Clinical trial results:
Nonmyeloablative Conditioning with Pre- and Post-Transplant Rituximab followed by Related or Unrelated Donor Hematopoietic Cell Transplantation for Patients with Advanced Chronic Lymphocytic Leukemia: A Multi-Center Trial

Summary

EudraCT number	2009-015968-34
Trial protocol	DK
Global end of trial date	28 July 2020

Results information

Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022
Summary attachment (see zip file)	Rituximab-based allogeneic transplant for chronic lymphocytic leukemia with comparison to historical experience (Public results of protocol 1840 eudract nr 200901596834.pdf)

Trial information

Trial identification

Sponsor protocol code	FHCRC1840

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fred Hutchinson Cancer Research Center
Sponsor organisation address	1100 Fairview Ave. N., Seattle, United States,
Public contact	Kim Drever , Fred Hutchinson Cancer Research Center, 1 (206) 667-6825, kdrever@fredhutch.org
Scientific contact	Mohamed Sorror, MD MSc , Fred Hutchinson Cancer Research Center, 1 (206) 667-2765, msorror@fredhutch.org

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	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2018
Global end of trial reached?	Yes
Global end of trial date	28 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine whether nonmyeloablative conditioning using rituximab and allogeneic HCT improves survival at 18 months for patients with fludarabine-refractory, FCR-failed, or del 17p CLL over that of historical controls

Protection of trial subjects:

Patient were followed closely in very specialized department of bone marrow transplant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	100 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	66
EEA total number of subjects	11

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)	54
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients and donors are screened using the protocol's inclusion/exclusion criteria and, if accepted, randomized to an arm by data management.

Period 1

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

Arms

Arm title	Treatment

Arm description:

Patients receive a conditioning regimen comprising fludarabine IV on days -4 to -2 and rituximab IV on days -3, 10, 24, and 38.

Patients undergo single fraction low-dose TBI on day 0. After completion of TBI, patients undergo allogeneic hematopoietic stem cell transplantation on day 0. Patients then receive rituximab IV on days 10, 24, and 38.

Patients receive an immunosuppressive regimen comprising cyclosporine PO BID on days -3 to 56 followed by a taper to day 180 (related recipients) or on days -3 to 100 followed by a taper to day 180 (unrelated recipients). Patients also receive mycophenolate mofetil PO BID on days 0-27 (related recipients) or TID on days 0-40 followed by a taper to day 96 (unrelated recipients).

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo HSCT

Cyclosporine: Given PO

Fludarabine Phosphate: Given IV

Laboratory Biomarker Analysis: Correlative studies

Mycophenolate Mofetil: Given PO

Peripheral Blood Stem Cell Transplantation:

Arm type	Experimental
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	2-F-ara-AMP, Beneflur, SH T 586
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive 30 mg/m^2 fludarabine administered over 30 minutes on Days -4, -3, and -2.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	Cellcept, MMF
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

MMF will be given based on adjusted body weight, at 15 mg/kg PO, 4-6 hours after HCT is complete. For related recipients MMF to be given at 15 mg/kg PO Q12 hrs, continue to day +27, then stop abruptly. For unrelated recipients MMF to be given at 15 mg/kg PO Q8 hrs, continue to day +40, then start to

taper to day +96.

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	CSP
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Commence CSP on Day –3 at 5.0 mg/kg PO Q12 hrs, continue to day +56 for related and day +100 for unrelated recipients, then taper to day +180. CSP should be routinely taken at 9:00 a.m. and 9:00 p.m.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive rituximab intravenously at a dose of 375 mg/m2 at three time points after stem cell transplantation. These time points are set up at days 10, 24, and 38. However, if there are clinical reasons that prohibit giving Rituximab at one of these specified time points the dose can be delayed to a maximum of 5 days. Following doses should be attempted to be given at the scheduled time points. If doses need to be delayed more than 5 days from the specified time points, then patient should only get the next scheduled dose Day 38+ dose can be delayed up to 100 days after HCT.

Number of subjects in period 1	Treatment
Started	66
Completed	66

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
Adults (18-64 years)	54	54	
From 65-84 years	12	12	
Age continuous Units: years			
median	59.6		
full range (min-max)	35.2 to 74.1	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	49	49	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

Patients receive a conditioning regimen comprising fludarabine IV on days -4 to -2 and rituximab IV on days -3, 10, 24, and 38.

Patients undergo single fraction low-dose TBI on day 0. After completion of TBI, patients undergo allogeneic hematopoietic stem cell transplantation on day 0. Patients then receive rituximab IV on days 10, 24, and 38.

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Allogeneic Hematopoietic Stem Cell Transplantation: Undergo HSCT

Cyclosporine: Given PO

Fludarabine Phosphate: Given IV

Laboratory Biomarker Analysis: Correlative studies

Mycophenolate Mofetil: Given PO

Peripheral Blood Stem Cell Transplantation:

Subject analysis set title	Patients with FCgammaRIIIa receptor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with polymorphisms of the FCgammaRIIIa receptor.

Subject analysis set title	Patients without FCgammaRIIIa receptor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants without polymorphisms of the FCgammaRIIIa receptor.

Subject analysis set title	Day 60 Rituxan testing group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The population of participants who had Rituxan Concentration testing performed at Day 60 post-transplant.

Subject analysis set title	Day 84 Rituxan testing group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The population of participants who had Rituxan Concentration testing performed at Day 84 post-transplant.

Subject analysis set title	Day 180 Rituxan testing group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The population of participants who had Rituxan Concentration testing performed at Day 180 post-transplant.

Subject analysis set title	1 Year Rituxan testing group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The population of participants who had Rituxan Concentration testing performed at 1 Year post-transplant.

Subject analysis set title	Arm 1
Subject analysis set type	Full analysis

Subject analysis set description:

All accrued subjects. This is a single-arm study and this analysis set was created as a workaround for the primary endpoint's statistical analysis.

Primary: Overall survival

End point title	Overall survival

End point description:

Estimated probability of overall survival at 3 years post-transplant.

End point type	Primary

End point timeframe:

3 years post-transplant

End point values	Treatment	Arm 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52[1]	52[2]		
Units: Subjects	34	34		

Notes:

[1] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

[2] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

Statistical analyses

Statistical analysis title	Kaplan-Meier point estimate of overall survival

Statistical analysis description:

Kaplan-Meier point estimate of overall survival at 3 years among all patients on trial

Comparison groups	Treatment v Arm 1
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Kaplan-Meier estimate
Point estimate	53
Confidence interval	
level	95 %
sides	2-sided
lower limit	38
upper limit	67

Notes:

[3] - Point estimate of 3-year overall survival

Secondary: Rate of relapse/progression

End point title	Rate of relapse/progression

End point description:

Cumulative incidence estimate of relapse/progression at 3 years post-transplant.

Relapse/Progression criteria for CLL
Progressive disease:
≥1 of: Physical exam/imaging studies ≥50% increase or new, circulating lymphocytes by morphology and/or flow cytometry ≥50% increase, and lymph node biopsy w/ Richter's transformation.
Relapsed disease:
Criteria of progression occurring 6 months after achievement of complete or partial remission

End point type	Secondary

End point timeframe:

3 years post-transplant

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	52[4]			
Units: Subjects	1			

Notes:

[4] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidences of Grade II-III / III-IV acute GVHD / chronic GVHD

End point title	Incidences of Grade II-III / III-IV acute GVHD / chronic GVHD

End point description:

Number of participants who developed grade II-III acute GVHD.
Number of participants who developed grade III-IV acute GVHD.
Number of participants who developed chronic extensive GVHD.

Acute GVHD grading:
Grade I +1 to +2 skin rash, No gut or liver involvement Grade II +1 to +3 skin rash, +1 gastrointestinal involvement and/or +1 liver involvement Grade III +2 to +4 gastrointestinal involvement and/or +2 to +4 liver involvement with or without a rash Grade IV Pattern and severity of GVHD similar to grade 3 with extreme constitutional symptoms or death

Chronic GVHD grading:
The diagnosis of chronic GVHD requires at least one manifestation that is distinctive for chronic GVHD as opposed to acute GVHD. In all cases, infection and others causes must be ruled out in the differential diagnosis of chronic GVHD.

End point type	Secondary

End point timeframe:

One year post-transplant

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	52[5]			
Units: Subjects				
Grade II-III acute GVHD	33			
Grade III-IV acute GVHD	12			
Chronic extensive GVHD	27			

Notes:

[5] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Regimen-related Toxicity and Infections

End point title	Number of Participants With Regimen-related Toxicity and Infections

End point description:

Number of Participants With Regimen-related Toxicity and Infections, reported using the adapted National Cancer Institute Common Toxicity Criteria.

End point type	Secondary

End point timeframe:

100 days post-transplant

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	52[6]			
Units: Subjects	46			

Notes:

[6] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-related Mortality

End point title	Number of Participants With Treatment-related Mortality

End point description:

Number of subjects expired without disease progression/relapse.

End point type	Secondary

End point timeframe:

One year post-transplant

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	52[7]			
Units: Subjects	14			

Notes:

[7] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Rituxan Concentration

End point title	Rituxan Concentration

End point description:

Median rituxan level at days 60, 84, 180, and 1 year.

End point type	Secondary

End point timeframe:

Days 60, 84, 180, and 1 year.

End point values	Day 60 Rituxan testing group	Day 84 Rituxan testing group	Day 180 Rituxan testing group	1 Year Rituxan testing group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	28	15	6
Units: Rituxan level				
median (full range (min-max))	109 (0.2 to 480.5)	51 (0.1 to 369)	1.3 (0 to 103.6)	0.03 (0 to 0.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Achieving Complete Response and Partial Response (Overall Response Rate)

End point title	Number of Patients Achieving Complete Response and Partial Response (Overall Response Rate)

End point description:

Complete Remission (CR):
Imaging studies (Xray, CT, MRI) (nodes, liver, and spleen): Normal Peripheral blood by flow cytometry: No clonal lymphocytes Bone marrow by morphology: No nodules; or if present, nodules are free from CLL cells by immunohistochemistry Duration: ≥2 months
CR with minimal residual disease Peripheral blood or bone marrow by flow cytometry: >0 - <1 CLL cells/1000 leukocytes (0.1%)
Partial Remission (PR):
Both criteria:
Absolute lymphocyte count in peripheral blood: ≥50% decrease Physical exam/Imaging studies (nodes, liver, and/or spleen): ≥50% decrease Duration: ≥2 months

End point type	Secondary

End point timeframe:

One year post-transplant

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	52[8]			
Units: Subjects	35			

Notes:

[8] - 14 enrolled subjects did not receive rituximab and not evaluated for outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Donor and Host Polymorphisms of the FCgammaRIIIa Receptor and CD32 and Their Impact on Disease Response and Relapse

End point title	Donor and Host Polymorphisms of the FCgammaRIIIa Receptor and CD32 and Their Impact on Disease Response and Relapse

End point description:

Number of participants without progressive disease and surviving at one year. Participants with FCgammaRIIIa receptor vs participants without FCgammaRIIIa receptor.

End point type	Secondary

End point timeframe:

One year post-transplant

End point values	Patients with FCgammaRIIIa receptor	Patients without FCgammaRIIIa receptor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	30		
Units: Subjects				
Surviving patients	2	21		
Progression free	2	19		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: Conditioning through Day 100
SAEs: Conditioning through Day 200

Assessment type	Systematic

Dictionary used

Dictionary name	Adapted CTC
Dictionary version	2.0

Reporting groups

Reporting group title	Rituxan group

Reporting group description: -

Serious adverse events	Rituxan group		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 52 (7.69%)		
number of deaths (all causes)	33		
number of deaths resulting from adverse events			
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Grade 4 GVHD			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Rituxan group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 52 (42.31%)		
Investigations			
Weight gain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Creatinine increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Cardiac disorders			
Heart Failure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Chest pain - cardiac			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	3		

Nervous system disorders Syncope subjects affected / exposed occurrences (all)	 3 / 52 (5.77%) 3		
Blood and lymphatic system disorders Febrile Neutropenia subjects affected / exposed occurrences (all)	 4 / 52 (7.69%) 7		
General disorders and administration site conditions Fever subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) Colitis subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Respiratory, thoracic and mediastinal disorders Hypoxia subjects affected / exposed occurrences (all)	 4 / 52 (7.69%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported