Clinical trial results:
Phase-II study evaluating midostaurin in induction, consolidation and maintenance therapy also after allogeneic blood stem cell transplantation
in patients with newly diagnosed acute myeloid leukemia exhibiting a FLT3 internal tandem duplication AMLSG 16-10

Summary

EudraCT number	2011-003168-63
Trial protocol	DE AT
Global end of trial date	26 February 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2021
First version publication date	12 March 2021

Trial information

Trial identification

Sponsor protocol code	AMLSG16-10/CPKC412ADE02T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01477606
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
Public contact	Hartmut Doehner, University Hospital Ulm, +49 73150045501, daniela.weber@uniklinik-ulm.de
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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	01 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2020
Global end of trial reached?	Yes
Global end of trial date	26 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective
To evaluate the impact of midostaurin given in combination with intensive induction, consolidation including allogeneic hematopoietic
stem cell transplantation and single agent maintenance therapy on event-free survival (EFS) in adult patients with AML exhibiting a FLT3- ITD.

Key-Secondary Efficacy Objective
- To evaluate the impact of midostaurin given in combination with intensive induction, consolidation including allogeneic hematopoietic stem cell transplantation and single agent maintenance therapy on OS in adult patients with AML exhibiting a FLT3-ITD.

To perform two predefined subgroup analyses in the age-groups 18-60 years and 61-70 years evaluating the impact of midostaurin given in combination with intensive induction, consolidation including allogeneic hematopoietic stem cell transplantation and single agent maintenance therapy on EFS and OS and in adult patients with AML exhibiting a FLT3-ITD.

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 39
Country: Number of subjects enrolled	Germany: 401
Worldwide total number of subjects	440
EEA total number of subjects	440

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)	373
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow was performed at baseline within 48 hours to make an enrollment possible.

Period 1

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

Arms

Arm title	AMLSG 16-10 study population

Arm description:

AMLSG 16-10 study population

Arm type	Experimental
Investigational medicinal product name	Midostaurin
Investigational medicinal product code	PKC412
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Midostaurin was administered orally in a dose of 50mg twice daily starting on day 8 during the induction chemotherapy cycles and on day 6 during the consolidation chemotherapy cycles, thereafter with continuous dosing until 48h before start of subsequent chemotherapy cycle. After allogeneic HSCT or after high-dose Cytarabine consolidation therapy, a maintenance therapy with Midostaurin was administered orally in a dose of 50mg twice daily for 365 days.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During induction chemotherapy, Cytarabine was administered by continuous intravenous infusion in a dose of 200 mg/m2 from day 1 up to day 7 for up to two cycles. During consolidation therapy four cycles high-dose Cytarabine was intended. Cytarabine was administered by intravenous infusion in a dose of 3 g/m2 twice a day on days 1, 3 and 5. For patients > 65 years of age, dose of Cytarabine was restrained to 1 g/m2.

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daunorubicin was administered by 1-hour intravenous infusion in a dose of 60 mg/m2 on days 1 up to day 3 during induction chemotherapy for up to two cycles.

Number of subjects in period 1	AMLSG 16-10 study population
Started	440
Completed	65
Not completed	375
Adverse event, serious fatal	41
Consent withdrawn by subject	8
Adverse event, non-fatal	113
Patient`s decision	62
Other reason	47
Lack of efficacy	104

Baseline characteristics

Reporting groups	
Reporting group title	AMLSG 16-10 study population
Reporting group description: AMLSG 16-10 study population	

Reporting group values	AMLSG 16-10 study population	Total	
Number of subjects	440	440	
Age categorical Units: Subjects			
<=60 years	312	312	
>60 years	128	128	
Age continuous Units: years			
median	54.1		
full range (min-max)	18.0 to 70.6	-	
Gender categorical Units: Subjects			
Female	249	249	
Male	191	191	
NPM1 mutation Units: Subjects			
mutated	266	266	
wildtype	174	174	
missing	0	0	
FLT3-ITD genescan ratio Units: Subjects			
<0.5	196	196	
>=0,5	242	242	
missing	2	2	
FLT3 TKD Units: Subjects			
positive	16	16	
negative	424	424	
missing	0	0	
Type of AML Units: Subjects			
de Novo	390	390	
sAML	31	31	
tAML	19	19	
missing	0	0	
ELN 2010 risk classification Units: Subjects			
intermediate-1	285	285	
intermediate-2	101	101	
high	26	26	
missing	28	28	

ECOG Units: Subjects			
ECOG 0	169	169	
ECOG 1	218	218	
ECOG 2	53	53	
HCTCI Score Units: Subjects			
Score 0	238	238	
Score 1	102	102	
Score 2	42	42	
Score 3	31	31	
Score >=4	25	25	
missing	2	2	
White blood cell count Units: G/l			
median	41.8		
full range (min-max)	0.3 to 420	-	
Blasts in bone marrow Units: percent			
median	80		
full range (min-max)	0 to 100	-	
Height Units: cm			
median	172		
full range (min-max)	153 to 197	-	
Weight Units: kilogram			
median	79.0		
full range (min-max)	44.0 to 163.0	-	
Lactate dehydrogenase Units: G/l			
median	573		
full range (min-max)	65 to 5930	-	
Platelets Units: G/L			
median	59		
full range (min-max)	5 to 681	-	
Hemoglobin Units: mg/dl			
median	9.0		
full range (min-max)	4.1 to 18.1	-	
Blasts in peripheral blood Units: percent			
median	52.5		
full range (min-max)	0 to 100	-	

Subject analysis sets

Subject analysis set title	Historical control
Subject analysis set type	Per protocol

Subject analysis set description:

- Historical control population served as a control group comprised of all AML cases with FLT3-ITD (excluding patients older than 70 years, or exhibiting translocation t(15;17)), or low cytogenetic risk profile according to ELN2010) from 5 previous AMLSG trials
  - AMLHD93 (R F Schlenk et al. 2003),
  - AMLHD98A (Richard F Schlenk et al. 2010),
  - HD98B (Richard F Schlenk et al. 2009),
  - AMLSG 06-04 (Tassara et al. 2014),
  - AMLSG 07-04 (Richard F Schlenk et al. 2016).

The above-mentioned trials were actively recruiting between 1993 and 2008 at the same centers also involved in the AMLSG 16-10 trial. Treatment in all patients consisted of induction therapy with idarubicin, cytarabine, etoposide, and up to 3 cycles of high- dose cytarabine-based consolidation therapy. Allogeneic HSCT in first CR was performed on investigators discretion.
The historical population included 415 intensively treated patients exhibiting a FLT3-ITD.

Reporting group values	Historical control		
Number of subjects	415		
Age categorical Units: Subjects			
<=60 years	352		
>60 years	63		
Age continuous Units: years			
median	50.5		
full range (min-max)	18.3 to 71.0		
Gender categorical Units: Subjects			
Female	222		
Male	193		
NPM1 mutation Units: Subjects			
mutated	229		
wildtype	178		
missing	8		
FLT3-ITD genescan ratio Units: Subjects			
<0.5	129		
>=0,5	165		
missing	121		
FLT3 TKD Units: Subjects			
positive	16		
negative	377		
missing	22		
Type of AML Units: Subjects			
de Novo	396		
sAML	6		
tAML	12		
missing	1		
ELN 2010 risk classification Units: Subjects			
intermediate-1	321		
intermediate-2	72		

high	22		
missing	0		
ECOG Units: Subjects			
ECOG 0	92		
ECOG 1	255		
ECOG 2	68		
HCTCI Score Units: Subjects			
Score 0	0		
Score 1	0		
Score 2	0		
Score 3	0		
Score >=4	0		
missing	0		
White blood cell count Units: G/l			
median	44.8		
full range (min-max)	0.2 to 440		
Blasts in bone marrow Units: percent			
median	85		
full range (min-max)	2 to 100		
Height Units: cm			
median	170		
full range (min-max)	149 to 199		
Weight Units: kilogram			
median	75.0		
full range (min-max)	42.0 to 189.0		
Lactate dehydrogenase Units: G/l			
median	599		
full range (min-max)	121 to 6910		
Platelets Units: G/L			
median	58		
full range (min-max)	6 to 734		
Hemoglobin Units: mg/dl			
median	9.0		
full range (min-max)	3.1 to 14.6		
Blasts in peripheral blood Units: percent			
median	60		
full range (min-max)	0 to 100		

End points

End points reporting groups

Reporting group title	AMLSG 16-10 study population
Reporting group description: AMLSG 16-10 study population	
Subject analysis set title	Historical control
Subject analysis set type	Per protocol

Subject analysis set description:

- Historical control population served as a control group comprised of all AML cases with FLT3-ITD (excluding patients older than 70 years, or exhibiting translocation t(15;17)), or low cytogenetic risk profile according to ELN2010) from 5 previous AMLSG trials
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  - AMLHD98A (Richard F Schlenk et al. 2010),
  - HD98B (Richard F Schlenk et al. 2009),
  - AMLSG 06-04 (Tassara et al. 2014),
  - AMLSG 07-04 (Richard F Schlenk et al. 2016).

The above-mentioned trials were actively recruiting between 1993 and 2008 at the same centers also involved in the AMLSG 16-10 trial. Treatment in all patients consisted of induction therapy with idarubicin, cytarabine, etoposide, and up to 3 cycles of high- dose cytarabine-based consolidation therapy. Allogeneic HSCT in first CR was performed on investigators discretion.
The historical population included 415 intensively treated patients exhibiting a FLT3-ITD.

Primary: Event-free Survival

End point title	Event-free Survival

End point description:

The primary endpoint of the AMLSG 16-10 trial was event-free survival (EFS), defined as the time from enrolment to induction failure (failure of achieving CR or CR with incomplete recovery (CRi)), death or relapse, whichever occurs first, based on response assessed by the investigator.

End point type	Primary

End point timeframe:

after 24 months

End point values	AMLSG 16-10 study population	Historical control		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	440	415		
Units: Rate				
number (confidence interval 95%)	0.41 (0.36 to 0.46)	0.21 (0.17 to 0.25)		

Attachments (see zip file)	Event-free survival acc. to population and ag/KM_EFS_popage. Event-free survival according to population/KM_EFS_pop.pdf

Statistical analyses

Statistical analysis title	Cox Regression on EFS
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.65
Variability estimate	Standard deviation
Dispersion value	0.08

Statistical analysis title	Cox Regression on EFS - patients <=60 years of age
Statistical analysis description:	
Subgroup analysis of patients <= 60 years of age (n=312 patients from the AMLSG 16-10 population and n=352 patients from the historical population)	
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.71
Variability estimate	Standard deviation
Dispersion value	0.1

Statistical analysis title	Cox Regression on EFS - patients >60 years of age
Statistical analysis description:	
Subgroup analysis of patients > 60 years of age (n=128 patients from the AMLSG 16-10 population and n=63 patients from the historical population)	
Comparison groups	AMLSG 16-10 study population v Historical control

Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.6
Variability estimate	Standard deviation
Dispersion value	0.17

Secondary: Overall Survival

End point title	Overall Survival

End point description:

The key secondary endpoint of the AMLSG 16-10 trial was overall survival (OS), defined as the time from enrolment to death from any cause in months.

End point type	Secondary

End point timeframe:

after 24 months

End point values	AMLSG 16-10 study population	Historical control		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	440	415		
Units: Rate				
number (confidence interval 95%)	0.55 (0.50 to 0.60)	0.38 (0.33 to 0.43)		

Attachments (see zip file)	Overall survival according to population/KM_OS_pop.pdf Overall survival according to population and age

Statistical analyses

Statistical analysis title	Cox Regression on OS
Comparison groups	AMLSG 16-10 study population v Historical control

Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.68
Variability estimate	Standard deviation
Dispersion value	0.09

Statistical analysis title	Cox Regression on OS in patients <= 60 yrs of age
Statistical analysis description:	
Subgroup analysis of patients <= 60 years of age (n=312 patients from the AMLSG 16-10 population and n=352 patients from the historical population)	
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.72
Variability estimate	Standard deviation
Dispersion value	0.11

Statistical analysis title	Cox Regression on OS in patients >60 yrs of age
Statistical analysis description:	
Subgroup analysis of patients > 60 years of age (n=128 patients from the AMLSG 16-10 population and n=63 patients from the historical population)	
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.68
Variability estimate	Standard deviation
Dispersion value	0.18

Secondary: Rate of complete remission / complete remission with incomplete hematological recovery

End point title	Rate of complete remission / complete remission with incomplete hematological recovery

End point description:

A patient was said to have achieved CR/CRi in two cases:
(a) when a patient's response after one cycle of induction was CR or CRi
(b) when a patient's response after one cycle of induction was partial remission then he/she might have received a second cycle and thereby achieved CR/CRi during the second cycle.

End point type	Secondary

End point timeframe:

after one or two induction cycles (within maximal 2 months)

End point values	AMLSG 16-10 study population	Historical control		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	440	415		
Units: Patients with CR/CRi	328	268		

Statistical analyses

Statistical analysis title	Logistic regression on CR/CRi rate
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	2.33

Variability estimate	Standard deviation
Dispersion value	0.16

Secondary: Relapse-free Survival

End point title	Relapse-free Survival

End point description:

Relapse-free survival (RFS) was defined as the time from first CR/CRi until relapse or death, whichever came first. RFS was defined only for patients achieving CR/CRi as a response to induction therapy.

End point type	Secondary

End point timeframe:

after 24 months

End point values	AMLSG 16-10 study population	Historical control		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	328	268		
Units: Rate				
number (confidence interval 95%)	0.52 (0.47 to 0.58)	0.32 (0.26 to 0.38)		

Attachments (see zip file)	Relapse-free survival according to population/KM_RFS_pop.pdf

Statistical analyses

Statistical analysis title	Cox Regression on RFS
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.62
Variability estimate	Standard deviation
Dispersion value	0.11

Secondary: Cumulative incidence of relapse

End point title	Cumulative incidence of relapse

End point description:

CIR was measured from the date of first CR/CRi until the date of relapse; patients not known to have relapsed were censored on the date they were last examined. Patients who died without relapse were counted as a competing cause of failure.

End point type	Secondary

End point timeframe:

after 24 months

End point values	AMLSG 16-10 study population	Historical control		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	328	268		
Units: Rate				
number (confidence interval 95%)	0.28 (0.23 to 0.33)	0.57 (0.51 to 0.63)		

Attachments (see zip file)	CIR according to population/CI_CIR_pop.pdf

Statistical analyses

Statistical analysis title	Cause-specific Cox regression on CIR
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.48
Variability estimate	Standard deviation
Dispersion value	0.13

Secondary: Cumulative incidence of death

End point title	Cumulative incidence of death

End point description:

CID was measured from the date of first CR/CRi until the date of death. Patients not known to have died were censored on the date they were last examined; patients who relapsed were counted as a

competing cause of failure.

End point type	Secondary

End point timeframe:
after 24 months

End point values	AMLSG 16-10 study population	Historical control		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	328	268		
Units: Rate				
number (confidence interval 95%)	0.20 (0.16 to 0.25)	0.12 (0.08 to 0.15)		

Attachments (see zip file)	CID according to population/CI_CID_pop.pdf

Statistical analyses

Statistical analysis title	Cause-specific Cox regression on CID
Comparison groups	AMLSG 16-10 study population v Historical control
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.643
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.68
Variability estimate	Standard deviation
Dispersion value	0.21

Secondary: Effect of allogeneic HSCT on EFS

End point title	Effect of allogeneic HSCT on EFS

End point description:

The analyses investigate the potential effect of an allogeneic HSCT in first CR/CRi on the event-free survival of the patients. Since the decision process for or against conducting alloHSCT in the historical cohort was inconsistent, this analysis is restricted to patients of the 16-10 trial. In a first step, EFS was compared between patients having been transplanted versus patients without transplantation, irrespective of the type of donor. In a second step, transplanted patients were differentiated between those receiving stem cells from a matched related donor and those being transplanted with stem cells from an unrelated donor.
Both multivariate models revealed alloHSCT as favorable prognostic factor for EFS 0.49 (P<.001). The

favorable impact of HSCT was higher in patients with a family donor (HR 0.39, P<.001) compared to patients with donor stem cells from an unrelated donor (HR 0.51, P<.001).

End point type	Secondary

End point timeframe:

within the first 6 months of treatment

End point values	AMLSG 16-10 study population			
Subject group type	Reporting group			
Number of subjects analysed	440			
Units: Hazard ratio				
number (confidence interval 95%)	0.49 (0.34 to 0.70)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Quality of life - Global health status

End point title	Quality of life - Global health status

End point description:

Quality of Life data was collected using the EORTC Quality of Life Core Questionnaire (QLQ-C30) at 5 timepoints throughout the AMLSG 16-10 study: before treatment starts, in first CR, after one year, 3 and 5 years after initial diagnosis. The scores of the questionnaire were computed according to the EORTC scoring manual transforming the raw scores into standardized scores ranging from 0 to 100. A higher score represents a higher ("better") level of functioning or a higher ("worse") level of symptoms. At diagnosis, median global health status was 41.7 (IQR: 16.7-62.5), at timepoint of first CR 50.0 (IQR: 41.7-66.7), after one year 58.3 (IQR: 50.0-70.8), after 3 years 66.7 (IQR:50.0-83.3) and after 5 years 50.0 (IQR:54.2-83.3).

End point type	Other pre-specified

End point timeframe:

at baseline, in first CR, after one year, 3 years and 5 years after initial diagnosis

End point values	AMLSG 16-10 study population			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: Standardised Quality score				
median (inter-quartile range (Q1-Q3))	41.7 (16.7 to 62.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period began upon signing of informed consent and ended 28 days after the last treatment administration or until all drug-related toxicities were resolved, or until the Investigators assessed AEs as chronic or stable.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Overall treatment period

Reporting group description: -

Serious adverse events	Overall treatment period		
Total subjects affected by serious adverse events			
subjects affected / exposed	284 / 440 (64.55%)		
number of deaths (all causes)	218		
number of deaths resulting from adverse events	49		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epstein-Barr virus associated lymphoma			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung cancer metastatic			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pancreatic carcinoma			

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Post transplant lymphoproliferative disorder				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Vascular disorders				
Capillary leak syndrome				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Circulatory collapse				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypertension				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				

subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venoocclusive disease			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Venous thrombosis			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	6 / 7		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Localised oedema			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Chest pain				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 35			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	2 / 3			
Fatigue				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Mucosal inflammation				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	1 / 4			
Oedema				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	19 / 440 (4.32%)			
occurrences causally related to treatment / all	7 / 20			
deaths causally related to treatment / all	2 / 2			
Systemic inflammatory response syndrome				

subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	9 / 440 (2.05%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 1		
Graft versus host disease in liver			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Graft versus host disease in skin			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypersensitivity			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Diaphragmatic paralysis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	10 / 440 (2.27%)			
occurrences causally related to treatment / all	5 / 12			
deaths causally related to treatment / all	3 / 5			
Lung disorder				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung infiltration				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	1 / 1			
Oropharyngeal pain				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Pulmonary edema				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory failure				
subjects affected / exposed	10 / 440 (2.27%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	2 / 3			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	13 / 440 (2.95%)			
occurrences causally related to treatment / all	13 / 15			
deaths causally related to treatment / all	1 / 1			
Aspartate aminotransferase increased				
subjects affected / exposed	8 / 440 (1.82%)			
occurrences causally related to treatment / all	9 / 10			
deaths causally related to treatment / all	1 / 1			
Blood alkaline phosphatase increased				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	7 / 8			
deaths causally related to treatment / all	0 / 0			

Blood bilirubin increased				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	2 / 2			
Blood creatinine increased				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 1			
C-reactive protein increased				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	16 / 440 (3.64%)			
occurrences causally related to treatment / all	23 / 26			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	15 / 440 (3.41%)			
occurrences causally related to treatment / all	16 / 19			
deaths causally related to treatment / all	1 / 1			
Haemoglobin decreased				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Prothrombin time prolonged				

subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Transaminases increased			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product administration error			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Venous injury			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Arrhythmia			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Arrhythmia supraventricular			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorder			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Extrasystoles			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocarditis			

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary valve disease				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Right ventricular dysfunction				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tachyarrhythmia				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				

subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal ganglia infarction			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral haemorrhage			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	2 / 4		
Cerebral infarction			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Demyelinating polyneuropathy			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis			

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial nerve disorder				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Leukoencephalopathy				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological symptom				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensorimotor neuropathy				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	15 / 440 (3.41%)			
occurrences causally related to treatment / all	19 / 24			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	25 / 440 (5.68%)			
occurrences causally related to treatment / all	23 / 30			
deaths causally related to treatment / all	0 / 0			
Haematotoxicity				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune thrombocytopenia				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intravascular haemolysis				

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Leukopenia				
subjects affected / exposed	41 / 440 (9.32%)			
occurrences causally related to treatment / all	51 / 70			
deaths causally related to treatment / all	1 / 1			
Lymphopenia				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	21 / 440 (4.77%)			
occurrences causally related to treatment / all	28 / 32			
deaths causally related to treatment / all	2 / 2			
Pancytopenia				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	58 / 440 (13.18%)			
occurrences causally related to treatment / all	86 / 107			
deaths causally related to treatment / all	2 / 3			
Thrombocytosis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombotic microangiopathy				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Bacterial sepsis				

subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal symptom			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute abdomen			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Ascites			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	1 / 1		
Colitis ulcerative			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	16 / 440 (3.64%)		
occurrences causally related to treatment / all	9 / 30		
deaths causally related to treatment / all	0 / 1		
Dysphagia			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Enteritis			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Enterocolitis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Gastritis haemorrhagic			

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	6 / 440 (1.36%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 2			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal stenosis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Large intestine perforation				

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mesenteric artery thrombosis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	10 / 440 (2.27%)			
occurrences causally related to treatment / all	7 / 10			
deaths causally related to treatment / all	0 / 0			
Neutropenic colitis				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Oesophageal haemorrhage				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	12 / 440 (2.73%)			
occurrences causally related to treatment / all	11 / 13			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Hepatic function abnormal				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic lesion				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disease				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatomegaly				

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	46 / 440 (10.45%)			
occurrences causally related to treatment / all	4 / 42			
deaths causally related to treatment / all	0 / 0			
Liver injury				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Venoocclusive liver disease				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Erythema multiforme				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity vasculitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed	7 / 440 (1.59%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Rash macular			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 1		
Cystitis haemorrhagic			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal disorder			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal failure			
subjects affected / exposed	17 / 440 (3.86%)		
occurrences causally related to treatment / all	7 / 17		
deaths causally related to treatment / all	1 / 3		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders				
Arthralgia				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Still's disease				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abscess sweat gland				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspergilloma				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Atypical pneumonia			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	2 / 440 (0.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 1		
Campylobacter infection			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridial infection			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			

subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Device related sepsis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Enterocolitis infectious				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	1 / 233			
deaths causally related to treatment / all	1 / 1			
Escherichia sepsis				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes virus infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	0 / 0			
Infection				

subjects affected / exposed	5 / 440 (1.14%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Large intestine infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic infection				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	40 / 440 (9.09%)			
occurrences causally related to treatment / all	26 / 45			
deaths causally related to treatment / all	9 / 14			
Pneumonia fungal				
subjects affected / exposed	6 / 440 (1.36%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	1 / 1			
Diabetic foot infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia influenzal				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia viral				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	32 / 440 (7.27%)			
occurrences causally related to treatment / all	21 / 33			
deaths causally related to treatment / all	14 / 20			
Septic shock				

subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Sinusitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheitis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Decreased appetite				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 440 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Diabetes mellitus				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	2 / 440 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperuricaemia				

subjects affected / exposed	3 / 440 (0.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 440 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall treatment period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	440 / 440 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Second primary malignancy			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	14		
Vascular disorders			
Angiopathy			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	6		
Flushing			
subjects affected / exposed	11 / 440 (2.50%)		
occurrences (all)	13		
Haematoma			
subjects affected / exposed	39 / 440 (8.86%)		
occurrences (all)	46		
Haemorrhage			
subjects affected / exposed	20 / 440 (4.55%)		
occurrences (all)	26		

Hot flush			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	15		
Hypertension			
subjects affected / exposed	133 / 440 (30.23%)		
occurrences (all)	261		
Hypotension			
subjects affected / exposed	45 / 440 (10.23%)		
occurrences (all)	51		
Phlebitis			
subjects affected / exposed	39 / 440 (8.86%)		
occurrences (all)	51		
Thrombosis			
subjects affected / exposed	12 / 440 (2.73%)		
occurrences (all)	30		
Vasculitis			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	6		
General disorders and administration site conditions			
Localised oedema			
subjects affected / exposed	16 / 440 (3.64%)		
occurrences (all)	18		
Chest pain			
subjects affected / exposed	35 / 440 (7.95%)		
occurrences (all)	40		
Chills			
subjects affected / exposed	41 / 440 (9.32%)		
occurrences (all)	52		
Fatigue			
subjects affected / exposed	142 / 440 (32.27%)		
occurrences (all)	306		
General physical health deterioration			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	10		
General symptom			

subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	7		
Injection site reaction			
subjects affected / exposed	69 / 440 (15.68%)		
occurrences (all)	110		
Mucosal inflammation			
subjects affected / exposed	236 / 440 (53.64%)		
occurrences (all)	362		
Oedema			
subjects affected / exposed	130 / 440 (29.55%)		
occurrences (all)	238		
Oedema peripheral			
subjects affected / exposed	111 / 440 (25.23%)		
occurrences (all)	178		
Pain			
subjects affected / exposed	119 / 440 (27.05%)		
occurrences (all)	203		
Pyrexia			
subjects affected / exposed	283 / 440 (64.32%)		
occurrences (all)	635		
Visceral oedema			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	4		
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	21 / 440 (4.77%)		
occurrences (all)	72		
Graft versus host disease in eye			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	7		
Graft versus host disease in gastrointestinal tract			

subjects affected / exposed	31 / 440 (7.05%)		
occurrences (all)	54		
Graft versus host disease in liver			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	4		
Graft versus host disease in skin			
subjects affected / exposed	62 / 440 (14.09%)		
occurrences (all)	127		
Hypersensitivity			
subjects affected / exposed	93 / 440 (21.14%)		
occurrences (all)	134		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	7		
Sexual dysfunction			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Rhinitis			
subjects affected / exposed	11 / 440 (2.50%)		
occurrences (all)	12		
Bronchospasm			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	106 / 440 (24.09%)		
occurrences (all)	173		
Dysphonia			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	72 / 440 (16.36%)		
occurrences (all)	101		
Hiccups			

subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	7		
Hypoxia			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	8		
Laryngeal pain			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Lung disorder			
subjects affected / exposed	22 / 440 (5.00%)		
occurrences (all)	27		
Nasal disorder			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Obstructive airways disorder			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	16		
Pleural effusion			
subjects affected / exposed	25 / 440 (5.68%)		
occurrences (all)	33		
Pleuritic pain			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Pneumonitis			
subjects affected / exposed	24 / 440 (5.45%)		
occurrences (all)	34		
Pneumothorax			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Pulmonary haemorrhage			
subjects affected / exposed	78 / 440 (17.73%)		
occurrences (all)	101		
Respiratory failure			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Psychiatric disorders			

Agitation			
subjects affected / exposed	46 / 440 (10.45%)		
occurrences (all)	66		
Anxiety			
subjects affected / exposed	51 / 440 (11.59%)		
occurrences (all)	84		
Confusional state			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	5		
Depression			
subjects affected / exposed	53 / 440 (12.05%)		
occurrences (all)	84		
Insomnia			
subjects affected / exposed	176 / 440 (40.00%)		
occurrences (all)	376		
Psychotic disorder			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	8		
Investigations			
Activated partial thromboplastin time shortened			
subjects affected / exposed	10 / 440 (2.27%)		
occurrences (all)	16		
Alanine aminotransferase increased			
subjects affected / exposed	62 / 440 (14.09%)		
occurrences (all)	165		
Antithrombin III			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	50 / 440 (11.36%)		
occurrences (all)	117		
Blood alkaline phosphatase increased			
subjects affected / exposed	21 / 440 (4.77%)		
occurrences (all)	42		
Blood bilirubin increased			

subjects affected / exposed	36 / 440 (8.18%)			
occurrences (all)	49			
Blood cholesterol increased				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences (all)	14			
Blood creatinine increased				
subjects affected / exposed	34 / 440 (7.73%)			
occurrences (all)	61			
Blood fibrinogen decreased				
subjects affected / exposed	11 / 440 (2.50%)			
occurrences (all)	14			
Blood lactate dehydrogenase increased				
subjects affected / exposed	26 / 440 (5.91%)			
occurrences (all)	54			
Coagulation factor XIII level decreased				
subjects affected / exposed	7 / 440 (1.59%)			
occurrences (all)	7			
C-reactive protein increased				
subjects affected / exposed	102 / 440 (23.18%)			
occurrences (all)	208			
Electrocardiogram QT prolonged				
subjects affected / exposed	30 / 440 (6.82%)			
occurrences (all)	60			
Gamma-glutamyltransferase increased				
subjects affected / exposed	50 / 440 (11.36%)			
occurrences (all)	115			
Hepatic enzyme increased				
subjects affected / exposed	15 / 440 (3.41%)			
occurrences (all)	47			
International normalised ratio decreased				
subjects affected / exposed	6 / 440 (1.36%)			
occurrences (all)	8			
pH urine increased				

subjects affected / exposed	16 / 440 (3.64%)		
occurrences (all)	23		
Prothrombin time prolonged			
subjects affected / exposed	23 / 440 (5.23%)		
occurrences (all)	32		
Troponin T increased			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	18 / 440 (4.09%)		
occurrences (all)	31		
Weight increased			
subjects affected / exposed	79 / 440 (17.95%)		
occurrences (all)	130		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Procedural haemorrhage			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	5		
Procedural pain			
subjects affected / exposed	18 / 440 (4.09%)		
occurrences (all)	21		
Vascular access site thrombosis			
subjects affected / exposed	20 / 440 (4.55%)		
occurrences (all)	26		
Wound complication			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	5		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Arrhythmia supraventricular			

subjects affected / exposed	46 / 440 (10.45%)		
occurrences (all)	70		
Cardiac disorder			
subjects affected / exposed	11 / 440 (2.50%)		
occurrences (all)	16		
Cardiac failure			
subjects affected / exposed	12 / 440 (2.73%)		
occurrences (all)	22		
Cardiac valve disease			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	7		
Myocardial ischaemia / Myocardial infarction			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Palpitations			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Pericardial effusion			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Tachycardia			
subjects affected / exposed	9 / 440 (2.05%)		
occurrences (all)	10		
Ventricular arrhythmia			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	10		
Oesophagitis			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	11		
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	9		
Dizziness			

subjects affected / exposed	82 / 440 (18.64%)		
occurrences (all)	122		
Dyskinesia			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	152 / 440 (34.55%)		
occurrences (all)	301		
Nervous system disorder			
subjects affected / exposed	13 / 440 (2.95%)		
occurrences (all)	17		
Neuralgia			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	6		
Peripheral sensory neuropathy			
subjects affected / exposed	20 / 440 (4.55%)		
occurrences (all)	47		
Seizure			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Speech disorder			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	16 / 440 (3.64%)		
occurrences (all)	21		
Tremor			
subjects affected / exposed	20 / 440 (4.55%)		
occurrences (all)	37		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	390 / 440 (88.64%)		
occurrences (all)	1460		

Blood disorder				
subjects affected / exposed	6 / 440 (1.36%)			
occurrences (all)	7			
Coagulopathy				
subjects affected / exposed	12 / 440 (2.73%)			
occurrences (all)	15			
Disseminated intravascular coagulation				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences (all)	5			
Erythropenia				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences (all)	22			
Febrile neutropenia				
subjects affected / exposed	195 / 440 (44.32%)			
occurrences (all)	355			
Leukocytosis				
subjects affected / exposed	22 / 440 (5.00%)			
occurrences (all)	38			
Leukopenia				
subjects affected / exposed	33 / 440 (7.50%)			
occurrences (all)	10002			
Lymphatic disorder				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences (all)	3			
Lymphopenia				
subjects affected / exposed	26 / 440 (5.91%)			
occurrences (all)	65			
Neutropenia				
subjects affected / exposed	198 / 440 (45.00%)			
occurrences (all)	445			
Neutrophilia				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences (all)	5			
Thrombocytopenia				

subjects affected / exposed	391 / 440 (88.86%)		
occurrences (all)	1289		
Ascites			
subjects affected / exposed	10 / 440 (2.27%)		
occurrences (all)	12		
Colitis			
subjects affected / exposed	34 / 440 (7.73%)		
occurrences (all)	42		
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	9 / 440 (2.05%)		
occurrences (all)	11		
Ear pain			
subjects affected / exposed	10 / 440 (2.27%)		
occurrences (all)	12		
Hypoacusis			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	12		
Tinnitus			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	5		
Eye disorders			
Cataract			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	16		
Diplopia			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Dry eye			
subjects affected / exposed	38 / 440 (8.64%)		
occurrences (all)	82		
Eye disorder			
subjects affected / exposed	28 / 440 (6.36%)		
occurrences (all)	35		
Eye pain			

subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Keratitis			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	6		
Ocular surface disease			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	12		
Photopsia			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	4		
Vision blurred			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	7		
Vitreous haemorrhage			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	6		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	32 / 440 (7.27%)		
occurrences (all)	36		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	9 / 440 (2.05%)		
occurrences (all)	9		
Abdominal pain upper			
subjects affected / exposed	182 / 440 (41.36%)		
occurrences (all)	320		
Abdominal pain			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	4		
Anal fissure			
subjects affected / exposed	13 / 440 (2.95%)		
occurrences (all)	15		
Constipation			

subjects affected / exposed	150 / 440 (34.09%)			
occurrences (all)	272			
Diarrhoea				
subjects affected / exposed	252 / 440 (57.27%)			
occurrences (all)	436			
Dry mouth				
subjects affected / exposed	17 / 440 (3.86%)			
occurrences (all)	30			
Dyspepsia				
subjects affected / exposed	41 / 440 (9.32%)			
occurrences (all)	78			
Dysphagia				
subjects affected / exposed	23 / 440 (5.23%)			
occurrences (all)	26			
Enteritis				
subjects affected / exposed	11 / 440 (2.50%)			
occurrences (all)	12			
Flatulence				
subjects affected / exposed	34 / 440 (7.73%)			
occurrences (all)	38			
Gastritis				
subjects affected / exposed	14 / 440 (3.18%)			
occurrences (all)	19			
Gastrointestinal disorder				
subjects affected / exposed	34 / 440 (7.73%)			
occurrences (all)	57			
Gastrointestinal fistula				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences (all)	3			
Gastrointestinal haemorrhage				
subjects affected / exposed	33 / 440 (7.50%)			
occurrences (all)	36			
Gingival pain				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences (all)	4			
Haemorrhoids				

subjects affected / exposed	30 / 440 (6.82%)		
occurrences (all)	44		
Ileus			
subjects affected / exposed	9 / 440 (2.05%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	351 / 440 (79.77%)		
occurrences (all)	1270		
Oral pain			
subjects affected / exposed	24 / 440 (5.45%)		
occurrences (all)	27		
Proctalgia			
subjects affected / exposed	14 / 440 (3.18%)		
occurrences (all)	16		
Proctitis			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Taste disorder			
subjects affected / exposed	14 / 440 (3.18%)		
occurrences (all)	17		
Toothache			
subjects affected / exposed	14 / 440 (3.18%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	201 / 440 (45.68%)		
occurrences (all)	598		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	5		
Hepatic function abnormal			
subjects affected / exposed	11 / 440 (2.50%)		
occurrences (all)	12		
Hepatobiliary disease			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	7		

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	23 / 440 (5.23%)		
occurrences (all)	35		
Dry skin			
subjects affected / exposed	26 / 440 (5.91%)		
occurrences (all)	39		
Erythema multiforme			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	5		
Hyperhidrosis			
subjects affected / exposed	32 / 440 (7.27%)		
occurrences (all)	50		
Nail disorder			
subjects affected / exposed	4 / 440 (0.91%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	58 / 440 (13.18%)		
occurrences (all)	108		
Skin burning sensation			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Skin disorder			
subjects affected / exposed	69 / 440 (15.68%)		
occurrences (all)	93		
Skin hyperpigmentation			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	13		
Skin ulcer			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	7		
Urticaria			
subjects affected / exposed	10 / 440 (2.27%)		
occurrences (all)	13		
Renal and urinary disorders			

Bladder pain			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	7		
Dysuria			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	6		
Haemorrhage urinary tract			
subjects affected / exposed	30 / 440 (6.82%)		
occurrences (all)	44		
Pollakiuria			
subjects affected / exposed	14 / 440 (3.18%)		
occurrences (all)	17		
Renal disorder			
subjects affected / exposed	11 / 440 (2.50%)		
occurrences (all)	16		
Renal failure			
subjects affected / exposed	33 / 440 (7.50%)		
occurrences (all)	55		
Renal pain			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Urinary incontinence			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	10		
Urinary retention			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	10		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	10		
Hypothyroidism			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	7		
Petechiae			

subjects affected / exposed	53 / 440 (12.05%)		
occurrences (all)	68		
Rash			
subjects affected / exposed	199 / 440 (45.23%)		
occurrences (all)	321		
Skin induration			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	44 / 440 (10.00%)		
occurrences (all)	64		
Arthritis			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	9		
Back pain			
subjects affected / exposed	84 / 440 (19.09%)		
occurrences (all)	114		
Bone pain			
subjects affected / exposed	42 / 440 (9.55%)		
occurrences (all)	57		
Muscular weakness			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	25		
Musculoskeletal chest pain			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	5		
Musculoskeletal disorder			
subjects affected / exposed	22 / 440 (5.00%)		
occurrences (all)	30		
Myalgia			
subjects affected / exposed	22 / 440 (5.00%)		
occurrences (all)	41		
Myopathy			

subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	17		
Neck pain			
subjects affected / exposed	26 / 440 (5.91%)		
occurrences (all)	35		
Osteoporosis			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	16		
Pain in extremity			
subjects affected / exposed	51 / 440 (11.59%)		
occurrences (all)	84		
Infections and infestations			
Abdominal infection			
subjects affected / exposed	3 / 440 (0.68%)		
occurrences (all)	3		
Anal infection			
subjects affected / exposed	11 / 440 (2.50%)		
occurrences (all)	11		
Bronchitis			
subjects affected / exposed	10 / 440 (2.27%)		
occurrences (all)	14		
Cellulitis			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	8		
Clostridium difficile infection			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	6		
Conjunctivitis			
subjects affected / exposed	21 / 440 (4.77%)		
occurrences (all)	25		
Cystitis			
subjects affected / exposed	24 / 440 (5.45%)		
occurrences (all)	30		
Cytomegalovirus infection			
subjects affected / exposed	41 / 440 (9.32%)		
occurrences (all)	75		

Device related infection				
subjects affected / exposed	67 / 440 (15.23%)			
occurrences (all)	85			
Enterococcal infection				
subjects affected / exposed	22 / 440 (5.00%)			
occurrences (all)	35			
Epstein-Barr virus infection				
subjects affected / exposed	12 / 440 (2.73%)			
occurrences (all)	13			
Eye infection				
subjects affected / exposed	7 / 440 (1.59%)			
occurrences (all)	9			
Folliculitis				
subjects affected / exposed	9 / 440 (2.05%)			
occurrences (all)	10			
Genital infection female				
subjects affected / exposed	7 / 440 (1.59%)			
occurrences (all)	9			
Hepatic infection				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences (all)	3			
Herpes virus infection				
subjects affected / exposed	19 / 440 (4.32%)			
occurrences (all)	19			
Herpes zoster				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences (all)	4			
Infection				
subjects affected / exposed	136 / 440 (30.91%)			
occurrences (all)	233			
Influenza				
subjects affected / exposed	5 / 440 (1.14%)			
occurrences (all)	7			
Large intestine infection				
subjects affected / exposed	14 / 440 (3.18%)			
occurrences (all)	15			

Lip infection				
subjects affected / exposed	37 / 440 (8.41%)			
occurrences (all)	43			
Nail infection				
subjects affected / exposed	4 / 440 (0.91%)			
occurrences (all)	9			
Neutropenic infection				
subjects affected / exposed	23 / 440 (5.23%)			
occurrences (all)	32			
Oral candidiasis				
subjects affected / exposed	8 / 440 (1.82%)			
occurrences (all)	13			
Oral infection				
subjects affected / exposed	18 / 440 (4.09%)			
occurrences (all)	21			
Otitis media				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences (all)	5			
Pharyngitis				
subjects affected / exposed	11 / 440 (2.50%)			
occurrences (all)	11			
Pleural infection				
subjects affected / exposed	3 / 440 (0.68%)			
occurrences (all)	3			
Pneumonia				
subjects affected / exposed	116 / 440 (26.36%)			
occurrences (all)	157			
Rhinitis				
subjects affected / exposed	21 / 440 (4.77%)			
occurrences (all)	27			
Sepsis syndrome				
subjects affected / exposed	49 / 440 (11.14%)			
occurrences (all)	63			
Sinusitis				
subjects affected / exposed	7 / 440 (1.59%)			
occurrences (all)	9			

Soft tissue infection			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	6		
Tooth infection			
subjects affected / exposed	5 / 440 (1.14%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	27 / 440 (6.14%)		
occurrences (all)	48		
Urinary tract infection			
subjects affected / exposed	41 / 440 (9.32%)		
occurrences (all)	56		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	7 / 440 (1.59%)		
occurrences (all)	9		
Decreased appetite			
subjects affected / exposed	71 / 440 (16.14%)		
occurrences (all)	131		
Diabetes mellitus			
subjects affected / exposed	13 / 440 (2.95%)		
occurrences (all)	27		
Folate deficiency			
subjects affected / exposed	8 / 440 (1.82%)		
occurrences (all)	12		
Hypercalcaemia			
subjects affected / exposed	6 / 440 (1.36%)		
occurrences (all)	10		
Hyperglycaemia			
subjects affected / exposed	30 / 440 (6.82%)		
occurrences (all)	62		
Hyperkalaemia			
subjects affected / exposed	24 / 440 (5.45%)		
occurrences (all)	31		
Hypernatraemia			

subjects affected / exposed	4 / 440 (0.91%)			
occurrences (all)	5			
Hypertriglyceridaemia				
subjects affected / exposed	30 / 440 (6.82%)			
occurrences (all)	4			
Hyperuricaemia				
subjects affected / exposed	61 / 440 (13.86%)			
occurrences (all)	98			
Hypoalbuminaemia				
subjects affected / exposed	21 / 440 (4.77%)			
occurrences (all)	25			
Hypocalcaemia				
subjects affected / exposed	42 / 440 (9.55%)			
occurrences (all)	67			
Hypokalaemia				
subjects affected / exposed	215 / 440 (48.86%)			
occurrences (all)	484			
Hypomagnesaemia				
subjects affected / exposed	90 / 440 (20.45%)			
occurrences (all)	175			
Hyponatraemia				
subjects affected / exposed	11 / 440 (2.50%)			
occurrences (all)	24			
Hypophosphataemia				
subjects affected / exposed	6 / 440 (1.36%)			
occurrences (all)	10			
Metabolic disorder				
subjects affected / exposed	38 / 440 (8.64%)			
occurrences (all)	59			
Tumour lysis syndrome				
subjects affected / exposed	8 / 440 (1.82%)			
occurrences (all)	10			
Vitamin B12 deficiency				
subjects affected / exposed	6 / 440 (1.36%)			
occurrences (all)	8			
Vitamin D deficiency				

subjects affected / exposed occurrences (all)	19 / 440 (4.32%) 44		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2013	• Implementation of Urgent Amendment (21 September 2012): No concomitant administration of Paracetamol during treatment with Midostaurin (due to risk of liver toxicities and hemolysis) • Implementation of new safety information (Investigator's Brochure Midostaurin Version 16) • Interaction of Midostaurin with strong CYP3A4 inhibitors
07 October 2014	• Increase of sample size from n=142 to n=284 patients; adaptation of sample size calculation and study duration • Integration of further study objectives: Primary objective: Integration of two predefined subgroup analyses for younger and older patients Secondary objective: Evaluation of relative impact of allogeneic stem cell transplantation as time-dependent covariable on survival endpoints
25 March 2015	• Implementation of new safety information from Investigator's Brochure Midostaurin Version 18: Prolongation of contraception from 3 months to 5 months after last administration of Midostaurin.
27 May 2015	• Implementation of new safety information from Investigator's Brochure Midostaurin Version 18: Integration of monitoring of Lipase levels during treatment cycles on day 15 and every three months during maintenance therapy.
07 November 2016	• Integration of "overall survival" as key secondary endpoint • Increase of sample size to 440 patients and adaption of sample size calculation • Integration and update of new information about the IMP Midostaurin • Update of adverse event reporting requirements of leukemia-associated events
18 July 2017	• Adaption of the overall study duration to 8 years and the follow-up period to 24 month after the enrollment of the last patient. • Harmonization of the dose modifications of midostaurin in the study protocol and informed consent form. Update of interaction with strong inhibitors of Cytochrome P450-3A4. • Integration of new safety information on the study drug midostaurin according to the Investigators Brochure Version 20, update of the risk-benefit assessment and integration of actual study results. Change of coordinating investigator (from Prof. Dr. Richard Schlenk to Prof. Dr. Hartmut Döhner)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 April 2014	Achievement of initial recruitment goal of n=142 patients. An amendment (No. 2) of the protocol was performed to increase sample size to 284 patients.	21 October 2014
20 September 2016	Achievement of recruitment goal of n=284 patients. An amendment (No.5) of the protocol was performed to increase sample size to n=440 patients.	22 November 2016

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30563875