ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 02/10/2014

Grantor: CDER IND/IDE Number: 4294 Serial Number: 408

Fludarabine (Fludara®) Plus Alemtuzumab (CAMPATH®, MabCampath®) vs Fludarabine Alone in B-Cell Chronic Lymphocytic Leukemia (B-CLL) Patients

This study has been completed.

Sponsor:	Genzyme, a Sanofi Company
Collaborators:	
Information provided by (Responsible Party):	Sanofi (Genzyme, a Sanofi Company)
ClinicalTrials.gov Identifier:	NCT00086580

Purpose

This is a Phase 3, prospective, multicenter, open-label, randomized, controlled study to evaluate and compare the efficacy and safety of fludarabine plus alemtuzumab versus fludarabine alone as second-line therapy for patients with relapsed or refractory B-cell chronic lymphocytic leukemia (B-CLL). Patients who meet all eligibility criteria and sign the informed consent document may be entered on the study.

Condition	Intervention	Phase
B-Cell Chronic Lymphocytic Leukemia	Biological/Vaccine: FluCAM [Fludara + Campath] Biological/Vaccine: fludarabine phosphate	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A Phase III Randomized Trial to Evaluate the Efficacy and Safety of Second-Line Therapy With Fludarabine Plus Alemtuzumab vs. Fludarabine Alone in Patients With B-Cell Chronic Lymphocytic Leukemia

Further study details as provided by Sanofi (Genzyme, a Sanofi Company):
Primary Outcome Measure:

- Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) Assessment [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Progression-free survival was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease (PD) as determined by the treatment-blinded IRRP, or death due to any cause. Results are expressed in months.

Secondary Outcome Measures:

- Participant Best Response to Treatment Assessed by the Independent Response Review Panel (IRRP) [Time Frame: Up to 9 months] [Designated as safety issue: No]
  Participants were evaluated by the IRRP according to National Cancer Institute (NCI) 1996 response criteria. The best response observed during the study is summarized. Response categories include Complete Response (CR) with normal physical exam, marrow cells and blood values, Partial Response (PR) with a >= 50% decrease from baseline in lymphocytes, lymphadenopathy and liver or spleen exam, Stable Disease (SD) without significant progression from baseline, or Progressive Disease (PD) with increased size/number of nodes, size of liver or spleen, increase in lymphocytes, aggressive histology.
- Kaplan-Meier Estimates of Overall Survival Time [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Overall survival was defined as the time in days from the date of randomization to the date of death due to any cause plus 1 day for all participants. Results are stated in months.
- Kaplan Meier Estimates for Time to Disease Progression Assessed by the Independent Response Review Panel (IRRP) [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Time to disease progression was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease as determined by IRRP. Results are stated in months.
- Kaplan-Meier Estimates for Duration of Response Assessed by the Independent Response Review Panel (IRRP) [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Duration of response was analyzed for participants who achieved a complete response (CR) or partial response (PR) and was defined as the number of days from the first date of documented response to the date of progressive disease as determined by IRRP or death due to any cause. Results are stated in months.
- Kaplan-Meier Estimates for Time to Alternative Therapy [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Time to alternative therapy was defined as the number of days from the date of randomization to the date of first alternative therapy for chronic lymphocytic leukemia (CLL) or death resulting from any cause. Participants who had not received alternative therapy as of the data cutoff date were censored at the last follow-up visit assessment date plus 1 day. Results are stated in months.
- Mean EQ-5D™ Index Scores to Measure Quality of Life at Baseline [Time Frame: Day 0 (baseline)] [Designated as safety issue: No]
  EQ-5D™ is a trademark of the EuroQol Group. EQ-5D™ is a standardized instrument for use as a measure of health outcome. The questionnaire asks about health status along 5 dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression, which are rated at three possible levels (no problems, some problems, extreme problems). The score ranges from best (+1) to worst (-0.59).
- Mean EQ-5D™ Index Scores to Measure Quality of Life at End of Treatment [Time Frame: up to month 6 (end of treatment)] [Designated as safety issue: No]
  EQ-5D™ is a trademark of the EuroQol Group. EQ-5D™ is a standardized instrument for use as a measure of health outcome. The questionnaire asks about health status along 5 dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression, which are rated at three possible levels (no problems, some problems, extreme problems). The score ranges from best (+1) to worst (-0.59).
- Mean EuroQol Visual Analogue Scale (EQ-VAS) Scores to Measure Quality of Life at Baseline [Time Frame: Day 0 (baseline)] [Designated as safety issue: No]
  The EuroQol Visual Analogue Scale (EQ-VAS) was also used to capture the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.
- Mean EuroQol Visual Analogue Scale (EQ-VAS) Scores to Measure Quality of Life at End of Treatment [Time Frame: up to month 6 (end of treatment)] [Designated as safety issue: No]

The EuroQol Visual Analogue Scale (EQ-VAS) was also used to capture the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.

- Summary of Participants With Adverse Experiences (AEs) [Time Frame: Up to 6 years] [Designated as safety issue: Yes]
  Number of participants with adverse events (AEs). AEs were graded by the investigator using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and were assessed for relatedness to study treatment (4 point scale from 'not related' to 'definitely related'). Categories reported include participant counts for treatment-emergent AEs, AEs for infections, serious AEs, AEs causing discontinuation of study drug(s), and deaths. Related AEs for the combination arm can be related to either fludarabine or alemtuzumab.
- Mean Systemic Clearance (CL) of Fludarabine [Time Frame: month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)] [Designated as safety issue: No]
  Clearance of drug from plasma is affected by the absorption, distribution, metabolism and elimination of the drug. Mean systemic clearance of fludarabine is derived from plasma concentration versus time data.
- Total Volume of Distribution (Vss) of Fludarabine [Time Frame: month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)] [Designated as safety issue: No]
  The total volume of distribution (Vss) is the apparent volume in which fludarabine is distributed immediately after it has been injected intravenously and equilibrated between plasma and the surrounding tissues. Total volume of distribution (Vss) of fludarabine is derived from plasma concentration versus time data.
- Area Under the Curve (AUC) of Fludarabine From (AUC 0-tau) [Time Frame: month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)] [Designated as safety issue: No]
  AUC (0-tau) is the area under the plasma concentration curve for fludarabine over the dosage interval (tau).
- Maximum Plasma Concentration (Cmax) of Fludarabine [Time Frame: month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)] [Designated as safety issue: No]
  Cmax is the maximum plasma concentration of fludarabine observed.
- Participants With Minimal Residual Disease (MRD) [Time Frame: up to 9 months] [Designated as safety issue: No]
  MRD negativity in this report was defined by the absence of tumor cells in bone marrow, using 4-color flow cytometry. MRD was assessed in participants with a clinical complete response (CR) or partial response (PR) without recovery of blood counts. MRD represents a very positive outcome.

Other Pre-specified Outcome Measures:

- Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage I-II [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Progression-free survival was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease (PD) as determined by the treatment-blinded IRRP, or death due to any cause. Results are expressed in months and include participants with Rai stage I or II.
- Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage III-IV [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Progression-free survival was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease (PD) as determined by the treatment-blinded IRRP, or death due to any cause. Results are expressed in months and include participants with Rai stage III or IV.
- Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage I-II [Time Frame: Up to 6 years] [Designated as safety issue: No]
  Overall survival was defined as the time in days from the date of randomization to the date of death due to any cause plus 1 day for all participants. Results are stated in months and include participants with Rai Stage I or II.
- Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage III-IV [Time Frame: Up to 6 years] [Designated as safety issue: No]

Overall survival was defined as the time in days from the date of randomization to the date of death due to any cause plus 1 day for all participants. Results are stated in months and include participants with Rai Stage III or IV.

Enrollment: 335
Study Start Date: July 2004
Primary Completion Date: June 2010
Study Completion Date: June 2010

Arms	Assigned Interventions
Experimental: Combination Arm (FluCAM)	Biological/Vaccine: FluCAM [Fludara + Campath] Phase A: Escalating Doses of alemtuzumab (Campath) Alone Day 1: alemtuzumab 3 mg intravenously (IV) over 2 hours. Day 2: alemtuzumab 10 mg IV over 2 hours if 3 mg was tolerated, else repeat 3 mg daily until tolerated. Day 3: alemtuzumab 30 mg IV over 2 hours if 10 mg was tolerated, else repeat 10 mg daily until tolerated. Participants were allowed 3-14 days to escalate to 30 mg. Once 30 mg was tolerated, the participant had to begin Phase B within 7 days. Phase B: FluCAM Cycle 1: Days 1,2,3 fludarabine phosphate administered at 30 mg/m^2 over 30 minutes IV, followed within 1 hour by alemtuzumab 30 mg IV over 2 hours. A similar schedule is set for Cycles 2 through 6; duration of alemtuzumab infusions vary from 2-6 hours. Each 28-day period is 1 cycle. Fludarabine phosphate dosage is based on participants' body surface area at the beginning of each cycle. FluCAM administered up to a maximum of 6 cycles, based upon participants' response to therapy and toxicity. Other Names: alemtuzumab fludarabine phosphate Fludara Campath
Active Comparator: Fludarabine Alone	Biological/Vaccine: fludarabine phosphate

Arms	Assigned Interventions
	Fludarabine phosphate (Fludara) is administered at a dose of 25 mg/m^2 IV over 15 to 30 minutes daily for 5 consecutive days (days 1 through 5) every 28 days (per package instructions). Each 28-day period is 1 cycle. The dose of fludarabine phosphate will be based on the participant's body surface area as calculated at the beginning of each cycle. Participants treated with fludarabine phosphate up to a maximum of 6 cycles, based upon their response to therapy and toxicity. Other Names: fludarabine phosphate Fludara

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- A diagnosis of B-cell chronic lymphocytic leukemia (B-CLL); according to the National Cancer Institute Working Group (NCI WG) criteria.
- Relapsed or refractory disease after 1 prior regimen except patients who were refractory to (i.e., progressed on) fludarabine or alemtuzumab therapy. Patients who previously responded (complete response or partial response) to fludarabine or alemtuzumab therapy, but who have relapsed at the time of study entry, may be eligible but response to fludarabine or alemtuzumab therapy must have lasted >12 months (i.e., >12 months from a documented response to a documented relapse).
- Binet stage A, stage B, or stage C or Rai Stage I through IV disease with evidence of progression as evidenced by the presence of one or more of the following:

I. Evidence of progressive marrow failure as manifested by: 1) a decrease in hemoglobin to <11g/dL, or 2) a decrease in platelet count to <100 x 10^9/L within the previous 6 months, or 3) a decrease in absolute neutrophil count (ANC) to <1.0 X 10^9/L.

II. Progressive splenomegaly to >2 cm below the left costal margin or other organomegaly.

III. Progressive lymphadenopathy.

IV. Progressive lymphocytosis with an increase of 50% over a 2-month period, or an anticipated doubling time of less than 6 months.

- World Health Organization (WHO) performance status (PS) of 0 or 1.
- Life expectancy >12 weeks.
- Anti-cancer therapy, major surgery, or irradiation was completed >3 weeks before randomization in this study. Patient must have recovered from the acute side effects incurred as a result of previous therapy.

- Serum creatinine less than or equal to 2.0 x institutional upper limits of normal (ULN) and calculated creatinine clearance (CrCl) greater than or equal to 30mL/min using the Cockroft and Gault formula.
- Adequate liver function as indicated by a total bilirubin, AST, and ALT less than or equal to 2 x the institutional ULN value, unless directly attributable to the patient's tumor.
- Female patients with childbearing potential must have a negative serum pregnancy test with 2 weeks of first dose of study drug(s). Male and female patients must agree to use an effective contraceptive method while on study treatment, if appropriate, and for a minimum of 6 months following study therapy.
- Signed, written informed consent.

Exclusion Criteria:

- Previously treated with >1 prior regimen for B-CLL.
- Previously treated with a fludarabine plus alemtuzumab (FluCAM) regimen for B-CLL.
- Positive Coombs test and actively hemolyzing.
- Absolute neutrophil count (ANC) <1.5 x 10^9/L or platelet count <75 x 10^9/L, unless due to bone marrow involvement.
- Medical condition requiring chronic use of pharmacologic doses of oral corticosteroids, i.e. anything other than replacement dose levels.
- History of anaphylaxis following exposure to monoclonal antibodies.
- Use of investigational agents within 6 weeks prior to study randomization.
- Active infection or history of severe infection (grade 4) within 3 months prior to study randomization.
- Known to be human immunodeficiency virus (HIV) positive.
- Autoimmune thrombocytopenia.
- Active second malignancy.
- Known central nervous system (CNS) involvement with B-CLL.
- Other severe, concurrent diseases, including tuberculosis, mental disorders, serious cardiac functional capacity (Class III or IV as defined by the New York Heart Association Classification), severe diabetes, severe hypertension, pulmonary disease (chronic obstructive pulmonary disease [COPD] with hypoxemia), or major organ malfunction (liver, kidney) that could interfere with the patient's ability to participate in the study.
- Pregnant or nursing women.
- Patients that have progressed with more aggressive B-cell cancers such as Richter's syndrome.
- Active hepatitis or a history of prior viral hepatitis B or hepatitis C, or positive hepatitis B serologies without prior immunization.

Contacts and Locations

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Lviv National Medical University named Danilo Galytcky
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Investigators

Study Director:	Medical Monitor	Genzyme Corporation

More Information

Results Publications:

Engert A, et al. Overall Survival Advantage and Acceptable Safety Profile with Fludarabine in Combination with Alemtuzumab (FluCam) in Previously Treated Patients with Advanced Stage Chronic Lymphocytic Leukemia. Poster Presentation at American Society of Hematology 10 December 2010; Blood (ASH Annual Meeting Abstracts), Nov 2010;116:919. http://ash.confex.com/ash/2010/webprogram/Paper31687.html

Engert A, et al. Improved Progression-free Survival (PFS) of Alemtuzumab (Campath®, MabCampath®) plus Fludarabine (Fludara®) versus Fludarabine Alone as Second-line Treatment of Patients with B-Cell Chronic Lymphocytic Leukemia: Preliminary Results from a Phase III Randomized Trial. 51st ASH Annual Meeting. Blood 2009;114. Abstract 537. http://ash.confex.com/ash/2009/webprogram/Paper21929.html

Engert A, et al. Fludarabine (FLU) plus Alemtuzumab (FluCAM) Improves Progression Free Survival versus Fludarabine in Previously Treated Chronic Lymphocytic Leukemia and Demonstrates Activity in High Risk Patients. Poster Presentation at European Hematology Association 12 June 2010. Abstract 0768. http://www.eventure-online.com/eventure/publicAbstractView.do?id=136964&congressId=3446

Responsible Party:	Genzyme, a Sanofi Company
Study ID Numbers:	CAM314 2004-000149-39 [EudraCT Number]
Health Authority:	United States: Food and Drug Administration Austria: Federal Ministry for Health and Women Bulgaria: Bulgarian Drug Agency

Canada: Health Canada
Croatia: Ministry of Health and Social Care
Czech Republic: State Institute for Drug Control
France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)
Germany: Federal Institute for Drugs and Medical Devices
Greece: National Organization of Medicines
Italy: Ministry of Health
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal: National Pharmacy and Medicines Institute
Romania: National Medicines Agency
Russia: Ministry of Health of the Russian Federation
Sweden: Medical Products Agency
Ukraine: State Pharmacological Center - Ministry of Health

Study Results

Participant Flow

Pre-Assignment Details	Treatment was from initiation of study drug(s) to 4 weeks after last administration of study drug. Follow-up was for those without disease progression and ended upon disease progression or primary endpoint analysis whichever came first. Observation included those with disease progression who were observed for alternative rx and overall survival.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Treatment Period

	Combination Arm (FluCAM)	Fludarabine Alone
Started	168	167
Safety Population	164 [1]	165 [2]
Completed	103 [3]	107 [4]

	Combination Arm (FluCAM)	Fludarabine Alone
Not Completed	65	60
Disease progression	9	8
Unable to comply with protocol	3	1
Withdrawal by Subject	7	8
Physician Decision	13	7
AE - not treatment related	7	7
Toxicity - treatment related	15	15
Anemia or thrombocytopenia	1	4
Death	5	7
Not specified	5	3

[1] Four participants did not receive treatment
[2] Two participants did not receive treatment
[3] Finished 6 cycles of study drugs
[4] Finished 6 cycles of study drug

Follow-up Period

	Combination Arm (FluCAM)	Fludarabine Alone
Started	141	137
Completed	37	18
Not Completed	104	119
Disease progression	72	99
Unable to comply with protocol	5	0
Withdrawal by Subject	6	6
Physician Decision	0	1
AE - not related	1	0
Death	13	7
Not specified	7	6

Observation Period

	Combination Arm (FluCAM)	Fludarabine Alone
Started	95	121
Completed	49	56
Not Completed	46	65
Unable to comply with protocol	1	1
Withdrawal by Subject	4	2
Death	33	55
Not specified	8	7

Baseline Characteristics

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Baseline Measures

	Combination Arm (FluCAM)	Fludarabine Alone	Total
Number of Participants	168	167	335
Age, Continuous [units: years] Mean (Standard Deviation)	60.0 (9.25)	60.8 (9.34)	60.4 (9.29)
Gender, Male/Female [units: participants]			
Female	59	59	118
Male	109	108	217
Race/Ethnicity, Customized [units: participants]			
White	167	167	334

	Combination Arm (FluCAM)	Fludarabine Alone	Total
Other	1	0	1
Height [units: centimeters] Mean (Standard Deviation)	169.0 (8.88)	169.4 (9.30)	169.2 (9.08)
Body Surface Area (BSA) [units: meters^2] Mean (Standard Deviation)	1.87 (0.213)	1.90 (0.218)	1.88 (0.216)
Maximum Lymph Node Size [1] [units: participants]			
<5 centimeters	134	136	270
>= 5 centimeters	34	31	65
World Health Organization (WHO) Performance Status [2] [units: participants]			
WHO Performance Status = 0	81	72	153
WHO Performance Status = 1	87	95	182
Rai Stage Group [3] [units: participants]			
Rai Stage 0	2	2	4
Rai Stage I - II	104	102	206
Rai Stage III - IV	62	63	125
Binet Stage [4] [units: participants]			
Binet Stage A	27	25	52
Binet Stage B	89	89	178
Binet Stage C	52	53	105
Disease Status [5] [units: participants]			
Relapsed	101	101	202
Refractory	67	66	133

	Combination Arm (FluCAM)	Fludarabine Alone	Total
Summary of Prior Therapy by Type of Therapy [6] [units: participants]			
Fludarabine-containing therapy	25	26	51
Non-fludarabine-containing therapy	143	141	284

[1] The number of participants whose largest lymph node by physical exam assessment during a baseline visit fell within two categories: <5 cm and >=5 cm. If there is no enlarged lymph node, then size is classified as <5 cm.

[2] Per protocol, all participants had a WHO performance status of 0 or 1. A WHO performance status of 0 is defined as "patient is able to carry out all normal activity without restriction," and status of 1 is "patient is ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours."

[3] Rai staging is a way to categorize the disease progression of chronic lymphocytic leukemia (CLL); higher stages reflect increasing severity.

Rai Stage 0: Lymphocytosis only, Rai Stage I: Lymphocytosis with lymphadenopathy, Rai Stage II: Lymphocytosis with hepatomegaly or splenomegaly, Rai Stage III: Lymphocytosis with anemia, Rai Stage IV: Lymphocytosis with thrombocytopenia.

Per protocol, the 4 participants with Rai Stage 0 were eligible for the study because they had Binet Stage A.

[4] Binet staging classifies CLL according to the number of lymphoid tissues involved, as well as the presence of low red blood cell count (anemia) or low number of blood platelets (thrombocytopenia).

Binet Stage A: fewer than three areas of enlarged lymphoid tissue. Enlarged lymph nodes of the neck, underarms, and groin, as well as the spleen, are each considered "one group," whether unilateral (one-sided) or bilateral (on both sides).

Binet Stage B: more than three areas of enlarged lymphoid tissue.

Binet Stage C: anemia plus thrombocytopenia (platelets <100 x 10^3/dL).

[5] Count of participants with refractory or relapsed disease at baseline (as reported by the investigator).

[6] Count of participants who had prior therapy categorized by type of therapy: fludarabine-containing therapy or non-fludarabine-containing therapy.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) Assessment

Measure Description	Progression-free survival was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease (PD) as determined by the treatment-blinded IRRP, or death due to any cause. Results are expressed in months.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	167
Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) Assessment [units: months] Median (95% Confidence Interval)	23.65 (19.180 to 28.360)	16.48 (12.500 to 21.220)

Statistical Analysis 1 for Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) Assessment

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]

	Method	Regression, Cox
	Comments	Cox proportional hazards model was stratified by Rai Stage Group

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.610
	Confidence Interval	(2-Sided) 95% 0.467 to 0.795
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Participant Best Response to Treatment Assessed by the Independent Response Review Panel (IRRP)
Measure Description	Participants were evaluated by the IRRP according to National Cancer Institute (NCI) 1996 response criteria. The best response observed during the study is summarized. Response categories include Complete Response (CR) with normal physical exam, marrow cells and blood values, Partial Response (PR) with a >= 50% decrease from baseline in lymphocytes, lymphadenopathy and liver or spleen exam, Stable Disease (SD) without significant progression from baseline, or Progressive Disease (PD) with increased size/number of nodes, size of liver or spleen, increase in lymphocytes, aggressive histology.
Time Frame	Up to 9 months
Safety Issue?	No

Analysis Population Description
Full analysis set

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	167
Participant Best Response to Treatment Assessed by the Independent Response Review Panel (IRRP)		

	Combination Arm (FluCAM)	Fludarabine Alone
[units: participants]		
Overall Response (CR+PR)	137	126
Complete Response (CR)	21	7
Partial Response (PR)	116	119
Progressive Disease (PD)	6	9
Stable Disease (SD)	12	21
Not Evaluable (NE)	13	11

Statistical Analysis 1 for Participant Best Response to Treatment Assessed by the Independent Response Review Panel (IRRP)

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	Comparison of Overall Response.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.178
	Comments	P-value presented is adjusted for multiple tests using Hochberg procedure for 3 clinically important secondary endpoints: ORR, CR rates and OS.
	Method	Cochran-Mantel-Haenszel
	Comments	CMH chi-square test for a difference in overall response rates between treatments stratified by Rai Stage Group.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.06
	Confidence Interval	(2-Sided) 95% -0.03 to 0.15
	Estimation Comments	Difference and confidence interval (CI) calculated using the recommended method by Altman et al.

Statistical Analysis 2 for Participant Best Response to Treatment Assessed by the Independent Response Review Panel (IRRP)

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	Comparison of complete response (CR).
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.018
	Comments	P-value presented is adjusted for multiple tests using Hochberg procedure for 3 clinically important secondary endpoints: ORR, CR rates and OS.
	Method	Cochran-Mantel-Haenszel
	Comments	CMH chi-square test for a difference in complete response rates between treatments stratified by Rai Stage Group.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.08
	Confidence Interval	(2-Sided) 95% 0.02 to 0.15
	Estimation Comments	Difference and confidence interval (CI) calculated using the recommended method by Altman et al.

3. Secondary Outcome Measure:

Measure Title	Kaplan-Meier Estimates of Overall Survival Time
Measure Description	Overall survival was defined as the time in days from the date of randomization to the date of death due to any cause plus 1 day for all participants. Results are stated in months.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	167
Kaplan-Meier Estimates of Overall Survival Time [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]	52.93 (40.890 to NA) [1]

[1] NA = values were not calculable since there were not enough events for the statistical estimation, ie, few participants died

Statistical Analysis 1 for Kaplan-Meier Estimates of Overall Survival Time

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.042
	Comments	P-value presented is adjusted for multiple tests using Hochberg procedure for 3 clinically important secondary endpoints: ORR, CR rates and OS.
	Method	Regression, Cox
	Comments	Cox proportional hazards model stratified by Rai Stage Group

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.648
	Confidence Interval	(2-Sided) 95% 0.449 to 0.937
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Kaplan Meier Estimates for Time to Disease Progression Assessed by the Independent Response Review Panel (IRRP)
Measure Description	Time to disease progression was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease as determined by IRRP. Results are stated in months.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	167
Kaplan Meier Estimates for Time to Disease Progression Assessed by the Independent Response Review Panel (IRRP) [units: months] Median (95% Confidence Interval)	27.96 (22.340 to 31.910)	18.68 (14.510 to 23.220)

Statistical Analysis 1 for Kaplan Meier Estimates for Time to Disease Progression Assessed by the Independent Response Review Panel (IRRP)

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Regression, Cox
	Comments	Cox regression model stratified by Rai Stage Group.

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.562
	Confidence Interval	(2-Sided) 95% 0.420 to 0.752
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Kaplan-Meier Estimates for Duration of Response Assessed by the Independent Response Review Panel (IRRP)
Measure Description	Duration of response was analyzed for participants who achieved a complete response (CR) or partial response (PR) and was defined as the number of days from the first date of documented response to the date of progressive disease as determined by IRRP or death due to any cause. Results are stated in months.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set of participants who achieved a complete response or a partial response as determined by the IRRP.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	135	124

	Combination Arm (FluCAM)	Fludarabine Alone
Kaplan-Meier Estimates for Duration of Response Assessed by the Independent Response Review Panel (IRRP) [units: months] Median (95% Confidence Interval)	25.10 (20.200 to 29.280)	19.14 (14.140 to 21.910)

6. Secondary Outcome Measure:

Measure Title	Kaplan-Meier Estimates for Time to Alternative Therapy
Measure Description	Time to alternative therapy was defined as the number of days from the date of randomization to the date of first alternative therapy for chronic lymphocytic leukemia (CLL) or death resulting from any cause. Participants who had not received alternative therapy as of the data cutoff date were censored at the last follow-up visit assessment date plus 1 day. Results are stated in months.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	167
Kaplan-Meier Estimates for Time to Alternative Therapy [units: months] Median (95% Confidence Interval)	25.43 (20.130 to 41.810)	22.01 (20.130 to 27.830)

Statistical Analysis 1 for Kaplan-Meier Estimates for Time to Alternative Therapy

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.021
	Comments	[Not specified]
	Method	Regression, Cox
	Comments	Cox proportional hazards model stratified by Rai Stage Group.

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.718
	Confidence Interval	(2-Sided) 95% 0.543 to 0.951
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Mean EQ-5D™ Index Scores to Measure Quality of Life at Baseline
Measure Description	EQ-5D™ is a trademark of the EuroQol Group. EQ-5D™ is a standardized instrument for use as a measure of health outcome. The questionnaire asks about health status along 5 dimensions: mobility, self care, usual activities, pain/ discomfort, and anxiety/depression, which are rated at three possible levels (no problems, some problems, extreme problems). The score ranges from best (+1) to worst (-0.59).
Time Frame	Day 0 (baseline)
Safety Issue?	No

Analysis Population Description

Full analysis dataset. Participants who provided valid answers on questionnaires are included.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	164
Mean EQ-5D™ Index Scores to Measure Quality of Life at Baseline [units: units on a scale] Mean (Standard Deviation)	0.7959 (0.1868)	0.7822 (0.2023)

8. Secondary Outcome Measure:

Measure Title	Mean EQ-5D™ Index Scores to Measure Quality of Life at End of Treatment
Measure Description	EQ-5D™ is a trademark of the EuroQol Group. EQ-5D™ is a standardized instrument for use as a measure of health outcome. The questionnaire asks about health status along 5 dimensions: mobility, self care, usual activities, pain/ discomfort, and anxiety/depression, which are rated at three possible levels (no problems, some problems, extreme problems). The score ranges from best (+1) to worst (-0.59).
Time Frame	up to month 6 (end of treatment)
Safety Issue?	No

Analysis Population Description

Full analysis dataset. Participants who provided valid answers on questionnaires are included.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	152	147
Mean EQ-5D™ Index Scores to Measure Quality of Life at End of Treatment [units: units on a scale] Mean (Standard Deviation)	0.8049 (0.2752)	0.7749 (0.2569)

9. Secondary Outcome Measure:

Measure Title	Mean EuroQol Visual Analogue Scale (EQ-VAS) Scores to Measure Quality of Life at Baseline
Measure Description	The EuroQol Visual Analogue Scale (EQ-VAS) was also used to capture the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.
Time Frame	Day 0 (baseline)
Safety Issue?	No

Analysis Population Description

Full analysis set. Participants who provided valid answers on questionnaires are included.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	167	161
Mean EuroQol Visual Analogue Scale (EQ-VAS) Scores to Measure Quality of Life at Baseline [units: units on a scale] Mean (Standard Deviation)	70.9 (18.01)	70.2 (17.24)

10. Secondary Outcome Measure:

Measure Title	Mean EuroQol Visual Analogue Scale (EQ-VAS) Scores to Measure Quality of Life at End of Treatment
Measure Description	The EuroQol Visual Analogue Scale (EQ-VAS) was also used to capture the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.
Time Frame	up to month 6 (end of treatment)
Safety Issue?	No

Analysis Population Description

Full analysis set. Participants who provided valid answers on questionnaires are included.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	152	146
Mean EuroQol Visual Analogue Scale (EQ-VAS) Scores to Measure Quality of Life at End of Treatment [units: units on a scale] Mean (Standard Deviation)	77.1 (19.41)	75.7 (17.98)

11. Secondary Outcome Measure:

Measure Title	Summary of Participants With Adverse Experiences (AEs)

Measure Description	Number of participants with adverse events (AEs). AEs were graded by the investigator using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and were assessed for relatedness to study treatment (4 point scale from 'not related' to 'definitely related'). Categories reported include participant counts for treatment-emergent AEs, AEs for infections, serious AEs, AEs causing discontinuation of study drug(s), and deaths. Related AEs for the combination arm can be related to either fludarabine or alemtuzumab.
Time Frame	Up to 6 years
Safety Issue?	Yes

Analysis Population Description

Safety population

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	164	165
Summary of Participants With Adverse Experiences (AEs) [units: participants]		
At least 1 treatment emergent AE	161	149
At least 1 related treatment emergent AE	159	125
At least 1 treatment-emergent infection	67	58
At least 1 drug-related infection	44	30
At least 1 serious AE	54	41
At least 1 related serious AE	47	28
Discontinuation of study drug due to AE	37	32
Discontinuation of study drug due to related AE	32	24
Deaths	10	12

	Combination Arm (FluCAM)	Fludarabine Alone
Patients who died due to a related AE	7	6
Patients who died within 30 days of the last dose	4	7

12. Secondary Outcome Measure:

Measure Title	Mean Systemic Clearance (CL) of Fludarabine
Measure Description	Clearance of drug from plasma is affected by the absorption, distribution, metabolism and elimination of the drug. Mean systemic clearance of fludarabine is derived from plasma concentration versus time data.
Time Frame	month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)
Safety Issue?	No

Analysis Population Description

Pharmacokinetic population

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	17	12
Mean Systemic Clearance (CL) of Fludarabine [units: liters/hour] Mean (Standard Deviation)	9.46 (4.31)	9.54 (3.10)

13. Secondary Outcome Measure:

Measure Title	Total Volume of Distribution (Vss) of Fludarabine
Measure Description	The total volume of distribution (Vss) is the apparent volume in which fludarabine is distributed immediately after it has been injected intravenously and equilibrated between plasma and the surrounding tissues. Total volume of distribution (Vss) of fludarabine is derived from plasma concentration versus time data.
Time Frame	month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)
Safety Issue?	No

Analysis Population Description
Pharmacokinetic population

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	17	12
Total Volume of Distribution (Vss) of Fludarabine [units: liters] Mean (Standard Deviation)	117 (64.3)	172 (91.3)

14. Secondary Outcome Measure:

Measure Title	Area Under the Curve (AUC) of Fludarabine From (AUC 0-tau)
Measure Description	AUC (0-tau) is the area under the plasma concentration curve for fludarabine over the dosage interval (tau).
Time Frame	month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)
Safety Issue?	No

Analysis Population Description
Pharmacokinetic population

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	17	12
Area Under the Curve (AUC) of Fludarabine From (AUC 0-tau) [units: ng*h/mL] Mean (Standard Deviation)	8203 (6531)	5669 (3888)

15. Secondary Outcome Measure:

Measure Title	Maximum Plasma Concentration (Cmax) of Fludarabine
Measure Description	Cmax is the maximum plasma concentration of fludarabine observed.
Time Frame	month 4 (cycle 4): first day of dosing (pre-dose, 0.5 hr end of infusion), second day of dosing (pre-dose, 0.5 hr end of infusion), third day of dosing (pre-dose, 0.25 hr, 0.5 hr end of infusion, 1,2,3,4,6,24,48,72 hr after start of fludarabine infusion)
Safety Issue?	No

Analysis Population Description
Pharmacokinetic population

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.

	Description
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	17	12
Maximum Plasma Concentration (Cmax) of Fludarabine [units: ng/mL] Mean (Standard Deviation)	4084 (6089)	1847 (1637)

16. Secondary Outcome Measure:

Measure Title	Participants With Minimal Residual Disease (MRD)
Measure Description	MRD negativity in this report was defined by the absence of tumor cells in bone marrow, using 4-color flow cytometry. MRD was assessed in participants with a clinical complete response (CR) or partial response (PR) without recovery of blood counts. MRD represents a very positive outcome.
Time Frame	up to 9 months
Safety Issue?	No

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	168	167

	Combination Arm (FluCAM)	Fludarabine Alone
Participants With Minimal Residual Disease (MRD) [units: participants]	6	0

Statistical Analysis 1 for Participants With Minimal Residual Disease (MRD)

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.014
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	CMH chi-square test for a difference in response rates between treatments stratified by Rai Stage Group.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.04
	Confidence Interval	(2-Sided) 95% 0.01 to 0.08
	Estimation Comments	[Not specified]

17. Other Pre-specified Outcome Measure:

Measure Title	Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage I-II
Measure Description	Progression-free survival was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease (PD) as determined by the treatment-blinded IRRP, or death due to any cause. Results are expressed in months and include participants with Rai stage I or II.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set of participants with Rai stage I or II

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	104	102
Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage I-II [units: months] Median (95% Confidence Interval)	23.75 (19.970 to 29.700)	20.76 (14.700 to 24.340)

Statistical Analysis 1 for Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage I-II

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.102
	Comments	[Not specified]
	Method	Regression, Cox
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.750

	Confidence Interval	(2-Sided) 95% 0.531 to 1.059
	Estimation Comments	[Not specified]

18. Other Pre-specified Outcome Measure:

Measure Title	Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage III-IV
Measure Description	Progression-free survival was defined as the number of days from the date of randomization to the date of first objective documentation of progressive disease (PD) as determined by the treatment-blinded IRRP, or death due to any cause. Results are expressed in months and include participants with Rai stage III or IV.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set of participants with Rai stage III or IV

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	62	63
Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage III-IV [units: months] Median (95% Confidence Interval)	20.53 (14.310 to 31.910)	11.51 (8.980 to 14.670)

Statistical Analysis 1 for Kaplan-Meier Estimates for Progression-free Survival (PFS) Based on Independent Response Review Panel (IRRP) for Participants With Rai Stage III-IV

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Regression, Cox
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.443
	Confidence Interval	(2-Sided) 95% 0.292 to 0.671
	Estimation Comments	[Not specified]

19. Other Pre-specified Outcome Measure:

Measure Title	Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage I-II
Measure Description	Overall survival was defined as the time in days from the date of randomization to the date of death due to any cause plus 1 day for all participants. Results are stated in months and include participants with Rai Stage I or II.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set of participants with Rai Stage I or II

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.

	Description
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	104	102
Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage I-II [units: months] Median (95% Confidence Interval)	NA (58.420 to NA) [1]	NA (57.430 to NA) [1]

[1] NA=values were not calculable since there were not enough events for the statistical estimation, ie, few participants died

Statistical Analysis 1 for Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage I-II

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.819
	Comments	[Not specified]
	Method	Regression, Cox
	Comments	Cox proportional hazards model

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	1.066
	Confidence Interval	(2-Sided) 95% 0.619 to 1.836
	Estimation Comments	[Not specified]

20. Other Pre-specified Outcome Measure:

Measure Title	Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage III-IV

Measure Description	Overall survival was defined as the time in days from the date of randomization to the date of death due to any cause plus 1 day for all participants. Results are stated in months and include participants with Rai Stage III or IV.
Time Frame	Up to 6 years
Safety Issue?	No

Analysis Population Description

Full analysis set of participants with Rai Stage III or IV

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Measured Values

	Combination Arm (FluCAM)	Fludarabine Alone
Number of Participants Analyzed	62	63
Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage III-IV [units: months] Median (95% Confidence Interval)	NA (32.140 to NA) [1]	23.52 (17.760 to 40.300)

[1] NA=values were not calculable since there were not enough events for the statistical estimation, ie, few participants died

Statistical Analysis 1 for Kaplan-Meier Estimates of Overall Survival Time for Participants With Rai Stage III-IV

Statistical Analysis Overview	Comparison Groups	Combination Arm (FluCAM), Fludarabine Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Regression, Cox

	Comments	Cox proportional hazards model

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.416
	Confidence Interval	(2-Sided) 95% 0.250 to 0.690
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	Up to 6 years
Additional Description	In the event a single participant has experienced both a serious and a non-serious form of the same adverse event term, the individual has been included in the numerator ("number of affected participants") of both adverse event tables.

Reporting Groups

	Description
Combination Arm (FluCAM)	Participants received both fludarabine (Fludara) and alemtuzumab (Campath) intravenously. Initial escalation of alemtuzumab from 3 to 30 mg (escalation can take up to 14 days). Up to six cycles of fludarabine 30 mg/m^2 intravenous (IV) followed by alemtuzumab 30 mg IV on the first 3 days of each 28 day cycle.
Fludarabine Alone	Participants received fludarabine monotherapy 25 mg/m^2 IV daily for the first 5 days of each 28 day cycle for up to 6 cycles.

Serious Adverse Events

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	54/164 (32.93%)	41/165 (24.85%)
Blood and lymphatic system disorders		
Anaemia [A] †	1/164 (0.61%)	6/165 (3.64%)
Anaemia haemolytic autoimmune [A] †	2/164 (1.22%)	2/165 (1.21%)
Autoimmune neutropenia [A] †	1/164 (0.61%)	0/165 (0%)
Autoimmune thrombocytopenia [A] †	0/164 (0%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Disseminated intravascular coagulation [A] †	0/164 (0%)	1/165 (0.61%)
Febrile neutropenia [A] †	5/164 (3.05%)	7/165 (4.24%)
Haemolytic anaemia [A] †	0/164 (0%)	2/165 (1.21%)
Haemolytic uraemic syndrome [A] †	0/164 (0%)	1/165 (0.61%)
Leukopenia [A] †	4/164 (2.44%)	1/165 (0.61%)
Neutropenia [A] †	8/164 (4.88%)	2/165 (1.21%)
Pancytopenia [A] †	2/164 (1.22%)	1/165 (0.61%)
Thrombocytopenia [A] †	5/164 (3.05%)	1/165 (0.61%)
Cardiac disorders		
Acute myocardial infarction [A] †	0/164 (0%)	1/165 (0.61%)
Angina pectoris [A] †	1/164 (0.61%)	0/165 (0%)
Cardiac arrest [A] †	1/164 (0.61%)	0/165 (0%)
Cardiac failure [A] †	0/164 (0%)	2/165 (1.21%)
Cardiogenic shock [A] †	0/164 (0%)	1/165 (0.61%)
Cardiopulmonary failure [A] †	1/164 (0.61%)	0/165 (0%)
Cardiovascular insufficiency [A] †	1/164 (0.61%)	2/165 (1.21%)
Left ventricular dysfunction [A] †	1/164 (0.61%)	0/165 (0%)
Pericardial effusion [A] †	1/164 (0.61%)	0/165 (0%)
Supraventricular tachycardia [A] †	1/164 (0.61%)	1/165 (0.61%)
Eye disorders		
Retinopathy [A] †	0/164 (0%)	1/165 (0.61%)
Gastrointestinal disorders		

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Anal fistula [A] †	0/164 (0%)	1/165 (0.61%)
Colitis [A] †	1/164 (0.61%)	0/165 (0%)
Diarrhoea [A] †	4/164 (2.44%)	0/165 (0%)
Enterocolitis [A] †	1/164 (0.61%)	0/165 (0%)
Femoral hernia, obstructive [A] †	1/164 (0.61%)	0/165 (0%)
Gastritis [A] †	1/164 (0.61%)	0/165 (0%)
Gastrointestinal hypermotility [A] †	1/164 (0.61%)	0/165 (0%)
Lower gastrointestinal haemorrhage [A] †	0/164 (0%)	1/165 (0.61%)
Nausea [A] †	1/164 (0.61%)	0/165 (0%)
Pancreatitis acute [A] †	1/164 (0.61%)	0/165 (0%)
Umbilical hernia [A] †	0/164 (0%)	1/165 (0.61%)
Vomiting [A] †	2/164 (1.22%)	0/165 (0%)
General disorders		
Fatigue [A] †	1/164 (0.61%)	0/165 (0%)
Infusion related reaction [A] †	3/164 (1.83%)	0/165 (0%)
Mucosal inflammation [A] †	1/164 (0.61%)	0/165 (0%)
Multi-organ failure [A] †	0/164 (0%)	1/165 (0.61%)
Pyrexia [A] †	5/164 (3.05%)	1/165 (0.61%)
Sudden cardiac death [A] †	0/164 (0%)	1/165 (0.61%)
Hepatobiliary disorders		
Hepatic failure [A] †	0/164 (0%)	1/165 (0.61%)
Hepatitis [A] †	1/164 (0.61%)	0/165 (0%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Hepatitis cholestatic [A] †	1/164 (0.61%)	0/165 (0%)
Hepatitis toxic [A] †	1/164 (0.61%)	0/165 (0%)
Hepatotoxicity [A] †	1/164 (0.61%)	0/165 (0%)
Immune system disorders		
Hypogammaglobulinaemia [A] †	1/164 (0.61%)	0/165 (0%)
Infections and infestations		
Bronchitis [A] †	3/164 (1.83%)	0/165 (0%)
Cellulitis [A] †	0/164 (0%)	1/165 (0.61%)
Cytomegalovirus infection [A] †	2/164 (1.22%)	0/165 (0%)
Erysipelas [A] †	0/164 (0%)	1/165 (0.61%)
Eye infection toxoplasmal [A] †	1/164 (0.61%)	0/165 (0%)
Fungaemia [A] †	0/164 (0%)	1/165 (0.61%)
Gastroenteritis escherichia coli [A] †	0/164 (0%)	1/165 (0.61%)
Hepatitis c [A] †	1/164 (0.61%)	0/165 (0%)
Herpes simplex [A] †	0/164 (0%)	1/165 (0.61%)
Herpes zoster [A] †	1/164 (0.61%)	0/165 (0%)
Infection [A] †	0/164 (0%)	1/165 (0.61%)
Oral fungal infection [A] †	0/164 (0%)	1/165 (0.61%)
Orchitis [A] †	0/164 (0%)	1/165 (0.61%)
Oropharyngeal candidiasis [A] †	1/164 (0.61%)	0/165 (0%)
Peritonsillar abscess [A] †	1/164 (0.61%)	0/165 (0%)
Pharyngitis [A] †	2/164 (1.22%)	0/165 (0%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Pharyngitis bacterial [A] †	0/164 (0%)	1/165 (0.61%)
Pneumococcal sepsis [A] †	0/164 (0%)	1/165 (0.61%)
Pneumocystis jiroveci infection [A] †	1/164 (0.61%)	0/165 (0%)
Pneumocystis jiroveci pneumonia [A] †	1/164 (0.61%)	0/165 (0%)
Pneumonia [A] †	5/164 (3.05%)	1/165 (0.61%)
Pneumonia bacterial [A] †	0/164 (0%)	1/165 (0.61%)
Pneumonia fungal [A] †	1/164 (0.61%)	2/165 (1.21%)
Pneumonia streptococcal [A] †	0/164 (0%)	1/165 (0.61%)
Pyelonephritis acute [A] †	1/164 (0.61%)	1/165 (0.61%)
Respiratory tract infection [A] †	0/164 (0%)	1/165 (0.61%)
Salmonella sepsis [A] †	1/164 (0.61%)	0/165 (0%)
Sepsis [A] †	0/164 (0%)	2/165 (1.21%)
Septic shock [A] †	0/164 (0%)	1/165 (0.61%)
Sinusitis [A] †	1/164 (0.61%)	1/165 (0.61%)
Tonsillitis [A] †	1/164 (0.61%)	0/165 (0%)
Tuberculosis [A] †	1/164 (0.61%)	0/165 (0%)
Investigations		
Cd4 lymphocytes decreased [A] †	1/164 (0.61%)	0/165 (0%)
Cytomegalovirus test positive [A] †	3/164 (1.83%)	0/165 (0%)
Pneumocystis test positive [A] †	1/164 (0.61%)	0/165 (0%)
Transaminases increased [A] †	1/164 (0.61%)	0/165 (0%)
Metabolism and nutrition disorders		

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Dehydration [A] †	1/164 (0.61%)	0/165 (0%)
Hypokalaemia [A] †	1/164 (0.61%)	0/165 (0%)
Tumour lysis syndrome [A] †	1/164 (0.61%)	0/165 (0%)
Musculoskeletal and connective tissue disorders		
Osteochondrosis [A] †	0/164 (0%)	1/165 (0.61%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Adenocarcinoma [A] †	0/164 (0%)	1/165 (0.61%)
Chronic lymphocytic leukaemia transformation [A] †	2/164 (1.22%)	0/165 (0%)
Gastric cancer [A] †	1/164 (0.61%)	0/165 (0%)
Hodgkin's disease [A] †	1/164 (0.61%)	0/165 (0%)
Malignant melanoma [A] †	0/164 (0%)	1/165 (0.61%)
Malignant peritoneal neoplasm [A] †	0/164 (0%)	1/165 (0.61%)
Malignant pleural effusion [A] †	1/164 (0.61%)	1/165 (0.61%)
Neuroendocrine carcinoma of the skin [A] †	0/164 (0%)	1/165 (0.61%)
Rectosigmoid cancer [A] †	0/164 (0%)	1/165 (0.61%)
Nervous system disorders		
Brain oedema [A] †	0/164 (0%)	1/165 (0.61%)
Cerebrovascular accident [A] †	0/164 (0%)	1/165 (0.61%)
Coma hepatic [A] †	1/164 (0.61%)	0/165 (0%)
Ischaemic cerebral infarction [A] †	0/164 (0%)	1/165 (0.61%)
Neuropathy peripheral [A] †	1/164 (0.61%)	0/165 (0%)
Peripheral sensory neuropathy [A] †	0/164 (0%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Radicular pain [A] †	1/164 (0.61%)	0/165 (0%)
Renal and urinary disorders		
Calculus urinary [A] †	1/164 (0.61%)	0/165 (0%)
Cystitis haemorrhagic [A] †	0/164 (0%)	1/165 (0.61%)
Nephrolithiasis [A] †	1/164 (0.61%)	0/165 (0%)
Renal failure [A] †	1/164 (0.61%)	0/165 (0%)
Renal failure acute [A] †	0/164 (0%)	1/165 (0.61%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] †	1/164 (0.61%)	0/165 (0%)
Acute respiratory failure [A] †	0/164 (0%)	1/165 (0.61%)
Bronchospasm [A] †	1/164 (0.61%)	0/165 (0%)
Chronic obstructive pulmonary disease [A] †	0/164 (0%)	1/165 (0.61%)
Pulmonary oedema [A] †	0/164 (0%)	1/165 (0.61%)
Skin and subcutaneous tissue disorders		
Dermatitis allergic [A] †	1/164 (0.61%)	0/165 (0%)
Dermatitis exfoliative [A] †	1/164 (0.61%)	0/165 (0%)
Pruritus [A] †	1/164 (0.61%)	0/165 (0%)
Urticaria [A] †	2/164 (1.22%)	0/165 (0%)
Vascular disorders		
Deep vein thrombosis [A] †	1/164 (0.61%)	0/165 (0%)
Hypertension [A] †	1/164 (0.61%)	0/165 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	160/164 (97.56%)	147/165 (89.09%)
Blood and lymphatic system disorders		
Anaemia [A] †	36/164 (21.95%)	39/165 (23.64%)
Autoimmune thrombocytopenia [A] †	0/164 (0%)	1/165 (0.61%)
Eosinophilia [A] †	1/164 (0.61%)	3/165 (1.82%)
Febrile neutropenia [A] †	1/164 (0.61%)	4/165 (2.42%)
Granulocytopenia [A] †	3/164 (1.83%)	1/165 (0.61%)
Haematotoxicity [A] †	0/164 (0%)	1/165 (0.61%)
Idiopathic thrombocytopenic purpura [A] †	1/164 (0.61%)	0/165 (0%)
Leukopenia [A] †	73/164 (44.51%)	25/165 (15.15%)
Lymphopenia [A] †	35/164 (21.34%)	7/165 (4.24%)
Neutropenia [A] †	82/164 (50%)	84/165 (50.91%)
Pancytopenia [A] †	0/164 (0%)	1/165 (0.61%)
Thrombocytopenia [A] †	44/164 (26.83%)	44/165 (26.67%)
Cardiac disorders		
Angina pectoris [A] †	0/164 (0%)	2/165 (1.21%)
Aortic valve calcification [A] †	1/164 (0.61%)	0/165 (0%)
Aortic valve incompetence [A] †	1/164 (0.61%)	0/165 (0%)
Arrhythmia [A] †	1/164 (0.61%)	0/165 (0%)
Arteriosclerosis coronary artery [A] †	0/164 (0%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Atrial fibrillation [A] †	1/164 (0.61%)	1/165 (0.61%)
Cardiac failure [A] †	1/164 (0.61%)	0/165 (0%)
Cardiomyopathy [A] †	0/164 (0%)	1/165 (0.61%)
Diastolic dysfunction [A] †	1/164 (0.61%)	0/165 (0%)
Hypertensive cardiomyopathy [A] †	1/164 (0.61%)	0/165 (0%)
Hypertensive heart disease [A] †	1/164 (0.61%)	0/165 (0%)
Left ventricular dysfunction [A] †	1/164 (0.61%)	0/165 (0%)
Mitral valve incompetence [A] †	1/164 (0.61%)	0/165 (0%)
Myocardial ischaemia [A] †	0/164 (0%)	1/165 (0.61%)
Palpitations [A] †	1/164 (0.61%)	3/165 (1.82%)
Pericardial effusion [A] †	2/164 (1.22%)	0/165 (0%)
Sinus tachycardia [A] †	2/164 (1.22%)	0/165 (0%)
Tachycardia [A] †	3/164 (1.83%)	0/165 (0%)
Ventricular arrhythmia [A] †	1/164 (0.61%)	0/165 (0%)
Ventricular extrasystoles [A] †	1/164 (0.61%)	0/165 (0%)
Congenital, familial and genetic disorders		
Accessory spleen [A] †	1/164 (0.61%)	0/165 (0%)
Kidney malformation [A] †	1/164 (0.61%)	0/165 (0%)
Ear and labyrinth disorders		
Deafness neurosensory [A] †	1/164 (0.61%)	1/165 (0.61%)
Hearing impaired [A] †	0/164 (0%)	1/165 (0.61%)
Tinnitus [A] †	0/164 (0%)	2/165 (1.21%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Vertigo [A] †	2/164 (1.22%)	1/165 (0.61%)
Endocrine disorders		
Goitre [A] †	2/164 (1.22%)	1/165 (0.61%)
Hypothyroidism [A] †	1/164 (0.61%)	1/165 (0.61%)
Eye disorders		
Cataract [A] †	0/164 (0%)	1/165 (0.61%)
Conjunctival haemorrhage [A] †	0/164 (0%)	1/165 (0.61%)
Conjunctivitis [A] †	1/164 (0.61%)	0/165 (0%)
Conjunctivitis allergic [A] †	1/164 (0.61%)	0/165 (0%)
Erythema of eyelid [A] †	0/164 (0%)	1/165 (0.61%)
Lacrimation increased [A] †	1/164 (0.61%)	0/165 (0%)
Retinopathy [A] †	0/164 (0%)	1/165 (0.61%)
Retinopathy hypertensive [A] †	0/164 (0%)	1/165 (0.61%)
Visual impairment [A] †	0/164 (0%)	1/165 (0.61%)
Gastrointestinal disorders		
Abdominal discomfort [A] †	1/164 (0.61%)	1/165 (0.61%)
Abdominal distension [A] †	0/164 (0%)	1/165 (0.61%)
Abdominal pain [A] †	4/164 (2.44%)	3/165 (1.82%)
Abdominal pain upper [A] †	0/164 (0%)	3/165 (1.82%)
Aphthous stomatitis [A] †	1/164 (0.61%)	0/165 (0%)
Ascites [A] †	1/164 (0.61%)	0/165 (0%)
Cheilitis [A] †	1/164 (0.61%)	0/165 (0%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Colitis [A] †	1/164 (0.61%)	0/165 (0%)
Constipation [A] †	6/164 (3.66%)	4/165 (2.42%)
Diarrhoea [A] †	15/164 (9.15%)	11/165 (6.67%)
Diverticulum intestinal [A] †	0/164 (0%)	1/165 (0.61%)
Dry mouth [A] †	1/164 (0.61%)	1/165 (0.61%)
Duodenal ulcer [A] †	0/164 (0%)	1/165 (0.61%)
Duodenitis [A] †	0/164 (0%)	1/165 (0.61%)
Dyspepsia [A] †	3/164 (1.83%)	3/165 (1.82%)
Enterocolitis [A] †	1/164 (0.61%)	0/165 (0%)
Erosive duodenitis [A] †	1/164 (0.61%)	0/165 (0%)
Flatulence [A] †	2/164 (1.22%)	3/165 (1.82%)
Gastric ulcer [A] †	1/164 (0.61%)	0/165 (0%)
Gastritis [A] †	1/164 (0.61%)	0/165 (0%)
Gastrooesophageal reflux disease [A] †	0/164 (0%)	1/165 (0.61%)
Gingival bleeding [A] †	0/164 (0%)	1/165 (0.61%)
Gingival pain [A] †	0/164 (0%)	1/165 (0.61%)
Gingivitis ulcerative [A] †	0/164 (0%)	1/165 (0.61%)
Haemorrhoids [A] †	3/164 (1.83%)	0/165 (0%)
Lower gastrointestinal haemorrhage [A] †	0/164 (0%)	1/165 (0.61%)
Nausea [A] †	20/164 (12.2%)	13/165 (7.88%)
Pancreatic disorder [A] †	0/164 (0%)	1/165 (0.61%)
Pancreatitis [A] †	3/164 (1.83%)	3/165 (1.82%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Pancreatitis acute [A] †	1/164 (0.61%)	0/165 (0%)
Periodontitis [A] †	1/164 (0.61%)	0/165 (0%)
Stomatitis [A] †	4/164 (2.44%)	0/165 (0%)
Toothache [A] †	1/164 (0.61%)	1/165 (0.61%)
Vomiting [A] †	15/164 (9.15%)	3/165 (1.82%)
General disorders		
Asthenia [A] †	4/164 (2.44%)	6/165 (3.64%)
Catheter site inflammation [A] †	1/164 (0.61%)	0/165 (0%)
Chest discomfort [A] †	1/164 (0.61%)	0/165 (0%)
Chills [A] †	49/164 (29.88%)	2/165 (1.21%)
Face oedema [A] †	0/164 (0%)	1/165 (0.61%)
Fatigue [A] †	10/164 (6.1%)	9/165 (5.45%)
Generalised oedema [A] †	1/164 (0.61%)	0/165 (0%)
Hyperpyrexia [A] †	2/164 (1.22%)	0/165 (0%)
Hyperthermia [A] †	6/164 (3.66%)	0/165 (0%)
Impaired healing [A] †	0/164 (0%)	1/165 (0.61%)
Influenza like illness [A] †	2/164 (1.22%)	0/165 (0%)
Infusion related reaction [A] †	20/164 (12.2%)	0/165 (0%)
Injection site extravasation [A] †	1/164 (0.61%)	0/165 (0%)
Injection site reaction [A] †	1/164 (0.61%)	0/165 (0%)
Localised oedema [A] †	0/164 (0%)	3/165 (1.82%)
Malaise [A] †	1/164 (0.61%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Mucosal inflammation [A] †	1/164 (0.61%)	1/165 (0.61%)
Non-cardiac chest pain [A] †	2/164 (1.22%)	0/165 (0%)
Oedema [A] †	0/164 (0%)	1/165 (0.61%)
Oedema peripheral [A] †	6/164 (3.66%)	4/165 (2.42%)
Pyrexia [A] †	96/164 (58.54%)	14/165 (8.48%)
Soft tissue inflammation [A] †	1/164 (0.61%)	0/165 (0%)
Hepatobiliary disorders		
Cholecystitis [A] †	1/164 (0.61%)	0/165 (0%)
Cholecystitis chronic [A] †	5/164 (3.05%)	2/165 (1.21%)
Cholelithiasis [A] †	0/164 (0%)	1/165 (0.61%)
Hepatic cyst [A] †	1/164 (0.61%)	0/165 (0%)
Hepatic steatosis [A] †	0/164 (0%)	1/165 (0.61%)
Hepatitis chronic active [A] †	0/164 (0%)	1/165 (0.61%)
Hepatitis toxic [A] †	1/164 (0.61%)	1/165 (0.61%)
Hepatomegaly [A] †	1/164 (0.61%)	0/165 (0%)
Hyperbilirubinaemia [A] †	4/164 (2.44%)	0/165 (0%)
Liver disorder [A] †	0/164 (0%)	1/165 (0.61%)
Immune system disorders		
Allergy to arthropod bite [A] †	1/164 (0.61%)	0/165 (0%)
Cytokine release syndrome [A] †	7/164 (4.27%)	0/165 (0%)
Drug hypersensitivity [A] †	1/164 (0.61%)	0/165 (0%)
Hypersensitivity [A] †	5/164 (3.05%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Mycotic allergy [A] †	1/164 (0.61%)	0/165 (0%)
Seasonal allergy [A] †	2/164 (1.22%)	0/165 (0%)
Infections and infestations		
Acute sinusitis [A] †	0/164 (0%)	1/165 (0.61%)
Ascariasis [A] †	1/164 (0.61%)	0/165 (0%)
Bronchitis [A] †	15/164 (9.15%)	5/165 (3.03%)
Bronchopneumonia [A] †	2/164 (1.22%)	0/165 (0%)
Bullous impetigo [A] †	0/164 (0%)	1/165 (0.61%)
Candidiasis [A] †	1/164 (0.61%)	0/165 (0%)
Conjunctivitis infective [A] †	0/164 (0%)	1/165 (0.61%)
Cystitis [A] †	1/164 (0.61%)	1/165 (0.61%)
Cytomegalovirus infection [A] †	2/164 (1.22%)	0/165 (0%)
Folliculitis [A] †	1/164 (0.61%)	0/165 (0%)
Herpes simplex [A] †	2/164 (1.22%)	1/165 (0.61%)
Herpes zoster [A] †	4/164 (2.44%)	3/165 (1.82%)
Infection [A] †	2/164 (1.22%)	0/165 (0%)
Influenza [A] †	2/164 (1.22%)	1/165 (0.61%)
Klebsiella bacteraemia [A] †	0/164 (0%)	1/165 (0.61%)
Laryngitis [A] †	1/164 (0.61%)	0/165 (0%)
Nasopharyngitis [A] †	7/164 (4.27%)	8/165 (4.85%)
Neutropenic infection [A] †	2/164 (1.22%)	1/165 (0.61%)
Oral fungal infection [A] †	1/164 (0.61%)	2/165 (1.21%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Oral herpes [A] †	3/164 (1.83%)	3/165 (1.82%)
Otitis media [A] †	1/164 (0.61%)	0/165 (0%)
Perirectal abscess [A] †	0/164 (0%)	1/165 (0.61%)
Pharyngitis [A] †	6/164 (3.66%)	5/165 (3.03%)
Pneumonia [A] †	6/164 (3.66%)	3/165 (1.82%)
Pulpitis dental [A] †	0/164 (0%)	1/165 (0.61%)
Respiratory tract infection [A] †	4/164 (2.44%)	5/165 (3.03%)
Respiratory tract infection viral [A] †	4/164 (2.44%)	2/165 (1.21%)
Rhinitis [A] †	3/164 (1.83%)	3/165 (1.82%)
Sinusitis [A] †	1/164 (0.61%)	3/165 (1.82%)
Skin candida [A] †	0/164 (0%)	1/165 (0.61%)
Staphylococcal infection [A] †	0/164 (0%)	1/165 (0.61%)
Tinea versicolour [A] †	1/164 (0.61%)	0/165 (0%)
Tonsillitis [A] †	1/164 (0.61%)	3/165 (1.82%)
Tooth infection [A] †	0/164 (0%)	1/165 (0.61%)
Tracheitis [A] †	2/164 (1.22%)	1/165 (0.61%)
Upper respiratory tract infection [A] †	3/164 (1.83%)	3/165 (1.82%)
Urinary tract infection [A] †	3/164 (1.83%)	1/165 (0.61%)
Urinary tract infection pseudomonal [A] †	0/164 (0%)	1/165 (0.61%)
Viral infection [A] †	0/164 (0%)	1/165 (0.61%)
Viral upper respiratory tract infection [A] †	3/164 (1.83%)	1/165 (0.61%)
Injury, poisoning and procedural complications		

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Arthropod bite [A] †	0/164 (0%)	1/165 (0.61%)
Injury [A] †	0/164 (0%)	1/165 (0.61%)
Joint sprain [A] †	1/164 (0.61%)	0/165 (0%)
Investigations		
Alanine aminotransferase increased [A] †	6/164 (3.66%)	5/165 (3.03%)
Aspartate aminotransferase increased [A] †	2/164 (1.22%)	2/165 (1.21%)
Beta 2 microglobulin decreased [A] †	1/164 (0.61%)	0/165 (0%)
Blood albumin decreased [A] †	0/164 (0%)	1/165 (0.61%)
Blood alkaline phosphatase increased [A] †	0/164 (0%)	1/165 (0.61%)
Blood bilirubin increased [A] †	2/164 (1.22%)	1/165 (0.61%)
Blood creatinine increased [A] †	4/164 (2.44%)	3/165 (1.82%)
Blood lactate dehydrogenase increased [A] †	3/164 (1.83%)	0/165 (0%)
Body temperature increased [A] †	2/164 (1.22%)	1/165 (0.61%)
Breath sounds abnormal [A] †	0/164 (0%)	1/165 (0.61%)
Cd4 lymphocytes decreased [A] †	4/164 (2.44%)	2/165 (1.21%)
Creatinine renal clearance decreased [A] †	5/164 (3.05%)	5/165 (3.03%)
Cytomegalovirus test positive [A] †	19/164 (11.59%)	1/165 (0.61%)
Gamma-glutamyltransferase increased [A] †	1/164 (0.61%)	2/165 (1.21%)
Haemoglobin decreased [A] †	4/164 (2.44%)	5/165 (3.03%)
Hepatic enzyme increased [A] †	0/164 (0%)	1/165 (0.61%)
Lymphocyte count decreased [A] †	2/164 (1.22%)	1/165 (0.61%)
Neutrophil count decreased [A] †	6/164 (3.66%)	7/165 (4.24%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Neutrophil pelger-huet anomaly present [A] †	1/164 (0.61%)	0/165 (0%)
Platelet count decreased [A] †	6/164 (3.66%)	10/165 (6.06%)
Urine uric acid increased [A] †	1/164 (0.61%)	0/165 (0%)
Weight decreased [A] †	2/164 (1.22%)	2/165 (1.21%)
Weight increased [A] †	1/164 (0.61%)	2/165 (1.21%)
White blood cell count decreased [A] †	7/164 (4.27%)	3/165 (1.82%)
Metabolism and nutrition disorders		
Decreased appetite [A] †	2/164 (1.22%)	1/165 (0.61%)
Dehydration [A] †	1/164 (0.61%)	0/165 (0%)
Diabetes mellitus [A] †	2/164 (1.22%)	0/165 (0%)
Fluid retention [A] †	2/164 (1.22%)	0/165 (0%)
Gout [A] †	1/164 (0.61%)	0/165 (0%)
Hyperglycaemia [A] †	3/164 (1.83%)	2/165 (1.21%)
Hyperkalaemia [A] †	0/164 (0%)	1/165 (0.61%)
Hypernatraemia [A] †	0/164 (0%)	1/165 (0.61%)
Hyperphosphataemia [A] †	0/164 (0%)	1/165 (0.61%)
Hyperproteinaemia [A] †	1/164 (0.61%)	0/165 (0%)
Hyperuricaemia [A] †	1/164 (0.61%)	4/165 (2.42%)
Hypoalbuminaemia [A] †	4/164 (2.44%)	1/165 (0.61%)
Hypokalaemia [A] †	4/164 (2.44%)	0/165 (0%)
Hypophosphataemia [A] †	1/164 (0.61%)	1/165 (0.61%)
Hypoproteinaemia [A] †	1/164 (0.61%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Tumour lysis syndrome [A] †	0/164 (0%)	2/165 (1.21%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	3/164 (1.83%)	2/165 (1.21%)
Arthritis [A] †	0/164 (0%)	1/165 (0.61%)
Arthritis reactive [A] †	0/164 (0%)	1/165 (0.61%)
Back pain [A] †	4/164 (2.44%)	3/165 (1.82%)
Bone pain [A] †	9/164 (5.49%)	0/165 (0%)
Gouty arthritis [A] †	0/164 (0%)	1/165 (0.61%)
Groin pain [A] †	0/164 (0%)	1/165 (0.61%)
Mastication disorder [A] †	1/164 (0.61%)	0/165 (0%)
Musculoskeletal pain [A] †	1/164 (0.61%)	2/165 (1.21%)
Myalgia [A] †	2/164 (1.22%)	1/165 (0.61%)
Myositis [A] †	1/164 (0.61%)	0/165 (0%)
Osteoarthritis [A] †	0/164 (0%)	1/165 (0.61%)
Osteochondrosis [A] †	3/164 (1.83%)	2/165 (1.21%)
Osteonecrosis of jaw [A] †	1/164 (0.61%)	0/165 (0%)
Pain in extremity [A] †	2/164 (1.22%)	2/165 (1.21%)
Rheumatoid arthritis [A] †	1/164 (0.61%)	0/165 (0%)
Rotator cuff syndrome [A] †	0/164 (0%)	1/165 (0.61%)
Scoliosis [A] †	0/164 (0%)	1/165 (0.61%)
Spinal deformity [A] †	1/164 (0.61%)	0/165 (0%)
Spinal osteoarthritis [A] †	1/164 (0.61%)	0/165 (0%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Adenocarcinoma [A] †	0/164 (0%)	1/165 (0.61%)
Benign lung neoplasm [A] †	1/164 (0.61%)	0/165 (0%)
Gastrointestinal carcinoma [A] †	0/164 (0%)	1/165 (0.61%)
Lipoma [A] †	1/164 (0.61%)	1/165 (0.61%)
Malignant pleural effusion [A] †	1/164 (0.61%)	1/165 (0.61%)
Metastases to liver [A] †	1/164 (0.61%)	0/165 (0%)
Paraneoplastic pemphigus [A] †	0/164 (0%)	1/165 (0.61%)
Paraproteinaemia [A] †	1/164 (0.61%)	0/165 (0%)
Seborrhoeic keratosis [A] †	1/164 (0.61%)	1/165 (0.61%)
Skin papilloma [A] †	1/164 (0.61%)	0/165 (0%)
Nervous system disorders		
Cognitive disorder [A] †	1/164 (0.61%)	0/165 (0%)
Dizziness [A] †	4/164 (2.44%)	5/165 (3.03%)
Dysaesthesia [A] †	0/164 (0%)	1/165 (0.61%)
Dysgeusia [A] †	1/164 (0.61%)	1/165 (0.61%)
Facial neuralgia [A] †	1/164 (0.61%)	0/165 (0%)
Headache [A] †	14/164 (8.54%)	4/165 (2.42%)
Hypoaesthesia [A] †	0/164 (0%)	2/165 (1.21%)
Memory impairment [A] †	1/164 (0.61%)	0/165 (0%)
Neuralgia [A] †	0/164 (0%)	1/165 (0.61%)
Neuropathy peripheral [A] †	0/164 (0%)	2/165 (1.21%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Paraesthesia [A] †	0/164 (0%)	2/165 (1.21%)
Peripheral sensory neuropathy [A] †	1/164 (0.61%)	3/165 (1.82%)
Post herpetic neuralgia [A] †	1/164 (0.61%)	0/165 (0%)
Radicular pain [A] †	1/164 (0.61%)	0/165 (0%)
Sciatica [A] †	0/164 (0%)	1/165 (0.61%)
Somnolence [A] †	0/164 (0%)	1/165 (0.61%)
Sphenopalatine neuralgia [A] †	1/164 (0.61%)	0/165 (0%)
Syncope [A] †	1/164 (0.61%)	0/165 (0%)
Toxic encephalopathy [A] †	0/164 (0%)	2/165 (1.21%)
Tremor [A] †	1/164 (0.61%)	0/165 (0%)
Psychiatric disorders		
Agitation [A] †	1/164 (0.61%)	1/165 (0.61%)
Anxiety [A] †	1/164 (0.61%)	0/165 (0%)
Confusional state [A] †	1/164 (0.61%)	0/165 (0%)
Depression [A] †	2/164 (1.22%)	1/165 (0.61%)
Disorientation [A] †	0/164 (0%)	1/165 (0.61%)
Hallucination [A] †	1/164 (0.61%)	0/165 (0%)
Insomnia [A] †	5/164 (3.05%)	2/165 (1.21%)
Sleep disorder [A] †	0/164 (0%)	1/165 (0.61%)
Renal and urinary disorders		
Calculus urinary [A] †	1/164 (0.61%)	0/165 (0%)
Chromaturia [A] †	1/164 (0.61%)	0/165 (0%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Crystalluria [A] †	1/164 (0.61%)	0/165 (0%)
Cystitis haemorrhagic [A] †	1/164 (0.61%)	0/165 (0%)
Dysuria [A] †	0/164 (0%)	1/165 (0.61%)
Leukocyturia [A] †	1/164 (0.61%)	0/165 (0%)
Nephrolithiasis [A] †	0/164 (0%)	1/165 (0.61%)
Nephroptosis [A] †	2/164 (1.22%)	0/165 (0%)
Pollakiuria [A] †	5/164 (3.05%)	3/165 (1.82%)
Renal failure [A] †	1/164 (0.61%)	0/165 (0%)
Renal failure acute [A] †	0/164 (0%)	1/165 (0.61%)
Renal impairment [A] †	2/164 (1.22%)	0/165 (0%)
Urinary retention [A] †	1/164 (0.61%)	0/165 (0%)
Reproductive system and breast disorders		
Benign prostatic hyperplasia [A] †	1/164 (0.61%)	2/165 (1.21%)
Calculus prostatic [A] †	0/164 (0%)	1/165 (0.61%)
Metrorrhagia [A] †	1/164 (0.61%)	0/165 (0%)
Vaginal haemorrhage [A] †	0/164 (0%)	1/165 (0.61%)
Respiratory, thoracic and mediastinal disorders		
Asthma [A] †	0/164 (0%)	1/165 (0.61%)
Bronchitis chronic [A] †	1/164 (0.61%)	0/165 (0%)
Bronchospasm [A] †	8/164 (4.88%)	0/165 (0%)
Cough [A] †	13/164 (7.93%)	8/165 (4.85%)
Dysphonia [A] †	1/164 (0.61%)	0/165 (0%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Dyspnoea [A] †	5/164 (3.05%)	1/165 (0.61%)
Epistaxis [A] †	1/164 (0.61%)	2/165 (1.21%)
Haemoptysis [A] †	1/164 (0.61%)	0/165 (0%)
Hiccups [A] †	3/164 (1.83%)	0/165 (0%)
Laryngeal polyp [A] †	1/164 (0.61%)	0/165 (0%)
Lung infiltration [A] †	1/164 (0.61%)	0/165 (0%)
Nasal dryness [A] †	1/164 (0.61%)	0/165 (0%)
Obstructive airways disorder [A] †	0/164 (0%)	1/165 (0.61%)
Oropharyngeal pain [A] †	0/164 (0%)	2/165 (1.21%)
Pleural effusion [A] †	3/164 (1.83%)	0/165 (0%)
Pleurisy [A] †	1/164 (0.61%)	0/165 (0%)
Pneumonitis [A] †	1/164 (0.61%)	0/165 (0%)
Pulmonary congestion [A] †	1/164 (0.61%)	0/165 (0%)
Respiratory alkalosis [A] †	0/164 (0%)	1/165 (0.61%)
Respiratory disorder [A] †	1/164 (0.61%)	1/165 (0.61%)
Respiratory failure [A] †	0/164 (0%)	1/165 (0.61%)
Sinus congestion [A] †	1/164 (0.61%)	0/165 (0%)
Throat irritation [A] †	1/164 (0.61%)	0/165 (0%)
Wheezing [A] †	0/164 (0%)	1/165 (0.61%)
Skin and subcutaneous tissue disorders		
Alopecia [A] †	1/164 (0.61%)	0/165 (0%)
Angioedema [A] †	0/164 (0%)	1/165 (0.61%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Dermatitis [A] †	1/164 (0.61%)	0/165 (0%)
Dermatitis allergic [A] †	13/164 (7.93%)	4/165 (2.42%)
Drug eruption [A] †	6/164 (3.66%)	0/165 (0%)
Dry skin [A] †	1/164 (0.61%)	0/165 (0%)
Eczema [A] †	1/164 (0.61%)	1/165 (0.61%)
Erythema [A] †	1/164 (0.61%)	3/165 (1.82%)
Exfoliative rash [A] †	1/164 (0.61%)	0/165 (0%)
Hyperhidrosis [A] †	3/164 (1.83%)	3/165 (1.82%)
Hyperkeratosis [A] †	1/164 (0.61%)	0/165 (0%)
Night sweats [A] †	2/164 (1.22%)	0/165 (0%)
Petechiae [A] †	0/164 (0%)	1/165 (0.61%)
Pruritus [A] †	13/164 (7.93%)	4/165 (2.42%)
Pruritus allergic [A] †	3/164 (1.83%)	1/165 (0.61%)
Pruritus generalised [A] †	1/164 (0.61%)	0/165 (0%)
Rash [A] †	25/164 (15.24%)	5/165 (3.03%)
Rash erythematous [A] †	1/164 (0.61%)	0/165 (0%)
Rash generalised [A] †	0/164 (0%)	1/165 (0.61%)
Rash macular [A] †	1/164 (0.61%)	0/165 (0%)
Rash maculo-papular [A] †	1/164 (0.61%)	0/165 (0%)
Rash papular [A] †	1/164 (0.61%)	0/165 (0%)
Seborrhoeic dermatitis [A] †	1/164 (0.61%)	0/165 (0%)
Skin exfoliation [A] †	0/164 (0%)	2/165 (1.21%)

	Combination Arm (FluCAM)	Fludarabine Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Skin hyperpigmentation [A] †	0/164 (0%)	2/165 (1.21%)
Skin lesion [A] †	0/164 (0%)	1/165 (0.61%)
Skin swelling [A] †	0/164 (0%)	1/165 (0.61%)
Skin ulcer [A] †	0/164 (0%)	1/165 (0.61%)
Swelling face [A] †	0/164 (0%)	1/165 (0.61%)
Urticaria [A] †	22/164 (13.41%)	4/165 (2.42%)
Urticaria vesiculosa [A] †	1/164 (0.61%)	0/165 (0%)
Vascular disorders		
Arteriosclerosis obliterans [A] †	1/164 (0.61%)	0/165 (0%)
Deep vein thrombosis [A] †	2/164 (1.22%)	0/165 (0%)
Flushing [A] †	1/164 (0.61%)	0/165 (0%)
Hot flush [A] †	1/164 (0.61%)	0/165 (0%)
Hypertension [A] †	11/164 (6.71%)	6/165 (3.64%)
Hypertensive crisis [A] †	1/164 (0.61%)	0/165 (0%)
Hypotension [A] †	3/164 (1.83%)	2/165 (1.21%)
Phlebitis [A] †	2/164 (1.22%)	0/165 (0%)
Systolic hypertension [A] †	1/164 (0.61%)	1/165 (0.61%)
Temporal arteritis [A] †	1/164 (0.61%)	0/165 (0%)
Varicose vein [A] †	1/164 (0.61%)	0/165 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.0

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.

In multi-site studies, PI can publish after an independent multi-investigator publication (in which the PI can participate) or 18 months after study completion. PI gives Genzyme a draft 60 days before publication. Genzyme can ask that confidential information be removed, and can defer publication another 60 days upon notifying PI that it will file a patent application on inventions contained in the draft.

Results Point of Contact:

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