Clinical trial results:
Estudio de pemetrexed y cisplatino como tratamiento de primera línea en pacientes con cáncer de pulmón no escamoso, avanzado: estudio farmacogenómico en fase IIA

(Study of pemetrexed disodium plus cisplatin as first-line therapy in patients with advanced non-squamous cell lung cancer: a phase IIA pharmacogenomic tria)

Summary

EudraCT number	2009-011327-31
Trial protocol	ES
Global end of trial date	26 February 2014

Results information

Result version number	v1 (current)
This version publication date	15 July 2020
First version publication date	15 July 2020
Summary attachment (see zip file)	GECP_PHALCIS_final report_summary (Resumen Informe final PHALCIS_Junio 2020_registro.pdf)

Trial information

Trial identification

Sponsor protocol code	GECP0901PHALCIS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01088906
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Cáncer de Pulmón
Sponsor organisation address	Avenida Meridiana 358, 6ª planta, Barcelona, Spain, 08027
Public contact	Eva Pereira Álvarez epereira@gecp.org, Grupo Español de Cáncer de Pulmón, 93 4302006, epereira@gecp.org
Scientific contact	Dr. Jose Miguel Sánchez Torres, Grupo Español de Cáncer de Pulmón, 93 4302006, epereira@gecp.org

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	29 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2014
Global end of trial reached?	Yes
Global end of trial date	26 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Valorar la eficacia de la combinación de pemetrexed y cisplatino como tratamiento de primera línea en apcientes con CPNM avanzado no escamoso

To assess the efficacy of the combination of pemetrexed and cisplatin as first-line treatment in patients with advanced non-squamous NSCLC.

Protection of trial subjects:

Las mujeres en edad fértil incluidas en el estudio deberán tener una prueba de embarazo negativa en los 3 días previos al inicio del estudio. Tanto hombres
como mujeres bajo esta condición deberán tomar medidas anticonceptivas durante el estudio y en los 3 meses siguientes a la última dosis del medicamento en estudio.

Women of childbearing age included in the study should have proof of negative pregnancy in the 3 days prior to the start of the study. Both men
as women under this condition they must take contraceptive measures during the study and in the 3 months following the last dose of study medication.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	28 January 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	Spain: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	42
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Dates of recruitment: start date :20/ 01/2010; ended 19/02/2014

All the patient were recruited in Spain

Pre-assignment

Screening details:

Not applicable

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

Arm title	Arm of study

Arm description:

Pemetrexed 500 mg / m2 IV will be administered as a 10-minute infusion on day 1 of each cycle. The cycles will last 21 days. For cisplatin the recommended dose is 75 mg / m2 in IV infusion for 2 hours. It will be administered approximately 30 minutes after pemetrexed, on day 1 of each cycle.
Patients will continue the study treatment until completing a maximum of 6 cycles or until disease progression, onset of toxicity unacceptable, rejection by the patient or delay in the administration of the treatment> 3 weeks.

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

Dosage and administration details:

Pemetrexed 500 mg / m2 IV will be administered as a 10-minute infusion on day 1 of each cycle.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin the recommended dose is 75 mg / m2 in IV infusion for 2 hours. It will be administered approximately 30 minutes after pemetrexed,
on day 1 of each cycle.

Number of subjects in period 1	Arm of study
Started	52
Completed	52

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
NSCLC patients non squamous stages IIIb and IV	

Reporting group values	Overall study	Total	
Number of subjects	52	52	
Age categorical			
Female and male			
Units: Subjects			
Adults (18-64 years)	42	42	
From 65-84 years	10	10	
Age continuous			
Units: years			
median	62		
full range (min-max)	53 to 72	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	39	39	
Smoking status			
Units: Subjects			
Never	5	5	
Former	31	31	
Smoker	16	16	
ECOG			
Units: Subjects			
ECOG 0	5	14	
ECOG 1	33	33	
ECOG UK	5	5	
Histology			
Units: Subjects			
Adenocarcinoma	51	51	
Large Cell Lung Carcinoma	1	1	
Treatment compliance			
Units: Subjects			
C1	1	1	
C2	7	7	
C3	6	6	
C4	8	8	
C5	4	4	
C6	26	26	

Subject analysis sets

Subject analysis set title	Final analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

NSCLC non squamous stage IIb and IV

Reporting group values	Final analysis		
Number of subjects	52		
Age categorical			
Female and male			
Units: Subjects			
Adults (18-64 years)	42		
From 65-84 years	10		
Age continuous			
Units: years			
median	62		
full range (min-max)	53 to 72		
Gender categorical			
Units: Subjects			
Female	13		
Male	39		
Smoking status			
Units: Subjects			
Never	5		
Former	31		
Smoker	16		
ECOG			
Units: Subjects			
ECOG 0	14		
ECOG 1	33		
ECOG UK	5		
Histology			
Units: Subjects			
Adenocarcinoma	51		
Large Cell Lung Carcinoma	1		
Treatment compliance			
Units: Subjects			
C1	1		
C2	7		
C3	6		
C4	8		
C5	4		
C6	26		

End points

End points reporting groups

Reporting group title	Arm of study

Reporting group description:

Pemetrexed 500 mg / m2 IV will be administered as a 10-minute infusion on day 1 of each cycle. The cycles will last 21 days. For cisplatin the recommended dose is 75 mg / m2 in IV infusion for 2 hours. It will be administered approximately 30 minutes after pemetrexed, on day 1 of each cycle.
Patients will continue the study treatment until completing a maximum of 6 cycles or until disease progression, onset of toxicity unacceptable, rejection by the patient or delay in the administration of the treatment> 3 weeks.

Subject analysis set title	Final analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

NSCLC non squamous stage IIb and IV

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

The percentage of patients who have experienced a tumor response since the start of treatment

The percentage of patients who have experienced tumor regression since the start of treatment (Complete response + Partial response) among the total of patients ORR = 34%
Disease control rate (Complete response + Partial Response + Stable Disease) = 78%
ORR: (%)
Stable disease:44
Partial response:22
Complete response:4
Progression:30

End point type	Primary

End point timeframe:

At the end of study

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 statistical analyses for this end point.
Conclusion : The combination of pemetrexed and cisplatin as first-line treatment in patients with Stage IV non-small cell lung cancer achieves a 34% response rate (complete response in 4.0% and partial response in 30%), and a control rate of 78% disease. The median progression-free survival was 5.63 months, and 11.27 months in overall survival.
No significant differences were found in PFS or OS according to expression of the BRCA1, RAP80 or TS genes

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: subjects				
Stable disease	22	22		
Partial response	12	12		
Complete response	2	2		
Progression	16	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

This interval is measured in months from the date of entry into the study until the first date of the appearance of new metastatic lesions or objective progression of the disease.

End point type	Secondary

End point timeframe:

At the end of study

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)	5.633 (4.180 to 7.087)	5.633 (4.180 to 7.087)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is measured from the date of enrollment to the date of death from any cause

End point type	Secondary

End point timeframe:

At the end of study.

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)	11.267 (9.141 to 13.392)	11.267 (9.141 to 13.392)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker BRCA1_Time to progression

End point title	Biomarker BRCA1_Time to progression

End point description:

This interval is measured from the date of entry into the study until the first date of the appearance of new metastatic lesions or objective progression of the disease.

End point type	Secondary

End point timeframe:

At the end of study

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52			
Units: Months				
median (confidence interval 95%)				
BRCA1 negative	5.270 (3.443 to 7.097)	5.270 (3.443 to 7.097)		
BRCA1 positive	3.430 (0.564 to 6.296)	3.430 (0.564 to 6.296)		
Global	5.270 (2.678 to 7.862)	5.270 (2.678 to 7.862)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker RAP80_Time to progression

End point title	Biomarker RAP80_Time to progression

End point description:

This interval is measured from the date of entry into the study until the first date of the appearance of new metastatic lesions or objective progression of the disease.

End point type	Secondary

End point timeframe:

At the end of study.

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)				
RAP80 negative	5.630 (2.416 to 8.844)	5.630 (2.416 to 8.844)		

RAP80 positive	3.430 (0.0 to 7.354)	3.430 (0.0 to 7.354)		
Global	5.370 (2.430 to 8.310)	5.370 (2.430 to 8.310)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker TS_Time to progression

End point title	Biomarker TS_Time to progression

End point description:

This interval is measured from the date of entry into the study until the first date of the appearance of new metastatic lesions or objective progression of the disease.

End point type	Secondary

End point timeframe:

At the end of study

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)				
TS negative	5.630 (0.249 to 11.011)	5.630 (0.249 to 11.011)		
TS positive	3.330 (2.590 to 4.070)	3.330 (2.590 to 4.070)		
Global	3.430 (1.738 to 5.122)	3.430 (1.738 to 5.122)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker BRCA1_Overall survival

End point title	Biomarker BRCA1_Overall survival

End point description:

Overall survival is measured from the date of enrollment to the date of death from any cause.

End point type	Secondary

End point timeframe:

At the end of study.

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)				
BRCA1 negative	12.270 (7.605 to 16.935)	12.270 (7.605 to 16.935)		
BRCA1 positive	8.400 (0.864 to 15.936)	8.400 (0.864 to 15.936)		
Global	10.570 (6.921 to 14.219)	10.570 (6.921 to 14.219)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker RAP80_ Overall survival

End point title	Biomarker RAP80_ Overall survival

End point description:

Overall survival is measured from the date of enrollment to the date of death from any cause.

End point type	Secondary

End point timeframe:

At the end of study.

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)				
RAP80 negative	10.570 (0.00 to 24.843)	10.570 (0.00 to 24.843)		
RAP80 positive	9.600 (4.787 to 14.413)	9.600 (4.787 to 14.413)		
Global	10.570 (5.865 to 15.275)	10.570 (5.865 to 15.275)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker TS_ Overall Survival

End point title	Biomarker TS_ Overall Survival

End point description:

Overall survival is measured from the date of enrollment to the date of death from any cause.

End point type	Secondary

End point timeframe:

At the end of study.

End point values	Arm of study	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months				
median (confidence interval 95%)				
TS negative	12.270 (2.136 to 22.404)	12.270 (2.136 to 22.404)		
TS positivie	8.400 (0.473 to 16.327)	8.400 (0.473 to 16.327)		
Global	11.270 (5.351 to 17.189)	11.270 (5.351 to 17.189)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV).

Adverse event reporting additional description:

Common terminology criteria for adverse events was used in this study (NCI CTCAE version 3.0). Consistent with EudraCT disclosure specifications, GECP has reported under the SAE field "number of deaths resulting from AE" 0 deaths, because there are not deemed to be causally related to treatment by the investigator. In total were 9 exitus.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Subjects per protocol

Reporting group description: -

Serious adverse events	Subjects per protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 52 (48.08%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Vascular disorders			
Lower member embolism			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stroke ischemic and pneumonia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute ischemia of lower limbs			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pulmonary thromboembolism			

subjects affected / exposed	4 / 52 (7.69%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Disorientation and loss motor control			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Hemoglobin	Additional description: Grade III		
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leukocytes (total WBC)	Additional description: Grade III		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophils/granulocytes (ANC/AGC)	Additional description: Grade III		
subjects affected / exposed	5 / 52 (9.62%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue	Additional description: Grade III		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyporexia	Additional description: grade III		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea and vomiting			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pain	Additional description: Poorly controlled pain		
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Anorexy			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Mucositis	Additional description: grade III		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea and fever			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal bleeding			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Grade III		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Impaired function renal	Additional description: Grade III		

subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary infection	Additional description: Before starting chemotherapy		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Oliguria	Additional description: Swelling abdominal and face.		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
General stiffness			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis	Additional description: Grade III		
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bilateral bronchopneumonia			
subjects affected / exposed	1 / 52 (1.92%)		
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	Subjects per protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 52 (76.92%)		
Nervous system disorders			

Neurotoxicity sensitive subjects affected / exposed occurrences (all)	8 / 52 (15.38%) 8		
Blood and lymphatic system disorders Haemoglobin subjects affected / exposed occurrences (all) Leukocytes subjects affected / exposed occurrences (all) Neutrophils subjects affected / exposed occurrences (all) Platelets subjects affected / exposed occurrences (all) Edema subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all)	 40 / 52 (76.92%) 40 20 / 52 (38.46%) 20 14 / 52 (26.92%) 14 6 / 52 (11.54%) 6 3 / 52 (5.77%) 3 2 / 52 (3.85%) 2		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all)	 35 / 52 (67.31%) 35 1 / 52 (1.92%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1		
Ear and labyrinth disorders Ototoxicity			

subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 3 / 52 (5.77%) 3		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Mucositis subjects affected / exposed occurrences (all) Nausea-vomiting subjects affected / exposed occurrences (all)	 7 / 52 (13.46%) 7 4 / 52 (7.69%) 4 13 / 52 (25.00%) 13 12 / 52 (23.08%) 12 40 / 52 (76.92%) 40		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 5 / 52 (9.62%) 5		
Renal and urinary disorders Impaired function renal subjects affected / exposed occurrences (all)	 3 / 52 (5.77%) 3		
Endocrine disorders Increase AST/ALT subjects affected / exposed occurrences (all)	 7 / 52 (13.46%) 7		
Metabolism and nutrition disorders Hyporexia			

subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Increase GGT			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Hyperglycemia			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Hyperkalemia			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Hyponatremia			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
LDH increase			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		

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
26 February 2014	This study had a premature discontinuation due to the low recruitment rate of the study, not for safety reasons of the participants.	-

Notes:

Limitations and caveats

None reported