Clinical trial results:
Randomized phase II trial on primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation vs. high-dose chemotherapy supported by autologous stem cells transplantation for immunocompetent patients with newly diagnosed primary cns lymphoma.

Summary

EudraCT number	2009-012432-32
Trial protocol	IT DE GB DK
Global end of trial date	19 December 2024

Results information

Result version number	v1 (current)
This version publication date	02 January 2026
First version publication date	02 January 2026
Summary attachment (see zip file)	IELSG32 Synopsis (Synopsis_Clinical Study Report_IELSG32.pdf)

Trial information

Trial identification

Sponsor protocol code	IELSG 32

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01011920
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	International Extranodal Lymphoma Study Group (IELSG)
Sponsor organisation address	Via Vincenzo Vela 6, Bellinzona, Switzerland, 6500
Public contact	Operations Office, IELSG, +41 58 666 73 21, ielsg@ior.usi.ch
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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	13 November 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2024
Global end of trial reached?	Yes
Global end of trial date	19 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective at first randomization: to compare in a prospective, randomized phase II trial the activity of primary chemotherapy containing high-dose methotrexate (HD-MTX) + high-dose cytarabine (HD-araC) vs. HD-MTX + HD-araC + rituximab vs. HD-MTX + HD-araC + rituximab + thiotepa, in patients with newly diagnosed PCNSL. Primary objective at second randomization: to compare the efficacy of two consolidation strategies: conventional whole-brain radiotherapy (WBRT) vs. high-dose chemotherapy supported by autologous stem cell transplantation (HDC+ASCT) in patients with newly diagnosed PCNSL.

Protection of trial subjects:

In case of hematological toxicity, dose modifications of primary chemotherapy were foreseen. In case of inadequate bone marrow recovery on the intended day of re-treatment, the start of the next cycle could be delayed for a maximum of 2 weeks. Thereafter, chemotherapy has to be discontinued, and patient referred to WBRT 40 Gy plus boost 9 Gy. The dose of cytostatic drug were determined according to the nadir neutrophil or platelet counts of the previous course.
Ara-C dose reduction consisted of the omission of the 4th dose of the drug (2nd dose of the day 3).
No dose reductions were required in case of CTC grade 1 or 2 non-hematological toxicities. In case of CTC grade 3-4 non-hematological toxicity, the total dose of drugs to be administered in the subsequent course was reduced as foreseen in the study protocol.
Rituximab infusion reactions were managed according to international guidelines.

Background therapy:

The following drugs: antiemetics, analgesics, antibiotics, anticonvulsants, sedatives, anti-hyperuricemic agents as well as other therapies to control metabolic and malnutrition disturbances were delivered.
Additional cytotoxic therapy, biological responsive modifiers and drugs possibly interfering in the action or pharmacokinetics of MTX, Ara-C, rituximab, BCNU or thiotepa were avoided.
The type and doses of anticonvulsants and corticosteroids had to be accurately registered.
Antimicrobial prophylaxis followed Institutional guidelines since the variability in endemic or epidemic distribution of infectious agents. However, oral antiviral (Acyclovir 400 mg x 2/d), antifungine (Fluconazole 400 mg/d per os once weekly), antipneumocystic (Trimethoprim 160 mg and sulfamethoxazole 800 mg; three times per week) were suggested.
Conventional doses of rHuG-CSF from day 7th - 14th of every course associated with antibiotic prophylaxis with Levofloxacin 500 mg/day (same period) was
strongly suggested.
Antimicrobial drugs were interrupted during chemotherapy administration to avoid potential negative pharmacological interactions.

Evidence for comparator: -

Actual start date of recruitment	19 February 2010
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	Switzerland: 2

Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Germany: 82
Country: Number of subjects enrolled	Italy: 93
Worldwide total number of subjects	227
EEA total number of subjects	186

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	187
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted from 19 February 2010 to 07 October 2014

Pre-assignment

Screening details:

227 patients were screened and enrolled

Period 1

Period 1 title	First randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase.
Patients in Arm A received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3. Treatment was repeated on a 21 day cycle for 4 cycles.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3.5 mg/m2 (0.5 g/m2 in 15 min, followed by 3 g/m2 in 3-hour infusion) in combination with Cytarabine on day 1 of a 3 week cycle, for 4 cycles

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

Dosage and administration details:

2 g/m2 (1-hour infusion, twice a day, every 12 h) in combination with Methotrexate, on days 2 and 3 of a 21 days cycle for 4 cycles

Arm title	Arm B

Arm description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase.
Patients in Arm B received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Methotrexate was administered at the dosage of 3.5 mg/m2 (0.5 g/m2 in 15 min, followed by 3 g/m2 in 3-hour infusion) in combination with Cytarabine and Rituximab on day 1 of a 3 week cycle, for 4 cycles

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

Dosage and administration details:

Cytarabine was administered at the dosage of 2 g/m2 (1-hour infusion, twice a day, every 12 h) in combination with Methotrexate and Rituximab, on days 2 and 3 of a 21 days cycle for 4 cycles

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

Dosage and administration details:

Rituximab was administered at the dosage of 375 mg/m2 (conventional infusion) on days - 6 and 0, in combination with Methotrexate and Cytarabine, in a 21 days cycle for 4 cycles

Arm title	Arm C

Arm description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase. Patients in Arm C received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles less

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Methotrexate was administered at the dosage of 3.5 mg/m2 (0.5 g/m2 in 15 min, followed by 3 g/m2 in 3-hour infusion) in combination with Cytarabine, Rituximab and Thiotepa on day 1 of a 3 week cycle, for 4 cycles

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

Dosage and administration details:

Cytarabine was administered at the dosage of 2 g/m2 (1-hour infusion, twice a day, every 12 h) in combination with Methotrexate, Rituximab and Thiotepa, on days 2 and 3 of a 21 days cycle for 4 cycles

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

Dosage and administration details:

Rituximab was administered at the dosage of 375 mg/m2 (conventional infusion) on days - 6 and 0, in combination with Methotrexate, Cytarabine and Thiotepa, in a 21 days cycle for 4 cycles

Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Thiotepa was administered at the dosage of 30 mg/m2 (30 minutes infusion) on day 4 of a 21 days cycle for 4 cycles

Number of subjects in period 1[1]	Arm A	Arm B	Arm C
Started	75	69	75
Completed	46	55	66
Not completed	29	14	9
Adverse event, serious fatal	7	3	3
Progressive Disease	22	11	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two hundreds and twenty seven patients were enrolled and treated in the IELSG32 study. Eight patients were excluded (five from arm B and three from arm C) because of misdiagnosis, systemic lymphoma, or concomitant cancer.

Period 2

Period 2 title	Second Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm D

Arm description:

Patients responsive, Complete Response (CR) or Partial Response (PR) or with Stable Disease (SD) after primary chemotherapy (patients treated either with Arm A, B, or C) were randomly assigned to Arm D or Arm E.
Patients in Arm D were treated with conventional whole-brain radiotherapy (WBRT) with 36 Gy in the case of CR to primary chemotherapy or the same WBRT dose followed by a tumor-bed boost of 9 Gy with 1-2 cm of margin surrounding enhanced residual lesion (total tumor-bed dose 45 Gy) in patients who achieved a PR or SD after primary chemotherapy.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Arm E

Arm description:

Patients responsive, Complete Response (CR) or Partial Response (PR), or with Stable Disease (SD) after primary chemotherapy (patients treated either with Arm A, B, or C) were randomly assigned to Arm D or Arm E. Treatment regimen for Arm E corresponds to the conditioning phase for autologous stem cell transplantation (ASCT).

Arm type	Experimental

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

Dosage and administration details:

Carmustine was administered at the dosage of 400 mg/m2 on day - 6 before re-infusion of Peripheral Blood Stem Cells

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

Dosage and administration details:

Thiotepa was administered at the dosage of 5 mg/Kg on days - 5 and -4 before re-infusion of Peripheral Blood Stem Cells

Number of subjects in period 2[2]	Arm D	Arm E
Started	55	58
Completed	52	54
Not completed	3	4
Adverse event, serious fatal	-	2
Progressive Disease	3	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 167 patients with responsive or stable disease were observed. Eighteen patients experienced PD before the second randomization, 12 were deemed unfit, and 15 had no harvest. Consequently, 122 patients were eligible and assessable for second randomization. Four patients refused the second randomization, leaving 59 patients allocated to Arm D and 59 to Arm E.
Of these, five patients refused consolidation resulting in 113 patients proceeding.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase. Patients in Arm A received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3. Treatment was repeated on a 21 day cycle for 4 cycles.	
Reporting group title	Arm B
Reporting group description:	
At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase. Patients in Arm B received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles	
Reporting group title	Arm C
Reporting group description:	
At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase. Patients in Arm C received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles less	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	75	69	75
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	59	56	64
From 65-84 years	16	13	11
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	29	25	29
Male	46	44	46
Performance Status (ECOG) Units: Subjects			
ECOG 0 - 1	48	46	51
ECOG > 1	27	23	24
Increased LDH			
Increased serum lactate dehydrogenase concentration			
Units: Subjects			
Increased LDH	37	26	25
No increased LDH	38	43	50
Deep lesions Units: Subjects			

Deep lesions	58	52	64
No deep lesions	17	17	11
Increased CSF protein			
Increased cerebrospinal fluid (CSF) protein			
Units: Subjects			
Increased CSF protein	33	33	35
No increased CSF protein	23	20	18
Not recorded	19	16	22
IELSG risk score			
International Extranodal Lymphoma Study Group (IELSG) risk score			
Units: Subjects			
Low	14	12	13
Intermediate	47	44	47
High	14	13	15
Intraocular disease			
Units: Subjects			
Intraocular disease	5	1	1
No Intraocular disease	70	68	74
Meningeal involvement			
Units: Subjects			
Meningeal involvement	11	10	13
No meningeal involvement	45	43	40
Not recorded	19	16	22
Multiple lesions			
Units: Subjects			
Multiple lesions	45	40	41
No Multiple lesions	30	29	34

Reporting group values	Total		
Number of subjects	219		
Age categorical			
Units: Subjects			
In utero	0		
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)	179		
From 65-84 years	40		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	83		
Male	136		
Performance Status (ECOG)			
Units: Subjects			
ECOG 0 - 1	145		
ECOG > 1	74		
Increased LDH			

Increased serum lactate dehydrogenase concentration			
Units: Subjects			
Increased LDH	88		
No increased LDH	131		
Deep lesions Units: Subjects			
Deep lesions	174		
No deep lesions	45		
Increased CSF protein			
Increased cerebrospinal fluid (CSF) protein			
Units: Subjects			
Increased CSF protein	101		
No increased CSF protein	61		
Not recorded	57		
IELSG risk score			
International Extranodal Lymphoma Study Group (IELSG) risk score			
Units: Subjects			
Low	39		
Intermediate	138		
High	42		
Intraocular disease Units: Subjects			
Intraocular disease	7		
No Intraocular disease	212		
Meningeal involvement Units: Subjects			
Meningeal involvement	34		
No meningeal involvement	128		
Not recorded	57		
Multiple lesions Units: Subjects			
Multiple lesions	126		
No Multiple lesions	93		

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase.
Patients in Arm A received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3. Treatment was repeated on a 21 day cycle for 4 cycles.

Reporting group title	Arm B

Reporting group description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase.
Patients in Arm B received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles

Reporting group title	Arm C

Reporting group description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase. Patients in Arm C received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles less

Reporting group title	Arm D

Reporting group description:

Patients responsive, Complete Response (CR) or Partial Response (PR) or with Stable Disease (SD) after primary chemotherapy (patients treated either with Arm A, B, or C) were randomly assigned to Arm D or Arm E.
Patients in Arm D were treated with conventional whole-brain radiotherapy (WBRT) with 36 Gy in the case of CR to primary chemotherapy or the same WBRT dose followed by a tumor-bed boost of 9 Gy with 1-2 cm of margin surrounding enhanced residual lesion (total tumor-bed dose 45 Gy) in patients who achieved a PR or SD after primary chemotherapy.

Reporting group title	Arm E

Reporting group description:

Patients responsive, Complete Response (CR) or Partial Response (PR), or with Stable Disease (SD) after primary chemotherapy (patients treated either with Arm A, B, or C) were randomly assigned to Arm D or Arm E. Treatment regimen for Arm E corresponds to the conditioning phase for autologous stem cell transplantation (ASCT).

Primary: Complete Remission (CR) Rate

End point title	Complete Remission (CR) Rate[1]

End point description:

End point type	Primary

End point timeframe:

After primary chemotherapy

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal comparison was planned among the groups involved and the randomised active control group (Arm A) was used for calibration purposes.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	69	75	
Units: Percentage				
number (confidence interval 95%)	23 (14 to 31)	30 (21 to 42)	49 (38 to 60)	

Statistical analyses

No statistical analyses for this end point

Primary: 2-year failure-free survival (2-yr FFS)

End point title	2-year failure-free survival (2-yr FFS)[2]

End point description:

End point type	Primary

End point timeframe:

From the time of study entry until disease progression or death from any cause until 2 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal comparison was planned between groups D and E. The randomised active control group was used for calibration purposes.

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	58		
Units: Percentage				
number (confidence interval 95%)	76 (65 to 87)	75 (64 to 86)		

Statistical analyses

No statistical analyses for this end point

Secondary: 2 year Progression Free survival (PFS)

End point title	2 year Progression Free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

From the time of study entry until disease progression or death from any cause until 2 years

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	69	75	
Units: Percentage				
number (confidence interval 95%)	36 (31 to 41)	46 (40 to 52)	61 (55 to 67)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2 year overall survival (OS)

End point title	2 year overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

From treatment starts until 2 years after

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	69	75	55
Units: Percentage				
number (confidence interval 95%)	42 (36 to 48)	56 (50 to 62)	69 (64 to 74)	76 (65 to 87)

End point values	Arm E			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Percentage				
number (confidence interval 95%)	75 (64 to 86)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signature of the informed consent to 30 days after the last dose of the study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5.1

Reporting groups

Reporting group title	Arm A

Reporting group description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase.
Patients in Arm A received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3. Treatment was repeated on a 21 day cycle for 4 cycles.

Reporting group title	Arm B

Reporting group description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase.
Patients in Arm B received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles

Reporting group title	Arm C

Reporting group description:

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as an induction phase. Patients in Arm C received: Methotrexate 3.5 g/m2 on day 1 + Cytarabine 2g/m2 on days 2 and 3 + Rituximab 375 mg/m2 on days - 5 and 0. Treatment was repeated on a 21 day cycle for 4 cycles less

Reporting group title	Arm D

Reporting group description: -

Reporting group title	Arm E

Reporting group description: -

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 75 (52.00%)	38 / 69 (55.07%)	39 / 75 (52.00%)
number of deaths (all causes)	56	41	33
number of deaths resulting from adverse events	7	3	3
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 69 (1.45%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			

subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Peripheral arterial ischemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Hemorrhage, CNS			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Haemorrhage, pulmonary			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (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 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
General disorders and administration site conditions			
Fever			
subjects affected / exposed	6 / 75 (8.00%)	1 / 69 (1.45%)	4 / 75 (5.33%)
occurrences causally related to treatment / all	6 / 6	1 / 1	2 / 4
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pain general			
subjects affected / exposed	0 / 75 (0.00%)	2 / 69 (2.90%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pain abdomen			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower extremity gait			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Multi-organ failure			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Pelvic pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Disease progression			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Immune system disorders			
Allergy			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory increased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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 insufficiency			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 75 (4.00%)	0 / 69 (0.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mood alteration			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Confusion			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Psychosis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Nervous system disorders			
Cerebrovascular Ischemia			

subjects affected / exposed	0 / 75 (0.00%)	2 / 69 (2.90%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Seizure			
subjects affected / exposed	2 / 75 (2.67%)	4 / 69 (5.80%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 2	3 / 5	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
cerebellar toxicity			
subjects affected / exposed	1 / 75 (1.33%)	2 / 69 (2.90%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Leukoencephalopathy			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Syncope			
subjects affected / exposed	2 / 75 (2.67%)	0 / 69 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory neuropathy			

subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 75 (0.00%)	2 / 69 (2.90%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhoids			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (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
Mucositis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (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
Enteritis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Nausea/Vomiting			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (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
Dehydration			

subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (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
Perforation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 75 (2.67%)	3 / 69 (4.35%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (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
Osteonecrosis			
subjects affected / exposed	2 / 75 (2.67%)	1 / 69 (1.45%)	0 / 75 (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
Infections and infestations			
Febrile Neutropenia			
subjects affected / exposed	8 / 75 (10.67%)	8 / 69 (11.59%)	16 / 75 (21.33%)
occurrences causally related to treatment / all	8 / 8	8 / 8	22 / 22
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Viral Encephalitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	12 / 75 (16.00%)	5 / 69 (7.25%)	5 / 75 (6.67%)
occurrences causally related to treatment / all	12 / 12	5 / 5	4 / 5
deaths causally related to treatment / all	6 / 6	2 / 2	0 / 0

Pneumonia			
subjects affected / exposed	5 / 75 (6.67%)	6 / 69 (8.70%)	8 / 75 (10.67%)
occurrences causally related to treatment / all	5 / 5	5 / 7	8 / 8
deaths causally related to treatment / all	1 / 1	3 / 3	0 / 0
Aspergillosis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 69 (1.45%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections general			
subjects affected / exposed	9 / 75 (12.00%)	7 / 69 (10.14%)	15 / 75 (20.00%)
occurrences causally related to treatment / all	7 / 9	7 / 10	12 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (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
Cellulitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 75 (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
Pseudomonas infection			

subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
ALT increased			
subjects affected / exposed	3 / 75 (4.00%)	1 / 69 (1.45%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 69 (1.45%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine increased			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D	Arm E	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 55 (9.09%)	10 / 58 (17.24%)	
number of deaths (all causes)	30	23	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Epistaxis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial ischemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hemorrhage, CNS			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage, pulmonary			
subjects affected / exposed	0 / 55 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 55 (1.82%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain general			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain abdomen			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower extremity gait			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multi-organ failure			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory increased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory insufficiency			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Mood alteration			
subjects affected / exposed	0 / 55 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Ischemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 55 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebellar toxicity			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory neuropathy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			

subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 55 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	0 / 55 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Enteritis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea/Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 55 (1.82%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 55 (1.82%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 55 (1.82%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile Neutropenia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Encephalitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 55 (0.00%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections general			
subjects affected / exposed	1 / 55 (1.82%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ALT increased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine increased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 75 (100.00%)	68 / 69 (98.55%)	74 / 75 (98.67%)
Vascular disorders			
Coagulation disorders			
subjects affected / exposed	9 / 75 (12.00%)	11 / 69 (15.94%)	7 / 75 (9.33%)
occurrences (all)	16	18	11
Nervous system disorders			
Neurological toxicity			
subjects affected / exposed	13 / 75 (17.33%)	18 / 69 (26.09%)	13 / 75 (17.33%)
occurrences (all)	34	38	27
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	66 / 75 (88.00%)	65 / 69 (94.20%)	71 / 75 (94.67%)
occurrences (all)	187	207	261
Neutropenia			
subjects affected / exposed	68 / 75 (90.67%)	65 / 69 (94.20%)	69 / 75 (92.00%)
occurrences (all)	129	158	198
Thrombocytopenia			
subjects affected / exposed	67 / 75 (89.33%)	65 / 69 (94.20%)	70 / 75 (93.33%)
occurrences (all)	177	203	248
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 75 (5.33%)	0 / 69 (0.00%)	0 / 75 (0.00%)
occurrences (all)	5	0	0
Pain			

subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	3 / 75 (4.00%)
occurrences (all)	0	0	6
Fever			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 75 (0.00%)	2 / 69 (2.90%)	7 / 75 (9.33%)
occurrences (all)	0	6	10
Ear and labyrinth disorders			
Hearing impairment			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 75 (17.33%)	22 / 69 (31.88%)	50 / 75 (66.67%)
occurrences (all)	16	44	30
Nausea/Vomiting			
subjects affected / exposed	13 / 75 (17.33%)	29 / 69 (42.03%)	30 / 75 (40.00%)
occurrences (all)	20	68	61
Stomatisis/Mucositis			
subjects affected / exposed	18 / 75 (24.00%)	20 / 69 (28.99%)	20 / 75 (26.67%)
occurrences (all)	23	41	46
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	41 / 75 (54.67%)	42 / 69 (60.87%)	39 / 75 (52.00%)
occurrences (all)	97	104	97
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	18 / 75 (24.00%)	22 / 69 (31.88%)	28 / 75 (37.33%)
occurrences (all)	18	22	28
Erithema			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrotoxicity			

subjects affected / exposed	14 / 75 (18.67%)	18 / 69 (26.09%)	11 / 75 (14.67%)
occurrences (all)	31	35	20
Infections and infestations			
Infections			
subjects affected / exposed	22 / 75 (29.33%)	18 / 69 (26.09%)	28 / 75 (37.33%)
occurrences (all)	22	18	32

Non-serious adverse events	Arm D	Arm E	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 55 (69.09%)	49 / 58 (84.48%)	
Vascular disorders			
Coagulation disorders			
subjects affected / exposed	5 / 55 (9.09%)	7 / 58 (12.07%)	
occurrences (all)	5	7	
Nervous system disorders			
Neurological toxicity			
subjects affected / exposed	10 / 55 (18.18%)	4 / 58 (6.90%)	
occurrences (all)	10	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 55 (16.36%)	40 / 58 (68.97%)	
occurrences (all)	9	40	
Neutropenia			
subjects affected / exposed	7 / 55 (12.73%)	49 / 58 (84.48%)	
occurrences (all)	7	58	
Thrombocytopenia			
subjects affected / exposed	2 / 55 (3.64%)	49 / 58 (84.48%)	
occurrences (all)	2	58	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 55 (10.91%)	0 / 58 (0.00%)	
occurrences (all)	6	0	
Pain			
subjects affected / exposed	0 / 55 (0.00%)	4 / 58 (6.90%)	
occurrences (all)	0	4	
Fever			

subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	4 / 58 (6.90%) 4	
Immune system disorders Allergic reaction subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	0 / 58 (0.00%) 0	
Ear and labyrinth disorders Hearing impairment subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4	0 / 58 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	19 / 58 (32.76%) 19	
Nausea/Vomiting subjects affected / exposed occurrences (all)	7 / 55 (12.73%) 7	16 / 58 (27.59%) 16	
Stomatisis/Mucositis subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	30 / 58 (51.72%) 30	
Hepatobiliary disorders Hepatotoxicity subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4	19 / 58 (32.76%) 19	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	16 / 55 (29.09%) 16	17 / 58 (29.31%) 17	
Erithema subjects affected / exposed occurrences (all)	7 / 55 (12.73%) 7	0 / 58 (0.00%) 0	
Renal and urinary disorders Nephrotoxicity subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	6 / 58 (10.34%) 6	
Infections and infestations			

Infections subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	13 / 58 (22.41%) 13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2009	Amendment N. 1 The main purposes of this amendment were: • A section on monitoring and audit has been added. • A section on "Publication policy" has been modified. • A pregnancy test has been added to the work-up procedures. • Anonymization procedures have been included. • The use of PET in staging procedures has been better specified
06 July 2011	Amendment N. 2 In the section Statistical Design and Sample Size, the wording The A'Hern-Fleming Single stage Phase II design was used was reported. It has been better specified that the clinical trial design used to assess the effectiveness of treatment is a "single-stage" design, meaning that all participants are enrolled and observed for a fixed period before an assessment of the treatment's efficacy is made. The "A'Hern-Fleming" part refers to the statistical methods used to analyze the data and make decisions about whether the treatment is promising enough to warrant further investigation in larger, more definitive phase III trials.
02 January 2013	Amendment N. 4 The statistical design for the second randomisation was reviewed to optimise power and precision of the estimates after the first 100 patients were enrolled. The design of the study was not changed. Accordingly, 52 patients per arm at the second randomisation were needed, and a new sample size for trial registration was estimated to be more than 200 patients.
30 October 2015	Amendment N. 6 This amendment included the following changes: • Modification of an inclusion criterion regarding the hepatic function • Change of definition of lethal SAE

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported