



Clinical trial results:

Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.

Summary

EudraCT number	2006-001533-17
Trial protocol	NL DE FR IT BE ES GB AT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	18 August 2021
First version publication date	18 August 2021

Trial information

Trial identification

Sponsor protocol code	EORTC26053-22054
-----------------------	------------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	83 Avenue Mounier, Brussels, Belgium, 1200
Public contact	Project Mgt & Regulatory Unit, European Organisation for Research and Treatment of Cancer (EORTC), 00 32 2774 10 72/, regulatory@eortc.be
Scientific contact	Project Mgt & Regulatory Unit, European Organisation for Research and Treatment of Cancer (EORTC), 00 32 2774 10 72/, 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	Interim
Date of interim/final analysis	07 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether concurrent radiotherapy with daily temozolomide chemotherapy improves overall survival as compared to no daily temozolomide in patients with non-1p/19q deleted anaplastic glioma. To assess whether adjuvant temozolomide chemotherapy improves survival as compared to no adjuvant temozolomide chemotherapy in patients with non-1p/19q deleted anaplastic glioma

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol was written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 2007
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	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 143
Country: Number of subjects enrolled	Netherlands: 72
Country: Number of subjects enrolled	Belgium: 73
Country: Number of subjects enrolled	France: 93
Country: Number of subjects enrolled	Germany: 70
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Switzerland: 26
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United States: 101
Country: Number of subjects enrolled	Australia: 82
Country: Number of subjects enrolled	Canada: 23
Worldwide total number of subjects	751
EEA total number of subjects	515

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)	696
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All patients were initially registered into the trial as soon as possible after surgery. After this point, material was sent for 1p/19q analysis and MGMT promoter methylation assay. Patients could only be randomized into the trial within 8 days from the start of radiotherapy; at this time, all baseline requirements for the study had to be fulfilled

Period 1

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

Blinding implementation details:

No blinding

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Radiotherapy
------------------	--------------

Arm description:

Arm 1: Radiotherapy and further treatment including chemotherapy if indicated at progression

Arm type	Radiotherapy
----------	--------------

No investigational medicinal product assigned in this arm

Arm title	TMZ/RT
------------------	--------

Arm description:

Arm 2: Radiotherapy & concurrent temozolomide

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Temozolomide
--	--------------

Investigational medicinal product code	
--	--

Other name	
------------	--

Pharmaceutical forms	Capsule
----------------------	---------

Routes of administration	Oral use
--------------------------	----------

Dosage and administration details:

Patients randomized to concomitant temozolomide received temozolomide continuously at a daily dose of 75 mg/m² during radiotherapy. The drug was administered orally 1 hour before each session of radiotherapy during weekdays. During weekends without radiotherapy, the drug was taken in the morning. The dose administered was determined using the body surface area (BSA) calculated at the beginning of the concomitant treatment. The daily dose was rounded to the nearest 5 mg. In case of high value of BSA, an upper limit of 2.1 m² is suggested to calculate the dose. Patients was told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of the treatment, no re-dosing of the patient was allowed before the next scheduled dose.

Arm title	RT->TMZ
------------------	---------

Arm description:

Arm 3: Radiotherapy + adjuvant temozolomide for 12 cycles

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Temozolomide
--	--------------

Investigational medicinal product code	
--	--

Other name	
------------	--

Pharmaceutical forms	Capsule
----------------------	---------

Routes of administration	Oral use
--------------------------	----------

Dosage and administration details:

Patients randomized to adjuvant temozolomide started adjuvant temozolomide after a 4 week resting period after the end of radiotherapy. Temozolomide was administered orally once a day for 5 consecutive days (days 1-5). The starting dose for the first cycle was 150 mg/m²/day with a single dose escalation to 200mg/m²/day in subsequent cycles if no significant toxicity was observed in the first cycle. One cycle was defined as 28 days and a maximum of 12 cycles was administered. Treatment could be discontinued earlier in case of significant toxicity interfering with further treatment and not responding to dose reductions, or at the patient wish. The dose administered was determined using the BSA calculated at the beginning of each treatment cycle. The dose was rounded to the nearest 5 mg. In case of high value of BSA, an upper limit of 2.1 m² was suggested to calculate the dose.

Arm title	TMZ/RT->TMZ
------------------	-------------

Arm description:

Arm 4: Radiotherapy & concurrent temozolomide + adjuvant temozolomide for 12 cycles

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

Dosage and administration details:

Both concomitant and adjuvant Temozolomide (see other corresponding arms for details)

Number of subjects in period 1	Radiotherapy	TMZ/RT	RT->TMZ
Started	189	188	186
Completed	175	163	109
Not completed	14	25	77
Consent withdrawn by subject	3	1	5
RT was prematurely stopped by mistake	1	-	-
Adverse event, non-fatal	1	7	14
Multiple reasons	1	6	7
Death not due to malign. disease or toxicity	-	1	-
Missing	-	-	1
Lack of efficacy	6	7	49
Missing reason	2	2	-
Protocol deviation	-	1	1

Number of subjects in period 1	TMZ/RT->TMZ
Started	188
Completed	93
Not completed	95
Consent withdrawn by subject	11
RT was prematurely stopped by mistake	-
Adverse event, non-fatal	28
Multiple reasons	13

Death not due to malign. disease or toxicity	-
Missing	-
Lack of efficacy	40
Missing reason	3
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Radiotherapy
Reporting group description:	
Arm 1: Radiotherapy and further treatment including chemotherapy if indicated at progression	
Reporting group title	TMZ/RT
Reporting group description:	
Arm 2: Radiotherapy & concurrent temozolomide	
Reporting group title	RT->TMZ
Reporting group description:	
Arm 3: Radiotherapy + adjuvant temozolomide for 12 cycles	
Reporting group title	TMZ/RT->TMZ
Reporting group description:	
Arm 4: Radiotherapy & concurrent temozolomide + adjuvant temozolomide for 12 cycles	

Reporting group values	Radiotherapy	TMZ/RT	RT->TMZ
Number of subjects	189	188	186
Age categorical			
Age at randomization			
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)	174	168	174
From 65-84 years	15	20	12
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	75	68	82
Male	114	120	104
Presence of oligodendroglial elements			
Presence of oligodendroglial elements (Yes vs No)			
Units: Subjects			
No oligodendroglial elements	146	144	143
Oligodendroglial elements	43	44	43
WHO Performance Status			
WHO Performance Status (PS >0 vs PS 0)			
Units: Subjects			
PS 0	111	110	108
PS >0	78	78	78
Presence of 1p LOH			
Presence of 1p LOH (Yes vs No)			
Units: Subjects			

1p no loss	175	176	172
1p loss	14	12	14
MGMT Methylation Status			
MGMT (Methylated/Unmethylated/Undetermined /invalid)			
Units: Subjects			
Methylated	62	55	66
Unmethylated	83	79	78
Undetermined/invalid	44	54	42

Reporting group values	TMZ/RT->TMZ	Total	
Number of subjects	188	751	
Age categorical			
Age at randomization			
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)	180	696	
From 65-84 years	8	55	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	82	307	
Male	106	444	
Presence of oligodendroglial elements			
Presence of oligodendroglial elements (Yes vs No)			
Units: Subjects			
No oligodendroglial elements	144	577	
Oligodendroglial elements	44	174	
WHO Performance Status			
WHO Performance Status (PS >0 vs PS 0)			
Units: Subjects			
PS 0	112	441	
PS >0	76	310	
Presence of 1p LOH			
Presence of 1p LOH (Yes vs No)			
Units: Subjects			
1p no loss	175	698	
1p loss	13	53	
MGMT Methylation Status			
MGMT (Methylated/Unmethylated/Undetermined /invalid)			
Units: Subjects			
Methylated	56	239	
Unmethylated	87	327	
Undetermined/invalid	45	185	

Subject analysis sets

Subject analysis set title	Intent to Treat with concomitant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients analyzed in the arm they were allocated by randomization. Patients with concomitant TMZ	
Subject analysis set title	Intent to Treat without concomitant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients analyzed in the arm they were allocated by randomization. Patients without concomitant TMZ	
Subject analysis set title	Intent to Treat with adjuvant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients analyzed in the arm they were allocated by randomization. Patients with adjuvant TMZ.	
Subject analysis set title	Intent to Treat without adjuvant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients analyzed in the arm they were allocated by randomization. Patients without adjuvant TMZ.	

Reporting group values	Intent to Treat with concomitant TMZ	Intent to Treat without concomitant TMZ	Intent to Treat with adjuvant TMZ
Number of subjects	376	375	374
Age categorical			
Age at randomization			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	348	348	354
From 65-84 years	28	27	20
85 years and over			
Gender categorical			
Units: Subjects			
Female	150	157	164
Male	126	218	210
Presence of oligodendroglial elements			
Presence of oligodendroglial elements (Yes vs No)			
Units: Subjects			
No oligodendroglial elements	288	289	187
Oligodendroglial elements	88	86	87
WHO Performance Status			
WHO Performance Status (PS >0 vs PS 0)			
Units: Subjects			
PS 0	222	219	220
PS >0	154	156	154

Presence of 1p LOH			
Presence of 1p LOH (Yes vs No)			
Units: Subjects			
1p no loss	351	347	347
1p loss	25	28	27
MGMT Methylation Status			
MGMT (Methylated/Unmethylated/Undetermined /invalid)			
Units: Subjects			
Methylated	111	128	122
Unmethylated	166	161	165
Undetermined/invalid	99	86	87

Reporting group values	Intent to Treat without adjuvant TMZ		
Number of subjects	377		
Age categorical			
Age at randomization			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	342		
From 65-84 years	35		
85 years and over			
Gender categorical			
Units: Subjects			
Female	143		
Male	234		
Presence of oligodendroglial elements			
Presence of oligodendroglial elements (Yes vs No)			
Units: Subjects			
No oligodendroglial elements	290		
Oligodendroglial elements	87		
WHO Performance Status			
WHO Performance Status (PS >0 vs PS 0)			
Units: Subjects			
PS 0	221		
PS >0	156		
Presence of 1p LOH			
Presence of 1p LOH (Yes vs No)			
Units: Subjects			
1p no loss	351		
1p loss	26		
MGMT Methylation Status			
MGMT (Methylated/Unmethylated/Undetermined /invalid)			
Units: Subjects			
Methylated	117		

Unmethylated	162		
Undetermined/invalid	98		

End points

End points reporting groups

Reporting group title	Radiotherapy
Reporting group description:	
Arm 1: Radiotherapy and further treatment including chemotherapy if indicated at progression	
Reporting group title	TMZ/RT
Reporting group description:	
Arm 2: Radiotherapy & concurrent temozolomide	
Reporting group title	RT->TMZ
Reporting group description:	
Arm 3: Radiotherapy + adjuvant temozolomide for 12 cycles	
Reporting group title	TMZ/RT->TMZ
Reporting group description:	
Arm 4: Radiotherapy & concurrent temozolomide + adjuvant temozolomide for 12 cycles	
Subject analysis set title	Intent to Treat with concomitant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients analyzed in the arm they were allocated by randomization. Patients with concomitant TMZ	
Subject analysis set title	Intent to Treat without concomitant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients analyzed in the arm they were allocated by randomization. Patients without concomitant TMZ	
Subject analysis set title	Intent to Treat with adjuvant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients analyzed in the arm they were allocated by randomization. Patients with adjuvant TMZ.	
Subject analysis set title	Intent to Treat without adjuvant TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients analyzed in the arm they were allocated by randomization. Patients without adjuvant TMZ.	

Primary: Overall Survival with concomitant TMZ

End point title	Overall Survival with concomitant TMZ
End point description:	
The duration of survival is the time interval between randomization and the date of death due to any cause. Patients not reported dead or lost to follow up will be censored at the date of the last follow up examination.	
End point type	Primary
End point timeframe:	
All patients had to be followed every 3 months until death.	

End point values	Intent to Treat with concomitant TMZ	Intent to Treat without concomitant TMZ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	375		
Units: Month				
median (confidence interval 95%)	66.9 (48.5 to 82.3)	60.4 (45.7 to 71.5)		

Statistical analyses

Statistical analysis title	Adjusted OS Cox model for concomitant TMZ question
Statistical analysis description: Cox overall survival model with question adjusted by the stratification factors at randomization	
Comparison groups	Intent to Treat with concomitant TMZ v Intent to Treat without concomitant TMZ
Number of subjects included in analysis	751
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	Other: 99.1 %
sides	2-sided
lower limit	0.73
upper limit	1.28

Primary: Overall Survival with adjuvant TMZ

End point title	Overall Survival with adjuvant TMZ
End point description: The duration of survival is the time interval between randomization and the date of death due to any cause. Patients not reported dead or lost to follow up will be censored at the date of the last follow up examination.	
End point type	Primary
End point timeframe: All patients hat to be followed every 3 months until death	

End point values	Intent to Treat with adjuvant TMZ	Intent to Treat without adjuvant TMZ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374	377		
Units: Month				
median (confidence interval 95%)	82.3 (67.2 to 116.6)	46.9 (37.9 to 56.9)		

Statistical analyses

Statistical analysis title	Adjusted Cox OS model for adjuvant TMZ
Statistical analysis description: Cox overall survival model with adjuvant TMZ question adjusted by the stratification factors at randomization	
Comparison groups	Intent to Treat with adjuvant TMZ v Intent to Treat without adjuvant TMZ
Number of subjects included in analysis	751
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.79

Secondary: Progression-free Survival with concomitant TMZ

End point title	Progression-free Survival with concomitant TMZ
End point description:	
End point type	Secondary
End point timeframe: MRI was obtained prior to surgery, post-surgery, prior to initiation of the concurrent radiation and temozolomide therapy, then within 72 hours prior to initiating adjuvant chemotherapy, then every 3 cycles, and at the time of neurologic deterioration.	

End point values	Radiotherapy	TMZ/RT	RT->TMZ	TMZ/RT->TMZ
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	189	188	186	188
Units: Months				
median (confidence interval 95%)	17.0 (11.3 to 20.9)	23.0 (15.0 to 34.9)	28.6 (20.6 to 46.4)	55.8 (32.2 to 77.0)

End point values	Intent to Treat with concomitant TMZ	Intent to Treat without concomitant TMZ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	375		
Units: Months				
median (confidence interval 95%)	33.0 (23.8 to 46.1)	20.9 (17.3 to 26.6)		

Statistical analyses

Statistical analysis title	Adjusted Cox PFS model for concomitant TMZ
Statistical analysis description: Adjusted Cox Progression-free Survival model for the concomitant TMZ question	
Comparison groups	Intent to Treat without concomitant TMZ v Intent to Treat with concomitant TMZ
Number of subjects included in analysis	751
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.03

Secondary: Progression-free Survival with adjuvant TMZ

End point title	Progression-free Survival with adjuvant TMZ
End point description:	
End point type	Secondary
End point timeframe: MRI was obtained prior to surgery, post-surgery, prior to initiation of the concurrent radiation and temozolomide therapy, then within 72 hours prior to initiating adjuvant chemotherapy, then every 3 cycles, and at the time of neurologic deterioration.	

End point values	Intent to Treat with adjuvant TMZ	Intent to Treat without adjuvant TMZ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374	377		
Units: Months				
median (confidence interval 95%)	42.8 (27.8 to 56.4)	19.1 (14.6 to 23.8)		

Statistical analyses

Statistical analysis title	Adjusted Cox PFS model for adjuvant TMZ
Statistical analysis description:	
Adjusted Cox PFS model for adjuvant TMZ question	
Comparison groups	Intent to Treat with adjuvant TMZ v Intent to Treat without adjuvant TMZ
Number of subjects included in analysis	751
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Before trt start, during radiotherapy trt, weekly visits, evaluation at week 4 and 6, evaluation 4 weeks after the end of radiotherapy, six monthly disease evaluation after the end of radiotherapy, prior to each cycle of adjuvant therapy.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (xx% AEs are reported as "other" and are not reported as not available from the list of SOC). AEs and SAEs are evaluated using CTC grading. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

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

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Radiotherapy
-----------------------	--------------

Reporting group description:

Radiotherapy

Reporting group title	RT->TMZ
-----------------------	---------

Reporting group description:

RT->TMZ

Reporting group title	TMZ/RT->TMZ
-----------------------	-------------

Reporting group description:

TMZ/RT->TMZ

Reporting group title	TMZ/RT
-----------------------	--------

Reporting group description:

TMZ/RT

Serious adverse events	Radiotherapy	RT->TMZ	TMZ/RT->TMZ
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 186 (6.99%)	32 / 183 (17.49%)	32 / 185 (17.30%)
number of deaths (all causes)	129	92	86
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
VASCULAR			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CONSTITUTIONAL SYMPTOMS			
alternative dictionary used: CTCAE 3			

subjects affected / exposed	0 / 186 (0.00%)	2 / 183 (1.09%)	2 / 185 (1.08%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 186 (1.08%)	4 / 183 (2.19%)	3 / 185 (1.62%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ALLERGY/IMMUNOLOGY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	2 / 183 (1.09%)	2 / 185 (1.08%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY/UPPER RESPIRATORY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	0 / 183 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CARDIAC(GENERAL)			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
NEUROLOGY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	9 / 186 (4.84%)	12 / 183 (6.56%)	10 / 185 (5.41%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
BLOOD			

alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 186 (1.08%)	2 / 183 (1.09%)	5 / 185 (2.70%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHATICS			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 186 (1.08%)	1 / 183 (0.55%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
OCULAR/VISUAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	0 / 183 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
GASTROINTESTINAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 186 (0.54%)	4 / 183 (2.19%)	5 / 185 (2.70%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DERMATOLOGY/SKIN			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	2 / 185 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL/GENITOURINARY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

MUSCULOSKELETAL/SOFT TISSUE alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations INFECTION alternative dictionary used: CTCAE 3			
subjects affected / exposed	6 / 186 (3.23%)	8 / 183 (4.37%)	6 / 185 (3.24%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders METABOLIC/LABORATORY alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 186 (0.54%)	1 / 183 (0.55%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TMZ/RT		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 185 (14.59%)		
number of deaths (all causes)	108		
number of deaths resulting from adverse events	0		
Vascular disorders VASCULAR alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions CONSTITUTIONAL SYMPTOMS alternative dictionary used: CTCAE 3			
subjects affected / exposed	7 / 185 (3.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

PAIN alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 185 (1.08%) 0 / 1 0 / 0		
Immune system disorders ALLERGY/IMMUNOLOGY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 185 (0.00%) 0 / 0 0 / 0		
Respiratory, thoracic and mediastinal disorders PULMONARY/UPPER RESPIRATORY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 185 (0.00%) 0 / 0 0 / 0		
Cardiac disorders CARDIAC(GENERAL) alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 185 (0.00%) 0 / 0 0 / 0		
Nervous system disorders NEUROLOGY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	15 / 185 (8.11%) 1 / 1 0 / 0		
Blood and lymphatic system disorders BLOOD alternative dictionary used: CTCAE 3			

subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
LYMPHATICS			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 185 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
OCULAR/VISUAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
GASTROINTESTINAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
DERMATOLOGY/SKIN			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
RENAL/GENITOURINARY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 185 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL/SOFT TISSUE			

alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 185 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations INFECTION			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	4 / 185 (2.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders METABOLIC/LABORATORY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Radiotherapy	RT->TMZ	TMZ/RT->TMZ
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 186 (97.85%)	182 / 183 (99.45%)	185 / 185 (100.00%)
Vascular disorders VASCULAR			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 186 (1.08%)	5 / 183 (2.73%)	7 / 185 (3.78%)
occurrences (all)	2	11	22
Surgical and medical procedures SURGERY/INTRA-OPERATIVE INJURY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 186 (0.00%)	0 / 183 (0.00%)	1 / 185 (0.54%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

<p>CONSTITUTIONAL SYMPTOMS</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>151 / 186 (81.18%)</p> <p>925</p>	<p>170 / 183 (92.90%)</p> <p>2182</p>	<p>176 / 185 (95.14%)</p> <p>2302</p>
<p>PAIN</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>129 / 186 (69.35%)</p> <p>656</p>	<p>138 / 183 (75.41%)</p> <p>1219</p>	<p>132 / 185 (71.35%)</p> <p>960</p>
<p>Immune system disorders</p> <p>ALLERGY/IMMUNOLOGY</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 186 (3.76%)</p> <p>16</p>	<p>11 / 183 (6.01%)</p> <p>19</p>	<p>15 / 185 (8.11%)</p> <p>45</p>
<p>Reproductive system and breast disorders</p> <p>SEXUAL/REPRODUCTIVE FUNCTION</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 186 (1.08%)</p> <p>4</p>	<p>7 / 183 (3.83%)</p> <p>33</p>	<p>13 / 185 (7.03%)</p> <p>23</p>
<p>Respiratory, thoracic and mediastinal disorders</p> <p>PULMONARY/UPPER RESPIRATORY</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 186 (4.30%)</p> <p>13</p>	<p>17 / 183 (9.29%)</p> <p>33</p>	<p>18 / 185 (9.73%)</p> <p>59</p>
<p>Cardiac disorders</p> <p>CARDIAC(GENERAL)</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 186 (4.84%)</p> <p>23</p>	<p>17 / 183 (9.29%)</p> <p>50</p>	<p>20 / 185 (10.81%)</p> <p>74</p>
<p>Nervous system disorders</p> <p>NEUROLOGY</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>147 / 186 (79.03%)</p> <p>1431</p>	<p>148 / 183 (80.87%)</p> <p>2026</p>	<p>154 / 185 (83.24%)</p> <p>1777</p>
Blood and lymphatic system disorders			

<p>BLOOD</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 186 (2.69%)</p> <p>11</p>	<p>10 / 183 (5.46%)</p> <p>15</p>	<p>14 / 185 (7.57%)</p> <p>44</p>
<p>LYMPHATICS</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 186 (6.45%)</p> <p>33</p>	<p>14 / 183 (7.65%)</p> <p>44</p>	<p>11 / 185 (5.95%)</p> <p>34</p>
<p>Ear and labyrinth disorders</p> <p>AUDITORY/EAR</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>30 / 186 (16.13%)</p> <p>75</p>	<p>33 / 183 (18.03%)</p> <p>157</p>	<p>39 / 185 (21.08%)</p> <p>185</p>
<p>Eye disorders</p> <p>OCULAR/VISUAL</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>51 / 186 (27.42%)</p> <p>207</p>	<p>48 / 183 (26.23%)</p> <p>253</p>	<p>56 / 185 (30.27%)</p> <p>271</p>
<p>Gastrointestinal disorders</p> <p>GASTROINTESTINAL</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>107 / 186 (57.53%)</p> <p>468</p>	<p>158 / 183 (86.34%)</p> <p>1428</p>	<p>161 / 185 (87.03%)</p> <p>1761</p>
<p>Hepatobiliary disorders</p> <p>HEPATOBIILIAR/PANCREAS</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 186 (0.00%)</p> <p>0</p>	<p>0 / 183 (0.00%)</p> <p>0</p>	<p>2 / 185 (1.08%)</p> <p>3</p>
<p>Skin and subcutaneous tissue disorders</p> <p>DERMATOLOGY/SKIN</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>146 / 186 (78.49%)</p> <p>881</p>	<p>147 / 183 (80.33%)</p> <p>1248</p>	<p>157 / 185 (84.86%)</p> <p>1259</p>
<p>Renal and urinary disorders</p> <p>RENAL/GENITOURINARY</p> <p>alternative dictionary used: CTCAE 3</p>			

subjects affected / exposed occurrences (all)	11 / 186 (5.91%) 24	16 / 183 (8.74%) 34	9 / 185 (4.86%) 19
Endocrine disorders ENDOCRINE alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	6 / 186 (3.23%) 27	9 / 183 (4.92%) 24	15 / 185 (8.11%) 41
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL/SOFT TISSUE alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	16 / 186 (8.60%) 39	23 / 183 (12.57%) 102	23 / 185 (12.43%) 101
Infections and infestations INFECTION alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	37 / 186 (19.89%) 57	72 / 183 (39.34%) 144	66 / 185 (35.68%) 131
Metabolism and nutrition disorders METABOLIC/LABORATORY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	7 / 186 (3.76%) 10	8 / 183 (4.37%) 10	10 / 185 (5.41%) 16

Non-serious adverse events	TMZ/RT		
Total subjects affected by non-serious adverse events subjects affected / exposed	183 / 185 (98.92%)		
Vascular disorders VASCULAR alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	7 / 185 (3.78%) 26		
Surgical and medical procedures SURGERY/INTRA-OPERATIVE INJURY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	0 / 185 (0.00%) 0		
General disorders and administration			

site conditions CONSTITUTIONAL SYMPTOMS alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	160 / 185 (86.49%) 1144		
PAIN alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	131 / 185 (70.81%) 738		
Immune system disorders ALLERGY/IMMUNOLOGY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	9 / 185 (4.86%) 14		
Reproductive system and breast disorders SEXUAL/REPRODUCTIVE FUNCTION alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	4 / 185 (2.16%) 4		
Respiratory, thoracic and mediastinal disorders PULMONARY/UPPER RESPIRATORY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	9 / 185 (4.86%) 14		
Cardiac disorders CARDIAC(GENERAL) alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	15 / 185 (8.11%) 43		
Nervous system disorders NEUROLOGY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	153 / 185 (82.70%) 1575		
Blood and lymphatic system disorders			

<p>BLOOD</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 185 (6.49%)</p> <p>64</p>		
<p>LYMPHATICS</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 185 (5.41%)</p> <p>40</p>		
<p>Ear and labyrinth disorders</p> <p>AUDITORY/EAR</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>23 / 185 (12.43%)</p> <p>67</p>		
<p>Eye disorders</p> <p>OCULAR/VISUAL</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>62 / 185 (33.51%)</p> <p>261</p>		
<p>Gastrointestinal disorders</p> <p>GASTROINTESTINAL</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>136 / 185 (73.51%)</p> <p>795</p>		
<p>Hepatobiliary disorders</p> <p>HEPATOBIILIAR/PANCREAS</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 185 (0.00%)</p> <p>0</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>DERMATOLOGY/SKIN</p> <p>alternative dictionary used: CTCAE 3</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>139 / 185 (75.14%)</p> <p>984</p>		
<p>Renal and urinary disorders</p> <p>RENAL/GENITOURINARY</p> <p>alternative dictionary used: CTCAE 3</p>			

subjects affected / exposed occurrences (all)	7 / 185 (3.78%) 22		
Endocrine disorders ENDOCRINE alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	8 / 185 (4.32%) 23		
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL/SOFT TISSUE alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	17 / 185 (9.19%) 63		
Infections and infestations INFECTION alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	35 / 185 (18.92%) 71		
Metabolism and nutrition disorders METABOLIC/LABORATORY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	7 / 185 (3.78%) 41		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported