



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 alkalinisation 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 Cyclophosphamide) 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 simultaneous administration of FMC-polychemotherapy and -Alemtuzumab with a subsequent Alemtuzumab-maintenance therapy 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, analysis 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 (ocurrence 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: <ul style="list-style-type: none">- Change of the start of the trial- Reduction of the Alemtuzumab dosing and change in the treatment intervals- Changes in the recommended CMV prophylaxis- Simplification of the Retreatment criteria and dose modification- Correction of the registration and screening process- Changes in the logistic procedures of Alemtuzumab- Changes for the immunophenotyping 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>