

**ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt**

Release Date: September 9, 2013

**ClinicalTrials.gov ID: NCT00281918**

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### Study Identification

Unique Protocol ID: CDR0000454560

Brief Title: Fludarabine and Cyclophosphamide With or Without Rituximab in Patients With Previously Untreated Chronic B-Cell Lymphocytic Leukemia ( CLL-8 )

Official Title: Phase III Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Chemotherapy With Fludarabine and Cyclophosphamide (FC) Alone in Patients With Previously Untreated Chronic Lymphocytic Leukaemia

Secondary IDs: GCLLSG-CLL-8  
EU-20560  
ML17102

### Study Status

Record Verification: September 2013

Overall Status: Completed

Study Start: July 2003 []

Primary Completion: July 2007 [Actual]

Study Completion: October 2011 [Actual]

### Sponsor/Collaborators

Sponsor: Hoffmann-La Roche

Responsible Party: Sponsor

Collaborators: German CLL Study Group

## Oversight

U.S. FDA-regulated Drug:

U.S. FDA-regulated Device:

Unapproved/Uncleared No  
Device:

U.S. FDA IND/IDE: No

Human Subjects Review: Board Status: Approved  
Approval Number: 138/2003  
Board Name: Ethikkommission der Universität Ulm Pharmakologie  
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Data Monitoring:

FDA Regulated Intervention: Yes

Section 801 Clinical Trial: Yes

## Study Description

Brief Summary: This randomized phase III trial is studying fludarabine, cyclophosphamide, and rituximab to see how well they work compared to fludarabine and cyclophosphamide in treating patients with B-cell chronic lymphocytic leukemia.

Detailed Description:

## Conditions

Conditions: Leukemia

Keywords: B-cell chronic lymphocytic leukemia  
stage I chronic lymphocytic leukemia  
stage II chronic lymphocytic leukemia  
stage III chronic lymphocytic leukemia  
stage IV chronic lymphocytic leukemia

## Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Interventional Study Model: Parallel Assignment

Number of Arms: 2

Masking: None (Open Label)

Allocation: Randomized

Enrollment: 817 [Actual]

## Arms and Interventions

| Arms   | Assigned Interventions   |
|--|--|
| Experimental: Fludarabine+Cyclophosphamide+Rituximab (FCR) | Drug: Rituximab<br>Intravenous repeating dose<br>Drug: Cyclophosphamide<br>Intravenous repeating dose<br>Drug: Fludarabine Phosphate<br>Intravenous repeating dose |
| Active Comparator: Fludarabine+Cyclophosphamide (FC)       | Drug: Cyclophosphamide<br>Intravenous repeating dose<br>Drug: Fludarabine Phosphate<br>Intravenous repeating dose  |

## Outcome Measures

[See Results Section.]

## Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: DISEASE CHARACTERISTICS:

- Diagnosed B-cell chronic lymphocytic leukemia (CLL) defined by the National Cancer Institute (NCI) Working Group criteria
- Meets 1 of the following criteria:
  - Binet stage C disease
  - Binet stage B disease AND  $\geq 1$  of the following signs or symptoms\*:
    - B symptoms (night sweats, weight loss  $\geq 10\%$  within the previous 6 months, fevers  $> 38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$  for  $\geq 2$  weeks without evidence of infection), or constitutional symptoms (fatigue)
    - Continuous progression (doubling of peripheral lymphocyte count within the past 6 months and absolute lymphocyte count  $> 50 \text{ G/l}$ )
    - Evidence of progressive marrow failure as manifested by the development/worsening of anemia and/or thrombocytopenia
    - Massive, progressive or painful splenomegaly or hypersplenism
    - Massive lymph nodes or lymph node clusters ( $> 10 \text{ cm}$  in longest diameter), danger of organ complications through large lymphoma (e.g., vascular compression or tracheal narrowing), or progressive lymphadenopathy
    - Occurrence of symptomatic hyperviscosity problems at leukocyte counts  $> 200 \text{ G/l}$  (symptomatic leukostasis)
- No Binet stage A disease
- No transformation to an aggressive B-cell malignancy (e.g., diffuse large cell lymphoma, Richter's syndrome, or prolymphocytic leukemia)

PATIENT CHARACTERISTICS:

- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Cumulative Illness Rating Scale (CIRS) score  $> 6$
- Life expectancy  $> 6$  months
- Bilirubin  $\leq 2$  times upper limit of normal (ULN)
- Alkaline phosphatase and transaminases  $\leq 2$  times ULN
- Creatinine clearance  $\geq 70 \text{ mL/min}$
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception during and for 2 months after study treatment
- No known hypersensitivity with anaphylactic reaction to humanized monoclonal antibodies or any of the study drugs
- No cerebral dysfunction that precludes chemotherapy
- No active bacterial, viral, or fungal infection
- No clinically significant autoimmune cytopenia or Coombs-positive hemolytic anemia
- No other active malignancy requiring concurrent treatment except basal cell carcinoma or tumors treated curatively by surgery
- No medical or psychological condition that would preclude study therapy
- No concurrent disease that requires prolonged ( $> 1$  month) therapy involving glucocorticoids

PRIOR CONCURRENT THERAPY:

- No previous treatment of CLL by chemotherapy, radiotherapy, or immunotherapy

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**IPDSharing**

Plan to Share IPD:

**References**

Citations:

Links: URL: <http://www.rocche-trials.com/studyResultGet.action?studyResultNumber=ML17102>

Description Clinical Study Report Synopsis

Available IPD/Information:

## Study Results

### Participant Flow

#### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

#### Overall Study

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
| Started                                | 409 <sup>[1]</sup>                | 408 <sup>[2]</sup>                           |
| Safety Population; Received Study Drug | 398                               | 402  |
| Completed                              | 267 <sup>[3]</sup>                | 300 <sup>[3]</sup>                           |
| Not Completed                          | 142                               | 108  |

[1] Informed consent unavailable for 2 patients at time of analysis; intent-to-treat population was 407.

[2] Informed consent unavailable for 5 patients at time of analysis; intent-to-treat population was 403.

[3] Completed all 6 cycles of study medication.

### Baseline Characteristics

#### Reporting Groups

|                                   | Description  |
|-----------------------------------|--|
| Fludarabine+Cyclophosphamide (FC) | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. |

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

### Baseline Measures

|  |                 | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) | Total            |
|--|-----------------|-----------------------------------|--|------------------|
| Overall Number of Participants   |                 | 407                               | 403  | 810              |
| <b>Age, Continuous</b><br>Mean (Standard Deviation)<br>Unit of years measure:                    | Number Analyzed | 407 participants                  | 403 participants                             | 810 participants |
|  |                 | 59.3 (8.55)                       | 59.6 (8.70)                                  | 59.5 (8.62)      |
| <b>Sex: Female, Male</b><br>Measure Count of Type: Participants<br>Unit of participants measure: | Number Analyzed | 407 participants                  | 403 participants                             | 810 participants |
|  | Female          | 105 25.8%                         | 105 26.05%                                   | 210 25.93%       |
|  | Male            | 302 74.2%                         | 298 73.95%                                   | 600 74.07%       |

## Outcome Measures

### 1. Primary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Progression-free Survival (PFS)  |
| Measure Description | Progression-free survival (PFS) was defined as the time between randomization and the date of first documented disease progression, relapse or death by any cause, whichever came first. |
| Time Frame          | Median observation time at time of analysis was approximately 21 months  |

### Analysis Population Description

The Intent-to-treat (ITT) population was comprised of all patients randomized in the study, irrespective of whether they received treatment or not. Informed consent was unavailable at the time of analysis for 2 patients in the FC group and 5 patients in the FCR group. ITT population: FC = 407; FCR = 403.

### Reporting Groups

|                                   | Description  |
|-----------------------------------|--|
| Fludarabine+Cyclophosphamide (FC) | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. |

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

#### Measured Values

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|---|-----------------------------------|---|
| Overall Number of Participants Analyzed   | 407                               | 403   |
| Progression-free Survival (PFS)<br>Median (Full Range)<br>Unit of measure: Days | 981.0 (1 to 1343)                 | 1212.0 (1 to 1372)                            |

#### Statistical Analysis 1 for Progression-free Survival (PFS)

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | <.0001  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |

#### 2. Primary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Final Analysis: Time to Progression-free Survival Event  |
| Measure Description | Progression-free survival was defined as the time between randomization and the date of first documented disease progression, relapse or death by any cause, whichever came first. |
| Time Frame          | Median observation time was approximately 66.4 months  |

#### Analysis Population Description

Participants from the Intent-to-treat population, that included all randomized participants, with PFS events.

## Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

## Measured Values

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|--|-----------------------------------|---|
| Overall Number of Participants Analyzed  | 297                               | 253   |
| Final Analysis: Time to Progression-free Survival Event<br>Median (95% Confidence Interval)<br>Unit of measure: Days | 998.0 (886 to 1129)               | 1703.0 (1543 to 1853)                         |

## Statistical Analysis 1 for Final Analysis: Time to Progression-free Survival Event

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | <.0001  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |
| Method of Estimation           | Estimation Parameter       | Hazard Ratio (HR)   |
|                                | Estimated Value            | 0.57  |
|                                | Confidence Interval        | (2-Sided) 95%<br>0.48 to 0.67   |

|  |                     |                 |
|--|---------------------|-----------------|
|  | Estimation Comments | [Not specified] |
|--|---------------------|-----------------|

### 3. Secondary Outcome Measure:

|                     |   |
|---------------------|---|
| Measure Title       | Event-free Survival (EFS)   |
| Measure Description | Event-free survival (EFS) was defined as the time between randomization and the date of disease progression, relapse, start of new CLL treatment or death by any cause. |
| Time Frame          | Median observation time at time of analysis was approximately 21 months   |

#### Analysis Population Description

The ITT population was comprised of all patients randomized in the study, irrespective of whether they received treatment or not. Informed consent was unavailable at the time of analysis for 2 patients in the FC group and 5 patients in the FCR group. ITT population: FC = 407; FCR = 403.

#### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

#### Measured Values

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|---|-----------------------------------|---|
| Overall Number of Participants Analyzed                                   | 407                               | 403   |
| Event-free Survival (EFS)<br>Median (Full Range)<br>Unit of measure: Days | 947.0 (1 to 1343)                 | 1212.0 (1 to 1372)                            |

#### Statistical Analysis 1 for Event-free Survival (EFS)

|                               |                            |   |
|-------------------------------|----------------------------|---|
| Statistical Analysis Overview | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                               | Comments                   | [Not specified]   |
|                               | Type of Statistical Test   | Superiority or Other (legacy)   |
|                               | Comments                   | [Not specified]   |

|                                |          |                 |
|--------------------------------|----------|-----------------|
| Statistical Test of Hypothesis | P-Value  | <.0001          |
|                                | Comments | [Not specified] |
|                                | Method   | Log Rank        |
|                                | Comments | [Not specified] |

#### 4. Secondary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Overall Survival (OS)  |
| Measure Description | Overall survival (OS) was defined as the time between randomization and the date of death due to any cause. Median OS was not reached. |
| Time Frame          | Median observation time at time of analysis was approximately 21 months  |

#### Analysis Population Description

The ITT population was comprised of all patients randomized in the study, irrespective of whether they received treatment or not. Informed consent was unavailable at the time of analysis for 2 patients in the FC group and 5 patients in the FCR group. ITT population: FC = 407; FCR = 403.

#### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

#### Measured Values

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|--|-----------------------------------|---|
| Overall Number of Participants Analyzed                                | 407                               | 403   |
| Overall Survival (OS)<br>Measure Type: Number<br>Unit of measure: Days |                                   |   |
| Minimum number of days to an event                                     | 5                                 | 4   |
| Maximum number of days to an event                                     | 1373                              | 1372  |

### Statistical Analysis 1 for Overall Survival (OS)

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | 0.0427  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |

### 5. Secondary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Disease-free Survival (DFS) of Patients With Confirmed Complete Response (CR).   |
| Measure Description | CR is defined by at least 8 weeks of: 1)Absence of lymphadenopathy 2)No hepatomegaly or splenomegaly 3)Absence of B-symptoms 4)Normal blood count 5)Bone marrow aspirate and biopsy 8 weeks after the clinical and laboratory results demonstrated that a CR was achieved. A marrow sample had to be normocellular for age with less than 30% lymphocytes. Lymphoid nodules had to be absent. If marrow was hypocellular,a repeat biopsy was taken 4 weeks later and samples were re-reviewed in conjunction with the prior pathology. DFS was calculated from time of CR to relapse or death. Median DFS was not reached. |
| Time Frame          | Median observation time at time of analysis was approximately 21 months  |

### Analysis Population Description

The ITT population was comprised of all patients randomized in the study, irrespective of whether they received treatment or not. Informed consent was unavailable at the time of analysis for 2 patients in the FC group and 5 patients in the FCR group. ITT population: FC = 407; FCR = 403.

### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

## Measured Values

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|---|-----------------------------------|---|
| Overall Number of Participants Analyzed   | 407                               | 403   |
| Disease-free Survival (DFS) of Patients With Confirmed Complete Response (CR).<br>Measure Type: Number<br>Unit of measure: Days to an event |                                   |   |
| Minimum number of days to an event  | 84                                | 91  |
| Maximum number of days to an event  | 1164                              | 1226  |

## Statistical Analysis 1 for Disease-free Survival (DFS) of Patients With Confirmed Complete Response (CR).

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | 0.7882  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |

## 6. Secondary Outcome Measure:

|                     |   |
|---------------------|---|
| Measure Title       | Final Analysis: Time to Overall Survival Event  |
| Measure Description | Overall survival (OS) was defined as the time between randomization and the date of death due to any cause. |
| Time Frame          | Median observation time was approximately 66.4 months   |

## Analysis Population Description

Participants from the Intent-to-treat population, that included all randomized participants who died.

## Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

## Measured Values

|   | Fludarabine+Cyclophosphamide (FC)  | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|---|------------------------------------|---|
| Overall Number of Participants Analyzed   | 154                                | 125   |
| Final Analysis: Time to Overall Survival Event<br>Median (95% Confidence Interval)<br>Unit of measure: Days | 2613.0 (2354 to NA) <sup>[1]</sup> | NA (2745 to NA) <sup>[2]</sup>                |

[1] Upper limit of the 95% confidence interval has not been reached.

[2] Median time to event and upper limit of the 95% confidence have not been reached.

## Statistical Analysis 1 for Final Analysis: Time to Overall Survival Event

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | 0.0010  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |
| Method of Estimation           | Estimation Parameter       | Hazard Ratio (HR)   |
|                                | Estimated Value            | 0.68  |
|                                | Confidence Interval        | (2-Sided) 95%   |

|  |                     |                 |
|--|---------------------|-----------------|
|  |                     | 0.54 to 0.86    |
|  | Estimation Comments | [Not specified] |

### 7. Secondary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Final Analysis: Time to Event-free Survival Event  |
| Measure Description | Event-free survival was defined as the time between randomization and the date of disease progression, relapse, start of new Chronic Lymphocytic Leukemia treatment or death by any cause. |
| Time Frame          | Median observation time was approximately 66.4 months  |

#### Analysis Population Description

Participants from the Intent-to-treat population, that included all randomized participants, with disease progression, relapse, start of new Chronic Lymphocytic Leukemia treatment or death.

#### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

#### Measured Values

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|--|-----------------------------------|---|
| Overall Number of Participants Analyzed  | 301                               | 257   |
| Final Analysis: Time to Event-free Survival Event<br>Median (95% Confidence Interval)<br>Unit of measure: Days | 951.0 (843 to 1039)               | 1666.0 (1415 to 1799)                         |

#### Statistical Analysis 1 for Final Analysis: Time to Event-free Survival Event

|                               |                            |   |
|-------------------------------|----------------------------|---|
| Statistical Analysis Overview | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                               | Comments                   | [Not specified]   |

|                                |                          |                               |
|--------------------------------|--------------------------|-------------------------------|
|                                | Type of Statistical Test | Superiority or Other (legacy) |
|                                | Comments                 | [Not specified]               |
| Statistical Test of Hypothesis | P-Value                  | <.0001                        |
|                                | Comments                 | [Not specified]               |
|                                | Method                   | Log Rank                      |
|                                | Comments                 | [Not specified]               |
| Method of Estimation           | Estimation Parameter     | Hazard Ratio (HR)             |
|                                | Estimated Value          | 0.57                          |
|                                | Confidence Interval      | (2-Sided) 95%<br>0.48 to 0.67 |
|                                | Estimation Comments      | [Not specified]               |

#### 8. Secondary Outcome Measure:

|                     |   |
|---------------------|---|
| Measure Title       | Final Analysis: Time to Disease-free Survival (DFS) Event in Participants With Complete Response (CR)   |
| Measure Description | CR is defined by at least 8 weeks of: 1)Absence of lymphadenopathy 2)No hepatomegaly or splenomegaly 3)Absence of B-symptoms 4)Normal blood count 5)Bone marrow aspirate and biopsy 8 weeks after the clinical and laboratory results demonstrated that a CR was achieved. A marrow sample had to be normocellular for age with less than 30% lymphocytes. Lymphoid nodules had to be absent. If marrow was hypocellular,a repeat biopsy was taken 4 weeks later and samples were re-reviewed in conjunction with the prior pathology. DFS was calculated from time of CR to relapse or death |
| Time Frame          | Median observation time was approximately 66.4 months   |

#### Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants, with complete response who experienced a disease free survival event (disease relapse or death).

#### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

## Measured Values

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|--|-----------------------------------|---|
| Overall Number of Participants Analyzed  | 58                                | 97  |
| Final Analysis: Time to Disease-free Survival (DFS) Event in Participants With Complete Response (CR)<br>Median (95% Confidence Interval)<br>Unit of measure: Days | 1488.0 (1198 to 1836)             | 1854.0 (1646 to 2208)                         |

## Statistical Analysis 1 for Final Analysis: Time to Disease-free Survival (DFS) Event in Participants With Complete Response (CR)

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | 0.0523  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |
| Method of Estimation           | Estimation Parameter       | Hazard Ratio (HR)   |
|                                | Estimated Value            | 0.73  |
|                                | Confidence Interval        | (2-Sided) 95%<br>0.52 to 1.02   |
|                                | Estimation Comments        | [Not specified]   |

## 9. Secondary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Final Analysis: Duration of Response   |
| Measure Description | Duration of response was defined as the time from the first documented Complete Response, Partial Response to disease progression or death by any cause. |
| Time Frame          | Median observation time was approximately 66.4 months  |

### Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants, with complete response or partial response who experienced an event (disease progression or death due to any cause).

### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

### Measured Values

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|---|-----------------------------------|---|
| Overall Number of Participants Analyzed   | 214                               | 207   |
| Final Analysis: Duration of Response<br>Median (95% Confidence Interval)<br>Unit of measure: Days | 1102.0 (977 to 1249)              | 1718.0 (1618 to 1859)                         |

### Statistical Analysis 1 for Final Analysis: Duration of Response

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | <.0001  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |
| Method of Estimation           | Estimation Parameter       | Hazard Ratio (HR)   |
|                                | Estimated Value            | 0.58  |

|  |                     |                               |
|--|---------------------|-------------------------------|
|  | Confidence Interval | (2-Sided) 95%<br>0.48 to 0.71 |
|  | Estimation Comments | [Not specified]               |

#### 10. Secondary Outcome Measure:

|                     |  |
|---------------------|--|
| Measure Title       | Final Analysis: Percentage of Participants With Complete Response (CR) and Partial Response  |
| Measure Description | CR is defined by at least 8 weeks of: 1)Absence of lymphadenopathy 2)No hepatomegaly or splenomegaly 3)Absence of B-symptoms 4)Normal blood count 5)Bone marrow aspirate and biopsy 8 weeks after the clinical and laboratory results demonstrated that a CR was achieved. A marrow sample had to be normocellular for age with less than 30% lymphocytes. Lymphoid nodules had to be absent. If marrow was hypocellular,a repeat biopsy was taken 4 weeks later and samples were re-reviewed in conjunction with the prior pathology. Partial response is defined as a decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment. |
| Time Frame          | Median observation time was approximately 66.4 months  |

#### Analysis Population Description

Intent-to-treat population included all randomized participants.

#### Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

#### Measured Values

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|--|-----------------------------------|---|
| Overall Number of Participants Analyzed  | 409                               | 408   |
| Final Analysis: Percentage of Participants With Complete Response (CR) and Partial Response<br>Number (95% Confidence Interval)<br>Unit of measure: Percentage of participants | 72.4 (67.8 to 76.7)               | 85.8 (82.0 to 89.0)                           |

Statistical Analysis 1 for Final Analysis: Percentage of Participants With Complete Response (CR) and Partial Response

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | <.0001  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Chi-squared   |
|                                | Comments                   | [Not specified]   |
| Method of Estimation           | Estimation Parameter       | Odds Ratio (OR)   |
|                                | Estimated Value            | 2.30  |
|                                | Confidence Interval        | (2-Sided) 95%<br>1.62 to 3.28   |
|                                | Estimation Comments        | [Not specified]   |

**11. Secondary Outcome Measure:**

|                     |   |
|---------------------|---|
| Measure Title       | Final Analysis: Time to New Treatment for Chronic Lymphocytic Leukemia(CLL) |
| Measure Description | The time from randomization to the start of a new treatment.                |
| Time Frame          | Median observation time was approximately 66.4 months                       |

Analysis Population Description

Participants from the Intent-to-treat population, that included all randomized participants, who started a new CLL treatment.

Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

## Measured Values

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide +Rituximab (FCR) |
|--|-----------------------------------|---|
| Overall Number of Participants Analyzed  | 251                               | 206   |
| Final Analysis: Time to New Treatment for Chronic Lymphocytic Leukemia(CLL)<br>Median (95% Confidence Interval)<br>Unit of measure: Days | 1455.0 (1324 to 1577)             | 2082.0 (1926 to 2253)                         |

## Statistical Analysis 1 for Final Analysis: Time to New Treatment for Chronic Lymphocytic Leukemia(CLL)

|                                |                            |   |
|--------------------------------|----------------------------|---|
| Statistical Analysis Overview  | Comparison Group Selection | Fludarabine+Cyclophosphamide (FC), Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|                                | Comments                   | [Not specified]   |
|                                | Type of Statistical Test   | Superiority or Other (legacy)   |
|                                | Comments                   | [Not specified]   |
| Statistical Test of Hypothesis | P-Value                    | <.0001  |
|                                | Comments                   | [Not specified]   |
|                                | Method                     | Log Rank  |
|                                | Comments                   | [Not specified]   |
| Method of Estimation           | Estimation Parameter       | Hazard Ratio (HR)   |
|                                | Estimated Value            | 0.59  |
|                                | Confidence Interval        | (2-Sided) 95%<br>0.49 to 0.72   |
|                                | Estimation Comments        | [Not specified]   |

## Reported Adverse Events

|                                     |   |
|-------------------------------------|---|
| Time Frame                          | Adverse Events were recorded until 28 days after completion of study treatment (median time approximately 21 months). Serious Adverse Events reported until 1 year post-treatment or initiation of new CLL treatment (median time approximately 42 months). |
| Adverse Event Reporting Description | The safety population included all participants who received at least one dose of study drug.   |

## Reporting Groups

|   | Description   |
|---|---|
| Fludarabine+Cyclophosphamide (FC)             | Fludarabine+cyclophosphamide (FC) intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV on Days 1, 2, 3 for 6 cycles.  |
| Fludarabine+Cyclophosphamide +Rituximab (FCR) | Rituximab intravenously for a total of 6 treatment cycles at intervals of 28 days. Cycle 1: 375 mg/m <sup>2</sup> IV on Day 0; Cycles 2-6: 500 mg/m <sup>2</sup> IV on Day 1. FC intravenously for a total of 6 treatment cycles at intervals of 28 days. Fludarabine: 25 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. Cyclophosphamide: 250 mg/m <sup>2</sup> IV over 15-30 min on Days 1, 2, 3 for 6 cycles. |

## All-Cause Mortality

|                           | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---------------------------|-----------------------------------|--|
|                           | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Total All-Cause Mortality | /                                 | /  |

## Serious Adverse Events

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---|-----------------------------------|--|
|   | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Total   | 164/398 (41.21%)                  | 186/402 (46.27%)                             |
| Blood and lymphatic system disorders              |                                   |  |
| Agranulocytosis <sup>A</sup> †                    | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Anaemia <sup>A</sup> †                            | 10/398 (2.51%)                    | 6/402 (1.49%)                                |
| Bone Marrow Failure <sup>A</sup> †                | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Coombs Positive Haemolytic Anaemia <sup>A</sup> † | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Evans Syndrome <sup>A</sup> †                     | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Febrile Bone Marrow Aplasia <sup>A</sup> †        | 0/398 (0%)                        | 3/402 (0.75%)                                |
| Febrile Neutropenia <sup>A</sup> †                | 22/398 (5.53%)                    | 31/402 (7.71%)                               |
| Granulocytopenia <sup>A</sup> †                   | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Haematotoxicity <sup>A</sup> †                    | 0/398 (0%)                        | 1/402 (0.25%)                                |

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---|-----------------------------------|--|
|   | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Haemolysis <sup>A †</sup>                     | 3/398 (0.75%)                     | 1/402 (0.25%)                                |
| Haemolytic Anaemia <sup>A †</sup>             | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Leukopenia <sup>A †</sup>                     | 3/398 (0.75%)                     | 9/402 (2.24%)                                |
| Lymphadenitis <sup>A †</sup>                  | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Neutropenia <sup>A †</sup>                    | 3/398 (0.75%)                     | 8/402 (1.99%)                                |
| Pancytopenia <sup>A †</sup>                   | 3/398 (0.75%)                     | 7/402 (1.74%)                                |
| Splenomegaly <sup>A †</sup>                   | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Thrombocytopenia <sup>A †</sup>               | 6/398 (1.51%)                     | 6/402 (1.49%)                                |
| <b>Cardiac disorders</b>                      |                                   |  |
| Acute Myocardial Infarction <sup>A †</sup>    | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Angina Pectoris <sup>A †</sup>                | 2/398 (0.5%)                      | 5/402 (1.24%)                                |
| Arrhythmia <sup>A †</sup>                     | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Cardiac Failure <sup>A †</sup>                | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Cardiac Failure Congestive <sup>A †</sup>     | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Cardiopulmonary Failure <sup>A †</sup>        | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Coronary Artery Disease <sup>A †</sup>        | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Myocardial Infarction <sup>A †</sup>          | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Myocardial Ischaemia <sup>A †</sup>           | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Sinus Bradycardia <sup>A †</sup>              | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Supraventricular Extrasystoles <sup>A †</sup> | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Tachyarrhythmia <sup>A †</sup>                | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Tachycardia <sup>A †</sup>                    | 0/398 (0%)                        | 2/402 (0.5%)                                 |

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---|-----------------------------------|--|
|   | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Ventricular Fibrillation <sup>A</sup> †     | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Ear and labyrinth disorders                 |                                   |  |
| Vertigo <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Eye disorders                               |                                   |  |
| Amaurosis Fugax <sup>A</sup> †              | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Dacryostenosis Acquired <sup>A</sup> †      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Retinal Detachment <sup>A</sup> †           | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Uveitis <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Vitreous Haemorrhage <sup>A</sup> †         | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Gastrointestinal disorders                  |                                   |  |
| Abdominal Pain <sup>A</sup> †               | 3/398 (0.75%)                     | 1/402 (0.25%)                                |
| Abdominal Symptom <sup>A</sup> †            | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Constipation <sup>A</sup> †                 | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Diarrhoea <sup>A</sup> †                    | 2/398 (0.5%)                      | 5/402 (1.24%)                                |
| Duodenal Ulcer Perforation <sup>A</sup> †   | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Gastrointestinal Ulcer <sup>A</sup> †       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Haematemesis <sup>A</sup> †                 | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Inguinal Hernia <sup>A</sup> †              | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Inguinal Hernia, Obstructive <sup>A</sup> † | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Nausea <sup>A</sup> †                       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Pancreatitis <sup>A</sup> †                 | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Tongue Ulceration <sup>A</sup> †            | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Vomiting <sup>A</sup> †                     | 2/398 (0.5%)                      | 3/402 (0.75%)                                |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| <b>General disorders</b>                             |                                   |  |
| Adverse Drug Reaction <sup>A</sup> †                 | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Chest Discomfort <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Chest Pain <sup>A</sup> †                            | 1/398 (0.25%)                     | 3/402 (0.75%)                                |
| Chills <sup>A</sup> †                                | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Death <sup>A</sup> †                                 | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Device occlusion <sup>A</sup> †                      | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| General Physical Health Deterioration <sup>A</sup> † | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| General Symptom <sup>A</sup> †                       | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Ill-Defined Disorder <sup>A</sup> †                  | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Mucosal Inflammation <sup>A</sup> †                  | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Multi-Organ Failure <sup>A</sup> †                   | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Pain <sup>A</sup> †                                  | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Pyrexia <sup>A</sup> †                               | 20/398 (5.03%)                    | 18/402 (4.48%)                               |
| <b>Hepatobiliary disorders</b>                       |                                   |  |
| Cholangitis <sup>A</sup> †                           | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Cholecystitis <sup>A</sup> †                         | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Cholecystitis Acute <sup>A</sup> †                   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Cholelithiasis <sup>A</sup> †                        | 2/398 (0.5%)                      | 1/402 (0.25%)                                |
| Drug-induced liver injury <sup>A</sup> †             | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Hepatic Siderosis <sup>A</sup> †                     | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Hepatitis <sup>A</sup> †                             | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Hepatotoxicity <sup>A</sup> †                        | 0/398 (0%)                        | 1/402 (0.25%)                                |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| <b>Immune system disorders</b>                 |                                   |  |
| Anaphylactic Reaction <sup>A †</sup>           | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Cytokine Release Syndrome <sup>A †</sup>       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Drug Hypersensitivity <sup>A †</sup>           | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Hypersensitivity <sup>A †</sup>                | 1/398 (0.25%)                     | 3/402 (0.75%)                                |
| <b>Infections and infestations</b>             |                                   |  |
| Abscess <sup>A †</sup>                         | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Appendicitis <sup>A †</sup>                    | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Bronchiolitis <sup>A †</sup>                   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Bronchitis <sup>A †</sup>                      | 5/398 (1.26%)                     | 5/402 (1.24%)                                |
| Bronchopneumonia <sup>A †</sup>                | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Cellulitis <sup>A †</sup>                      | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Cerebral Toxoplasmosis <sup>A †</sup>          | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Chronic Sinusitis <sup>A †</sup>               | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Cytomegalovirus Infection <sup>A †</sup>       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Device related infection <sup>A †</sup>        | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Diverticulitis <sup>A †</sup>                  | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Endophthalmitis <sup>A †</sup>                 | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Enterococcal Bacteraemia <sup>A †</sup>        | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Erysipelas <sup>A †</sup>                      | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Gastroenteritis <sup>A †</sup>                 | 3/398 (0.75%)                     | 2/402 (0.5%)                                 |
| Gastroenteritis Cryptosporidial <sup>A †</sup> | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Hepatitis B <sup>A †</sup>                     | 2/398 (0.5%)                      | 1/402 (0.25%)                                |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Hepatitis C <sup>A</sup> †                       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Hepatobiliary Infection <sup>A</sup> †           | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Herpes Simplex <sup>A</sup> †                    | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Herpes Virus Infection <sup>A</sup> †            | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Herpes Zoster <sup>A</sup> †                     | 6/398 (1.51%)                     | 8/402 (1.99%)                                |
| Herpes Zoster Ophthalmic <sup>A</sup> †          | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Infected Skin Ulcer <sup>A</sup> †               | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Infection <sup>A</sup> †                         | 2/398 (0.5%)                      | 5/402 (1.24%)                                |
| Infectious pleural effusion <sup>A</sup> †       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Lower Respiratory Tract Infection <sup>A</sup> † | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Lung Infection <sup>A</sup> †                    | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Lung Infection Pseudomonal <sup>A</sup> †        | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Neutropenic Infection <sup>A</sup> †             | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Neutropenic Sepsis <sup>A</sup> †                | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Oesophageal Candidiasis <sup>A</sup> †           | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Oral Herpes <sup>A</sup> †                       | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Orchitis <sup>A</sup> †                          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Osteomyelitis <sup>A</sup> †                     | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Otitis Media <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Periorbital Cellulitis <sup>A</sup> †            | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Pneumocystis Jiroveci Infection <sup>A</sup> †   | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Pneumocystis Jiroveci Pneumonia <sup>A</sup> †   | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Pneumonia <sup>A</sup> †                             | 21/398 (5.28%)                    | 18/402 (4.48%)                               |
| Pneumonia Fungal <sup>A</sup> †                      | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Pneumonia Primary Atypical <sup>A</sup> †            | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Pneumonia Respiratory Syncytial Viral <sup>A</sup> † | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Pseudomonal Sepsis <sup>A</sup> †                    | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Respiratory Tract Infection <sup>A</sup> †           | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Sepsis <sup>A</sup> †                                | 8/398 (2.01%)                     | 5/402 (1.24%)                                |
| Septic Shock <sup>A</sup> †                          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Sinusitis <sup>A</sup> †                             | 1/398 (0.25%)                     | 4/402 (1%)                                   |
| Skin Infection <sup>A</sup> †                        | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Staphylococcal Infection <sup>A</sup> †              | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Subcutaneous Abscess <sup>A</sup> †                  | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Tonsillitis <sup>A</sup> †                           | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Tuberculosis <sup>A</sup> †                          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Urosepsis <sup>A</sup> †                             | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Viral Infection <sup>A</sup> †                       | 0/398 (0%)                        | 3/402 (0.75%)                                |
| Injury, poisoning and procedural complications       |                                   |  |
| Humerus Fracture <sup>A</sup> †                      | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Post Procedural Complication <sup>A</sup> †          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Investigations                                       |                                   |  |
| Body Temperature Increased <sup>A</sup> †            | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Catheterisation Cardiac <sup>A</sup> †               | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Metabolism and nutrition disorders                   |                                   |  |

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---|-----------------------------------|--|
|   | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Dehydration <sup>A</sup> †  | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Gout <sup>A</sup> †   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Hyperuricaemia <sup>A</sup> †                                       | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Tumour Lysis Syndrome <sup>A</sup> †                                | 2/398 (0.5%)                      | 1/402 (0.25%)                                |
| Musculoskeletal and connective tissue disorders                     |                                   |  |
| Intervertebral Disc Protrusion <sup>A</sup> †                       | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Kyphosis <sup>A</sup> †   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |  |
| Acute Myeloid Leukaemia <sup>A</sup> †                              | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Adenocarcinoma <sup>A</sup> †                                       | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Anogenital warts <sup>A</sup> †                                     | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Basal Cell Carcinoma <sup>A</sup> †                                 | 2/398 (0.5%)                      | 1/402 (0.25%)                                |
| Bladder Cancer <sup>A</sup> †                                       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Breast Cancer <sup>A</sup> †  | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Central Nervous System Lymphoma <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Histiocytosis Haematophagic <sup>A</sup> †                          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Hodgkin's Disease <sup>A</sup> †                                    | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Lung Neoplasm Malignant <sup>A</sup> †                              | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Lung Squamous Cell Carcinoma Stage Unspecified <sup>A</sup> †       | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Lymphoma <sup>A</sup> †   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Lymphoma Transformation <sup>A</sup> †                              | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Malignant Melanoma <sup>A</sup> †                                   | 2/398 (0.5%)                      | 1/402 (0.25%)                                |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Non-Small Cell Lung Cancer <sup>A</sup> †          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Pancreatic Carcinoma <sup>A</sup> †                | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Pharyngeal Cancer Stage Unspecified <sup>A</sup> † | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Prostate Cancer <sup>A</sup> †                     | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Rectal Cancer <sup>A</sup> †                       | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Skin Cancer <sup>A</sup> †                         | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Squamous Cell Carcinoma <sup>A</sup> †             | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Squamous Cell Carcinoma of Skin <sup>A</sup> †     | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Transitional Cell Carcinoma <sup>A</sup> †         | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Nervous system disorders                           |                                   |  |
| Cerebral Infarction <sup>A</sup> †                 | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Cerebrovascular Accident <sup>A</sup> †            | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Convulsion <sup>A</sup> †                          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Diabetic Neuropathy <sup>A</sup> †                 | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Encephalitis <sup>A</sup> †                        | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Epilepsy <sup>A</sup> †                            | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Headache <sup>A</sup> †                            | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Hemiparesis <sup>A</sup> †                         | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Hydrocephalus <sup>A</sup> †                       | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Migraine <sup>A</sup> †                            | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Optic Neuritis <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Stupor <sup>A</sup> †                              | 1/398 (0.25%)                     | 0/402 (0%)                                   |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Syncope <sup>A</sup> †                               | 2/398 (0.5%)                      | 2/402 (0.5%)                                 |
| Transient Ischaemic Attack <sup>A</sup> †            | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Psychiatric disorders                                |                                   |  |
| Completed Suicide <sup>A</sup> †                     | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Renal and urinary disorders                          |                                   |  |
| Calculus Ureteric <sup>A</sup> †                     | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Cystitis Haemorrhagic <sup>A</sup> †                 | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Nephrolithiasis <sup>A</sup> †                       | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Renal Failure <sup>A</sup> †                         | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Renal Failure Acute <sup>A</sup> †                   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Urinary Retention <sup>A</sup> †                     | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Urinary Tract Obstruction <sup>A</sup> †             | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Reproductive system and breast disorders             |                                   |  |
| Benign Prostatic Hyperplasia <sup>A</sup> †          | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Respiratory, thoracic and mediastinal disorders      |                                   |  |
| Alveolitis <sup>A</sup> †                            | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Alveolitis Allergic <sup>A</sup> †                   | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Bronchospasm <sup>A</sup> †                          | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Chronic Obstructive Pulmonary Disease <sup>A</sup> † | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Chylothorax <sup>A</sup> †                           | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Dyspnoea <sup>A</sup> †                              | 2/398 (0.5%)                      | 1/402 (0.25%)                                |
| Dyspnoea Exertional <sup>A</sup> †                   | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Dyspnoea at Rest <sup>A</sup> †                      | 0/398 (0%)                        | 1/402 (0.25%)                                |

|  | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|--|-----------------------------------|--|
|  | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Epistaxis <sup>A †</sup>                   | 2/398 (0.5%)                      | 1/402 (0.25%)                                |
| Interstitial Lung Disease <sup>A †</sup>   | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Laryngeal Stenosis <sup>A †</sup>          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Lung Disorder <sup>A †</sup>               | 0/398 (0%)                        | 2/402 (0.5%)                                 |
| Lung Infiltration <sup>A †</sup>           | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Pleural Effusion <sup>A †</sup>            | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Pulmonary Embolism <sup>A †</sup>          | 2/398 (0.5%)                      | 2/402 (0.5%)                                 |
| Respiration Abnormal <sup>A †</sup>        | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Skin and subcutaneous tissue disorders     |                                   |  |
| Dermatitis Allergic <sup>A †</sup>         | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Dermatitis Exfoliative <sup>A †</sup>      | 1/398 (0.25%)                     | 1/402 (0.25%)                                |
| Drug Eruption <sup>A †</sup>               | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Erythema <sup>A †</sup>                    | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Leukocytoclastic Vasculitis <sup>A †</sup> | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Pruritus <sup>A †</sup>                    | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Pustular Psoriasis <sup>A †</sup>          | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Rash <sup>A †</sup>                        | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Skin Ulcer <sup>A †</sup>                  | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Urticaria <sup>A †</sup>                   | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Surgical and medical procedures            |                                   |  |
| Cholecystectomy <sup>A †</sup>             | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Coronary Revascularisation <sup>A †</sup>  | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Haemorrhoid Operation <sup>A †</sup>       | 1/398 (0.25%)                     | 0/402 (0%)                                   |

|                                       | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---------------------------------------|-----------------------------------|--|
|                                       | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Prostatectomy <sup>A †</sup>          | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Surgery <sup>A †</sup>                | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| <b>Vascular disorders</b>             |                                   |  |
| Circulatory Collapse <sup>A †</sup>   | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Deep Vein Thrombosis <sup>A †</sup>   | 2/398 (0.5%)                      | 0/402 (0%)                                   |
| Hypotension <sup>A †</sup>            | 1/398 (0.25%)                     | 2/402 (0.5%)                                 |
| Thrombosis <sup>A †</sup>             | 1/398 (0.25%)                     | 0/402 (0%)                                   |
| Vasculitis Necrotising <sup>A †</sup> | 0/398 (0%)                        | 1/402 (0.25%)                                |
| Venous Thrombosis Limb <sup>A †</sup> | 0/398 (0%)                        | 1/402 (0.25%)                                |

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (15.0)

### Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

|   | Fludarabine+Cyclophosphamide (FC) | Fludarabine+Cyclophosphamide+Rituximab (FCR) |
|---|-----------------------------------|--|
|   | Affected/At Risk (%)              | Affected/At Risk (%)                         |
| Total                                       | 122/398 (30.65%)                  | 185/402 (46.02%)                             |
| <b>Blood and lymphatic system disorders</b> |                                   |  |
| Leukopenia <sup>A †</sup>                   | 45/398 (11.31%)                   | 88/402 (21.89%)                              |
| Neutropenia <sup>A †</sup>                  | 71/398 (17.84%)                   | 116/402 (28.86%)                             |
| Thrombocytopenia <sup>A †</sup>             | 35/398 (8.79%)                    | 21/402 (5.22%)                               |

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (15.0)

### Limitations and Caveats

[Not specified]

## More Information

### **Certain Agreements:**

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

### **Results Point of Contact:**

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Organization: Hoffmann-LaRoche

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