Clinical trial results:
Phase II Trial of Combined Immunochemotherapy with Fludarabine, Mitoxantrone, Cyclophosphamide and Alemtuzumab (FMC-Alemtuzumab) in Patients with Previously Treated or Untreated T-Prolymphocytic Leukemia

Summary

EudraCT number	2008-001421-34
Trial protocol	DE AT
Global end of trial date	29 May 2014

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	TPLL2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01186640
WHO universal trial number (UTN)	-
Other trial identifiers	PEI: 962/01

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Information Desk, German CLL Study Group, 0049 22147888220, cll-studie@uk-koeln.de
Scientific contact	Information Desk, German CLL Study Group, 0049 22147888220, cll-studie@uk-koeln.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	02 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2014
Global end of trial reached?	Yes
Global end of trial date	29 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the T-PLL2-study is to assess remission rate, number of serious adverse events, number of life-threatening infections of simultaneous FMC-Alemtuzumab administration followed by Alemtuzumab-maintenance therapy in patients with T-PLL.

Protection of trial subjects:

I. Premedication
Patients should be treated with
- Antihistamine (e.g. Diphenhydramine/Tavegil® 2mg i.v.)
- Paracetamol/Acetaminophen (1000mg p.o.)
- Prednisolone (e.g. Solu-Decortin® 100mg i.v.)
30 minutes before the administration of Alemtuzumab during the first cycle and on the first day of the subsequent cycles of A-FMC and Alemtuzumab-maintenance treatment, plus in cases this premedication is clinically indicated (e.g., when there are adverse effects due to an infusion).
If a patient did not show any adverse effects, the premedication could be omitted on day 2 and 3 of each cycle.
Any patient considered being at risk of an infusion related reaction and/or tumour lysis syndrome (pts. with a lymphocytosis > 100,000/l) should have received appropriate hydration, urine alkalisation with intravenous bicarbonate and allopurinol before the beginning of treatment and thereafter until the risk is ruled out.

II. Infection prevention
Patients should have received
- Trimethoprim / Sulfamethoxazole (e.g. two tablets Cotrim forte® three times a week)
- Valgancyclovir (. 2x 450mg p.o./day)
or equivalent medications from the beginning until 4 months after the end of the treatment.
Prophylactic antifungal medication, e.g., with 100 mg Fluco-nazole, and use of growth factors like G-CSF and Erythropo-etin could be administered according to institutional standards.
No live vaccines should have been administered during the treatment; responses to inactivated, recombinant and cell wall-vaccines were unreliable and suboptimal in these patients.

Background therapy:

As the median survival time of patients with T-PLL is less than 12 months, the treatment of T-PLL is a special challenge.
The overall response rates with conventional chemotherapy or Deoxycoformycin were low (about 30% and 40%), with the monoclonal antibody Alemtuzumab response rates of 50% to 70% were achieved, but the duration of the response was short.
In the previous trial (T-PLL 1), the efficacy of the FMC regi-men (FMC = Fludarabine, Mitoxantrone and Cyclophos-phamide) was tested, a preliminary analysis of 16 patients revealed a response rate of more than 60% after FMC-poly-chemotherapy and 83% after the subsequent administration of Alemtuzumab.
The goal of the T-PLL2-protocol is to assess if the simulta-neous administration of FMC-polychemotherapy and -Alem-tuzumab with a subsequent Alemtuzumab-maintenance the-rapy is capable of improving the remission rate and the disease-free survival time in patients with T-PLL.

Evidence for comparator:

n/a

Actual start date of recruitment	01 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	7
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to enroll 16 patients. In total 18 patients were enrolled between 06/2010 and 05/2014

Pre-assignment

Screening details:

20 T-PLL patients were registered for the
trial. The central screening was performed by the GCLLSG central study office in Cologne, Germany and included immunophenotyping, anaylsis of TCL1 signaling and cytogenetic analysis. Of those 20 patients, 2 patient were assessed as screening failure, 18 patients were enrolled.

Pre-assignment period milestones

Number of subjects started	20[1]
Number of subjects completed	18

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: All patients who meet the eligibility criteria for the study entry can be enrolled into the trial. To verify the eligibility of patients, a patient screening by a medical review of the pretherapeutic staging as well as a central immunophenotyping, analysis of the TCL1 signaling and the cytogenetics will be performed before randomization.
20 patients started pre-assignment period, 2 patient were assessed as screening failure, 18 patients were enrolled.

Period 1

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

Arms

Arm title	FMC-Alemtuzumab

Arm description:

All patients received a combination therapy of Fludarabine,
Mitoxantrone, Cyclophosphamide and Alemtuzumab (A-FMC), followed
by Alemtuzumab maintenance treatment.

Arm type	Experimental
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

First treatment phase Chemoimmunotherapy A-FMC: 20 mg/m2 i.v., days 1-3; Repeat day 29, maximum 4 cycles.

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	09393
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

First treatment phase Chemoimmunotherapy A-FMC: 6 mg/m2 i.v., day 1; Repeat day 29, maximum 4 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	1001995601
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

First treatment phase Chemoimmunotherapy A-FMC: 200 mg/m2 i.v., days 1-3; Repeat day 29, maximum 4 cycles.

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

Dosage and administration details:

First treatment phase Chemoimmunotherapy A-FMC
Cycle 1+2:
10 mg s.c., days 1-3
Cycle 3+4:
CR: 10 mg s.c., days 1-3
PR/SD: 30 mg s.c., days 1-3
Second treatment phase Maintenance-treatment with 30mg Alemtuzumab s.c. for patients in CR, PR or SD; The maintenance therapy started one month after the Final Staging
and was administered monthly during the first six months plus once in
month 10 and 13.

Number of subjects in period 1	FMC-Alemtuzumab
Started	18
Completed	0
Not completed	18
Adverse event, serious fatal	5
Physician decision	12
non-cooperation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	7	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
median	68		
inter-quartile range (Q1-Q3)	57.8 to 73.5	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	10	10	

End points

End points reporting groups

Reporting group title	FMC-Alemtuzumab

Reporting group description:

All patients received a combination therapy of Fludarabine, Mitoxantrone, Cyclophosphamide and Alemtuzumab (A-FMC), followed by Alemtuzumab maintenance treatment.

Primary: Overall response rate

End point title	Overall response rate[1]

End point description:

Remission rate (ocurence of CRs, CRis, nPRs and PRs)

End point type	Primary

End point timeframe:

Overall response rate was analysed within the final analysis in 2014 (data cut-off was 03.09.2014) . This analysis was not repeated for the final clinical study.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the hypothesis states that the efficacy of the TPLL2 regimen is assessed uninteresting if the ORR rate is less than 50% and is confirmed if the ORR is at least 50% and as there are no further comparisons between different treatment arms, a frequency tabulation with no further statistical analyses was sufficient. So there are no statistical values available to provide.

End point values	FMC-Alemtuzumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (confidence interval 95%)	66.7 (44.0 to 89.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	FMC-A

Reporting group description: -

Serious adverse events	FMC-A		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 18 (66.67%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	4		
Vascular disorders			
Shock haemorrhagic	Additional description: Shock haemorrhagic		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Aplastic anaemia	Additional description: Aplastic anaemia		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Neutropenia	Additional description: Neutropenia		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome	Additional description: Systemic inflammatory response syndrome		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus chorioretinitis	Additional description: Cytomegalovirus chorioretinitis		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection	Additional description: Cytomegalovirus infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic infection	Additional description: Neutropenic infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral	Additional description: Pneumonia respiratory syncytial viral		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection	Additional description: Urinary tract infection		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial	Additional description: Urinary tract infection bacterial		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	FMC-A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)		
Investigations			
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	7 / 18 (38.89%)		
occurrences (all)	7		
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	12 / 18 (66.67%)		
occurrences (all)	30		
Neutropenia	Additional description: Neutropenia		

subjects affected / exposed	14 / 18 (77.78%)		
occurrences (all)	36		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	12 / 18 (66.67%)		
occurrences (all)	15		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Subileus	Additional description: Subileus		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Tongue ulceration	Additional description: Tongue ulceration		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	3		
Infections and infestations			
Aspergillus infection	Additional description: Aspergillus infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Giardiasis	Additional description: Giardiasis		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infection	Additional description: Infection		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Lip infection	Additional description: Lip infection		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Metapneumovirus infection	Additional description: Metapneumovirus infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2010	Amendment 1: - Change of the start of the trial - Reduction of the Alemtuzumab dosing and change in the treatment intervals - Changes in the recomennded CMV prophylaxis - Simplification of the Retreatment criteria and dose modification - Correction of the registration and screening process - Changes in the logisitic procedures of Alemtuzumab - Changes for the immunophenotypig samples

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/30234404