Clinical trial results:
An Open-Label, Multicenter, Phase III Trial of ABI-007 vs Dacarbazine in Previously Untreated Patients with Metastatic Malignant Melanoma

Summary

EudraCT number	2007-004097-32
Trial protocol	GB DE NL FR ES IT
Global end of trial date	31 January 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CA033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00864253
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States,
Public contact	Clinical Trial Disclosure, Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, 1 888-260-1599, clinicaltrialsdisclosure@celgene.com
Scientific contact	Ileana Elias, Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, 1 6479684300, ielias@celgene.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	Interim
Date of interim/final analysis	30 June 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2012
Global end of trial reached?	Yes
Global end of trial date	31 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the following regimens with respect to antitumor activity in patients who are previously untreated with cytotoxic chemotherapy for metastatic malignant melanoma:
• ABI-007 150 mg/m^2 Days 1, 8, and 15 every 4 weeks
• Dacarbazine 1000 mg/m^2 every 3 weeks

Protection of trial subjects:

Protection of patient confidentiality
Protection of biomarker information by a secure database

Background therapy:

Dacarbazine remains the standard of treatment

Evidence for comparator: -

Actual start date of recruitment	23 April 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	38 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Germany: 56
Country: Number of subjects enrolled	Italy: 82
Country: Number of subjects enrolled	United States: 186
Country: Number of subjects enrolled	Australia: 70
Country: Number of subjects enrolled	Canada: 45
Worldwide total number of subjects	529
EEA total number of subjects	228

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)	289
From 65 to 84 years	234
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted by investigators in 9 countries: Australia, Canada, France, Germany, Italy, Netherlands, Spain, United Kingdom and the United States (US) and treatment was given on an outpatient basis. First participant enrolled 30 April 2011, last participant enrolled June 2011.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio. Randomization was stratified based on metastatic stage (M1a, M1b, and M1c), region (North America, Western Europe and Australia), and baseline lactate dehydrogenase (LDH) Upper Limit of Normal (ULN) (< 0.8 x ULN, 0.8-1.1 x ULN, >1.1-2 x ULN).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ABI-007

Arm description:

ABI-007 150mg/m^2 intravenously over approximately 30 minutes on Days 1, 8 and 15 of each 28 day cycle

Arm type	Experimental
Investigational medicinal product name	ABI-007
Investigational medicinal product code	
Other name	Nab-Paclitaxel; Abraxane
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

ABI-007 150mg/m^2 intravenously over approximately 30 minutes on Days 1, 8 and 15 of each 28 day cycle

Arm title	Dacarbazine

Arm description:

Dacarbazine 1000mg/m^2 intravenously over approximately 30-60 minutes on Day 1 of each 21 day cycle.

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous drip use

Dosage and administration details:

Dacarbazine 1000mg/m^2 intravenously over approximately 30-60 minutes on Day 1 of each 21 day cycle.

Number of subjects in period 1	ABI-007	Dacarbazine
Started	264	265
Treated	257	258
Therapy Ongoing	2	3
Therapy Discontinued	255	255
Completed	2	3
Not completed	262	262
Physician decision	11	15
Consent withdrawn by subject	18	18
Adverse event, non-fatal	3	11
Death	1	-
Progressive Disease	165	207
Unrelated Adverse Event	-	1
Untreated	7	7
Unacceptable Toxicity	56	-
Lost to follow-up	1	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ABI-007
Reporting group description:	
ABI-007 150mg/m^2 intravenously over approximately 30 minutes on Days 1, 8 and 15 of each 28 day cycle	
Reporting group title	Dacarbazine
Reporting group description:	
Dacarbazine 1000mg/m^2 intravenously over approximately 30-60 minutes on Day 1 of each 21 day cycle.	

Reporting group values	ABI-007	Dacarbazine	Total
Number of subjects	264	265	529
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Adults (18-64 years)	154	135	289
From 65-84 years	107	127	234
85 years and over	3	3	6
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Age continuous			
Units: years			
median	62	64	
full range (min-max)	21 to 85	28 to 87	-
Gender categorical			
Units: Subjects			
Female	91	91	182
Male	173	174	347
Eastern Cooperative Oncology Group Performance Status (ECOG)			
ECOG-Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active (Most Favorable Activity); 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, No self-care (Least Favorable Activity)			
Units: Subjects			
0 = Fully Active	195	181	376
1= Restrictive but Ambulatory	68	82	150
2 = Ambulatory but Unable to Work	1	2	3
3 = Limited Self-Care	0	0	0
4 = Completely Disabled	0	0	0
Baseline Lactate Dehydrogenase value			
The serum level of Lactate Dehydrogenase (LDH) is considered a risk factor for overall survival in			

participants with metastatic melanoma. LDH is a blood test used as a general indicator of the existence and severity of acute or chronic tissue damage and used to monitor cancers such as metastatic melanoma. The baseline LDH value was considered to be the last central laboratory LDH value before randomization. If the central laboratory data was not available, the last non-missing local laboratory value before randomization was used.			
Units: Subjects			
<0.8 * Upper Limit of Normal (ULN)	138	139	277
0.8-1.1 * ULN	72	69	141
>1.1-2 * ULN	51	56	107
>2 * ULN	3	1	4
Metastatic Stage of Disease			
Distant Metastatic (M) Stages: MX: Distant metastasis cannot be assessed; M0: No distant metastasis; M1= Distant metastasis; M1a: Metastasis to skin, subcutaneous tissues or distant lymph nodes; M1b: metastasis to lung; M1c: metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehyrogenase.			
Units: Subjects			
M1a	27	21	48
M1b	66	69	135
M1c	171	175	346
BRAF Mutation Status			
BRAF is a mutation biomarker for melanoma, a human gene that makes the protein B-Raf. The gene is referred to as a protoco-oncogene B Raf and vRaf murine sarcoma viral oncogene homolog B1, while the protein is known as serine/threonine-protein kinase B-Raf. The protein is involved in sending signals inside cells and in directing cell growth. These BRAF mutations were associated with features of high risk melanoma, including truncal primary, earlier age of onset, lack of chronic skin damage and shortened survival. The BRAF statuses included: Wild type and V600E mutation			
Units: Subjects			
Wild Type (mutation negative)	116	108	224
Unknown	83	90	173
V 600 E Mutation	65	67	132

End points

End points reporting groups

Reporting group title	ABI-007
Reporting group description:	
ABI-007 150mg/m^2 intravenously over approximately 30 minutes on Days 1, 8 and 15 of each 28 day cycle	
Reporting group title	Dacarbazine
Reporting group description:	
Dacarbazine 1000mg/m^2 intravenously over approximately 30-60 minutes on Day 1 of each 21 day cycle.	

Primary: Primary: Progression Free Survival (PFS) Based on a Blinded Radiology Assessment of Response Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 Guidelines

End point title	Primary: Progression Free Survival (PFS) Based on a Blinded Radiology Assessment of Response Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 Guidelines
End point description:	
PFS was defined as the time from the randomization date to the start of disease progression or patient death, whichever occurred first. Participants who did not have disease progression or had not died were censored at the last known time that the patient was progression free. In the event of palliative radiotherapy or surgery, they were censored at the last assessment where they were documented to be progression-free prior to the date of radiotherapy or surgery. In follow up, participants who began new anticancer therapy prior to documented progression were censored at the last assessment where they were documented as progression free. Those with two or more missing response assessments prior to a visit with documented disease progression (or death) were censored at the last visit where they were documented to be progression free. RECIST defines progressive disease as a ≥ 20% increase taking as reference the smallest sum of the longest diameters recorded since the treatment began.	
End point type	Primary
End point timeframe:	
Response assessment completed every 8 weeks until disease progression for up to 106 weeks; data cut off 30 June 2012	

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: Months				
median (confidence interval 95%)	4.8 (3.7 to 5.5)	2.5 (2 to 3.6)		

Statistical analyses

Statistical analysis title	Progression Free Survival
Statistical analysis description:	
Two hundred fifty-seven (257) patients were to be randomized to each treatment group for a total of 514 patients. This sample size was chosen to provide at least 80% power for the final analysis (with a two-sided type I error of 0.049) to reject the null hypothesis that the ABI 007/dacarbazine hazard ratio (HR) for PFS is equal to 1.0. This sample size calculation was based on estimates of HR = 0.750.	

Comparison groups	ABI-007 v Dacarbazine
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.044 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.631
upper limit	0.992

Notes:

[1] - An interim safety review was performed by DMC. An alpha spending function was utilized to preserve the overall Type 1 error at 0.050. The spending function allocated alpha of 0.001 and 0.049 to the interim and final analyses of PFS, respectively.

[2] - P-value is based on a stratified log-rank test stratified by geographic region, metastatic stage, and LDH category.

Secondary: Participant Survival

End point title	Participant Survival

End point description:

Survival was defined as the time from the date of randomization to the date of death (any cause). Participants were censored at the last known time that they were alive.

End point type	Secondary

End point timeframe:

Up to 38 months; Up to data cut off of 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: months				
median (confidence interval 95%)	12.8 (11.3 to 14.6)	10.7 (9.6 to 12.5)		

Statistical analyses

Statistical analysis title	Participant Survival

Statistical analysis description:

For the participant survival, at the time at least 417 events are recorded, this sample size provides at least 80% power with a two-sided Type 1 error of 0.049 to reject the null hypothesis that the ABI-007/dacarbazine hazard ratio is equal to 1.0. This was based on a HR = 0.760. Proportional hazards were assumed.

Comparison groups	ABI-007 v Dacarbazine

Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.831
Confidence interval	
level	Other: 99.9 %
sides	2-sided
lower limit	0.578
upper limit	1.196

Notes:

[3] - The treatment difference was tested using the stratified log-rank test, stratified by metastatic stage, region, and baseline LDH.

Secondary: Summary of Treatment-emergent Adverse Events (AEs)

End point title	Summary of Treatment-emergent Adverse Events (AEs)

End point description:

A Treatment Emergent AE (TEAE) was any AE that began or worsened after the start of the study drug through 30 days after the last dose of study drug or end of study whichever is later. A treatment related toxicity was one considered by the investigator to be possibly, probably or definitely related to study drug. AE's were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 3.0 criteria and the following scale:
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life threatening, and Grade 5 = Death A SAE is any untoward medical occurrence at any dose that is fatal or life threatening, results in persistent or significant disability or incapacity; requires prolonged hospitalizations; is a congenital anomaly birth defect in the offspring of a patient, and conditions not included in the above that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

End point type	Secondary

End point timeframe:

Maximum exposure to study drug was 106 weeks; up to data cut off of 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	258		
Units: participants				
≥1 TEAE	255	239		
≥1 TEAE related to study drug	250	212		
≥1 NCI CTCAE Grade (GR) 3 or above	167	117		
≥1 NCI CTCAE GR 3 or above TEAE to study drug	129	71		
≥1 TEAE with outcome of death	8	1		
≥1 drug related TEAE with outcome of death	2	1		
≥1 serious TEAE	62	54		
≥1 serious TEAE related to study drug	23	17		
≥1 TEAE leading to a dose reduction of study	81	51		
≥1 related TEAE leading to dose reduction	80	49		
≥1 TEAE leading to drug interruption	4	16		

≥1 drug related TEAE leading to drug interrup	3	15		
≥1 TEAE leading to dose delay of study drug	124	84		
≥1 drug related TEAE leading to dose delay	106	77		
≥1 TEAE leading to drug discontinuation	59	12		
≥1 drug related TEAE leading to drug disconti	56	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Dose Reductions, or Dose Interruptions, or Dose Delays of Study Drug

End point title	Number of Participants Experiencing Dose Reductions, or Dose Interruptions, or Dose Delays of Study Drug

End point description:

The number of participants with dose reductions, dose interruptions and dose delays that occurred during the treatment period. Dose reductions, interruptions and delays are typically caused by clinically significant laboratory abnormalities and /or treatment emergent adverse events/toxicities

End point type	Secondary

End point timeframe:

Maximum study drug exposure 106 weeks; data cut off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	258		
Units: participants				
Dose Reductions	81	51		
Dose Interruptions	6	17		
Dose Delay	145	105		

Statistical analyses

No statistical analyses for this end point

Secondary: Nadir for the Absolute Neutrophil Count (ANC) Measurements

End point title	Nadir for the Absolute Neutrophil Count (ANC) Measurements

End point description:

Maximal degree of myelosuppression during study drug dosing was represented by the nadir in ANC measurements over all treatment cycles. Treated Population = consisted of all randomized participants who received at least one dose of study drug and with at least one post-baseline central laboratory result were included.

End point type	Secondary

End point timeframe:

Day 1 up to 106 weeks; up to data cut off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	246		
Units: 10^9/L				
median (full range (min-max))	1.5 (0.1 to 20)	2.4 (0 to 13.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nadir for White Blood Cells (WBCs) Measurements

End point title	Nadir for White Blood Cells (WBCs) Measurements

End point description:

Maximal degree of myelosuppression was represented by the nadir in white blood cells (WBCs) count measurements over all treatment cycles. Treated population = consisted of all randomized participants who received at least one dose of study drug and with at least one post-baseline central laboratory result were included

End point type	Secondary

End point timeframe:

Day 1 up to 106 weeks; up to data cut off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	246		
Units: 10^9/L				
median (full range (min-max))	3 (0.6 to 22.8)	4.1 (0.5 to 14.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nadir for Platelet Count Measurements.

End point title	Nadir for Platelet Count Measurements.

End point description:

Maximal degree of myelosuppression was represented by the nadir in platelet count measurements over all treatment cycles. Treated population = consisted of all randomized participants who received at least one dose of study drug and with at least one post-baseline central laboratory result were included

End point type	Secondary

End point timeframe:

Day 1 up to 106 weeks; up to data cut off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	246		
Units: 10^9/L				
median (full range (min-max))	228.5 (112 to 437)	153 (9 to 723)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nadir for the Hemoglobin Count Measurements

End point title	Nadir for the Hemoglobin Count Measurements

End point description:

Maximal degree of myelosuppression during study drug dosing was represented by the nadir in hemoglobin count measurements over all treatment cycles. Treated population = consisted of all randomized participants who received at least one dose of study drug and with at least one post-baseline central laboratory result were included.

End point type	Secondary

End point timeframe:

Day 1 up to 106 weeks; up to data cut off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	246		
Units: g/L				
median (full range (min-max))	109 (65 to 137)	122 (65 to 161)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameters

End point title	Pharmacokinetic Parameters

End point description:

Patients randomized to receive ABI-007 treatment in Australia, Canada, Europe, United Kingdom and United States had the option to participate in sparse PK sampling in this study. Only 44 participants consented to participate, an insufficient number to support the planned population PK analysis hence these analyses were not performed

End point type	Secondary

End point timeframe:

On Cycle 1, Day 1 blood samples were taken at 0.25, 3.5, and 24 hr post-infusion end of the initial dose

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[4] - PK Analyses was not performed as the PK portion was optional. Insufficient numbers of subject sample

[5] - PK Analysis was not performed on participants in the dacarbazine treatment arm.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free Survival (PFS) Based on Investigator Assessment Using RECIST Response Guidelines

End point title	Progression-free Survival (PFS) Based on Investigator Assessment Using RECIST Response Guidelines

End point description:

PFS was defined as the time from the randomization date to the start of disease progression or patient death, whichever occurred first. Participants who did not have disease progression or had not died were censored at the last known time that the patient was progression free. In the event of palliative radiotherapy or surgery, they were censored at the last assessment where they were documented to be progression-free prior to the date of radiotherapy or surgery. In follow up, patients who began new anticancer therapy prior to documented progression were censored at the last assessment where they were documented as progression free. Those with two or more missing response assessments prior to a visit with documented disease progression (or death) were censored at the last visit where they were documented to be progression free.

End point type	Other pre-specified

End point timeframe:

Response assessments completed every 8 weeks until disease progression; up to data cut off 30 June 2012; 38 months

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: months				
median (confidence interval 95%)	3.7 (3.1 to 3.9)	2.1 (1.9 to 2.5)		

Statistical analyses

Statistical analysis title	PFS Based on Investigator Assessment Using RECIST
Comparison groups	ABI-007 v Dacarbazine
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.696
upper limit	1.025

Notes:

[6] - P-value is based on a stratified log-rank test stratified by geographic region, metastatic stage, and LDH category

Other pre-specified: Percent of Participants Who Achieve an Objective Confirmed Complete or Partial Response Based on Blinded Radiology Assessment of Response by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0

End point title	Percent of Participants Who Achieve an Objective Confirmed Complete or Partial Response Based on Blinded Radiology Assessment of Response by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0

End point description:

RECIST defines complete response (CR): The disappearance of all known disease and no new sites or disease related symptoms confirmed at least 4 weeks after initial documentation. All sites must be assessed, including non-measurable sites, such as effusions, or markers. Disappearance of all non-target lesions. The normalization of tumor marker level confirmed at least 4 weeks after initial documentation. Partial response (PR): At least a 30% decrease in the sum of the longest diameters of target lesions, taking as a reference the baseline sum of the longest diameters confirmed at least 4 weeks after initial documentation. PR is also recorded when all measurable disease has completely disappeared, but a non-measurable component (i.e., ascites) is still present but not progressing. As well as persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits.

End point type	Other pre-specified

End point timeframe:

every 8 weeks; up to data cut off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: percentage of participants				
number (not applicable)				
Complete Response (CR)	0	0		
Partial Response (PR)	15	11		

Statistical analyses

Statistical analysis title	Confirmed Complete or Partial Response
Comparison groups	ABI-007 v Dacarbazine
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	Chi-squared
Parameter estimate	Response Rate Ratio
Point estimate	1.305
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.837
upper limit	2.035

Other pre-specified: Percent of Participants With Stable Disease (SD) for ≥ 16 Weeks, or Confirmed Complete or Partial Response (i.e., Disease Control) Based on a Blinded Radiology Assessment of Response

End point title	Percent of Participants With Stable Disease (SD) for ≥ 16 Weeks, or Confirmed Complete or Partial Response (i.e., Disease Control) Based on a Blinded Radiology Assessment of Response

End point description:

Disease control is stable disease (SD) for >=16 weeks + complete response (CR) + partial response (PR). See Outcome #4 for definitions of CR and PR.
RECIST defines SD for target lesions as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, no occurrence of progression disease for non-target lesions, and no new lesions.

End point type	Other pre-specified

End point timeframe:

Response assessment completed every 8 weeks until disease progression; up to data cut-off 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: percent of participants				
number (not applicable)	39	27		

Statistical analyses

Statistical analysis title	Those With Stable Disease (SD) for ≥ 16 Weeks
Comparison groups	ABI-007 v Dacarbazine

Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Chi-squared
Parameter estimate	Response Rate Ratio
Point estimate	1.442
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.123
upper limit	1.852

Other pre-specified: Duration of Response (DOR) in Responding Participants

End point title	Duration of Response (DOR) in Responding Participants

End point description:

Duration of response (DOR) as measured by PFS based on radiological review for those who achieved an objective confirmed response of CR or PR. DOR was defined as PFS in responders, i.e. as the time between the start of a complete response (CR) or partial response (PR) and the start of progressive disease (PD) or participants death from any cause, whichever occurred first. Those that did not have progression or had not died were censored at the last known time the participant was progression free. Participants that had initiated other anticancer therapy prior to progression were censored at the time when new anticancer therapy was initiated. Complete response (CR) and partial response (PR) are defined in outcome #4. PD was defined as at least a 20% increase in the sum of the longest diameters of target lesions; or the appearance of one or more new lesions; or the unequivocal progression of a non-target lesion. Includes ITT with a confirmed complete or partial overall response

End point type	Other pre-specified

End point timeframe:

Up to the data cut off of 30 June 2012

End point values	ABI-007	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[7]	30[8]		
Units: months				
median (confidence interval 95%)	11.1 (7.3 to 9999)	16.4 (11 to 21.8)		

Notes:

[7] - ITT of participants with a confirmed complete or partial overall response

[8] - ITT of participants with a confirmed complete or partial overall response

Statistical analyses

Statistical analysis title	DOR in Responding Participants
Comparison groups	Dacarbazine v ABI-007

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.959
upper limit	5.053

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event (AE) that started at any time from the time the signing of the informed consent to 30 days after the last dose of study drug or End of Study was followed and reported; maximum drug exposure 106 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	ABI-007

Reporting group description:

ABI-007 150mg/m^2 intravenously over approximately 30 minutes on Days 1, 8 and 15 of each 28 day cycle

Reporting group title	Dacarbazine

Reporting group description:

Dacarbazine 1000mg/m^2 intravenously over approximately 30-60 minutes on Day 1 of each 21 day cycle.

Serious adverse events	ABI-007	Dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 257 (24.12%)	54 / 258 (20.93%)	
number of deaths (all causes)	160	175	
number of deaths resulting from adverse events	8	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemorrhagic tumour necrosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 257 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Extravasation			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site thrombosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 257 (0.78%)	5 / 258 (1.94%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 257 (0.00%)	2 / 258 (0.78%)	
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 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 257 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic brain injury			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 257 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	1 / 257 (0.39%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 257 (0.39%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Palpitations			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebrovascular stenosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hemiparesis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			

subjects affected / exposed	2 / 257 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 257 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 257 (0.39%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 257 (1.17%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maculopathy			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	2 / 257 (0.78%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	3 / 257 (1.17%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 257 (0.78%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (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			
Urticaria			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar spinal stenosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 257 (1.17%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	3 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 257 (1.17%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 257 (1.56%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 257 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swine influenza			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 257 (1.17%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 257 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ABI-007	Dacarbazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	255 / 257 (99.22%)	239 / 258 (92.64%)	
Vascular disorders			
Flushing			
subjects affected / exposed	8 / 257 (3.11%)	16 / 258 (6.20%)	
occurrences (all)	8	20	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 257 (15.18%)	28 / 258 (10.85%)	
occurrences (all)	64	49	
Chills			
subjects affected / exposed	12 / 257 (4.67%)	15 / 258 (5.81%)	
occurrences (all)	18	19	
Fatigue			

subjects affected / exposed	134 / 257 (52.14%)	110 / 258 (42.64%)	
occurrences (all)	237	187	
Infusion site pain			
subjects affected / exposed	2 / 257 (0.78%)	13 / 258 (5.04%)	
occurrences (all)	3	21	
Mucosal inflammation			
subjects affected / exposed	20 / 257 (7.78%)	13 / 258 (5.04%)	
occurrences (all)	24	15	
Oedema peripheral			
subjects affected / exposed	54 / 257 (21.01%)	24 / 258 (9.30%)	
occurrences (all)	78	29	
Pain			
subjects affected / exposed	20 / 257 (7.78%)	10 / 258 (3.88%)	
occurrences (all)	22	10	
Pyrexia			
subjects affected / exposed	32 / 257 (12.45%)	30 / 258 (11.63%)	
occurrences (all)	43	46	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	59 / 257 (22.96%)	33 / 258 (12.79%)	
occurrences (all)	68	41	
Dyspnoea			
subjects affected / exposed	39 / 257 (15.18%)	38 / 258 (14.73%)	
occurrences (all)	49	46	
Epistaxis			
subjects affected / exposed	34 / 257 (13.23%)	5 / 258 (1.94%)	
occurrences (all)	39	5	
Oropharyngeal pain			
subjects affected / exposed	17 / 257 (6.61%)	9 / 258 (3.49%)	
occurrences (all)	20	11	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	16 / 257 (6.23%)	19 / 258 (7.36%)	
occurrences (all)	19	21	
Insomnia			

subjects affected / exposed	42 / 257 (16.34%)	31 / 258 (12.02%)	
occurrences (all)	51	42	
Investigations			
Weight decreased			
subjects affected / exposed	16 / 257 (6.23%)	10 / 258 (3.88%)	
occurrences (all)	22	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 257 (12.45%)	30 / 258 (11.63%)	
occurrences (all)	41	43	
Dysgeusia			
subjects affected / exposed	62 / 257 (24.12%)	24 / 258 (9.30%)	
occurrences (all)	76	28	
Headache			
subjects affected / exposed	42 / 257 (16.34%)	38 / 258 (14.73%)	
occurrences (all)	53	52	
Neuropathy peripheral			
subjects affected / exposed	98 / 257 (38.13%)	6 / 258 (2.33%)	
occurrences (all)	236	8	
Paraesthesia			
subjects affected / exposed	41 / 257 (15.95%)	8 / 258 (3.10%)	
occurrences (all)	61	10	
Peripheral sensory neuropathy			
subjects affected / exposed	52 / 257 (20.23%)	9 / 258 (3.49%)	
occurrences (all)	108	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	39 / 257 (15.18%)	28 / 258 (10.85%)	
occurrences (all)	64	47	
Leukopenia			
subjects affected / exposed	31 / 257 (12.06%)	23 / 258 (8.91%)	
occurrences (all)	49	69	
Neutropenia			
subjects affected / exposed	66 / 257 (25.68%)	63 / 258 (24.42%)	
occurrences (all)	130	138	
Thrombocytopenia			

subjects affected / exposed	1 / 257 (0.39%)	43 / 258 (16.67%)	
occurrences (all)	1	99	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	17 / 257 (6.61%)	4 / 258 (1.55%)	
occurrences (all)	17	4	
Vision blurred			
subjects affected / exposed	19 / 257 (7.39%)	6 / 258 (2.33%)	
occurrences (all)	23	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	34 / 257 (13.23%)	28 / 258 (10.85%)	
occurrences (all)	45	31	
Abdominal pain upper			
subjects affected / exposed	17 / 257 (6.61%)	14 / 258 (5.43%)	
occurrences (all)	19	19	
Constipation			
subjects affected / exposed	83 / 257 (32.30%)	89 / 258 (34.50%)	
occurrences (all)	104	130	
Diarrhoea			
subjects affected / exposed	103 / 257 (40.08%)	45 / 258 (17.44%)	
occurrences (all)	156	67	
Dyspepsia			
subjects affected / exposed	24 / 257 (9.34%)	20 / 258 (7.75%)	
occurrences (all)	30	29	
Nausea			
subjects affected / exposed	104 / 257 (40.47%)	130 / 258 (50.39%)	
occurrences (all)	154	244	
Stomatitis			
subjects affected / exposed	18 / 257 (7.00%)	8 / 258 (3.10%)	
occurrences (all)	22	9	
Vomiting			
subjects affected / exposed	53 / 257 (20.62%)	56 / 258 (21.71%)	
occurrences (all)	79	89	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	177 / 257 (68.87%)	9 / 258 (3.49%)	
occurrences (all)	235	9	
Dry skin			
subjects affected / exposed	24 / 257 (9.34%)	5 / 258 (1.94%)	
occurrences (all)	25	6	
Erythema			
subjects affected / exposed	16 / 257 (6.23%)	5 / 258 (1.94%)	
occurrences (all)	19	5	
Nail disorder			
subjects affected / exposed	52 / 257 (20.23%)	2 / 258 (0.78%)	
occurrences (all)	72	2	
Photosensitivity reaction			
subjects affected / exposed	3 / 257 (1.17%)	13 / 258 (5.04%)	
occurrences (all)	3	17	
Pruritus			
subjects affected / exposed	31 / 257 (12.06%)	17 / 258 (6.59%)	
occurrences (all)	37	22	
Rash			
subjects affected / exposed	72 / 257 (28.02%)	18 / 258 (6.98%)	
occurrences (all)	110	26	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	48 / 257 (18.68%)	24 / 258 (9.30%)	
occurrences (all)	81	36	
Back pain			
subjects affected / exposed	24 / 257 (9.34%)	26 / 258 (10.08%)	
occurrences (all)	30	35	
Musculoskeletal pain			
subjects affected / exposed	16 / 257 (6.23%)	16 / 258 (6.20%)	
occurrences (all)	21	22	
Myalgia			
subjects affected / exposed	44 / 257 (17.12%)	10 / 258 (3.88%)	
occurrences (all)	69	12	
Pain in extremity			

subjects affected / exposed	33 / 257 (12.84%)	20 / 258 (7.75%)	
occurrences (all)	47	21	
Muscular weakness			
subjects affected / exposed	16 / 257 (6.23%)	5 / 258 (1.94%)	
occurrences (all)	24	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 257 (5.45%)	10 / 258 (3.88%)	
occurrences (all)	17	12	
Upper respiratory tract infection			
subjects affected / exposed	18 / 257 (7.00%)	13 / 258 (5.04%)	
occurrences (all)	21	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	68 / 257 (26.46%)	52 / 258 (20.16%)	
occurrences (all)	85	56	
Hypokalaemia			
subjects affected / exposed	13 / 257 (5.06%)	10 / 258 (3.88%)	
occurrences (all)	22	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2008	1. Added optional biomarker analysis as additional efficacy endpoint, including SPARC testing, of tumor tissue and blood has in order to further study the correlation between expression of molecular biomarkers and clinical outcome. 2. In response to the FDA Clinical Pharmacology Reviewer's recommendation, added sparse PK sampling and sampling rationale.
13 March 2009	1. References to dacarbazine brand names have been removed throughout the document. 2. Language added to clarify that participation in PK sampling is optional. 3. Added clarification that patients who stopped treatment prior to developing disease progression were to be followed without further treatment until progressive disease was documented or until the treating physician felt that additional treatment was required (in which case documentation was to be made in the Case Report Form as to the compelling reason(s) for starting a new treatment in the absence of progressive disease). 4. Added procedures for collection and preparation of specimens for biomarker analyses. 5. Updated storage and preparation information for dacarbazine. 6. The Every-8-Weeks assessment of CBC, differential and platelet count has been removed from both arms as it was erroneous. 7. Added clarification that PK was an optional procedure. 8. The list of tests to be included in the clinical chemistry panel was detailed. 9. Sponsor Signatories page has been updated.
15 April 2009	1.Change of Medical Monitor 2. Clarified that pharmacokinetic evaluations are for the ABI-007 arm only. 3. Added clarification that patients should have cutaneous malignant melanoma for entry into the study. 4. Updated language to reflect expression of SPARC in metastatic melanoma and its association with a poor prognosis. 5. Added details regarding premedication for dacarbazine arm (Arm B). 6. Deleted paragraph regarding patients who received chemotherapy or an investigational drug 3 weeks prior to first dose since prior cytotoxic chemotherapy and prior adjuvant cytotoxic chemotherapy were not permitted for patients in this study. 7. CT scan or MRI of head assessment added for consistency. 8. Added outline of planned interim safety review. 9. Added a section to outline the establishment of a Data Monitoring Committee

02 September 2009	1. Changed time window for dacarbazine infusion from 15 – 60 minutes to 30 – 60 minutes. 2. The following changes were made to inclusion criteria: - Inclusion Criterion 2 was updated to clarify the timeframe by which sites should allow a patient to enter the study upon completing prior treatment. - Inclusion Criterion 3 was updated to clarify the guidelines regarding contraception during and after treatment in the protocol, and to be consistent with the Summary of Product Characteristics and Prescribing Information. - Inclusion Criterion 4 was updated to clarify the length of time and types of previous malignancies that are and are not acceptable for entry into the study. - Inclusion Criterion 5 was modified with language to reinforce that any patients who enrolled into the trial were healthy enough to complete the study. The following changes were made to exclusion criteria: - Exclusion 8 was added to ensure that patients with hypersensitivity reactions to any of the investigational products or comparators were not enrolled. 3. Text for blood collection for biomarkers was modified to ensure that sites were allowed to minimize any extra stress put on the patient by having multiple blood draws in a compressed time frame. 4. Clarification was added regarding participation in other investigational trials while participating in the current study, and also regarding radiotherapy with reference to Treatment for Brain Metastases section. 5. Language was updated to allow sites to use their standard practice for study drug administration while ensuring that any major changes in body weight were accounted for in the BSA calculations for dosing the patient. 6. Added BSA calculation at Baseline. 7. Added guidance for abnormal lymph nodes identified as target lesions, for target lesions documented via digital photography and for the assessment of progressive disease for pleural fluid, ascites, pericardial effusions, and other fluid collections.
25 March 2011	1. Changes were made throughout the protocol to reflect the acquisition of Abraxis BioScience by Celgene Corporation. 2. Added text to clarify the acceptable window for ABI-007 infusion time (30 – 40 minutes). 3. Added language to clarify that because pharmacokinetic information was not being collected for the dacarbazine treatment arm in this study, the infusion time window for dacarbazine could be determined by guidelines followed at the clinical site. 4. Removed text specific to United States and Canada from the PK sections to allow study sites from additional regions to participate. 5. Added clarification that PK sampling participation was to be determined by the patient. 6. Inclusion criteria were modified to allow enrollment of patients with other malignancies if they were cured by surgery with radiotherapy. 7. Text modified to clarify that the biomarker assays were part of a sub-study involving a subset of patients and that the assays performed were for exploratory purposes and were not validated. 8. Added clarification that follow-up of non-serious AEs will not continue if patient initiates another anti-cancer therapy.

12 June 2012	1. Updated the IND number on the protocol to IND 115025. IND 115025 administratively split the malignant melanoma indication from the existing IND 055974 for ABI-007 at the request of FDA as a result of the reorganization at the FDA Office of Oncology Drug Products in September 2011. 2. Updated Contact Information to reflect the acquisition of Abraxis BioScience by Celgene Corporation. 3. Added a final patient contact for follow-up OS status. 4. Clarified that lack of efficacy (disease progression) is not considered an AE or SAE. 5. An administrative change to update the safety reporting contact information and the methods for reporting to Celgene Drug Safety instead of Abraxis. 6. Updated the Study Design, Randomization, Sample Size, Power, and Interim Safety Review section (Section 8.1) to reflect the change in timing (and rationale) for the final analysis of the primary endpoint of independently assessed PFS as a result of independent statistical review. 7. Independent review of pooled PFS events revealed that the final event total would be lower than originally planned 379. Thus the final analysis of PFS was performed one year after the last patient was randomized (data cutoff date of 30 Jun 2012). Based on a projected 320 total PFS events, the power to reject the null hypothesis that the ABI-007/dacarbazine HR for PFS is equal to 1.0 will be approximately 72% for HR = 0.750 utilizing the remaining two-sided alpha of 0.049 for the final analysis instead of at least 80% (with a two-sided type I error of 0.049).
12 December 2012	1. An administrative change to reflect approval of study drug for the indication of non-small cell lung cancer patients in the US since last protocol revision. 2. Updated OS follow-up to continue to collect survival status beyond 24 months from treatment discontinuation, until death or study termination in all patients. 3. Safety reporting procedures have been broadened to reflect the extended overall survival follow-up period. 4. Administrative change to update signature page with personnel at Celgene Corporation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported