Clinical trial results:
A Phase II Study of Pemetrexed in Children with Recurrent Malignancies

Summary

EudraCT number	2017-000095-28
Trial protocol	Outside EU/EEA
Global end of trial date	03 February 2010

Results information

Result version number	v1 (current)
This version publication date	16 April 2017
First version publication date	16 April 2017

Trial information

Trial identification

Sponsor protocol code	H3E-MC-JMHW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00520936
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 10294

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 February 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the response rate of pemetrexed given every 21 days for the treatment of children with relapsed or refractory osteosarcoma, Ewing's sarcoma/peripheral primitive neuroectodermal tumors (PNET), rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET or non-brain stem high-grade glioma.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2007
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	Canada: 11
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	72
EEA total number of subjects	0

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)	37
Adolescents (12-17 years)	20
Adults (18-64 years)	15
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

No Text Entered

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Osteosarcoma

Arm description:

Pemetrexed 1910 milligrams per meters squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Rhabdomyosarcoma

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Neuroblastoma (Measureable Disease)

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Ependymoma

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Arm title	Non-Brainstem High-Grade Glioma

Arm description:

Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1910 milligrams per meter squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old), intravenous (IV), for 21 days x 17 cycles

Number of subjects in period 1	Osteosarcoma	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors	Rhabdomyosarcoma
Started	10	11	9
Completed	10	7	7
Not completed	0	4	2
Adverse event, serious fatal	-	-	-
Physician decision	-	2	1
Consent withdrawn by subject	-	-	-
Toxicity Requiring Removal from Study	-	1	-
Protocol deviation	-	1	1

Number of subjects in period 1	Neuroblastoma (Measureable Disease)	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)	Ependymoma
Started	5	6	10
Completed	5	5	10
Not completed	0	1	0
Adverse event, serious fatal	-	-	-
Physician decision	-	-	-
Consent withdrawn by subject	-	-	-
Toxicity Requiring Removal from Study	-	-	-
Protocol deviation	-	1	-

Number of subjects in period 1	Medulloblastoma/Supratentorial	Non-Brainstem High-Grade Glioma

	Primitive Neuroectodermal Tumor	
Started	11	10
Completed	7	9
Not completed	4	1
Adverse event, serious fatal	1	-
Physician decision	-	-
Consent withdrawn by subject	-	1
Toxicity Requiring Removal from Study	2	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Osteosarcoma
Reporting group description:	
Pemetrexed 1910 milligrams per meters squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old)	
Reporting group title	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Rhabdomyosarcoma
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Neuroblastoma (Measureable Disease)
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Ependymoma
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Non-Brainstem High-Grade Glioma
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	

Reporting group values	Osteosarcoma	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors	Rhabdomyosarcoma
Number of subjects	10	11	9
Age categorical Units: Subjects			
Gender, Male/Female Units:			
Female	4	8	6
Male	6	3	3
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	0	1	0
Black or African American	4	0	0
White	4	8	7
Other	1	1	0
Unknown	1	1	0

Region of Enrollment Units: Subjects			
United States	7	7	8
Canada	3	4	1
Karnofsky Performance Score			
Classifies patients according to their functional impairment. Scores range from 0-100, the lower the score, the worse the survival for most serious illnesses. 100 - Normal no complaints; no evidence of disease 90 - Normal activity; minor signs of disease 80 - Activity with effort; some signs of disease 70 - Unable to carry on normal activity <=60 Needs increasing assistance up to Death (0)			
Units: Subjects			
100	0	2	0
90	3	3	0
80	0	1	0
70	0	1	0
50	1	0	0
Not Recorded	6	4	9
Lansky Play Score			
100=fully active, normal. 90=minor restrictions in physically strenuous activity. 80=active, but tires more quickly. 70=both greater restriction of and less time spent in play activity. 60=up and around, but minimal active play; keeps busy with quieter activities. 50=gets dressed, but lies around much of the day; no active play, able to participate in all quiet play activities. 40=mostly in bed; participates in quiet activities. 30=in bed; needs assistance even for quiet play. 20=often sleeping; play entirely limited to very passive activities. 10=No play; does not get out of bed.			
Units: Subjects			
100	1	1	3
90	1	3	3
80	2	0	2
70	0	0	0
60	1	0	1
50	1	0	0
Not Recorded	4	7	0
Age Units: Years			
arithmetic mean	14.94	18.24	8.74
standard deviation	± 4.28	± 3.35	± 4.96

Reporting group values	Neuroblastoma (Measureable Disease)	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)	Ependymoma
Number of subjects	5	6	10
Age categorical Units: Subjects			
Gender, Male/Female Units:			
Female	1	1	3
Male	4	5	7
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0

Black or African American	2	1	1
White	2	4	9
Other	1	0	0
Unknown	0	1	0
Region of Enrollment Units: Subjects			
United States	5	5	9
Canada	0	1	1
Karnofsky Performance Score			
Classifies patients according to their functional impairment. Scores range from 0-100, the lower the score, the worse the survival for most serious illnesses. 100 - Normal no complaints; no evidence of disease 90 - Normal activity; minor signs of disease 80 - Activity with effort; some signs of disease 70 - Unable to carry on normal activity <=60 Needs increasing assistance up to Death (0)			
Units: Subjects			
100	0	0	1
90	0	1	0
80	0	0	0
70	0	0	0
50	0	0	0
Not Recorded	5	5	9
Lansky Play Score			
100=fully active, normal. 90=minor restrictions in physically strenuous activity. 80=active, but tires more quickly. 70=both greater restriction of and less time spent in play activity. 60=up and around, but minimal active play; keeps busy with quieter activities. 50=gets dressed, but lies around much of the day; no active play, able to participate in all quiet play activities. 40=mostly in bed; participates in quiet activities. 30=in bed; needs assistance even for quiet play. 20=often sleeping; play entirely limited to very passive activities. 10=No play; does not get out of bed.			
Units: Subjects			
100	4	2	2
90	1	1	2
80	0	2	3
70	0	0	1
60	0	0	1
50	0	0	0
Not Recorded	0	1	1
Age Units: Years			
arithmetic mean	6.23	9.62	8.42
standard deviation	± 2.98	± 5.38	± 4.59

Reporting group values	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor	Non-Brainstem High-Grade Glioma	Total
Number of subjects	11	10	72
Age categorical Units: Subjects			
Gender, Male/Female Units:			
Female	4	5	32
Male	7	5	40

Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	0	1	2
Black or African American	3	3	14
White	8	6	48
Other	0	0	3
Unknown	0	0	3
Region of Enrollment Units: Subjects			
United States	10	10	61
Canada	1	0	11
Karnofsky Performance Score			
Classifies patients according to their functional impairment. Scores range from 0-100, the lower the score, the worse the survival for most serious illnesses. 100 - Normal no complaints; no evidence of disease 90 - Normal activity; minor signs of disease 80 - Activity with effort; some signs of disease 70 - Unable to carry on normal activity <=60 Needs increasing assistance up to Death (0)			
Units: Subjects			
100	0	0	3
90	1	1	9
80	0	1	2
70	1	0	2
50	1	0	2
Not Recorded	8	8	54
Lansky Play Score			
100=fully active, normal. 90=minor restrictions in physically strenuous activity. 80=active, but tires more quickly. 70=both greater restriction of and less time spent in play activity. 60=up and around, but minimal active play; keeps busy with quieter activities. 50=gets dressed, but lies around much of the day; no active play, able to participate in all quiet play activities. 40=mostly in bed; participates in quiet activities. 30=in bed; needs assistance even for quiet play. 20=often sleeping; play entirely limited to very passive activities. 10=No play; does not get out of bed.			
Units: Subjects			
100	2	3	18
90	3	4	18
80	2	0	11
70	0	1	2
60	1	0	4
50	0	0	1
Not Recorded	3	2	18
Age Units: Years			
arithmetic mean	12	12.75	
standard deviation	± 7.13	± 5.15	-

End points

End points reporting groups

Reporting group title	Osteosarcoma
Reporting group description:	
Pemetrexed 1910 milligrams per meters squared (mg/m^2) (or 60 milligrams per kilogram [mg/kg] if patient <12 months old)	
Reporting group title	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Rhabdomyosarcoma
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Neuroblastoma (Measureable Disease)
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Ependymoma
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	
Reporting group title	Non-Brainstem High-Grade Glioma
Reporting group description:	
Pemetrexed 1910 mg/m^2 (or 60 mg/kg if patient <12 months old)	

Primary: Percentage of Participants with Overall Tumor Response (Response Rate)

End point title	Percentage of Participants with Overall Tumor Response (Response Rate)[1]

End point description:

Response using Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Complete Response = disappearance of all target lesions. Partial Response = 30% decrease in sum of longest diameter of target lesions. Response rate (percent [%])= (number of participants with complete response (CR) or partial response (PR) in stratum/number of participants in stratum)*100.

Population Description: All treated participants

End point type	Primary

End point timeframe:

baseline to measured progressive disease (up to 1 year)

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: The primary objective was to estimate the response rates to pemetrexed and to further define and describe the toxicities of pemetrexed. There were no responders (neither CR nor PR) in this study.

End point values	Osteosarcoma	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors	Rhabdomyosarcoma	Neuroblastoma (Measureable Disease)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	9	5
Units: Percentage of Participants				
number (not applicable)	0	0	0	0

End point values	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)	Ependymoma	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor	Non-Brainstem High-Grade Glioma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	10	11	10
Units: Percentage of Participants				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Adverse Events, Discontinuations, or Deaths Possibly Due to Study Drug

End point title	Number of Patients with Adverse Events, Discontinuations, or Deaths Possibly Due to Study Drug

End point description:

AdEERS= Adverse Event Expedited Reporting System; AE = adverse event.
Patients may be counted in more than 1 category.
Includes events that were considered possibly related to study drug (PRSD) as judged by the investigator.

Population Description: All treated participants

End point type	Secondary

End point timeframe:

every cycle (up to 2 years and 7 months)

End point values	Osteosarcoma	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors	Rhabdomyosarcoma	Neuroblastoma (Measureable Disease)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	9	5
Units: Participants				
>=1 AdEERs possibly related to study drug	3	2	0	2

Discontinued due to AE possibly related to drug	0	1	0	0
Died on therapy possibly related to study drug	0	0	0	0
Died within 31 days of last dose of drug PRSD	0	0	0	0

End point values	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)	Ependymoma	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor	Non-Brainstem High-Grade Glioma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	10	11	10
Units: Participants				
>=1 AdEERs possibly related to study drug	3	2	2	2
Discontinued due to AE possibly related to drug	0	0	2	0
Died on therapy possibly related to study drug	0	0	0	0
Died within 31 days of last dose of drug PRSD	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacogenomics - measure the response of genes related to toxicity

End point title	Pharmacogenomics - measure the response of genes related to toxicity

End point description:

The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrahydrofolate reductase gene and the presence of a polymorphism in the thymidylate synthase (TS) gene and/or gene promoter and toxicity were optional and will not be reported here. Results of this optional research may be reported in the future by the Children's Oncology Group in the peer-reviewed literature.

Population Description: The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrahydrofolate reductase gene and the presence of a polymorphism in the thymidylate synthase (TS) gene and/or gene promoter and toxicity were optional and will not be reported here.

End point type	Secondary

End point timeframe:

baseline

End point values	Osteosarcoma	Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumors	Rhabdomyosarcoma	Neuroblastoma (Measureable Disease)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: Correlation coefficient				
number (not applicable)				

Notes:

[2] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

[3] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

[4] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

[5] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

End point values	Neuroblastoma (Metaiodobenzylguanidine Positive Evaluable)	Ependymoma	Medulloblastoma/Supratentorial Primitive Neuroectodermal Tumor	Non-Brainstem High-Grade Glioma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	0[8]	0[9]
Units: Correlation coefficient				
number (not applicable)				

Notes:

[6] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

[7] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

[8] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

[9] - The pharmacogenomics outcomes examining the correlation between the presence of the methylene tetrah

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

H3E-MC-JMHW

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Pemetrexed

Reporting group description: -

Serious adverse events	Pemetrexed		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 72 (29.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
ggt			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
hemorrhage, cns			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
hydrocephalus			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
hypotension				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
mood alteration: depression				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
syncope				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
febrile neutropenia				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	4 / 72 (5.56%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
hemoglobin				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
infection				
alternative dictionary used: MedDRA 13.0				

subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
infection with normal anc or grade 1				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	4 / 72 (5.56%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
leukocytes				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
lymphopenia				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
neutrophils/granulocytes				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
platelets				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
fever				
alternative dictionary used: MedDRA 13.0				

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
flushing				
alternative dictionary used: MedDRA 11.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
pain: extremity-limb				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
nausea				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
pain: tumor pain				
alternative dictionary used: MedDRA 12.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ulceration				
alternative dictionary used: MedDRA 11.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
vomiting				
alternative dictionary used: MedDRA 13.0				

subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
death not associated with ctcae term				
alternative dictionary used: MedDRA 11.0				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
rash: erythema multiforme				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
dyspnea				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
rash/desquamation				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
albumin, serum-low				
alternative dictionary used: MedDRA 13.0				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
calcium, serum-low				
alternative dictionary used: MedDRA 13.0				

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
dehydration			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
phosphate, serum-low			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
potassium, serum-low			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Pemetrexed		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 72 (13.89%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
seizure			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Congenital, familial and genetic disorders			
sodium, serum-low			
alternative dictionary used: MedDRA 11.0			

subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Cardiac disorders			
dermatology/skin - other			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
pulmonary/upper respiratory - other			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
thrombosis/thrombus/embolism			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
General disorders and administration site conditions			
fever			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
infection with normal anc or grade 1			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Gastrointestinal disorders			
diarrhea			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
hemorrhage, gi: rectum			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
pain: tumor pain			

alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Respiratory, thoracic and mediastinal disorders hypoxia alternative dictionary used: MedDRA 13.0 subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
Renal and urinary disorders hemorrhage, gu: urinary nos alternative dictionary used: MedDRA 13.0 subjects affected / exposed occurrences (all) renal failure alternative dictionary used: MedDRA 13.0 subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1 1 / 72 (1.39%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported