Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

Summary

EudraCT number	2015-005256-97
Trial protocol	DE BE HU ES GB FR PL SE DK IT
Global end of trial date	01 June 2020

Results information

Result version number	v2 (current)
This version publication date	06 August 2023
First version publication date	13 June 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	SGI-110-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02920008
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astex Pharmaceuticals, Inc.
Sponsor organisation address	4420 Rosewood Dr., Pleasanton, United States, 94588
Public contact	Clinical trial info. ASTRAL-2, Astex Pharmaceuticals, Inc., ASTRAL-2@astx.com
Scientific contact	Clinical trial info. ASTRAL-2, Astex Pharmaceuticals, Inc., ASTRAL-2@astx.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	01 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2020
Global end of trial reached?	Yes
Global end of trial date	01 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess and compare overall survival (OS) between guadecitabine and treatment choice (TC) in adults with previously treated acute myeloid leukemia (AML).

TC options are:
• High intensity (intermediate or high dose cytarabine [HiDAC]; mitoxantrone, etoposide, and cytarabine [MEC]; or fludarabine, cytarabine, granulocyte colony stimulating factor [G-CSF], +/- idarubicin [FLAG/FLAG-Ida])
• Low intensity (low dose cytarabine [LDAC], decitabine, or azacitidine)
• Best Supportive Care (BSC)

BSC will be provided to all subjects as per standard and institutional practice.

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	United States: 57

Country: Number of subjects enrolled	Ukraine: 4
Worldwide total number of subjects	302
EEA total number of subjects	149

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)	164
From 65 to 84 years	138
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 358 participants were assessed for study inclusion. Of these 56 failed screening assessments. A total of 302 participants were randomized (148 guadecitabine, 154 treatment choice [TC]). Of the randomized participants, 10 did not receive study drug (3 guadecitabine, 7 TC).

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	Guadacitabine

Arm description:

Guadecitabine was administered subcutaneously (SC) at a dose of 60 milligrams per meter square (mg/m^2) for 10 days on Days 1-5 and Days 8-12 or on Days 1-10 in the first cycle. Second cycle was 60 mg/m^2 for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by end of Cycle 1. For Cycles ≥3, guadecitabine, 60 mg/m^2 was given for 5 days only (Days 1-5). Each cycle = 28 days.

Arm type	Experimental
Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	
Other name	SGI-110
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg/m^2 subcutaneously (SC) daily on Days 1-5 and Days 8-12 or on Days 1-10 of the first 28-day cycle. Second cycle could have been 60 mg/m^2 for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by Day ≥28. For Cycles ≥3, guadecitabine was given for 5 days only (60 mg/m^2/day, Days 1-5).

Arm title	Treatment Choice

Arm description:

Intermediate or high dose cytarabine (HiDAC), mitoxantrone, etoposide and cytarabine (MEC) and granulocyte colony-stimulating factors (G-CSF)/fludarabine, cytarabine, G-CSF and idarubicin (FLAG/FLAG-Ida), low dose cytarabine (LDAC), decitabine, azacitidine, or best supportive care (BSC) was administered only. High intensity: Intermediate or HiDAC, recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, max. 36 g/m^2 per cycle; MEC: eg.: mitoxantrone 6-12 mg/m^2 IV, etoposide 80-200 mg/m^2 IV, and cytarabine 1000 mg/m^2 IV; each daily for 5 days; FLAG/FLAG-Ida: eg.: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days; G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5. Low intensity: LDAC 20 mg SC or IV twice daily on Days 1-10; Decitabine 20 mg/m^2 IV daily on Days 1-5; Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7. Best supportive care only.

Arm type	Active comparator
Investigational medicinal product name	Various treatment choice products
Investigational medicinal product code	
Other name	cytarabine, mitoxantrone, etoposide, fludarabine, idarubicin, decitabine, azacitidine
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

High intensity: Intermediate or high dose cytarabine (HiDAC), recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, maximum 36 g/m^2 per cycle; MEC: For example: mitoxantrone 6-12 mg/m^2 IV (recommended 8 mg/m^2), etoposide 80-200 mg/m^2 IV (recommended 100 mg/m^2), and cytarabine 1000 mg/m^2 IV; each daily for 5 days (Days 1-5); FLAG/FLAG-Ida: For example: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days (recommended to be given for 4 hours after fludarabine); G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5.

Low intensity: LDAC 20 mg SC or IV twice daily on Days 1-10; Decitabine 20 mg/m^2 IV daily on Days 1-5; Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7.

Best supportive care only.

Number of subjects in period 1	Guadacitabine	Treatment Choice
Started	148	154
Completed	28	20
Not completed	120	134
Consent withdrawn by subject	3	6
Death	117	127
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Guadacitabine
Reporting group description:	
Guadecitabine was administered subcutaneously (SC) at a dose of 60 milligrams per meter square (mg/m^2) for 10 days on Days 1-5 and Days 8-12 or on Days 1-10 in the first cycle. Second cycle was 60 mg/m^2 for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by end of Cycle 1. For Cycles ≥3, guadecitabine, 60 mg/m^2 was given for 5 days only (Days 1-5). Each cycle = 28 days.	
Reporting group title	Treatment Choice
Reporting group description:	
Intermediate or high dose cytarabine (HiDAC), mitoxantrone, etoposide and cytarabine (MEC) and granulocyte colony-stimulating factors (G-CSF)/fludarabine, cytarabine, G-CSF and idarubicin (FLAG/FLAG-Ida), low dose cytarabine (LDAC), decitabine, azacitidine, or best supportive care (BSC) was administered only. High intensity: Intermediate or HiDAC, recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, max. 36 g/m^2 per cycle; MEC: eg.: mitoxantrone 6-12 mg/m^2 IV, etoposide 80-200 mg/m^2 IV, and cytarabine 1000 mg/m^2 IV; each daily for 5 days; FLAG/FLAG-Ida: eg.: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days; G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5. Low intensity: LDAC 20 mg SC or IV twice daily on Days 1-10; Decitabine 20 mg/m^2 IV daily on Days 1-5; Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7. Best supportive care only.	

Reporting group values	Guadacitabine	Treatment Choice	Total
Number of subjects	148	154	302
Age categorical Units: Subjects			
Adults (18-64 years)	72	92	164
From 65-84 years	76	62	138
Age continuous Units: years			
arithmetic mean	61.8	59.8	
standard deviation	± 12.2	± 13.1	-
Gender categorical Units: Subjects			
Female	62	76	138
Male	86	78	164

End points

End points reporting groups

Reporting group title	Guadacitabine

Reporting group description:

Guadecitabine was administered subcutaneously (SC) at a dose of 60 milligrams per meter square (mg/m^2) for 10 days on Days 1-5 and Days 8-12 or on Days 1-10 in the first cycle. Second cycle was 60 mg/m^2 for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by end of Cycle 1. For Cycles ≥3, guadecitabine, 60 mg/m^2 was given for 5 days only (Days 1-5). Each cycle = 28 days.

Reporting group title	Treatment Choice

Reporting group description:

Intermediate or high dose cytarabine (HiDAC), mitoxantrone, etoposide and cytarabine (MEC) and granulocyte colony-stimulating factors (G-CSF)/fludarabine, cytarabine, G-CSF and idarubicin (FLAG/FLAG-Ida), low dose cytarabine (LDAC), decitabine, azacitidine, or best supportive care (BSC) was administered only. High intensity: Intermediate or HiDAC, recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, max. 36 g/m^2 per cycle; MEC: eg.: mitoxantrone 6-12 mg/m^2 IV, etoposide 80-200 mg/m^2 IV, and cytarabine 1000 mg/m^2 IV; each daily for 5 days; FLAG/FLAG-Ida: eg.: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days; G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5. Low intensity: LDAC 20 mg SC or IV twice daily on Days 1-10; Decitabine 20 mg/m^2 IV daily on Days 1-5; Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7. Best supportive care only.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as number of days from day of randomization to date of death, regardless of cause. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Primary

End point timeframe:

From the date of randomization until the date of death, or approximately 34 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: days				
median (confidence interval 95%)	191.0 (141.0 to 253.0)	163.0 (131.0 to 213.0)		

Statistical analyses

Statistical analysis title	Guadecitabine Vs Treatment Choice (TC)
Comparison groups	Guadacitabine v Treatment Choice

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3287
Method	Stratified log-rank

Secondary: Event Free Survival

End point title	Event Free Survival

End point description:

Event-free survival is defined as number of days from randomization to earliest date of treatment discontinuation (for reasons other than initiation of hematopoietic cell transplant [HCT]), start of alternative anti-leukemia therapy (except HCT), or death. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of death, or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Days				
median (confidence interval 95%)	90.0 (73.0 to 105.0)	71.5 (53.0 to 78.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Long-term Survival

End point title	Long-term Survival

End point description:

Survival rate at 1 year after randomization; subjects were also followed to estimate 2-year survival rate. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: proportion				
number (confidence interval 95%)				
12-month survival rate	0.32 (0.25 to 0.40)	0.26 (0.20 to 0.34)		
24-month survival rate	0.19 (0.12 to 0.26)	0.10 (0.05 to 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion Independence Rate

End point title	Transfusion Independence Rate

End point description:

Number of subjects without red blood cells (RBC) or platelet transfusion for any 8-week period after treatment divided by total number of subjects in efficacy analysis. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Baseline up to approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: percentage of subjects				
number (not applicable)				
Overall transfusion independence	20.3	13.0		
Platelet transfusion independence	23.6	21.4		
RBC transfusion independence	21.6	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Alive and Out of the Hospital (NDAOH)

End point title	Number of Days Alive and Out of the Hospital (NDAOH)

End point description:

Number of days subjects alive and out of hospital during first 6 months of the study. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: days				
least squares mean (confidence interval 95%)	73.2 (53.2 to 93.2)	73.9 (53.8 to 94.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

The Complete response (CR) rate based on modified International Working Group (IWG) 2003 AML Response Criteria was calculated as the number of subjects with a best response of CR divided by the total number of subjects included in the efficacy analysis. CR as per modified 2003 IWG AML Response Criteria is absolute neutrophil count (ANC) ≥1000/µL, platelets ≥100,000/µL, independence from red blood cells (RBC) and platelet transfusions over the past week, no leukemic blasts in peripheral blood and bone marrow should contain less than 5% blast cells. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Baseline to end of treatment, or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: percentage of subjects				
number (not applicable)	12.8	7.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of combined CR and CR With Partial Hematologic Recovery (CRh)

End point title	Duration of combined CR and CR With Partial Hematologic Recovery (CRh)

End point description:

Time from first CR or CRh to time of relapse; the date of the earliest of the following 3 events: (1) relapse (defined as the earliest time point whereby BM assessment or PB assessment by the investigator indicate relapse/disease progression due to confirmed reappearance of leukemic blasts in PB or ≥5% leukemic blasts in BM, or clinical progression determined by the investigator), (2) start of alternative therapy (except HCT) or (3) death. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Baseline to end of treatment, or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	12		
Units: days				
median (confidence interval 95%)	124 (73.0 to 315.0)	63 (8.0 to 71.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematopoietic cell transplant (HCT) Rate

End point title	Hematopoietic cell transplant (HCT) Rate

End point description:

Number of subjects who received HCT after randomization divided by total number of subjects in efficacy analysis. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Baseline to long term follow-up or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: percentage of subjects				
number (not applicable)	17.6	16.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Combined Complete Response and Complete Response With Partial Hematologic Recovery Rate

End point title	Combined Complete Response and Complete Response With Partial Hematologic Recovery Rate

End point description:

The combined CR and CR with partial hematologic recovery rate based on modified International Working Group (IWG) 2003 AML Response Criteria was calculated as number of subjects with CR and CR with partial hematologic recovery divided by the total number of subjects included in the efficacy analysis. CR as per modified 2003 IWG AML Response Criteria is absolute neutrophil count (ANC) ≥1000/µL, platelets ≥100,000/µL, independence from red blood cells (RBC) and platelet transfusions over the past week, no leukemic blasts in peripheral blood and bone marrow should contain less than 5% blast cells. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Baseline to end of treatment, or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: percentage of subjects				
number (not applicable)	16.9	7.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL-5 Dimension 5 Level (EQ-5D-5L) Index Scores

End point title	Change From Baseline in EuroQoL-5 Dimension 5 Level (EQ-5D-5L) Index Scores

End point description:

Index score is calculated based on 5-level version of the EQ-5D descriptive system using the value set for England. The range of index score is from -0.281 (for the worst health state, score of 5 for all categories) to 1 (for the best health state, score of 1 for all categories). The efficacy analysis set included data from all participants randomly assigned to study treatment. Overall number of participants analyzed is the number of participants with data available for analysis in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Cycle 2 Day 1(n=107,102)	-0.027 (-0.061 to 0.007)	-0.034 (-0.068 to 0.001)		
Cycle 3 Day 1(n=80,77)	-0.026 (-0.063 to 0.011)	-0.028 (-0.066 to 0.010)		
Cycle 4 Day 1(n=71,55)	-0.008 (-0.050 to 0.034)	-0.061 (-0.108 to -0.015)		
Cycle 5 Day 1(n=57,48)	-0.022 (-0.072 to 0.027)	-0.072 (-0.126 to -0.019)		
Cycle 6 Day 1(n=48,38)	-0.027 (-0.071 to 0.017)	-0.070 (-0.188 to -0.022)		
Cycle 7 Day 1(n=37,31)	-0.020 (-0.071 to 0.030)	-0.022 (-0.076 to 0.033)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal finding in laboratory tests or other diagnostic procedures), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. The safety analysis set included data from all subjects randomly assigned to study treatment who received any amount of study treatment or any component of a multi-dose study treatment regimen.

End point type	Secondary

End point timeframe:

From first dose until 30 days after the last dose of study drug, or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	147		
Units: percentage of subjects				
number (not applicable)	96.6	97.3		

Statistical analyses

No statistical analyses for this end point

Secondary: All-Cause Mortality

End point title	All-Cause Mortality

End point description:

All-cause mortality in the first 30 days and first 60 days after the start of treatment divided by the total number of subjects receiving at least one dose of study treatment. The efficacy analysis set included data from all participants randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

From the first dose until 60 days after the first dose of study drug

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	147		
Units: Percentage of subjects				
number (not applicable)				
Within 30 days	11.7	9.5		
Within 60 days	24.8	20.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EQ-5D-5L Visual Analogue Scale (VAS) Score

End point title	Change in EQ-5D-5L Visual Analogue Scale (VAS) Score

End point description:

VAS score is obtained using vertical 20-cm visual analogue scale with the top value of 100 labelled as 'the best health you can imagine' and the bottom value of 0 labelled as 'the worst health you can imagine'. The efficacy analysis set included data from all subjects randomly assigned to study treatment. Overall number of subjects analysed is the number of subjects with data available for analysis in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	147		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Cycle 2 Day 1(n=107,102)	-2.80 (-6.26 to 0.65)	-1.86 (-5.40 to 1.67)		
Cycle 3 Day 1(n=80,77)	-0.61 (-4.08 to 2.87)	-1.47 (-5.02 to 2.08)		

Cycle 4 Day 1(n=71,56)	1.13 (-2.24 to 4.51)	-2.37 (-6.04 to 1.29)		
Cycle 5 Day 1(n=57,48)	1.28 (-2.88 to 5.44)	-2.30 (-6.83 to 2.22)		
Cycle 6 Day 1(n=47,38)	0.67 (-3.51 to 4.85)	-1.42 (-6.04 to 3.21)		
Cycle 7 Day 1(n=37,31)	-0.44 (-5.66 to 4.78)	-0.77 (-6.46 to 4.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Complete Response Rate

End point title	Composite Complete Response Rate

End point description:

Composite complete response rate based on modified IWG 2003 AML Response Criteria defined as number of subjects with best response of CR, CR with incomplete platelet recovery (CRp), or CR with incomplete blood count recovery (CRi) divided by total number of subjects in efficacy analysis. CR as per modified 2003 IWG AML Response Criteria is ANC ≥1000/µL, platelets ≥100,000/µL, independence from RBC and platelet transfusions over the past week, no leukemic blasts in peripheral blood and bone marrow should contain less than 5% blast cells. CRp is defined as ANC ≥1000/µL, Platelets <100,000/µL, independence from RBC transfusions over the past week, no leukemic blasts and bone marrow should contain less than 5% blast cells. CRi is defined as ANC <1000/µL, no leukemic blasts and bone marrow should contain less than 5% blast cells. The efficacy analysis set included data from all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Baseline to end of treatment, or approximately 38 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: percentage of subjects				
number (not applicable)	27.0	14.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until 30 days after the last dose of study drug, or approximately 38 months

Adverse event reporting additional description:

All-cause mortality is reported for enrolled participants in the study. The serious and other adverse events is reported for safety analysis set which included data from all participants randomly assigned to study treatment who received any amount of study treatment or any component of a multi-dose study treatment regimen.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Guadacitabine

Reporting group description:

Guadecitabine was administered SC at a dose of 60 mg/m^2 for 10 days on Days 1-5 and Days 8-12 or on Days 1-10 in the first cycle. Second cycle was 60 mg/m^2 for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by end of Cycle 1. For Cycles ≥3, guadecitabine, 60 mg/m^2 was given for 5 days only (Days 1-5). Each cycle = 28 days.

Reporting group title	Treatment Choice

Reporting group description:

Intermediate or high dose cytarabine (HiDAC), mitoxantrone, etoposide and cytarabine (MEC) and granulocyte colony-stimulating factors (G-CSF)/fludarabine, cytarabine, G-CSF and idarubicin (FLAG/FLAG-Ida), low dose cytarabine (LDAC), decitabine, azacitidine, or best supportive care (BSC) was administered only. High intensity: Intermediate or HiDAC, recommended as 1-1.5 g/m^2 every 12 hours or up to 6 g/m^2/day for ≤6 days, max. 36 g/m^2 per cycle; MEC: eg.: mitoxantrone 6-12 mg/m^2 IV, etoposide 80-200 mg/m^2 IV, and cytarabine 1000 mg/m^2 IV; each daily for 5 days; FLAG/FLAG-Ida: eg.: fludarabine 25-30 mg/m^2 IV daily Days 1-5; cytarabine 1-2 g/m^2 IV daily for up to 5 days; G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m^2 IV daily on Days 3 to 5. Low intensity: LDAC 20 mg SC or IV twice daily on Days 1-10; Decitabine 20 mg/m^2 IV daily on Days 1-5; Azacitidine 75 mg/m^2 IV or SC daily on Days 1-7. Best supportive care only.

Serious adverse events	Guadacitabine	Treatment Choice	
Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 145 (77.93%)	91 / 147 (61.90%)	
number of deaths (all causes)	117	129	
number of deaths resulting from adverse events	40	30	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
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	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Pyrexia			
subjects affected / exposed	5 / 145 (3.45%)	6 / 147 (4.08%)	
occurrences causally related to treatment / all	1 / 5	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 145 (2.07%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung infiltration			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			

Suicidal ideation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Myocardial infarction			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 145 (2.07%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac arrest			
subjects affected / exposed	4 / 145 (2.76%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Nervous system disorders			

Hydrocephalus			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain stem infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	2 / 145 (1.38%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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			

Febrile bone marrow aplasia			
subjects affected / exposed	4 / 145 (2.76%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	4 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	41 / 145 (28.28%)	33 / 147 (22.45%)	
occurrences causally related to treatment / all	33 / 67	11 / 42	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 145 (2.07%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral mucosal erythema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal mucosal tear			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland enlargement			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue oedema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
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			
Arthritis			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	4 / 145 (2.76%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Bartholinitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	4 / 145 (2.76%)	5 / 147 (3.40%)	
occurrences causally related to treatment / all	1 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			

subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 145 (1.38%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	4 / 145 (2.76%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecthyma			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	4 / 145 (2.76%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermo-hypodermitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corynebacterium bacteraemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Disseminated varicella zoster vaccine virus infection			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective myositis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal sepsis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	27 / 145 (18.62%)	25 / 147 (17.01%)	
occurrences causally related to treatment / all	9 / 31	7 / 32	
deaths causally related to treatment / all	1 / 6	2 / 8	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory tract infection			

subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	15 / 145 (10.34%)	16 / 147 (10.88%)	
occurrences causally related to treatment / all	6 / 18	5 / 16	
deaths causally related to treatment / all	0 / 4	3 / 7	
Septic shock			
subjects affected / exposed	7 / 145 (4.83%)	5 / 147 (3.40%)	
occurrences causally related to treatment / all	2 / 8	4 / 7	
deaths causally related to treatment / all	0 / 3	1 / 2	
Sinusitis fungal			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 145 (0.00%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus B19 infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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	2 / 145 (1.38%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
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	Guadacitabine	Treatment Choice	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 145 (95.17%)	137 / 147 (93.20%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	19 / 145 (13.10%)	11 / 147 (7.48%)	
occurrences (all)	20	14	
Hypertension			
subjects affected / exposed	15 / 145 (10.34%)	4 / 147 (2.72%)	
occurrences (all)	20	4	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	23 / 145 (15.86%)	23 / 147 (15.65%)	
occurrences (all)	28	28	
Asthenia			
subjects affected / exposed	11 / 145 (7.59%)	15 / 147 (10.20%)	
occurrences (all)	15	20	
Fatigue			
subjects affected / exposed	20 / 145 (13.79%)	27 / 147 (18.37%)	
occurrences (all)	23	32	
Injection site reaction			
subjects affected / exposed	29 / 145 (20.00%)	12 / 147 (8.16%)	
occurrences (all)	35	12	
Pyrexia			
subjects affected / exposed	33 / 145 (22.76%)	36 / 147 (24.49%)	
occurrences (all)	50	50	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			

subjects affected / exposed	4 / 145 (2.76%)	9 / 147 (6.12%)	
occurrences (all)	8	9	
Epistaxis			
subjects affected / exposed	16 / 145 (11.03%)	16 / 147 (10.88%)	
occurrences (all)	22	30	
Dyspnoea			
subjects affected / exposed	20 / 145 (13.79%)	17 / 147 (11.56%)	
occurrences (all)	21	18	
Cough			
subjects affected / exposed	22 / 145 (15.17%)	27 / 147 (18.37%)	
occurrences (all)	28	31	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 145 (9.66%)	13 / 147 (8.84%)	
occurrences (all)	16	14	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	8 / 145 (5.52%)	9 / 147 (6.12%)	
occurrences (all)	14	11	
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 145 (4.14%)	8 / 147 (5.44%)	
occurrences (all)	6	15	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 145 (7.59%)	8 / 147 (5.44%)	
occurrences (all)	13	12	
Alanine aminotransferase increased			
subjects affected / exposed	12 / 145 (8.28%)	7 / 147 (4.76%)	
occurrences (all)	15	15	
Blood creatinine increased			
subjects affected / exposed	8 / 145 (5.52%)	4 / 147 (2.72%)	
occurrences (all)	11	6	
Weight decreased			
subjects affected / exposed	5 / 145 (3.45%)	9 / 147 (6.12%)	
occurrences (all)	6	10	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	11 / 145 (7.59%)	6 / 147 (4.08%)	
occurrences (all)	11	7	
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 145 (20.69%)	20 / 147 (13.61%)	
occurrences (all)	39	26	
Dizziness			
subjects affected / exposed	8 / 145 (5.52%)	11 / 147 (7.48%)	
occurrences (all)	9	14	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	43 / 145 (29.66%)	46 / 147 (31.29%)	
occurrences (all)	77	137	
Neutropenia			
subjects affected / exposed	47 / 145 (32.41%)	28 / 147 (19.05%)	
occurrences (all)	87	55	
Leukopenia			
subjects affected / exposed	14 / 145 (9.66%)	14 / 147 (9.52%)	
occurrences (all)	23	19	
Febrile neutropenia			
subjects affected / exposed	25 / 145 (17.24%)	29 / 147 (19.73%)	
occurrences (all)	32	35	
Anaemia			
subjects affected / exposed	37 / 145 (25.52%)	41 / 147 (27.89%)	
occurrences (all)	68	108	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 145 (24.83%)	32 / 147 (21.77%)	
occurrences (all)	46	40	
Abdominal pain			
subjects affected / exposed	11 / 145 (7.59%)	11 / 147 (7.48%)	
occurrences (all)	12	16	
Dyspepsia			
subjects affected / exposed	12 / 145 (8.28%)	5 / 147 (3.40%)	
occurrences (all)	12	5	
Haemorrhoids			

subjects affected / exposed	11 / 145 (7.59%)	9 / 147 (6.12%)	
occurrences (all)	12	9	
Nausea			
subjects affected / exposed	42 / 145 (28.97%)	38 / 147 (25.85%)	
occurrences (all)	58	52	
Stomatitis			
subjects affected / exposed	16 / 145 (11.03%)	20 / 147 (13.61%)	
occurrences (all)	21	21	
Vomiting			
subjects affected / exposed	24 / 145 (16.55%)	20 / 147 (13.61%)	
occurrences (all)	35	33	
Constipation			
subjects affected / exposed	33 / 145 (22.76%)	33 / 147 (22.45%)	
occurrences (all)	36	42	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	12 / 145 (8.28%)	7 / 147 (4.76%)	
occurrences (all)	13	8	
Rash			
subjects affected / exposed	11 / 145 (7.59%)	9 / 147 (6.12%)	
occurrences (all)	12	17	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	8 / 145 (5.52%)	2 / 147 (1.36%)	
occurrences (all)	9	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	11 / 145 (7.59%)	7 / 147 (4.76%)	
occurrences (all)	15	13	
Myalgia			
subjects affected / exposed	8 / 145 (5.52%)	5 / 147 (3.40%)	
occurrences (all)	9	5	
Back pain			
subjects affected / exposed	15 / 145 (10.34%)	12 / 147 (8.16%)	
occurrences (all)	16	13	
Arthralgia			

subjects affected / exposed	12 / 145 (8.28%)	10 / 147 (6.80%)	
occurrences (all)	14	11	
Infections and infestations			
Pneumonia			
subjects affected / exposed	15 / 145 (10.34%)	14 / 147 (9.52%)	
occurrences (all)	16	17	
Oral herpes			
subjects affected / exposed	8 / 145 (5.52%)	5 / 147 (3.40%)	
occurrences (all)	8	5	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	13 / 145 (8.97%)	9 / 147 (6.12%)	
occurrences (all)	21	20	
Hyponatraemia			
subjects affected / exposed	10 / 145 (6.90%)	3 / 147 (2.04%)	
occurrences (all)	19	4	
Hypomagnesaemia			
subjects affected / exposed	14 / 145 (9.66%)	16 / 147 (10.88%)	
occurrences (all)	26	25	
Hypokalaemia			
subjects affected / exposed	29 / 145 (20.00%)	38 / 147 (25.85%)	
occurrences (all)	47	63	
Hypocalcaemia			
subjects affected / exposed	9 / 145 (6.21%)	5 / 147 (3.40%)	
occurrences (all)	12	5	
Hypoalbuminaemia			
subjects affected / exposed	10 / 145 (6.90%)	7 / 147 (4.76%)	
occurrences (all)	12	8	
Hyperkalaemia			
subjects affected / exposed	9 / 145 (6.21%)	3 / 147 (2.04%)	
occurrences (all)	11	8	
Decreased appetite			
subjects affected / exposed	27 / 145 (18.62%)	20 / 147 (13.61%)	
occurrences (all)	32	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2017	•Incorporated the changes from previous region-specific amendments • Clarified clinical response assessment using bone marrow and peripheral blood samples. • Clarified inclusion and exclusion criteria. • Clarified what was meant by "alternative anti-leukemia therapy" in this protocol and when the safety follow-up visit was to be performed. • Provided information and references on cytogenetics-based risk classification. • Amended the timing of the planned primary analysis of overall survival if the number of death events had not occurred within a reasonable duration. • Clarified when electrocardiogram (ECG) and vital sign safety assessments were performed for subjects in the BSC group. • Clarified long-term follow-up procedures. • Implemented administrative updates.
14 February 2018	• Added the efficacy variable "complete response with partial hematological recovery (CRh)" based on recent Food and Drug Administration (FDA) marketing approvals for relapsed/refractory (r/r) AML treatments based on this variable. • Combined CRh with CR for calculation of duration of response to include important response criteria in the duration calculation. • Allowed subjects randomly assigned to guadecitabine to receive hydroxyurea in the first 30 days of treatment to enable subjects to receive at least 2 cycles of study treatment, as guadecitabine may not adequately control proliferative disease from one cycle only. • Excluded subjects with high PB blasts >50% AND poor ECOG PS of 2, which indicates highly aggressive proliferative disease, as subjects may be at imminent risk of death. • Clarified that, after discontinuing study treatment, subjects should not withdraw consent just because they wished to participate in another experimental study. • Allowed the 10-day regimen of guadecitabine to be given on Days 1-10 (rather than Days 1-5 and 8-12) to facilitate quicker control of apparent progression in the first 2 cycles. • Allowed concomitant intrathecal treatment to control central nervous system (CNS) disease, as study treatment is not active in CNS disease. • Allowed donor lymphocytes infusion (DLI) if it was part of standard practice in certain subjects with r/r AML.
29 October 2018	• Study closed to further enrollment based on recommendation from DMC. • Revised plan for interim analysis to describe futility analysis. • Specified study follow-up stop date to be Q3 2019 or when the last subject was off study and removed provision for subjects to continue receiving guadecitabine after study completion. • Administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

12 September 2018	Based on data from 278 randomly assigned subjects, the Data Monitoring Committee (DMC) recommended to stop further enrollment into the trial based on futility analysis that showed the trial was unlikely to show superiority of guadecitabine over treatment choice (TC) for the primary endpoint of overall survival (OS). Consequently, the study was closed to further enrollment in September 2018 (Amendment 4).	-

Notes:

Limitations and caveats

None reported