Clinical trial results:
Evaluation of the impact of remission induction chemotherapy prior to allogeneic stem cell transplantation in relapsed and poor-response patients with AML

Summary

EudraCT number	2014-003124-44
Trial protocol	DE
Global end of trial date	05 April 2022

Results information

Result version number	v1 (current)
This version publication date	13 July 2024
First version publication date	13 July 2024

Trial information

Trial identification

Sponsor protocol code	DKMS-14-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02461537
WHO universal trial number (UTN)	-
Other trial identifiers	clinicaltrials.gov: NCT02461537

Notes:

Sponsors

Sponsor organisation name	DKMS Group gGmbH
Sponsor organisation address	Kressbach 1, Tuebingen, Germany, 72072
Public contact	CTU Study Manager, DKMS Group gGmbH, 0049 3512107980, etal3asap@dkms.de
Scientific contact	CTU Study Manager, DKMS Group gGmbH, 0049 3512107980, etal3asap@dkms.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	19 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2022
Global end of trial reached?	Yes
Global end of trial date	05 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to compare outcome of two treatment strategies for patients with high-risk AML who failed to achieve or maintain a complete remission with standard therapy.

Protection of trial subjects:

All investigations are clinical standard diagnostic procedures, recommended in diagnostic and treatment guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 281
Worldwide total number of subjects	281
EEA total number of subjects	281

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)	190
From 65 to 84 years	91
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

No central screening process was implemented. Only patients who fulfill all eligibility criteria can be enrolled in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	DISC

Arm description:

Disease Control Strategy: The DISC arm aims at disease-monitoring and control until start of the conditioning regimen prior to transplantation. The aim is not to induce a remission but to prevent complications from AML with the least toxic approach. Disease-monitoring without anti-leukemic therapy ("Watch and wait") is the preferred approach except for those patients with rapidly proliferating AML (see definitions). Transplantation should be scheduled as soon as possible. Pharmacologic options aimed at disease control in patients with rapidly proliferating AML comprise low-dose AraC (LDAC) or single-dose mitoxantrone.

Arm type	Experimental
Investigational medicinal product name	Cytarabin
Investigational medicinal product code	SUB06880MIG
Other name	ARA-cell
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Injection

Dosage and administration details:

LDAC: cytarabine 20 mg/ m2 s.c. once a day for 10 days

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	SUB03309MIG
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Mitoxantrone 10 mg/ m2 i.v. given as single intravenous infusion

Arm title	RIST

Arm description:

The remission-induction strategy encompasses the administration of aggressive induction chemotherapy (HAM) and remission control after hematopoietic recovery.

Arm type	Active comparator
Investigational medicinal product name	Cytarabin
Investigational medicinal product code	SUB06880MIG
Other name	ARA-cell
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Patients ≤ 60y: 3 g/m2 over 3h every 12 hours on 3 consecutive days

Patients > 60y: 1 g/m2 over 3h every 12 hours on 3 consecutive days

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	SUB03309MIG
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Patients ≤60y: 10 mg/m2 on 3 consequtive days starting at the last day of Cytarabin administration
Patients >60y: 10 mg/m2 on 3 consequtive days starting at the last day of Cytarabin administration

Number of subjects in period 1	DISC	RIST
Started	140	141
Completed	139	137
Not completed	1	4
Consent withdrawn by subject	1	1
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	DISC

Reporting group description:

Disease Control Strategy: The DISC arm aims at disease-monitoring and control until start of the conditioning regimen prior to transplantation. The aim is not to induce a remission but to prevent complications from AML with the least toxic approach. Disease-monitoring without anti-leukemic therapy ("Watch and wait") is the preferred approach except for those patients with rapidly proliferating AML (see definitions). Transplantation should be scheduled as soon as possible. Pharmacologic options aimed at disease control in patients with rapidly proliferating AML comprise low-dose AraC (LDAC) or single-dose mitoxantrone.

Reporting group title	RIST

Reporting group description:

The remission-induction strategy encompasses the administration of aggressive induction chemotherapy (HAM) and remission control after hematopoietic recovery.

Reporting group values	DISC	RIST	Total
Number of subjects	140	141	281
Age categorical Units: Subjects			
Adults (≥ 18y)	140	141	281
Age continuous Units: years			
median	61	61	
full range (min-max)	18 to 75	19 to 74	-
Gender categorical Units: Subjects			
Female	64	61	125
Male	76	80	156

Subject analysis sets	
Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population consists of all randomized patients who did not withdraw their informed consent or who violated inclusion-exclusion criteria of trial protocol version 6.0. This opulation was defined also as full analysis set (FAS). The ITT population defined the primary efficacy population. Patients were analyzed in ITT as randomized.

Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The population for the per protocol primary efficacy analysis (PP population) consisted of patients in the FAS who received the initial treatment to which they were randomized, and received the first dose of Cytarabine in RIST arm in line with protocol, or received the first day of study intervention (including watch and wait) in DisC arm.

Reporting group values	Intent-to-Treat Population	Per-Protocol Population	
Number of subjects	276	272	

Age categorical Units: Subjects			
Adults (≥ 18y)	276	272	
Age continuous Units: years			
median	61	61	
full range (min-max)	18 to 75	18 to 75	
Gender categorical Units: Subjects			
Female	121	117	
Male	155	146	

End points

End points reporting groups

Reporting group title	DISC

Reporting group description:

Disease Control Strategy: The DISC arm aims at disease-monitoring and control until start of the conditioning regimen prior to transplantation. The aim is not to induce a remission but to prevent complications from AML with the least toxic approach. Disease-monitoring without anti-leukemic therapy ("Watch and wait") is the preferred approach except for those patients with rapidly proliferating AML (see definitions). Transplantation should be scheduled as soon as possible. Pharmacologic options aimed at disease control in patients with rapidly proliferating AML comprise low-dose AraC (LDAC) or single-dose mitoxantrone.

Reporting group title	RIST

Reporting group description:

The remission-induction strategy encompasses the administration of aggressive induction chemotherapy (HAM) and remission control after hematopoietic recovery.

Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population consists of all randomized patients who did not withdraw their informed consent or who violated inclusion-exclusion criteria of trial protocol version 6.0. This opulation was defined also as full analysis set (FAS). The ITT population defined the primary efficacy population. Patients were analyzed in ITT as randomized.

Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The population for the per protocol primary efficacy analysis (PP population) consisted of patients in the FAS who received the initial treatment to which they were randomized, and received the first dose of Cytarabine in RIST arm in line with protocol, or received the first day of study intervention (including watch and wait) in DisC arm.

Primary: Rate of treatment success

End point title	Rate of treatment success

End point description:

End point type	Primary

End point timeframe:

defined as documented complete remission on day 56 after allogeneic HSCT

End point values	DISC	RIST	Intent-to-Treat Population	Per-Protocol Population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	139	137	276	272
Units: N success				
number (not applicable)	116	111	227	225

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Statistical analysis description: Dichotomous success rate	
Comparison groups	RIST v DISC
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.054
Method	Farrington and Manning

Adverse events

Adverse events information

Timeframe for reporting adverse events:

within 28 days after the end of study treatment, or without treatment until start of subsequent anti-leukemic treatment (start of bridging therapy)/ start of the conditioning regimen

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	DISC

Reporting group description:

Disease Control Strategy: The DISC arm aims at disease-monitoring and control until start of the conditioning regimen prior to transplantation. The aim is not to induce a remission but to prevent complications from AML with the least toxic approach. Disease-monitoring without anti-leukemic therapy ("Watch and wait") is the preferred approach except for those patients with rapidly proliferating AML (see definitions). Transplantation should be scheduled as soon as possible. Pharmacologic options aimed at disease control in patients with rapidly proliferating AML comprise low-dose AraC (LDAC) or single-dose mitoxantrone.

Reporting group title	RIST

Reporting group description:

The remission-induction strategy encompasses the administration of aggressive induction chemotherapy (HAM) and remission control after hematopoietic recovery.

Serious adverse events	DISC	RIST	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 139 (15.83%)	19 / 137 (13.87%)	
number of deaths (all causes)	66	58	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage			

unspecified			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
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			
Subdural haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock haemorrhagic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac disorders			
Myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (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 neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 139 (1.44%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Administration site extravasation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fissure haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis haemorrhagic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (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			
Epistaxis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (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			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection reactivation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 139 (1.44%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection in an immunocompromised host			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Postoperative wound infection			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (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			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DISC	RIST	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 139 (20.14%)	99 / 137 (72.26%)	
Cardiac disorders			
Cardiac disorder	Additional description: CTCAE Grade 3-5		
subjects affected / exposed	0 / 139 (0.00%)	11 / 137 (8.03%)	
occurrences (all)	0	12	
Infections and infestations			
Infection	Additional description: CTCAE Grade 3-5		
subjects affected / exposed	22 / 139 (15.83%)	78 / 137 (56.93%)	
occurrences (all)	27	107	
Metabolism and nutrition disorders			
Metabolic disorder	Additional description: CTCAE Grade 3-5		
subjects affected / exposed	6 / 139 (4.32%)	10 / 137 (7.30%)	
occurrences (all)	6	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2015	Non-substantial: Mitoxantrone dosing modification, instructions detailed early induction response, serum chemistry assessment in bridging therapy visit, transplant report and other assessments added.
02 July 2015	Substantial: Changes in the CTA Form submitted to the authorities to indicate a change in the cytarabine concentration to be used in order to make reconstitution of the cytarabine solution feasible for the pharmacy service.
26 February 2016	Substantial: Addition of inclusion criteria for the poor responder stratum and modification of the potential donor matching grade for eligibility, ancillary research implemented, safety consideration that cytopenia reflects underlying disease, information added on how to document and report pregnancy
14 March 2017	Substantial: Rewording of an exclusion to an inclusion criterion, information on how to deal with subjects that participate at more than one trial site.
24 May 2019	Substantial: Addition of inclusion criteria for poor responders.
10 February 2021	Non-substantial: Recruitment prolongation.
11 March 2022	Substantial: Adoption of timelines for final analysis – new study termination criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38583455