



Clinical trial results:

Phase 1b/2a Study Combining LY2157299 with Standard Temozolomide-based Radiochemotherapy in Patients with Newly Diagnosed Malignant Glioma

Summary

EudraCT number	2010-022160-13
Trial protocol	DE
Global end of trial date	23 November 2016

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017

Trial information

Trial identification

Sponsor protocol code	H9H-MC-JBAI
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01220271
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 11585

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Mon - Fri 9 AM - 5 PM Eastern time (UTC/GMT - 5 hours, EST), Eli Lilly and Company, 1 8772854559,
Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	23 November 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1b: To determine the safe and tolerable dose of galunisertib in combination with radiochemotherapy with temozolomide in participants with glioma eligible to receive radiochemotherapy with temozolomide (e.g. newly diagnosed malignant glioma World Health Organization Grade III and IV).

Phase 2a: To confirm the tolerability and evaluate the pharmacodynamic effect of Galunisertib in combination with standard radiochemotherapy in participants with newly diagnosed glioblastoma.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

Radiation therapy.

Evidence for comparator: -

Actual start date of recruitment	21 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	35 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 35
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Spain: 22
Worldwide total number of subjects	75
EEA total number of subjects	40

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)	55
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Completers included participants who died from any cause and participants who were alive but off study treatment at study conclusion.

Pre-assignment

Screening details:

No Text Entered

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: 160 mg Galunisertib +TMZ+RTX

Arm description:

During Radiation therapy:

- Radiation(RTX):Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.
- Temozolomide(TMZ): 75 mg/m2 taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.
- Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.
- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.

Arm type	Experimental
Investigational medicinal product name	Galunisertib
Investigational medicinal product code	
Other name	LY2157299
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During Radiation therapy:

- Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.

After Radiation Therapy:

- Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.

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

Dosage and administration details:

After Radiation Therapy:

- Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib

Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Arm title	Phase 1: 300 mg Galunisertib +TMZ+RTX
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Arm description:

During Radiation therapy:

- Radiation: Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: 150 mg taken twice orally daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.
- Temozolomide: 75 mg/m² taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.
- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.
- Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Galunisertib
Investigational medicinal product code	
Other name	LY2157299
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During Radiation therapy:

- Galunisertib: 150 mg taken twice orally daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.

After Radiation Therapy:

- Galunisertib: 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.

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

Dosage and administration details:

During Radiation therapy:

- Temozolomide: 75 mg/m² taken orally daily for 6 weeks.

After Radiation Therapy:

- Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Arm title	Phase 2: 300 mg Galunisertib +TMZ+RTX
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Arm description:

During Radiation therapy:

- Radiation: Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.
- Temozolomide: 75 mg/m² taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days

of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.

- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.
- Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Galunisertib
Investigational medicinal product code	
Other name	LY2157299
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During Radiation therapy:

- Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.

After Radiation Therapy:

- Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.

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

Dosage and administration details:

During Radiation therapy:

- Temozolomide: 75 mg/m² taken orally daily for 6 weeks.

After Radiation Therapy:

- Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Arm title	Phase 2: TMZ+RTX
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Arm description:

During Radiation therapy:

- Radiation: Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Temozolomide: 75 mg/m² taken orally daily for 6 weeks.

After Radiation Therapy:

Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

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

Dosage and administration details:

After Radiation Therapy:

Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Number of subjects in period 1	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX	Phase 2: 300 mg Galunisertib +TMZ+RTX
Started	10	9	40
Received at Least one dose of study drug	10	9	40
Completed	5	9	38
Not completed	5	0	2
Consent withdrawn by subject	4	-	2
Lost to follow-up	1	-	-

Number of subjects in period 1	Phase 2: TMZ+RTX
Started	16
Received at Least one dose of study drug	16
Completed	16
Not completed	0
Consent withdrawn by subject	-
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1: 160 mg Galunisertib +TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation(RTX):Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.• Temozolomide(TMZ): 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
<ul style="list-style-type: none">• Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.• Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.• For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.	
Reporting group title	Phase 1: 300 mg Galunisertib +TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Galunisertib: 150 mg taken twice orally daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.• Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
<ul style="list-style-type: none">• Galunisertib: 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.• For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.• Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.	
Reporting group title	Phase 2: 300 mg Galunisertib +TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.• Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
<ul style="list-style-type: none">• Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.• For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.• Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.	
Reporting group title	Phase 2: TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.	

Reporting group values	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX	Phase 2: 300 mg Galunisertib +TMZ+RTX
Number of subjects	10	9	40
Age categorical			
All participants who received at least one dose of study drug.			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
All participants who received at least one dose of study drug.			
Units: years			
arithmetic mean standard deviation	52.3 ± 8.1	57.6 ± 12.3	58.7 ± 8.9
Gender categorical			
All participants who received at least one dose of study drug.			
Units: Subjects			
Female Male	3 7	4 5	18 22
Sex: Female, Male			
All participants who received at least one dose of study drug.			
Units: Subjects			
Female Male	3 7	4 5	18 22
Race (NIH/OMB)			
All participants who received at least one dose of study drug.			
Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported	0 0 0 0 10 0 0	0 0 0 0 9 0 0	0 1 0 0 39 0 0
Region of Enrollment			
All participants who received at least one dose of study drug.			
Units: Subjects			
United States Germany Spain	2 4 4	2 4 3	25 6 9

Reporting group values	Phase 2: TMZ+RTX	Total	
Number of subjects	16	75	

Age categorical			
All participants who received at least one dose of study drug.			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age Continuous			
All participants who received at least one dose of study drug.			
Units: years			
arithmetic mean	57.8		
standard deviation	± 11.6	-	
Gender categorical			
All participants who received at least one dose of study drug.			
Units: Subjects			
Female	5	30	
Male	11	45	
Sex: Female, Male			
All participants who received at least one dose of study drug.			
Units: Subjects			
Female	5	30	
Male	11	45	
Race (NIH/OMB)			
All participants who received at least one dose of study drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	15	73	
More than one race	0	0	
Unknown or Not Reported	0	0	
Region of Enrollment			
All participants who received at least one dose of study drug.			
Units: Subjects			
United States	6	35	
Germany	4	18	
Spain	6	22	

End points

End points reporting groups

Reporting group title	Phase 1: 160 mg Galunisertib +TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation(RTX):Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.• Temozolomide(TMZ): 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
<ul style="list-style-type: none">• Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.• Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.• For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.	
Reporting group title	Phase 1: 300 mg Galunisertib +TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Galunisertib: 150 mg taken twice orally daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.• Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
<ul style="list-style-type: none">• Galunisertib: 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.• For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.• Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.	
Reporting group title	Phase 2: 300 mg Galunisertib +TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.• Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
<ul style="list-style-type: none">• Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles.• For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.• Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.	
Reporting group title	Phase 2: TMZ+RTX
Reporting group description:	
During Radiation therapy:	
<ul style="list-style-type: none">• Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.• Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.	
After Radiation Therapy:	
Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.	

Subject analysis set title	Phase 1b Participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

During Radiation therapy:

- Radiation(RTX):Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose= 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: 80 mg or 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days
- Temozolomide(TMZ): 75 mg/m² taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: 80 mg or 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for 6 cycles
- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.
- Temozolomide: 150 mg/m² and then 200 mg/m² orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Primary: Phase 1b: Recommended Dose for Phase 2a Portion : Maximum Tolerated Dose (MTD)

End point title	Phase 1b: Recommended Dose for Phase 2a Portion : Maximum Tolerated Dose (MTD) ^[1]
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End point description:

MTD was determined by evaluation of overall safety, dose reductions, omissions,& PK information from Phase1b.Toxicities were graded according to the National Cancer Institute's(NCI)Common Terminology Criteria for Adverse Events (CTCAE) v4.0. If multiple toxicities are seen, the presence of Dose-limiting toxicities (DLT)was based on the most severe toxicity experienced. DLTs were defined as any of the following events, which occur during radiochemotherapy & galunisertib attributable to galunisertib or the combination of galunisertib with radiation and/or TMZ and which last longer than 7 days: any Grade > 3 thrombocytopenia, and Grade 4 anemia and neutropenia any non-hematologic Grade > 3 toxicity(including nausea, vomiting, or diarrhea which can't be controlled with optimal medical management within 48 hours)any Grade 4 radiation-induced skin changes failure to recover from toxicities to be eligible for retreatment with galunisertib.

End point type	Primary
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End point timeframe:

Baseline to phase 1 Completion (Up to 10 Weeks)

Analysis Population Description (APD): Phase 1b: All participants who received at least one dose of study drug.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No arm comparison analyses were planned or conducted.

End point values	Phase 1b Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: mg				
number (not applicable)	300			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Relationship of Change in Response Biomarkers to Clinical

Benefit (Overall Survival (OS) of Change in Biomarkers)

End point title	Phase 2a: Relationship of Change in Response Biomarkers to Clinical Benefit (Overall Survival (OS) of Change in Biomarkers) ^[2]
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End point description:

Change from baseline in the biomarker at the end of cycle 5 for each participant was calculated and each participant was then classified as being 'less than' or 'greater than or equal to' the median change from baseline. Median overall survival (months) and 90% confidence intervals (where participant's numbers allowed) were estimated for each treatment/biomarker category combination.

APD: All phase 2a participants randomized onto one of the study treatment arms and who completed 5 cycles of treatment. 4 participants in the control arm were combined into 300 mg Galunisertib + TMZ+RTX arm since there was insufficient data to estimate parameters in control arm.

TRegs= CD4+CD25+CD127-/LOFOX P3+

9999= Not estimable. Too few data to estimate. Data were estimated from a Kaplan-Meier Model and not raw data.

End point type	Secondary
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End point timeframe:

Baseline Through Discontinuation From Study For Any Cause (Up To 35 Months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31 ^[3]	4 ^[4]		
Units: Months				
median (confidence interval 90%)				
OS;CD3+ change in biomarker<median change(n=15,2)	20.0 (13.4 to 25.2)	9999 (9999 to 9999)		
OS;CD3+ change in biomarker>=median change(n=16,2)	18.7 (15.3 to 28.5)	9999 (9999 to 9999)		
OS;CD4+ change in biomarker<median change(n=15,2)	19.2 (12.8 to 24.4)	9999 (9999 to 9999)		
OS;CD4+ change in biomarker>=median change(n=16,2)	19.6 (17.2 to 28.5)	9999 (9999 to 9999)		
OS;CD8+ change in biomarker<median change(n=15,2)	22.3 (19.2 to 9999)	9999 (9999 to 9999)		
OS;CD8+ change in biomarker>=median change(n=16,2)	16.3 (11.6 to 22.0)	9999 (9999 to 9999)		
OS;TRegs change in biomarker<median change(n=15,2)	15.3 (11.7 to 20.0)	9999 (9999 to 9999)		
OS;TRegs change biomarker>=median change(n=16,2)	25.2 (18.2 to 9999)	9999 (9999 to 9999)		
OS;YKL-40 change biomarker<median change(n=16,2)	18.7 (11.7 to 26.3)	9999 (9999 to 9999)		
OS;YKL-40 change biomarker>=median change(n=16,2)	19.9 (15.3 to 28.5)	9999 (9999 to 9999)		

Notes:

[3] - 9999= Not estimable. Too few data to estimate.

[4] - 9999= Not estimable. Too few data to estimate.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Pharmacokinetics (PK) - Maximum Observed Drug Concentration at Steady (Cmax ss)

End point title	Phase 1b: Pharmacokinetics (PK) - Maximum Observed Drug Concentration at Steady (Cmax ss) ^[5]
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End point description:

Maximum Observed Drug Concentration (Cmax ss).

APD: Phase 1b: All participants who received at least one dose of study drug and had evaluable PK data.

Geometric coefficient of variation is a % and not \pm . Due to system limitation we could not add a %.

End point type	Secondary
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End point timeframe:

Cycle 1: Day 14, Predose, 0.5,2,3,6 h; Day 15 (morning, 24h postdose), Day 16 (morning, 48h postdose); Cycle 2 and Cycle 3: Day 14: Predose, 0.5,2,3,6 h; Day 15 (morning,24h postdose)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 1b.

End point values	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: Nanograms/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1(n=10,8)	653 (\pm 91)	1620 (\pm 70)		
Cycle 2(n=8,8)	580 (\pm 75)	1160 (\pm 48)		
Cycle 3(n=5,7)	728 (\pm 67)	1550 (\pm 47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: PK - Time of Maximum Observed Drug Concentration at Steady State (Tmax ss)

End point title	Phase 1b: PK - Time of Maximum Observed Drug Concentration at Steady State (Tmax ss) ^[6]
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End point description:

Time of Maximum Observed Drug Concentration (Tmax ss)

APD: Phase 1b: All participants who received at least one dose of study drug and had evaluable PK data.

End point type	Secondary
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End point timeframe:

Cycle 1: Day 14, Predose, 0.5,2,3,6 h; Day 15 (morning, 24h postdose), Day 16 (morning, 48h postdose); Cycle 2 and Cycle 3: Day 14: Predose, 0.5,2,3,6 h; Day 15 (morning,24h postdose)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analyses were only planned for Phase 1b.

End point values	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: Hours (h)				
median (full range (min-max))				
Cycle 1 (n=10,8)	1.29 (0.5 to 3)	1.21 (0.5 to 3)		
Cycle 2 (n=8,8)	1.13 (0.5 to 3)	1.5 (0.5 to 2)		
Cycle 3 (n=5,7)	0.75 (0.48 to 2)	1 (0.5 to 2.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: PK - Area Under the Concentration-Time Curve at Steady State From Time Zero to Infinity (AUC[0-∞],ss)

End point title	Phase 1b: PK - Area Under the Concentration-Time Curve at Steady State From Time Zero to Infinity (AUC[0-∞],ss) ^[7]
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End point description:

Area Under the Concentration-Time Curve From Time Zero to Infinity.

APD: Phase 1b: All participants who received at least one dose of study drug and had evaluable PK data.

Geometric coefficient of variation is a % and not ±. Due to system limitation we could not add a %.

End point type	Secondary
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End point timeframe:

Cycle 1: Day 14, Predose, 0.5,2,3,6 h; Day 15 (morning, 24h postdose), Day 16 (morning, 48h postdose); Cycle 2 and Cycle 3: Day 14: Predose, 0.5,2,3,6 h; Day 15 (morning,24h postdose)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analyses were only planned for Phase 1b.

End point values	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: Hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 (n=10,8)	1860 (± 93)	6290 (± 70)		
Cycle 2(n=8,8)	1910 (± 89)	4940 (± 35)		
Cycle 3(n=5,7)	1920 (± 104)	5510 (± 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Overall Response Rate[ORR])

End point title	Phase 1b: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Overall Response Rate[ORR])[⁸]
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End point description:

ORR rate is the best response of complete response(CR) or partial response(PR) as classified by the investigators according to the Response Evaluation Criteria In Solid Tumors(RECIST v1.1).CR is the complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks and participants must be off corticosteroids and stable or improved clinically.PR is greater than or equal to 50% decrease,compared to baseline,in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. Progression(PD) was defined as having at least a 25% increase in the sum of the longest diameter of target lesions. Stable disease(SD) occurred when a participant did not qualify for CR,PR, or PD. ORR calculated as sum of the number of participants with PRs and CRs divided by the number of patients treated, expressed as a percentage.

APD: Phase 1b: All participants who received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline to Progressive Disease (Up to 46 Months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analyses were only planned for Phase 1b.

End point values	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: Percentage of participants				
number (not applicable)	10.00	11.11		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Percentage Overall Survival at 12 Months

End point title	Phase 2a: Percentage Overall Survival at 12 Months[⁹]
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End point description:

Overall survival duration is measured from the date of randomization to the date of death from any cause. For each participant who is not known to have died as of the data-inclusion cut-off date for a

particular analysis, overall survival duration was censored for that analysis at the date of last prior contact.

APD: Phase 2a: All participants who received at least one dose of study drug. Number of participants censored were Galunisertib + TMZ+RTX= 9 and TMZ+RTX= 5.

End point type	Secondary
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End point timeframe:

Randomization to Date of Death from any Cause at 12 Months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	16		
Units: Percentage alive at 12 months				
arithmetic mean (confidence interval 90%)	74 (59 to 83)	80 (56 to 92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Overall Survival

End point title	Phase 2a: Overall Survival ^[10]
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End point description:

Overall survival duration is measured from the date of randomization to the date of death from any cause. For each participant who is not known to have died as of the data-inclusion cut-off date for a particular analysis, overall survival duration will be censored for that analysis at the date of last prior contact.

APD: Phase 2a: All participants who received at least one dose of study drug. Number of participants censored were Galunisertib + TMZ+RTX= 9 and TMZ+RTX= 5.

End point type	Secondary
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End point timeframe:

Randomization to Date of Death from Any Cause (Up to 35 Months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	16		
Units: Months				
median (confidence interval 95%)	18.2 (13.4 to 20.6)	17.9 (10.7 to 24.0)		

Statistical analyses

Statistical analysis title	statistical_analysis_Overall Survival
Statistical analysis description: Regression Cox methodology was used to calculate the hazard ratio.	
Comparison groups	Phase 2: TMZ+RTX v Phase 2: 300 mg Galunisertib +TMZ+RTX
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	2.1

Secondary: Phase 2a: Progression Free Survival (PFS)

End point title	Phase 2a: Progression Free Survival (PFS) ^[11]
End point description: PFS is defined as the date of randomization to the first date of progression of disease or of death from any cause. For each participant who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, PFS will be censored at the date of last prior contact. PFS will be calculated and analyzed twice: (1) including clinical progressions of disease not based on lesion measurements, and (2) excluding clinical progressions. Progression(PD) was defined as having at least a 25% increase in the sum of the longest diameter of target lesions. APD: Phase 2a: All participants who received at least one dose of study drug. Number of participants censored were Galunisertib + TMZ+RTX = 3 and TMZ+RTX= 3.	
End point type	Secondary
End point timeframe: Randomization to Measured Progressive Disease or Death From Any Cause(Up to 35 Months)	
Notes: [11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analyses were only planned for Phase 2a.	

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	16		
Units: Months				
median (confidence interval 95%)	7.6 (6.1 to 10.4)	11.5 (5.4 to 15.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point title	Phase 2a: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])[12]
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End point description:

ORR rate is the best response of complete response(CR) or partial response(PR) as classified by the investigators according to the Response Evaluation Criteria In Solid Tumors(RECIST v1.1).CR is the complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks and participants must be off corticosteroids and stable or improved clinically.PR is greater than or equal to 50% decrease,compared to baseline,in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. Progression(PD) was defined as having at least a 25% increase in the sum of the longest diameter of target lesions. Stable disease(SD) occurred when a participant did not qualify for CR,PR, or PD.ORR calculated as sum of the number of participants with PRs and CRs divided by the number of patients treated, expressed as a percentage.

APD: Phase 2a : All participants who received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Randomization to Measured Progressive Disease(Up to 35 Months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	16		
Units: Percentage of participants				
number (not applicable)	7.50	0.00		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Duration of tumor Response

End point title	Phase 2a: Duration of tumor Response[13]
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End point description:

APD: Zero participants were analyzed.The data were not evaluable.Only three participants were responders and so duration of tumor was not evaluable.

End point type	Secondary
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End point timeframe:

Time of Response to Measured Progressive Disease or Death Due to any Cause(Up To 35 Months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[14]	0 ^[15]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[14] - Zero participants were analyzed.The data were not evaluable.

[15] - Zero participants were analyzed.The data were not evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Time to Treatment Failure

End point title	Phase 2a: Time to Treatment Failure ^[16]
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End point description:

Time to treatment failure is measured from the date of randomization until the date of discontinuation of study treatment due to adverse event, progression of disease, or death from any cause. For each participant who discontinued study treatment for any other reason, time to treatment failure will be censored at the date of discontinuation of study treatment. If a participant is still on study treatment as of the data-inclusion cut-off date for the particular analysis, time to treatment failure will be censored for that participant at that cut-off date. Progression(PD) was defined as having at least a 25% increase in the sum of the longest diameter of target lesions.

APD: Phase 2a: All participants who received at least one dose of study drug. Number of participants censored were Galunisertib + TMZ+RTX=9 and TMZ+RTX= 9.

End point type	Secondary
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End point timeframe:

Randomization to the Date of Discontinuation of Study Treatment Due to Adverse Event, Progression of Disease, or Death from Any Cause(Up to 35 Months)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	16 ^[17]		
Units: Months				
median (confidence interval 95%)	7.1 (5.5 to 8.9)	8.8 (5.1 to 9999)		

Notes:

[17] - 9999= Not estimable. Too many censored values.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Change from baseline in MD Anderson Symptom Inventory Brain Tumor (MDASI-BT) - Brain Tumor Symptoms, Core Symptoms, Interference Symptoms

End point title	Phase 2a: Change from baseline in MD Anderson Symptom Inventory Brain Tumor (MDASI-BT) - Brain Tumor Symptoms, Core Symptoms, Interference Symptoms ^[18]
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End point description:

The MDASI-BT consists of 22 symptom items (13 items of the core MDASI plus 9 items specific to brain tumors) plus 6 interference items, all with 11-point rating scales. For the symptom items, 0 equals "not present" and 10 equals "as bad as you can imagine." For the interference items, 0 equals "did not interfere" and 10 equals "interfered completely. The brain tumor symptoms, core symptoms and interference symptoms range 0 to 10 with lower scores indicating that the participant is reporting fewer symptoms or less interference.

APD: Phase 2a: All participants who received at least one dose of study drug and had a baseline and at least one post-baseline measurement.

End point type	Secondary
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End point timeframe:

Baseline, 30 Day Post Study Day Follow-Up

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analyses were only planned for Phase 2a.

End point values	Phase 2: 300 mg Galunisertib +TMZ+RTX	Phase 2: TMZ+RTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Brain Tumor Symptoms	0.2 (± 1.3)	0.2 (± 1.7)		
Core Symptoms	0.7 (± 1.1)	0.6 (± 1.4)		
Interference Symptoms	0.8 (± 2.1)	0.2 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Phase 1b/2a - Entire Study

Adverse event reporting additional description:

All participants who received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Phase 1: 160 mg Galunisertib +TMZ+RTX
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Reporting group description:

During Radiation therapy:

- Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.
- Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: 80 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for a 6 cycles.
- Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.
- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.

Reporting group title	Phase 1: 300 mg Galunisertib +TMZ+RTX
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Reporting group description:

During Radiation therapy:

- Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: 150 mg taken twice orally daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.
- Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: 150 mg taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for a 6 cycles.
- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.
- Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Reporting group title	Phase 2: 300 mg Galunisertib +TMZ+RTX
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Reporting group description:

During Radiation therapy:

- Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days.
- Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.

After Radiation Therapy:

- Galunisertib: Phase 1 established dose taken orally twice daily for 14 days on followed 14 days of pause. This on/off schedule constitutes a cycle of 28 days. Taken for a 6 cycles.
- For participants benefiting from therapy, treatment may continue in 2 cycle segments as long as benefit continues.
- Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib.

Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Reporting group title	Phase 2: TMZ+RTX
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Reporting group description:

During Radiation therapy:

- Radiation:Approximate 1.8 - 2.0 Gy x 30 fractions taken 5 days per week. Approximate total dose = 60.0 Gy per week for 6 weeks. Radiation was administered as approved.
- Temozolomide: 75 mg/m2 taken orally daily for 6 weeks.

After Radiation Therapy:

Temozolomide: 150 mg/m2 and then 200 mg/m2 orally daily during the off time of galunisertib. Starting 28 days after the completion of radiation therapy. Taken for 5 days followed by 23 days of rest for 6 cycles.

Serious adverse events	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX	Phase 2: 300 mg Galunisertib +TMZ+RTX
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	2 / 9 (22.22%)	20 / 40 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastases to spine			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tumour haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
pyrexia			

alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
pneumonia aspiration			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary embolism			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mental status changes			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
alanine aminotransferase increased			

alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutrophil count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
platelet count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
white blood cell count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
postoperative fever			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac failure			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ataxia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
brain oedema			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
central nervous system necrosis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebral haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
epilepsy			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemorrhage intracranial			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neurological symptom			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
seizure			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
febrile neutropenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombocytopenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
enteritis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
large intestine perforation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
retroperitoneal haemorrhage			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
pain in extremity			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
gastroenteritis viral			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
septic shock			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
wound infection			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
hypokalaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: TMZ+RTX		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 16 (31.25%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastases to spine			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
tumour haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
pyrexia			
alternative dictionary used:			

MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
pneumonia aspiration			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
pneumonitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
pulmonary embolism			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
mental status changes			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
alanine aminotransferase increased			
alternative dictionary used:			

MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
neutrophil count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
platelet count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
white blood cell count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
postoperative fever			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cardiac failure			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
ataxia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
brain oedema			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
central nervous system necrosis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cerebral haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
epilepsy			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
haemorrhage intracranial			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
neurological symptom			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
seizure			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
syncope			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
febrile neutropenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
neutropenia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
thrombocytopenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
enteritis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
large intestine perforation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
nausea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
retroperitoneal haemorrhage			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
pain in extremity			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
gastroenteritis viral			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pneumonia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
septic shock			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
wound infection			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
hypokalaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1: 160 mg Galunisertib +TMZ+RTX	Phase 1: 300 mg Galunisertib +TMZ+RTX	Phase 2: 300 mg Galunisertib +TMZ+RTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	9 / 9 (100.00%)	39 / 40 (97.50%)
Vascular disorders			
arterial haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
deep vein thrombosis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 40 (5.00%)
occurrences (all)	0	1	4
haematoma			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
hypertension			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
hypotension			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
lymphoedema			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
orthostatic hypotension			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
thrombophlebitis superficial			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	3 / 10 (30.00%)	1 / 9 (11.11%)	6 / 40 (15.00%)
occurrences (all)	3	1	6
face oedema			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
fatigue			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	5 / 10 (50.00%)	6 / 9 (66.67%)	24 / 40 (60.00%)
occurrences (all)	6	8	27
gait disturbance			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	5 / 40 (12.50%)
occurrences (all)	1	0	6
influenza like illness			
alternative dictionary used: MedDRA 19.1			

<p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 10 (0.00%)</p> <p>0</p>	<p>1 / 9 (11.11%)</p> <p>1</p>	<p>2 / 40 (5.00%)</p> <p>4</p>
<p>localised oedema</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 10 (0.00%)</p> <p>0</p>	<p>1 / 9 (11.11%)</p> <p>1</p>	<p>1 / 40 (2.50%)</p> <p>1</p>
<p>malaise</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 10 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p>	<p>0 / 40 (0.00%)</p> <p>0</p>
<p>oedema peripheral</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 10 (10.00%)</p> <p>1</p>	<p>0 / 9 (0.00%)</p> <p>0</p>	<p>3 / 40 (7.50%)</p> <p>4</p>
<p>pyrexia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 10 (10.00%)</p> <p>1</p>	<p>1 / 9 (11.11%)</p> <p>1</p>	<p>3 / 40 (7.50%)</p> <p>4</p>
<p>Immune system disorders</p> <p>hypersensitivity</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 10 (10.00%)</p> <p>1</p>	<p>0 / 9 (0.00%)</p> <p>0</p>	<p>2 / 40 (5.00%)</p> <p>2</p>
<p>Respiratory, thoracic and mediastinal disorders</p> <p>benign prostatic hyperplasia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed^[1]</p> <p>occurrences (all)</p> <p>cough</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dyspnoea</p> <p>alternative dictionary used: MedDRA 19.1</p>	<p>0 / 7 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>2</p>	<p>0 / 5 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p>	<p>0 / 22 (0.00%)</p> <p>0</p> <p>5 / 40 (12.50%)</p> <p>5</p>

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
nasal congestion			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
paranasal sinus discomfort			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
productive cough			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Psychiatric disorders			
aggression			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
anxiety			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	3
bulimia nervosa			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
confusional state			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	5 / 40 (12.50%)
occurrences (all)	0	1	9
depression			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	4 / 40 (10.00%)
occurrences (all)	0	1	4
insomnia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	8 / 40 (20.00%)
occurrences (all)	1	1	8
irritability			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 10 (20.00%)	1 / 9 (11.11%)	7 / 40 (17.50%)
occurrences (all)	2	1	11
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	4 / 40 (10.00%)
occurrences (all)	1	1	7
blood bilirubin increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
blood creatinine increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
lipase increased			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	4 / 40 (10.00%)
occurrences (all)	1	1	6
lymphocyte count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	7 / 40 (17.50%)
occurrences (all)	3	2	15
neutrophil count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	10
platelet count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	11 / 40 (27.50%)
occurrences (all)	0	1	17
weight decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	7 / 40 (17.50%)
occurrences (all)	1	2	8
weight increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	5 / 40 (12.50%)
occurrences (all)	0	0	5
white blood cell count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	12 / 40 (30.00%)
occurrences (all)	1	0	30
Injury, poisoning and procedural complications			
contusion			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
fall			
alternative dictionary used: MedDRA 19.1			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>radiation skin injury</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>wound</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 10 (0.00%)</p> <p>0</p> <p>5 / 10 (50.00%)</p> <p>5</p> <p>0 / 10 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>1 / 9 (11.11%)</p> <p>1</p>	<p>7 / 40 (17.50%)</p> <p>9</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>0 / 40 (0.00%)</p> <p>0</p>
<p>Cardiac disorders</p> <p>palpitations</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>sinus tachycardia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 10 (0.00%)</p> <p>0</p> <p>0 / 10 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p>	<p>0 / 40 (0.00%)</p> <p>0</p> <p>0 / 40 (0.00%)</p> <p>0</p>
<p>Nervous system disorders</p> <p>amnesia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>aphasia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ataxia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>balance disorder</p> <p>alternative dictionary used: MedDRA 19.1</p>	<p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>1</p> <p>0 / 10 (0.00%)</p> <p>0</p>	<p>1 / 9 (11.11%)</p> <p>1</p> <p>2 / 9 (22.22%)</p> <p>2</p> <p>0 / 9 (0.00%)</p> <p>0</p>	<p>1 / 40 (2.50%)</p> <p>1</p> <p>10 / 40 (25.00%)</p> <p>10</p> <p>3 / 40 (7.50%)</p> <p>3</p>

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
cognitive disorder			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 40 (5.00%)
occurrences (all)	0	1	2
dizziness			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	6 / 40 (15.00%)
occurrences (all)	1	1	12
dysarthria			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	4 / 40 (10.00%)
occurrences (all)	0	1	4
dysgeusia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3
facial paralysis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	4
headache			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	5 / 10 (50.00%)	4 / 9 (44.44%)	15 / 40 (37.50%)
occurrences (all)	10	4	23
hemiparesis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	6 / 40 (15.00%)
occurrences (all)	0	0	7
hypoesthesia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3

memory impairment			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	8 / 40 (20.00%)
occurrences (all)	0	0	8
monoparesis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 40 (0.00%)
occurrences (all)	1	2	0
myoclonus			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
paraesthesia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
paresis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	4
quadriplegia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
seizure			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	7 / 40 (17.50%)
occurrences (all)	0	1	10
sinus headache			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
somnolence			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
syncope			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
tremor			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	5 / 40 (12.50%)
occurrences (all)	1	0	5
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	6 / 40 (15.00%)
occurrences (all)	2	0	8
haemorrhagic diathesis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
leukopenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
lymphadenopathy			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
lymphopenia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	4 / 9 (44.44%) 4	6 / 40 (15.00%) 14
neutropenia alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 9 (33.33%) 3	2 / 40 (5.00%) 3
thrombocytopenia alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 9	3 / 9 (33.33%) 3	7 / 40 (17.50%) 8
Ear and labyrinth disorders hypoacusis alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	1 / 40 (2.50%) 2
vertigo alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 40 (0.00%) 0
Eye disorders blindness alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 40 (0.00%) 0
lacrimation increased alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 40 (0.00%) 0
vision blurred alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	3 / 40 (7.50%) 4
vitreous haemorrhage alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
abdominal pain			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 10 (20.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	2	0	3
abdominal pain upper			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
anal incontinence			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
constipation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	4 / 10 (40.00%)	1 / 9 (11.11%)	20 / 40 (50.00%)
occurrences (all)	8	2	26
diarrhoea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	5
dry mouth			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
dyspepsia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	6 / 40 (15.00%)
occurrences (all)	2	2	6
dysphagia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
eructation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
flatulence			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
nausea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	8 / 10 (80.00%)	2 / 9 (22.22%)	21 / 40 (52.50%)
occurrences (all)	13	2	34
paraesthesia oral			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
stomatitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
toothache			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

vomiting alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	5 / 9 (55.56%) 7	13 / 40 (32.50%) 24
Skin and subcutaneous tissue disorders alopecia alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 4	1 / 9 (11.11%) 1	15 / 40 (37.50%) 15
decubitus ulcer alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0	0 / 40 (0.00%) 0
dermatitis acneiform alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	2 / 9 (22.22%) 2	3 / 40 (7.50%) 3
dermatitis allergic alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	2 / 40 (5.00%) 2
dermatitis bullous alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 40 (0.00%) 0
dry skin alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	4 / 40 (10.00%) 5
ecchymosis alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	2 / 40 (5.00%) 2
erythema alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	3
erythema multiforme			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
pruritus			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	5 / 40 (12.50%)
occurrences (all)	1	0	6
rash			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	5 / 40 (12.50%)
occurrences (all)	0	0	9
rash maculo-papular			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	3 / 10 (30.00%)	1 / 9 (11.11%)	5 / 40 (12.50%)
occurrences (all)	3	1	7
skin exfoliation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
skin lesion			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
dysuria			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
nocturia			
alternative dictionary used: MedDRA 19.1			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>polyuria</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>urinary incontinence</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>urinary retention</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>1</p> <p>0 / 10 (0.00%)</p> <p>0</p> <p>0 / 10 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p>	<p>0 / 40 (0.00%)</p> <p>0</p> <p>0 / 40 (0.00%)</p> <p>0</p> <p>4 / 40 (10.00%)</p> <p>4</p> <p>3 / 40 (7.50%)</p> <p>3</p>
<p>Endocrine disorders</p> <p>hypothyroidism</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 10 (10.00%)</p> <p>1</p>	<p>1 / 9 (11.11%)</p> <p>1</p>	<p>0 / 40 (0.00%)</p> <p>0</p>
<p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>back pain</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>joint range of motion decreased</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>muscular weakness</p> <p>alternative dictionary used: MedDRA 19.1</p>	<p>0 / 10 (0.00%)</p> <p>0</p> <p>0 / 10 (0.00%)</p> <p>0</p> <p>0 / 10 (0.00%)</p> <p>0</p>	<p>1 / 9 (11.11%)</p> <p>1</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>1 / 9 (11.11%)</p> <p>1</p>	<p>6 / 40 (15.00%)</p> <p>7</p> <p>7 / 40 (17.50%)</p> <p>8</p> <p>0 / 40 (0.00%)</p> <p>0</p>

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
musculoskeletal pain			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 40 (2.50%)
occurrences (all)	2	1	1
myalgia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	5
pain in extremity			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 40 (2.50%)
occurrences (all)	0	1	4
tendonitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
candida infection			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	5
herpes simplex			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
oral herpes			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
rhinitis			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
tooth infection			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
upper respiratory tract infection			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
urinary tract infection			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	5 / 10 (50.00%)	1 / 9 (11.11%)	11 / 40 (27.50%)
occurrences (all)	5	1	18
hypercalcaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
hyperglycaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 10 (20.00%)	1 / 9 (11.11%)	6 / 40 (15.00%)
occurrences (all)	3	1	7
hypermagnesaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
hypernatraemia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	2 / 40 (5.00%)
occurrences (all)	0	1	3
hypertriglyceridaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
hypokalaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	4 / 40 (10.00%)
occurrences (all)	1	1	7
hyponatraemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
hypophosphataemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
polydipsia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Phase 2: TMZ+RTX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders			
arterial haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
deep vein thrombosis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		

<p>haematoma</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 16 (0.00%)</p> <p>0</p>		
<p>hypertension</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 16 (0.00%)</p> <p>0</p>		
<p>hypotension</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 16 (0.00%)</p> <p>0</p>		
<p>lymphoedema</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 16 (0.00%)</p> <p>0</p>		
<p>orthostatic hypotension</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 16 (0.00%)</p> <p>0</p>		
<p>thrombophlebitis superficial</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 16 (0.00%)</p> <p>0</p>		
<p>General disorders and administration site conditions</p> <p>asthenia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>face oedema</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>fatigue</p> <p>alternative dictionary used:</p>	<p>3 / 16 (18.75%)</p> <p>3</p> <p>0 / 16 (0.00%)</p> <p>0</p>		

MedDRA 19.1			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	10		
gait disturbance			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
influenza like illness			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
localised oedema			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
malaise			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
oedema peripheral			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
pyrexia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

benign prostatic hyperplasia alternative dictionary used: MedDRA 19.1 subjects affected / exposed ^[1] occurrences (all)	1 / 11 (9.09%) 1		
cough alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
dyspnoea alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
nasal congestion alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
paranasal sinus discomfort alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
productive cough alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
Psychiatric disorders aggression alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
anxiety alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
bulimia nervosa alternative dictionary used: MedDRA 19.1			

<p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>confusional state</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>depression</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>3 / 16 (18.75%)</p> <p>occurrences (all)</p> <p>3</p>			
<p>insomnia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>6 / 16 (37.50%)</p> <p>occurrences (all)</p> <p>6</p>			
<p>irritability</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Investigations</p> <p>alanine aminotransferase increased</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>2 / 16 (12.50%)</p> <p>occurrences (all)</p> <p>4</p> <p>aspartate aminotransferase increased</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>4</p> <p>blood bilirubin increased</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>blood creatinine increased</p> <p>alternative dictionary used: MedDRA 19.1</p>			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
lipase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
lymphocyte count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
neutrophil count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
platelet count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	9		
weight decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
weight increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
white blood cell count decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	5		

<p>Injury, poisoning and procedural complications</p> <p>contusion</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>fall</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>radiation skin injury</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>wound</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Cardiac disorders</p> <p>palpitations</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>sinus tachycardia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Nervous system disorders</p> <p>amnesia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>aphasia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			

ataxia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
balance disorder			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
cognitive disorder			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
dizziness			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences (all)	10		
dysarthria			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
dysgeusia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
facial paralysis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
headache			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	8		
hemiparesis			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
hypoesthesia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
memory impairment			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
monoparesis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
myoclonus			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
paraesthesia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
paresis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
quadriplegia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

seizure alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
sinus headache alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
somnolence alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
syncope alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
tremor alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Blood and lymphatic system disorders anaemia alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
haemorrhagic diathesis alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
leukopenia alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
lymphadenopathy alternative dictionary used: MedDRA 19.1			

<p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>lymphopenia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>2</p> <p>neutropenia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>3</p> <p>thrombocytopenia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Ear and labyrinth disorders</p> <p>hypoacusis</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>vertigo</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Eye disorders</p> <p>blindness</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>lacrimation increased</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>vision blurred</p> <p>alternative dictionary used: MedDRA 19.1</p>			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
vitreous haemorrhage			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
abdominal pain			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
abdominal pain upper			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
anal incontinence			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
constipation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	8		
diarrhoea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
dry mouth			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
dyspepsia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
dysphagia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
eructation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
flatulence			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
nausea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	10 / 16 (62.50%)		
occurrences (all)	13		
paraesthesia oral			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
stomatitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		

toothache alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
vomiting alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	6 / 16 (37.50%) 6		
Skin and subcutaneous tissue disorders alopecia alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3		
decubitus ulcer alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
dermatitis acneiform alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
dermatitis allergic alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
dermatitis bullous alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
dry skin alternative dictionary used: MedDRA 19.1 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
ecchymosis alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
erythema			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
erythema multiforme			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
pruritus			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
rash			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
rash maculo-papular			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
skin exfoliation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
skin lesion			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
dysuria			
alternative dictionary used: MedDRA 19.1			

<p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>nocturia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>polyuria</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>urinary incontinence</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>urinary retention</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Endocrine disorders</p> <p>hypothyroidism</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>back pain</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>joint range of motion decreased</p> <p>alternative dictionary used: MedDRA 19.1</p>			

<p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>muscular weakness</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>2 / 16 (12.50%)</p> <p>occurrences (all)</p> <p>3</p>			
<p>musculoskeletal pain</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>myalgia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>pain in extremity</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>tendonitis</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Infections and infestations</p> <p>candida infection</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>herpes simplex</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>oral herpes</p> <p>alternative dictionary used: MedDRA 19.1</p>			

<p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>rhinitis</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>tooth infection</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>upper respiratory tract infection</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>urinary tract infection</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Metabolism and nutrition disorders</p> <p>decreased appetite</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>3 / 16 (18.75%)</p> <p>occurrences (all)</p> <p>3</p> <p>hypercalcaemia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>hyperglycaemia</p> <p>alternative dictionary used: MedDRA 19.1</p> <p>subjects affected / exposed</p> <p>2 / 16 (12.50%)</p> <p>occurrences (all)</p> <p>2</p> <p>hypermagnesaemia</p> <p>alternative dictionary used: MedDRA 19.1</p>			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
hypernatraemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	4		
hypertriglyceridaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
hypokalaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	5		
hyponatraemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
hypophosphataemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
polydipsia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2013	Amendment b - With the growing understanding of the safety profile of LY2157299 across all studies and to ensure that appropriate data are being collected, the following changes to the protocol have been made: 1. Pharmacodynamics (PD) markers which were identified in other studies to provide no scientific information on the activity of LY2157299, were removed. 2. While ECHO cardiography/Doppler will remain unchanged for this study, ECG (except for screening at baseline) and ECG chemistry will be removed because no medically significant changes were observed with the administration of LY2157299 (ie,PK-associated QTc prolongations). 3. Clarification, updates and information on the Phase 1b safety review was included.
08 July 2014	Amendment c The protocol was amended to reduce the number of visits and tests required for patients on Cycles 15 and beyond. Based on the current safety profile of LY2157299, the reduction in the number of visits and tests would have no influence on the risk assessment. Additionally, continued access to LY2157299 was offered to participants who continued to experience clinical benefit, had no undue risks, and were on study treatment at the time of study completion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported