Clinical trial results:
Phase III study of chemotherapy in combination with ATRA with or without gemtuzumab ozogamicin in patients with acute myeloid leukemia and NPM1 gene mutation

Summary

EudraCT number	2009-011889-28
Trial protocol	DE AT
Global end of trial date	01 September 2021

Results information

Result version number	v1 (current)
This version publication date	16 September 2022
First version publication date	16 September 2022

Trial information

Trial identification

Sponsor protocol code	AMLSG09-09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00893399
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
Public contact	AMLSG clinical trial office, University of Ulm, 049 731500 56072, daniela.weber@uniklinik-ulm.de
Scientific contact	AMLSG clinical trial office, University of Ulm, 3150045980 731500 56072, daniela.weber@uniklinik-ulm.de

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 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2021
Global end of trial reached?	Yes
Global end of trial date	01 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective
- Evaluation of efficacy based on short-term event-free survival (EFS) and overall survival (OS) after induction and consolidation chemotherapy plus all-trans retinoic acid (ATRA) with or without gemtuzumab ozogamicin (GO) in adult patients with acute myeloid leu-kemia (AML) and nucleophosmin-1 (NPM1) mutation

Secondary Efficacy Objectives
- Evaluation of efficacy based on complete remission (CR, CR/CRh, CR/CRi) rates, event-free survival (EFS), cumulative incidences of relapse (CIR) and death (CID) in CR/CRi

Safety and QoL Objectives
- Evaluation of safety based on toxicity induced by gemtuzumab ozogamicin (GO)
- Evaluation of safety based on duration of neutropenia and leukopenia after consolidation therapy, incidence of infection, duration of hospitalization
- Assessment of quality of life

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2010
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	Austria: 59
Country: Number of subjects enrolled	Germany: 529
Worldwide total number of subjects	588
EEA total number of subjects	588

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	398
From 65 to 84 years	190
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 12.05.2010
Last patient last visit: 01.09.2021
Recruitment was interrupted 3 times during the study:
1st interruption 01.06.2010 - 14.10.2010 due to withdrawal of marketing authorization of GO
2nd interruption 22.12.2011 - 23.04.2012 due to urgent amendment
3rd interruption 27.09.2013 - 20.12.2013 due increase of sample size

Pre-assignment

Screening details:

Screening details:
Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow was performed at baseline within 48 hours to make an enrollment possible.

Pre-assignment period milestones

Number of subjects started	588
Number of subjects completed	588

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: ATRA

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, cytarabine was administered by continuous intravenous infusion in a dose of 100 mg/m2 from day 1 to day 7. In the second induction cycle, cytarabine was administered by intravenous infusion in a dose of 100 mg/m2 from day 1 to day 5. In all consolidation cycles, cytarabine was administered by intravenous infusion in a dose of 3 g/m2 twice a day on days 1, 2 and 3. For patients > 60 years of age, dose of cytarabine was reduced to 1 g/m2.

Investigational medicinal product name	Idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

In the first induction cycle, idarubicin was administered by intravenous push in a dose of 12 mg/m2 on days 1, 3 and 5 in patients ≤ 60 years of age and on day 1 and day 3 in patients > 60 years of age. In the second induction cycle, idarubicin was administered by intravenous push in a dose of 10 mg/m2 on days 1 and 3 for both patients ≤ 60 years of age and patients > 60 years of age.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, etoposide was administered by intravenous infusion in a dose of 100 mg/m2 on days 1, 2 and 3. For patients > 60 years of age administration of etoposide was scheduled only on day 1 and day 3. In the second induction cycle, etoposide was scheduled on day 1 and day 3 in a dose of 100 mg/m2.

Investigational medicinal product name	All-trans retinoic acid (ATRA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In the induction cycles, ATRA was administered orally in a daily dose of 45 mg/m2 from day 6 to day 8 and thereafter in a daily dose of 15 mg/m2 from day 9 to day 21. During consolidation cycles, ATRA was administered orally in a daily dose of 15 mg/m2 from day 4 up to day 21.

Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegfilgrastim was administered subcutaneously in a dose of 6 mg on day 10 in the consolidation cycles.

Arm title	Arm B: GO+ATRA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, cytarabine was administered by continuous intravenous infusion in a dose of 100 mg/m2 from day 1 to day 7. In the second induction cycle, cytarabine was administered by intravenous infusion in a dose of 100 mg/m2 from day 1 to day 5. In all consolidation cycles, cytarabine was administered by intravenous infusion in a dose of 3 g/m2 twice a day on days 1, 2 and 3. For patients > 60 years of age, dose of cytarabine was reduced to 1 g/m2.

Investigational medicinal product name	Idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

In the first induction cycle, idarubicin was administered by intravenous push in a dose of 12 mg/m2 on days 1, 3 and 5 in patients ≤ 60 years of age and on day 1 and day 3 in patients > 60 years of age. In the second induction cycle, idarubicin was administered by intravenous push in a dose of 10 mg/m2 on days 1 and 3 for both patients ≤ 60 years of age and patients > 60 years of age.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, etoposide was administered by intravenous infusion in a dose of 100 mg/m2 on days 1, 2 and 3. For patients > 60 years of age administration of etoposide was scheduled only on day 1 and day 3. In the second induction cycle, etoposide was scheduled on day 1 and day 3 in a dose of 100 mg/m2.

Investigational medicinal product name	All-trans retinoic acid (ATRA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In the induction cycles, ATRA was administered orally in a daily dose of 45 mg/m2 from day 6 to day 8 and thereafter in a daily dose of 15 mg/m2 from day 9 to day 21. During consolidation cycles, ATRA was administered orally in a daily dose of 15 mg/m2 from day 4 up to day 21.

Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegfilgrastim was administered subcutaneously in a dose of 6 mg on day 10 in the consolidation cycles.

Investigational medicinal product name	Gemtuzumab ozogamicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemtuzumab ozogamicin was administered by intravenous infusion in a dose of 3 mg/m2 on day 1 of the treatment cycle, in the first and second induction cycle and the first consolidation cycle.

Number of subjects in period 1	Arm A: ATRA	Arm B: GO+ATRA
Started	296	292
Completed	194	170
Not completed	102	122
Adverse event, serious fatal	18	35
Consent withdrawn by subject	6	3
Allogeneic HCT	23	22
Death before start of treatment	1	2
Adverse event, non-fatal	25	42
Other reason	3	2
Lack of efficacy	26	16

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: ATRA
Reporting group description: -	
Reporting group title	Arm B: GO+ATRA
Reporting group description: -	

Reporting group values	Arm A: ATRA	Arm B: GO+ATRA	Total
Number of subjects	296	292	588
Age categorical Units: Subjects			
18 - 60 years	165	160	325
>60 years	131	132	263
Age continuous Units: years			
median	58.8	58.7	
full range (min-max)	20.9 to 80.2	18.4 to 82.3	-
Gender categorical Units: Subjects			
Female	152	163	315
Male	144	129	273
Ethnicity Units: Subjects			
Caucasian	291	285	576
Asian	1	0	1
North African / Arabian / Turk	4	5	9
Other African	0	1	1
Other	0	1	1
History of AML Units: Subjects			
De novo AML	276	271	547
sAML	3	7	10
tAML	17	14	31
ELN risk 2010 Units: Subjects			
Favorable	194	193	387
Intermediate-I	37	42	79
Intermediate-II	29	35	64
Adverse	3	3	6
Missing values	33	19	52
Normal karyotype Units: Subjects			
No	32	38	70
Yes	231	235	466
Missing values	33	19	52
FLT3-ITD mutation status Units: Subjects			

Negative	247	242	489
Positive	49	50	99
FLT3-TKD mutation status			
Units: Subjects			
Negative	262	250	512
Positive	34	42	76
DNMT3A			
Units: Subjects			
Negative	153	129	282
Positive	141	158	299
Missing values	2	5	7
White blood cell count			
Units: Giga/l			
median	20.5	16.9	
full range (min-max)	0.00204 to 296	0.0615 to 279	-
Hemoglobin			
Units: g/dl			
median	9.35	9.10	
full range (min-max)	4.3 to 19.3	4.4 to 15.0	-
Platelets			
Units: Giga/l			
median	69.5	74.0	
full range (min-max)	3 to 660	7 to 404	-
Bone marrow blast count			
Units: Percent (%)			
median	71	76.5	
full range (min-max)	3 to 100	0 to 100	-
Peripheral blood count			
Units: Percent (%)			
median	25	26	
full range (min-max)	0 to 99	0 to 99	-
LDH			
Units: U/l			
median	439	426	
full range (min-max)	86 to 5650	137 to 9670	-

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population comprises all randomized eligible patients. Patients were analyzed according to the treatment group allocated at randomization.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set includes all patients from the ITT population who have received at least one dose of any study medication. Treatment arms are aligned according to what treatment the patients actually have received.

Reporting group values	ITT population	Safety population	
Number of subjects	588	585	
Age categorical Units: Subjects			
18 - 60 years	325		
>60 years	263		
Age continuous Units: years			
median	58.7		
full range (min-max)	18.4 to 82.3		
Gender categorical Units: Subjects			
Female	315		
Male	273		
Ethnicity Units: Subjects			
Caucasian	576		
Asian	1		
North African / Arabian / Turk	9		
Other African	1		
Other	1		
History of AML Units: Subjects			
De novo AML	547		
sAML	10		
tAML	31		
ELN risk 2010 Units: Subjects			
Favorable	387		
Intermediate-I	79		
Intermediate-II	64		
Adverse	6		
Missing values	52		
Normal karyotype Units: Subjects			
No	70		
Yes	466		
Missing values	52		
FLT3-ITD mutation status Units: Subjects			
Negative	489		
Positive	99		
FLT3-TKD mutation status Units: Subjects			
Negative	512		
Positive	76		
DNMT3A Units: Subjects			
Negative	282		
Positive	299		
Missing values	7		

White blood cell count Units: Giga/l median full range (min-max)	 19.1 0.00204 to 296		
Hemoglobin Units: g/dl median full range (min-max)	 9.2 4.3 to 19.3		
Platelets Units: Giga/l median full range (min-max)	 73.0 3 to 660		
Bone marrow blast count Units: Percent (%) median full range (min-max)	 74 0 to 100		
Peripheral blood count Units: Percent (%) median full range (min-max)	 26 0 to 99		
LDH Units: U/l median full range (min-max)	 437 86 to 9670		

End points

End points reporting groups

Reporting group title	Arm A: ATRA
Reporting group description: -	
Reporting group title	Arm B: GO+ATRA
Reporting group description: -	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT population comprises all randomized eligible patients. Patients were analyzed according to the treatment group allocated at randomization.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set includes all patients from the ITT population who have received at least one dose of any study medication. Treatment arms are aligned according to what treatment the patients actually have received.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Primary
End point timeframe:	
after 48 months	

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	296	292	588	
Units: Rate				
number (confidence interval 95%)	0.61 (0.55 to 0.66)	0.64 (0.58 to 0.69)	0.62 (0.58 to 0.66)	

Attachments (see zip file)	Overall survival (all patients)/minimal-OS_desc2-1.pdf Overall survival (according to treatment arm)/minimal- Overall survival (according to treatment and age)/minimal-

Statistical analyses

Statistical analysis title	Primary analysis Overall Survival (univariate)
Statistical analysis description:	
Univariate analysis	
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA

Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.427
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.16

Statistical analysis title	Cox Regression on OS
Statistical analysis description: multivariate analysis	
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.713
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.23

Secondary: Event-free survival (original definition, ELN 2017)

End point title	Event-free survival (original definition, ELN 2017)

End point description:

Patients with no response after induction cycle 1 had an event at the date of response assessment after induction 1. Patients with refractory disease after induction cycle 2 had an event at the date of response assessment after induction 2. Patients with relapse after achieving CR/CRi by the end of induction treatment had an event at the date of relapse. Patients who died during induction of after achieving CR/CRi by the end of induction therapy had an event at the date of death. Non-events are censored at the date of last known alive.

End point type	Secondary

End point timeframe:

after 48 months

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	296	292	588	
Units: Rate				
number (confidence interval 95%)	0.47 (0.41 to 0.52)	0.53 (0.47 to 0.59)	0.50 (0.45 to 0.54)	

Attachments (see zip file)	EFS original definition (all patients)/minimal-EFSorig_desc2-1. EFS original definition (acc. to treatment arm)/minimal- EFS original definition (acc. treatment and age)/minimal-

Statistical analyses

Statistical analysis title	Univariate analysis on EFS (original definition)
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.03

Statistical analysis title	Cox Regression on EFS (original definition)
Statistical analysis description: multivariate analysis	
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.03

Secondary: Event-free survival (ELN 2022)

End point title	Event-free survival (ELN 2022)

End point description:

Patients who failed to achieve CR/CRi by the end of induction treatment had an event on day 1 post randomization. Patient with morphologic relapse after achieving CR/CRi by end of induction treatment had an event at the date of relapse. Patients who died without a relapse after achieving CR/CRi by the end of induction treatment had an event at the date of death. Patients who started a new non-study treatment due to confirmed molecular progression or relapse without prior morphologic relapse after achieving a CR/CRi by the end of induction treatment had an event at the date of start of new treatment. Non-events were censored at the date of last response evaluation. If no response assessment after study inclusion: Day 1 post-randomization.

End point type	Secondary

End point timeframe:

after 48 months

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	296	292	588	
Units: Rate				
number (confidence interval 95%)	0.41 (0.35 to 0.47)	0.48 (0.42 to 0.54)	0.45 (0.40 to 0.49)	

Attachments (see zip file)	Event-free survival - ELN 2022 (all patients)/minimal- EFS ELN 2022 (according to treatment arm)/minimal- EFS ELN 2022 (acc. treatment and age)/minimal-

Statistical analyses

Statistical analysis title	Univariate analysis on EFS (ELN 2022 definition)
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.03

Statistical analysis title	Cox Regression on EFS (ELN 2022) multivariate
Statistical analysis description: multivariate analysis	
Comparison groups	Arm B: GO+ATRA v Arm A: ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.02

Secondary: Rate of CR	
End point title	Rate of CR
End point description:	
End point type	Secondary
End point timeframe: within two months (after induction therapy)	

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	296	292	588	
Units: Rate				
number (not applicable)	58.1	46.6	52.4	

Statistical analyses

Statistical analysis title	Mantel-Haenszel Test Rate of CR
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA

Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.87

Statistical analysis title	Logistic regression on CR rate
Statistical analysis description: multivariate analysis	
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.87

Secondary: Rate of CR/CRi	
End point title	Rate of CR/CRi
End point description:	

End point type	Secondary
End point timeframe: within 2 months (after induction therapy)	

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	296	292	588	
Units: Rate				
number (not applicable)	90.2	86.0	88.1	

Statistical analyses

Statistical analysis title	Mantel-Haenszel Test Rate of CR/CRi
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.11

Statistical analysis title	Logistic regression on CR/CRi rate
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.06

Secondary: Rate of CR/CRh

End point title	Rate of CR/CRh

End point description:

End point type	Secondary

End point timeframe:
within 2 months (after induction therapy)

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	296	292	588	
Units: Rate				
number (not applicable)	72.3	66.8	69.6	

Statistical analyses

Statistical analysis title	Mantel-Haenszel Test Rate of CR/CRh
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.178
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.1

Statistical analysis title	Logistic regression on CR/CRh rate
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.08

Secondary: Cumulative incidence of relapse	
End point title	Cumulative incidence of relapse
End point description:	

End point type	Secondary
End point timeframe: after 48 months	

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	267	251	518	
Units: Rate				
number (confidence interval 95%)	0.42 (0.36 to 0.48)	0.30 (0.25 to 0.36)	0.36 (0.32 to 0.40)	

Attachments (see zip file)	CIR (all patients)/minimal-comprisk_plots-1.pdf CIR (according to treatment arm)/minimal-comprisk_plots-2. CIR (acc. treatment and age)/minimal-

Statistical analyses

Statistical analysis title	Cause-specific Cox regression on CIR
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.86

Statistical analysis title	Cox regression on CIR multivariate
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.81

Secondary: Cumulative incidence of death

End point title	Cumulative incidence of death
End point description:	

End point type	Secondary
End point timeframe: after 48 months	

End point values	Arm A: ATRA	Arm B: GO+ATRA	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	267	251	518	
Units: Rate				
number (confidence interval 95%)	0.07 (0.05 to 0.11)	0.08 (0.05 to 0.12)	0.08 (0.06 to 0.11)	

Attachments (see zip file)	CID (all patients)/minimal-comprisk_plots-1.pdf CID (according to treatment arm)/minimal-comprisk_plots-3. CID (acc. to treatment and age)/minimal-

Statistical analyses

Statistical analysis title	Cause-specific Cox regression on CID
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.907
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.81

Statistical analysis title	Cox regression on CID multivariate
Comparison groups	Arm A: ATRA v Arm B: GO+ATRA
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.816
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.9

Secondary: 30-day mortality	
End point title	30-day mortality
End point description:	

End point type	Secondary
End point timeframe:	
30 days	

End point values	Arm A: ATRA	Arm B: GO+ATRA	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	295	290	585	
Units: Rate				
number (confidence interval 95%)	0.04 (0.02 to 0.06)	0.07 (0.04 to 0.10)	0.05 (0.03 to 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: 60-day mortality

End point title	60-day mortality

End point description:

End point type	Secondary

End point timeframe:

60 days

End point values	Arm A: ATRA	Arm B: GO+ATRA	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	295	290	585	
Units: Rate				
number (confidence interval 95%)	0.05 (0.03 to 0.08)	0.08 (0.05 to 0.11)	0.07 (0.05 to 0.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery induction cycle 1

End point title	Hematological recovery induction cycle 1

End point description:

In the first induction cycle, there were no major differences between the two treatment arms regarding hematological recovery of neutrophils and platelets.

		Arm A: ATRA N=298		Arm B: GO + ATRA N=287	
Component	Time [days]	Rate	95% CI	Rate	95% CI
ANC recovery (> 0.5 G/l)	28	0.59	(0.53, 0.65)	0.61	(0.55, 0.67)
ANC recovery (> 1.5 G/l)	28	0.37	(0.31, 0.43)	0.36	(0.3, 0.43)
Platelet recovery (> 20 G/l)	28	0.80	(0.75, 0.85)	0.80	(0.74, 0.84)
Platelet recovery (> 50 G/l)	28	0.74	(0.69, 0.8)	0.69	(0.63, 0.74)
Platelet recovery (> 100 G/l)	28	0.62	(0.56, 0.68)	0.57	(0.51, 0.64)

End point type	Secondary

End point timeframe:

Induction cycle 1

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	585			
Units: Recovery rates				
number (not applicable)	0			

Attachments (see zip file)	Recovery of neutrophils_induction 1/0.jpg Recovery of platelets_induction 1/0.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery induction cycle 2

End point title	Hematological recovery induction cycle 2

End point description:

Recovery rates of platelets >20 G/l, >50 G/l and >100 G/l at day 28 were remarkably lower in the investigational arm (GO+ATRA) (0.55, 0.39 and 0.25) compared to the standard arm (ATRA) (0.76, 0.63 and 0.49).

		Arm A: ATRA N=274		Arm B: GO + ATRA N=223	
Component	Time [days]	Rate	95% CI	Rate	95% CI
ANC recovery (> 0.5 G/l)	28	0.67	(0.61, 0.73)	0.60	(0.53, 0.67)
ANC recovery (> 1.5 G/l)	28	0.42	(0.36, 0.49)	0.38	(0.32, 0.46)
Platelet recovery (> 20 G/l)	28	0.76	(0.7, 0.81)	0.55	(0.48, 0.62)
Platelet recovery (> 50 G/l)	28	0.63	(0.57, 0.7)	0.39	(0.32, 0.46)
Platelet recovery (> 100 G/l)	28	0.49	(0.43, 0.56)	0.25	(0.19, 0.32)

End point type	Secondary

End point timeframe:

Induction cycle 2

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	585			
Units: Rate of recovery				
number (not applicable)	0			

Attachments (see zip file)	Recovery of neutrophils_induction 2/0.jpg Recovery of platelets_induction 2/0.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 1

End point title	Hematological recovery consolidation cycle 1

End point description:

Recovery rates of platelets >20 G/l, >50 G/l and >100 G/l at day 28 were remarkably lower in the investigational arm (GO+ATRA) (0.57, 0.38 and 0.23) compared to the standard arm (ATRA) (0.77, 0.55 and 0.33).

		Arm A: ATRA N=268		Arm B: GO + ATRA N=180	
Component	Time [days]	Rate	95% CI	Rate	95% CI
ANC recovery (> 0.5 G/l)	28	0.87	(0.82, 0.91)	0.83	(0.76, 0.88)
ANC recovery (> 1.5 G/l)	28	0.70	(0.64, 0.76)	0.68	(0.6, 0.76)
Platelet recovery (> 20 G/l)	28	0.77	(0.71, 0.83)	0.57	(0.49, 0.65)
Platelet recovery (> 50 G/l)	28	0.55	(0.48, 0.62)	0.38	(0.3, 0.46)
Platelet recovery (> 100 G/l)	28	0.33	(0.27, 0.4)	0.23	(0.17, 0.31)

End point type	Secondary

End point timeframe:

Consolidation cycle 1

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	585			
Units: Rate of recovery				
number (not applicable)	0			

Attachments (see zip file)	Recovery of platelets_consolidation 1/0.jpg Recovery of neutrophils_consolidation 1/0.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 2

End point title	Hematological recovery consolidation cycle 2

End point description:

In the second consolidation cycle, there were no major differences between the two treatment arms regarding the hematological recovery of neutrophils and platelets.

		Arm A: ATRA N=249		Arm B: GO + ATRA N=158	
Component	Time [days]	Rate	95% CI	Rate	95% CI
ANC recovery (> 0.5 G/l)	28	0.89	(0.84, 0.93)	0.87	(0.8, 0.92)
ANC recovery (> 1.5 G/l)	28	0.75	(0.69, 0.81)	0.77	(0.69, 0.84)
Platelet recovery (> 20 G/l)	28	0.73	(0.66, 0.79)	0.67	(0.59, 0.75)
Platelet recovery (> 50 G/l)	28	0.50	(0.43, 0.57)	0.43	(0.35, 0.52)
Platelet recovery (> 100 G/l)	28	0.27	(0.21, 0.34)	0.25	(0.19, 0.34)

End point type	Secondary

End point timeframe:

Consolidation cycle 2

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	585			
Units: Rates of recovery				
number (not applicable)	0			

Attachments (see zip file)	Recovery of neutrophils_consolidation 2/0.jpg Recovery of platelets_consolidation 2/0.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 3

End point title	Hematological recovery consolidation cycle 3

End point description:

In the third consolidation cycle, there were no major differences between the two treatment arms regarding the hematological recovery of neutrophils and platelets.

		Arm A: ATRA N=225		Arm B: GO + ATRA N=143	
Component	Time [days]	Rate	95% CI	Rate	95% CI
ANC recovery (> 0.5 G/l)	28	0.90	(0.85, 0.94)	0.85	(0.78, 0.91)
ANC recovery (> 1.5 G/l)	28	0.74	(0.67, 0.8)	0.77	(0.68, 0.84)
Platelet recovery (> 20 G/l)	28	0.78	(0.71, 0.84)	0.67	(0.57, 0.76)
Platelet recovery (> 50 G/l)	28	0.51	(0.43, 0.59)	0.49	(0.39, 0.59)
Platelet recovery (> 100 G/l)	28	0.36	(0.29, 0.45)	0.27	(0.19, 0.37)

End point type	Secondary

End point timeframe:

Consolidation cycle 3

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	585			
Units: Rates of recovery				
number (not applicable)	0			

Attachments (see zip file)	Recovery of neutrophils_consolidation 3/0.jpg Recovery of platelets_consolidation 3/0.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period began upon signing of informed consent and ended 28 days after the last treatment administration or until all drug-related toxicities were resolved, or until the Investigators assessed AEs as chronic or stable.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Arm A: ATRA
Reporting group description: -	
Reporting group title	Arm B: GO+ATRA
Reporting group description: -	

Serious adverse events	Arm A: ATRA	Arm B: GO+ATRA	
Total subjects affected by serious adverse events			
subjects affected / exposed	125 / 295 (42.37%)	160 / 290 (55.17%)	
number of deaths (all causes)	21	36	
number of deaths resulting from adverse events	21	36	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Appendicectomy			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon operation			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
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			
Fatigue			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (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	7 / 295 (2.37%)	10 / 290 (3.45%)	
occurrences causally related to treatment / all	7 / 8	8 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 295 (0.68%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 295 (0.34%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 295 (0.34%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	2 / 295 (0.68%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Pulmonary infarction			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	2 / 295 (0.68%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 295 (0.34%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sputum discoloured			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin			
subjects affected / exposed	2 / 295 (0.68%)	4 / 290 (1.38%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate			

subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin			
subjects affected / exposed	8 / 295 (2.71%)	9 / 290 (3.10%)	
occurrences causally related to treatment / all	9 / 10	19 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count			
subjects affected / exposed	1 / 295 (0.34%)	3 / 290 (1.03%)	
occurrences causally related to treatment / all	0 / 1	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	10 / 295 (3.39%)	21 / 290 (7.24%)	
occurrences causally related to treatment / all	21 / 22	45 / 45	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
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			
Arterial injury			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	1 / 295 (0.34%)	3 / 290 (1.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrioventricular block			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 295 (0.68%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 295 (0.00%)	3 / 290 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	2 / 295 (0.68%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 295 (0.68%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion			

subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
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	3 / 295 (1.02%)	6 / 290 (2.07%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	0 / 1	1 / 2	
Cerebrovascular accident			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow disorder			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	15 / 295 (5.08%)	24 / 290 (8.28%)	
occurrences causally related to treatment / all	18 / 21	24 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	12 / 295 (4.07%)	10 / 290 (3.45%)	
occurrences causally related to treatment / all	19 / 20	25 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 295 (0.34%)	3 / 290 (1.03%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 295 (1.02%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	2 / 295 (0.68%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	2 / 295 (0.68%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			

subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis ulcerative			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 295 (1.36%)	6 / 290 (2.07%)	
occurrences causally related to treatment / all	1 / 4	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lip swelling			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			

subjects affected / exposed	2 / 295 (0.68%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oral pain			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal tenesmus			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatorenal syndrome			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 295 (0.68%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal disorder			

subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 295 (0.34%)	4 / 290 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Renal injury			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal disorder			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			

subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	2 / 295 (0.68%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 295 (0.68%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 295 (0.68%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			

subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			

subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	4 / 295 (1.36%)	3 / 290 (1.03%)	
occurrences causally related to treatment / all	1 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 295 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Muscle abscess			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	4 / 295 (1.36%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opportunistic infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Orchitis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			

subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	23 / 295 (7.80%)	33 / 290 (11.38%)	
occurrences causally related to treatment / all	15 / 33	22 / 37	
deaths causally related to treatment / all	1 / 4	2 / 4	
Pseudomonas infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis dental			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purulent pericarditis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 295 (1.02%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	28 / 295 (9.49%)	46 / 290 (15.86%)	
occurrences causally related to treatment / all	20 / 29	30 / 54	
deaths causally related to treatment / all	6 / 8	8 / 16	
Septic shock			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			

subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	2 / 295 (0.68%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 295 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 295 (0.68%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 295 (0.00%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Arm A: ATRA	Arm B: GO+ATRA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	295 / 295 (100.00%)	290 / 290 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	25 / 295 (8.47%)	36 / 290 (12.41%)	
occurrences (all)	50	52	
Haemorrhage			
subjects affected / exposed	11 / 295 (3.73%)	7 / 290 (2.41%)	
occurrences (all)	17	7	
Phlebitis			
subjects affected / exposed	44 / 295 (14.92%)	41 / 290 (14.14%)	
occurrences (all)	59	47	
Thrombosis			
subjects affected / exposed	25 / 295 (8.47%)	14 / 290 (4.83%)	
occurrences (all)	36	29	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	23 / 295 (7.80%)	62 / 290 (21.38%)	
occurrences (all)	39	103	

Fatigue			
subjects affected / exposed	83 / 295 (28.14%)	92 / 290 (31.72%)	
occurrences (all)	193	198	
Hyperhidrosis			
subjects affected / exposed	17 / 295 (5.76%)	14 / 290 (4.83%)	
occurrences (all)	32	18	
Injection site reaction			
subjects affected / exposed	61 / 295 (20.68%)	71 / 290 (24.48%)	
occurrences (all)	120	158	
Pain			
subjects affected / exposed	81 / 295 (27.46%)	53 / 290 (18.28%)	
occurrences (all)	128	80	
Pyrexia			
subjects affected / exposed	173 / 295 (58.64%)	173 / 290 (59.66%)	
occurrences (all)	416	448	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	59 / 295 (20.00%)	68 / 290 (23.45%)	
occurrences (all)	90	110	
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	19 / 295 (6.44%)	24 / 290 (8.28%)	
occurrences (all)	31	30	
Cough			
subjects affected / exposed	64 / 295 (21.69%)	65 / 290 (22.41%)	
occurrences (all)	82	95	
Dyspnoea			
subjects affected / exposed	45 / 295 (15.25%)	50 / 290 (17.24%)	
occurrences (all)	60	63	
Oropharyngeal pain			
subjects affected / exposed	34 / 295 (11.53%)	32 / 290 (11.03%)	
occurrences (all)	44	40	
Pleural effusion			
subjects affected / exposed	12 / 295 (4.07%)	19 / 290 (6.55%)	
occurrences (all)	18	23	
Pneumonitis			

subjects affected / exposed	15 / 295 (5.08%)	14 / 290 (4.83%)	
occurrences (all)	17	16	
Pulmonary haemorrhage			
subjects affected / exposed	76 / 295 (25.76%)	87 / 290 (30.00%)	
occurrences (all)	120	174	
Psychiatric disorders			
Agitation			
subjects affected / exposed	33 / 295 (11.19%)	32 / 290 (11.03%)	
occurrences (all)	44	52	
Anxiety			
subjects affected / exposed	25 / 295 (8.47%)	22 / 290 (7.59%)	
occurrences (all)	44	27	
Confusional state			
subjects affected / exposed	18 / 295 (6.10%)	17 / 290 (5.86%)	
occurrences (all)	23	24	
Depression			
subjects affected / exposed	22 / 295 (7.46%)	33 / 290 (11.38%)	
occurrences (all)	45	54	
Insomnia			
subjects affected / exposed	92 / 295 (31.19%)	107 / 290 (36.90%)	
occurrences (all)	213	230	
Investigations			
Alanine aminotransferase			
subjects affected / exposed	26 / 295 (8.81%)	34 / 290 (11.72%)	
occurrences (all)	59	53	
Aspartate aminotransferase			
subjects affected / exposed	22 / 295 (7.46%)	37 / 290 (12.76%)	
occurrences (all)	40	60	
Blood alkaline phosphatase			
subjects affected / exposed	11 / 295 (3.73%)	16 / 290 (5.52%)	
occurrences (all)	19	34	
Blood bilirubin			
subjects affected / exposed	20 / 295 (6.78%)	26 / 290 (8.97%)	
occurrences (all)	26	29	
Blood creatine			

subjects affected / exposed	5 / 295 (1.69%)	24 / 290 (8.28%)	
occurrences (all)	15	42	
Blood lactate dehydrogenase increased			
subjects affected / exposed	8 / 295 (2.71%)	11 / 290 (3.79%)	
occurrences (all)	18	22	
C-reactive protein increased			
subjects affected / exposed	73 / 295 (24.75%)	60 / 290 (20.69%)	
occurrences (all)	160	137	
Gamma-glutamyltransferase			
subjects affected / exposed	36 / 295 (12.20%)	49 / 290 (16.90%)	
occurrences (all)	76	99	
General physical condition			
subjects affected / exposed	18 / 295 (6.10%)	24 / 290 (8.28%)	
occurrences (all)	20	27	
Haemoglobin			
subjects affected / exposed	260 / 295 (88.14%)	255 / 290 (87.93%)	
occurrences (all)	1092	981	
Neutrophil count			
subjects affected / exposed	124 / 295 (42.03%)	120 / 290 (41.38%)	
occurrences (all)	403	358	
Platelet count decreased			
subjects affected / exposed	262 / 295 (88.81%)	254 / 290 (87.59%)	
occurrences (all)	1029	979	
Prothrombin time prolonged			
subjects affected / exposed	14 / 295 (4.75%)	17 / 290 (5.86%)	
occurrences (all)	19	21	
Weight increased			
subjects affected / exposed	47 / 295 (15.93%)	52 / 290 (17.93%)	
occurrences (all)	90	101	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	44 / 295 (14.92%)	41 / 290 (14.14%)	
occurrences (all)	70	70	
Hypertension			

subjects affected / exposed	66 / 295 (22.37%)	84 / 290 (28.97%)	
occurrences (all)	113	161	
Hypotension			
subjects affected / exposed	27 / 295 (9.15%)	32 / 290 (11.03%)	
occurrences (all)	44	48	
Nervous system disorders			
Dizziness			
subjects affected / exposed	47 / 295 (15.93%)	51 / 290 (17.59%)	
occurrences (all)	78	102	
Headache			
subjects affected / exposed	92 / 295 (31.19%)	116 / 290 (40.00%)	
occurrences (all)	188	272	
Syncope			
subjects affected / exposed	19 / 295 (6.44%)	18 / 290 (6.21%)	
occurrences (all)	23	27	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	7 / 295 (2.37%)	14 / 290 (4.83%)	
occurrences (all)	8	18	
Febrile neutropenia			
subjects affected / exposed	124 / 295 (42.03%)	131 / 290 (45.17%)	
occurrences (all)	194	255	
Leukopenia			
subjects affected / exposed	230 / 295 (77.97%)	217 / 290 (74.83%)	
occurrences (all)	915	826	
Lymphopenia			
subjects affected / exposed	13 / 295 (4.41%)	15 / 290 (5.17%)	
occurrences (all)	45	42	
Eye disorders			
Dry eye			
subjects affected / exposed	17 / 295 (5.76%)	10 / 290 (3.45%)	
occurrences (all)	21	14	
Eye haemorrhage			
subjects affected / exposed	9 / 295 (3.05%)	20 / 290 (6.90%)	
occurrences (all)	11	28	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	72 / 295 (24.41%)	84 / 290 (28.97%)	
occurrences (all)	99	114	
Abdominal pain upper			
subjects affected / exposed	43 / 295 (14.58%)	43 / 290 (14.83%)	
occurrences (all)	62	66	
Colitis			
subjects affected / exposed	24 / 295 (8.14%)	30 / 290 (10.34%)	
occurrences (all)	34	34	
Constipation			
subjects affected / exposed	115 / 295 (38.98%)	113 / 290 (38.97%)	
occurrences (all)	257	233	
Diarrhoea			
subjects affected / exposed	158 / 295 (53.56%)	150 / 290 (51.72%)	
occurrences (all)	266	243	
Dyspepsia			
subjects affected / exposed	25 / 295 (8.47%)	24 / 290 (8.28%)	
occurrences (all)	31	30	
Enteritis			
subjects affected / exposed	8 / 295 (2.71%)	10 / 290 (3.45%)	
occurrences (all)	8	12	
Flatulence			
subjects affected / exposed	21 / 295 (7.12%)	23 / 290 (7.93%)	
occurrences (all)	27	34	
Gastric haemorrhage			
subjects affected / exposed	23 / 295 (7.80%)	46 / 290 (15.86%)	
occurrences (all)	25	73	
Gastrointestinal inflammation			
subjects affected / exposed	137 / 295 (46.44%)	145 / 290 (50.00%)	
occurrences (all)	214	277	
Haemorrhoids			
subjects affected / exposed	17 / 295 (5.76%)	19 / 290 (6.55%)	
occurrences (all)	24	26	
Nausea			
subjects affected / exposed	179 / 295 (60.68%)	197 / 290 (67.93%)	
occurrences (all)	405	499	

Oral pain			
subjects affected / exposed	12 / 295 (4.07%)	11 / 290 (3.79%)	
occurrences (all)	13	12	
Proctalgia			
subjects affected / exposed	20 / 295 (6.78%)	17 / 290 (5.86%)	
occurrences (all)	24	22	
Toothache			
subjects affected / exposed	11 / 295 (3.73%)	12 / 290 (4.14%)	
occurrences (all)	13	12	
Vomiting			
subjects affected / exposed	50 / 295 (16.95%)	102 / 290 (35.17%)	
occurrences (all)	97	245	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	16 / 295 (5.42%)	22 / 290 (7.59%)	
occurrences (all)	25	37	
Dry skin			
subjects affected / exposed	17 / 295 (5.76%)	21 / 290 (7.24%)	
occurrences (all)	20	28	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	10 / 295 (3.39%)	17 / 290 (5.86%)	
occurrences (all)	16	28	
Petechiae			
subjects affected / exposed	53 / 295 (17.97%)	72 / 290 (24.83%)	
occurrences (all)	109	140	
Pruritus			
subjects affected / exposed	46 / 295 (15.59%)	25 / 290 (8.62%)	
occurrences (all)	63	39	
Rash			
subjects affected / exposed	110 / 295 (37.29%)	103 / 290 (35.52%)	
occurrences (all)	210	182	
Skin lesion			
subjects affected / exposed	14 / 295 (4.75%)	22 / 290 (7.59%)	
occurrences (all)	17	30	
Renal and urinary disorders			

Fluid retention			
subjects affected / exposed	131 / 295 (44.41%)	125 / 290 (43.10%)	
occurrences (all)	262	275	
Haemorrhage urinary tract			
subjects affected / exposed	22 / 295 (7.46%)	28 / 290 (9.66%)	
occurrences (all)	27	39	
Renal failure			
subjects affected / exposed	9 / 295 (3.05%)	10 / 290 (3.45%)	
occurrences (all)	9	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 295 (10.51%)	30 / 290 (10.34%)	
occurrences (all)	41	44	
Back pain			
subjects affected / exposed	59 / 295 (20.00%)	53 / 290 (18.28%)	
occurrences (all)	97	73	
Bone pain			
subjects affected / exposed	40 / 295 (13.56%)	33 / 290 (11.38%)	
occurrences (all)	63	47	
Myalgia			
subjects affected / exposed	15 / 295 (5.08%)	13 / 290 (4.48%)	
occurrences (all)	21	15	
Neck pain			
subjects affected / exposed	12 / 295 (4.07%)	15 / 290 (5.17%)	
occurrences (all)	13	15	
Pain in extremity			
subjects affected / exposed	28 / 295 (9.49%)	31 / 290 (10.69%)	
occurrences (all)	35	41	
Infections and infestations			
Anal infection			
subjects affected / exposed	10 / 295 (3.39%)	11 / 290 (3.79%)	
occurrences (all)	14	15	
Cellulitis			
subjects affected / exposed	28 / 295 (9.49%)	35 / 290 (12.07%)	
occurrences (all)	34	40	
Device related infection			

subjects affected / exposed	33 / 295 (11.19%)	39 / 290 (13.45%)	
occurrences (all)	45	50	
Enterococcal infection			
subjects affected / exposed	11 / 295 (3.73%)	15 / 290 (5.17%)	
occurrences (all)	30	29	
Enterocolitis infectious			
subjects affected / exposed	15 / 295 (5.08%)	9 / 290 (3.10%)	
occurrences (all)	23	11	
Fungal infection			
subjects affected / exposed	11 / 295 (3.73%)	12 / 290 (4.14%)	
occurrences (all)	13	14	
Gingivitis			
subjects affected / exposed	9 / 295 (3.05%)	9 / 290 (3.10%)	
occurrences (all)	13	10	
Herpes virus infection			
subjects affected / exposed	19 / 295 (6.44%)	23 / 290 (7.93%)	
occurrences (all)	24	26	
Infection			
subjects affected / exposed	53 / 295 (17.97%)	42 / 290 (14.48%)	
occurrences (all)	89	61	
Lip infection			
subjects affected / exposed	31 / 295 (10.51%)	23 / 290 (7.93%)	
occurrences (all)	42	31	
Pharyngitis			
subjects affected / exposed	7 / 295 (2.37%)	13 / 290 (4.48%)	
occurrences (all)	14	14	
Pneumonia			
subjects affected / exposed	74 / 295 (25.08%)	79 / 290 (27.24%)	
occurrences (all)	104	112	
Rhinitis			
subjects affected / exposed	8 / 295 (2.71%)	12 / 290 (4.14%)	
occurrences (all)	10	18	
Sepsis			
subjects affected / exposed	76 / 295 (25.76%)	84 / 290 (28.97%)	
occurrences (all)	101	124	
Staphylococcal infection			

subjects affected / exposed	10 / 295 (3.39%)	92 / 290 (31.72%)	
occurrences (all)	10	12	
Urinary tract infection			
subjects affected / exposed	24 / 295 (8.14%)	29 / 290 (10.00%)	
occurrences (all)	29	35	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 295 (14.58%)	51 / 290 (17.59%)	
occurrences (all)	66	82	
Hyperglycaemia			
subjects affected / exposed	16 / 295 (5.42%)	19 / 290 (6.55%)	
occurrences (all)	20	24	
Hyperkalaemia			
subjects affected / exposed	9 / 295 (3.05%)	10 / 290 (3.45%)	
occurrences (all)	10	11	
Hyperuricaemia			
subjects affected / exposed	23 / 295 (7.80%)	22 / 290 (7.59%)	
occurrences (all)	32	39	
Hypoalbuminaemia			
subjects affected / exposed	17 / 295 (5.76%)	22 / 290 (7.59%)	
occurrences (all)	20	29	
Hypocalcaemia			
subjects affected / exposed	26 / 295 (8.81%)	26 / 290 (8.97%)	
occurrences (all)	33	29	
Hypokalaemia			
subjects affected / exposed	150 / 295 (50.85%)	180 / 290 (62.07%)	
occurrences (all)	336	439	
Hypomagnesaemia			
subjects affected / exposed	13 / 295 (4.41%)	27 / 290 (9.31%)	
occurrences (all)	19	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2010	Amendment No. 1 (dated 29 June 2010) to the protocol was issued after 5 patients were enrolled. The following major procedural changes (not all-inclusive) were made to the protocol: • Pfizer Pharma GmbH had become the legal successor of Wyeth Pharma GmbH • Implementation of the withdrawal of the market approval of gemtuzumab ozogamicin in the USA in June 2010 • Adaption and extension of reporting responsibilities regarding drug-associated risks and other reportable events
13 April 2012	Amendment No. 2 (dated 13 April 2012) to the protocol was issued after 141 patients were enrolled. The following major procedural changes (not all-inclusive) were made to the protocol: • Implementation of dose reduction of cytarabine, etoposide and idarubicin in the second induction cycle (urgent amendment on 23 December 2011) due to increased rates of prolonged thrombocytopenia and neutropenia and corresponding increased rates of severe infections detected within the continuous safety assessment • Addition of new information regarding measurable residual disease (MRD) and implementation of the option to perform an allogeneic HCT after consolidation cycle 2 or 3 in patients with persistently high MRD values
19 June 2012	Amendment No. 3 (dated 19 June 2012) to the protocol was issued after 154 patients were enrolled. The following major procedural changes (not all-inclusive) were made to the protocol: • Implementation of instructions regarding the concominant administration of antimycotic prophylaxis with azoles and definition of re-start of azoles for day 6 of second induction cycle (urgent amendment on 27 April 2012)
31 October 2013	Amendment No. 4 (dated 31 October 2013) to the protocol was issued after 295 patients were enrolled. The following major procedural changes (not all-inclusive) were made to the protocol: • Increase of sample size from 276 to 588 patients • Addition of OS as second primary endpoint • Integration of new information regarding capillary leak syndrome with Pegfilgrastim from June 2013 • Integration of new information from investigator’s brochure of gemtuzumab ozogamicin from June 2013
10 November 2016	Amendment No. 5 (dated 10 November 2016) to the protocol was issued after 520 patients were enrolled. The following major procedural changes (not all-inclusive) were made to the protocol: • Change of coordinating investigator from Prof. Richard Schlenk to Prof. Hartmut Döhner • Integration of urgent amendment from 07 June 2016 for the investigational arm: In case of prolonged thrombocytopenia grade 3/4 > day 35 during induction therapy, gemtuzumab ozogamicin will not be administered in the subsequent treatment cycles.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 June 2010	First interruption was performed due to with-drawal of marketing authorization for gemtuzumab ozogamicin and the associated need for a protocol and ICF amendment.	14 October 2010
22 December 2011	Second interruption took place due to implementation of dose reduction of cytarabine, etoposide and idarubicin in the second induction cycle (urgent amendment on 23 December 2011) due to increased rates of prolonged throm-bocytopenia and neutropenia and corresponding increased rates of severe infections detected within the continuous safety assessment.	23 April 2012
27 September 2013	The third interruption took place due to achievement of recruitment goals until the protocol amendment with the increase of sample size (from n=276 to n=588 patients), change of primary study endpoint (from EFS to OS), integration of new information regarding capillary leak syndrome with pegfilgrastim from June 2013 and integration of new information from investigator's brochure of gemtuzumab ozogamicin from June 2013 was approved.	20 December 2013

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31851556

http://www.ncbi.nlm.nih.gov/pubmed/33367545