# Clinical trial results:
# A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2016-002244-16 |
| Trial protocol | IE |
| Global end of trial date | |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 26 January 2025 |
| First version publication date | 26 January 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | NRG-HN002 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02254278 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Cancer Trials Ireland |
| Sponsor organisation address | RCSI House, Dublin, Ireland, D02 H903 |
| Public contact | Clinical Program Leader , Irish Clinical Oncology Research Group CLG, trading as Cancer Trials Ireland, +353 16677211, info@cancertrials.ie |
| Scientific contact | Clinical Program Leader , Irish Clinical Oncology Research Group CLG, trading as Cancer Trials Ireland, 0876654933 16677211, info@cancertrials.ie |
| Sponsor organisation name | NRG Oncology |
| Sponsor organisation address | 1818 Market Street, Suite 1720, Philadelphia, United States, PA 19103 |
| Public contact | Clinical Project Manager, NRG Oncology, +1 267-519-6630, info@nrgoncology.org |
| Scientific contact | Clinical Project Manager, NRG Oncology, +1 267-519-6630, info@nrgoncology.org |

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 | Interim |
| Date of interim/final analysis | 25 June 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 June 2019 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

To select the arm(s) achieving a 2-year progression-free survival rate of >= 85% without unacceptable swallowing toxicity at 1 year.

Protection of trial subjects:

The Trial was conducted in accordance with International Conference on Harmonization Good Clinical Practice Guidelines and principles of the Declaration of Helsinki of 1964. An independent, unblinded data and safety monitoring committee reviewed safety and efficacy data at predefined data points. Patients provided written informed consent before undergoing any trial-related procedures.

Background therapy:

None

Evidence for comparator:

This randomized phase II trial studies the side effects and how well modestly reduced-dose intensity-modulated radiation therapy (IMRT) with or without cisplatin works in treating patients with oropharyngeal cancer that has spread to other places in the body (advanced). Radiation therapy uses high energy x rays to kill tumor cells. Drugs used in chemotherapy, such as cisplatin, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. It is not yet known whether IMRT is more effective with or without cisplatin in treating patients with oropharyngeal cancer.

| | |
|---|---|
| Actual start date of recruitment | 01 October 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 7 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 61 |
| Country: Number of subjects enrolled | United States: 243 |
| Country: Number of subjects enrolled | Saudi Arabia: 1 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Worldwide total number of subjects | 306 |
| EEA total number of subjects | 1 |

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) | 215 |
| From 65 to 84 years | 91 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

From October 27th 2014 to February 7th 2017, a total of 316 patients were enrolled and 308 were randomized, of whom 2 were subsequently determined to ineligible

### Pre-assignment

Screening details:

After first step registration and prior to randomization, patients were tested for p16. Only patients with p16-positive tumors continued on to randomization. In total, 316 patients were enrolled and 308 were randomized.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 308[1] |
| Number of subjects completed | 306 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Protocol deviation: 2 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 308 subjects were randomized but only 306 subjects were randomized and eligible.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | IMRT 6 Weeks + Cisplatin |

Arm description:

Cisplatin: 40 mg/m2 IV (intravenously) weekly for 6 weeks
IMRT 6 weeks: Intensity-modulated radiation therapy (IMRT), 30 fractions over 6 weeks, 5 fractions per week, 2 Gray per fraction to total dose of 60 Gy

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

40 mg/m2 IV (intravenously) weekly for 6 weeks
Radiation: IMRT 6 weeks, 30 fractions over 6 weeks, 5 fractions per week, 2 Gray per fraction to total dose of 60 Gy

| | |
|---|---|
| **Arm title** | IMRT 5 weeks |

Arm description:

Intensity-modulated radiation therapy (IMRT), 30 fractions over 5 weeks, 6 fractions per week, 2 Gray per fraction to total dose of 60 Gy

| | |
|---|---|
| Arm type | Intenisty-modulated Radiotherapy |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks |
|---|---|---|
| Started | 157 | 149 |
| Completed | 157 | 149 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | IMRT 6 Weeks + Cisplatin |
| Reporting group description: | |
| Cisplatin: 40 mg/m2 IV (intravenously) weekly for 6 weeks<br>IMRT 6 weeks: Intensity-modulated radiation therapy (IMRT), 30 fractions over 6 weeks, 5 fractions per week, 2 Gray per fraction to total dose of 60 Gy | |
| Reporting group title | IMRT 5 weeks |
| Reporting group description: | |
| Intensity-modulated radiation therapy (IMRT), 30 fractions over 5 weeks, 6 fractions per week, 2 Gray per fraction to total dose of 60 Gy | |

| Reporting group values | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | Total |
|---|---|---|---|
| Number of subjects | 157 | 149 | 306 |
| Age categorical | | | |
| Randomized and eligible patients | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 108 | 107 | 215 |
| From 65-84 years | 49 | 42 | 91 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 25 | 49 |
| Male | 133 | 124 | 257 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 3 | 7 | 10 |
| Not Hispanic or Latino | 143 | 130 | 273 |
| Unknown or Not Reported | 11 | 12 | 23 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 0 | 4 | 4 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 2 | 3 |
| White | 151 | 130 | 281 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 4 | 12 | 16 |
| Zubrod performance status<br>Units: Subjects | | | |
| 0: Asymptomatic | 132 | 113 | 245 |

| | | | |
|---|---|---|---|
| 1: Symptomatic but completely ambulatory | 25 | 36 | 61 |
| Smoking history (pack years) | | | |
| Smoking history as measured in pack-years, calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. | | | |
| Units: Subjects | | | |
| =0 | 112 | 101 | 213 |
| >0-<5 | 26 | 32 | 58 |
| 5-10 | 19 | 16 | 35 |
| T Stage | | | |
| Tumor stage per the American Joint Committee on Cancer (AJCC) 7th ed. refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b. | | | |
| Units: Subjects | | | |
| T1 | 64 | 51 | 115 |
| T2 | 67 | 80 | 147 |
| T3 | 26 | 18 | 44 |
| N Stage | | | |
| Regional lymph nodes staging per American Joint Committee on Cancer (AJCC) 7th ed. refers to the number and/or extent of spread of lymph nodes that contain cancer. The higher the number after the N, the greater the involvement of regional lymph nodes. | | | |
| Units: Subjects | | | |
| N0 | 6 | 7 | 13 |
| N1 | 28 | 34 | 62 |
| N2a | 24 | 19 | 43 |
| N2b | 99 | 89 | 188 |
| Primary tumor site<br>Units: Subjects | | | |
| Oropharynx NOS | 4 | 13 | 17 |
| Tonsillar fossa | 83 | 78 | 161 |
| Base of tongue | 68 | 58 | 126 |
| Pharyngeal oropharynx | 1 | 0 | 1 |
| Posterior pharyngeal wll | 1 | 0 | 1 |
| Radiation Therapy (RT) planning (as stratified) | | | |
| Radiation therapy plan included unilateral or bilateral radiation to the neck, as provided by the treating site at stratification. | | | |
| Units: Subjects | | | |
| Unilateral | 52 | 47 | 99 |
| Bilateral | 105 | 102 | 207 |
| RT planning (per central review) | | | |
| Radiation therapy plan included unilateral or bilateral radiation to the neck, as provided by central review by the study radiation oncologist. | | | |
| Units: Subjects | | | |
| Unilateral | 16 | 21 | 37 |
| Bilateral | 136 | 125 | 261 |
| Unknown | 5 | 3 | 8 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | IMRT 6 Weeks + Cisplatin |
| Reporting group description: | |
| Cisplatin: 40 mg/m2 IV (intravenously) weekly for 6 weeks<br>IMRT 6 weeks: Intensity-modulated radiation therapy (IMRT), 30 fractions over 6 weeks, 5 fractions per week, 2 Gray per fraction to total dose of 60 Gy | |
| Reporting group title | IMRT 5 weeks |
| Reporting group description: | |
| Intensity-modulated radiation therapy (IMRT), 30 fractions over 5 weeks, 6 fractions per week, 2 Gray per fraction to total dose of 60 Gy | |
| Subject analysis set title | Both Arms Combined |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| IMRT 6 Weeks + Cisplatin (Arm 1)and IMRT 5 weeks (Arm 2) combined | |
| Subject analysis set title | Both Arms Combined |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| IMRT 6 Weeks + Cisplatin (Arm 1)and IMRT 5 weeks (Arm 2) combined<br>This subject set is created as a workaround for reporting statistical analysis. | |
| Subject analysis set title | IMRT 6 Weeks + Cisplatin (Arm 1) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| This subject analysis set is being set up for a workaround for reporting statistical analysis | |
| Subject analysis set title | IMRT 5 Weeks (Arm 2) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| This subject analysis set is set up as a workaround to report statistical analysis | |
| Subject analysis set title | IMRT 6 Weeks + Cisplatin (Arm 1) 1 month post-RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Subject analysis set Arm 1 - 1 month post RT | |
| Subject analysis set title | IMRT 5 Weeks (Arm 2) 1 month post RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Subject analysis set - Arm 2 1 month Post RT | |
| Subject analysis set title | IMRT 6 Weeks + Cisplatin (Arm 1) 6 months post-RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| 6 months after end of radiation therapy (RT) | |
| Subject analysis set title | IMRT 5 weeks (Arm 2) 6 months post RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| 6 months after end of radiation therapy (RT) | |
| Subject analysis set title | IMRT 6 Weeks + Cisplatin (Arm 1) 1 year post-RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| 1 year after end of Radiation therapy (RT) | |
| Subject analysis set title | IMRT 5 weeks (Arm 2) 1 year post RT |
| Subject analysis set type | Sub-group analysis |

| | |
|---|---|
| Subject analysis set description:<br>1 year after end of radiation therapy (RT) | |
| Subject analysis set title | IMRT 6 Weeks + Cisplatin (Arm 1) 2 years post-RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description:<br>2 years after end of radiation therapy (RT) | |
| Subject analysis set title | IMRT 5 weeks (Arm 2) 2 years post RT |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description:<br>2 years after end of radiation therapy (RT) | |

## Primary: Percentage of Participants Alive Without Progression at Two Years (Progression-free Survival)

| | |
|---|---|
| End point title | Percentage of Participants Alive Without Progression at Two Years (Progression-free Survival) |

End point description:

Progression is defined as local, regional, or distant disease progression or death due to any cause.
Percentage is estimated using the binomial distribution.
Two-year data was available for 147/157 (Arm 1) and 145/149 (Arm 2) randomized and eligible participants.
One-side confidence interval

| | |
|---|---|
| End point type | Primary |
| End point timeframe:<br>From randomization to 2 years | |

| **End point values** | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 147 | 145 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 90.5 | 87.6 | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Assuming a binomial distribution, 140 eligible patients per arm were required for 80% power and 1-sided type I error rate of 10% to test the null hypothesis of 2-year progression-free survival (PFS) rate ≤ 85% against the alternative hypothesis of > 85% with a binomial test. The arms are not compared to each other; they are each tested separately against the null hypothesis.

| | |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin v IMRT 5 weeks |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 [1] |
| Method | Binomial |

Notes:

[1] - One-sided significance level=0.10

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Assuming a binomial distribution, 140 eligible patients per arm were required for 80% power and 1-sided type I error rate of 10% to test the null hypothesis of 2-year PFS rate ≤ 85% against the alternative hypothesis of > 85% with a binomial test. The arms are not compared to each other; they are each tested separately against the null hypothesis.

| | |
|---|---|
| Comparison groups | IMRT 5 weeks v IMRT 6 Weeks + Cisplatin |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | Binomial |
| Confidence interval | |
| level | Other: 10 % |
| sides | 1-sided |

## Secondary: Percentage of Participants With Local-regional Failure

| End point title | Percentage of Participants With Local-regional Failure |
|---|---|

End point description:

Local-regional failure is defined as local or regional progression, salvage surgery of the primary tumor with tumor present/unknown, salvage neck dissection with tumor present/unknown > 20 weeks after the end of radiation therapy, death due to study cancer without documented progression, or death due to unknown causes without documented progression. Distant metastasis and death due to other causes are considered competing risks. Local-regional failure time is defined as time from randomization to the date of first progression/death or last known follow-up (censored). Rates are estimated by the cumulative incidence method.

| End point type | Secondary |
|---|---|

End point timeframe:

From randomization to 2 years

| **End point values** | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157 | 149 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Six months | 0.7 (0.1 to 3.3) | 2.0 (0.6 to 5.4) | | |
| Two Years | 3.3 (1.2 to 7.1) | 9.5 (5.5 to 15.0) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | IMRT 5 weeks v IMRT 6 Weeks + Cisplatin |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.17 |
| upper limit | 0.9 |

Notes:

[2] - Two-sided significance level = 0.05

## Secondary: Percentage of Participants With Distant Metastasis

| End point title | Percentage of Participants With Distant Metastasis |
|---|---|

End point description:

Distant metastasis is defined as distant progression. Local-regional failure and death due to any cause are considered competing risks. Distant metastasis time is defined as time from randomization to the date of progression/death or last known follow-up (censored). Rates are estimated by the cumulative incidence method.

| End point type | Secondary |
|---|---|

End point timeframe:

From randomization to 2 years

| End point values | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157 | 149 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Six months | 0 (0 to 0) | 0 (0 to 0) | | |
| Two years | 4 (1.6 to 8.0) | 2.1 (0.6 to 5.5) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin v IMRT 5 weeks |

| | |
|---|---|
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.58 [4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 5.08 |

Notes:

[3] - Estimation Comments Reference level = IMRT 5 weeks

[4] - Two-sided significance level = 0.05

## Secondary: Percentage of Participants Alive

| | |
|---|---|
| End point title | Percentage of Participants Alive |

End point description:

Overall survival time is defined as time from randomization to the date of death or last known follow-up (censored). Overall survival rates are estimated by the Kaplan-Meier method.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From randomization to 2 years

| End point values | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157 | 149 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Six months | 99.3 (98.1 to 100) | 98.0 (95.7 to 100) | | |
| Two years | 96.7 (93.9 to 99.5) | 97.3 (94.6 to 99.9) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin v IMRT 5 weeks |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.93 [6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 2.95 |

Notes:

[5] - Estimation Comments Reference level = IMRT 5 weeks

[6] - Two-side significance level = 0.05

## Secondary: Percentage of Participants With Grade 3+ Adverse Events (End of RT)

| End point title | Percentage of Participants With Grade 3+ Adverse Events (End of RT) |
|---|---|

End point description:

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade refers to the severity of the AE. The CTCAE v4.0 assigns Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening or disabling, Grade 5 Death related to AE.

| End point type | Secondary |
|---|---|

End point timeframe:

End of radiation therapy (RT) (approximately 6 weeks for Arm 1 and 5 weeks for Arm 2).

| **End point values** | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 152 | 147 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 73.7 (65.9 to 80.5) | 46.3 (38.0 to 54.7) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

End of RT

| Comparison groups | IMRT 6 Weeks + Cisplatin v IMRT 5 weeks |
|---|---|
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | < 0.0001 [8] |
| Method | Fisher exact |

Notes:

[7] - End of RT

[8] - Two-sided significance level = 0.05

## Secondary: Mean One-year Total MD Anderson Dysphagia Inventory (MDADI) Score (Patient-reported Swallowing Outcome)

| End point title | Mean One-year Total MD Anderson Dysphagia Inventory (MDADI) Score (Patient-reported Swallowing Outcome) |
|---|---|

End point description:

The MDADI is a 20-item tool with each item scored as Strongly agree; Agree; No opinion; Disagree; or Strongly disagree. There is 1 global item (G1), 6 emotional subscale items (E2-E7), 5 functional subscale items (F1-F5), and 8 physical subscale items (P1-P8). For all items except E7 and F2, Strongly agree corresponds to a score of 1, Agree 2, No opinion 3, Disagree 4, and Strongly disagree 5. For E7 and F2, the scores are reversed; these 2 items are rescored to match the others before calculating summary scores. The composite (total) score is the mean of the 19 items (other than G1) X 20. Composite scores range from 20 to 100 with higher scores indicating less dysphagia.

| End point type | Secondary |
|---|---|

End point timeframe:

One year post-RT. Radiation therapy (RT) ends at approximately 6 weeks for Arm 1 and 5 weeks for Arm 2

| **End point values** | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 121[9] | 106[10] | | |
| Units: Score on scale | | | | |
| arithmetic mean (confidence interval 95%) | 85.3 (82.5 to 88.1) | 81.8 (79.0 to 84.5) | | |

Notes:

[9] - 121 Arm 1 participants had one year post-RT data.

[10] - 106 Arm 2 participants had one year post-RT data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Negative Predictive Value (NPV) of Post-treatment FDG-PET/CT Scan [Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/Computed Tomography (CT)] for Progression-free Survival and Local-regional Control at Two Years

| End point title | Negative Predictive Value (NPV) of Post-treatment FDG-PET/CT Scan [Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/Computed Tomography (CT)] for Progression-free Survival and Local-regional Control at Two Years |
|---|---|

End point description:

NPV is the percentage of participants alive and failure-free at 2 years among those with a negative post-treatment scan, as evaluated by central review. Negative scan determined as follows: primary site, right neck, left neck evaluated using a 5-point ordinal scale: 1-Definite complete metabolic response (CMR), 2-Likely CMR, 3-Likely inflammatory, 4-Likely residual metabolic disease (RMD), and 5-Definite RMD. 'Negative'= 1 or 2, 'Indeterminate'=3, 'Positive' = 4 or 5. 'Negative' for all three evaluation sites = overall score of 'Negative.' Progression (failure) is defined as local, regional, or distant disease progression (PR) or any death. Local-regional progression (failure) is defined as local or regional PR, salvage surgery of the primary tumor with tumor present/unknown, salvage neck dissection with tumor present/unknown > 20 weeks post RT, death due to study cancer or unknown causes without documented PR. The protocol specified that both arms would be combined for analysis.

| End point type | Secondary |
|---|---|

End point timeframe:

3 months (scan) and two years after the end of RT (approximately 6 weeks for Arm 1 and 5 weeks for Arm 2)

| End point values | Both Arms Combined | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 115 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Progression-free Survival | 92.0 | | | |
| Local-regional failure | 94.5 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Grade 3+ Adverse Events (1 month Post RT)

| End point title | Percentage of Participants With Grade 3+ Adverse Events (1 month Post RT) |
|---|---|

End point description:

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade refers to the severity of the AE. The CTCAE v4.0 assigns Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening or disabling, Grade 5 Death related to AE.

| End point type | Secondary |
|---|---|

End point timeframe:

1 month post radiation therapy (RT)

| End point values | IMRT 6 Weeks + Cisplatin (Arm 1) 1 month post-RT | IMRT 5 Weeks (Arm 2) 1 month post RT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 144 | 142 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 36.1 (28.3 to 44.5) | 28.2 (21.0 to 36.3) | | |

### Statistical analyses

| Statistical analysis title | One month after end of RT |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin (Arm 1) 1 month post-RT v IMRT 5 Weeks (Arm 2) 1 month post RT |

| | |
|---|---|
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 [11] |
| Method | Fisher exact |

Notes:

[11] - Two-sided significance level = 0.05

## Secondary: Percentage of Participants With Grade 3+ Adverse Events (6 months Post RT)

| | |
|---|---|
| End point title | Percentage of Participants With Grade 3+ Adverse Events (6 months Post RT) |

End point description:

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade refers to the severity of the AE. The CTCAE v4.0 assigns Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening or disabling, Grade 5 Death related to AE.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

6 months post Radiation therapy (RT)

| End point values | IMRT 6 Weeks + Cisplatin (Arm 1) 6 months post-RT | IMRT 5 weeks (Arm 2) 6 months post RT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 140 | 126 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 17.9 (11.9 to 25.2) | 11.1 (6.2 to 17.9) | | |

### Statistical analyses

| Statistical analysis title | 6 months after end of RT |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin (Arm 1) 6 months post-RT v IMRT 5 weeks (Arm 2) 6 months post RT |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.16 |
| Method | Fisher exact |

Notes:

[12] - Two-side significance level = 0.05

## Secondary: Percentage of Participants With Grade 3+ Adverse Events (1 year Post RT)

| | |
|---|---|
| End point title | Percentage of Participants With Grade 3+ Adverse Events (1 year Post RT) |

End point description:

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade refers to the severity of the AE. The CTCAE v4.0 assigns Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening or disabling, Grade 5 Death related to AE.

| End point type | Secondary |
|---|---|

End point timeframe:

1 year after end of radiation therapy (RT)

| **End point values** | IMRT 6 Weeks + Cisplatin (Arm 1) 1 year post-RT | IMRT 5 weeks (Arm 2) 1 year post RT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 143 | 134 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 14.0 (8.8 to 20.8) | 9.0 (4.7 to 15.1) | | |

**Statistical analyses**

| **Statistical analysis title** | 1 year after end of RT |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin (Arm 1) 1 year post-RT v IMRT 5 weeks (Arm 2) 1 year post RT |
| Number of subjects included in analysis | 277 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.26 |
| Method | Fisher exact |

Notes:

[13] - Two-sided significance level =0.05

## Secondary: Percentage of Participants With Grade 3+ Adverse Events (2 years Post RT)

| End point title | Percentage of Participants With Grade 3+ Adverse Events (2 years Post RT) |
|---|---|

End point description:

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade refers to the severity of the AE. The CTCAE v4.0 assigns Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening or disabling, Grade 5 Death related to AE.

| End point type | Secondary |
|---|---|

End point timeframe:

2 years after end of radiation therapy (RT)

| End point values | IMRT 6 Weeks + Cisplatin (Arm 1) 2 years post-RT | IMRT 5 weeks (Arm 2) 2 years post RT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 128 | 122 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 8.6 (4.4 to 14.9) | 7.4 (3.4 to 13.5) | | |

**Statistical analyses**

| Statistical analysis title | 2 years after end of RT |
|---|---|
| Comparison groups | IMRT 6 Weeks + Cisplatin (Arm 1) 2 years post-RT v IMRT 5 weeks (Arm 2) 2 years post RT |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[14] |
| P-value | = 0.82 |
| Method | Fisher exact |

Notes:

[14] - Two-side significance level = 0.05

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Weekly during treatment, 1 & 3 months after EOT, then every 3 months from end of treatment for 2 years, every 6 months from end of treatment for 3 years, then annually until study completion. Maximum follow-up at time of reporting was 4.1 years.

Adverse event reporting additional description:

The Assessment type for the Adverse Events documented was both Systematic and Non-Systematic.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | IMRT 6 Weeks + Cisplatin |

Reporting group description:

IMRT 6 weeks: Intensity-modulated radiation therapy (IMRT), 30 fractions over 6 weeks, 5 fractions per week, 2 Gray per fraction to total dose of 60 Gy

| | |
|---|---|
| Reporting group title | IMRT 5 weeks |

Reporting group description:

Intensity-modulated radiation therapy (IMRT), 30 fractions over 5 weeks, 6 fractions per week, 2 Gray per fraction to total dose of 60 Gy

| Serious adverse events | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 152 (20.39%) | 11 / 147 (7.48%) | |
| number of deaths (all causes) | 6 | 6 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thromboemboloic event | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 6 / 152 (3.95%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| alternative assessment type: Non- | | | |

| | | | |
|---|---|---|---|
| systematic | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flu like symptoms | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 147 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngeal mucositis | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngolaryngeal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Sore throat | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Creatinine increased | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Heart failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dysarthria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 147 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal detachment | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 2 / 147 (1.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Esophagitis | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Neck soft tissue necrosis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (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 | | | |
| Appendicitis | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Hypocalcaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | IMRT 6 Weeks + Cisplatin | IMRT 5 weeks | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 152 / 152 (100.00%) | 147 / 147 (100.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 10 / 152 (6.58%) | 11 / 147 (7.48%) | |
| occurrences (all) | 25 | 21 | |
| Lymphoedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 11 / 147 (7.48%) | |
| occurrences (all) | 13 | 13 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 138 / 152 (90.79%) | 117 / 147 (79.59%) | |
| occurrences (all) | 280 | 245 | |
| Fever | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 2 / 147 (1.36%) | |
| occurrences (all) | 9 | 2 | |
| Neck edema | | | |

| | | | |
|---|---|---|---|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 10 / 147 (6.80%) | |
| occurrences (all) | 6 | 12 | |
| Pain | | | |
| subjects affected / exposed | 115 / 152 (75.66%) | 121 / 147 (82.31%) | |
| occurrences (all) | 226 | 262 | |
| General disorders and administration site conditions - Other | | | |
| subjects affected / exposed | 6 / 152 (3.95%) | 11 / 147 (7.48%) | |
| occurrences (all) | 13 | 14 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 38 / 152 (25.00%) | 37 / 147 (25.17%) | |
| occurrences (all) | 62 | 57 | |
| Hiccups | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 0 / 147 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Hoarseness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 18 / 152 (11.84%) | 19 / 147 (12.93%) | |
| occurrences (all) | 25 | 25 | |
| Respiratory, thoracic and mediastinal disorders - Other | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 8 / 147 (5.44%) | |
| occurrences (all) | 9 | 9 | |
| Sore throat | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 42 / 152 (27.63%) | 28 / 147 (19.05%) | |
| occurrences (all) | 55 | 39 | |
| Voice alteration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 13 / 147 (8.84%) | |
| occurrences (all) | 11 | 14 | |
| Pharyngeal mucosistis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 29 / 152 (19.08%) | 44 / 147 (29.93%) | |
| occurrences (all) | 39 | 61 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 15 / 147 (10.20%) | |
| occurrences (all) | 12 | 18 | |
| Depression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 12 / 152 (7.89%) | 7 / 147 (4.76%) | |
| occurrences (all) | 20 | 9 | |
| Insomnia | | | |
| subjects affected / exposed | 44 / 152 (28.95%) | 34 / 147 (23.13%) | |
| occurrences (all) | 62 | 55 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 14 / 152 (9.21%) | 7 / 147 (4.76%) | |
| occurrences (all) | 15 | 8 | |
| Aspartate aminotransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 12 / 152 (7.89%) | 7 / 147 (4.76%) | |
| occurrences (all) | 12 | 9 | |
| Blood bilirubin increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 5 / 147 (3.40%) | |
| occurrences (all) | 13 | 7 | |
| Creatinine increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 26 / 152 (17.11%) | 3 / 147 (2.04%) | |
| occurrences (all) | 28 | 3 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 118 / 152 (77.63%) | 87 / 147 (59.18%) | |
| occurrences (all) | 248 | 158 | |
| Neutrophil count decreased | | | |

| | | | |
|---|---|---|---|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 33 / 152 (21.71%) | 3 / 147 (2.04%) | |
| occurrences (all) | 40 | 3 | |
| Platelet count decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 53 / 152 (34.87%) | 8 / 147 (5.44%) | |
| occurrences (all) | 70 | 12 | |
| Weight loss | | | |
| subjects affected / exposed | 119 / 152 (78.29%) | 101 / 147 (68.71%) | |
| occurrences (all) | 235 | 186 | |
| White blood cell count decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 56 / 152 (36.84%) | 13 / 147 (8.84%) | |
| occurrences (all) | 90 | 14 | |
| Injury, poisoning and procedural complications | | | |
| Dermatitis radiation | | | |
| subjects affected / exposed | 113 / 152 (74.34%) | 109 / 147 (74.15%) | |
| occurrences (all) | 147 | 135 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 15 / 152 (9.87%) | 8 / 147 (5.44%) | |
| occurrences (all) | 17 | 8 | |
| Dysgeusia | | | |
| subjects affected / exposed | 142 / 152 (93.42%) | 132 / 147 (89.80%) | |
| occurrences (all) | 312 | 281 | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 12 / 152 (7.89%) | 11 / 147 (7.48%) | |
| occurrences (all) | 13 | 14 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 29 / 152 (19.08%) | 15 / 147 (10.20%) | |
| occurrences (all) | 51 | 29 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 92 / 152 (60.53%) | 35 / 147 (23.81%) | |
| occurrences (all) | 172 | 49 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 4 / 147 (2.72%) | |
| occurrences (all) | 10 | 4 | |
| Hearing impaired | | | |
| subjects affected / exposed | 43 / 152 (28.29%) | 34 / 147 (23.13%) | |
| occurrences (all) | 95 | 72 | |
| Tinnitus | | | |
| subjects affected / exposed | 65 / 152 (42.76%) | 41 / 147 (27.89%) | |
| occurrences (all) | 119 | 75 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 92 / 152 (60.53%) | 53 / 147 (36.05%) | |
| occurrences (all) | 118 | 75 | |
| Diarrhoea | | | |
| subjects affected / exposed | 26 / 152 (17.11%) | 14 / 147 (9.52%) | |
| occurrences (all) | 30 | 17 | |
| Dry mouth | | | |
| subjects affected / exposed | 150 / 152 (98.68%) | 142 / 147 (96.60%) | |
| occurrences (all) | 391 | 365 | |
| Dyspepsia | | | |
| subjects affected / exposed | 42 / 152 (27.63%) | 31 / 147 (21.09%) | |
| occurrences (all) | 57 | 52 | |
| Dysphagia | | | |
| subjects affected / exposed | 124 / 152 (81.58%) | 119 / 147 (80.95%) | |
| occurrences (all) | 259 | 282 | |
| Gastrooesophageal reflux disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 3 / 147 (2.04%) | |
| occurrences (all) | 9 | 6 | |
| Gastrointestinal disorder | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 16 / 152 (10.53%) | 13 / 147 (8.84%) | |
| occurrences (all) | 29 | 19 | |
| Mucositis oral | | | |
| subjects affected / exposed | 131 / 152 (86.18%) | 121 / 147 (82.31%) | |
| occurrences (all) | 193 | 172 | |
| Nausea | | | |
| subjects affected / exposed | 109 / 152 (71.71%) | 62 / 147 (42.18%) | |
| occurrences (all) | 145 | 84 | |
| Oral pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 9 / 147 (6.12%) | |
| occurrences (all) | 11 | 13 | |
| Vomiting | | | |
| subjects affected / exposed | 51 / 152 (33.55%) | 30 / 147 (20.41%) | |
| occurrences (all) | 61 | 37 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 28 / 152 (18.42%) | 25 / 147 (17.01%) | |
| occurrences (all) | 34 | 34 | |
| Dry skin | | | |
| subjects affected / exposed | 36 / 152 (23.68%) | 35 / 147 (23.81%) | |
| occurrences (all) | 54 | 45 | |
| Skin and subcutaneous tissue disorders - Other | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 12 / 152 (7.89%) | 10 / 147 (6.80%) | |
| occurrences (all) | 15 | 13 | |
| Skin hyperpigmentation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 9 / 147 (6.12%) | |
| occurrences (all) | 3 | 9 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 18 / 152 (11.84%) | 16 / 147 (10.88%) | |
| occurrences (all) | 28 | 23 | |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 7 / 152 (4.61%) | 11 / 147 (7.48%) | |
| occurrences (all) | 7 | 15 | |
| Trismus | | | |
| subjects affected / exposed | 22 / 152 (14.47%) | 25 / 147 (17.01%) | |
| occurrences (all) | 31 | 36 | |
| Infections and infestations | | | |
| Infections and infestations - Other | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 12 / 152 (7.89%) | 7 / 147 (4.76%) | |
| occurrences (all) | 12 | 9 | |
| Mucosal infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 10 / 152 (6.58%) | 10 / 147 (6.80%) | |
| occurrences (all) | 11 | 14 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 81 / 152 (53.29%) | 69 / 147 (46.94%) | |
| occurrences (all) | 116 | 96 | |
| Dehydration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 23 / 152 (15.13%) | 11 / 147 (7.48%) | |
| occurrences (all) | 28 | 12 | |
| Hyperglycaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 27 / 152 (17.76%) | 13 / 147 (8.84%) | |
| occurrences (all) | 35 | 16 | |
| Hyperkalaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 4 / 147 (2.72%) | |
| occurrences (all) | 11 | 5 | |
| Hypoalbuminaemia | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 23 / 152 (15.13%) | 11 / 147 (7.48%) | |
| occurrences (all) | 26 | 11 | |
| Hypocalcaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 14 / 152 (9.21%) | 4 / 147 (2.72%) | |
| occurrences (all) | 14 | 4 | |
| Hypokalaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 16 / 152 (10.53%) | 4 / 147 (2.72%) | |
| occurrences (all) | 22 | 8 | |
| Hypomagnesaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 31 / 152 (20.39%) | 3 / 147 (2.04%) | |
| occurrences (all) | 40 | 3 | |
| Hyponatraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 33 / 152 (21.71%) | 9 / 147 (6.12%) | |
| occurrences (all) | 44 | 11 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 September 2016 | SA01 Protocol Amendment 2 24-May-2016 which included the addition of an optional modified barium swallow sub study and changes to the open eligibility checklist. |
| 12 February 2018 | Protocol Amendment 3 20-Dec-2017 was submitted as a non-substantial amendment. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes:

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/33507809