



## 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 |
|-----------------------|----------|

#### 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:

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## 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:

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## 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:

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## 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:

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### 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                          |
| <b>Arm title</b>             | Nimorazole plus radiotherapy |

Arm description:

Therapeutic arm. Radiotherapy as per control arm. In addition, 1.2 g/m<sup>2</sup> 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/m<sup>2</sup> body surface (see table) in connection with the first daily radiation treatments. Total dose over the entire radiation period should be approximately 36 g/m<sup>2</sup> and must not exceed 40 g/m<sup>2</sup> or a total of 75 g.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Placebo plus radiotherapy |
|------------------|---------------------------|

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 |
|----------|---------|

|  |                        |
|--|------------------------|
| 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.

| <b>Number of subjects in period 1</b> | Nimorazole plus radiotherapy | Placebo plus radiotherapy |
|---------------------------------------|------------------------------|---------------------------|
| Started                               | 168                          | 170                       |
| Completed                             | 168                          | 170                       |

## Baseline characteristics

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Nimorazole plus radiotherapy |
|-----------------------|------------------------------|

Reporting group description:

Therapeutic arm. Radiotherapy as per control arm. In addition, 1.2 g/m<sup>2</sup> 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 |
|-----------------------|---------------------------|

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<br>Units: Subjects  |   |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |   |  |  |
| Age continuous<br>Units: years  |   |  |  |
| median  | 72  | 72   |  |
| full range (min-max)  | 50 to 88  | 45 to 84                                     |  |
| Gender categorical<br>Units: Subjects   |   |  |  |
| Female  |   |  |  |
| Male  |   |  |  |
| Tumour site<br>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 |
|-----------------------|------------------------------|

#### Reporting group description:

Therapeutic arm. Radiotherapy as per control arm. In addition, 1.2 g/m<sup>2</sup> 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 |
|-----------------------|---------------------------|

#### 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 |
|----------------------------|---|

|                           |                             |
|---------------------------|-----------------------------|
| 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 ≤ 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 ≤ 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 |
|-----------------|--|

#### 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 |
| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>   |
| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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    |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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              |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.0   |

### Reporting groups

|                                |                              |
|--------------------------------|------------------------------|
| Reporting group title          | Placebo plus Radiotherapy    |
| Reporting group description: - |                              |
| Reporting group title          | Nimorazole plus Radiotherapy |
| 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 %

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

|   |  |                    |  |
|---|--|--------------------|--|
| subjects affected / exposed                     | 56 / 170 (32.94%)                            | 69 / 168 (41.07%)  |  |
| occurrences (all)                               | 63   | 76                 |  |
| Respiratory, thoracic and mediastinal disorders |  |                    |  |
| HOARSENESS                                      | Additional description: HOARSENESS           |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 14 / 170 (8.24%)                             | 20 / 168 (11.90%)  |  |
| occurrences (all)                               | 16   | 24                 |  |
| Skin and subcutaneous tissue disorders          |  |                    |  |
| EDEMA NECK                                      | Additional description: EDEMA NECK           |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 17 / 170 (10.00%)                            | 17 / 168 (10.12%)  |  |
| occurrences (all)                               | 17   | 17                 |  |
| MUCOSITIS                                       | Additional description: MUCOSITIS            |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 130 / 170 (76.47%)                           | 119 / 168 (70.83%) |  |
| occurrences (all)                               | 196  | 173                |  |
| RADIATION DERMATITIS                            | Additional description: RADIATION DERMATITIS |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 5 / 170 (2.94%)                              | 6 / 168 (3.57%)    |  |
| occurrences (all)                               | 5  | 7                  |  |
| SKIN RASH                                       | Additional description: SKIN RASH            |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 37 / 170 (21.76%)                            | 41 / 168 (24.40%)  |  |
| occurrences (all)                               | 43   | 43                 |  |
| Infections and infestations                     |  |                    |  |
| INFECTION                                       | Additional description: INFECTION            |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 70 / 170 (41.18%)                            | 66 / 168 (39.29%)  |  |
| occurrences (all)                               | 88   | 79                 |  |
| Metabolism and nutrition disorders              |  |                    |  |
| ANOREXIA  | Additional description: ANOREXIA             |                    |  |
| alternative assessment type: Non-systematic     |  |                    |  |
| subjects affected / exposed                     | 98 / 170 (57.65%)                            | 97 / 168 (57.74%)  |  |
| occurrences (all)                               | 143  | 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</p> <p>Changes made to the protocol and supporting documents are as follows:</p> <ul style="list-style-type: none"><li>• Dr Mererid Evans added to trial personnel at the front of the protocol</li><li>• Change to the physics QA advisors</li><li>• Sponsor contact deleted Angela Ball's name and added Gillian Heap.</li><li>• Change to 2 PIs at other centres – Cheltenham and Belfast</li><li>• Unblinding procedure details added now that they are known.</li></ul> <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"><li>• Section 7 radiotherapy treatment details all updated in line with QA procedure - large changes throughout this section.</li><li>• Clarification that drug will take 3 working days to arrive at sites and not 2 as previously recorded.</li><li>• Clarification that translational research samples will not be required for screen failure patients. Any collected before screen failure status is known will be destroyed.</li><li>• 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</li></ul> |
| 28 October 2014  | <p>Substantial amendment 02:</p> <ul style="list-style-type: none"><li>• Change to PI at Royal Surrey centre</li><li>• Addition of new site: Hertfordshire</li><li>• Removal of existing site: Mount Vernon Hospital</li><li>• Update to protocol section around translational research tissue (includes greater detail of what the translational analysis entails)</li><li>• 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.</li></ul>  |
| 11 February 2015 | <p>Substantial amendment 03:</p> <ul style="list-style-type: none"><li>• Change to PI at Belfast City hospital</li><li>• Introduction of PIC site participant identification pathway</li></ul>  |
| 07 July 2015     | <p>Substantial amendment 04:</p> <ul style="list-style-type: none"><li>• Change to the PI at Addenbrookes hospital</li><li>• Addition of York, Bradford, UCL, Middleborough, Leicester, Coventry as new sites</li><li>• Removal of Belfast and Preston as sites.</li></ul>  |
| 29 June 2017     | <p>Substantial amendment 05:</p> <ul style="list-style-type: none"><li>• Addition of Belfast as a site</li><li>• Change to the PI at Glasgow</li><li>• Removal of Newcastle as a site</li></ul>   |

|                  |  |
|------------------|--|
| 13 November 2017 | <p>Substantial amendment 06:</p> <ul style="list-style-type: none"> <li>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.</li> <li>Updated protocol information to reflect changes to trial personnel and contact information.</li> <li>Supplementary information added for IMP from the investigators brochure</li> <li>Correction of several typographical errors from previous protocol version.</li> </ul>  |
| 15 November 2017 | <p>Substantial amendment 07:</p> <ul style="list-style-type: none"> <li>Documents updated due to change in PI at the Leicester site</li> </ul>   |
| 03 May 2018      | <p>Substantial amendment 08:</p> <ul style="list-style-type: none"> <li>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.</li> </ul>   |
| 28 March 2019    | <p>Substantial amendment 09:</p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>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.</li> <li>The overall recruitment target reduced from 470 to 340.</li> <li>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.</li> <li>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).</li> <li>The Chief Investigator for the study was changed to Dr David Thomson</li> </ul> |
| 03 July 2019     | <p>Substantial amendment 10:</p> <ul style="list-style-type: none"> <li>Documents updated due to change in PI at the Bradford site</li> </ul>  |
| 16 October 2019  | <p>Substantial amendment 11:</p> <ul style="list-style-type: none"> <li>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.<br/>(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)).</li> </ul>   |
| 29 April 2020    | <p>Substantial amendment 12:</p> <ul style="list-style-type: none"> <li>Document updates due to change in PI at the Coventry site</li> </ul>   |
| 20 December 2020 | <p>Substantial amendment 13:</p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>Change to the PI at Sheffield Teaching Hospitals NHS Foundation Trust (from Dr Foran to Dr Lester)</li> </ul>  |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported