Clinical trial results:
A pilot study to assess the effect of regulatory T-cell depletion on 5T4-containing MVA(TroVax®)vaccination in patients with inoperable metastatic colorectal cancer

Summary

EudraCT number	2010-024380-41
Trial protocol	GB
Global end of trial date	23 June 2016

Results information

Result version number	v1 (current)
This version publication date	22 March 2019
First version publication date	22 March 2019

Trial information

Trial identification

Sponsor protocol code	SPON868-10

Additional study identifiers

ISRCTN number	ISRCTN54669986
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	MacKenzie House, Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Chris Shaw, Cardiff University, 44 (0)29 208 79130, shawc3@cardiff.ac.uk
Scientific contact	Andrew Godkin, Cardiff University, 44 (0)29 2068 7003, godkinaj@cardiff.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	23 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2015
Global end of trial reached?	Yes
Global end of trial date	23 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to investigate whether an immune cell population that acts against the clinical benefit of the patient (i.e. in favour of the development of cancer) can be specifically reduced. This would lead to enhanced anti-tumour immune responses observed, as it has already been observed in rodents.

The research question will be asked in patients with inoperable metastatic colorectal cancer.

Protection of trial subjects:

All subjects received the treatment in a side-room away from contact with other subjects

At regular intervals subjects were screened for the following safety parameters:
General physical examination (vital signs / heart / lungs / abdomen)
Full blood count
Urea and electrolytes
Liver function tests

Background therapy:

none

Evidence for comparator:

Colorectal cancer (CRC) is the second leading cause of death from cancer. Although early stages are often cured by surgical resection, the prognosis for patients with metastatic colorectal cancer (mCRC) is very poor, with a 5-year survival rate of 7%. More than 96% of patients with mCRC have microsatellite stable tumors that do not respond to current immunotherapies, possibly owing to decreased incidence of neoantigens. We hypothesized that in these patients, a well-targeted immune response against an up-regulated tumor antigen with minimal expression on healthy background tissues represents a potentially more effective therapy. One candidate is 5T4, a trophoblast glycoprotein with restricted expression to several human adenocarcinomas, including more than 90% of CRCs.7 Previous studies demonstrated that 5T4-specific interferon-γ–positive (IFN-γ+) T-cell responses correlate with tumor stage, providing protection against metastasis.
Herein, we sought to improve 5T4 immune responses in patients with mCRC through vaccination with an immunogenic, nonreplicating modified vaccinia Ankara–5T4 (MVA-5T4; TroVax; Oxford BioMedica, plc). This vaccine has demonstrated efficacy in preclinical models of colon cancer via the induction of humoral anti-5T4 responses. Early indications in mCRC demonstrated an excellent safety profile, with the induction of anti-5T4 responses correlating with disease control, thus warranting further studies in randomized clinical trials. Given that activation of the adaptive immune response may concurrently stimulate tumor-specific regulatory T (Treg) cells, we also sought to test the hypothesis that the effectiveness of cancer vaccines is improved by prior administration of a Treg-depleting agent. In low doses, cyclophosphamide has demonstrated numerous immune-potentiating effects, including the depletion and reduced functionality of Tregs. However, to date, low-dose metronomic cyclophosphamide treatment has not been evaluated in a randomized trial.

Actual start date of recruitment	09 July 2012
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: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	26
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From July 9, 2012, through February 8, 2016, 55 patients were recruited and randomized in a single center in the Clinical Research Facility, University Hospital of Wales, Cardiff.

Pre-assignment

Screening details:

55 patients were screened and all were randomised. One patient from group 3 withdrew consent before receiving the allocated intervention, and 1 patient each from groups 1 and 3 were later found to have undergone a curative procedure before enrolment.

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: watch and wait

Arm description:

watch and wait

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Group 2: cyclophosphamide only

Arm description:

cyclophosphamide only

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

Dosage and administration details:

Cyclophosphamide (Pharmacia Ltd) was orally administered in doses of 50 mg twice per day on treatment days 1 to 7 and 15 to 21 or until the patient experienced relapse

Arm title	Group 3: MVA-5T4 only

Arm description:

MVA-5T4

Arm type	Experimental
Investigational medicinal product name	MVA-5T4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

MVA-5T4 was administered in an intramuscular injection at a dose of 1 × 109 50% tissue culture infectious dose (TCID50) on treatment days 22, 36, 50, 64, 78, and 106.

Arm title	Group 4: cyclophosphamide and MVA-5T4
Arm description: cyclophosphamide and MVA-5T4	
Arm type	Experimental
Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Cyclophosphamide (Pharmacia Ltd) was orally administered in doses of 50 mg twice per day on treatment days 1 to 7 and 15 to 21 or until the patient experienced relapse	
Investigational medicinal product name	MVA-5T4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use
Dosage and administration details: MVA-5T4 was administered in an intramuscular injection at a dose of 1 × 109 50% tissue culture infectious dose (TCID50) on treatment days 22, 36, 50, 64, 78, and 106.	

Number of subjects in period 1	Group 1: watch and wait	Group 2: cyclophosphamide only	Group 3: MVA-5T4 only
Started	8	9	17
Completed	8	9	17

Number of subjects in period 1	Group 4: cyclophosphamide and MVA-5T4
Started	18
Completed	18

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: watch and wait
Reporting group description: watch and wait	
Reporting group title	Group 2: cyclophosphamide only
Reporting group description: cyclophosphamide only	
Reporting group title	Group 3: MVA-5T4 only
Reporting group description: MVA-5T4	
Reporting group title	Group 4: cyclophosphamide and MVA-5T4
Reporting group description: cyclophosphamide and MVA-5T4	

Reporting group values	Group 1: watch and wait	Group 2: cyclophosphamide only	Group 3: MVA-5T4 only
Number of subjects	8	9	17
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age			
Units: years			
arithmetic mean	62.5	64.6	63.4
standard deviation	± 11.41	± 5.94	± 10.67
Gender categorical Units: Subjects			
Female	2	5	3
Male	6	4	14

Reporting group values	Group 4: cyclophosphamide and MVA-5T4	Total	
Number of subjects	18	52	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age			
Units: years			
arithmetic mean	65.5		
standard deviation	± 11.18	-	
Gender categorical			
Units: Subjects			
Female	4	14	
Male	14	38	

End points

End points reporting groups

Reporting group title	Group 1: watch and wait
Reporting group description: watch and wait	
Reporting group title	Group 2: cyclophosphamide only
Reporting group description: cyclophosphamide only	
Reporting group title	Group 3: MVA-5T4 only
Reporting group description: MVA-5T4	
Reporting group title	Group 4: cyclophosphamide and MVA-5T4
Reporting group description: cyclophosphamide and MVA-5T4	

Primary: Immunological response

End point title	Immunological response[1]

End point description:

Immunological response defined as an increase from baseline to any point up to day 29 of 105 IFN-γ sport forming T-cells per 100,000 cultured PBMC

End point type	Primary

End point timeframe:

Start of treatment to day 22

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: Please see the linked papers in "More information" for full details of the analysis of this study

End point values	Group 1: watch and wait	Group 2: cyclophosphamide only	Group 3: MVA-5T4 only	Group 4: cyclophosphamide and MVA-5T4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	17	18
Units: Patients with response	0	8	0	11

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Weekly for the first 4 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4
Reporting groups	
Reporting group title	Group 1: watch and wait
Reporting group description: watch and wait	
Reporting group title	Group 2: cyclophosphamide only
Reporting group description: cyclophosphamide only	
Reporting group title	Group 3: MVA-5T4 only
Reporting group description: MVA-5T4	
Reporting group title	Group 4: cyclophosphamide and MVA-5T4
Reporting group description: cyclophosphamide and MVA-5T4	

Serious adverse events	Group 1: watch and wait	Group 2: cyclophosphamide only	Group 3: MVA-5T4 only
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	3 / 17 (17.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4: cyclophosphamide and MVA-5T4		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1: watch and wait	Group 2: cyclophosphamide only	Group 3: MVA-5T4 only
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	7 / 9 (77.78%)	13 / 17 (76.47%)
Investigations			
Raised ALP			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Injection site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	7 / 17 (41.18%)
occurrences (all)	0	0	7
Stoma site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Transient ischaemic attack			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nervous system disorders			
Paresthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			

Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	2 / 17 (11.76%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Infection			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	7 / 17 (41.18%)
occurrences (all)	1	2	7
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	2 / 17 (11.76%)
occurrences (all)	2	2	2

Non-serious adverse events	Group 4:		

	cyclophosphamide and MVA-5T4		
Total subjects affected by non-serious adverse events subjects affected / exposed	16 / 18 (88.89%)		
Investigations Raised ALP subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0		
Injury, poisoning and procedural complications Injection site reaction subjects affected / exposed occurrences (all) Stoma site pain subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 5 1 / 18 (5.56%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Transient ischaemic attack subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 0 / 18 (0.00%) 0		
Nervous system disorders Paresthesia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2 1 / 18 (5.56%) 1		
Blood and lymphatic system disorders Haematochezia subjects affected / exposed occurrences (all) Embolism	2 / 18 (11.11%) 0		

subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0 2 / 18 (11.11%) 2		
Ear and labyrinth disorders Dizziness subjects affected / exposed occurrences (all)	 2 / 18 (11.11%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Aphthous ulcer subjects affected / exposed occurrences (all)	 6 / 18 (33.33%) 6 1 / 18 (5.56%) 1 2 / 18 (11.11%) 2 2 / 18 (11.11%) 2 1 / 18 (5.56%) 1		
Respiratory, thoracic and mediastinal disorders Infection subjects affected / exposed occurrences (all)	 2 / 18 (11.11%) 2		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	 0 / 18 (0.00%) 0		
Renal and urinary disorders Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 5 / 18 (27.78%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2013	Patient schedule amended, 13 week samples removed,
14 July 2014	Admin Version number, page numbers, contact details 'tidied', Tim Elliott's name 1 t added, the word 'be' inserted paragraph 7.2.2 Inclusion criteria 'Responding or stable disease as defined by oncologist following chemotherapy for metastatic disease, as demonstrated on CT scan in comparison with pretreatment CT scan (RECIST), within 4 weeks of trial entry' to 'Responding or stable disease as defined by an oncologist within 4 weeks of trial entry. The stable disease is assessed on the basis of clinical judgment and review of radiological imaging' Exclusion criteria Subject has clinically apparent/active autoimmune disease (prior confirmed diagnosis or treatment for autoimmune disease including Systemic Lupus Erythematosis, Grave's disease, active Hashimoto's thyroiditis, multiple sclerosis, insulin dependent diabetes mellitus and rheumatoid arthritis). Note: subjects with non-insulin dependent diabetes mellitus can be included, as can subjects with controlled and rarely flaring rheumatoid disease and endstage insulin dependent diabetes mellitus controlled on insulin." to "Subject has clinically active autoimmune disease (prior confirmed diagnosis or treatment for autoimmune disease including Systemic Lupus Erythematosis, Grave's disease, active Hashimoto's thyroiditis, multiple sclerosis, new on-set insulin dependent diabetes mellitus and rheumatoid arthritis). Note: subjects can be included with controlled and rarely flaring rheumatoid disease, endstage/advanced insulin dependent diabetes mellitus controlled on insulin, and burnt out/previously treated (e.g. radioactive iodine, thyroidectomy) autoimmune thyroid disease now stable on replacement therapy." PIS The PIS has also been updated to reflect the changes in visits for bloods which was in the last amendment but was not updated at the time - the PIS now reflects the protocol and also Consent Form, page 8 Version number (point one) has been updated.

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/28880972

http://www.ncbi.nlm.nih.gov/pubmed/28855352