Clinical trial results:
An Exploratory Phase 2 Study of Pemetrexed/Cisplatin as Pre-operative Chemotherapy in the treatment of Stage IIIAN2 Nonsquamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2009-018148-45
Trial protocol	IT
Global end of trial date	05 April 2016

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	13621

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01165021
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: H3E-EW-JMIP

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	05 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to assess how well the combination of pemetrexed with cisplatin can reduce tumor size.

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	16 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	12
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participant Flow reports participants who discontinued from study treatment. Completed participants were those who had a baseline tumor assessment, finished 3 cycles (Cy) of pre-operative chemotherapy (chemo), and had a second tumor assessment following chemo.

Period 1

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

Arms

Arm title	Pemetrexed + Cisplatin

Arm description:

Pemetrexed: 500 milligrams per square meter (mg/m²) administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles

Cisplatin: 75 mg/m² administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles.

All participants that entered into the study were also administered folic acid, vitamin B12 supplementation and dexamethasone prophylaxis.

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

Dosage and administration details:

500 milligram per square meter (mg/m²) administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m² administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles

Investigational medicinal product name	Folic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally.

Investigational medicinal product name	Vitamin B12
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection

Routes of administration	Intramuscular use
Dosage and administration details: Administered Intramuscular injection.	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Administered orally.	

Number of subjects in period 1	Pemetrexed + Cisplatin
Started	19
≥1 Dose Chemo	19
≥1 dose chemo, baseline, Cy 3 assessment	17 [1]
3 cycles of Chemo, then Surgery	15 [2]
Completed	18
Not completed	1
Adverse event, serious fatal	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 17 participants had >=1 dose of chemotherapy, baseline and cycle 3 assessment.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 15 participants had 3 cycles of chemotherapy and then surgery.

Baseline characteristics

Reporting groups	
Reporting group title	Pemetrexed + Cisplatin

Reporting group description:

Pemetrexed: 500 milligrams per square meter (mg/m²) administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles

Cisplatin: 75 mg/m² administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles.

All participants that entered into the study were also administered folic acid, vitamin B12 supplementation and dexamethasone prophylaxis.

Reporting group values	Pemetrexed + Cisplatin	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	62.5		
standard deviation	± 9.32	-	
Gender, Male/Female Units: participants			
Female	6	6	
Male	13	13	
Race/Ethnicity, Customized Units: Subjects			
White	19	19	
Region of Enrollment Units: Subjects			
Italy	19	19	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG classifies participants according to their functional impairment. Scores range from 0 (fully active) to 5 (death). 0 (fully active, able to carry on all pre-disease performance without restriction) and 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).			
Units: Subjects			
ECOG 0	15	15	
ECOG 1	4	4	
Initial Pathological Diagnosis			
Initial cancer diagnosis confirmed by tissue biopsy.			
Units: Subjects			
Adenocarcinoma, Lung	17	17	
Carcinoma, Large Cell, Lung	1	1	
Carcinoma, Non-Small Cell, Lung	1	1	
Tumor-Node-Metastasis (TNM) Stage of Disease			
Tumor size: T1=surrounded by lung or visceral pleura with no evidence of invasion more proximal than lobar bronchus; T1a ≤2 centimeters (cm) at greatest dimension (GD); T1b >2 cm, ≤3 cm at GD; T2=involves main bronchus, ≥2 cm distal to carina; invades visceral pleura, associated with atelectasis			

or obstructive pneumonitis extends to hilar but not entire lung; T2a >3 cm, ≤5 cm at GD; T2b >5 cm, ≤7 cm at GD; T3= >7 cm or 1 that invades the thoracic cavity. Nodal status (N): N2 =Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes. Distant metastasis (M): M0 =No distant metastasis.			
Units: Subjects			
T1aN2M0	3	3	
T1bN2M0	2	2	
T2aN2M0	3	3	
T2bN2M0	3	3	
T3N2M0	8	8	
Tobacco Consumption Status Units: Subjects			
Current Tobacco User	4	4	
Former Tobacco User	12	12	
Never Used Tobacco	3	3	

End points

End points reporting groups

Reporting group title	Pemetrexed + Cisplatin

Reporting group description:

Pemetrexed: 500 milligrams per square meter (mg/m²) administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles

Cisplatin: 75 mg/m² administered as an intravenous infusion on Day 1 of 21-day cycles, for 3 cycles.

All participants that entered into the study were also administered folic acid, vitamin B12 supplementation and dexamethasone prophylaxis.

Primary: Percentage of participants with complete response (CR) or partial response (PR) [Overall Response Rate (ORR)]

End point title	Percentage of participants with complete response (CR) or partial response (PR) [Overall Response Rate (ORR)][1]

End point description:

Response was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.1) criteria. CR was defined as the disappearance of all target and non-target lesions and all target and non-target lymph nodes were non-pathological or normal in size [<10 millimeter (mm) short axis]. PR was defined as having at least a 30% decrease in sum of longest diameter of target lesions taking as reference the baseline sum diameters. ORR calculated as: (sum of the number of participants with PRs and CRs) divided by (number of evaluable participants) multiplied by 100.

Analysis Population Description: Participants who received at least 1 dose of preoperative chemotherapy and had baseline and Cycle 3 scans for tumor assessment.

End point type	Primary

End point timeframe:

From study enrollment until disease progression or recurrence up to completion of 3 cycles (21-day cycles) of 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: Unable to provide statistical analysis for single-arm study with no comparison group due to system limitations.

End point values	Pemetrexed + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of participants				
number (confidence interval 95%)	41.2 (18.4 to 67.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with No viable tumor cells in resected lung tissue [Pathological Complete Remission (pCR)]

End point title	Percentage of participants with No viable tumor cells in

	resected lung tissue [Pathological Complete Remission (pCR)]

End point description:

pCR after the participant has undergone surgery was calculated as: (total number of participants with pCR) divided by (the total number of participants in pathological response population) multiplied by 100.

Analysis Population Description: Participants who received at least 1 dose of preoperative chemotherapy and had surgical tumor tissue samples available.

End point type	Secondary

End point timeframe:

At the time of surgery (within 3 to 6 weeks of Day 1 of Cycle 3 [21-day cycles] of chemotherapy)

End point values	Pemetrexed + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percentage of participants				
number (confidence interval 95%)	93.3 (68.1 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who exhibit a downward shift in tumor extent from stage IIIAN2 to stages IIIA, II, I, or Stage 0

End point title	Percentage of participants who exhibit a downward shift in tumor extent from stage IIIAN2 to stages IIIA, II, I, or Stage 0

End point description:

Tumor downstaging compared to baseline (Stage IIIAN2) were those participants who exhibited a downward shift in tumor extent from Stage IIIAN2 to Stages IIIA, II, I, or 0 were reported. Downstaging was based on radiological examination. Stage IIIAN2 was locally advanced and/or involved lymph nodes, metastasis in ipsilateral mediastinal and or subcarinal lymph nodes, tumors were ≤2 centimeters (cm) up to 5 cm in greatest dimension; Stage IIIA was locally advanced and/or involved lymph nodes, tumor extension was restricted to the affected lung; Stage II was locally advanced and/or involved lymph nodes; Stage I was small localized cancers, usually curable; Stage 0 the cancer did not spread beyond the inner lining of the lung. Missing responses were also reported. Percentage of participants calculated as: (number of participants with a downward shift in extent of their tumor) divided by (total number of evaluable participants) multiplied by 100.

End point type	Secondary

End point timeframe:

From study enrollment until disease progression or recurrence up to completion of 3 cycles(cy)(21-day cy) of chemotherapy(CTH)

Population:Participants who received at least 1 dose of preoperative CTH and had baseline and Cy 3 scans for tumor assessment

End point values	Pemetrexed + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of participants				
number (confidence interval 95%)				
No Change or Worsening of Tumor Stage	29.4 (10.3 to 56)			
Change to Stage IIIA	29.4 (10.3 to 56)			
Change to Stage II	11.8 (1.5 to 36.4)			
Change to Stage I	17.6 (3.8 to 43.4)			
Missing	11.8 (1.5 to 36.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as duration from the date of study enrollment to the date of death from any cause. Participants not known to have died as of the data inclusion cut-off date were censored at the date of last contact. The last contact for participants in post-discontinuation was the last date participant was known to be alive.

Analysis Population Description : All participants who received 1 or more doses of preoperative chemotherapy. Participants censored=8.

End point type	Secondary

End point timeframe:

Enrollment until the date of death from any cause up to 64 months

End point values	Pemetrexed + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	19[2]			
Units: months				
median (confidence interval 95%)	34.6 (10.8 to 9999)			

Notes:

[2] - 9999 = NA. Upper range of 95% confidence interval were not calculated due to high censoring rate.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time from date of first dose to the first observation of disease progression or death due to any cause. For participants not known to have died or did not have objective progressive disease (PD) as of the data inclusion cut-off date, PFS was censored at the date of the last objective progression-free disease assessment. PD was defined using RECIST v1.1 criteria as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Analysis Population Description: All participants who received 1 or more doses of preoperative chemotherapy. Participants censored=3.

End point type	Secondary

End point timeframe:

Enrollment until the first date of objectively determined PD or death up to 64 months

End point values	Pemetrexed + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: months				
median (confidence interval 95%)	12.4 (7 to 21.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Treatment	
Adverse event reporting additional description: H3E-EW-JMIP	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Pemetrexed+Cisplatin

Reporting group description: -

Serious adverse events	Pemetrexed+Cisplatin		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
paraneoplastic syndrome			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
acute abdomen			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pemetrexed+Cisplatin		
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 19 (78.95%)		
Vascular disorders hypotension alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3		
General disorders and administration site conditions asthenia alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3		
fatigue alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 7		
oedema peripheral alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
pyrexia alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3		
Respiratory, thoracic and mediastinal disorders dyspnoea alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Psychiatric disorders depression alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

depressive symptom alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all) irritability alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Investigations neutrophil count decreased alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all) platelet count decreased alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	 4 / 19 (21.05%) 6 2 / 19 (10.53%) 2		
Injury, poisoning and procedural complications anaemia postoperative alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Nervous system disorders dysgeusia alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all) headache alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all) syncope alternative dictionary used: MedDRA 18.1 subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 2 / 19 (10.53%) 2		

Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
apical granuloma			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
dysphagia			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
haemorrhoids			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
oral dysaesthesia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
stomatitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
cafe au lait spots			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Renal and urinary disorders			
cystitis noninfective			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

myalgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
herpes zoster			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
tooth abscess			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	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? Yes

Date	Interruption	Restart date
28 March 2013	Enrollment was stopped due to difficulties identifying suitable participants and enrollment delays.	-

Notes:

Limitations and caveats

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

Due to difficulties identifying suitable participants and enrollment delays, entries were closed after 26 of planned 33 participants signed consent. Results based on 19 participants who received ≥1 dose of chemotherapy. View results with caution.

Notes: