Clinical trial results:
Nitroglycerin's effect on perfusion and hypoxia in human non small cell lung cancer: proof of principle, a phase II trial

Summary

EudraCT number	2010-023120-24
Trial protocol	NL
Global end of trial date	18 June 2018

Results information

Result version number	v1 (current)
This version publication date	12 April 2023
First version publication date	12 April 2023
Summary attachment (see zip file)	2010-023120-24 Result (2010-023120-24 Nitroglycerin's effect on perfusion and hypoxia in human non small cell lung cancer proof of principle, a phase II trial RESULT.pdf)

Trial information

Trial identification

Sponsor protocol code	Nitro1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01210378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Maastro
Sponsor organisation address	Dr. Tanslaan 29, Maastricht, Netherlands, 6229 ET
Public contact	Chantal Overhof, Maastro, 0031 884455863, chantal.overhof@maastro.nl
Scientific contact	Chantal Overhof, Maastro, 0031 884455863, chantal.overhof@maastro.nl

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 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2018
Global end of trial reached?	Yes
Global end of trial date	18 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate an absolute increase in 2 year overall survival of 15 % vs historical controls with a nitroglycerin patch by enhancement of tumor perfusion

Protection of trial subjects:

- Patient had a minimum of three days to think about participating in the trial;
- Independent physician, who can be consulted with questions;
- Annual safety reporting;
- Monitoring.

Background therapy:

Patients enrolled in the trial will be requested to undergo repeat scanning with perfusion CT (DCE-CT) scans and hypoxia PET-scans at 2 separate occasions before treatment start;

"Baseline" scans: 1 DCE-CT and 1 HX4-PET-scan

"Nitroglycerin" scans: 1 DCE-CT and 1 HX-4 PET-scan after administration of nitroglycerin

After the first 40 patients completing all scans, the subsequently included 20 patients will only be requested to undergo the baseline scans to evaluate the prognostic value of DCE-CT and hypoxia scanning.

The number of 40 patients is chosen to have a sample size which gives a flavour of the normal Gaussian distribution in our patient population.

Evidence for comparator:

If no clear improvement of the OS is observed compared to historical controls, there is no need to embark a more complex randomized phase II and subsequent phase III trial.

Actual start date of recruitment	01 December 2011
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	Netherlands: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	28
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the Netherlands, patients were included in the period from November 2011 until June 2016.
From 47 patients enrolled, 42 were eligible. Three patients withdrew their consent and 2 patients were included incorrectly.

Pre-assignment

Screening details:

Inclusion criteria:
- Non-small cell lung cancer stage IB-IV amenable for radiotherapy with curative intent.
- Patients not included in PET-boost trial
- WHO performance status 0-2
- Willing and able to comply with the study prescriptions
- 18 years or older

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Arm title	Nitroglycerin patch

Arm description:

Patient underwent repeated scans, before and after placing a nitroglycerin patch

Arm type	Experimental
Investigational medicinal product name	HX4
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Step I: 15ug HX-4
Step II: 27 ug HX-4

Number of subjects in period 1	Nitroglycerin patch
Started	42
Completed	42

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
From 47 patients enrolled, 42 were eligible	

Reporting group values	Overall trial	Total	
Number of subjects	42	42	
Age categorical			
Age (mean, range; years) 60 (36–82)			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	28	
From 65-84 years	14	14	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	24	24	
Age continuous			
Units: years			
median	61.14		
standard deviation	± 11.39	-	

End points

End points reporting groups

Reporting group title	Nitroglycerin patch
Reporting group description:	
Patient underwent repeated scans, before and after placing a nitroglycerin patch	

Primary: 2-year overall survival

End point title	2-year overall survival[1]
End point description:	
2-year overall survival	
End point type	Primary
End point timeframe:	
2-year overall survival	

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: As discussed with Sjennie Daelmans, as the study was prematurely ended and has only one group. The analysis is not possible/mandatory.

End point values	Nitroglycerin patch			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: mortality				
mortality	21			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
2 years	
Adverse event reporting additional description:	
Physician assessment of CTCAE 4.0, WHO performance status, weight, blood pressure before radiotherapy (RT), weekly during RT, one month after RT, every 3 months thereafter	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	all patients
Reporting group description:	
all patients	

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 42 (50.00%)		
number of deaths (all causes)	21		
number of deaths resulting from adverse events	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 42 (2.38%)		
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 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Epidermolysis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Herpes ophthalmic			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	all patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)		
Injury, poisoning and procedural complications			
Contrast media allergy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	6		
Memory impairment			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Sensory level abnormal			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Fever neonatal			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	16 / 42 (38.10%)		
occurrences (all)	22		
Rib fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Sight disability			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Appetite disorder			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	27 / 42 (64.29%)		
occurrences (all)	41		
Nausea			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 42 (57.14%)		
occurrences (all)	32		
dyspnea			
subjects affected / exposed	25 / 42 (59.52%)		
occurrences (all)	33		
Haemoptysis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Infections and infestations Cystitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2011	Logistical change (timpoint of the scans)
15 February 2012	Adding the HX-4 administration protocol to the study protocol
29 August 2012	Adaptation of the inclusion criteria and adding a voluntary scan
12 March 2014	Reduction of HX-4, reduction of scanning time, new IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32021913