Clinical trial results:
A Phase II Trial to Assess the Activity of NY-ESO-1 Targeted T Cells in Advanced Oesophagogastric Cancer

Summary

EudraCT number	2012-005327-33
Trial protocol	GB
Global end of trial date	30 November 2017

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information

Trial identification

Sponsor protocol code	CFTSp0603

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01795976
WHO universal trial number (UTN)	-
Other trial identifiers	REC REF number: 13/SS/0041, Sponsor number: 12_DOG14_22

Notes:

Sponsors

Sponsor organisation name	The Christie NHS FoundationTrust
Sponsor organisation address	Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	The Christie NHS Foundation Trust, The Christie NHS Foundation Trust, +44 01613067041, Christiesponsoredresearch@christie.nhs.uk
Scientific contact	The Christie NHS Foundation Trust, The Christie NHS Foundation Trust, +44 01613067041, Christiesponsoredresearch@christie.nhs.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	30 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2017
Global end of trial reached?	Yes
Global end of trial date	30 November 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Is using the patient's own engineered cells as a therapy effective in treating oesophago-gastric cancer (as an example of a common epithelial malignancy) where there is a clear need for more effective therapies?
Primary objective: To evaluate the response rate in Oesophagogastric cancer patients who are NYESO-1 and HLA-A2 positive to adoptive cell therapy targeted to NYESO-1

Protection of trial subjects:

Potential subjects will need to have a screening blood test for HLAA0201
positivity prior to consenting to the study,
therefore a second consent form will be required for this proceedure.
Subjects data will be shared amongst study collaborators in the European Union and The United States, where data
protection laws may differ. There will be a statement on the consent form for the patient to agree to this.
There will be 3rd party access to patient data, by Adaptimmune Limited who are providing the vector for the modified Tcells.
This information will be conveyed to the patient via the patient information sheet, and there will be a statement
on the consent form for the patient to agree to this.
Subjects will be receiving a novel therapy, which has limited toxicity data from similar studies performed in the United
States. This information will be conveyed to the patient via the patient information sheet.
Subjects will be receiving more CT scans during the study period then they would as standard of care, therefore they
will recieve a higher radiation dose. A dose and risk assessment wil be performed by a trained radiologist, and this
information will be conveyed to the patient via the patient information sheet.
There is a high risk of Toxicity from the Preconditioning
Chemotherapy and subsequent IL2 therapy. This information
will be conveyed to the patient via the patient information sheet.

Background therapy:

NY-ESO-1 T cells are T cells engineered to target the tumour antigen NY-ESO-1. Autologous T cells are obtained from eligible patients who have NY-ESO-1 positive tumours and who are HLA-A*0201 positive. The T cells undergo lentiviral transduction with NY-ESO-1 specific nucleic acid under GMP conditions. The patient will then undergo preconditioning chemotherapy with a regime of cyclophosphamide 60mg/kg/day day -7 and -6 followed by fludarabine 25mg/m2 day -5 to -1. They will receive autologous NY-ESO-1 T cells on day 0 and following on from that they will receive up to 12 doses of intravenous IL-2 at a dose of 100,000 units per kg. Due to the risk of toxicities from the preconditioning chemotherapy, such as immune suppression, prophylactic and supportive medication will be administered

Evidence for comparator:

Interleukin-2 (IL2) is a well-accepted component in the treatment regimes of recent adoptive cell therapy trials. It has been shown to promote the survival and proliferation of T cells and has been widely used in experimental cell therapy with LAK cells and TILs (Rosenberg, et al 1993).

Cyclophosphamide 60mg/kg/day (Day -7 and -6) and Fludarabine 25mg/m2/day (Day -5 to -1) will be used in this study. This non-myeloablative regime was used in the pilot adoptive T cell therapy study (Rosenberg et al., 2011) and a well-established pre-conditioning chemotherapy regime for adoptive cell therapy studies in recent times. There is considerable justification for the use of pre-conditioning chemotherapy.

The T cell dose used in the two NY-ESO-1 T cell studies has been in the range of 1-130 billion cells (1-10 billion in Kalos et al study and 16-130 billion in Robbins et al), both showed good efficacy and tolerance. We have chosen the intermediate dose of 5-50 billion (i.e. 5x109 to 5x1010). This is also based on the realistic estimate of achievable cell production from the experience of our cell production units.

Actual start date of recruitment	01 May 2014
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: 2
Worldwide total number of subjects	2
EEA total number of subjects	2

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)	1
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial opened to recruitment on 30th September 2014. Patients were recruited from one hospital site in the United Kingdom. All patients gave written informed consent before any trial related procedures were carried out.

Pre-assignment

Screening details:

Eligible patients have advanced gastro-esophageal malignancies, have received at least one line of prior palliative chemotherapy, are HLA-A*02:01+, and have NY-ESO-1 expression in malignant cells detected by immunohistochemistry (IHC).

Period 1

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

Blinding implementation details:

Not Applicable

Arms

Arm title	NY-ESO-1 T-cell treatment

Arm description:

This is a single arm trial of adoptive T cell therapy using autologous T cells genetically engineered to target the tumour associated antigen NY-ESO-1. Eligible patients will undergo leukapheresis to retrieve sufficient T cells which will be gene modified and expanded in the laboratory. Patients will undergo preconditioning chemotherapy with cyclophosphamide (60mg/kg) day -7 and day -6, followed by fludarabine (25mg/m2) day -5 to day -1. The NY-ESO-1 gene modified cells will be re-infused on day 0 and the patients will receive up to 12 doses of intravenous IL2 (100,000 U/kg) from day 0 to day 4. Each participant will receive one cycle of treatment only.

Arm type	Single arm
Investigational medicinal product name	autologous primary T-lymphocytes
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NY-ESO-1 T cells
(5x109 to 5x1010 cells).
Volume: ~270ml

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

60mg/kg/day

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
25mg/m2/day

Number of subjects in period 1	NY-ESO-1 T-cell treatment
Started	2
Completed	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	2	2	
Age categorical 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)	1	1	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	62		
full range (min-max)	55 to 69	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	2	2	

End points

End points reporting groups

Reporting group title	NY-ESO-1 T-cell treatment

Reporting group description:

This is a single arm trial of adoptive T cell therapy using autologous T cells genetically engineered to target the tumour associated antigen NY-ESO-1. Eligible patients will undergo leukapheresis to retrieve sufficient T cells which will be gene modified and expanded in the laboratory. Patients will undergo preconditioning chemotherapy with cyclophosphamide (60mg/kg) day -7 and day -6, followed by fludarabine (25mg/m2) day -5 to day -1. The NY-ESO-1 gene modified cells will be re-infused on day 0 and the patients will receive up to 12 doses of intravenous IL2 (100,000 U/kg) from day 0 to day 4. Each participant will receive one cycle of treatment only.

Primary: Response rate by RECIST v1.1 in oesophagogastric cancer patients who are NY-ESO-1 and HLA-A*0201 positive to adoptive cell therapy targeted to NY-ESO-1.

End point title	Response rate by RECIST v1.1 in oesophagogastric cancer patients who are NY-ESO-1 and HLA-A*0201 positive to adoptive cell therapy targeted to NY-ESO-1.[1]

End point description:

Two patients were infused with NY-ESO-1-specific TCR-T cells as per protocol. Both patients experienced symptoms consistent with cytokine release syndrome in the first two weeks post infusion, which resolved with supportive regimens. Whilst Patient 1 recovered, Patient 2 subsequently developed enterocolitis and bone marrow failure from which was fatal, despite immunosuppressive therapy. Immunological assays detected outgrowth in the peripheral blood and tissues of T cell clones. Notably the dominant clone was not associated with the transduced NY-ESO-1 TCR.
Both patients achieved stable disease as best response. Patient 1 maintained disease stability until month 7 post infusion. Patient 2 demonstrated a 23% reduction in target lesions on imaging at 4 weeks post infusion. At week 6 this had reduced to 10%.

End point type	Primary

End point timeframe:

Baseline to end of study

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: This is a single arm study and no comparison has been made. This study was terminated early and descriptive statistics only has been performed.

End point values	NY-ESO-1 T-cell treatment			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: number of patients	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until End of Trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	NY-ESO-1

Reporting group description: -

Serious adverse events	NY-ESO-1		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Chest Pain	Additional description: Chest Pain		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Oedema	Additional description: Pulmonary Oedema		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)	Additional description: Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Bone Marrow Failure	Additional description: Bone Marrow Failure		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Immune system disorders			
Cytokine Release Syndrome	Additional description: Cytokine Release Syndrome		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain	Additional description: Abdominal Pain		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation	Additional description: Constipation		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis Infectious	Additional description: Enterocolitis Infectious		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage	Additional description: Gastrointestinal Haemorrhage		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic Sepsis	Additional description: Neutropenic Sepsis		

subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	NY-ESO-1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
General disorders and administration site conditions			
Agitation	Additional description: Agitation		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Peripheral Oedema	Additional description: Peripheral Oedema		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Lower Respiratory Tract Infection	Additional description: Lower Respiratory Tract Infection		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Respiratory Secretions	Additional description: Respiratory Secretions		

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Investigations			
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hyperbilirubinaemia	Additional description: Hyperbilirubinaemia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypomagnesemia	Additional description: Hypomagnesemia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Cardiac disorders			
Atrial Fibrillation	Additional description: Atrial Fibrillation		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Heart Failure	Additional description: Heart Failure		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypertension	Additional description: Hypertension		

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Confusion	Additional description: Confusion		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Peripheral Neuropathy	Additional description: Peripheral Neuropathy		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Myoclinical Jerks	Additional description: Myoclinical Jerks		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Eye disorders			
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Macular Degeneration	Additional description: Macular Degeneration		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal Pain	Additional description: Abdominal Pain		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Dry Mouth	Additional description: Dry Mouth		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Nausea	Additional description: Nausea		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Oral Dysethesia	Additional description: Oral Dysethesia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Maculopapular Rash	Additional description: Maculopapular Rash		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute Kidney Injury	Additional description: Acute Kidney Injury		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Infections and infestations			
Fever	Additional description: Fever		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		

General Infection	Additional description: General Infection		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Lower Respiratory Tract Infection	Additional description: Lower Respiratory Tract Infection		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2014	Substantial amendment 2 Simplify the inclusion criteria parameters for ALT and AST. The patient information sheet and consent form has been amended in order to clarify that anonomysed trial data will be sent to a subsidiary of the trial vector supplier Adaptimmune.
26 September 2014	Substantial amendment 3 The Protocol has been amended to incorporate changes requested by the Swedish regulatory authority, as part of the trial authorisation submission there. The version of the protocol approved in Sweden alone is version 5, and has been provided for reference. There has been a change in Chief Investigator for the trial, with Dr Fiona Thistlethwaite returning to the position, replacing Dr Was Mansoor. This change, along with the changes requested by the Swedish regulator is incorporated into version 6 of the protocol. The Investigator's Brochure has had a number of changes requested by the Swedish regulatory authority, as part of the trial authorisation submission there. There has also been updated information provided by the vector supplier Adaptimmune. The Main Study Patient Information Sheet and Consent Form has been amended as anonymised trial data will now be being sent to GSK as well as the trial vector supplier Adaptimmune. Adaptimmune have entered into a strategic collaboration and licensing agreement with GlaxoSmithKline (GSK)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 August 2015	Suspension of recruitment due to patient death	-

Notes:

Limitations and caveats

None reported