



Clinical trial results:

Prospective randomized multicenter phase II trial of low-dose decitabine (DAC) administered alone or in combination with the histone deacetylase inhibitor valproic acid (VPA) and all-trans retinoic acid (ATRA) in patients > 60 years with acute myeloid leukemia who are ineligible for induction chemotherapy

Summary

EudraCT number	2009-009916-33
Trial protocol	DE
Global end of trial date	23 February 2016

Results information

Result version number	v1
This version publication date	30 August 2019
First version publication date	30 August 2019

Trial information

Trial identification

Sponsor protocol code	00332/AMLSG14-09
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00867672
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany,
Public contact	Prof Dr Michael Luebbert, Medical Center - University of Freiburg, +49 76127032790, michael.luebbert@uniklinik-freiburg.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	07 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2016
Global end of trial reached?	Yes
Global end of trial date	23 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective is to answer the research question of whether a combination of low-dose DAC combined with the histone deacetylase inhibitor VPA and / or ATRA is able to increase the objective response rate to low-dose-DAC alone in AML of the elderly. The hypothesis that the combination is more active than single-agent DAC is based on a plethora of in vitro data indicating a synergism between both epigenetic modifiers (Cameron et al., 1999)

Protection of trial subjects:

An independent Data Monitoring Committee (DMC) was established. The DMC consisted of three hemato-oncologists and one statistician.

The function of the DMC was to monitor the course of the study and if necessary to give a recommendation to the steering committee for discontinuation, modification or continuation of the study. The underlying principles for the DMC were ethical and safety aspects for the patients. It was the task of the DMC to examine whether the conduct of the study was still ethically justifiable, whether security of the patients was ensured, and whether the process of the study is acceptable. For this purpose, the DMC had to be informed about the adherence to the protocol, the patient recruitment, the observed serious adverse events, and deaths. The DMC received the interim analysis report at the time point of the planned interim analysis. After the interim analysis, a DMC meeting was conducted and recommendations on the further continuation of the study and on early stopping of one or more of the treatment arms were given to the sponsor. In addition, serious adverse events were reported to the DMC at regular intervals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 December 2011
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	Germany: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	7
From 65 to 84 years	186
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 27 December 2011 (randomisation of the first patient) and ended on 23 February 2015 (randomisation of the last patient). The study was initiated in 29 study centres in Germany (one site did not enrol patients).

Pre-assignment

Screening details:

Patients with primary or secondary AML according to WHO ($\geq 20\%$ blasts in the peripheral blood (pB) or bone marrow (BM)) who are not expected to benefit from standard remission-induction chemotherapy

Pre-assignment period milestones

Number of subjects started	200
Number of subjects completed	200

Period 1

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

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: DAC

Arm description:

intravenous Decitabine 20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks

Arm title	Arm B: DAC + VPA
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Arm description:

intravenous Decitabine 20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks, and VPA (p.o.) from day 6 of first cycle continuously throughout all treatment cycles

Arm type	Experimental
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks

Investigational medicinal product name	Valproic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Starting dose 500mg, target serum levels 50 to 110 mg/l, from day 6 of first cycle continuously throughout all treatment cycles	
Arm title	Arm C: DAC + ATRA
Arm description:	
intravenous DAC 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks and ATRA (45 mg/m ² p.o.) from day 6 to day 28 of each treatment cycle	
Arm type	Experimental
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks	
Investigational medicinal product name	All-trans retinoic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details:	
45 mg/m ² p.o. from day 6 to day 28 of each treatment cycle	
Arm title	Arm D: DAC + VPA + ATRA
Arm description:	
intravenous DAC 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks and VPA (starting dose 500 mg p.o.) from day 6 continuously throughout all treatment cycles and ATRA (45 mg/m ² p.o.), from day 6 to day 28 of each treatment cycle	
Arm type	Experimental
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks	
Investigational medicinal product name	Valproic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Starting dose 500mg, target serum levels 50 to 110 mg/l, from day 6 of first cycle continuously throughout all treatment cycles	
Investigational medicinal product name	All-trans retinoic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

45 mg/m² p.o. from day 6 to day 28 of each treatment cycle

Number of subjects in period 1	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA
Started	47	57	46
Completed	47	57	46

Number of subjects in period 1	Arm D: DAC + VPA + ATRA
Started	50
Completed	50

Baseline characteristics

Reporting groups

Reporting group title	Arm A: DAC
Reporting group description: intravenous Decitabine 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks	
Reporting group title	Arm B: DAC + VPA
Reporting group description: intravenous Decitabine 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks, and VPA (p.o.) from day 6 of first cycle continuously throughout all treatment cycles	
Reporting group title	Arm C: DAC + ATRA
Reporting group description: intravenous DAC 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks and ATRA (45 mg/m ² p.o.) from day 6 to day 28 of each treatment cycle	
Reporting group title	Arm D: DAC + VPA + ATRA
Reporting group description: intravenous DAC 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks and VPA (starting dose 500 mg p.o.) from day 6 continuously throughout all treatment cycles and ATRA (45 mg/m ² p.o.), from day 6 to day 28 of each treatment cycle	

Reporting group values	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA
Number of subjects	47	57	46
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	75	76	77
inter-quartile range (Q1-Q3)	72 to 79	72 to 77	73 to 80
Gender categorical Units: Subjects			
Female	16	19	18
Male	31	38	28

Reporting group values	Arm D: DAC + VPA + ATRA	Total	
Number of subjects	50	200	
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	77		
inter-quartile range (Q1-Q3)	74 to 80	-	
Gender categorical			
Units: Subjects			
Female	19	72	
Male	31	128	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) included all randomised patients for whom any study treatment was started, and patients were analysed as belonging to their randomised arm (A: DAC, B: DAC+VPA, C: DAC+ATRA, or D: DAC+VPA+ATRA), regardless of whether they refused or discontinued therapy, or whether other protocol deviations are known.

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

Subject analysis set description:

The safety analysis set (SAF) included all randomised patients who received at least one dose of trial medication, and patients are analysed according to the received treatment. Patients were analyzed as belonging to

Arm A (DAC), if treatment with DAC was started, and no treatment with VPA and ATRA was started

Arm B (DAC+VPA), if treatment with VPA was started, and no treatment with ATRA was started

Arm C (DAC+ATRA), if treatment with ATRA was started, and no treatment with VPA was started

Arm D (DAC+VPA+ATRA), if treatment with VPA and with ATRA was started

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	200	200	
Age categorical			
Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	76	76	
inter-quartile range (Q1-Q3)	72 to 79	72 to 79	

Gender categorical			
Units: Subjects			
Female	72	72	
Male	128	128	

End points

End points reporting groups

Reporting group title	Arm A: DAC
Reporting group description: intravenous Decitabine 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks	
Reporting group title	Arm B: DAC + VPA
Reporting group description: intravenous Decitabine 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks, and VPA (p.o.) from day 6 of first cycle continuously throughout all treatment cycles	
Reporting group title	Arm C: DAC + ATRA
Reporting group description: intravenous DAC 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks and ATRA (45 mg/m ² p.o.) from day 6 to day 28 of each treatment cycle	
Reporting group title	Arm D: DAC + VPA + ATRA
Reporting group description: intravenous DAC 20 mg/m ² over 1h, 5 days (total dose 100 mg/m ²), repeated every 4 weeks and VPA (starting dose 500 mg p.o.) from day 6 continuously throughout all treatment cycles and ATRA (45 mg/m ² p.o.), from day 6 to day 28 of each treatment cycle	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) included all randomised patients for whom any study treatment was started, and patients were analysed as belonging to their randomised arm (A: DAC, B: DAC+VPA, C: DAC+ATRA, or D: DAC+VPA+ATRA), regardless of whether they refused or discontinued therapy, or whether other protocol deviations are known.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set (SAF) included all randomised patients who received at least one dose of trial medication, and patients are analysed according to the received treatment. Patients were analyzed as belonging to Arm A (DAC), if treatment with DAC was started, and no treatment with VPA and ATRA was started Arm B (DAC+VPA), if treatment with VPA was started, and no treatment with ATRA was started Arm C (DAC+ATRA), if treatment with ATRA was started, and no treatment with VPA was started Arm D (DAC+VPA+ATRA), if treatment with VPA and with ATRA was started	

Primary: Objective best overall response

End point title	Objective best overall response
End point description: Objective best overall response is defined as complete remission (CR, including CRi) or partial remission (PR). Patients were counted as responders if they achieve a CR, CRi or a PR. All other patients were counted as non-responders.	
End point type	Primary
End point timeframe: Whole study period	

End point values	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA	Arm D: DAC + VPA + ATRA
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	57	46	50
Units: patients' number				
Objective best overall response	4	10	12	9
No objective best overall response	43	47	34	41

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	200			
Units: patients' number				
Objective best overall response	35			
No objective best overall response	165			

Statistical analyses

Statistical analysis title	Primary efficacy analysis VPA vs no VPA
Statistical analysis description:	
The primary efficacy analysis was performed according to the intention-to-treat principle, based on the full analysis set, including all randomised patients who received any investigational product. The effect of VPA vs no VPA was analyzed by a comparison of arms (B+D) vs. arms (A+C).	
Comparison groups	Arm A: DAC v Arm B: DAC + VPA v Arm D: DAC + VPA + ATRA v Arm C: DAC + ATRA
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 ^[1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	2.21

Notes:

[1] - One-sided p-value for comparison of arms (B+D) vs arms (A+C)

Statistical analysis title	Primary efficacy analysis ATRA vs no ATRA
Statistical analysis description:	
The primary efficacy analysis was performed according to the intention-to-treat principle, based on the full analysis set, including all randomised patients who received any investigational product. The effect of ATRA vs no ATRA was analyzed by a comparison of arms (C+D) vs. arms (A+B).	
Comparison groups	Arm A: DAC v Arm B: DAC + VPA v Arm D: DAC + VPA + ATRA v Arm C: DAC + ATRA

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 ^[2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	3.79

Notes:

[2] - One-sided p-value for comparison of arms (C+D) vs arms (A+B)

Secondary: Overall best response

End point title	Overall best response
End point description:	
Overall best response was defined as CR, CRi, PR, or antileukemic effect (ALE). Patients were counted as responders if they achieve a CR or a PR or a ALE. All other patients were counted as non-responders.	
End point type	Secondary
End point timeframe:	
Whole study period	

End point values	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA	Arm D: DAC + VPA + ATRA
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	57	46	50
Units: patients number				
Overall best response responders	16	23	23	20
Overall best response non-responders	31	34	23	30

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	200			
Units: patients number				
Overall best response responders	82			
Overall best response non-responders	118			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description: The overall survival (OS) time from randomisation until death of the patients. For patients being alive at the end of the study, the OS time was censored at the time of the last visit or follow-up contact.	
End point type	Secondary
End point timeframe: Whole study period	

End point values	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA	Arm D: DAC + VPA + ATRA
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	57	46	50
Units: days				
median (inter-quartile range (Q1-Q3))	146 (55 to 317)	187 (58 to 335)	255 (96 to 553)	233 (96 to 715)

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	200			
Units: days				
median (inter-quartile range (Q1-Q3))	190.5 (72 to 425)			

Statistical analyses

Statistical analysis title	Efficacy analysis VPA vs no VPA
Statistical analysis description: The efficacy analysis was performed according to the intention-to-treat principle, based on the full analysis set, including all randomised patients who received any investigational product. The effect of VPA vs no VPA was analyzed by a comparison of arms (B+D) vs. arms (A+C).	
Comparison groups	Arm A: DAC v Arm B: DAC + VPA v Arm C: DAC + ATRA v Arm D: DAC + VPA + ATRA
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.28

Notes:

[3] - Two-sided p-value for comparison of arms (B+D) vs. arms (A+C).

Statistical analysis title	Efficacy analysis ATRA vs no ATRA
Statistical analysis description: The efficacy analysis was performed according to the intention-to-treat principle, based on the full analysis set, including all randomised patients who received any investigational product. The effect of ATRA vs no ATRA was analyzed by a comparison of arms (C+D) vs. arms (A+B).	
Comparison groups	Arm A: DAC v Arm B: DAC + VPA v Arm C: DAC + ATRA v Arm D: DAC + VPA + ATRA
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.89

Notes:

[4] - Two-sided p-value for comparison of arms (C+D) vs. arms (A+B).

Secondary: Progression free survival (PFS)	
End point title	Progression free survival (PFS)
End point description: Progression free survival (PFS) time from randomisation until relapse/progression or death of the patients. For patients being progression-free and alive at the end of the study, the PFS time was censored at the time of the last evaluation of bone marrow.	
End point type	Secondary
End point timeframe: Whole study period	

End point values	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA	Arm D: DAC + VPA + ATRA
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	57	46	50
Units: days				
median (inter-quartile range (Q1-Q3))	110 (39 to 236)	117 (51 to 350)	231 (75 to 497)	146 (56 to 440)

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	200			

Units: days				
median (inter-quartile range (Q1-Q3))	136 (49 to 357)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first administration until 4 weeks after the last administration of study drugs

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Arm A: DAC
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Reporting group description:

intravenous Decitabine 20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks

Reporting group title	Arm B: DAC + VPA
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Reporting group description:

intravenous Decitabine 20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks, and VPA (p.o.) from day 6 of first cycle continuously throughout all treatment cycles

Reporting group title	Arm C: DAC + ATRA
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Reporting group description:

intravenous DAC 20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks and ATRA (45 mg/m² p.o.) from day 6 to day 28 of each treatment cycle

Reporting group title	Arm D: DAC + VPA + ATRA
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Reporting group description:

intravenous DAC 20 mg/m² over 1h, 5 days (total dose 100 mg/m²), repeated every 4 weeks and VPA (starting dose 500 mg p.o.) from day 6 continuously throughout all treatment cycles and ATRA (45 mg/m² p.o.), from day 6 to day 28 of each treatment cycle

Serious adverse events	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 47 (80.85%)	46 / 57 (80.70%)	36 / 46 (78.26%)
number of deaths (all causes)	43	51	35
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic infiltration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatic carcinoma			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 47 (12.77%)	6 / 57 (10.53%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	3 / 9	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sudden death			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Condition aggravated			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site thrombosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Haemothorax			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolar proteinosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine increased			

subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prothrombin time prolonged			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ilium fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergic transfusion reaction			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transfusion reaction			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrial flutter			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral ischaemia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neurological symptom			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	12 / 47 (25.53%)	10 / 57 (17.54%)	7 / 46 (15.22%)
occurrences causally related to treatment / all	8 / 13	5 / 13	4 / 7
deaths causally related to treatment / all	0 / 0	1 / 3	0 / 1
Neutropenia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 57 (1.75%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	2 / 3	0 / 1	2 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Thrombocytopenia			
subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenic purpura			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemorrhagic anaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ileus			

subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nausea			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Hypersensitivity vasculitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 47 (6.38%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Synovitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	13 / 47 (27.66%)	10 / 57 (17.54%)	9 / 46 (19.57%)
occurrences causally related to treatment / all	7 / 16	0 / 16	3 / 9
deaths causally related to treatment / all	1 / 5	0 / 8	1 / 3
Infection			
subjects affected / exposed	4 / 47 (8.51%)	1 / 57 (1.75%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 47 (6.38%)	5 / 57 (8.77%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	1 / 3	0 / 5	0 / 3
deaths causally related to treatment / all	1 / 2	0 / 4	0 / 2
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Neutropenic infection			
subjects affected / exposed	0 / 47 (0.00%)	3 / 57 (5.26%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Lung infection			

subjects affected / exposed	2 / 47 (4.26%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 2
Urogenital infection bacterial			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Enterococcal sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia fungal			
subjects affected / exposed	2 / 47 (4.26%)	2 / 57 (3.51%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal sepsis			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Atypical pneumonia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess jaw			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	2 / 47 (4.26%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mycosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			

subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			

subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord abscess			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 57 (1.75%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D: DAC + VPA + ATRA		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 50 (88.00%)		
number of deaths (all causes)	40		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic infiltration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Meningioma			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Phlebitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tooth extraction			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Death			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Performance status decreased			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion site thrombosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypercapnia			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Epistaxis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alveolar proteinosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory acidosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood creatine increased			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prothrombin time prolonged			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ilium fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Overdose			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Allergic transfusion reaction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transfusion reaction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac failure				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Myocardial infarction				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Angina unstable				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Arrhythmia				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral infarction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neurological symptom			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Somnolence			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	10 / 50 (20.00%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Thrombocytopenic purpura			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bicytopenia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
haemorrhagic anaemia			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemolysis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic infarction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal angiodysplasia				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hypersensitivity vasculitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Acute kidney injury			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Synovitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	10 / 50 (20.00%) 2 / 12 0 / 2		
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 50 (10.00%) 2 / 5 0 / 0		
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 50 (4.00%) 0 / 2 0 / 2		
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 50 (6.00%) 0 / 3 0 / 0		
Pulmonary sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 0 / 1 0 / 1		
Neutropenic infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 50 (0.00%) 0 / 0 0 / 0		
Device related sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 50 (2.00%) 0 / 1 0 / 0		
Lung infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 50 (0.00%) 0 / 0 0 / 0		
Septic shock			

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urogenital infection bacterial				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterococcal sepsis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Endocarditis				

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abscess jaw				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary mycosis				

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis clostridial				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall abscess				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal abscess				

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterococcal infection			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr virus infection			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord abscess				

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A: DAC	Arm B: DAC + VPA	Arm C: DAC + ATRA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 47 (97.87%)	53 / 57 (92.98%)	42 / 46 (91.30%)
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	3 / 47 (6.38%)	3 / 57 (5.26%)	2 / 46 (4.35%)
occurrences (all)	3	3	2
Haematoma			
subjects affected / exposed	0 / 47 (0.00%)	5 / 57 (8.77%)	2 / 46 (4.35%)
occurrences (all)	0	6	2
Hypertension			
subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	3 / 46 (6.52%)
occurrences (all)	0	2	4
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	9 / 47 (19.15%)	12 / 57 (21.05%)	6 / 46 (13.04%)
occurrences (all)	9	16	11
Fatigue			
subjects affected / exposed	7 / 47 (14.89%)	8 / 57 (14.04%)	8 / 46 (17.39%)
occurrences (all)	8	13	11
Pyrexia			
subjects affected / exposed	9 / 47 (19.15%)	7 / 57 (12.28%)	9 / 46 (19.57%)
occurrences (all)	10	10	11
General physical health deterioration			

subjects affected / exposed	4 / 47 (8.51%)	5 / 57 (8.77%)	3 / 46 (6.52%)
occurrences (all)	4	6	3
Mucosal inflammation			
subjects affected / exposed	0 / 47 (0.00%)	3 / 57 (5.26%)	5 / 46 (10.87%)
occurrences (all)	0	4	5
Asthenia			
subjects affected / exposed	2 / 47 (4.26%)	5 / 57 (8.77%)	1 / 46 (2.17%)
occurrences (all)	3	5	1
Pain			
subjects affected / exposed	3 / 47 (6.38%)	2 / 57 (3.51%)	2 / 46 (4.35%)
occurrences (all)	3	2	3
Oedema			
subjects affected / exposed	3 / 47 (6.38%)	1 / 57 (1.75%)	1 / 46 (2.17%)
occurrences (all)	3	1	1
Infusion site extravasation			
subjects affected / exposed	0 / 47 (0.00%)	3 / 57 (5.26%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 47 (10.64%)	5 / 57 (8.77%)	9 / 46 (19.57%)
occurrences (all)	5	6	10
Epistaxis			
subjects affected / exposed	2 / 47 (4.26%)	6 / 57 (10.53%)	1 / 46 (2.17%)
occurrences (all)	2	6	1
Cough			
subjects affected / exposed	4 / 47 (8.51%)	3 / 57 (5.26%)	2 / 46 (4.35%)
occurrences (all)	4	3	2
Dyspnoea exertional			
subjects affected / exposed	3 / 47 (6.38%)	2 / 57 (3.51%)	3 / 46 (6.52%)
occurrences (all)	3	2	3
Lung infiltration			
subjects affected / exposed	3 / 47 (6.38%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences (all)	3	0	1
Psychiatric disorders			

Confusional state subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 57 (1.75%) 1	3 / 46 (6.52%) 3
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	3 / 57 (5.26%) 5	5 / 46 (10.87%) 8
Weight decreased subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	1 / 57 (1.75%) 1	2 / 46 (4.35%) 2
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	3 / 57 (5.26%) 4	3 / 46 (6.52%) 4
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	2 / 57 (3.51%) 2	5 / 46 (10.87%) 7
Blood creatine increased subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	3 / 57 (5.26%) 3	3 / 46 (6.52%) 3
C-reactive protein increased subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	5 / 57 (8.77%) 5	1 / 46 (2.17%) 1
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	6 / 57 (10.53%) 6	2 / 46 (4.35%) 2
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	0 / 57 (0.00%) 0	1 / 46 (2.17%) 1
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 7	6 / 57 (10.53%) 6	4 / 46 (8.70%) 6
Headache			

subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	0 / 57 (0.00%) 0	7 / 46 (15.22%) 12
Syncope subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	1 / 57 (1.75%) 1	2 / 46 (4.35%) 2
Tremor subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	4 / 57 (7.02%) 5	0 / 46 (0.00%) 0
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed occurrences (all)	10 / 47 (21.28%) 26	15 / 57 (26.32%) 24	14 / 46 (30.43%) 42
Anaemia subjects affected / exposed occurrences (all)	12 / 47 (25.53%) 31	14 / 57 (24.56%) 17	19 / 46 (41.30%) 26
Leukopenia subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 7	14 / 57 (24.56%) 16	12 / 46 (26.09%) 36
Neutropenia subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 6	8 / 57 (14.04%) 9	7 / 46 (15.22%) 31
Leukocytosis subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	3 / 57 (5.26%) 3	2 / 46 (4.35%) 2
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	2 / 57 (3.51%) 2	1 / 46 (2.17%) 1
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 9	5 / 57 (8.77%) 8	7 / 46 (15.22%) 9
Diarrhoea subjects affected / exposed occurrences (all)	8 / 47 (17.02%) 11	9 / 57 (15.79%) 9	5 / 46 (10.87%) 7
Constipation			

subjects affected / exposed	4 / 47 (8.51%)	8 / 57 (14.04%)	4 / 46 (8.70%)
occurrences (all)	4	10	4
Vomiting			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	5 / 46 (10.87%)
occurrences (all)	2	2	6
Stomatitis			
subjects affected / exposed	2 / 47 (4.26%)	3 / 57 (5.26%)	3 / 46 (6.52%)
occurrences (all)	2	3	3
Abdominal pain			
subjects affected / exposed	1 / 47 (2.13%)	3 / 57 (5.26%)	1 / 46 (2.17%)
occurrences (all)	1	3	1
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	3 / 47 (6.38%)	4 / 57 (7.02%)	5 / 46 (10.87%)
occurrences (all)	3	4	9
Rash			
subjects affected / exposed	2 / 47 (4.26%)	1 / 57 (1.75%)	4 / 46 (8.70%)
occurrences (all)	3	1	4
Pruritus			
subjects affected / exposed	1 / 47 (2.13%)	1 / 57 (1.75%)	2 / 46 (4.35%)
occurrences (all)	1	1	2
Dry skin			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Erythema			
subjects affected / exposed	1 / 47 (2.13%)	3 / 57 (5.26%)	2 / 46 (4.35%)
occurrences (all)	1	3	3
Skin ulcer			
subjects affected / exposed	0 / 47 (0.00%)	3 / 57 (5.26%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Alopecia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Urinary incontinence			

subjects affected / exposed	2 / 47 (4.26%)	2 / 57 (3.51%)	1 / 46 (2.17%)
occurrences (all)	2	2	1
Nocturia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 47 (0.00%)	3 / 57 (5.26%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 47 (4.26%)	3 / 57 (5.26%)	3 / 46 (6.52%)
occurrences (all)	2	3	3
Arthralgia			
subjects affected / exposed	0 / 47 (0.00%)	4 / 57 (7.02%)	2 / 46 (4.35%)
occurrences (all)	0	4	2
Pain in extremity			
subjects affected / exposed	1 / 47 (2.13%)	2 / 57 (3.51%)	3 / 46 (6.52%)
occurrences (all)	1	2	4
Neck pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 57 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 47 (4.26%)	3 / 57 (5.26%)	1 / 46 (2.17%)
occurrences (all)	2	3	1
Urinary tract infection			
subjects affected / exposed	3 / 47 (6.38%)	4 / 57 (7.02%)	4 / 46 (8.70%)
occurrences (all)	3	4	4
Oral herpes			
subjects affected / exposed	3 / 47 (6.38%)	2 / 57 (3.51%)	2 / 46 (4.35%)
occurrences (all)	3	2	2
Nasopharyngitis			
subjects affected / exposed	3 / 47 (6.38%)	3 / 57 (5.26%)	1 / 46 (2.17%)
occurrences (all)	5	4	1
Oral candidiasis			

subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	0 / 57 (0.00%) 0	0 / 46 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 47 (4.26%)	4 / 57 (7.02%)	3 / 46 (6.52%)
occurrences (all)	2	4	3
Hypokalaemia			
subjects affected / exposed	0 / 47 (0.00%)	2 / 57 (3.51%)	3 / 46 (6.52%)
occurrences (all)	0	2	3

Non-serious adverse events	Arm D: DAC + VPA + ATRA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 50 (98.00%)		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Haematoma			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	18		
Pyrexia			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	8		
General physical health deterioration			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	7		

Mucosal inflammation subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 5		
Asthenia subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Pain subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Oedema subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	8 / 50 (16.00%) 10		
Epistaxis subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 6		
Cough subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 4		
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Lung infiltration subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Investigations			

Platelet count decreased subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 10		
Weight decreased subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 6		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Blood creatine increased subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 2		
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5 5 / 50 (10.00%) 5 0 / 50 (0.00%) 0		

Tremor subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed occurrences (all)	13 / 50 (26.00%) 44		
Anaemia subjects affected / exposed occurrences (all)	12 / 50 (24.00%) 24		
Leukopenia subjects affected / exposed occurrences (all)	8 / 50 (16.00%) 15		
Neutropenia subjects affected / exposed occurrences (all)	9 / 50 (18.00%) 14		
Leukocytosis subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	10 / 50 (20.00%) 16		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 8		
Constipation subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5		
Vomiting subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 8		
Stomatitis			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Skin ulcer			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Nocturia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Renal failure			

subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	5		
Oral herpes			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	9		
Hypokalaemia			

subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2010	The main reasons for Amendment 01 dated 04.10.2010 (see Appendix 15.2.1.2) was a modification of DAC-administration schedule. At the time of amendment preliminary results of a clinical trial comparing low-dose DAC (5-day outpatient dosing, repeated every 4 weeks) with conventional care in elderly AML patients, (DAC 0016 trial) have shown similar efficacy and toxicity compared to the 6-week schedule (3 doses of DAC/day for 3 days every 6 weeks). This information led to modification of the initial protocol of this study and to the switch to the 5-day DAC-administration in 4-week cycles. The following additional specifications of initial CTP were performed: adaptation of the study flow chart to new DAC administration schedule, detailed definition of examinations at study visits, addition of secondary endpoints (progression-free survival (PFS) and number of nights in hospital), and submission of new centers, completion of DMC, update of phone/fax numbers and correction of typing errors.
07 February 2011	The main reasons of Amendment 02 dated 07.02.2011 (see Appendix 15.2.1.3) were the following: specification of DMC members, and involvement of the Institute of Pathology of the Medical Center - University of Freiburg for the central assessment instead of Den Haag. There were no active centers in the study at the moment: study sites were not initiated; no patients have been included into the study. That is why all modifications compared to the initial protocol were implemented directly into the text of the initial protocol in order to avoid potential misunderstanding/errors at study centers.

31 July 2012	The main goal of the Amendment 03 dated 31.07.2012 (see Appendix 15.2.1.4) was to clarify issues that arose during study conduct and to enhance the recruitment rate: some inclusion criteria were loosed or specified, e.g. patients with prior autologous transplantation were allowed to participate in the study. Furthermore, in the complex field of haematological malignancies it could not be avoided that patients participate simultaneously in registry or different diagnostic trials as long as they are compatible with the protocol of the given study; participation in such trials was allowed. Additional BM puncture after cytoreduction was cancelled. DAC and ATRA doses had to be calculated using actual body weight regardless of obesity status; neither capping of the body surface area (BSA) nor adjustment using ideal body weight had to be performed (Griggs et al. 2012). Ara-C was included as further allowed medication due to the fact that it is routinely used at several centers for cytoreduction. The CTP and Patient Informed Consent for translational project were modified in corresponding sections due to the fact that it was decided to include in this project also the patients who decline additional BM puncture on day 15. The end of treatment visit had to be performed as soon as possible after the termination of study treatment and not 4 weeks after its last administration, due to high probability of patient death during the time period of four weeks.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported