



## Clinical trial results:

### Neoadjuvant IntraviTreal Ranibizumab treatment in high risk Ocular melanoma patients: A two stage single centre Phase II single arm study (NITRO Trial)

#### Summary

EudraCT number	2011-000961-10
Trial protocol	GB
Global end of trial date	29 October 2014

#### Results information

Result version number	v1 (current)
This version publication date	28 February 2019
First version publication date	28 February 2019

#### Trial information

##### Trial identification

Sponsor protocol code	NITRO Protocol
-----------------------	----------------

##### Additional study identifiers

ISRCTN number	ISRCTN35236442
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor (RLBUHT): 3921

Notes:

##### Sponsors

Sponsor organisation name	Royal Liverpool and Broadgreen Hospitals NHS Trust
Sponsor organisation address	Prescot Street, Liverpool, United Kingdom, L7 8XP
Public contact	Charlotte Rawcliffe, Liverpool Cancer Trials Unit, 0151 794 8167, C.Rawcliffe@liverpool.ac.uk
Scientific contact	Victoria Shaw, GCLP Labs, 0151 706 4180 , Victoria.Shaw@liverpool.ac.uk

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	17 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2014
Global end of trial reached?	Yes
Global end of trial date	29 October 2014
Was the trial ended prematurely?	Yes

Notes:

---

## General information about the trial

Main objective of the trial:

To determine the safety and efficacy (effectiveness) of intravitreal Ranibizumab, in the neoadjuvant (before surgery) setting, in high risk ocular melanoma patients.

Protection of trial subjects:

Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

Source data will be identified and documented in the NITRO Trial Monitoring Plan. Any data to be recorded directly on the CRFs (i.e. no prior electronic or written record of the data), is to be considered to be source data e.g. questionnaires.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial.

Background therapy: -

Evidence for comparator:

No previous clinical trial had been done in this tumour type and setting. It is not known how anti-VEGF treatment would influence uveal melanomas in vivo. Several preclinical studies suggested antiangiogenic therapies, incl. anti-VEGF targeted therapies, could have a significant clinical impact in ocular melanoma. e.g, Clark transplanted cells from the murine uveal melanoma cell line (99E1) into the right eye of athymic nude BALB/c mice, which were subsequently treated with topical anecortave acetate (an angiostatic agent that inhibits endothelial cell migration) for 28 days; tumour growth inhibition was achieved. In another study, Yang injected murine recombinant angiostatin (another endothelial cell inhibitor) into the posterior compartment of the eye of C57BL/6 using three murine ocular melanoma cell lines (Queens, B16F10 and B16LS9). That was followed by enucleation and several more adjuvant doses. The sizes of hepatic metastasis and apoptosis ratios were significantly decreased in treated mice. Kim also showed that potent VEGF blockade with VEGF-Trap caused regression of coopted vessels in a xenograft model of neuroblastoma. Holash used the same drug to treat mice implanted with several cell lines, which included a melanoma cell line (mouse B16F10.9 melanoma), to find largely avascular tumours after treatment. More recently, Chan used the tyrosine kinase inhibitor Sunitinib, which targets the VEGF receptor as well as c-kit in ten patients with metastatic uveal melanoma. One partial response was achieved and 7 patients had stable disease with a median duration of response of 3.9 months. On the basis of the above, we believe that by using the treatment window opportunity offered by the neoadjuvant period we can study the effects of angiogenesis inhibition in this rare and aggressive tumour type, collect useful clinical and pathological information before and after treatment, and perhaps offering the patients the possibility of eye and sight preserving treatments.

Actual start date of recruitment	01 December 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	United Kingdom: 7
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	3
From 65 to 84 years	4
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

7 patients were registered onto the study.

### Pre-assignment

Screening details:

Patients screened = 60

### Period 1

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

Blinding implementation details:

N/A

### Arms

Arm title	Ranibizumab
-----------	-------------

Arm description:

Ranibizumab

Arm type	Single arm
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	Ranibizumab
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Ranibizumab will be administered by intravitreal injection and must be administered by a qualified Ophthalmologist. Patients will receive an initial dose of 0.5mg in 0.05ml Ranibizumab as a single intravitreal injection. Patients then receive the same dose once monthly (subject to tumour assessment) for a maximum of 6 months.

Number of subjects in period 1	Ranibizumab
Started	7
Completed	0
Not completed	7
Consent withdrawn by subject	2
Lack of efficacy	5

## Baseline characteristics

### Reporting groups

Reporting group title	Ranibizumab
-----------------------	-------------

Reporting group description:
------------------------------

Ranibizumab
-------------

Reporting group values	Ranibizumab	Total	
Number of subjects	7	7	
Age categorical			
All patients must be 18 years or older			
Units: Subjects			
Adults (18-64 years)	3	3	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous			
Units: years			
median	66		
full range (min-max)	50 to 84	-	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	5	5	
WHO performance status			
WHO performance status at baseline. (0,1, or 2)			
Units: Subjects			
WHO 0	7	7	
WHO 1	0	0	
WHO 2	0	0	

### Subject analysis sets

Subject analysis set title	Full Analysis Set
----------------------------	-------------------

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:
-----------------------------------

All patients registered into the study
--

Reporting group values	Full Analysis Set		
Number of subjects	7		
Age categorical			
All patients must be 18 years or older			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median			

full range (min-max)			
----------------------	--	--	--

Gender categorical			
Units: Subjects			
Female			
Male			
WHO performance status			
WHO performance status at baseline. (0,1, or 2)			
Units: Subjects			
WHO 0	7		
WHO 1	0		
WHO 2	0		

## End points

### End points reporting groups

Reporting group title	Ranibizumab
Reporting group description:	
Ranibizumab	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients registered into the study	

### Primary: Overall response rate

End point title	Overall response rate
End point description:	
To determine response rate of intravitreal ranibizumab, in the neoadjuvant setting, in large primary ocular melanoma patients. The overall response rate is defined as: (Number achieving complete response + number achieving partial responses)/number evaluable for response at 3 months.	
This was to be presented with an exact 95% confidence interval. An exact one-sided test with significance level 0.05 was also to be carried out of the null-hypothesis that the response rate is less than 20%. However, conclusions about the trial will not be based solely on the results of this test and must take into account issues with recruitment.	
TSC minutes dated 06/11/13 confirmed that if a patient chose enucleation before reaching 3 months they were to be classed as having progressive disease.	
Because of poor recruitment the final analysis is performed on only 7 patients.	
End point type	Primary
End point timeframe:	
From registration to end of study	

End point values	Ranibizumab	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	7		
Units: Subjects				
CR	0	0		
PR	0	0		
SD	0	0		
PD	7	7		
Not Assessable	0	0		
Missing	0	0		

### Statistical analyses

Statistical analysis title	Estimation of complete response rate
Comparison groups	Ranibizumab v Full Analysis Set

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	< 0.05
Method	Estimation
Parameter estimate	percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	41
Variability estimate	Standard deviation

Notes:

[1] - Estimation of the complete response rate



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Whole trial

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

### Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4
--------------------	---

### Reporting groups

Reporting group title	Ranibizumab
-----------------------	-------------

Reporting group description:

Ranibizumab

Serious adverse events	Ranibizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Ranibizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)		
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vitreous haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Eye disorder	Additional description: Other		
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2013	Amendment 3 - Change in Chief Investigator from Professor Bertil Damato to Professor Heinrich Heinmann (Approval states Amendment 1)

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported