Clinical trial results:
A Phase II, Multi-centre, Open-Label, Parallel Group, Randomised Study To Compare the Efficacy of selumetinib (AZD6244, ARRY-142886). vs Temozolomide in Patients with Unresectable AJCC Stage 3 or 4 Malignant Melanoma

Summary

EudraCT number	2006-001456-12
Trial protocol	GB AT DK FR
Global end of trial date	24 July 2013

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	06 July 2016

Trial information

Trial identification

Sponsor protocol code	D1532C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00338130
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Alderley Park, Macclesfield, United Kingdom, SK10 4TG
Public contact	AstraZeneca, AstraZeneca, AZTrial_results_posting@AstraZeneca.com
Scientific contact	Selumetinib Global Clinical Lead, MD, AstraZeneca, AZTrial_results_posting@AstraZeneca.com

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	20 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2007
Global end of trial reached?	Yes
Global end of trial date	24 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of selumetinib (AZD6244, ARRY-142886). versus TMZ in
patients with unresectable AJCC Stage 3 or 4 malignant melanoma by evaluation of Progression Free Survival (PFS)

Protection of trial subjects:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Switzerland: 28
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	200
EEA total number of subjects	68

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)	142
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female or male patients aged 18 years and over, with unresectable AJCC Stage 3 or 4 malignant melanoma. Patients were to have at least 1 measurable site of disease as defined by RECIST, World Health Organisation (WHO) performance status 0 to 2.

Pre-assignment

Screening details:

Two hundred and thirty nine patients were enrolled, of whom 200 were randomised. Of the 39 patients who failed screening and were not randomised, the majority (27) failed inclusion/exclusion criteria.

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	AZD6244

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD6244/Selumetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

AZD6244 100mg twice daily

Arm title	TMZ_

Arm description: -

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

Dosage and administration details:

TMZ 200mg/m2 per day for 5 days every 28 days

Number of subjects in period 1	AZD6244	TMZ_
Started	104	96
Received treatment	99	95
Completed	3	3
Not completed	101	93
Clinical progression	-	2

Physician decision	1	3
Symptomatic deterioration	1	-
Adverse event, non-fatal	10	2
Elegibility criteria not fulled	-	1
Undergo resection & follow-up with other treatment	1	-
Did not receive treatment	5	1
Patients were given maximum 6 cycles	-	3
Disease Progression	78	81
Not willing to continue study treatment	5	-

Baseline characteristics

Reporting groups	
Reporting group title	AZD6244
Reporting group description: -	
Reporting group title	TMZ_
Reporting group description: -	

Reporting group values	AZD6244	TMZ_	Total
Number of subjects	104	96	200
Age Categorical			
Min			
Units: Subjects			
From 18 - 64 years	74	68	142
From 65 – 84 years	30	28	58
Age Continuous			
Age Continuous			
Units: years			
arithmetic mean	57.1	57	
standard deviation	± 14	± 13.4	-
Gender Categorical			
Units: Subjects			
Female	49	31	80
Male	55	65	120
World Health Organisation Performance Status			
WHO Performance Status assessed at baseline			
Units: Subjects			
0 (Normal activity)	67	71	138
1 (Restricted activity)	34	23	57
2 (In bed </= 50% of the time)	1	2	3
Performance Status unknown	2	0	2
American Joint committee on Cancer Staging			
AJCC assessed at baseline			
Units: Subjects			
Stage 3	3	3	6
Stage 4	99	92	191
AJCC stage unknown	2	1	3
Lactate dehydrogenase level at baseline			
Lactate dehydrogenase level at baseline			
Units: Subjects			
<2 x upper limit of normal	79	79	158
>/= 2 x upper limit normal	17	15	32
unknown	8	2	10
Primary tumour type			
Primary tumour type			
Units: Subjects			
Uveal	7	13	20

Mucosal	6	0	6
Cutaneous	75	72	147
Unknown primary tumour	16	11	27
Mutation Status Units: Subjects			
BRAF positive	45	28	73
NRAS positive	10	18	28
Wild-type for both	29	28	57
Mutation status unknown	20	22	42

Subject analysis sets

Subject analysis set title	AZD6244
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomised to AZD6244	
Subject analysis set title	TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomised to TMZ	

Reporting group values	AZD6244	TMZ	
Number of subjects	104	96	
Age Categorical			
Min			
Units: Subjects			
From 18 - 64 years	74	68	
From 65 – 84 years	30	28	
Age Continuous			
Age Continuous			
Units: years			
arithmetic mean	57.1	57	
standard deviation	± 14	± 13.4	
Gender Categorical Units: Subjects			
Female	49	31	
Male	55	65	
World Health Organisation Performance Status			
WHO Performance Status assessed at baseline			
Units: Subjects			
0 (Normal activity)	67	71	
1 (Restricted activity)	34	23	
2 (In bed </= 50% of the time)	1	2	
Performance Status unknown	2	0	
American Joint committee on Cancer Staging			
AJCC assessed at baseline			
Units: Subjects			
Stage 3	3	3	
Stage 4	99	92	
AJCC stage unknown	2	1	

Lactate dehydrogenase level at baseline			
Lactate dehydrogenase level at baseline			
Units: Subjects			
<2 x upper limit of normal	79	79	
>/= 2 x upper limit normal	17	15	
unknown	8	2	
Primary tumour type			
Primary tumour type			
Units: Subjects			
Uveal	7	13	
Mucosal	6	0	
Cutaneous	75	72	
Unknown primary tumour	16	11	
Mutation Status Units: Subjects			
BRAF positive	45	28	
NRAS positive	10	18	
Wild-type for both	29	28	
Mutation status unknown	20	22	

End points

End points reporting groups	
Reporting group title	AZD6244
Reporting group description: -	
Reporting group title	TMZ_
Reporting group description: -	
Subject analysis set title	AZD6244
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomised to AZD6244	
Subject analysis set title	TMZ
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomised to TMZ	

Primary: PFS	
End point title	PFS
End point description:	
End point type	Primary
End point timeframe: Assessment by RECIST criteria conducted at baseline, week 6, week 12 and then every 8 weeks until progression	

End point values	AZD6244	TMZ_		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	96		
Units: days				
median (not applicable)	78 (± 0)	80 (± 0)		

Statistical analyses

Statistical analysis title	PFS in the Overall Population
Statistical analysis description: PFS was analysed using a Cox Proportional Hazards model.	
Comparison groups	AZD6244 v TMZ_
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.65 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.86
upper limit	1.32

Notes:

[1] - Overall ITT population

[2] - 1-sided p-value

Statistical analysis title	PFS in BRAF mutant subpopulation

Statistical analysis description:

PFS was analysed using a Cox Proportional Hazards Model

Comparison groups	AZD6244 v TMZ_
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.537 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.71
upper limit	1.49

Notes:

[3] - BRAF mutant subpopulation

[4] - 1-sided p-value

Statistical analysis title	PFS in BRAF and/or NRAS mutant subpopulation

Statistical analysis description:

PFS was analysed using a Cox Proportional Hazards Model

Comparison groups	AZD6244 v TMZ_
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.547 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.76
upper limit	1.38

Notes:

[5] - BRAF and/or NRAS mutant subpopulation

[6] - 1-sided p-value

Secondary: Time To Death

End point title	Time To Death

End point description: Assessed following 130 deatjs	
End point type	Secondary
End point timeframe: Time from randomisation until Death	

End point values	AZD6244	TMZ_		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	96		
Units: Days				
median (not applicable)	284 (± 0)	369 (± 0)		

Statistical analyses

Statistical analysis title	TTD in the Overall Population
Statistical analysis description: Cox Proportional Hazards Model	
Comparison groups	AZD6244 v TMZ_
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.95 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.351
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.07
upper limit	1.71

Notes:
[7] - Overall Population
[8] - 1-sided p-value

Statistical analysis title	TTD in BRAF mutant subpopulation
Statistical analysis description: Time To Death analysed using Cox Proportional Hazards Model	
Comparison groups	AZD6244 v TMZ_
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.949 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.654

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.12
upper limit	2.45

Notes:

[9] - BRAF mutant subpopulation

[10] - 1-sided p-value

Statistical analysis title	TTD in BRAF and/or NRAS mutant subpopulation

Statistical analysis description:

Time To Death analysed using a Cox Proportional Hazards Model

Comparison groups	AZD6244 v TMZ_
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.973 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.621
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.18
upper limit	2.23

Notes:

[11] - BRAF and/or NRAS mutant subpopulation

[12] - 1-sided

Secondary: Objective Tumour response

End point title	Objective Tumour response

End point description:

End point type	Secondary

End point timeframe:

Assessment by RECIST criteria conducted at baseline, week 6, week 12 and then every 8 weeks until progression

End point values	AZD6244	TMZ_		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	96		
Units: No. Patients				
In overall Population	6	9		
In BRAF mutant subpopulation	5	3		
In BRAF and NRAS mutant subpopulation	5	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected throughout the study. SAEs were collected until disease progression or 30 days after withdrawal from treatment, whichever was the latest.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Temozolomide

Reporting group description:

Temozolomide was administered without food, as described in the national prescribing information

Reporting group title	AZD6244

Reporting group description:

AZD6244 was administered orally with 15 mL of Captisol® Aqueous solution (25% w/v) prior to breakfast and an evening meal

Serious adverse events	Temozolomide	AZD6244	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 95 (16.84%)	32 / 99 (32.32%)	
number of deaths (all causes)	57	73	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to biliary tract			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to gastrointestinal tract			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			

subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour haemorrhage			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	0 / 95 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 95 (1.05%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocturnal dyspnoea			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 95 (1.05%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 95 (2.11%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Patella fracture			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio respiratory arrest			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Left ventricular dysfunction			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphasia			

subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 95 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 95 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 95 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 95 (0.00%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric Vein Thrombosis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 95 (1.05%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 95 (2.11%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 95 (1.05%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			

subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 95 (1.05%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas			
subjects affected / exposed	0 / 95 (0.00%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type two Diabetes mellitus			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Temozolomide	AZD6244	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 95 (96.84%)	99 / 99 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 95 (2.11%)	8 / 99 (8.08%)	
occurrences (all)	2	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 95 (5.26%)	7 / 99 (7.07%)	
occurrences (all)	5	7	
Face oedema			
subjects affected / exposed	1 / 95 (1.05%)	7 / 99 (7.07%)	
occurrences (all)	1	8	
Fatigue			
subjects affected / exposed	40 / 95 (42.11%)	29 / 99 (29.29%)	
occurrences (all)	45	34	
Non-cardiac chest pain			
subjects affected / exposed	1 / 95 (1.05%)	5 / 99 (5.05%)	
occurrences (all)	1	5	
Oedema peripheral			
subjects affected / exposed	5 / 95 (5.26%)	40 / 99 (40.40%)	
occurrences (all)	5	62	
Pyrexia			
subjects affected / exposed	10 / 95 (10.53%)	15 / 99 (15.15%)	
occurrences (all)	10	22	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 95 (5.26%)	9 / 99 (9.09%)	
occurrences (all)	5	11	
Dyspnoea exertional			
subjects affected / exposed	6 / 95 (6.32%)	13 / 99 (13.13%)	
occurrences (all)	6	15	
Pharyngolaryngeal pain			

subjects affected / exposed	4 / 95 (4.21%)	9 / 99 (9.09%)	
occurrences (all)	4	9	
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 95 (5.26%)	7 / 99 (7.07%)	
occurrences (all)	5	7	
Insomnia			
subjects affected / exposed	6 / 95 (6.32%)	10 / 99 (10.10%)	
occurrences (all)	6	10	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 95 (2.11%)	7 / 99 (7.07%)	
occurrences (all)	2	8	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 95 (0.00%)	8 / 99 (8.08%)	
occurrences (all)	0	8	
Haemoglobin decreased			
subjects affected / exposed	4 / 95 (4.21%)	6 / 99 (6.06%)	
occurrences (all)	4	6	
Weight decreased			
subjects affected / exposed	6 / 95 (6.32%)	4 / 99 (4.04%)	
occurrences (all)	7	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 95 (7.37%)	8 / 99 (8.08%)	
occurrences (all)	10	10	
Headache			
subjects affected / exposed	23 / 95 (24.21%)	20 / 99 (20.20%)	
occurrences (all)	27	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 95 (6.32%)	9 / 99 (9.09%)	
occurrences (all)	6	10	
Thrombocytopenia			
subjects affected / exposed	7 / 95 (7.37%)	2 / 99 (2.02%)	
occurrences (all)	7	2	

Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 95 (2.11%)	8 / 99 (8.08%)	
occurrences (all)	2	8	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 95 (3.16%)	8 / 99 (8.08%)	
occurrences (all)	3	9	
Abdominal pain			
subjects affected / exposed	12 / 95 (12.63%)	12 / 99 (12.12%)	
occurrences (all)	14	13	
Abdominal pain upper			
subjects affected / exposed	4 / 95 (4.21%)	7 / 99 (7.07%)	
occurrences (all)	7	9	
Constipation			
subjects affected / exposed	45 / 95 (47.37%)	12 / 99 (12.12%)	
occurrences (all)	60	13	
Diarrhoea			
subjects affected / exposed	20 / 95 (21.05%)	55 / 99 (55.56%)	
occurrences (all)	27	77	
Dry mouth			
subjects affected / exposed	6 / 95 (6.32%)	8 / 99 (8.08%)	
occurrences (all)	6	8	
Dyspepsia			
subjects affected / exposed	4 / 95 (4.21%)	11 / 99 (11.11%)	
occurrences (all)	4	13	
Flatulence			
subjects affected / exposed	1 / 95 (1.05%)	7 / 99 (7.07%)	
occurrences (all)	1	7	
Nausea			
subjects affected / exposed	61 / 95 (64.21%)	49 / 99 (49.49%)	
occurrences (all)	79	64	
Stomatitis			
subjects affected / exposed	1 / 95 (1.05%)	9 / 99 (9.09%)	
occurrences (all)	1	12	
Vomiting			

subjects affected / exposed	42 / 95 (44.21%)	26 / 99 (26.26%)	
occurrences (all)	56	35	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 95 (0.00%)	5 / 99 (5.05%)	
occurrences (all)	0	7	
Alopecia			
subjects affected / exposed	1 / 95 (1.05%)	7 / 99 (7.07%)	
occurrences (all)	2	7	
Dermatitis acneiform			
subjects affected / exposed	3 / 95 (3.16%)	58 / 99 (58.59%)	
occurrences (all)	3	70	
Dry skin			
subjects affected / exposed	0 / 95 (0.00%)	9 / 99 (9.09%)	
occurrences (all)	0	10	
Eczema			
subjects affected / exposed	0 / 95 (0.00%)	5 / 99 (5.05%)	
occurrences (all)	0	5	
Exfoliative rash			
subjects affected / exposed	0 / 95 (0.00%)	7 / 99 (7.07%)	
occurrences (all)	0	9	
Periorbital oedema			
subjects affected / exposed	1 / 95 (1.05%)	14 / 99 (14.14%)	
occurrences (all)	1	15	
Pruritus			
subjects affected / exposed	3 / 95 (3.16%)	10 / 99 (10.10%)	
occurrences (all)	3	11	
Rash			
subjects affected / exposed	1 / 95 (1.05%)	7 / 99 (7.07%)	
occurrences (all)	1	12	
Rash erythematous			
subjects affected / exposed	2 / 95 (2.11%)	6 / 99 (6.06%)	
occurrences (all)	2	7	
Rash macular			
subjects affected / exposed	0 / 95 (0.00%)	5 / 99 (5.05%)	
occurrences (all)	0	5	

Skin fissures			
subjects affected / exposed	0 / 95 (0.00%)	7 / 99 (7.07%)	
occurrences (all)	0	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 95 (7.37%)	5 / 99 (5.05%)	
occurrences (all)	7	7	
Back pain			
subjects affected / exposed	9 / 95 (9.47%)	5 / 99 (5.05%)	
occurrences (all)	14	5	
Musculoskeletal pain			
subjects affected / exposed	6 / 95 (6.32%)	2 / 99 (2.02%)	
occurrences (all)	7	2	
Pain in extremity			
subjects affected / exposed	7 / 95 (7.37%)	9 / 99 (9.09%)	
occurrences (all)	7	9	
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 95 (1.05%)	5 / 99 (5.05%)	
occurrences (all)	1	7	
Paronychia			
subjects affected / exposed	0 / 95 (0.00%)	5 / 99 (5.05%)	
occurrences (all)	0	6	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	12 / 95 (12.63%)	9 / 99 (9.09%)	
occurrences (all)	12	9	
Decreased appetite			
subjects affected / exposed	4 / 95 (4.21%)	11 / 99 (11.11%)	
occurrences (all)	4	12	
Hypokalaemia			
subjects affected / exposed	3 / 95 (3.16%)	5 / 99 (5.05%)	
occurrences (all)	3	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported