

**Clinical trial results:**

A randomised phase II trial of [18F]fluorothymidine and the standard tracer [18F]Fluorodeoxyglucose in the assessment of systemic therapy response in triple negative breast cancer and their utility compared to conventional MRI imaging response, early ADC change and biopsy derived biomarkers

Summary

EudraCT number	2011-004220-34
Trial protocol	GB
Global end of trial date	23 August 2017

Results information

Result version number	v1 (current)
This version publication date	21 August 2019
First version publication date	21 August 2019
Summary attachment (see zip file)	RESULTS SUMMARY (TN PET.pdf)

Trial information**Trial identification**

Sponsor protocol code	TNPET01
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor Andrew Tutt, King's College London, +44 02071884988, andrew.tutt@kcl.ac.uk
Scientific contact	Professor Andrew Tutt, King's College London, +44 02071884988, andrew.tutt@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
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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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2017
Global end of trial reached?	Yes
Global end of trial date	23 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To confirm repeatability of Positron Emission Tomography (PET) scan SUV measurement before chemotherapy in triple negative breast cancer using [18F]FLT and [18F]FDG tracers

Parts A and B:

To evaluate PET imaging using [18F]FLT or [18F]FDG as a method for evaluating response to systemic therapy in primary triple negative breast cancer

Protection of trial subjects:

Women of childbearing potential must have documented negative pregnancy test within the 2 weeks prior to day 1 chemotherapy and agree to use a medically acceptable birth control during the duration of their chemotherapy.

Background therapy:

All Participants will receive 6-8 cyclophosphamide (x3-4) cycles standard sequential consisting of anthracycline/ and taxane (x-3-4) components chemotherapy prior to surgery.

Evidence for comparator: -

Actual start date of recruitment	01 November 2012
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	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from a single centre in the UK between 2012 and 2017

Pre-assignment

Screening details:

A total of 25 patients with triple negative breast cancer will be enrolled:-

n=10 Part A,

n=15 Part B.

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

Are arms mutually exclusive?	Yes
Arm title	PART A - FDG

Arm description:

FDG - 3 scans in total:

5 patients scanned using FDG

PET component, 200 MBq of FDG: 4mSv

CT component for attenuation correction and localisation of dynamic and 1st static PET scan: 1.5 mSv

CT component for second static PET scan: 1.5 mSv CT component for third static PET scan: 1.5 mSv

(CT parameters for all patients in this group 2FOV, 140 kVp, 32mAs, coll = 40 mm, pitch = 1.375)

Total effective dose per session: 8.5 mSv

Total effective dose for three sessions: 25.5 mSv

Arm type	Active comparator
Investigational medicinal product name	MetaTrace FDG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

FDG tracer administration will be in accordance with the SmPC and patients will receive a maximum radioactivity dose of 200 MBq (-10%) [¹⁸F]-FDG by intravenous administration.

Arm title	PART A - FLT
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Arm description:

5 patients to be scanned using FLT. 3 scans in total

PET component, 200 MBq FLT: 6.5 mSv (1)

CT component for dynamic and static PET scan(2FOV, 140 kVp, 42mAs, coll = 40 mm, pitch = 1.375): 2 mSv

Total effective dose per session: 8.5 mSv Total effective dose for three sessions: 26 mSv

Arm type	Experimental
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Investigational medicinal product name	[18F]FLT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Aseptic technique is employed when preparing the drug for administration.

The clinical dose of FLT will contain a maximum of 50 µg of [18F]-FLT, and radioactivity concentration.

The volume will be adjusted to account for the radioactive concentration of the product at the time of administration. Participants will receive a maximum radioactivity dose of 200 MBq (-10%)

[18F]FLT,, equating to a maximum chemical dose of less than 50 µg [18F]-FLT.

Arm title	PART B - FDG
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Arm description:

On confirmation of tracer repeatability in Part A analysis , a further 15 participants were expected to be recruited to Part B. All participants in Part B will be imaged using the tracer, FDG which met the repeatability criteria at the end of part A.

Arm type	Experimental
Investigational medicinal product name	MetaTrace FDG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

FDG tracer administration will be in accordance with the SmPC and patients will receive a maximum radioactivity dose of 200 MBq (-10%) [18F]-FDG by intravenous administration.

Number of subjects in period 1	PART A - FDG	PART A - FLT	PART B - FDG
Started	5	6	11
Completed	5	4	10
Not completed	0	2	1
Consent withdrawn by subject	-	1	1
FLT production failure - no IMP received	-	1	-

Baseline characteristics

Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	22	22	
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)	22	22	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	0	0	

End points

End points reporting groups

Reporting group title	PART A - FDG
Reporting group description: FDG - 3 scans in total: 5 patients scanned using FDG PET component, 200 MBq of FDG: 4mSv CT component for attenuation correction and localisation of dynamic and 1st static PET scan: 1.5 mSv CT component for second static PET scan: 1.5 mSv CT component for third static PET scan: 1.5 mSv (CT parameters for all patients in this group 2FOV, 140 kVp, 32mAs, coll = 40 mm, pitch = 1.375) Total effective dose per session: 8.5 mSv Total effective dose for three sessions: 25.5 mSv	
Reporting group title	PART A - FLT
Reporting group description: 5 patients to be scanned using FLT. 3 scans in total PET component, 200 MBq FLT: 6.5 mSv (1) CT component for dynamic and static PET scan(2FOV, 140 kVp, 42mAs, coll = 40 mm, pitch = 1.375): 2 mSv Total effective dose per session: 8.5 mSv Total effective dose for three sessions: 26 mSv	
Reporting group title	PART B - FDG
Reporting group description: On confirmation of tracer repeatability in Part A analysis , a further 15 participants were expected to be recruited to Part B. All participants in Part B will be imaged using the tracer, FDG which met the repeatability criteria at the end of part A.	

Primary: PART A

End point title	PART A ^[1]
End point description: To confirm PET scan SUV measurement repeatability using [18F]FDG and [18F]FLT tracers. Repeatability for both tracers will be within +/-15% (second scan at 3 days after first PET +/- 10% of baseline)	
End point type	Primary
End point timeframe: End of study is defined as day of surgery. Patients will proceed to definitive surgery according to usual practice at 3 to 6 weeks after their final chemotherapy.	
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 attached document	

Attachments (see zip file)	PART A RESULTS/Publication - Annals of Oncology.pdf
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Statistical analyses

No statistical analyses for this end point

Primary: PART B

End point title	PART B ^[2]
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End point description:

To evaluate PET-CT imaging using [18F]FLT or [18F]FDG as methods for evaluating response to systemic therapy in primary triple negative breast cancer. Correlation of SUV response for tracer with conventional MRI RECIST response assessment after 3 cycles neoadjuvant chemotherapy

End point type	Primary
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End point timeframe:

End of study is defined as day of surgery. Patients will proceed to definitive surgery according to usual practice at 3 to 6 weeks after their final chemotherapy.

Notes:

[2] - 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 attached document

End point values	PART A - FDG	PART A - FLT	PART B - FDG	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	4	10	
Units: whole	5	4	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoints

End point title	Secondary Endpoints
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End point description:

*The Time point in triple negative breast cancer where tumour SUV peaks

*Correlate PET imaging response in breast and axillary lymph nodes with residual cancer burden (RCB) at definitive surgery

*Correlate PET imaging response using each tracer with blood and biopsy derived biomarkers. These will include proliferation biomarkers, HER2:HER3 dimer (FRET Efficiency), apoptosis biomarkers, tumour genomic profiling analyses and blood derivatives for DNA, RNA and protein markers of the cancers biology

*Non invasive assessment of Ki and k1 from this data set

*Assess nodal response using PET imaging

*Evaluate the ability of tracer to predict subsequent MRI response as a function of integrated ADC & size change.

*Evaluate the ability of early MRI size and ADC change to predict subsequent MRI response.

*Confirm the safety of [18F]FLT in patients with breast cancer.

*Correlate MRI imaging ADC change with blood & biopsy derived proliferation biomarkers & apoptosis biomarkers

End point type	Secondary
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End point timeframe:

End of trial

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Until the end of trial (Day of surgery)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	PART A - FDG
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Reporting group description: -

Reporting group title	PART A - [18F]FLT
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Reporting group description: -

Reporting group title	PART B - FDG
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Reporting group description: -

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: No non-serious adverse events were reported.

Serious adverse events	PART A - FDG	PART A - [18F]FLT	PART B - FDG
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever, headache, Lethargy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Shortness of breath on minimal excursion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Iatrogenic pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PART A - FDG	PART A - [18F]FLT	PART B - FDG
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2014	Change from 30 to 25 participants sample size and change to reflect single tracer progressing to part B with increased power for this tracer

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported