Clinical trial results:
Gemcitabine in Combination with the Oral Irreversible ErbB Inhibitor Afatinib versus Gemcitabine Alone in Patients with Metastatic Pancreatic Cancer: an Explorative Randomized Phase II Trial

Summary

EudraCT number	2011-004063-77
Trial protocol	DE
Global end of trial date	02 February 2018

Results information

Result version number	v1 (current)
This version publication date	23 February 2019
First version publication date	23 February 2019

Trial information

Trial identification

Sponsor protocol code	ACCEPT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Klinikum der Universität München-Großhadern
Sponsor organisation address	Marchioninistr. 15, München, Germany, 81377
Public contact	Study Office, Klinikum der Universität München - Großhadern, +49 89440072208, Matthias.Wolff@med.uni-muenchen.de
Scientific contact	Study Office, Klinikum der Universität München - Großhadern, +49 89440072208, Matthias.Wolff@med.uni-muenchen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2018
Global end of trial reached?	Yes
Global end of trial date	02 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the combination of afatinib plus gemcitabine is superior to gemcitabine alone in the treatment of metastatic pancreatic cancer.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable European and national regulations (including European Directive 2001/20/EC and German Drug Law (AMG)) and with the ethical principles laid down in the Declaration of Helsinki. Participating subjects signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	23 April 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 119
Worldwide total number of subjects	119
EEA total number of subjects	119

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	91
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

34 investigational sites in Germany were participating. 119 subjects were screened and enrolled at 25 of these 34 investigational sites.
The first patient was enrolled on 23-Apr-2013, the last patient on 31-Jan-2017.

Pre-assignment

Screening details:

Patients with histologically (not cytologically) confirmed diagnosis of metastatic pancreatic adenocarcinoma (stage IV according to UICC 2009 classification: each T, each N, M1), who were treatment-naive for locally advanced and metastatic disease.
- ECOG 0-1.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The randomization ratio is set to 2:1 for the experimental arm (with gemcitabine plus afatinib).

Arms

Are arms mutually exclusive?	Yes
Arm title	Gemcitabine plus Afatinib

Arm description:

Intravenous administration of 1000 mg/m² BSA gemcitabine on D1, D8, D15 of each 28-day treatment cycle and oral administration of 40 mg afatinib daily.
Treatment was continued until disease progression, unacceptable toxicity or other reasons (e.g. patient's wish, investigator's decision).

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg afatinib flat dose, p.o. once daily.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion, Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration of 1000 mg/m² BSA, 30 min intravenous infusion on Day1, Day8, and D15. Repetition of the cycle every 4 weeks.

Arm title	Gemcitabine

Arm description:

Intravenous administration of 1000 mg/m² BSA gemcitabine on D1, D8, D15 of each 28-day treatment cycle.
Treatment was continued until disease progression, unacceptable toxicity or other reasons (e.g. patient's wish, investigator's decision).

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion, Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration of 1000 mg/m² BSA, 30 min infusion, on Day1, Day 8, Day 15.
Repetition of the cycles every four weeks.

Number of subjects in period 1[1]	Gemcitabine plus Afatinib	Gemcitabine
Started	77	38
Completed	0	0
Not completed	77	38
Physician decision	7	4
Adverse event, non-fatal	8	3
Death	13	4
Progression	33	20
Lack of compliance	-	1
Lost to follow-up	1	-
Patients' wish	11	4
Protocol deviation	4	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Four patients had not been treated, two patients in arm "Gemcitabine plus Afatinib" and two patients in arm "Gemcitabine".

Baseline characteristics

Reporting groups	
Reporting group title	Gemcitabine plus Afatinib
Reporting group description:	
Intravenous administration of 1000 mg/m² BSA gemcitabine on D1, D8, D15 of each 28-day treatment cycle and oral administration of 40 mg afatinib daily. Treatment was continued until disease progression, unacceptable toxicity or other reasons (e.g. patient's wish, investigator's decision).	

Reporting group title	Gemcitabine
Reporting group description:	
Intravenous administration of 1000 mg/m² BSA gemcitabine on D1, D8, D15 of each 28-day treatment cycle. Treatment was continued until disease progression, unacceptable toxicity or other reasons (e.g. patient's wish, investigator's decision).	

Reporting group values	Gemcitabine plus Afatinib	Gemcitabine	Total
Number of subjects	77	38	115
Age categorical Units: Subjects			
Adults (18-64 years)	17	6	23
From 65-84 years	57	32	89
85 years and over	3	0	3
Age continuous			
Note: Age at time of randomisation.			
Units: years median full range (min-max)	 73.0 37 to 89	 72.5 55 to 84	 -
Gender categorical Units: Subjects			
Female	33	17	50
Male	44	21	65
ECOG Performance status Units: Subjects			
ECOG 0	46	21	67
ECOG 1	31	17	48
Stratification factor - CA 19-9			
Note: Stratification factor at the time of randomisation. It is possible that in the CRF another value is documented during baseline.			
Units: Subjects			
≤ 1000 U/mL	41	18	59
> 1000 U/mL	36	20	56
Stratification factor - Bilirubin			
Note: Stratification factor at the time of randomisation. It is possible that in the CRF another value is documented during baseline.			
Units: Subjects			
Bilirubin normal (≤ 1 x ULN)	70	33	103
Bilirubin elevated (1.1 - <2xULN, <5xULN)	7	5	12
Combination of the stratification factors			

Note: Stratification factor at time of randomisation. It is possible that in the CRF another value is documented during baseline.			
Units: Subjects			
CA19-9 ≤ 1000 U/mL, Bilirubin ≤ 1 x ULN	39	17	56
CA19-9 ≤ 1000 U/mL, Bilirubin 1.1 - <2xULN,<5xULN	2	1	3
CA19-9 > 1000 U/mL, Bilirubin ≤ 1 x ULN	31	16	47
CA19-9 > 1000 U/mL, Bilirubin 1.1 - <2xULN,<5xULN	5	4	9

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients, who have been treated with at least one dose of the study medication (gemcitabine, afatinib).

Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Full Analysis Set is a subset of the safety analysis set, which included only patients, who had received at least one dose of study drug in this study and fulfilled the selection criteria of the study. Seven patients were excluded from the statistical analysis because they had not fulfilled the selection criteria and/or their baseline data were not available and it was impossible to verify proper inclusion according to selection criteria. These patients were determined in a blinded review in cooperation between the CRO and the sponsor representative.

Subject analysis set title	Per-Protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Patients of the Full Analysis Set, who passed at least two cycles of therapy according to the protocol and reached the first staging (unless their treatment had to be interrupted because of early progression or early death).
The Per-Protocol set is a subset of the safety analysis set and the full analysis set.

Reporting group values	Safety set	Full Analysis Set	Per-Protocol set
Number of subjects	115	108	92
Age categorical Units: Subjects			
Adults (18-64 years)	23	21	19
From 65-84 years	89	84	71
85 years and over	3	3	2
Age continuous			
Note: Age at time of randomisation.			
Units: years			
median	73.0	73.0	73.5
full range (min-max)	37 to 89	37 to 89	37 to 89
Gender categorical Units: Subjects			
Female	50	47	40
Male	65	61	52
ECOG Performance status Units: Subjects			
ECOG 0	67	64	53

ECOG 1	48	44	39
Stratification factor - CA 19-9			
Note: Stratification factor at the time of randomisation. It is possible that in the CRF another value is documented during baseline.			
Units: Subjects			
≤ 1000 U/mL	59	54	41
> 1000 U/mL	56	54	51
Stratification factor - Bilirubin			
Note: Stratification factor at the time of randomisation. It is possible that in the CRF another value is documented during baseline.			
Units: Subjects			
Bilirubin normal (≤ 1 x ULN)	103	97	81
Bilirubin elevated (1.1 - <2xULN, <5xULN)	12	11	11
Combination of the stratification factors			
Note: Stratification factor at time of randomisation. It is possible that in the CRF another value is documented during baseline.			
Units: Subjects			
CA19-9 ≤ 1000 U/mL, Bilirubin ≤ 1 x ULN	56	52	39
CA19-9 ≤ 1000 U/mL, Bilirubin 1.1 - <2xULN,<5xULN	3	2	2
CA19-9 > 1000 U/mL, Bilirubin ≤ 1 x ULN	47	45	42
CA19-9 > 1000 U/mL, Bilirubin 1.1 - <2xULN,<5xULN	9	9	9

End points

End points reporting groups

Reporting group title	Gemcitabine plus Afatinib

Reporting group description:

Intravenous administration of 1000 mg/m² BSA gemcitabine on D1, D8, D15 of each 28-day treatment cycle and oral administration of 40 mg afatinib daily.
Treatment was continued until disease progression, unacceptable toxicity or other reasons (e.g. patient's wish, investigator's decision).

Reporting group title	Gemcitabine

Reporting group description:

Intravenous administration of 1000 mg/m² BSA gemcitabine on D1, D8, D15 of each 28-day treatment cycle.
Treatment was continued until disease progression, unacceptable toxicity or other reasons (e.g. patient's wish, investigator's decision).

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients, who have been treated with at least one dose of the study medication (gemcitabine, afatinib).

Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Full Analysis Set is a subset of the safety analysis set, which included only patients, who had received at least one dose of study drug in this study and fulfilled the selection criteria of the study. Seven patients were excluded from the statistical analysis because they had not fulfilled the selection criteria and/or their baseline data were not available and it was impossible to verify proper inclusion according to selection criteria. These patients were determined in a blinded review in cooperation between the CRO and the sponsor representative.

Subject analysis set title	Per-Protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Patients of the Full Analysis Set, who passed at least two cycles of therapy according to the protocol and reached the first staging (unless their treatment had to be interrupted because of early progression or early death).
The Per-Protocol set is a subset of the safety analysis set and the full analysis set.

Primary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The overall survival (OS) was defined as the duration from the first administration of gemcitabine/afatinib to death. Patients without events were censored at the date of their last contact.

End point type	Primary

End point timeframe:

Survival status was recorded up to 12 months after the end of treatment.

End point values	Gemcitabine plus Afatinib	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	37		
Units: months				
median (confidence interval 80%)	7.3 (6.2 to 8.4)	7.4 (6.0 to 9.1)		

Statistical analyses

Statistical analysis title	null hypothesis test of the primary endpoint (FAS)
Comparison groups	Gemcitabine plus Afatinib v Gemcitabine
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8038 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.058
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.791
upper limit	1.414

Notes:

[1] - HR > 1 favors Gemcitabine/Afatinib.

[2] - OS was defined as the duration from first the administration of gemcitabine and or afatinib to death. Patients without events were censored at the date of their last contact.

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Survival status of each participating patient was recorded up to 12 months after the end of treatment. Additional statistical analyses: 2-sided log-rank test with 95% CI for HR, stratified by the baseline values of CA 19-9. Of note, HR > 1 favours "≤ 1000 U/mL.

Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within each treatment arm:
Within the experimental arm in the FAS (N=71):
median(≤1000 U/ml)=4.7,
median(>1000U/ml)= 3.0;
p= 0.0042, HR= 2.057 (CI: 1.240 to 3.413).

Within the control arm in the FAS (N=37):
median(≤1000 U/ml)= 5.3,
median (>1000U/ml)= 3.8;
p= 0.0836, HR= 1.825 (CI: 0.910 to 3.663).

Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within the FAS (N=108):
median(≤1000 U/ml)= 5.2,
median (>1000U/ml)= 3.4;
p= 0.0009, HR= 1.952 (CI: 1.301 to 2.929).

End point type	Secondary

End point timeframe:

PFS was defined as the duration from the date of first administration of Gemcitabine/Afatinib to first

progression (acc. to RECIST 1.1) or death, whichever occurred first. Patients without an event were censored at the last tumour staging by imaging.

End point values	Gemcitabine plus Afatinib	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	37		
Units: months				
median (confidence interval 95%)	3.9 (3.2 to 5.2)	3.9 (2.0 to 5.8)		

Statistical analyses

Statistical analysis title	Kaplan-Meier analysis of PFS
Comparison groups	Gemcitabine plus Afatinib v Gemcitabine
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.4282 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.558
upper limit	1.283

Notes:

[3] - exploratory only

[4] - log-rank test (2-sided, alpha=0.05)

Secondary: One-year overall survival rate

End point title	One-year overall survival rate

End point description:

One-year overall survival rate was calculated as the percentage of patients who were alive one year after the first administration of gemcitabine and or afatinib.

End point type	Secondary

End point timeframe:

The timeframe of the One-year overall survival rate was defined as the time from the first administration to one year after the first administration of afatinib and/or gemcitabine.

End point values	Gemcitabine plus Afatinib	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	37		
Units: Number of subjects analysed				
25.4% for the exp. arm	18	0		
21.6% for the contr. arm	0	8		

Statistical analyses

Statistical analysis title	One-year overall survival rate
Comparison groups	Gemcitabine plus Afatinib v Gemcitabine
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.8135
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	3.177

Notes:

[5] - exploratory analysis only

Secondary: CA 19-9 tumor marker response - OS

End point title	CA 19-9 tumor marker response - OS

End point description:

Stratification factor at the time of randomisation, an analysis of its prognostic influence on the overall survival.

Additional statistical analyses: 2-sided log-rank test with 95% CI for HR, stratified by the baseline values of CA 19-9. Of note, HR > 1 favours ≤ 1000 U/mL
Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within each treatment arm:
Within the experimental arm in the FAS (N=71):
median(≤1000 U/ml)=8.2,
median(>1000U/ml)= 5.6;
p= 0.0893, HR= 1.564 (CI: 0.929 to 2.632).

Within the control arm in the FAS (N=37):
median(≤1000 U/ml)= 8.4,
median (>1000U/ml)= 5.0;
p= 0.0531, HR= 2.033 (CI: 0.977 to 4.230).

Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within the FAS (N=108):
median(≤1000 U/ml)= 8.4,
median (>1000U/ml)= 5.6;
p= 0.0531, HR= 2.033 (CI: 0.977 to 4.230).

End point type	Secondary

End point timeframe:

OS was defined as the duration from first administration of the gemcitabine and/or afatinib to death. Patients without events were censored at the date of their last contact.

End point values	Gemcitabine plus Afatinib	Gemcitabine	Full Analysis Set	Per-Protocol set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	71	37	108	92
Units: months				
median (confidence interval 95%)				
≤ 1000 U/ml	8.2 (6.2 to 12.7)	8.4 (6.0 to 13.9)	8.4 (6.7 to 11.3)	9.9 (7.0 to 12.7)
> 1000 U/ml	5.6 (3.9 to 8.6)	5.0 (3.4 to 9.3)	5.6 (3.9 to 7.5)	6.2 (4.3 to 8.6)

Statistical analyses

No statistical analyses for this end point

Secondary: CA 19-9 tumor marker -PFS

End point title	CA 19-9 tumor marker -PFS

End point description:

Stratification factor at the time of randomisation, an analysis of its prognostic influence on the progression-free survival.

Additional statistical analyses: 2-sided log-rank test with 95% CI for HR, stratified by the baseline values of CA 19-9. Of note, HR > 1 favours ≤ 1000 U/mL
Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within each treatment arm:
Within the experimental arm in the FAS (N=71):
median(≤1000 U/ml)=4.7,
median(>1000U/ml)= 3.0;
p= 0.0042, HR= 2.057 (95% CI: 1.240 to 3.413).

Within the control arm in the FAS (N=37):
median(≤1000 U/ml)= 5.3,
median (>1000U/ml)= 3.8;
p= 0.0836, HR= 1.825 (95% CI: 0.910 to 3.663).

Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within the FAS (N=108):
median(≤1000 U/ml)= 5.2,
median (>1000U/ml)= 3.4;
p= 0.0009, HR= 1.952 (CI: 1.301 to 2.929).

End point type	Secondary

End point timeframe:

PFS was defined as the duration from the first administration of gemcitabine and or afatinib to first progression (acc. to RECIST 1.1) or death, whichever occurred first.

End point values	Gemcitabine plus Afatinib	Gemcitabine	Full Analysis Set	Per-Protocol set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	71	37	108	92
Units: months				
median (confidence interval 95%)				
≤ 1000 U/ml	4.7 (3.6 to 6.6)	5.3 (2.1 to 7.2)	5.2 (3.7 to 6.2)	5.4 (3.8 to 6.7)
> 1000 U/ml	3.0 (1.6 to 4.5)	3.8 (1.6 to 5.6)	3.4 (1.7 to 4.5)	3.4 (1.7 to 4.5)

Statistical analyses

No statistical analyses for this end point

Secondary: CA 19-9 tumor marker -1-year overall survival rate

End point title	CA 19-9 tumor marker -1-year overall survival rate

End point description:

Stratification factor at the time of randomisation, an analysis of its prognostic influence on one-year overall survival rate.

Additional statistical analyses: 2-sided fisher's exact test with 95% CI for OR, stratified by the baseline values of CA 19-9.
Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within each treatment arm:
Within the experimental arm in the FAS (N=71):
For ≤1000 U/ml=32.4% (N=12/37),
For >1000U/ml= 17.6% (N=6/34);
p= 0.1808, OR= 2.240 (CI: 0.732 to 6.856).

Within the control arm in the FAS (N=37):
For ≤1000 U/ml= 35.3% (N=6/17),
For >1000U/ml= 10.0% (N=2/20);
p= 0.1090, OR= 4.909 (CI: 0.838 to 28.745).

Comparison of the groups after stratification by CA 19-9 value ≤ 1000 U/ml and > 1000 U/ml within the FAS (N=108):
For ≤1000 U/ml= 33.3% (N=18/54),
For >1000U/ml= 14.8% (N=8/54);
p= 0.0416, OR= 2.875 (CI: 1.123 to 7.361).

End point type	Secondary

End point timeframe:

Stratification factor at the time of randomisation.

End point values	Gemcitabine plus Afatinib	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	37		
Units: Subjects				
32.4% for ≤1000 U/ml (exp. arm)	12	0		
17.6% for >1000U/ml (exp. arm)	6	0		
35.3% for ≤1000 U/ml (contr. arm)	0	6		
10.0% for >1000U/ml (contr. arm)	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the informed consent onwards through the observational phase and within 28 days after the last drug administration of the study medication.

Adverse event reporting additional description:

Information on all adverse events, with particular emphasis on potential dose-limiting toxicities. Missing data were imputed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Gemcitabine plus Afatinib

Reporting group description:

Intravenous administration of 1000 mg/m² gemcitabine on D1, D8, D15 of each 28-day treatment cycle and oral administration of 40 mg afatinib daily.
Treatment was continued until disease progression, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

Reporting group title	Gemcitabine

Reporting group description:

Treatment with 1000 mg/m² gemcitabine on D1, D8, D15 of each 28-day treatment cycle.
Treatment was continued until disease progression, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

Serious adverse events	Gemcitabine plus Afatinib	Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 77 (68.83%)	22 / 38 (57.89%)	
number of deaths (all causes)	15	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	6 / 77 (7.79%)	4 / 38 (10.53%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 6	0 / 4	
Metastases to peritoneum			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			

Thrombosis	Additional description: In the analysis listing, the term 'thromboembolic event' is used as a preprinted term. It comprises the PTs 'thrombosis' and 'pulmonary embolism'. Here, the events of pulmonary embolism are subtracted.		
subjects affected / exposed	1 / 77 (1.30%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 77 (1.30%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Stent placement			
subjects affected / exposed	0 / 77 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	7 / 77 (9.09%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 77 (6.49%)	4 / 38 (10.53%)	
occurrences causally related to treatment / all	2 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 77 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			

subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Death			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 77 (3.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema	Additional description: In the analysis listing, the term 'Oedema (lower leg)' is used as a preprinted term.		
subjects affected / exposed	3 / 77 (3.90%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 77 (5.19%)	3 / 38 (7.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism	Additional description: In the analysis listing, the term 'thromboembolic event' is used as a preprinted term. It comprises the PTs 'thrombosis' and 'pulmonary embolism'. Here, the events of thrombosis are subtracted.		
subjects affected / exposed	3 / 77 (3.90%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 77 (3.90%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease	Additional description: Substitute for the preprinted term: "ILD-like syndrome (pneumonitis, pulmonary infiltrates)".		
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Respiratory failure			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Bilirubin conjugated increased			
subjects affected / exposed	4 / 77 (5.19%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 77 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	2 / 77 (2.60%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	6 / 77 (7.79%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	6 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	0 / 77 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 77 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 77 (7.79%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	5 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 77 (3.90%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	4 / 77 (5.19%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 77 (2.60%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	1 / 77 (1.30%)	4 / 38 (10.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hypersensitivity vasculitis	Additional description: According to MedDRA 21.0 is "hypersensitivity vasculitis" the new PT for the outdated MedDRA 16.1 PT "Leukocytoclastic vasculitis".		
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury	Additional description: According to MedDRA 21.0 is "acute kidney injury" the new PT for the outdated MedDRA 16.1 PT "renal failure acute".		
subjects affected / exposed	1 / 77 (1.30%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			

subjects affected / exposed	19 / 77 (24.68%)	8 / 38 (21.05%)	
occurrences causally related to treatment / all	9 / 24	3 / 13	
deaths causally related to treatment / all	1 / 2	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Gemcitabine plus Afatinib	Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 77 (100.00%)	37 / 38 (97.37%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 77 (1.30%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 77 (5.19%)	1 / 38 (2.63%)	
occurrences (all)	6	3	

Thrombosis	Additional description: In the analysis listing, the term 'thromboembolic event' is used as a preprinted term. It comprises the PTs 'thrombosis' and 'pulmonary embolism'. Events of pulmonary embolism were substrated and occurred in less than 5% of the patients.		
subjects affected / exposed	7 / 77 (9.09%)	1 / 38 (2.63%)	
occurrences (all)	7	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 77 (3.90%)	1 / 38 (2.63%)	
occurrences (all)	3	1	
Chills			
subjects affected / exposed	4 / 77 (5.19%)	3 / 38 (7.89%)	
occurrences (all)	4	3	
Fatigue			
subjects affected / exposed	3 / 77 (3.90%)	2 / 38 (5.26%)	
occurrences (all)	3	2	
General physical health deterioration			
subjects affected / exposed	5 / 77 (6.49%)	0 / 38 (0.00%)	
occurrences (all)	6	0	
Oedema	Additional description: (lower leg)		
subjects affected / exposed	23 / 77 (29.87%)	12 / 38 (31.58%)	
occurrences (all)	28	13	
Pain			
subjects affected / exposed	36 / 77 (46.75%)	21 / 38 (55.26%)	
occurrences (all)	50	34	
Swelling	Additional description: In the analysis listing the preferred term is "local swelling".		
subjects affected / exposed	1 / 77 (1.30%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	13 / 77 (16.88%)	11 / 38 (28.95%)	
occurrences (all)	20	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 77 (6.49%)	1 / 38 (2.63%)	
occurrences (all)	5	3	
Dyspnoea			

subjects affected / exposed	7 / 77 (9.09%)	1 / 38 (2.63%)	
occurrences (all)	7	1	
Dyspnoea exertional			
subjects affected / exposed	4 / 77 (5.19%)	1 / 38 (2.63%)	
occurrences (all)	7	1	
Epistaxis			
subjects affected / exposed	7 / 77 (9.09%)	0 / 38 (0.00%)	
occurrences (all)	31	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	4 / 77 (5.19%)	2 / 38 (5.26%)	
occurrences (all)	4	2	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	23 / 77 (29.87%)	9 / 38 (23.68%)	
occurrences (all)	26	9	
Lymphocyte count decreased			
subjects affected / exposed	6 / 77 (7.79%)	2 / 38 (5.26%)	
occurrences (all)	7	3	
Blood alkaline phosphatase decreased			
subjects affected / exposed	5 / 77 (6.49%)	2 / 38 (5.26%)	
occurrences (all)	5	2	
Bilirubin conjugated increased			
subjects affected / exposed	8 / 77 (10.39%)	5 / 38 (13.16%)	
occurrences (all)	9	6	
C-reactive protein increased			
subjects affected / exposed	3 / 77 (3.90%)	1 / 38 (2.63%)	
occurrences (all)	3	1	
Alanine aminotransferase increased	Additional description: In the analysis listing, the term 'Liver value ALT' is used as a preprinted term.		
subjects affected / exposed	34 / 77 (44.16%)	20 / 38 (52.63%)	
occurrences (all)	58	28	
Aspartate aminotransferase increased	Additional description: In the analysis listing, the term 'Liver value increased AST' is used as a preprinted term.		
subjects affected / exposed	31 / 77 (40.26%)	16 / 38 (42.11%)	
occurrences (all)	47	36	
Weight decreased			

subjects affected / exposed	26 / 77 (33.77%)	6 / 38 (15.79%)	
occurrences (all)	27	6	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 77 (2.60%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 77 (7.79%)	2 / 38 (5.26%)	
occurrences (all)	6	2	
Dysgeusia			
subjects affected / exposed	6 / 77 (7.79%)	1 / 38 (2.63%)	
occurrences (all)	6	1	
Somnolence			
subjects affected / exposed	40 / 77 (51.95%)	22 / 38 (57.89%)	
occurrences (all)	49	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	57 / 77 (74.03%)	23 / 38 (60.53%)	
occurrences (all)	66	24	
Leukopenia			
subjects affected / exposed	12 / 77 (15.58%)	11 / 38 (28.95%)	
occurrences (all)	17	20	
Lymphopenia			
subjects affected / exposed	1 / 77 (1.30%)	2 / 38 (5.26%)	
occurrences (all)	3	2	
Neutropenia			
subjects affected / exposed	26 / 77 (33.77%)	20 / 38 (52.63%)	
occurrences (all)	65	46	
Thrombocytopenia			
subjects affected / exposed	42 / 77 (54.55%)	19 / 38 (50.00%)	
occurrences (all)	84	43	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	5 / 77 (6.49%)	1 / 38 (2.63%)	
occurrences (all)	6	1	
Dry eye			

subjects affected / exposed	4 / 77 (5.19%)	1 / 38 (2.63%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Cheilitis			
subjects affected / exposed	5 / 77 (6.49%)	0 / 38 (0.00%)	
occurrences (all)	5	0	
Constipation			
subjects affected / exposed	14 / 77 (18.18%)	12 / 38 (31.58%)	
occurrences (all)	14	13	
Diarrhoea			
subjects affected / exposed	55 / 77 (71.43%)	5 / 38 (13.16%)	
occurrences (all)	79	8	
Dry mouth			
subjects affected / exposed	9 / 77 (11.69%)	2 / 38 (5.26%)	
occurrences (all)	9	2	
Flatulence			
subjects affected / exposed	4 / 77 (5.19%)	0 / 38 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	38 / 77 (49.35%)	17 / 38 (44.74%)	
occurrences (all)	58	23	
Stomatitis	Additional description: Also PT Stomatitis of the SOC General disorders and administration site conditions		
subjects affected / exposed	30 / 77 (38.96%)	3 / 38 (7.89%)	
occurrences (all)	38	4	
Vomiting			
subjects affected / exposed	23 / 77 (29.87%)	9 / 38 (23.68%)	
occurrences (all)	30	9	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 77 (9.09%)	1 / 38 (2.63%)	
occurrences (all)	8	3	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	4 / 77 (5.19%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Dry skin			

subjects affected / exposed	18 / 77 (23.38%)	4 / 38 (10.53%)	
occurrences (all)	23	5	
Pruritus			
subjects affected / exposed	11 / 77 (14.29%)	1 / 38 (2.63%)	
occurrences (all)	12	1	
Dermatitis acneiform	Additional description: In the analysis listing the PT is "Acneiform exanthema (rash).		
subjects affected / exposed	50 / 77 (64.94%)	2 / 38 (5.26%)	
occurrences (all)	68	2	
Nail disorder	Additional description: In the analysis listings the PT is "Other nail changes (e.g. grooved nails, panaritium)".		
subjects affected / exposed	14 / 77 (18.18%)	0 / 38 (0.00%)	
occurrences (all)	15	0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 77 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Infections and infestations			
Paronychia			
subjects affected / exposed	9 / 77 (11.69%)	0 / 38 (0.00%)	
occurrences (all)	11	0	
Infection			
subjects affected / exposed	35 / 77 (45.45%)	16 / 38 (42.11%)	
occurrences (all)	35	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 77 (31.17%)	7 / 38 (18.42%)	
occurrences (all)	26	7	
Dehydration			
subjects affected / exposed	2 / 77 (2.60%)	1 / 38 (2.63%)	
occurrences (all)	2	2	
Hyperkalaemia			
subjects affected / exposed	10 / 77 (12.99%)	1 / 38 (2.63%)	
occurrences (all)	11	2	
Hyponatraemia			
subjects affected / exposed	4 / 77 (5.19%)	4 / 38 (10.53%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2013	Adaption of the section "listed adverse events for afatinib" according to the Investigator´s Brochure (IB) V. 14 of afatinib Implementation of recommendations on wound healing disorders during afatinib treatment and application of afatinib via a gastric tube Changes regarding laboratory test required before starting treatment. Laboratory tests do not need to be repeated on Cycle 1 day 1 if performed within 72 hours before treatment start
14 September 2015	Due to several updates of the IB for afatinib, V.16.0, the section listing "adverse events" were removed from the protocol. Instead, a referral to the most recent IB which was available at all centres The section listing "adverse events" for gemcitabine was removed from the trial protocol. Instead, it is referred to the most recent version of the German "Fachinformation" (Summary of Product Characteristics – SPC) which was available at all centres Adaptions concerning number of study centres, study period, publications, requirements for starting a new cycle with gemcitabine

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The endpoint "duration of response" could not be analysed statistically, because the number of patients achieving CR and/or PR was too low for the calculation of the median and related confidence interval (due to the indication mPDAC).

Notes: