



Clinical trial results:

A study to select rational therapeutics based on the analysis of matched tumor and normal biopsies in subjects with advanced malignancies

Summary

EudraCT number	2013-000914-38
Trial protocol	ES
Global end of trial date	31 December 2015

Results information

Result version number	v1 (current)
This version publication date	13 November 2021
First version publication date	13 November 2021

Trial information

Trial identification

Sponsor protocol code	WINTHER
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01856296
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, +34 934894779, joaquin.lopez.soriano@vhir.org
Scientific contact	Clinical Trials Office, Vall d'Hebron Institute of Oncology (VHIO), +34 9327460004922, gsala@vhio.net

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	31 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the individual outcome of patients with advanced malignancies, by comparing the progression-free survival (PFS) using a treatment regimen selected by a molecular analysis of a patient's tumor with the PFS for the most recent regimen on which the patient had experienced progression

- ARM A : PFS2/PFS1 >1.5 in 50% of patients
- ARM B : PFS2/PFS1 >1.5 in 40% of patients

Protection of trial subjects:

Patients had a fresh biopsy of tumor and corresponding normal tissue after they enrolled in the study, and these biopsies were used for the genomic and transcriptomic assays, which determined the treatment

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
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	Spain: 60
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	France: 20
Worldwide total number of subjects	107
EEA total number of subjects	80

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)	80
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were accrued at four centers located in four countries: Spain, Israel, France and Canada, from April 2013 to December 2015. Patients had advanced cancers that had progressed on standard treatment.

Pre-assignment

Screening details:

Consented patients underwent a dual biopsy from the metastasis and from the histologically matched normal tissue

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

Arms

Are arms mutually exclusive?	Yes
Arm title	DNA screening

Arm description:

Tumor specimens collected for tissue NGS analysis were sent directly to Foundation Medicine. The FoundationOne genomic assay (<http://www.foundationone.com/>) (Clinical Laboratory Improvement Assessment-approved standards) assessed genetic alterations from the entire coding sequence of 236 cancer-related genes, plus rearrangements found in introns of an additional 28 cancer-related genes. Equivocal amplification in this assay refers to copy number 6 or 7, whereas amplification means copy number ≥ 8 (except for ERBB2, for which equivocal amplification means copy number 5 or 6 and amplification means copy number ≥ 7). To be reported by the FoundationOne assay, specific alterations must have been identifiable in at least 10% of tumor DNA and a sequencing coverage of 500 x

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	ERBB2 antibody
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Depending on patient and center

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

Dosage and administration details:

Depending of patient and center

Arm title	RNA screening
------------------	---------------

Arm description:

All patients included in the study, whatever the status of their DNA analysis, had an analysis of their transcriptome attempted. But, per protocol, the transcriptomic information was only considered for navigation to a therapy in cases that had no match found or therapy available per arm A (DNA). The drug selection in arm B is based on the biological characteristics of the tumor of the individual to be treated in comparison to a normal sample from the same individual. Based on a score calculated (examining deregulated target genes), the match between genes deregulated to a literature-derived knowledge base of gene-drug-directed connections, the relative efficacy of the drugs was predicted for

the individual.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	ERBB2 antibody
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Depending on patient and center

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

Dosage and administration details:

Depending of patient and center

Number of subjects in period 1	DNA screening	RNA screening
Started	69	38
Completed	69	38

Baseline characteristics

End points

End points reporting groups

Reporting group title	DNA screening
-----------------------	---------------

Reporting group description:

Tumor specimens collected for tissue NGS analysis were sent directly to Foundation Medicine. The FoundationOne genomic assay (<http://www.foundationone.com/>) (Clinical Laboratory Improvement Assessment-approved standards) assessed genetic alterations from the entire coding sequence of 236 cancer-related genes, plus rearrangements found in introns of an additional 28 cancer-related genes. Equivocal amplification in this assay refers to copy number 6 or 7, whereas amplification means copy number ≥ 8 (except for ERBB2, for which equivocal amplification means copy number 5 or 6 and amplification means copy number ≥ 7). To be reported by the FoundationOne assay, specific alterations must have been identifiable in at least 10% of tumor DNA and a sequencing coverage of 500 ×

Reporting group title	RNA screening
-----------------------	---------------

Reporting group description:

All patients included in the study, whatever the status of their DNA analysis, had an analysis of their transcriptome attempted. But, per protocol, the transcriptomic information was only considered for navigation to a therapy in cases that had no match found or therapy available per arm A (DNA). The drug selection in arm B is based on the biological characteristics of the tumor of the individual to be treated in comparison to a normal sample from the same individual. Based on a score calculated (examining deregulated target genes), the match between genes deregulated to a literature-derived knowledge base of gene-drug-directed connections, the relative efficacy of the drugs was predicted for the individual.

Primary: PFS2/PFS1>1.5

End point title	PFS2/PFS1>1.5
-----------------	---------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

End of study

End point values	DNA screening	RNA screening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	38		
Units: percent				
number (confidence interval 5%)	20.3 (11.6 to 31.7)	26.3 (13.4 to 43.1)		

Statistical analyses

Statistical analysis title	PFS2/PFS1 > 1.5
----------------------------	-----------------

Comparison groups	DNA screening v RNA screening
-------------------	-------------------------------

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.48
Method	Fisher exact

Secondary: Median PFS

End point title	Median PFS
End point description:	
End point type	Secondary
End point timeframe:	
All the study	

End point values	DNA screening	RNA screening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	38		
Units: month				
number (not applicable)	2.01	1.94		

Statistical analyses

No statistical analyses for this end point

Secondary: Stable Disease

End point title	Stable Disease
End point description:	
End point type	Secondary
End point timeframe:	
All the study	

End point values	DNA screening	RNA screening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	38		
Units: month				
number (not applicable)	16	12		

Statistical analyses

Statistical analysis title	Stable Disease
Comparison groups	DNA screening v RNA screening
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.37
Method	Fisher exact

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

End of study

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	22
--------------------	----

Reporting groups

Reporting group title	Spanish patients
-----------------------	------------------

Reporting group description:

Assay was only considered as a Clinical Trial in Spain. So only data are available in this country on adverse events.

No non-serious events were reported.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Given the status of patients, all the detected adverse events were considered as serious.

Serious adverse events	Spanish patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 60 (23.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolism			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Fever			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever without focus			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alveolar haemorrhage			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal insufficiency			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Femur fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Spanish patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Patients had heavily pretreated disease, which may have limited capacity for response. Number of patients per arm was small. Trial was not designed to compare arms. Participating centers were located over a wide geographical territory.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31011205>