



Clinical trial results:

A randomised placebo-controlled trial of synchronous NIMorazole versus RADiotherapy alone in patients with locally advanced head and neck squamous cell carcinoma not suitable for synchronous chemotherapy or cetuximab.

Summary

EudraCT number	2013-002466-39
Trial protocol	GB
Global end of trial date	07 January 2021

Results information

Result version number	v1 (current)
This version publication date	19 January 2024
First version publication date	19 January 2024

Trial information

Trial identification

Sponsor protocol code	CFTSp032
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01950689
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference: 13/EE/0397

Notes:

Sponsors

Sponsor organisation name	The Christie NHS Foundation Trust
Sponsor organisation address	Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	Clare Griffin, The Christie NHS Foundation Trust, 0161 4463619, clare.griffin1@nhs.net
Scientific contact	Clare Griffin, The Christie NHS Foundation Trust, 0161 4463619, clare.griffin1@nhs.net

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	05 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2021
Global end of trial reached?	Yes
Global end of trial date	07 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine whether patients with locally advanced head and neck squamous cell carcinoma, unsuitable for either cisplatin chemotherapy or monoclonal antibody therapy, benefit from the addition of nimorazole to standard definitive radiotherapy in terms of increased locoregional control without additional serious toxicity.

Protection of trial subjects:

The trial will be conducted in accordance with the principles of good clinical practice (GCP) and the Declaration of Helsinki. The sponsor and MCTU will ensure that the study protocol, participant information sheet, participant consent form, GP letter and submitted supporting documents have been approved by the research ethics committee(s) prior to any subject recruitment.

Patients will be assigned a unique trial ID via the MCTU trials line which will be used throughout their participation in the trial. Any personal data recorded will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Investigators and trial site staff must not provide any participant-identifying data (e.g. name, address, hospital reference number) to the MCTU during the course of the trial, unless with prior approval by the Research Ethics Committee. Any participant-identifying data received by the MCTU will be redacted or destroyed, and the sender notified.

The MCTU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. The Investigator and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.

Risk-based on-site monitoring is permitted in order to verify that the rights and well-being of patients/participants are protected.

It is recommended to temporarily interrupt dosing with nimorazole if side effects of grade 3-4 severity, in terms of nausea and vomiting, are not controllable with anti-emetics. Dosing can be resumed when grade is \leq grade 1. Based on previous trials it is not expected that patients will have a severe allergic reaction but if this is experienced, nimorazole/placebo should be discontinued.

Background therapy:

Patients must be treated using IMRT (including fixed-beam or rotational arc therapy -VMAT, Rapid Arc, Tomotherapy) and immobilised in a 5 point fixation shell. The radiotherapy planning CT scan should be up to 3mm slice thickness and use of intravenous contrast is recommended.

If nausea and vomiting occur as a side effect of Nimorazole, patients should be managed using anti-emetics in accordance with local practice. For skin rash, patients should be treated with antihistamines.

Evidence for comparator:

Nimorazole belongs to a class of chemicals known as 5-nitroimidazoles. Nitroimidazoles are being used therapeutically as anti-infective drugs due to their antiprotozoal, antitrichomonal and antibacterial activity targeting anaerobic bacteria and protozoan infections. Nimorazole is also a hypoxic radiosensitizer with high electron affinity enabling the drug to mimic the effect of oxygen in rendering hypoxic cells radiosensitive. Nimorazole has been selected as the drug of choice to pursue further as a hypoxic radiosensitizer due to its good bioavailability in tumours following oral administration, its short half-life and good therapeutic ratio compared

to other nitroimidazoles.

The benefit of hypoxic radiosensitization was tested in clinical studies in more than 10,000 patients with various solid tumours. The highest benefit was seen in squamous cell cancers – specifically head and neck squamous cell carcinoma (HNSCC).

Actual start date of recruitment	01 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 338
Worldwide total number of subjects	338
EEA total number of subjects	0

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)	35
From 65 to 84 years	300
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Eligible patients were identified in the respective head and neck multi-disciplinary meetings and out-patient clinics at participating sites. 338 patients were randomised by 19 UK centres from May 2014 to May 2019.

Pre-assignment

Screening details:

Potential trial participants were screened up to 10 weeks prior to the planned treatment start date to ensure eligibility based on inclusion / exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The Manchester CTU were to coordinate randomisation and blinding and inform Azanta (the manufacturer) via the automated randomisation service of treatment allocation. Each patient received a high density polyethylene bottle of 150 tablets of nimorazole, 500 mg or placebo. Bottles were labelled generically containing only directions for administration and site and participant Identifier information.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nimorazole plus radiotherapy

Arm description:

Therapeutic arm. Radiotherapy as per control arm. In addition, 1.2 g/m² of nimorazole in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Arm type	Experimental
Investigational medicinal product name	Nimorazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Soluble tablet
Routes of administration	Oral use

Dosage and administration details:

Nimorazole in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

The IMP was administered in doses of approximately 1.2 g/m² body surface (see table) in connection with the first daily radiation treatments. Total dose over the entire radiation period should be approximately 36 g/m² and must not exceed 40 g/m² or a total of 75 g.

Arm title	Placebo plus radiotherapy
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Arm description:

Control arm. 30 fractions of radiotherapy, each of 2.17 Gy given once a day, 5 days a week, for 6 weeks, totalling 65 Gy. In addition, a placebo in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Arm type	Placebo
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Investigational medicinal product name	Matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Soluble tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

30 fractions of radiotherapy, each of 2.17 Gy given once a day, 5 days a week, for 6 weeks, totalling 65 Gy. In addition, a placebo in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Number of subjects in period 1	Nimorazole plus radiotherapy	Placebo plus radiotherapy
Started	168	170
Completed	168	170

Baseline characteristics

Reporting groups

Reporting group title	Nimorazole plus radiotherapy
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Reporting group description:

Therapeutic arm. Radiotherapy as per control arm. In addition, 1.2 g/m² of nimorazole in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Reporting group title	Placebo plus radiotherapy
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Reporting group description:

Control arm. 30 fractions of radiotherapy, each of 2.17 Gy given once a day, 5 days a week, for 6 weeks, totalling 65 Gy. In addition, a placebo in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Reporting group values	Nimorazole plus radiotherapy	Placebo plus radiotherapy	Total
Number of subjects	168	170	338
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			
Units: years			
median	73	73	
full range (min-max)	44 to 88	44 to 88	-
Gender categorical			
Units: Subjects			
Female	35	41	76
Male	133	129	262
Tumour site			
Units: Subjects			
Oropharynx	110	97	207
Hypopharynx	25	26	51
Larynx	33	47	80
HPV P16 status			
Units: Subjects			
NEG	88	97	185
POS	75	67	142
Missing	5	6	11
TNM stage			

Units: Subjects			
II	7	8	15
III	52	51	103
IVA	99	99	198
IVB	10	12	22
Tumour differentiation			
Units: Subjects			
well differentiated	5	6	11
well & moderately differentiated	0	4	4
moderately differentiated	65	68	133
moderately & poorly differentiated	5	3	8
poorly differentiated	71	65	136
undifferentiated	2	2	4
missing	20	22	42
WHO Performance Status			
Units: Subjects			
00	73	64	137
01	69	80	149
02	26	26	52
Neck dissection			
Units: Subjects			
No	164	165	329
Yes	4	5	9
Dose volumes			
Units: Subjects			
2 doses	86	87	173
3 doses	76	79	155
Missing	6	4	10
Smoking status			
Units: Subjects			
Never smoked	25	27	52
Ex-smoker stopped for 1 year or more	80	87	167
Ex-smoker stopped for less than 1 year	30	19	49
Current smoker	32	37	69
Missing	1	0	1
Alcohol intake			
Units: Subjects			
Never heavy	121	111	232
Ex-heavy	25	35	60
Current heavy	22	24	46
Hypoxia score obtained			
Units: Subjects			
No	24	28	52
Yes	144	142	286
Hypoxia score			
Units: Score			
median	0.08	0.08	
full range (min-max)	0.02 to 0.36	0.02 to 0.30	-

Subject analysis sets

Subject analysis set title	Nimorazole plus radiotherapy more hypoxic group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

During conduct it became apparent that the original recruitment target of 470 cases was not achievable within the resources available and the primary objective was reconsidered in the light of this. It was anticipated that the benefit, if any, of hypoxia modifying therapy would be most pronounced in participants with "more hypoxic" tumours and it was decided to focus the primary trial arm comparison to this "enriched" group. The median hypoxia score (HS) for the first 50 samples analysed was 0.079 and this value was used to label participants' tumours as either "less hypoxic ($HS \leq 0.079$)" or "more hypoxic ($HS > 0.079$)". There was no matching of individual hypoxia scores with outcome data in arriving at this definition. The revised primary outcome is loco-regional progression in the enriched (more hypoxic) group.

The enriched ("more hypoxic") subgroup is comprised of 139 patients, 70 and 69 of which are in the Nimorazole and placebo arm, respectively.

Subject analysis set title	Placebo plus radiotherapy more hypoxic group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

During conduct it became apparent that the original recruitment target of 470 cases was not achievable within the resources available and the primary objective was reconsidered in the light of this. It was anticipated that the benefit, if any, of hypoxia modifying therapy would be most pronounced in participants with "more hypoxic" tumours and it was decided to focus the primary trial arm comparison to this "enriched" group. The median hypoxia score (HS) for the first 50 samples analysed was 0.079 and this value was used to label participants' tumours as either "less hypoxic ($HS \leq 0.079$)" or "more hypoxic ($HS > 0.079$)". There was no matching of individual hypoxia scores with outcome data in arriving at this definition. The revised primary outcome is loco-regional progression in the enriched (more hypoxic) group.

The enriched ("more hypoxic") subgroup is comprised of 139 patients, 70 and 69 of which in the Nimorazole and placebo arm, respectively.

Reporting group values	Nimorazole plus radiotherapy more hypoxic group	Placebo plus radiotherapy more hypoxic group	
Number of subjects	70	69	
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 Units: years			
median	72	72	
full range (min-max)	50 to 88	45 to 84	
Gender categorical Units: Subjects			
Female			
Male			
Tumour site Units: Subjects			
Oropharynx	40	31	

Hypopharynx	14	15	
Larynx	16	23	
HPV P16 status			
Units: Subjects			
NEG	46	51	
POS	24	18	
Missing	0	0	
TNM stage			
Units: Subjects			
II	3	2	
III	29	27	
IVA	36	36	
IVB	2	4	
Tumour differentiation			
Units: Subjects			
well differentiated	4	4	
well & moderately differentiated	0	2	
moderately differentiated	39	35	
moderately & poorly differentiated	0	1	
poorly differentiated	19	25	
undifferentiated	0	0	
missing	8	2	
WHO Performance Status			
Units: Subjects			
00	28	26	
01	30	33	
02	12	10	
Neck dissection			
Units: Subjects			
No	70	66	
Yes	0	3	
Dose volumes			
Units: Subjects			
2 doses	39	41	
3 doses	29	28	
Missing	2	0	
Smoking status			
Units: Subjects			
Never smoked	7	8	
Ex-smoker stopped for 1 year or more	30	30	
Ex-smoker stopped for less than 1 year	14	11	
Current smoker	19	20	
Missing	0	0	
Alcohol intake			
Units: Subjects			
Never heavy	51	41	
Ex-heavy	10	20	
Current heavy	9	8	
Hypoxia score obtained			
Units: Subjects			

No	0	0	
Yes	70	69	

Hypoxia score			
Units: Score			
median	0.11	0.12	
full range (min-max)	0.08 to 0.30	0.08 to 0.36	

End points

End points reporting groups

Reporting group title	Nimorazole plus radiotherapy
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Reporting group description:

Therapeutic arm. Radiotherapy as per control arm. In addition, 1.2 g/m² of nimorazole in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Reporting group title	Placebo plus radiotherapy
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Reporting group description:

Control arm. 30 fractions of radiotherapy, each of 2.17 Gy given once a day, 5 days a week, for 6 weeks, totalling 65 Gy. In addition, a placebo in tablet (solid or dispersible) preparation given orally (or via a feeding tube with an outer diameter of at least 4.0mm) once a day, 5 days a week for 6 weeks, 90 minutes pre intensity-modulated radiotherapy.

Subject analysis set title	Nimorazole plus radiotherapy more hypoxic group
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

During conduct it became apparent that the original recruitment target of 470 cases was not achievable within the resources available and the primary objective was reconsidered in the light of this. It was anticipated that the benefit, if any, of hypoxia modifying therapy would be most pronounced in participants with "more hypoxic" tumours and it was decided to focus the primary trial arm comparison to this "enriched" group. The median hypoxia score (HS) for the first 50 samples analysed was 0.079 and this value was used to label participants' tumours as either "less hypoxic (HS ≤ 0.079)" or "more hypoxic (HS > 0.079)". There was no matching of individual hypoxia scores with outcome data in arriving at this definition. The revised primary outcome is loco-regional progression in the enriched (more hypoxic) group.

The enriched ("more hypoxic") subgroup is comprised of 139 patients, 70 and 69 of which are in the Nimorazole and placebo arm, respectively.

Subject analysis set title	Placebo plus radiotherapy more hypoxic group
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

During conduct it became apparent that the original recruitment target of 470 cases was not achievable within the resources available and the primary objective was reconsidered in the light of this. It was anticipated that the benefit, if any, of hypoxia modifying therapy would be most pronounced in participants with "more hypoxic" tumours and it was decided to focus the primary trial arm comparison to this "enriched" group. The median hypoxia score (HS) for the first 50 samples analysed was 0.079 and this value was used to label participants' tumours as either "less hypoxic (HS ≤ 0.079)" or "more hypoxic (HS > 0.079)". There was no matching of individual hypoxia scores with outcome data in arriving at this definition. The revised primary outcome is loco-regional progression in the enriched (more hypoxic) group.

The enriched ("more hypoxic") subgroup is comprised of 139 patients, 70 and 69 of which in the Nimorazole and placebo arm, respectively.

Primary: Freedom from loco-regional progression: Nimorazole plus RT vs Placebo plus RT enriched group

End point title	Freedom from loco-regional progression: Nimorazole plus RT vs Placebo plus RT enriched group
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End point description:

The primary endpoint was loco-regional control (freedom from locoregional progression, FFLRP), initially restricted to the enriched (more hypoxic) sub-group - in patients with hypoxic tumours, defined as greater than or equal to the median hypoxia score of the first 50 patients analysed (≥0.079), using a validated 26-gene signature. The focus is on the treatment effect (Nimorazole vs placebo) on Freedom from loco-regional progression (FFLRP) after adjusting for the following factors:

- Disease stage [TNM v7]; (2 or 3) vs 4.
- WHO PS (0 or 1) vs 2.
- Neck dissection: no vs yes.
- RT intermediate dose level (60 Gy) being used: no vs yes.
- Human papilloma virus (HPV)/p16 status: negative vs positive.
- o If present, HPV information is used.

- o If HPV is missing, then p16 is used.

End point type	Primary
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End point timeframe:

Freedom from loco-regional progression (FFLRP) is a censored time to event variable measuring the time from randomisation to the first of a local or nodal progression.

End point values	Nimorazole plus radiotherapy more hypoxic group	Placebo plus radiotherapy more hypoxic group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	69		
Units: Total number of progression events				
number (not applicable)	14	22		

Statistical analyses

Statistical analysis title	FFLRP Treatment
Comparison groups	Nimorazole plus radiotherapy more hypoxic group v Placebo plus radiotherapy more hypoxic group
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.354
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.44

Notes:

[1] - analyses used a Cox proportional hazards regression model

Statistical analysis title	FFLRP cancer stage
Comparison groups	Nimorazole plus radiotherapy more hypoxic group v Placebo plus radiotherapy more hypoxic group
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.419
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	2.63

Statistical analysis title	FFLRP WHO performance status
Comparison groups	Nimorazole plus radiotherapy more hypoxic group v Placebo plus radiotherapy more hypoxic group
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	3.34

Statistical analysis title	FFLRP neck dissection
Comparison groups	Nimorazole plus radiotherapy more hypoxic group v Placebo plus radiotherapy more hypoxic group
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	5.03

Statistical analysis title	FFLRP RT intermediate dose level
Comparison groups	Nimorazole plus radiotherapy more hypoxic group v Placebo plus radiotherapy more hypoxic group

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	3.11

Statistical analysis title	FFLRP HPV p16 status
Comparison groups	Nimorazole plus radiotherapy more hypoxic group v Placebo plus radiotherapy more hypoxic group
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.68

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occur between randomisation and 6 weeks post end of trial treatment must be recorded in the patient notes. Adverse event data will be collected in the CRF from baseline.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo plus Radiotherapy
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Reporting group description: -

Reporting group title	Nimorazole plus Radiotherapy
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Reporting group description: -

Serious adverse events	Placebo plus Radiotherapy	Nimorazole plus Radiotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 170 (6.47%)	21 / 168 (12.50%)	
number of deaths (all causes)	66	60	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 170 (0.00%)	1 / 168 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DIARRHOEA	Additional description: DIARRHOEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 170 (0.59%)	2 / 168 (1.19%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TESTS (ELEVATED)	Additional description: LIVER FUNCTION TESTS (ELEVATED)		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 170 (0.00%)	1 / 168 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 170 (2.94%)	5 / 168 (2.98%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 170 (2.35%)	5 / 168 (2.98%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
MUCOSITIS	Additional description: MUCOSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 170 (0.59%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INFECTION	Additional description: INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 170 (2.35%)	11 / 168 (6.55%)	
occurrences causally related to treatment / all	4 / 4	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 170 (0.59%)	1 / 168 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT LOSS	Additional description: WEIGHT LOSS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 170 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Placebo plus Radiotherapy	Nimorazole plus Radiotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 170 (82.94%)	138 / 168 (82.14%)	
Nervous system disorders			
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	109 / 170 (64.12%)	111 / 168 (66.07%)	
occurrences (all)	191	196	
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	132 / 170 (77.65%)	119 / 168 (70.83%)	
occurrences (all)	209	180	
PARAESTHESIA	Additional description: PARAESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 170 (7.06%)	6 / 168 (3.57%)	
occurrences (all)	15	6	
PERIPHERAL NEUROPATHY	Additional description: PERIPHERAL NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 170 (8.82%)	11 / 168 (6.55%)	
occurrences (all)	18	13	
Blood and lymphatic system disorders			
ANAEMIA	Additional description: ANAEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	46 / 170 (27.06%)	44 / 168 (26.19%)	
occurrences (all)	56	51	
Immune system disorders			
ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	14 / 170 (8.24%) 15	15 / 168 (8.93%) 15	
Gastrointestinal disorders			
Additional description: ALTERED TASTE			
ALTERED TASTE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	119 / 170 (70.00%) 211	118 / 168 (70.24%) 204	
Additional description: CONSTIPATION			
CONSTIPATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	50 / 170 (29.41%) 62	37 / 168 (22.02%) 42	
Additional description: DRY MOUTH			
DRY MOUTH alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	127 / 170 (74.71%) 234	117 / 168 (69.64%) 212	
Additional description: DIARRHOEA			
DIARRHOEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	49 / 170 (28.82%) 54	39 / 168 (23.21%) 45	
Additional description: DYSPHAGIA			
DYSPHAGIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	113 / 170 (66.47%) 198	107 / 168 (63.69%) 184	
Additional description: LIVER FUNCTION TESTS (ELEVATED)			
LIVER FUNCTION TESTS (ELEVATED) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 170 (2.35%) 5	1 / 168 (0.60%) 1	
Additional description: NAUSEA			
NAUSEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	80 / 170 (47.06%) 95	111 / 168 (66.07%) 122	
Additional description: VOMITING			
VOMITING alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	56 / 170 (32.94%) 63	69 / 168 (41.07%) 76	
Respiratory, thoracic and mediastinal disorders			
HOARSENESS	Additional description: HOARSENESS		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	14 / 170 (8.24%) 16	20 / 168 (11.90%) 24	
Skin and subcutaneous tissue disorders			
EDEMA NECK	Additional description: EDEMA NECK		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	17 / 170 (10.00%) 17	17 / 168 (10.12%) 17	
MUCOSITIS	Additional description: MUCOSITIS		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	130 / 170 (76.47%) 196	119 / 168 (70.83%) 173	
RADIATION DERMATITIS	Additional description: RADIATION DERMATITIS		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 170 (2.94%) 5	6 / 168 (3.57%) 7	
SKIN RASH	Additional description: SKIN RASH		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	37 / 170 (21.76%) 43	41 / 168 (24.40%) 43	
Infections and infestations			
INFECTION	Additional description: INFECTION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	70 / 170 (41.18%) 88	66 / 168 (39.29%) 79	
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	98 / 170 (57.65%) 143	97 / 168 (57.74%) 146	
WEIGHT LOSS	Additional description: WEIGHT LOSS		

alternative assessment type: Non-systematic			
subjects affected / exposed	123 / 170 (72.35%)	111 / 168 (66.07%)	
occurrences (all)	196	171	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2014	<p>Substantial amendment 01: Protocol updated to V3.0 07/02/2014 Changes made to the protocol and supporting documents are as follows:</p> <ul style="list-style-type: none">• Dr Mererid Evans added to trial personnel at the front of the protocol• Change to the physics QA advisors• Sponsor contact deleted Angela Ball's name and added Gillian Heap.• Change to 2 PIs at other centres – Cheltenham and Belfast• Unblinding procedure details added now that they are known. <p>Pharmacist/out of hours pharmacist will cover 24 hour unblinding. Procedure for completion of forms, confirming identity of caller and emails are detailed.</p> <ul style="list-style-type: none">• Section 7 radiotherapy treatment details all updated in line with QA procedure - large changes throughout this section.• Clarification that drug will take 3 working days to arrive at sites and not 2 as previously recorded.• Clarification that translational research samples will not be required for screen failure patients. Any collected before screen failure status is known will be destroyed.• Update to the dose and risk assessment. This had previously stated there would be PET-CT which had been left in from previous drafts of the protocol. Updated document by medical physics expert shows that this test has been removed and was not included in the calculations
28 October 2014	<p>Substantial amendment 02:</p> <ul style="list-style-type: none">• Change to PI at Royal Surrey centre• Addition of new site: Hertfordshire• Removal of existing site: Mount Vernon Hospital• Update to protocol section around translational research tissue (includes greater detail of what the translational analysis entails)• Update to protocol allowing sites that use PET-CT scanning as standard, to continue doing so to allow for accurate mirroring of standard care where ever possible, and to avoid logistical issues around sole CT scanning.
11 February 2015	<p>Substantial amendment 03:</p> <ul style="list-style-type: none">• Change to PI at Belfast City hospital• Introduction of PIC site participant identification pathway
07 July 2015	<p>Substantial amendment 04:</p> <ul style="list-style-type: none">• Change to the PI at Addenbrookes hospital• Addition of York, Bradford, UCL, Middleborough, Leicester, Coventry as new sites• Removal of Belfast and Preston as sites.
29 June 2017	<p>Substantial amendment 05:</p> <ul style="list-style-type: none">• Addition of Belfast as a site• Change to the PI at Glasgow• Removal of Newcastle as a site

13 November 2017	<p>Substantial amendment 06:</p> <ul style="list-style-type: none"> Update to protocol information specifying that any new primary cancers at follow-up visits should be recorded within the trial CRFs and to allow for this data to be captured retrospectively. Updated protocol information to reflect changes to trial personnel and contact information. Supplementary information added for IMP from the investigators brochure Correction of several typographical errors from previous protocol version.
15 November 2017	<p>Substantial amendment 07:</p> <ul style="list-style-type: none"> Documents updated due to change in PI at the Leicester site
03 May 2018	<p>Substantial amendment 08:</p> <ul style="list-style-type: none"> Update to the reference safety information section of the Investigator Brochure (IB) so the expected ADR table includes: only those ADRs reported as serious; the frequency in numbers for each of the ADRs has been clarified; confirmation that none of these ADRs are reported as fatal.
28 March 2019	<p>Substantial amendment 09:</p> <ul style="list-style-type: none"> The recruitment period was extended for a further year until May 2019. The follow up of the last participant reduced from 2 years to 18 months giving an overall study extension of 6 months. Following slower than anticipated recruitment, and the importance of the NIMRAD biomarker work, the primary endpoint was changed from 'Loco-regional control' to 'Loco-regional control in the enriched population'. The enriched population being those patients with more hypoxic tumours. Due to the change in the primary endpoint it is now mandatory for all patients to consent to their diagnostic tumour block to be collected during screening and tested to determine if it is hypoxic. The overall recruitment target reduced from 470 to 340. The patient information sheet and informed consent form have been updated as the provision of the diagnostic tissue biopsy is now mandatory for participation in the study. The Investigator Brochure has been updated by the drug manufacturer, Azanta, and the Chief Investigator has reviewed this 7th edition. There are no changes to the risk/benefit assessment for the study. However, there are changes to the reference safety information (RSI) and we intend to use this RSI for the DSUR reporting period (Jan 2019 – Jan 2020). The Chief Investigator for the study was changed to Dr David Thomson
03 July 2019	<p>Substantial amendment 10:</p> <ul style="list-style-type: none"> Documents updated due to change in PI at the Bradford site
16 October 2019	<p>Substantial amendment 11:</p> <ul style="list-style-type: none"> Update to the Investigators Brochure (IB) and Reference Safety Information (RSI) from IB 7th edition, dated 20th April 2019 to IB 8th edition, dated 08th July 2019. <p>(Note: The RSI in IB 7th edition will continue to be used to assess expectedness for the current DSUR reporting period (January 2019 – January 2020)).</p>
29 April 2020	<p>Substantial amendment 12:</p> <ul style="list-style-type: none"> Document updates due to change in PI at the Coventry site
20 December 2020	<p>Substantial amendment 13:</p> <ul style="list-style-type: none"> Share tissue micro array slides generated from the FFPE tumour cores collected from patients enrolled on the NIMRAD trial with the Medicines Discovery Catapult. This is purely of translational interest and would not contribute to or alter any of the study end-points or objectives. Update to the Investigators Brochure (IB) and Reference Safety Information (RSI) from IB 8th edition, dated 08th July 2019 to IB 9th edition, dated 16th December 2020. Change to the PI at Sheffield Teaching Hospitals NHS Foundation Trust (from Dr Foran to Dr Lester)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported