Clinical trial results:
Double blind randomized phase III study of maintenance Pazopanib versus placebo in NSCLC patients non progressive after first line chemotherapy. MAPPING, an EORTC Lung group study.

Summary

EudraCT number	2010-018566-23
Trial protocol	BE NL DE GB GR SI
Global end of trial date	26 June 2015

Results information

Result version number	v1 (current)
This version publication date	30 July 2016
First version publication date	30 July 2016
Summary attachment (see zip file)	Summary 08092 (Summary-08092.docx)

Trial information

Trial identification

Sponsor protocol code	08092

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01208064
WHO universal trial number (UTN)	-
Other trial identifiers	MAPPING: 08092

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11 , Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 February 2014
Global end of trial reached?	Yes
Global end of trial date	26 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the therapeutic benefit of maintenance pazopanib versus placebo after first-line treatment for Non-Small Cell Lung Cancer (NSCLC).

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP).
The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

The small molecule VEGFR inhibitor, pazopanib is in clinical development in the treatment of a variety of human cancers. Pazopanib (GW786034) is an orally active, multi-target tyrosine kinase inhibitor (TKI) with a potent and selective in vitro activity against VEGF receptor (VEGF receptor-1, -2, and -3), platelet-derived growth factor (PDGF) receptor-α and -β, and stem cell factor receptor (CD-117 or c-Kit ligand). In pre-clinical angiogenesis models, pazopanib inhibited VEGF-dependent angiogenesis in a dose-dependent manner. In xenograft tumor models, twice-daily administration of pazopanib significantly inhibited tumor growth in mice implanted with various human tumor cells. By targeting a wide range of tyrosine kinases both in the vasculature and stroma, pazopanib has the potential to be effective in lung cancer. Proof of concept has been established for pazopanib monotherapy in early stage NSCLC (ELCAP study; VEG105290) where 30 out of 35 (86%) patients achieved a reduction in tumor volume after pazopanib preoperative treatment. Pazopanib has now been approved by the U.S. Food and Drug Administration FDA for the treatment of patients with advanced renal cell carcinoma (NDA number 022465).

Approximately 3000 subjects with cancer have been enrolled in clinical studies of pazopanib as of 09 September 2009. Data collected to date show that oral pazopanib is absorbed after administration and that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings.

Evidence for comparator:

While pemetrexed and erlotinib have demonstrated efficacy as maintenance therapy they are not considered standard of care in the general NSCLC patient population. Currently there is no standard treatment in the broad NSCLC population (squamous and non-squamous histologies) in the maintenance setting. Consequently, placebo is considered an appropriate comparator for Phase III.

Actual start date of recruitment	18 July 2011
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	Netherlands: 4
Country: Number of subjects enrolled	Slovenia: 10
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Egypt: 13
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	102
EEA total number of subjects	89

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)	54
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient recruited on 18 July, 2011
Last patient recruited on 25 October, 2013

Pre-assignment

Screening details:

- Stage IIIB- IV (as per TNM version VII) newly diagnosed or recurrent NSCLC (after surgery or radical radiotherapy) proven on cytology or histology before induction chemotherapy
- Patients must not have progressed during the four to six cycles of initial chemotherapy
(all the selection criteria are given in the summary attachment)

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To blind the treatment allocation after the randomization procedure, the EORTC Headquarters uses the concept of “treatment box”. The drugs are packed in "boxes" displaying only a code. The program used for registering patients and running the minimization algorithm is identical to the one used for open label studies. A box containing the allocated treatment available at the institution is subsequently identified, and its code is displayed by the randomization program.

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Pazopanib

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	GW786034B
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The investigational product, pazopanib monohydrochloride salt (coded as GW786034B) tablets is provided as 200 mg tablets.

Pazopanib treatment is starting at 600mg for 2 weeks then increasing to 800 mg daily till disease progression, unacceptable toxicity, best patient interest or patient refusal

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets matching the 200 mg pazopanib tablets will be used for the study as control and will be given daily till disease progression, unacceptable toxicity, best patient interest or patient refusal

Number of subjects in period 1	Maintenance Pazopanib	Placebo
Started	50	52
Started allocated treatment	50	50
Completed	45	50
Not completed	5	2
still on treatment by the time of final analysis	5	-
Treatment never started	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Maintenance Pazopanib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Maintenance Pazopanib	Placebo	Total
Number of subjects	50	52	102
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	27	54
From 65-84 years	23	25	48
85 years and over	0	0	0
Age continuous Units: years			
median	64.2	64.6	
full range (min-max)	28.4 to 81.1	25.9 to 80.7	-
Gender categorical			
Collected at baseline			
Units: Subjects			
Female	29	27	56
Male	21	25	46
Histology			
Stratification factor			
Units: Subjects			
squamous	9	11	20
non-squamous	41	41	82
Tobacco Use Units: Subjects			
Never	11	10	21
Past	26	35	61
Current	11	4	15
Missing	2	3	5
Prior Surgery			
Did the patient previously undergo surgery for NSCLC?			
Units: Subjects			
no	42	49	91
yes	8	3	11
Prior Radiotherapy			

Did the patient receive prior radiotherapy			
Units: Subjects			
no	43	44	87
yes, palliative radiotherapy	6	6	12
yes, radical radiotherapy	1	1	2
both radical and palliative	0	1	1
Performance Status			
Stratification factor			
Units: Subjects			
PS 0	18	11	29
PS 1	32	39	71
PS 2	0	2	2
Response after the last cycle of induction therapy			
Stratification factor			
Units: Subjects			
Partial response	16	14	30
Stable disease	34	38	72

End points

End points reporting groups

Reporting group title	Maintenance Pazopanib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is measured from the time between the date of randomization and the date of death. Patients who are still alive when last traced are censored at the date of last follow-up.

End point type	Primary

End point timeframe:

Overall survival rate at 1 year

End point values	Maintenance Pazopanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Percentages				
number (confidence interval 95%)	57.2 (41.2 to 70.3)	51.2 (34.2 to 65.9)		

Attachments (see zip file)	OS 08092/OS-08092.jpg

Statistical analyses

Statistical analysis title	OS comparison in ITT population

Statistical analysis description:

Comparison of overall survival maintenance pazopanib versus placebo in intent-to-treat (ITT) population (all randomized patient according to allocated treatment) and adjusted by stratification factors (histology, performance status, response after the last cycle of induction therapy).

Comparison groups	Maintenance Pazopanib v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.28

Notes:

[1] - OS was the primary endpoint, yet at the interim analysis, decision to continue was based on the Progression Free Survival (PFS)

[2] - Adjusted by stratification factors. Out of 3 stratification factors only Histology and Response after the last cycle of induction therapy were used in the adjustment. PS status (0/1 vs. 2) was not used since only 2 patients had PS=2

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression free survival is defined as the time between the date of randomization after completion of induction chemotherapy and the date of disease progression or death.

End point type	Secondary

End point timeframe:

Median progression-free survival

End point values	Maintenance Pazopanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Months				
median (confidence interval 95%)	4.3 (2.99 to 7.43)	3.22 (2.07 to 5.09)		

Attachments (see zip file)	PFS-08092/PFS-08092.jpg

Statistical analyses

Statistical analysis title	PFS comparison in ITT population

Statistical analysis description:

Comparison of progression-free survival of maintenance pazopanib versus placebo in intent-to-treat (ITT) population (all randomized patient according to allocated treatment) and adjusted by stratification factors (histology, performance status, response after the last cycle of induction therapy).

Comparison groups	Maintenance Pazopanib v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [3]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.03

Notes:

[3] - Adjusted by stratification factors. Out of 3 stratification factors only Histology and Response after the last cycle of induction therapy were used in the adjustment. PS status (0/1 vs. 2) was not used since only 2 patients had PS=2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on a CRF to be submitted at pre-specified timepoint : prior to maintenance, after 2 weeks of maintenance, during maintenance every 4 weeks, at the end of maintenance

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (1% of AEs are reported as "other" and are not reported as not available from the list of SOC).
AEs are evaluated using CTC v4, SAEs using MedDra. Non-SAEs has not been collected specifically, therefore all AEs (any grade) will be reported in non-SAE section.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Maintenance Pazopanib

Reporting group description:

Safety population: patients who started maintenance Pazopanib

Reporting group title	Placebo

Reporting group description:

Safety population: patients who started placebo

Serious adverse events	Maintenance Pazopanib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 50 (24.00%)	5 / 50 (10.00%)	
number of deaths (all causes)	20	26	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased	Additional description: From pharmacovigilance database		
subjects affected / exposed	2 / 50 (4.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased	Additional description: From pharmacovigilance database		
subjects affected / exposed	2 / 50 (4.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant	Additional description: From pharmacovigilance database		

subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertension	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: From pharmacovigilance database		

subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: From pharmacovigilance database		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: From pharmacovigilance database		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia	Additional description: From pharmacovigilance database		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection	Additional description: From pharmacovigilance database		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: From pharmacovigilance database		
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Tracheobronchitis	Additional description: From pharmacovigilance database		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Varicella	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia	Additional description: From pharmacovigilance database		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Maintenance Pazopanib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 50 (98.00%)	49 / 50 (98.00%)	
Vascular disorders			
Hypertension	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	40 / 50 (80.00%)	30 / 50 (60.00%)	
occurrences (all)	230	109	
Thromboembolic event	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 50 (14.00%)	4 / 50 (8.00%)	
occurrences (all)	21	6	
General disorders and administration site conditions			

Fatigue	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	33 / 50 (66.00%)	24 / 50 (48.00%)	
occurrences (all)	171	86	
Fever	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Non cardiac chest pain	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 50 (24.00%)	6 / 50 (12.00%)	
occurrences (all)	29	21	
Other GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 50 (18.00%)	8 / 50 (16.00%)	
occurrences (all)	35	21	
Reproductive system and breast disorders			
Other REPRODUCTIVE SYSTEM AND BREAST DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	
occurrences (all)	6	3	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	15 / 50 (30.00%)	15 / 50 (30.00%)	
occurrences (all)	57	50	
Dyspnea	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	15 / 50 (30.00%)	15 / 50 (30.00%)	
occurrences (all)	69	47	
Other RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	14 / 50 (28.00%)	12 / 50 (24.00%)	
occurrences (all)	51	42	
Pleural effusion	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)	2 / 50 (4.00%)	
occurrences (all)	3	7	
Psychiatric disorders			
Other PSYCHIATRIC DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 50 (12.00%)	5 / 50 (10.00%)	
occurrences (all)	26	7	
Investigations			
Electrocardiogram	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 50 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Other INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Cardiac disorders			
Heart failure	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Myocardial infarction	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)	0 / 50 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	6 / 50 (12.00%)	3 / 50 (6.00%)	
occurrences (all)	19	7	
Other NERVOUS SYSTEM DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	14 / 50 (28.00%)	6 / 50 (12.00%)	
occurrences (all)	57	15	
Peripheral motor neuropathy	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 50 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	5	
Peripheral sensory neuropathy	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	13 / 50 (26.00%)	9 / 50 (18.00%)	
occurrences (all)	71	35	
Ear and labyrinth disorders			
Other EAR AND LABYRINTH DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 50 (8.00%)	4 / 50 (8.00%)	
occurrences (all)	13	11	
Eye disorders			
Other EYE DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 50 (14.00%)	5 / 50 (10.00%)	
occurrences (all)	41	14	
Gastrointestinal disorders			
Abdominal pain	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	11 / 50 (22.00%)	6 / 50 (12.00%)	
occurrences (all)	25	11	
Diarrhea	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	24 / 50 (48.00%)	6 / 50 (12.00%)	
occurrences (all)	133	12	

Nausea	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	20 / 50 (40.00%)	13 / 50 (26.00%)	
occurrences (all)	56	35	
Other GASTROINTESTINAL DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	19 / 50 (38.00%)	15 / 50 (30.00%)	
occurrences (all)	103	76	
Vomiting	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 50 (24.00%)	9 / 50 (18.00%)	
occurrences (all)	25	18	
Skin and subcutaneous tissue disorders			
Other SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	20 / 50 (40.00%)	16 / 50 (32.00%)	
occurrences (all)	177	57	
Rash	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 50 (14.00%)	8 / 50 (16.00%)	
occurrences (all)	30	18	
Renal and urinary disorders			
Other RENAL AND URINARY DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 50 (8.00%)	1 / 50 (2.00%)	
occurrences (all)	10	4	
Endocrine disorders			
Other ENDOCRINE DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			

Other MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	20 / 50 (40.00%)	14 / 50 (28.00%)	
occurrences (all)	125	54	
Infections and infestations			
Other INFECTIONS AND INFESTATIONS	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 50 (24.00%)	16 / 50 (32.00%)	
occurrences (all)	24	34	
Metabolism and nutrition disorders			
Anorexia	Additional description: From clinical database: all clinical adverse events (any grade)		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	20 / 50 (40.00%)	12 / 50 (24.00%)	
occurrences (all)	103	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2012	The main rationale for this amendment is to update the protocol according to the comments received by the French Competent Authorities. This amendment has been discussed and agreed by the EORTC lung Group and the EORTC HQ. The comments made by the French authorities in their letter dated April 24, 2011 do not stop protocol for being activated but do request that the protocol be upgraded. The changes are not considered as altering profoundly the protocol and could be beneficial in any case to the whole protocol. The French authorities basically required additional safety checks at the time of dose increase and an additional visit has been introduced. Inclusion criteria do now request normal potassium and additional checks are inserted for QTc surveillance. A list of agents potentially interfering with QTc was provided. Several protocol timeframes were difficult to meet. There was an agreement to include protocol modifications making the timelines more close to clinical reality such as tumor assessment/documentation of non-progression and maintenance treatment start. We clarified that no confirmation CT/MRI is required and clarified the time window allowed for maintenance treatment initiation. The IB was also updated to version 9, as well as the Patient Information Sheet/Informed Consent to version 3.0.
24 September 2012	The following changes have been made to the protocol: • Some timelines have been modified so they are closer to clinical reality e.g. time interval from start of adjuvant treatment to induction chemotherapy for metastatic disease, and time interval from radical RT to initiation of chemotherapy for metastatic disease. • Clarification that concomitant treatment with statins is acceptable • Clarifications regarding other concomitant medication • New translational objective added (circulating tumour cell analysis). The following changes have been made to the PIS/IC: • Updated to include details of Circulating Tumor Cells (CTC) analysis.
23 April 2014	Updated Investigator's Brochure for the IMP Pazopanib (version 11, dated January 2014). The changes to this document have been assessed and it was concluded that a protocol amendment is not required, as the safety of participants and the risk-benefit assessment of the study has not been altered.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

06 August 2013	Temporary halt of the trial. The EORTC was informed on 21 December 2012 by GSK of their intention to withdraw their support to the study because of insufficient efficacy and/or poor tolerability of Pazopanib in lung cancer patients, and that accrual was considerably behind target. After discussions it was agreed that the study should remain open until 102 patients have been recruited or 53 events have been reported, and that an interim analysis should be performed to assess the future of the trial based on strong and reliable scientific evidence. The agreed target of 102 patients was reached on 06 August 2013 and all investigators have been notified that recruitment was on-hold. 25 October 2013: Decision to stop recruitment permanently. An Interim Analysis has been performed and the results have been reviewed by the EORTC IDMC. The Interim Analysis plan was conducted according to a modified futility test revised this year, towards a stringent futility stopping rule, due to emerging evidence from other Non-Small Cell Lung Cancer (NSCLC) pazopanib studies. Those studies were closed for various reasons, among others: poor recruitment, excess of toxicity, insufficient treatment adherence and efficacy. In addition, studies testing other tyrosine kinase inhibitors in NSCLC have shown there was no benefit for patients. Based on the data available in the current study, the IDMC has recommended stopping the trial since the efficacy results for the primary endpoint fulfill the extreme stopping rule for futility specified in the revised interim analysis plan. Moreover data have indicated that the adherence to the planned dosing of the experimental treatment beyond week 2 was rather poor. EORTC has accepted these recommendations and all investigators have been informed. As recruitment was stopped prematurely the trial never reached the End of Trial defined in the protocol. Therefore, the last patient’s last treatment was considered as the EoT.	-

Notes:

Limitations and caveats

None reported