonia fungal	All AEs	1	(2)	0		1	(1)
	Rhinitis	All AEs	1	(2)	0		1	(1)
	Sinusitis	All AEs	1	(2)	0		1	(1)
	Soft tissue infection	All AEs	0		1	(2)	1	(1)
	Tooth infection	All AEs	1	(2)	1	(2)	2	(2)
	Upper respiratory tract infection	All AEs	1	(2)	0		1	(1)
	Urinary tract infection	Grade 3+4	2	(5)	2	(5)	4	(5)
		All AEs	3	(7)	5	(11)	8	(9)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Grade 3+4	0		2	(5)	2	(2)
		All AEs	4	(9)	5	(11)	9	(10)
	Metastatic pain	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Neoplasm progression	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Neoplasm swelling	All AEs	0		1	(2)	1	(1)
	Tumour pain	Grade 3+4	0		1	(2)	1	(1)
		All AEs	3	(7)	3	(7)	6	(7)
	Tumour ulceration	All AEs	1	(2)	0		1	(1)
Blood and lymphatic system disorders		Grade 3+4	27	(63)	1	(2)	28	(32)
		All AEs	36	(84)	8	(18)	44	(51)
	Anaemia	Grade 3+4	4	(9)	0		4	(5)
		All AEs	16	(37)	4	(9)	20	(23)
	Anaemia of malignant disease	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Febrile neutropenia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Granulocytopenia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Haemolytic uraemic syndrome	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Leukopenia	Grade 3+4	14	(33)	1	(2)	15	(17)
		All AEs	20	(47)	3	(7)	23	(26)
	Lymph node pain	All AEs	2	(5)	0		2	(2)
	Neutropenia	Grade 3+4	9	(21)	0		9	(10)
		All AEs	11	(26)	2	(5)	13	(15)
	Pancytopenia	All AEs	1	(2)	0		1	(1)
	Thrombocytopenia	Grade 3+4	17	(40)	0		17	(20)
		All AEs	25	(58)	6	(14)	31	(36)
	Thrombotic microangiopathy	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
Endocrine disorders		All AEs	7	(16)	5	(11)	12	(14)
	Hypothyroidism	All AEs	7	(16)	5	(11)	12	(14)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Metabolism and nutrition disorders		Grade 3+4	7	(16)	0		7	(8)
		All AEs	19	(44)	11	(25)	30	(34)
	Abnormal loss of weight	All AEs	3	(7)	2	(5)	5	(6)
	Cachexia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	2	(5)	0		2	(2)
	Decreased appetite	Grade 3+4	2	(5)	0		2	(2)
		All AEs	12	(28)	8	(18)	20	(23)
	Dehydration	All AEs	1	(2)	0		1	(1)
	Diabetes mellitus	All AEs	1	(2)	0		1	(1)
	Hypercalcaemia	All AEs	0		1	(2)	1	(1)
	Hyperkalaemia	All AEs	1	(2)	1	(2)	2	(2)
	Hyperuricaemia	Grade 3+4	3	(7)	0		3	(3)
		All AEs	3	(7)	0		3	(3)
	Hypoalbuminaemia	All AEs	1	(2)	0		1	(1)
	Hypoglycaemia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Hypokalaemia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	4	(9)	0		4	(5)
	Hyponatraemia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Hypoproteinaemia	All AEs	1	(2)	0		1	(1)
	Metabolic disorder	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
Psychiatric disorders		Grade 3+4	1	(2)	0		1	(1)
		All AEs	7	(16)	3	(7)	10	(11)
	Abnormal behaviour	All AEs	0		1	(2)	1	(1)
	Anxiety	All AEs	1	(2)	0		1	(1)
	Confusional state	All AEs	1	(2)	0		1	(1)
	Depression	All AEs	2	(5)	0		2	(2)
	Hallucination	All AEs	0		1	(2)	1	(1)
	Initial insomnia	All AEs	1	(2)	0		1	(1)
	Insomnia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	2	(5)	3	(3)
	Restlessness	All AEs	0		1	(2)	1	(1)
	Sleep disorder	All AEs	2	(5)	1	(2)	3	(3)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Nervous system disorders		Grade 3+4	2	(5)	2	(5)	4	(5)
		All AEs	30	(70)	24	(55)	54	(62)
	Amnesia	All AEs	0		1	(2)	1	(1)
	Balance disorder	All AEs	1	(2)	1	(2)	2	(2)
	Burning sensation	All AEs	2	(5)	0		2	(2)
	Dizziness	All AEs	4	(9)	1	(2)	5	(6)
	Dysaesthesia	All AEs	0		1	(2)	1	(1)
	Dysgeusia	All AEs	5	(12)	7	(16)	12	(14)
	Headache	All AEs	7	(16)	3	(7)	10	(11)
	Hyperaesthesia	All AEs	0		1	(2)	1	(1)
	Hypoaesthesia	All AEs	3	(7)	2	(5)	5	(6)
	Hypogeusia	All AEs	1	(2)	0		1	(1)
	Migraine	All AEs	1	(2)	0		1	(1)
	Paraesthesia	All AEs	1	(2)	3	(7)	4	(5)
	Paraparesis	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Polyneuropathy	All AEs	1	(2)	1	(2)	2	(2)
	Presyncope	All AEs	1	(2)	0		1	(1)
	Somnolence	Grade 3+4	1	(2)	0		1	(1)
		All AEs	19	(44)	11	(25)	30	(34)
	Syncope	Grade 3+4	1	(2)	1	(2)	2	(2)
		All AEs	1	(2)	1	(2)	2	(2)
	Transient ischaemic attack	All AEs	1	(2)	0		1	(1)
Eye disorders		Grade 3+4	0		1	(2)	1	(1)
		All AEs	7	(16)	3	(7)	10	(11)
	Accommodation disorder	All AEs	0		1	(2)	1	(1)
	Cataract	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Conjunctival haemorrhage	All AEs	1	(2)	0		1	(1)
	Conjunctivitis	All AEs	1	(2)	0		1	(1)
	Diplopia	All AEs	0		1	(2)	1	(1)
	Dry eye	All AEs	1	(2)	0		1	(1)
	Ocular icterus	All AEs	1	(2)	0		1	(1)
	Photopsia	All AEs	1	(2)	0		1	(1)
	Visual impairment	All AEs	2	(5)	0		2	(2)
	Vitreous haemorrhage	All AEs	1	(2)	0		1	(1)
Ear and labyrinth disorders		All AEs	3	(7)	0		3	(3)
	Deafness unilateral	All AEs	1	(2)	0		1	(1)
	Ear discomfort	All AEs	1	(2)	0		1	(1)
	Hearing impaired	All AEs	1	(2)	0		1	(1)
	Vertigo	All AEs	1	(2)	0		1	(1)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Cardiac disorders		Grade 3+4	3	(7)	0		3	(3)
		All AEs	5	(12)	2	(5)	7	(8)
	Atrial flutter	All AEs	1	(2)	0		1	(1)
	Bradycardia	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Cardiac failure	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Cardiomegaly	All AEs	1	(2)	0		1	(1)
	Cardiomyopathy	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Sinus tachycardia	All AEs	1	(2)	1	(2)	2	(2)
	Tachycardia	All AEs	0		1	(2)	1	(1)
Vascular disorders		Grade 3+4	6	(14)	3	(7)	9	(10)
		All AEs	13	(30)	11	(25)	24	(28)
	Haematoma	All AEs	3	(7)	0		3	(3)
	Hot flush	All AEs	1	(2)	0		1	(1)
	Hypertension	Grade 3+4	5	(12)	2	(5)	7	(8)
		All AEs	8	(19)	9	(20)	17	(20)
	Hypertensive crisis	All AEs	0		1	(2)	1	(1)
	Lymphoedema	All AEs	1	(2)	0		1	(1)
	Subclavian vein thrombosis	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Thrombosis	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Vena cava thrombosis	All AEs	0		1	(2)	1	(1)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Respiratory, thoracic and mediastinal disorders		Grade 3+4	7	(16)	4	(9)	11	(13)
		Grade 5	1	(2)	0		1	(1)
		All AEs	25	(58)	19	(43)	44	(51)
	Acute respiratory distress syndrome	Grade 5	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Cough	All AEs	15	(35)	8	(18)	23	(26)
	Dysphonia	All AEs	1	(2)	2	(5)	3	(3)
	Dyspnoea	Grade 3+4	2	(5)	2	(5)	4	(5)
		All AEs	9	(21)	6	(14)	15	(17)
	Dyspnoea exertional	All AEs	4	(9)	4	(9)	8	(9)
	Epistaxis	Grade 3+4	2	(5)	0		2	(2)
		All AEs	7	(16)	0		7	(8)
	Haemoptysis	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	1	(2)	2	(2)
	Hiccups	All AEs	0		1	(2)	1	(1)
	Oropharyngeal pain	All AEs	2	(5)	2	(5)	4	(5)
	Pleural effusion	Grade 3+4	3	(7)	0		3	(3)
		All AEs	4	(9)	2	(5)	6	(7)
	Pneumothorax	Grade 3+4	1	(2)	2	(5)	3	(3)
		All AEs	2	(5)	3	(7)	5	(6)
	Pulmonary embolism	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Pulmonary oedema	All AEs	1	(2)	0		1	(1)
	Respiratory distress	All AEs	4	(9)	1	(2)	5	(6)
	Throat irritation	All AEs	1	(2)	0		1	(1)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Gastrointestinal disorders		Grade 3+4	5	(12)	3	(7)	8	(9)
		All AEs	40	(93)	32	(73)	72	(83)
	Abdominal discomfort	All AEs	0		1	(2)	1	(1)
	Abdominal distension	All AEs	5	(12)	3	(7)	8	(9)
	Abdominal pain	Grade 3+4	1	(2)	0		1	(1)
		All AEs	6	(14)	6	(14)	12	(14)
	Abdominal pain lower	All AEs	4	(9)	1	(2)	5	(6)
	Abdominal pain upper	Grade 3+4	0		1	(2)	1	(1)
		All AEs	5	(12)	6	(14)	11	(13)
	Abdominal tenderness	All AEs	1	(2)	1	(2)	2	(2)
	Anal fistula	All AEs	1	(2)	0		1	(1)
	Aphthous stomatitis	All AEs	1	(2)	0		1	(1)
	Ascites	All AEs	0		1	(2)	1	(1)
	Colitis	All AEs	0		1	(2)	1	(1)
	Constipation	All AEs	12	(28)	3	(7)	15	(17)
	Diarrhoea	Grade 3+4	2	(5)	1	(2)	3	(3)
		All AEs	26	(60)	18	(41)	44	(51)
	Dry mouth	Grade 3+4	1	(2)	0		1	(1)
		All AEs	3	(7)	1	(2)	4	(5)
	Dyspepsia	All AEs	2	(5)	3	(7)	5	(6)
	Dysphagia	All AEs	1	(2)	0		1	(1)
	Enteritis	All AEs	1	(2)	0		1	(1)
	Epigastric discomfort	All AEs	0		1	(2)	1	(1)
	Flatulence	All AEs	1	(2)	1	(2)	2	(2)
	Gastric ulcer	All AEs	0		1	(2)	1	(1)
	Gastrointestinal haemorrhage	Grade 3+4	0		1	(2)	1	(1)
		All AEs	1	(2)	1	(2)	2	(2)
	Gastrointestinal motility disorder	All AEs	1	(2)	0		1	(1)
	Gastrooesophageal reflux disease	All AEs	1	(2)	1	(2)	2	(2)
	Glossitis	All AEs	1	(2)	0		1	(1)
	Glossodynia	All AEs	0		1	(2)	1	(1)
	Nausea	All AEs	22	(51)	18	(41)	40	(46)
	Oral discomfort	All AEs	1	(2)	0		1	(1)
	Oral pain	All AEs	1	(2)	0		1	(1)
	Proctitis	All AEs	1	(2)	0		1	(1)
	Retching	All AEs	1	(2)	1	(2)	2	(2)
	Stomatitis	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	1	(2)	2	(2)
	Subileus	All AEs	0		1	(2)	1	(1)
	Toothache	All AEs	1	(2)	0		1	(1)
	Vomiting	Grade 3+4	2	(5)	0		2	(2)
		All AEs	11	(26)	8	(18)	19	(22)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Hepatobiliary disorders		Grade 3+4	1	(2)	2	(5)	3	(3)
		All AEs	2	(5)	3	(7)	5	(6)
	Cholecystitis	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Hepatotoxicity	Grade 3+4	0		1	(2)	1	(1)
		All AEs	1	(2)	2	(5)	3	(3)
	Jaundice cholestatic	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
Skin and subcutaneous tissue disorders		Grade 3+4	0		1	(2)	1	(1)
		All AEs	17	(40)	17	(39)	34	(39)
	Alopecia	All AEs	2	(5)	1	(2)	3	(3)
	Cold sweat	All AEs	0		1	(2)	1	(1)
	Erythema	All AEs	3	(7)	2	(5)	5	(6)
	Hair colour changes	All AEs	4	(9)	3	(7)	7	(8)
	Hair growth abnormal	All AEs	0		1	(2)	1	(1)
	Hyperhidrosis	All AEs	1	(2)	2	(5)	3	(3)
	Nail disorder	All AEs	0		2	(5)	2	(2)
	Night sweats	All AEs	4	(9)	3	(7)	7	(8)
	Palmar-plantar erythrodysaesthesia syndrome	All AEs	2	(5)	2	(5)	4	(5)
	Petechiae	All AEs	2	(5)	1	(2)	3	(3)
	Pruritus	Grade 3+4	0		1	(2)	1	(1)
		All AEs	2	(5)	2	(5)	4	(5)
	Pruritus generalised	All AEs	1	(2)	0		1	(1)
	Rash	All AEs	4	(9)	2	(5)	6	(7)
	Scar pain	All AEs	0		1	(2)	1	(1)
	Skin atrophy	All AEs	1	(2)	0		1	(1)
	Skin hypopigmentation	All AEs	1	(2)	0		1	(1)
	Skin induration	All AEs	0		1	(2)	1	(1)
	Skin lesion	All AEs	0		1	(2)	1	(1)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Musculoskeletal and connective tissue disorders		Grade 3+4	2	(5)	1	(2)	3	(3)
		All AEs	18	(42)	20	(45)	38	(44)
	Arthralgia	All AEs	2	(5)	2	(5)	4	(5)
	Back pain	Grade 3+4	0		1	(2)	1	(1)
		All AEs	5	(12)	5	(11)	10	(11)
	Bone pain	All AEs	1	(2)	0		1	(1)
	Fistula	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Flank pain	All AEs	1	(2)	1	(2)	2	(2)
	Groin pain	All AEs	0		1	(2)	1	(1)
	Inguinal mass	All AEs	1	(2)	0		1	(1)
	Limb discomfort	All AEs	0		1	(2)	1	(1)
	Muscle spasms	All AEs	4	(9)	4	(9)	8	(9)
	Muscular weakness	Grade 3+4	1	(2)	0		1	(1)
		All AEs	2	(5)	0		2	(2)
	Musculoskeletal chest pain	All AEs	2	(5)	0		2	(2)
	Musculoskeletal pain	All AEs	2	(5)	4	(9)	6	(7)
	Myalgia	All AEs	0		3	(7)	3	(3)
	Pain in extremity	All AEs	2	(5)	7	(16)	9	(10)
Renal and urinary disorders		Grade 3+4	3	(7)	0		3	(3)
		All AEs	9	(21)	3	(7)	12	(14)
	Bladder perforation	All AEs	0		1	(2)	1	(1)
	Dysuria	All AEs	2	(5)	1	(2)	3	(3)
	Nocturia	All AEs	3	(7)	0		3	(3)
	Proteinuria	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	1	(2)	2	(2)
	Renal failure	Grade 3+4	2	(5)	0		2	(2)
		All AEs	3	(7)	0		3	(3)
	Renal failure acute	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Renal impairment	All AEs	1	(2)	0		1	(1)
	Urinary incontinence	All AEs	0		1	(2)	1	(1)
	Urinary tract obstruction	All AEs	1	(2)	0		1	(1)
Reproductive system and breast disorders		All AEs	4	(9)	0		4	(5)
	Breast inflammation	All AEs	1	(2)	0		1	(1)
	Breast pain	All AEs	1	(2)	0		1	(1)
	Vaginal discharge	All AEs	1	(2)	0		1	(1)
	Vaginal haemorrhage	All AEs	1	(2)	0		1	(1)
Congenital, familial and genetic disorders		All AEs	1	(2)	0		1	(1)
	Atrial septal defect	All AEs	1	(2)	0		1	(1)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
General disorders and administration site conditions		Grade 3+4	7	(16)	2	(5)	9	(10)
		Grade 5	0		3	(7)	3	(3)
		All AEs	31	(72)	28	(64)	59	(68)
	Application site haematoma	All AEs	0		1	(2)	1	(1)
	Asthenia	All AEs	1	(2)	1	(2)	2	(2)
	Catheter site pain	All AEs	1	(2)	0		1	(1)
	Chest pain	Grade 3+4	1	(2)	0		1	(1)
		All AEs	4	(9)	4	(9)	8	(9)
	Chills	All AEs	2	(5)	0		2	(2)
	Condition aggravated	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Disease progression	Grade 5	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Fatigue	Grade 3+4	3	(7)	0		3	(3)
		All AEs	14	(33)	17	(39)	31	(36)
	Feeling hot	All AEs	1	(2)	0		1	(1)
	General physical health deterioration	Grade 5	0		1	(2)	1	(1)
		All AEs	4	(9)	1	(2)	5	(6)
	Generalised oedema	All AEs	1	(2)	0		1	(1)
	Impaired healing	All AEs	1	(2)	0		1	(1)
	Local swelling	All AEs	1	(2)	2	(5)	3	(3)
	Localised oedema	All AEs	2	(5)	0		2	(2)
	Malaise	All AEs	1	(2)	0		1	(1)
	Medical device pain	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Mucosal inflammation	All AEs	3	(7)	3	(7)	6	(7)
	Multi-organ failure	Grade 5	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Oedema	Grade 3+4	1	(2)	0		1	(1)
		All AEs	2	(5)	3	(7)	5	(6)
	Oedema peripheral	All AEs	10	(23)	0		10	(11)
	Pain	Grade 3+4	0		1	(2)	1	(1)
		All AEs	4	(9)	4	(9)	8	(9)
	Pyrexia	All AEs	10	(23)	2	(5)	12	(14)
	Swelling	All AEs	1	(2)	0		1	(1)
	Thrombosis in device	All AEs	1	(2)	0		1	(1)
	Ulcer	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Investigations		Grade 3+4	11	(26)	7	(16)	18	(21)
		All AEs	27	(63)	21	(48)	48	(55)
	Alanine aminotransferase increased	Grade 3+4	3	(7)	2	(5)	5	(6)
		All AEs	10	(23)	5	(11)	15	(17)
	Aspartate aminotransferase increased	Grade 3+4	1	(2)	1	(2)	2	(2)
		All AEs	11	(26)	4	(9)	15	(17)
	Blood alkaline phosphatase increased	All AEs	7	(16)	2	(5)	9	(10)
	Blood bilirubin increased	Grade 3+4	1	(2)	0		1	(1)
		All AEs	4	(9)	1	(2)	5	(6)
	Blood creatinine increased	Grade 3+4	2	(5)	0		2	(2)
		All AEs	5	(12)	0		5	(6)
	Blood lactate dehydrogenase increased	All AEs	1	(2)	0		1	(1)
	Blood pressure increased	All AEs	0		1	(2)	1	(1)
	Blood pressure systolic increased	All AEs	1	(2)	0		1	(1)
	Blood thyroid stimulating hormone increased	All AEs	0		1	(2)	1	(1)
	Body temperature increased	All AEs	1	(2)	0		1	(1)
	C-reactive protein increased	All AEs	1	(2)	0		1	(1)
	Escherichia test positive	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Gamma-glutamyltransferase increased	Grade 3+4	3	(7)	2	(5)	5	(6)
		All AEs	10	(23)	4	(9)	14	(16)
	Glomerular filtration rate increased	Grade 3+4	1	(2)	0		1	(1)
		All AEs	1	(2)	0		1	(1)
	Hepatic enzyme increased	Grade 3+4	0		1	(2)	1	(1)
		All AEs	0		1	(2)	1	(1)
	Neutrophil count decreased	All AEs	1	(2)	0		1	(1)
	Platelet count decreased	Grade 3+4	3	(7)	0		3	(3)
		All AEs	3	(7)	0		3	(3)
	Protein urine present	All AEs	1	(2)	0		1	(1)
	Transaminases increased	Grade 3+4	1	(2)	1	(2)	2	(2)
		All AEs	1	(2)	1	(2)	2	(2)
	Weight decreased	Grade 3+4	0		1	(2)	1	(1)
		All AEs	12	(28)	11	(25)	23	(26)
	White blood cell count decreased	Grade 3+4	2	(5)	0		2	(2)
		All AEs	2	(5)	0		2	(2)

Adverse Events by SOC, PT and Grade			Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
			N	(%)	N	(%)	N	(%)
Injury, poisoning and procedural complications		Grade 3+4	2	(5)	1	(2)	3	(3)
		All AEs	7	(16)	4	(9)	11	(13)
	Excoriation	All AEs	1	(2)	0		1	(1)
	Fall	All AEs	1	(2)	0		1	(1)
	Humerus fracture	Grade 3+4	2	(5)	0		2	(2)
		All AEs	2	(5)	0		2	(2)
	Joint injury	All AEs	1	(2)	0		1	(1)
	Ligament sprain	All AEs	0		1	(2)	1	(1)
	Lumbar vertebral fracture	All AEs	0		1	(2)	1	(1)
	Periorbital haematoma	All AEs	1	(2)	0		1	(1)
	Post procedural swelling	All AEs	1	(2)	0		1	(1)
	Postoperative wound complication	Grade 3+4	0		1	(2)	1	(1)
		All AEs	1	(2)	1	(2)	2	(2)
	Tongue injury	All AEs	0		1	(2)	1	(1)
Surgical and medical procedures		All AEs	1	(2)	0		1	(1)
	Tooth extraction	All AEs	1	(2)	0		1	(1)

In arm A (Pazopanib+GEM), 511/482 of 908 AEs were related to pazopanib/gemcitabine; in arm B (Pazopanib) 272 of 452 AEs related to pazopanib.
The most frequent AEs – regarding the number of affected patients – related to pazopanib/gemcitabine were thrombocytopenia in 23/24 of 43 patients, diarrhea in 17/14 patients, nausea in 16/16 patients, leucopenia in 15/20 patients, anemia in 13/13 patients, fatigue in 12/11 patients, increased aspartate aminotransferase in 11/10 patients, increased alanine aminotransferase in 10/10 patients, increased gamma-glutamyltransferase in 9/9 patients and neutropenia in 8/11 of 43 patients in arm A (Pazopanib+GEM); related to pazopanib fatigue in 17 patients, nausea in 16 patients and diarrhea in 15 of 44 patients in arm B (Pazopanib).
The only grade 5 AE in arm A (Pazopanib+GEM), acute respiratory distress syndrome, was evaluated as related to pazopanib and not related to gemcitabine. None of the 3 grade 5 AEs in arm B (Pazopanib) were related to pazopanib.
In arm A (Pazopanib+GEM), AEs related to pazopanib/gemcitabine with grade 4 were thrombocytopenia in 9/9 of 43 patients, neutropenia and leucopenia in 3/4 patients each, anemia, increased blood creatinine, decreased platelet count, metabolic disorder and acute renal failure in 1/1 patient each, diverticulitis and hypertension in 1/0 patient each; with grade 3 thrombocytopenia in 13/12 patients, leucopenia in 8/11 patients, neutropenia in 5/7 patients, increased alanine aminotransferase in 3/3 patients, anemia, increased gamma-glutamyltransferase and decreased platelet count in 3/2 patients each, increased blood creatinine in 2/2 patients, decreased white blood cell count, diarrhea, fatigue and epistaxis in 2/1 patients each, hyperuricaemia in 1/2 patients, granulocytopenia, increased trans-aminases, febrile neutropenia, haemolytic uraemic syndrome, bradycardia, cardiomyopathy, stomatitis, vomiting, aspartate increased aminotransferase, increased glomerular filtration rate, pulmonary embolism and hypertension in 1/1 patient each, anemia of malignant disease, aggravated condition, decreased appetite, syncope, proteinuria, renal failure and thrombosis in 1/0 patient each, dyspnoea and thrombotic microangiopathy in 0/1 patient each.
In arm B (Pazopanib), grade 4 AEs related to pazopanib were hepatotoxicity and pneumo-thorax in 1 patient each; related grade 3 AEs were increased gamma-glutamyltransferase, increased alanine aminotransferase, pneumothorax and hypertension in 2 patients each,

leucopenia, diarrhea, urinary tract infection, increased aspartate aminotransferase, increased transaminases, increased hepatic enzyme, syncope and pruritus in 1 patient each.

Serious Adverse Events

The number of patients suffering serious adverse events (SAE) and the number of SAEs are displayed in table 22.
In arm A (Pazopanib+GEM), in total, 49 SAEs were reported in 26 of 43 patients; in arm B (Pazopanib), 26 SAEs in 22 of 44 patients. In both arms, the most frequent SAE was pneumothorax (6/4 SAEs in 2/3 patients in arm A/B).

Table 22: SAEs by SOC and PT, Safety n=87

N: Number of patients with SAE, N SAE: Number of SAEs

SAEs by SOC and PT		Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
		N	N SAE	N	N SAE	N	N SAE
Any SAE		26	49	22	26	48	75
Infections and infestations		5	6	2	2	7	8
	Abdominal abscess	.	.	1	1	1	1
	Diverticulitis	1	1	.	.	1	1
	Infection	2	3	.	.	2	3
	Pneumonia	2	2	.	.	2	2
	Urinary tract infection	.	.	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		.	.	2	3	2	3
	Metastatic pain	.	.	1	1	1	1
	Neoplasm progression	.	.	1	1	1	1
	Tumour pain	.	.	1	1	1	1
Blood and lymphatic system disorders		2	4	.	.	2	4
	Anaemia	1	1	.	.	1	1
	Febrile neutropenia	1	2	.	.	1	2
	Thrombocytopenia	1	1	.	.	1	1
Metabolism and nutrition disorders		1	1	.	.	1	1
	Metabolic disorder	1	1	.	.	1	1
Nervous system disorders		2	2	2	2	4	4
	Paraparesis	.	.	1	1	1	1
	Somnolence	1	1	.	.	1	1
	Syncope	1	1	1	1	2	2
Eye disorders		1	1	.	.	1	1
	Vitreous haemorrhage	1	1	.	.	1	1
Cardiac disorders		1	1	.	.	1	1
	Bradycardia	1	1	.	.	1	1
Vascular disorders		2	2	.	.	2	2
	Hypertension	1	1	.	.	1	1
	Thrombosis	1	1	.	.	1	1

SAEs by SOC and PT		Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
		N	N SAE	N	N SAE	N	N SAE
Respiratory, thoracic and mediastinal disorders		5	10	4	5	9	15
	Acute respiratory distress syndrome	1	1	.	.	1	1
	Cough	.	.	1	1	1	1
	Pleural effusion	2	2	.	.	2	2
	Pneumothorax	2	6	3	4	5	10
	Pulmonary embolism	1	1	.	.	1	1
Gastrointestinal disorders		4	6	2	2	6	8
	Abdominal pain	1	1	.	.	1	1
	Abdominal pain upper	.	.	1	1	1	1
	Anal fistula	1	1	.	.	1	1
	Diarrhoea	1	1	.	.	1	1
	Gastrointestinal haemorrhage	1	1	1	1	2	2
	Vomiting	2	2	.	.	2	2
Hepatobiliary disorders		2	2	2	2	4	4
	Cholecystitis	1	1	.	.	1	1
	Hepatotoxicity	1	1	1	1	2	2
	Jaundice cholestatic	.	.	1	1	1	1
Musculoskeletal and connective tissue disorders		2	2	2	2	4	4
	Back pain	.	.	2	2	2	2
	Fistula	1	1	.	.	1	1
	Muscular weakness	1	1	.	.	1	1
Renal and urinary disorders		2	2	1	1	3	3
	Bladder perforation	.	.	1	1	1	1
	Renal failure	1	1	.	.	1	1
	Renal failure acute	1	1	.	.	1	1
General disorders and administration site conditions		5	7	3	3	8	10
	Chest pain	1	1	.	.	1	1
	Disease progression	.	.	1	1	1	1
	Fatigue	2	2	.	.	2	2
	General physical health deterioration	1	1	1	1	2	2
	Impaired healing	1	1	.	.	1	1
	Multi-organ failure	.	.	1	1	1	1
	Pyrexia	2	2	.	.	2	2
Investigations		1	1	3	3	4	4
	Alanine aminotransferase increased	.	.	1	1	1	1
	Hepatic enzyme increased	.	.	1	1	1	1
	Transaminases increased	1	1	1	1	2	2
Injury, poisoning and procedural complications		2	2	1	1	3	3
	Humerus fracture	2	2	.	.	2	2
	Postoperative wound complication	.	.	1	1	1	1

In arm A (Pazopanib+GEM) with 24/13 pazopanib/gemcitabine related SAEs in 15/7 of 43 patients, 7 patients had more than one pazopanib and/or gemcitabine related SAE. These patients were one with pazopanib and gemcitabine related acute renal failure, metabolic disorder and bradycardia, another one with pazopanib and gemcitabine related anaemia, thrombocytopenia and pulmonary embolism, another one with pazopanib related impaired healing, renal failure and fatigue, another one with pazopanib and gemcitabine related diarrhea, gemcitabine related gastrointestinal haemorrhage and pazopanib related vomiting, another one with pazopanib and gemcitabine related febrile neutropenia and gemcitabine related febrile neutropenia, another one with pazopanib related pneumothorax and acute respiratory distress syndrome, and another one with pazopanib related hepatotoxicity and vitreous haemorrhage. The other related SAEs occurred in different patients and were pazopanib and gemcitabine related increased transaminases, pyrexia and vomiting, and pazopanib related thrombosis, hypertension, syncope, diverticulitis and general physical health deterioration.
In arm B (Pazopanib), the 9 pazopanib related SAEs in 8 of 44 patients were pneumothorax (4 SAEs in 3 patients), hepatotoxicity, increased alanine aminotransferase, increased transaminases, increased hepatic enzyme and syncope (in 1 but not the same patient each).

Deaths

8 patients, 3 in arm A (Pazopanib+GEM) and 5 in arm B (Pazopanib), had SAEs with fatal outcome, see table 23. The fatal SAEs were pazopanib related acute respiratory distress syndrome, pazopanib related general physical health deterioration and neither pazopanib nor gemcitabine related somnolence in arm A (Pazopanib+GEM); and the following not pazopanib related SAEs in arm B (Pazopanib): neoplasm progression, multi-organ failure, paraparesis, disease progression and general physical health deterioration.

Table 23: SAEs with fatal outcome by SOC and PT, Safety n=87

N: Number of patients with fatal SAE. N SAE: Number of fatal SAEs

SAEs with fatal outcome by SOC and PT		Arm A Pazopanib+ GEM n=43		Arm B Pazopanib n=44		Total n=87	
		N	N SAE	N	N SAE	N	N SAE
Any fatal SAE		3	3	5	5	8	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		.	.	1	1	1	1
	Neoplasm progression	.	.	1	1	1	1
Nervous system disorders		1	1	1	1	2	2
	Paraparesis	.	.	1	1	1	1
	Somnolence	1	1	.	.	1	1
Respiratory, thoracic and mediastinal disorders		1	1	.	.	1	1
	Acute respiratory distress syndrome	1	1	.	.	1	1
General disorders and administration site conditions		1	1	3	3	4	4
	Disease progression	.	.	1	1	1	1
	General physical health deterioration	1	1	1	1	2	2
	Multi-organ failure	.	.	1	1	1	1

During study treatment and follow-up, 34 of 43 patients in arm A (Pazopanib+GEM) and 37 of 44 patients in arm B (Pazopanib) died, most of them due to tumour/progressive disease (table 24).

Table 24: Death and its causes, Safety n=87

Death and cause of death		Arm A Pazopanib+GEM n=43	Arm B Pazopanib n=44	Total n=87
		N	N	N
Death	No	9	7	16
	Yes	34	37	71
	Total	43	44	87
Cause of death	Tumour/sign of prior PD	31	33	64
	Toxicity/AE	1	0	1
	other SAE	2	2	4
	other cause	1	0	1
	unknown cause	1	4	5

References

[1] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001

20.3 Conclusions

Summary

The PAPAGEMO-trial meets its primary endpoint of a significant improvement of the "PFSR" (progression free survival rate) at 12 weeks" from 55% to 74% (p=0.006) (adjusted for liposacoma; N evaluable 85). The PFS is also significantly improved from 2.0 to 5.6 months with an HR of 0.58 (p=0,02). The "Per Protocol"-analysis (N PP evaluable 59) does result in the same significant improvement.
The improvement of the PFS is mainly driven by the subgroups liposarcoma and, to a less extend, leiomyosarcoma. This is important since in the first trial on single agent pazopanib (EORTC 62043) these typor subtypes had low benefit and liposarcoma was therefore excided from the Palette Trial. The improvement within the subgroups is, although relatively strong, only borderline significant due to the small number of patients (p=O.72). In contrast to the PFS-improvement, the OS is not improved. This is very likely due to post-trial crossover to gemcitabine in the control arm; this will be a matter of further evaluation.
The response rate is improved from 5% to 11 %, however this difference did not reach statistical significance. The NC rate is 63% in the combination arm vs. 47%, with a total improvement of the rate of responders including stabilization from 51% to 75%.
The toxicity is very tolerable with a low rate of grade 4 adverse events, but with, as expected, somewhat more pronounced bone marrow toxicity in the combination arm. The SAE-rate was higher (60%) in the combination vs. 50% in the control arm, including 2 potentially related

lethal events in the combination arm vs. 0 in the control arm. This were rather unspecific events (general physical health deterioration; acute respiratory distress syndrome). 8 SUSARs occurred, 4 in each arm.
The Quality of life analysis is still ongoing.

Conclusions

The outcome of the control arm is very close to the reference trial "PALETTE", and to the previous phase 11 trial. The efficacy of the combination arm is significantly higher in terms of PFS and not significantly also in response rate. Both are comparable to the outcome in the trial investigating gemcitabine + DTIC, however both trials are difficult to compare. However, the improvement still did not translate into improved OS, although the final follow up (currently 83% still alive) has to be expected, as well as the data of further line treatments to evaluate the effect of salvage treatment with gemcitabine in the control arm. The improvement was strong in the liposarcoma and leiomyosarcoma group - different from single agent pazopanib in the first trial EORTC 62043, which was only weekly active in this histology and therefore excluded from the Palette-Trial. This new regimen seems to be an other potentially treatment option in anthracycline and / or ifosfamide refractory soft-tissue sarcoma, with particular efficacy in leio-and liposarcoma and low and acceptable toxicity.
A head to head comparison of Pazopano+Gemcitabine with Pazopanib +DTIC might be interesting, but even more the development into a tri pie combination, based on the non overlapping toxicity of pazopanib.

21 Appendix

21.1 CONSORT Flow Diagramm