Clinical trial results:
A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of squamous cell carcinoma of the head and neck.

Summary

EudraCT number	2013-002441-12
Trial protocol	BE NL PL
Global end of trial date	06 September 2019

Results information

Result version number	v1 (current)
This version publication date	05 December 2020
First version publication date	05 December 2020

Trial information

Trial identification

Sponsor protocol code	1219

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01880359
WHO universal trial number (UTN)	-
Other trial identifiers	DAHANCA: DAHANCA-29

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	83 Avenue Emmanuel Mounier, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dep , European Organisation for Research and Treatment of Cancer, +32 27741542, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dep , European Organisation for Research and Treatment of Cancer, +32 27741542, regulatory@eortc.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2018
Global end of trial reached?	Yes
Global end of trial date	06 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

There are two primary objectives in this study:
- to evaluate in a blinded randomized trial, whether the hypoxic cell radiosensitizer nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with cisplatin given to patients with locally advanced (HNSCC) larynx, hypopharynx and HPV/p16 negative oropharynx.
- To investigate if patients who may have such benefit can be predicted by the use of a hypoxic gene profile, i.e. if the treatment benefit is larger and essentially restricted to the subset of patients who are hypoxic cell signature positive.

Protection of trial subjects:

The responsible investigator ensures that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).
The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Accelerated radiotherapy (70 Gy, 6 fractions/week) + Cisplatin (as either a weekly schedule of 40 mg/m2 (delivered
on 5 days) or 100 mg/m2 (delivered on day 1 and 22))

Evidence for comparator: -

Actual start date of recruitment	25 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 43
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Belgium: 42
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Canada: 5

Worldwide total number of subjects	194
EEA total number of subjects	165

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)	137
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 194 patients were randomized between 19th August 2014 and 9th January 2018 in 19 institutions from 8 countries.

Pre-assignment

Screening details:

- Newly diagnosed tumors stage III-IV located in the larynx, oropharynx and hypopharynx
· Histopathological diagnosis of invasive SCC in the primary tumor
· M0
· HPV/p16 negative for tumors of the oropharynx (larynx & hypopharynx regardless of the HPV status)
· WHO performance status 0-2
- Material for hypoxic gene signature test

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nimorazole - Cisplatin 40mg

Arm description: -

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

Dosage and administration details:

Nimorazole/placebo is to be administered in doses of approximately 1.2 g/m2 body surface area prior to daily irradiation treatments (first daily irradiation treatment if there are 2 given on that day). Total dose over the entire irradiation period should be approximately 36 g/m2 and must not exceed 40 g/m2 or a total of 75 g. This dose level provides maximum radiotherapy enhancement ratio and is the maximum tolerated dose level.

Table 1: Nimorazole dose prescription

Body surface1	# tablets/intake	Dose of nimorazole/intake	Total dose
< 1.6 m2	3	1.5 g	45 g
1.6–1.9 m2	4	2.0 g	60 g
> 1.9 m2	5	2.5 g	75 g

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

Dosage and administration details:

Cisplatin 40 mg/m² i.v. on day 1, 8, 15, 22, 29 of radiotherapy.

Arm title	Placebo - Cisplatin 40mg

Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 40 mg/m² i.v. on day 1, 8, 15, 22, 29 of radiotherapy.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nimorazole/placebo is to be administered in doses of approximately 1.2 g/m2 body surface area prior to daily irradiation treatments (first daily irradiation treatment if there are 2 given on that day). Total dose over the entire irradiation period should be approximately 36 g/m2 and must not exceed 40 g/m2 or a total of 75 g. This dose level provides maximum radiotherapy enhancement ratio and is the maximum tolerated dose level.

Table 1: Nimorazole dose prescription

Body surface1	# tablets/intake	Dose of nimorazole/intake	Total dose
< 1.6 m2	3	1.5 g	45 g
1.6–1.9 m2	4	2.0 g	60 g
> 1.9 m2	5	2.5 g	75 g

Arm title	Nimorazole - Cisplatin 100mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nimorazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nimorazole/placebo is to be administered in doses of approximately 1.2 g/m2 body surface area prior to daily irradiation treatments (first daily irradiation treatment if there are 2 given on that day). Total dose over the entire irradiation period should be approximately 36 g/m2 and must not exceed 40 g/m2 or a total of 75 g. This dose level provides maximum radiotherapy enhancement ratio and is the maximum tolerated dose level.

Table 1: Nimorazole dose prescription

Body surface1	# tablets/intake	Dose of nimorazole/intake	Total dose
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1.6–1.9 m2	4	2.0 g	60 g
> 1.9 m2	5	2.5 g	75 g

Investigational medicinal product name	Cisplatin 100mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 100 mg/m² i.v. on day 1 and 22 of radiotherapy

Arm title	Placebo - Cisplatin 100mg

Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nimorazole/placebo is to be administered in doses of approximately 1.2 g/m2 body surface area prior to daily irradiation treatments (first daily irradiation treatment if there are 2 given on that day). Total dose over the entire irradiation period should be approximately 36 g/m2 and must not exceed 40 g/m2 or a total of 75 g. This dose level provides maximum radiotherapy enhancement ratio and is the maximum tolerated dose level.

Table 1: Nimorazole dose prescription

Body surface1	# tablets/intake	Dose of nimorazole/intake	Total dose
< 1.6 m2	3	1.5 g	45 g
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> 1.9 m2	5	2.5 g	75 g

Investigational medicinal product name	Cisplatin 100mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 100 mg/m² i.v. on day 1 and 22 of radiotherapy

Number of subjects in period 1	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg
Started	60	62	37
Completed	33	47	26
Not completed	27	15	11
Patient decision	9	3	2
Start of new anti-cancer treatment	-	-	-
Adverse event, non-fatal	12	3	6
Other	5	7	2
Death	-	1	-
Both toxicity and patient decision	-	-	1
Did not start allocated treatment	1	1	-

Number of subjects in period 1	Placebo - Cisplatin 100mg
Started	35
Completed	29
Not completed	6
Patient decision	2
Start of new anti-cancer treatment	1
Adverse event, non-fatal	3

Other	-
Death	-
Both toxicity and patient decision	-
Did not start allocated treatment	-

Baseline characteristics

Reporting groups	
Reporting group title	Nimorazole - Cisplatin 40mg
Reporting group description: -	
Reporting group title	Placebo - Cisplatin 40mg
Reporting group description: -	
Reporting group title	Nimorazole - Cisplatin 100mg
Reporting group description: -	
Reporting group title	Placebo - Cisplatin 100mg
Reporting group description: -	

Reporting group values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg
Number of subjects	60	62	37
Age categorical 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)	38	44	30
From 65-84 years	22	18	7
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	13	15	4
Male	47	47	33
WHO PS			
PS = Performance Status			
Units: Subjects			
PS=0	35	37	21
PS=1	23	24	16
PS=2	2	1	0
Smoking habit Units: Subjects			
never smoked	0	2	2
stopped > 20 years before diagnosis	6	2	3
stopped < 20 years before diagnosis	27	31	15
current smoker	27	26	17
Missing	0	1	0
Alcohol habit Units: Subjects			
never drank alcohol	6	3	2
drank alcohol in the past	23	20	11

current drinker of alcohol	30	39	21
Missing	1	0	3
History of past oncological disease Units: Subjects			
NO	57	57	37
Yes	3	5	0
Location of newly diagnosed tumors Units: Subjects			
larynx	18	10	6
oropharynx	24	32	21
hypopharynx	18	20	10
Clinical T stage			
AJCC 7th edition			
Units: Subjects			
T1	1	1	2
T2	12	12	9
T3	21	21	13
T4	26	28	13
Clinical N stage Units: Subjects			
N0	8	18	8
N1	7	5	7
N2	44	38	22
N3	1	1	0
Presence of distant metastases Units: Subjects			
No	60	62	37
Yes	0	0	0
Stage UICC 7th edition Units: Subjects			
Stage 3	10	11	11
Stage 4	50	51	26
HPV/p16 negative (<=70% positively stained cells) Units: Subjects			
No	1	0	0
Yes	52	53	37
Unknown	7	9	0
Hypoxic gene signature - final results Units: Subjects			
Negative	35	37	29
Positive	25	25	8

Reporting group values	Placebo - Cisplatin 100mg	Total	
Number of subjects	35	194	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	137	
From 65-84 years	10	57	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	7	39	
Male	28	155	
WHO PS			
PS = Performance Status			
Units: Subjects			
PS=0	22	115	
PS=1	13	76	
PS=2	0	3	
Smoking habit			
Units: Subjects			
never smoked	0	4	
stopped > 20 years before diagnosis	1	12	
stopped < 20 years before diagnosis	21	94	
current smoker	13	83	
Missing	0	1	
Alcohol habit			
Units: Subjects			
never drank alcohol	2	13	
drank alcohol in the past	9	63	
current drinker of alcohol	24	114	
Missing	0	4	
History of past oncological disease			
Units: Subjects			
NO	35	186	
Yes	0	8	
Location of newly diagnosed tumors			
Units: Subjects			
larynx	9	43	
oropharynx	15	92	
hypopharynx	11	59	
Clinical T stage			
AJCC 7th edition			
Units: Subjects			
T1	3	7	
T2	7	40	
T3	12	67	
T4	13	80	
Clinical N stage			
Units: Subjects			
N0	9	43	
N1	3	22	

N2	22	126	
N3	1	3	
Presence of distant metastases Units: Subjects			
No	35	194	
Yes	0	0	
Stage UICC 7th edition Units: Subjects			
Stage 3	6	38	
Stage 4	29	156	
HPV/p16 negative (<=70% positively stained cells) Units: Subjects			
No	0	1	
Yes	35	177	
Unknown	0	16	
Hypoxic gene signature - final results Units: Subjects			
Negative	25	126	
Positive	10	68	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients will be analyzed in the arm they were allocated by randomization.

Reporting group values	ITT		
Number of subjects	194		
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)	137		
From 65-84 years	57		
85 years and over	0		
Gender categorical Units: Subjects			
Female	39		
Male	155		
WHO PS			
PS = Performance Status			
Units: Subjects			
PS=0	115		
PS=1	76		

PS=2	3		
Smoking habit Units: Subjects			
never smoked	4		
stopped > 20 years before diagnosis	12		
stopped < 20 years before diagnosis	94		
current smoker	83		
Missing	1		
Alcohol habit Units: Subjects			
never drank alcohol	13		
drank alcohol in the past	63		
current drinker of alcohol	114		
Missing	4		
History of past oncological disease Units: Subjects			
NO	186		
Yes	8		
Location of newly diagnosed tumors Units: Subjects			
larynx	43		
oropharynx	92		
hypopharynx	59		
Clinical T stage			
AJCC 7th edition			
Units: Subjects			
T1	7		
T2	40		
T3	67		
T4	80		
Clinical N stage Units: Subjects			
N0	43		
N1	22		
N2	126		
N3	3		
Presence of distant metastases Units: Subjects			
No	194		
Yes	0		
Stage UICC 7th edition Units: Subjects			
Stage 3	38		
Stage 4	156		
HPV/p16 negative (<=70% positively stained cells) Units: Subjects			
No	1		
Yes	177		
Unknown	16		

Hypoxic gene signature - final results Units: Subjects			
Negative	126		
Positive	68		

End points

End points reporting groups

Reporting group title	Nimorazole - Cisplatin 40mg
Reporting group description: -	
Reporting group title	Placebo - Cisplatin 40mg
Reporting group description: -	
Reporting group title	Nimorazole - Cisplatin 100mg
Reporting group description: -	
Reporting group title	Placebo - Cisplatin 100mg
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients will be analyzed in the arm they were allocated by randomization.

Primary: Locoregional recurrence rate at 2 years

End point title	Locoregional recurrence rate at 2 years

End point description:

Estimated using cumulative incidence rates.
Time to locoregional recurrence is counted from the day of randomization to the day of the first record of appearance of local or regional progression. Patients without any of the listed events (i.e. events of interest or competing risks events) are censored at the date of the most recent follow-up examination. Distant recurrence/progression and second cancers diagnosed before locoregional recurrence and death in absence of locoregional recurrence are considered as competing risk events in the analysis of this endpoint.
- Patients with no assessment performed at 3 months were considered to be not assessable and were censored at the date of randomization.
- Residual mass at 3 months was considered an event for this endpoint. Date of residual mass was, by convention, defined as the date of randomization.

End point type	Primary

End point timeframe:

Disease status assessed at three months after the end of treatment and yearly basis up to 5 years after end of treatment, or in case of clinical suspicion of relapse or residual disease.

End point values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg	Placebo - Cisplatin 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	62	37	35
Units: Percentage				
number (confidence interval 95%)	37.4 (23.0 to 51.8)	22.3 (11.6 to 35.2)	36.1 (20.9 to 51.5)	35 (19.7 to 50.7)

Statistical analyses

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 40mg)

Statistical analysis description:

The effect of treatment on the time to locoregional recurrence is estimated with a Fine&Gray model

adjusted for the stratification factors (except institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 40mg v Placebo - Cisplatin 40mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	3.91

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 100mg)

Statistical analysis description:

The effect of treatment on the time to locoregional recurrence is estimated with a Fine&Gray model adjusted for the stratification factors (except institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 100mg v Placebo - Cisplatin 100mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	2.44

Secondary: Overall survival rate at 2 years

End point title	Overall survival rate at 2 years

End point description:

Estimated using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Overall survival will be measured from the date of randomization to the date of death whatever the cause of death. Patients who are alive are censored at the date of the most recent follow-up examination.

End point values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg	Placebo - Cisplatin 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	62	37	35
Units: Percentage				
number (confidence interval 95%)	70.6 (54.2 to 82.1)	80.3 (64.2 to 89.7)	68.5 (50.2 to 81.2)	81.5 (63.2 to 91.2)

Statistical analyses

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 40mg)
Statistical analysis description:	
A Cox proportional hazard regression model adjusted for the stratification factors was fitted to estimate the effect size using hazard ratios (HR) and the associated 95% confidence interval	
Comparison groups	Nimorazole - Cisplatin 40mg v Placebo - Cisplatin 40mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2.42

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 100mg)
Statistical analysis description:	
A Cox proportional hazard regression model adjusted for the stratification factors was fitted to estimate the effect size using hazard ratios (HR) and the associated 95% confidence interval	
Comparison groups	Nimorazole - Cisplatin 100mg v Placebo - Cisplatin 100mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	3.96

Secondary: Distant-metastases rate at 2 years

End point title	Distant-metastases rate at 2 years

End point description:

Estimated using cumulative incidence rates.
Time to distant-metastases is counted from the day of randomization to the day of the first record of appearance of distant recurrence/progression. "Locoregional-only" progression or second cancers diagnosed before the distant metastases and death in absence of distant metastases are not considered events of interest for this endpoint. Patients without any of the events of interest are censored at the date of the most recent follow-up examination. Death in absence of distant-metastases is considered as a competing risk event in the analysis of this endpoint."
In addition, it was agreed with the study team that deaths due to progressive disease would be considered as competing risks, because the CRF did not allow to distinguish between death due to locoregional progression or due to distant metastasis.

End point type	Secondary

End point timeframe:

Disease status assessed at three months after the end of treatment and yearly basis up to 5 years after end of treatment, or in case of clinical suspicion of relapse or residual disease.

End point values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg	Placebo - Cisplatin 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	62	37	35
Units: Percentage				
number (confidence interval 95%)	34.2 (21.0 to 47.8)	12.4 (4.9 to 23.6)	10.8 (3.4 to 23.1)	21.3 (9.4 to 36.4)

Statistical analyses

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 40mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Placebo - Cisplatin 40mg v Nimorazole - Cisplatin 40mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	8.17

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 100mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors

(except institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 100mg v Placebo - Cisplatin 100mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.33

Secondary: Recurrence or death rate at 2 years

End point title	Recurrence or death rate at 2 years

End point description:

Estimated using cumulative incidence rates.

Time to recurrence or death is measured from the date of randomization to the date of first occurrence of any of the following events:
- any locoregional recurrence (i.e. local recurrence in the tumor bed or any positive node in the contralateral or ipsilateral neck).
- distant recurrence/progression.
- death due to any cause.

Patients alive and free of disease recurrence/progression (as defined above) are censored at the date of the most recent follow-up examination."
In addition, second cancer in absence of locoregional or distant recurrence is considered as a competing risk event for the analysis of this endpoint.

End point type	Secondary

End point timeframe:

Disease status assessed at three months after the end of treatment and yearly basis up to 5 years after end of treatment, or in case of clinical suspicion of relapse or residual disease.

End point values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg	Placebo - Cisplatin 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	62	37	35
Units: Percentage				
number (confidence interval 95%)	59.2 (42.7 to 72.4)	44.7 (28.9 to 59.3)	46.9 (30.1 to 62.1)	52.7 (34.9 to 67.7)

Statistical analyses

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 100mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except the institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 100mg v Placebo - Cisplatin 100mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	2.01

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 40mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except the institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 40mg v Placebo - Cisplatin 40mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.85

Secondary: Death due to HNSCC rate at 2 years

End point title	Death due to HNSCC rate at 2 years

End point description:

Disease-specific survival is measured from the date of randomization to the date of death due to primary HNSCC. Patients alive are censored at the date of the most recent follow-up examination. Death from causes other than primary HNSCC is considered as a competing risk event in the analysis of this endpoint.

End point type	Secondary

End point timeframe:

Disease-specific survival is measured from the date of randomization to the date of death due to primary HNSCC. Patients alive are censored at the date of the most recent follow-up examination. Death from causes other than primary HNSCC is considered

End point values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg	Placebo - Cisplatin 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	62	37	35
Units: Percentage				
number (confidence interval 95%)	19.6 (9.6 to 32.4)	6.0 (1.6 to 14.9)	25.7 (12.7 to 40.9)	12.5 (3.9 to 26.2)

Statistical analyses

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 100mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except the institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 100mg v Placebo - Cisplatin 100mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	5.47

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 40mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except the institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 40mg v Placebo - Cisplatin 40mg

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	3.93

Secondary: Cumulative incidence of second cancer at 2 years

End point title	Cumulative incidence of second cancer at 2 years

End point description:

End point type	Secondary

End point timeframe:

Disease status assessed at three months after the end of treatment and yearly basis up to 5 years after end of treatment, or in case of clinical suspicion of relapse or residual disease.

End point values	Nimorazole - Cisplatin 40mg	Placebo - Cisplatin 40mg	Nimorazole - Cisplatin 100mg	Placebo - Cisplatin 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	62	37	35
Units: Percentage				
number (confidence interval 95%)	11.3 (4.0 to 22.7)	9.7 (3.0 to 21.2)	8.7 (2.2 to 20.9)	3.0 (0.2 to 13.4)

Statistical analyses

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 100mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except the institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 100mg v Placebo - Cisplatin 100mg

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	4.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	33.23

Statistical analysis title	Comparison Nimorazole vs Placebo (Cisplatin 40mg)

Statistical analysis description:

The effect of treatment is estimated with a Fine&Gray model adjusted for the stratification factors (except the institution). As the protocol treatment changed after IDMC recommendations made on the 23/05/2016, the analysis is also adjusted according to the date of the urgent safety amendment (ie patient randomized before vs after 02/06/2016).

Comparison groups	Nimorazole - Cisplatin 40mg v Placebo - Cisplatin 40mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	5.68

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, laboratory and physical abnormalities were collected till three months after the end of treatment. Afterwards, only treatment related AE are collected. For SAEs: all SAEs till 30 days after end of treatment; afterwards, only related SAEs.

Adverse event reporting additional description:

AEs are evaluated using CTC grading, SAEs using MedDRA. Non-SAEs have not been collected specifically, all AEs including laboratory and physical abnormalities will be reported in non-SAE section. AEs are tabulated for each arm (Nimorazole versus Placebo), with both cisplatin regimens pooled together, for consistency with SAE reporting.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Nimorazole

Reporting group description:

Concomitantly with radiotherapy and cisplatin (both regimens pooled)

Reporting group title	Placebo

Reporting group description:

Concomitantly with radiotherapy and cisplatin (both regimens pooled)

Serious adverse events	Nimorazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 96 (56.25%)	50 / 96 (52.08%)	
number of deaths (all causes)	26	20	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
HYPOTENSION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 96 (3.13%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
INFUSION SITE EXTRAVASATION			
alternative dictionary used:			

MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	5 / 96 (5.21%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL NECROSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBSTRUCTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 96 (2.08%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ULCER			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 96 (4.17%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGEAL NECROSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
LARYNGEAL OEDEMA			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 96 (2.08%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGEAL HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
PHARYNGEAL SWELLING			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRODUCTIVE COUGH			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

STRIDOR			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ANXIETY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
RADIATION NECROSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION SKIN INJURY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

BRADYCARDIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (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			
BASAL GANGLIA HAEMORRHAGE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CEREBROVASCULAR ACCIDENT			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSGEUSIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROPATHY PERIPHERAL			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOCAL CORD PARALYSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPEPSIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 96 (9.38%)	15 / 96 (15.63%)	
occurrences causally related to treatment / all	9 / 9	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAECALOMA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PERFORATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NAUSEA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 96 (4.17%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	4 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ODYNOPHAGIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL FISTULA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL MOTILITY DISORDER			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL PAIN			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 96 (4.17%)	5 / 96 (5.21%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATOTOXICITY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
RASH			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 96 (8.33%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	10 / 11	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 96 (4.17%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BRONCHITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS BACTERIAL			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGITIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 96 (5.21%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	

SEPSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 96 (3.13%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 96 (1.04%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
METABOLIC ACIDOSIS			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
REFEEDING SYNDROME			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nimorazole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 96 (100.00%)	96 / 96 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOR PAIN			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	7 / 96 (7.29%)	2 / 96 (2.08%)	
occurrences (all)	8	3	
Vascular disorders			
FLUSHING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
HOT FLASHES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
HYPERTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	35 / 96 (36.46%)	28 / 96 (29.17%)	
occurrences (all)	80	67	
HYPOTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 96 (11.46%)	2 / 96 (2.08%)	
occurrences (all)	16	3	
LYMPHEDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	4 / 96 (4.17%)	
occurrences (all)	8	5	
SUPERFICIAL THROMBOPHLEBITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	5 / 96 (5.21%)	
occurrences (all)	4	6	
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
DIFFICULTY SWALLOWING TABLETS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
EDEMA FACE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	2 / 96 (2.08%)	
occurrences (all)	6	5	
EDEMA LIMBS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
FACIAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
FATIGUE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	40 / 96 (41.67%)	45 / 96 (46.88%)	
occurrences (all)	61	66	
FEVER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	17 / 96 (17.71%)	25 / 96 (26.04%)	
occurrences (all)	21	28	
GENERAL DETERIORATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
GENERALIZED EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	

INFUSION SITE EXTRAVASATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	1 / 96 (1.04%)	
occurrences (all)	5	1	
MALAISE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
NECK EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	3 / 96 (3.13%)	
occurrences (all)	15	7	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences (all)	2	1	
PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	4 / 96 (4.17%)	
occurrences (all)	4	4	
PICC OCCLUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
SUDDEN DEATH NOS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Immune system disorders			

ALLERGIC REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	4 / 96 (4.17%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
AGGRAVATED MUCUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
AGGRAVATED MUCUS PRODUCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
ASPIRATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	4 / 96 (4.17%)	
occurrences (all)	2	4	
ASPIRATION PNEUMONIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
BILATERAL VOCAL CORD PALSY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 96 (7.29%)	7 / 96 (7.29%)	
occurrences (all)	7	8	
DYSPNEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	12 / 96 (12.50%)	7 / 96 (7.29%)	
occurrences (all)	16	9	
EPISTAXIS			
alternative dictionary used: CTCAE			

4			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences (all)	1	3	
HEMORRHAGE DUE TO RADIONECROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	2	
HICCUPS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
HOARSENESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	20 / 96 (20.83%)	19 / 96 (19.79%)	
occurrences (all)	34	32	
INCREASED ODYNOPHAGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
LARYNGEAL EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 96 (10.42%)	12 / 96 (12.50%)	
occurrences (all)	11	20	
LARYNGEAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
LARYNGEAL INFLAMMATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	6 / 96 (6.25%)	
occurrences (all)	2	16	
LARYNGEAL MUCOSITIS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 96 (3.13%)	2 / 96 (2.08%)	
occurrences (all)	7	3	
LARYNGEAL NECROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
LARYNGEAL STENOSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
MUCOUS CONGESTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
MUCUS PRODUCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
PHARYNGEAL EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
PHARYNGEAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	2 / 96 (2.08%)	
occurrences (all)	3	4	
PHARYNGEAL MUCOSITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	15 / 96 (15.63%)	14 / 96 (14.58%)	
occurrences (all)	44	35	
PHARYNGOLARYNGEAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	5 / 96 (5.21%)	
occurrences (all)	8	9	

PNEUMONIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
PNEUMONITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	4 / 96 (4.17%)	
occurrences (all)	1	4	
PNEUMOTHORAX			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
POSTNASAL DRIP			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	4 / 96 (4.17%)	
occurrences (all)	1	4	
PRODUCTIVE COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 96 (9.38%)	9 / 96 (9.38%)	
occurrences (all)	10	11	
RESPIRATORY FAILURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences (all)	2	2	
SORE THROAT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 96 (10.42%)	13 / 96 (13.54%)	
occurrences (all)	16	26	
STRIDOR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	3 / 96 (3.13%)	
occurrences (all)	0	3	
VOICE ALTERATION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	14 / 96 (14.58%)	9 / 96 (9.38%)	
occurrences (all)	26	11	
WHEEZING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
AGITATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	1 / 96 (1.04%)	
occurrences (all)	5	1	
ANXIETY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	4 / 96 (4.17%)	
occurrences (all)	4	4	
CONFUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	3 / 96 (3.13%)	
occurrences (all)	3	4	
DELIRIUM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
DEPRESSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
HALLUCINATIONS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	0 / 96 (0.00%)	
occurrences (all)	4	0	
INSOMNIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	5 / 96 (5.21%)	5 / 96 (5.21%)	
occurrences (all)	6	9	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	23 / 96 (23.96%)	20 / 96 (20.83%)	
occurrences (all)	48	40	
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	22 / 96 (22.92%)	14 / 96 (14.58%)	
occurrences (all)	48	33	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	23 / 96 (23.96%)	24 / 96 (25.00%)	
occurrences (all)	43	47	
BLOOD BILIRUBIN INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	8 / 96 (8.33%)	
occurrences (all)	7	12	
BLOOD UREA NITROGEN DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
CHOLESTEROL HIGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
CRCL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	49 / 96 (51.04%)	48 / 96 (50.00%)	
occurrences (all)	276	176	
CREATININE INCREASED			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	76 / 96 (79.17%)	72 / 96 (75.00%)	
occurrences (all)	558	606	
GGT INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	35 / 96 (36.46%)	23 / 96 (23.96%)	
occurrences (all)	119	73	
INR INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	4 / 96 (4.17%)	
occurrences (all)	5	12	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	37 / 96 (38.54%)	32 / 96 (33.33%)	
occurrences (all)	62	42	
PLATELET COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 96 (10.42%)	8 / 96 (8.33%)	
occurrences (all)	17	10	
URINE OUTPUT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	0 / 96 (0.00%)	
occurrences (all)	3	0	
WEIGHT GAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	27 / 96 (28.13%)	30 / 96 (31.25%)	
occurrences (all)	146	140	
WEIGHT LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	89 / 96 (92.71%)	75 / 96 (78.13%)	
occurrences (all)	829	758	

WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	49 / 96 (51.04%)	55 / 96 (57.29%)	
occurrences (all)	91	104	
Injury, poisoning and procedural complications			
BURIED BUMPER SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
DERMATITIS RADIATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	79 / 96 (82.29%)	83 / 96 (86.46%)	
occurrences (all)	163	170	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
OBSTRUCTION PEG			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ORPHARYNGEAL NECROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	2	
PAIN OF PROCEDURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
POOR WOUND HEALING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
RADIONECROSIS			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
TRACHEAL OBSTRUCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
TRACHEOSTOMY SITE BLEEDING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
ATRIAL FIBRILLATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ATRIOVENTRICULAR BLOCK FIRST DEGREE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
CARDIAC ARREST			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
MYOCARDIAL INFARCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
PALPITATIONS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
SINUS BRADYCARDIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
SINUS TACHYCARDIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences (all)	2	2	
VENTRICULAR ARRHYTHMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
BRACHIAL PLEXOPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
CONCENTRATION IMPAIRMENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
DIZZINESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 96 (7.29%)	3 / 96 (3.13%)	
occurrences (all)	7	3	
DYSARTHRIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 96 (3.13%)	1 / 96 (1.04%)	
occurrences (all)	5	4	
DYSESTHESIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
DYSGEUSIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	46 / 96 (47.92%)	46 / 96 (47.92%)	
occurrences (all)	71	78	
FACIAL MUSCLE WEAKNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
HEADACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	3 / 96 (3.13%)	
occurrences (all)	7	3	
INTRACRANIAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
LETHARGY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
MEMORY IMPAIRMENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
NEURALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	2	

PARESTHESIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	2 / 96 (2.08%)	
occurrences (all)	4	2	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	8 / 96 (8.33%)	7 / 96 (7.29%)	
occurrences (all)	14	11	
SOMNOLENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
SYNCOPE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	0 / 96 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	50 / 96 (52.08%)	35 / 96 (36.46%)	
occurrences (all)	197	100	
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	2 / 96 (2.08%)	
occurrences (all)	4	2	
Ear and labyrinth disorders			
AURICULAR HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
BLEEDING SKIN EAR			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
EAR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 96 (7.29%)	1 / 96 (1.04%)	
occurrences (all)	7	1	
HEARING IMPAIRED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 96 (9.38%)	11 / 96 (11.46%)	
occurrences (all)	13	13	
MIDDLE EAR INFLAMMATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
TINNITUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 96 (9.38%)	11 / 96 (11.46%)	
occurrences (all)	11	12	
Eye disorders			
BLURRED VISION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences (all)	3	2	
ANAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
BLOATING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
CONSTIPATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	29 / 96 (30.21%)	26 / 96 (27.08%)	
occurrences (all)	38	27	
DENTAL CARIES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
DIARRHEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	13 / 96 (13.54%)	11 / 96 (11.46%)	
occurrences (all)	15	12	
DRY MOUTH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	70 / 96 (72.92%)	68 / 96 (70.83%)	
occurrences (all)	124	127	
DUODENAL PERFORATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
DYSPEPSIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	4 / 96 (4.17%)	
occurrences (all)	5	4	
DYSPHAGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	74 / 96 (77.08%)	80 / 96 (83.33%)	
occurrences (all)	204	193	

ENTEROCOLITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
ESOPHAGEAL FISTULA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ESOPHAGEAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	1 / 96 (1.04%)	
occurrences (all)	8	2	
ESOPHAGITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
EXCESSIVE SALIVA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
GASTRO-INTESTINAL OTHER; ENLARGED VALLECULA ORAL CAVITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
GASTROINTESTINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
GLOBUS SENSATION THROAT			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
HEMORRHOIDS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
INDIGESTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
IRRADIATION ULCER VALLECULA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	68 / 96 (70.83%)	74 / 96 (77.08%)	
occurrences (all)	156	156	
NAUSEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	53 / 96 (55.21%)	45 / 96 (46.88%)	
occurrences (all)	79	61	
ORAL CAVITY - ULCER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ORAL CAVITY ULCER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ORAL DYSESTHESIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	

ORAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	26 / 96 (27.08%)	23 / 96 (23.96%)	
occurrences (all)	47	52	
PERIODONTAL DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
SALIVARY DUCT INFLAMMATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	3 / 96 (3.13%)	
occurrences (all)	6	5	
STOMACH PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
THICK SECRETIONS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences (all)	2	6	
TOOTHACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
UPPER GASTROINTESTINAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	3	
VOMITING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	29 / 96 (30.21%)	26 / 96 (27.08%)	
occurrences (all)	42	31	
Hepatobiliary disorders			

CHOLESTASIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences (all)	2	3	
ERYTHEMA MULTIFORME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
NAIL LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
PRURITUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
RASH ACNEIFORM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	4 / 96 (4.17%)	
occurrences (all)	3	5	
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	2	
SKIN ATROPHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	3 / 96 (3.13%)	
occurrences (all)	4	5	
SKIN HYPERPIGMENTATION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	5 / 96 (5.21%)	1 / 96 (1.04%)	
occurrences (all)	8	1	
SKIN HYPOPIGMENTATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	2	
SKIN INDURATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
TELANGIECTASIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	3	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	69 / 96 (71.88%)	70 / 96 (72.92%)	
occurrences (all)	552	619	
CHRONIC KIDNEY DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
HEMATURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
RENAL IMPAIRMENT			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
URINARY RETENTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences (all)	2	1	
URINARY TRACT PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
Endocrine disorders			
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	1 / 96 (1.04%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
FIBROSIS DEEP CONNECTIVE TISSUE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences (all)	3	3	
FLANK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
HEAD SOFT TISSUE NECROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	4	
MYALGIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	2 / 96 (2.08%)	2 / 96 (2.08%)	
occurrences (all)	2	2	
NECK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	2 / 96 (2.08%)	
occurrences (all)	1	2	
NECK SOFT TISSUE NECROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
OSTEONECROSIS OF JAW			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 96 (6.25%)	2 / 96 (2.08%)	
occurrences (all)	6	2	
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
RIGHT CERVICAL SCLEROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
SUPERFICIAL SOFT TISSUE FIBROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 96 (11.46%)	11 / 96 (11.46%)	
occurrences (all)	22	20	
TRISMUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 96 (10.42%)	7 / 96 (7.29%)	
occurrences (all)	13	11	
Infections and infestations			
BLADDER INFECTION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
BREAST INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
BRONCHIAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	2 / 96 (2.08%)	
occurrences (all)	3	2	
CATHETER RELATED INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 96 (7.29%)	5 / 96 (5.21%)	
occurrences (all)	7	5	
CRP INCREASED/ INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ESOPHAGEAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	3 / 96 (3.13%)	
occurrences (all)	0	3	
INCREASED CRP			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences (all)	2	1	
INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	
occurrences (all)	2	1	
INFECTION OF THE TRACHEOSTOMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	

INFECTION WITH UNKNOWN FOCUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
LARYNGITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	0 / 96 (0.00%)	
occurrences (all)	5	0	
LIP INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	1	1	
LUNG INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 96 (6.25%)	2 / 96 (2.08%)	
occurrences (all)	7	2	
MUCOSAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 96 (9.38%)	10 / 96 (10.42%)	
occurrences (all)	15	11	
PHARYNGITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	4 / 96 (4.17%)	
occurrences (all)	4	5	
SEPSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 96 (3.13%)	1 / 96 (1.04%)	
occurrences (all)	3	1	
SEPTIC SHOCK			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
SKIN INFECTION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 96 (3.13%)	1 / 96 (1.04%)	
occurrences (all)	3	2	
SOFT TISSUE INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	2	
STOMA SITE INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
TOOTH INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
TRACHEITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	2 / 96 (2.08%)	
occurrences (all)	0	3	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	1 / 96 (1.04%)	
occurrences (all)	2	1	
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	0 / 96 (0.00%)	
occurrences (all)	6	0	
Metabolism and nutrition disorders			
ACIDOSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
ANOREXIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	12 / 96 (12.50%)	16 / 96 (16.67%)	
occurrences (all)	19	17	
CHLORIDE LOW			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
DEHYDRATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 96 (7.29%)	10 / 96 (10.42%)	
occurrences (all)	9	11	
HYPERCALCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	16 / 96 (16.67%)	14 / 96 (14.58%)	
occurrences (all)	35	29	
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 96 (5.21%)	0 / 96 (0.00%)	
occurrences (all)	13	0	
HYPERKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	45 / 96 (46.88%)	45 / 96 (46.88%)	
occurrences (all)	138	103	
HYPERMAGNESEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 96 (7.29%)	5 / 96 (5.21%)	
occurrences (all)	19	7	
HYPERNATREMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 96 (4.17%)	4 / 96 (4.17%)	
occurrences (all)	6	5	
HYPOALBUMINEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	4 / 96 (4.17%)	
occurrences (all)	0	13	

HYPOCALCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	45 / 96 (46.88%)	31 / 96 (32.29%)	
occurrences (all)	98	72	
HYPOGLYCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
HYPOKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	31 / 96 (32.29%)	31 / 96 (32.29%)	
occurrences (all)	61	71	
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	59 / 96 (61.46%)	47 / 96 (48.96%)	
occurrences (all)	189	187	
HYPONATREMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	58 / 96 (60.42%)	65 / 96 (67.71%)	
occurrences (all)	218	236	
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	39 / 96 (40.63%)	37 / 96 (38.54%)	
occurrences (all)	81	72	
LOW CHLORIDE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
REFEEDING SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	
occurrences (all)	0	1	
UNDERNUTRITION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1	0 / 96 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2015	This was a scientific amendment agreed between the leading group DAHANCA, the EORTC (Sponsor) and the pharmaceutical company Azanta. Data from DAHANCA on laryngeal and hypopharyngeal Squamous Cell Carcinoma (SCC) patients treated with radiotherapy did not show the prognostic value of p16-positivity on the contrary to data available for oropharyngeal SCC [Lassen P, Primdahl H, Johansen J, et al; Danish Head and Neck Cancer Group (DAHANCA). Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. Radiother Oncol. 2014; 113(3):310-6]. Similar data have been presented by G. D'Souza at the 5th World congress of the International Academy of Oral Oncology in Sao-Paulo (Brazil) in July 2015. In this context, it was decided to include all laryngeal and hypopharyngeal SCC irrespective of the HPV status as this will neither add any hetereogeneity to the study population or any bias whereas it will increase the feasibility of the study. This has led to a change in the title. Moreover, several clarifications were introduced in the eligibility criteria, treatment planning and schedule and dose modification so to improve the compliance to the protocol, based on the data of medical review. Finally, updates has been made on the administration of nimorazole to comply with the modification in the new version of the Investigator Brochure.
21 September 2016	In January 2016, the 1219 EORTC HQ team asked advice to EORTC IDMC experts concerning an excess of Serious Adverse Events in the patients treated with the 100mg/m2 cisplatin schedule. Following two subsequent IDMC safety reviews (1st IDMC meeting: 29/02/2016, 2nd IDMC meeting: 23/05/2016) with access to unblind safety reports and additional documentation produced by the unblind EORTC Headquarters team, the IDMC experts formulated recommendations to the Study Management Group and EORTC ROG and HNCG (see chapter 2.3). The protocol was amended so to include all the recommendations made by the IDMC. • Chapter 5.4 "cisplatin treatment" was updated to allow only weekly 40mg/m² regimen. • Assessment of the premedication for cisplatin were now part of the clinical evaluation during treatment (chapter 6.2) • A chapter specific to the evaluation of severe kidney injury (chapter 7.2.6) was added including the stopping rule to go back to IDMC. Furthermore, a clarification on the dose prescription of Nimorazole was added. This amendment was discussed and agreed by the study team, the study coordinators and the trial steering committee as well as the supportive company. After the rejection of the amendment by the IPRM, the protocol and PISIC were further amended. The amendment was implemented as an outcome of the urgent safety review of the IDMC in May 2016 due to the increased renal toxicity of patients who received cisplatin 100mg/m2. Based on the above facts, the Headquarters (HQ) team and the Study Coordinator(s) (SC) together with the Steering Committee have immediately suspended the use of this treatment schedule, implemented all recommendations of IDMC (as per previous PRC submission) and PRC, and in addition: 1. added liver function monitoring 2. included a nephrologist in the steering committee 3. added additional guidelines on prevention and management of chemotherapy induced renal toxicity 4. updated the informed consent accordingly

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 February 2018	The study was closed definitively for patient recruitment on 13th February 2018 with 194 randomized patients, instead of the planned number of 640. This decision was motivated by several factors: The independent data monitoring committee (IDMC) of EORTC requested to review the study by the end of 2017 in order to assess whether the assumptions used in the initial sample size, regarding loco-regional control and competing event rates were still justified. This review was held on January 22, 2018. Based on their analysis of unblinded data, they recommended closing the study. This recommendation was motivated by the weak conditional power for the hypothesized treatment effect. In November 2017 the financial sponsor of the trial decided to withdraw its financial support. The slow accrual possibly explained by competing industry-sponsored trials and the increasing incidence of HPV-driven oropharyngeal tumors was also part of the IDMC motivation.	-

Notes:

Limitations and caveats

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

The cisplatin regimen of 100mg/m2 was not allowed after the 2016 Amendment, to high toxicity. But in this report, AEs are tabulated for each arm (Nimorazole and Placebo), with both cisplatin regimens pooled , for consistency with SAEs reporting.

Notes: