Clinical trial results:
Phase II trial of oral vinorelbine in Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (NSCLC) patients with Epidermal Growth Factor Receptor (EGFR) positive mutation after a failure to treatment with EGFR Tyrosine Kinase Inhibitors (TKI) in first line.

Summary

EudraCT number	2012-003361-18
Trial protocol	AT PL
Global end of trial date	17 April 2015

Results information

Result version number	v1 (current)
This version publication date	20 February 2019
First version publication date	20 February 2019

Trial information

Trial identification

Sponsor protocol code	PM0259CA229J1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Médicament
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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	15 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the disease control rate (CR, PR, SD) of oral vinorelbine as a single agent in patients with lung cancer and a EGFR positive mutation, previously treated with tyrosine kinase inhibitor.

Protection of trial subjects:

The study was conducted according to Good Clinical Practice (GCP) (CPMP/ICH/135/95), the principles stated in the Declaration of Helsinki (1964) and its subsequent amendments thereto, and national regulations. The request for authorization by the Competent Authority or its notification (depending on National Regulations) was carried out by the Sponsor. The study protocol and related documents, including the informed consent forms (ICFs), were submitted for approval to independent, local or national Independent Ethics Committees (IECs) and to competent authorities (CAs) before the study set-up, according to national regulations.

Background therapy:

Oral vinorelbine is a drug with moderate emetogenic risk (emetic risk: 30-90 %). Anti-emetic prophylaxis with oral 5-HT3 antagonists was recommended from the first cycle before each oral vinorelbine intake. The use of corticosteroids as antiemetic was also allowed. Patients had to receive full supportive care including antibiotics, anti-diarrhoeals, analgesics, transfusion of blood products, when appropriate. The use of drugs with laxative properties had to be avoided.

Evidence for comparator:

No control arm was planned as the study aimed at evaluating the efficacy of oral vinorelbine as a proof of concept in this selected population of patients.

Actual start date of recruitment	01 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Singapore: 8
Worldwide total number of subjects	30
EEA total number of subjects	22

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	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was planned in a total of 55 patients with locally advanced or metastatic EGFR mutation positive NSCLC after failure to 1st line EGFR-TKI therapy and with at least 1 measurable disease . A 2nd cohort was opened to include patients with asymptomatic brain metastases incidentally found during screening process (no local treatment needed).

Pre-assignment

Screening details:

Due to a slow recruitment, the Sponsor decided to halt permanently recruitment of patients into the study and terminate the study. Only a total of 30 patients were enrolled, all were eligible and received at least one dose of study treatment.

Period 1

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

Arms

Arm title	ITT Population

Arm description:

A total of 30 patients were enrolled, all were eligible and received at least one dose of study treatment.

Arm type	Experimental
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	Navelbine
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral Vinorelbine was given at 60mg/m2 weekly, for cycle 1, then 80 mg/ m2 weekly for subsequent cycles according to haematological tolerance (a cycle is a treatment period between 3 administrations of weekly oral vinorelbine on day 1, day 8 and day 15). The study treatment was to be continued at least 4 cycles unless documented disease progression, unacceptable toxicity or patient’s refusal. This treatment regimen is within the frame of the market authorization of oral Vinorelbine.

Number of subjects in period 1	ITT Population
Started	30
Completed	0
Not completed	30
Drug related toxicity	2
Investigator decision (no further benefit expected	1
Drug administration delay	1
Non-drug related toxicity	3
Patient's decision to stop	3
Documented progressive disease (radiological)	20

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	18	18	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	67.8		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	14	14	
Comorbidities Units: Subjects			
<2	20	20	
≥2	10	10	
Smoking History Units: Subjects			
Never smoked	16	16	
Stopped smoking < 10 years	6	6	
Stopped smoking ≥ 10 years	8	8	
Primary tumor (histological type) Units: Subjects			
Adenocarcinoma	29	29	
Giant cell carcinoma	1	1	
Number of metastatic sites at study entry2 Units: Subjects			
Zero	2	2	
One	9	9	
Two	9	9	
Three	6	6	
Four	4	4	
Prior surgery Units: Subjects			
Yes	7	7	
No	23	23	
Prior radiotherapy Units: Subjects			
Yes	13	13	

No	17	17	
Prior EGFR targeted therapy Units: Subjects			
Gefitinib	22	22	
Erlotinib	5	5	
Afatinib	3	3	
TNM staging at initial diagnosis Units: Subjects			
IA	1	1	
IB	1	1	
IIIA	1	1	
IIIB	4	4	
IV	23	23	
Best response to prior EGFR-TKI Units: Subjects			
Partial Response (PR)	1	1	
Complete Response (CR)	16	16	
Stable Disease (SD)	10	10	
Progressive Disease (PD)	2	2	
Non -evaluable (NE)	1	1	
Karnofsky Performance Status Units: percentage			
arithmetic mean	89.0		
standard deviation	± 8.4	-	
Delay between diagnosis and study entry Units: months			
median	12.6		
full range (min-max)	3.6 to 58.5	-	

End points

End points reporting groups

Reporting group title	ITT Population

Reporting group description:

A total of 30 patients were enrolled, all were eligible and received at least one dose of study treatment.

Primary: Disease control rate (DCR)

End point title	Disease control rate (DCR)[1]

End point description:

DCR was defined as by Recist v1.1 (CR+PR+SD) rates in the ITT population (all registered and treated patients) with 95% CI calculated following the exact method. Overall, in the ITT population, two PR (N=2/30), one PR not confirmed (SD), and 16 SD were achieved, yielding a DCR of 63.3% [95%CI: 43.8-80.1].

End point type	Primary

End point timeframe:

Tumor assessment was performed at baseline, then every 6 weeks according to RECIST v1.1 until progressive disease documented by the investigator.

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 analysis has been specified because the studu is a single-arm study

End point values	ITT Population			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: pourcentage				
number (confidence interval 95%)	63.3 (43.8 to 80.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

End point title	Overall response rate

End point description:

Overall Response rate (ORR) was defined as the sum of CR and PR (using the best confirmed response recorded from the date of randomisation to the end of treatment) in the ITT population. There were 2 confirmed PR (N=2/30), and 1 not confirmed PR, yielding an ORR of 6.7%.

End point type	Secondary

End point timeframe:

Overall Response rate (ORR) was evaluated at specified timelines (every 6 weeks until the end of study) in the ITT population by the investigator.

End point values	ITT Population			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: patients				
PD	11			
SD <24 weeks	9			
SD 24 weeks	7			
PR confirmed	2			
PR not confirmed	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control

End point title	Duration of disease control

End point description:

The disease control rate (sum of confirmed CR, confirmed PR and stabilisation rate) was evaluated for the ITT population using Kaplan Meier curves and Confidence intervals on the median duration of disease control were calculated using the reflected method. Patients who were lost to follow-up without progression, or have reached the
time point of analysis without a known record of progression or death had the duration of disease control censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occured last. Patients who received a new anti-tumoral treatment, whatever the type of treatment, before their disease progression were censored at the start date of this new anti-tumoral treatment.

End point type	Secondary

End point timeframe:

The duration of disease control (CR, PR and stabilization of at least 3 months) was measured from the date of registration until the criteria for disease progression is met or the date of death or start of new anticancer therapy.

End point values	ITT Population			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: months				
arithmetic mean (full range (min-max))	5.4 (3.3 to 9.5)			

Attachments (see zip file)	KM curve of the Duration of Disease Control/Kaplan Meier DDC.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease

End point title	Duration of stable disease

End point description:

The duration of stable disease was estimated on the ITT population using Kaplan Meier curves and Confidence intervals on the median were calculated using the reflected method. Patients who were lost to follow-up without progression, or reach the time point of analysis without a known record of progression or death had the duration of disease control censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occur last. Patients who received a new anti-tumoral treatment, whatever the type of treatment, before their disease progression were censored at the start date of this new anti-tumoral treatment.

End point type	Secondary

End point timeframe:

The duration of stable disease was measured from the date of registration until the criteria for disease progression was met or the date of death (whatever the reason of of death) or start of new anticancer therapy.

End point values	ITT Population			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: months				
arithmetic mean (full range (min-max))	5.0 (3.3 to 9.5)			

Attachments (see zip file)	Kaplan Meier Stable disease/Kaplan Meier SD.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Analyses of Overall Survival were performed with the Kaplan-Meier method. At the time of data base lock, a total of 24/30 (80%) patients died, all due to disease progression, 4/30 (13.3%) patients were still alive and 2/30 (6.7) patients were lost to follow-up. Overall survival of patients lost to follow-up or without a known record of death was censored at the date of last news.

End point type	Secondary

End point timeframe:

Overall survival was evaluated from the date of registration to the date of death due to any cause in the ITT population.

End point values	ITT Population			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: months				
median (full range (min-max))	13.1 (6.1 to 15.8)			

Attachments (see zip file)	Kaplan - Meier Survival time in months /Kaplan Meier OS.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each patient was assessed for occurrence of AEs throughout the study period. At the time of the database lock, all patients discontinued study treatment, 24/30 patients died due to disease progression, 4 patients were still alive and 2 were lost to FUP.

Adverse event reporting additional description:

A total of 166 cycles were administered for a mean number of cycles of 5.5 (± 5.2), with one third (33.3%) of the patients having received at least 6 cycles of the study medication. Approximately one fifth (23.3%) of the patients received > 90% of the planned dose of oral vinorelbine. The median relative dose intensity was 77.6% [range:46.8-105.0].

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 30 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3.3 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 30 (93.33%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	19 / 30 (63.33%)		
occurrences (all)	41		
Pyrexia			

subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Dysphonia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pleuritic pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	6		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	14		
Investigations			
Weight decreased			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			

Femoral neck fracture subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Nervous system disorders Amnesia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Peripheral motor neuropathy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 2 / 30 (6.67%) 2 3 / 30 (10.00%) 3 1 / 30 (3.33%) 1 1 / 30 (3.33%) 2 4 / 30 (13.33%) 17		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 26 / 30 (86.67%) 102 3 / 30 (10.00%) 3 1 / 30 (3.33%) 1		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) Vertigo	 1 / 30 (3.33%) 2		

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	15		
Diarrhoea			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	15		
Dry mouth			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Gastrointestinal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	10 / 30 (33.33%)		
occurrences (all)	17		
Pancreatic cyst			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Stomatitis			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2 11 / 30 (36.67%) 12		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 3 / 30 (10.00%) 23 1 / 30 (3.33%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) bone pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Osteoporosis subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2 2 / 30 (6.67%) 2 8 / 30 (26.67%) 21 2 / 30 (6.67%) 13 1 / 30 (3.33%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Urinary tract infection	 2 / 30 (6.67%) 2 1 / 30 (3.33%) 1		

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Gout subjects affected / exposed occurrences (all)	 9 / 30 (30.00%) 30 1 / 30 (3.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2013	Local requirement for performing pregnancy tests to all women of childbearing potential on a regular basis throughout the treatment period (every cycles) Not implemented –Country abandoned (Refusal of study in Dec ,13 by ANMAT Competent Authorities)
28 March 2014	Inclusion of patients with brain metastases (if asymptomatic and steroid free) in a new cohort of 55 patients Wash out period of 2 weeks for patients previously treated with an approved EGFR-TKI in the frame of a clinical trial, instead of 4 weeks; 2 weeks interval from radiotherapy before starting with oral vinorelbine, instead of 4 weeks. Prolongation of inclusion until Q1 2015

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported