Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplemental Appendix for

Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia

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Eligibility Criteria and Indications for Treatment

Documentation of Disease:

Patients must be diagnosed with CLL in accordance with IWCLL 2008 criteria[1] or SLL according to the WHO criteria that includes documentation of:

- Biopsy-proven small lymphocytic leukemia

OR

- $\geq 5x10^9$ lymphocytes ($5x10^9$/L) in the peripheral blood
- Immunophenotype (performed locally) consistent with CLL defined as:
    - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc).
    - Clonality as evidenced by **κ** or **λ** light chain restriction (typically dim immunoglobulin expression)
    - Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate) or negative immunohistochemical stains for cyclin D1 staining on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy.

Indication for Therapy

- Patients must meet criteria for treatment as defined by IWCLL 2008 guidelines[1] which includes at least one of the following criteria:
    - Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hg < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10^9/L) that was not attributable to autoimmune hemolytic anemia or thrombocytopenia)
    - Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
    - Constitutional symptoms attributable to CLL, which include one or more of the following disease-related symptoms:
        - Weight loss ≥ 10% within the previous 6 months
        - Grade 2 or 3 fatigue attributed to CLL
        - Fevers >100.5°F for 2 weeks without evidence of infection
        - Clinically significant night sweats without evidence of infection
    - Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months.

Prior Treatment

- Patients must not have had prior chemotherapy, BTK inhibitor therapy, or monoclonal anti-body therapy for treatment of CLL or SLL.
- No previous use of glucocorticoids for autoimmune complications that have developed since the initial diagnosis of CLL. Prior use of glucocorticoids for reasons other than treatment of autoimmune complications is allowed.
- No radiation therapy ≤ 4 weeks before registration

No current use of glucocorticoids

- EXCEPTION: Low doses of steroids (< 10 mg of prednisone or equivalent dose of other steroid) used for treatment of non-hematologic medical condition (e.g. chronic adrenal insufficiency) is permitted.

Patients must not be on any other systemic immunosuppressant therapy (other than glucocorticoids) within 28 days of the first dose of study drug

Age ≥ 18 years and ≤70 years

Eastern Cooperative Oncology Group Performance Status 0-2

Life expectancy of ≥12 months

No deletion of 17p13 on cytogenetic analysis by FISH

No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment

No other active primary malignancy (other than non-melanomatous skin cancer or carcinoma in situ of the cervix) requiring treatment or limiting expected survival to ≤2 years

- Patients who have a positive Coombs test but no evidence of hemolysis are NOT excluded from participation

Patients with HIV infection are eligible provided they meet the following criteria:

CD4-positive cell count	≥ Lower limit of institutional normal
Viral load	<10,000 copies HIV RNA/mL (if not on anti-HIV therapy) OR <50 copies HIV RNA/mL (if on anti-HIV therapy)
Hepatitis B or C	No evidence of infection
AIDS-defining condition	No history of an AIDS-defining condition

Women must not be pregnant or breast-feeding

- Women must not be pregnant or breast-feeding since this study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown.
- Female patients of childbearing potential must have a negative serum pregnancy test within 2 weeks before registration to rule out pregnancy.

Women of childbearing potential and sexually active males

Must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for 90 days after the last dose of study drug

Other conditions

Patients must not have any of the following conditions:

- Congestive heart failure or New York Heart Association Functional Classification III or IV congestive heart failure
- History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months before registration.
- Recent infections requiring systemic treatment; need to have completed anti-biotic therapy >14 days before the first dose of study drug.
- Cerebral vascular accident or intracranial bleed within the last 6 months
- Infection with known chronic, active hepatitis C.
- Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) before enrollment (PCR positive patients will be excluded).
- Patients with any known bleeding disorders (e.g. von Willebrand's disease) or hemophilia.
- Patient must not have currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the NCI/Child Pugh classification

Active systemic anticoagulation

Patients must not be receiving active systemic anticoagulation with warfarin. Patients must be off warfarin therapy for at least 30 days before enrollment.

Patients must not be vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.

CYP3A4/5 inhibitor or inducer

Patients must not have continued requirement for treatment with a strong CYP3A inhibitor.

Prior Surgery

Patients may not have had major surgery within 4 week (28 days) of the first dose of the study drug or minor surgery within 3 days of first dose of study drug

Patients must not be on any other investigational agents

Initial laboratory values

Patients must meet the following required initial laboratory values obtained ≤14 days before registration:

AST or ALT	≤ 3.0 x upper limits of normal
Bilirubin	≤ 2.5 x upper limits of normal (unless due to Gilbert's disease). For those with a total bilirubin >2.5 x upper limit of normal, a direct bilirubin should be performed and must be <1.5 mg/dL for Gilbert's to be diagnosed
Creatinine Clearance	>40 mL/min*
PT/INR	<1.5 x upper limits of normal
PTT (aPTT)	<1.5 x upper limits of normal

* To be calculated by modified Cockcroft-Gault formula as follows:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age in years}) \times \text{actual wt (in kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad \times .85 \text{ (for female patients)}$$

Ability to tolerate FCR based therapy

Ability to swallow capsules

- Patients must be able to swallow capsules and not have the following conditions:
    - Disease significantly affecting gastrointestinal function
    - Prior resection of the stomach or small bowel
    - Symptomatic inflammatory bowel disease
    - Ulcerative colitis
    - Partial or complete bowel obstruction

Ability to adhere to the study visit schedule and other protocol requirements

Hematopoietic Growth Factor Support

Growth factor support was permitted per the ASCO guidelines.[2] The most relevant aspect of these guidelines for patients treated in E1912 included:

● Growth factors are recommended for primary prophylaxis beginning with the first and subsequent cycles of chemotherapy for patients with a 20% or higher risk for febrile neutropenia.

● Growth factors are recommended for secondary prophylaxis in patients who develop a neutropenic complication from a prior cycle of treatment during which primary prophylaxis was not administered if a dose reduction or treatment delay may impact clinical outcome (PFS, OS).

● Growth factors are not recommended for patients with neutropenia who are afebrile.

● Growth factors are not recommended as an adjunctive with antibiotic therapy for patients with fever and neutropenia unless they are at high risk for infection-associated complications.

IWCLL Grading Scale for Hematologic Toxicity

Hematologic toxicity was graded according to IWCLL 2008 criteria[1], which account for pretreatment cytopenias. These are graded as follows:

Grade	Decrease in Platelets* or Hgb** from pretreatment value	Absolute Neutrophil Count (ANC) (uL)***
0	No change – 10%	≥2000
1	11%-24%	≥1500 and <2000
2	25%-49%	≥1000 and <1500
3	50%-74%	≥500 and <1000
4	≥75%	<500

*Platelet counts must be below normal levels for any grade toxicity to be recorded. If platelet count is $<20x10^{12}$/L, this will be considered grade 4 toxicity unless the initial platelet count was ≤20,000 uL in which case the patient is unevaluable for toxicity referable to platelet counts.

**Hgb levels must be below normal levels for any grade toxicity to be recorded. Baseline and subsequent hemoglobin determinations must be immediately before any transfusions.

***If ANC is <1000 before study, the patient is not evaluable for toxicity assessment based on ANC.

Treatment and Dose Modifications

Patients were evaluated clinically every cycle while on treatment, and then every 3 cycles after treatment discontinuation until the time of disease progression. CT scans were performed at baseline, and the time of the 12 month response evaluation. Bone marrow biopsy was performed at baseline, the time of the 12 month response evaluation.

Treatment Plan

Arm A: Ibrutinib/Rituximab (IR)

Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each 28-day cycle. Patients also received rituximab during cycles 2-7. During cycle 2, 50 mg/m^2 of rituximab will be administered on day 1 and 325 mg/m^2 on day 2. During Cycle 2 3-7, 500 mg/m^2 on day 1. Ibrutinib will be continued past cycle 6 until disease progression. It should be noted that it is common for CLL patients treated with Ibrutinib to experience a transient increase in lymphocytosis due to redistribution of lymphocytes from the lymph nodes and spleen to the peripheral blood circulation. This lymphocytosis is not a marker of disease progression or Richter's transformation and typically resolves over several months. For this reason, before the 12 month response evaluation, patients on both arms will not be considered to have disease progression based on an increased absolute lymphocyte count if they simultaneously have unequivocal improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (Hgb or platelet count), or disease-related symptoms. Questions regarding an increase in the absolute lymphocyte count after initiation of therapy should be discussed with the study PI.

- Recommended/prohibited ancillary therapy is outlined in the protocol

  All patients will be given PO allopurinol 300 mg/day from day 1 to day 14 (a total of 14 days) of Cycles 1 and 2 unless they are allergic. Treatment with allopurinol may continue beyond 14 days during Cycles 1 and 2 at the discretion of the treating physician. Use of allopurinol with subsequent cycles will be at the discretion of the treating physician.

  Patients with a baseline platelet counts below 20x10^9/L should receive platelet transfusion prior cycle 2, day 1 rituximab therapy. As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < 50x10^9/L, before receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

  Patients on both study arms will receive Bactrim DS 1 tablet (or alternative Pneumocystis pneumonia prophylaxis) on Monday/Wednesday/Friday AND acyclovir 400 mg p.o. twice per day (or equivalent) beginning with cycle 1 and continuing until the time of response evaluation (52 weeks after start of cycle 1). Even if patients discontinue protocol treatment. they should remain on these prophylactic antibiotics until this timepoint.

Neutrophil growth factors and red blood cell growth factors are permitted per American Society of Clinical Oncology Guidelines.[3] Use of colony stimulating factors (e.g., filgrastim, sargramostim, PEG-filgrastim) in this protocol is permitted during therapy as required for the treatment of febrile neutropenia. Colony stimulating factors may not be used to avoid dose reductions (e.g. to boost counts immediately before a starting a treatment cycle).

- Premedication

Unless otherwise indicated, premedication before all doses of rituximab (Cycles 2-7) will include the following:

- Hydrocortisone 100 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of rituximab during Cycle 2 of therapy. Thereafter, it should only be administered if patients have infusion reactions or nausea that is not controlled by alternative anti-emetics.
- Diphenhydramine 50 mg IV or PO (or alternative anti-histamine) and acetaminophen 650 mg PO should be administered 30 minutes before rituximab to reduce infusion reactions. Patients with allergic reactions to diphenhydramine and other anti-histamines may have anti-histamines held at the discretion of the treating physician

Use of antiemetic therapy will be left to the discretion of the treating physician

- Drug administration

Full administration guidelines are outlined in the protocol. Ibrutinib is administered orally as three capsules daily, and rituximab is administered intravenously. Patients on ibrutinib will keep a daily drug administration record with dates and times taken. If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to normal schedule the following day.

- Dose modifications/dose delays are outlined in the protocol

- Supportive care

Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion mediated graft versus host disease in CLL patients receiving potentially T-cell suppressive therapy.

All supportive measures consistent with optimal patient care will be given throughout the study.

Patients with a pre-treatment platelet counts below $20x10^9$/L should receive platelet transfusion prior cycle 1, day 1 rituximab therapy. Patients whose pre-treatment platelet count is below $20x10^9$/L should have repeat CBC on day 3.

As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < 50 $x10^9$/L before receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

Arm B: Fludarabine, cyclophosphamide and rituximab (FCR)

Treatment on Arm B consists of six 28-day cycles. Each cycle consists of intravenous fludarabine (25 mg/m^2 days 1-3), cyclophosphamide (250 mg/m^2 days 1-3) along with rituximab. During cycle 1, 50 mg/m^2 of rituximab will be administered on day 1 and 325 mg/m^2 on day 2. During Cycle 2-6, 500 mg/m^2 of rituximab will be administered on day 1.

- Recommended/prohibited ancillary therapy is outlined in the protocol

The following premedication will be administered before Cycles 1 and 2:

All patients will be given PO allopurinol 300 mg/day from day 1 to day 14 (a total of 14 days) of Cycles 1 and 2 unless they are allergic. Treatment with allopurinol may continue beyond 14 days during Cycles 1 and 2 at the discretion of the treating physician. Use of allopurinol with subsequent cycles will be at the discretion of the treating physician.

Patients with a baseline platelet counts below 20x10^9/L should receive platelet transfusion prior cycle 1, day 1 rituximab therapy. As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < 50x10^9/L, before receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

Patients on both study arms will receive Bactrim DS 1 tablet (or alternative Pneumocystis pneumonia prophylaxis) on Monday/Wednesday/Friday AND acyclovir 400 mg p.o. twice per day (or equivalent) beginning with cycle 1 and continuing until the time of response evaluation (52 weeks after start of cycle 1). Even if patients discontinue protocol treatment. they should remain on these prophylactic anti-biotics until this timepoint.

Neutrophil growth factor support is permitted per American Soceity of Clnical Onoclogy Guidelines.[3] Use of colony stimulating factors (e.g., filgrastim, sargramostim, PEG-filgrastim) in this protocol is permitted during therapy as required for the treatment of febrile neutropenia. Colony stimulating factors may not be used to avoid dose reductions (e.g. to boost counts immediately before a starting a treatment cycle).

Recommended/prohibited ancillary therapy is outlined in the protocol

Unless otherwise indicated, premedication before all doses of rituximab (Cycles 1-6) will include the following:

- Hydrocortisone 100 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of rituximab

during Cycle 2 of therapy. Thereafter, it should only be administered if patients have infusion reactions or nausea that is not controlled by alternative anti-emetics.

- Diphenhydramine 50 mg IV or PO (or alternative anti-histamine) and acetaminophen 650 mg PO should be administered 30 minutes before rituximab to reduce infusion reactions. Patients with allergic reactions to diphenhydramine and other anti-histamines may have anti-histamines held at the discretion of the treating physician

Antiemetic medications such as Granisetron 1 mg PO (or substitute) should be given thirty minutes to 1 hour before chemotherpay (fludarabine and/or cyclophosphamide. Additional prophylactic antiemetic therpay will be left to the discretion of the treating physician

All patients should be well hydrated before each cycle of therpay. Patients should be encouraged to drink fluids the night before treatment and will receive approximately 500 to 1000 mL of intravenous hydration over 1 hour before chemotherapy on days they receive fludarabine and cyclophsphamide.

- Drug administration

  Full administration guidelines are outlined in the protocol. Fludarabine, cyclophosphamide and rituximab are all administered intravenously. Fludarabine and cyclophosphamide should be administered before rituximab on days that they are all three drugs given.

- Dose modifications/dose delays are outlined in the protocol

- Supportive care

  Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion mediated graft versus host disease in CLL patients receiving potentially T-cell suppressive therapy.

  All supportive measures consistent with optimal patient care will be given throughout the study.

  Patients with a pre-treatment platelet counts below $20x10^9$/L should receive platelet transfusion prior cycle 1, day 1 rituximab therapy. Patients whose pre-treatment platelet count is below $20x10^9$/L should have repeat CBC on day 3.

  As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < $50\ x10^9$/L before receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

- Dose modifications/dose delays after cycle 1 are outlined in the protocol

Arm A: Ibrutinib and rituximab

Dose Modifications for Hematologic Toxicity: Dose modifications should be made based on day 1 values for each cycle, or the presence of significant bleeding or febrile neutropenia.

Neutropenia:

For Grade 4 neutropenia (ANC < 0.5 x 10^9/L [ie, < 500/ µL]) lasting > 7 days, follow the actions outlined in the table:

Occurrence	Action
1st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4th	Discontinue Ibrutinib

In patients whose baseline (i.e., before starting protocol therapy) ANC is < 1000/µL, the above Ibrutinib dose modifications, if required, would not be applied until Cycle 3.

If Ibrutinib is interrupted for a reason on other than toxicity (e.g. unrelated illness) it must be restarted within 60 days. If interrupted for more than 60 days, study medication should be discontinued permanently

If the dose of ibrutinib is reduced, at the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study documentation.

Febrile neutropenia

For febrile neutropenia, hold Ibrutinib until fever resolves and ANC ≥ 1000/µL, then resume Ibrutinib at the previous dose. If Ibrutinib is delayed for febrile neutropenia, rituximab should also be delayed.

Thrombocytopenia

Grade 3 thrombocytopenia (platelets <50 x 10^9/L [i.e., < 50,000/mL]); or in subjects with baseline thrombocytopenia a platelet decrease of 50% to 74% from baseline that is associated with clinically significant bleeding follow the actions outlined in the table:

Occurrence	Action
1st	Hold Ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level (420 mg daily)
2nd	Hold Ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (280 mg daily)
3rd	Hold Ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (140 mg daily)
4th	Discontinue Ibrutinib

For grade 4 thrombocytopenia (platelets < 25 x 10^9/L [i.e., < 25,000/mL]); or in subjects with baseline thrombocytopenia a decrease of > 75% from baseline or < 20 x 10^9/L, whichever is higher follow the actions outlined in the table:

Occurrence	Action
1st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4th	Discontinue Ibrutinib

If the dose of ibrutinib is reduced, at the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study

Dose Modifications for Atrial Fibrillation

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.

If the dose of ibrutinib is reduced, at the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study documentation.

Dose Adjustments for Non-Hematologic Toxicity

Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrheal therapy) or any other Grade 4 toxicity (with the exception of hair loss or drug related chills)or any unmanageable Grade 3 toxicity follow the actions outlined in the table:

Occurrence	Action
1st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4th	Discontinue Ibrutinib

If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.

Dose modifications are for adverse events attributed to study treatment. Dose modifications are not required for adverse events unrelated to study treatment.

Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

If Ibrutinib is interrupted for a reason other than toxicity (e.g. unrelated illness) the first instance of interruption must be restarted within 42 days. Subsequent study medication interruptions lasting more than 42 days ibrutinib should be discontinued permanently.

If the dose of ibrutinib is reduced, at the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study documentation.

If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO) should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.

If treating provider feels that a dose reduction needs to be made based on first occurrence (e.g. without restarting at original dose level) this must be discussed with study PI who can who can approve this request at their discretion.

If the dose of ibrutinib is reduced, at the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study documentation.

Arm B : Fludarabine, cyclophosphamide and rituximab

Dose Modifications for Hematologic Toxicity: Dose modifications should be made based on day 1 values for each cycle, or the presence of significant bleeding or febrile neutropenia.

Neutropenia:

ANC must be ≥ 1000/µL on day 1 of a cycle. For ANC < 1000/µL, hold fludarabine and cyclophosphamide until ANC ≥ 1000/µL, then resume both at one dose level lower than previous dose (see Table) If dose reduction to less than dose level -2 is required for neutropenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine and cyclophosphamide are delayed for neutropenia, rituximab should also be delayed. If counts have not recovered to adequate levels to permit retreatment by 8 weeks (56 days) from day 1 of the most recent cycle, then the patient will discontinue active treatment.

Dose Level	**IV Fludarabine Dose Level**	**Oral Fludarabine Dose Level (Canada Only)**	**Cyclophosphamide Dose Level**
0 (Starting Level)	25 mg/m^2/day	40 mg/m^2/day	250 mg/m^2/day
-1	18.75 mg/m^2/day	30 mg/m^2/day	200 mg/m^2/day
-2	12.5 mg/m^2/day	20 mg/m^2/day	150 /m^2/day

If the modifications indicate that either Fludarabine or Cyclophosphamide should be held, all drugs in the cycle should be held (e.g. the entire cycle delayed) until patient fulfills the indicated criteria for retreatment. Accordingly, there will not be any "missed" doses of medication.

There are no dose modifications for rituximab. If rituximab needs to be held, patients can continue to receive other treatment as prescribed by their assigned arm.

NOTE: Patients on Arm B who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels

Febrile Neutropenia

For febrile neutropenia, hold fludarabine and cyclophosphamide until fever resolves and ANC ≥ 1000/µL, then resume both at one dose level lower than the previous dose. If dose reduction to less than dose level -2 is required for febrile neutropenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine and cyclophosphamide are delayed for febrile neutropenia, rituximab should also be delayed. If counts have not recovered to adequate levels to permit retreatment by 8 weeks (56 days) from day 1 of the most recent cycle, then the patient will discontinue active treatment.

NOTE: Patients on Arm B who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels

Thrombocytopenia

Platelets must be ≥ 100,000/μL or > 80% of baseline value (i.e., > 80% of the value before protocol therapy started) on day 1 of a cycle. For platelets < 100,000/μL or < 80% of baseline, hold fludarabine and cyclophosphamide until platelets ≥ 100,000/μL or > 80% of baseline, then resume both at one dose level lower than the previous dose. If dose reduction to less than dose level -2 is required for thrombocytopenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine is delayed for thrombocytopenia, rituximab should also be delayed. If counts have not recovered to adequate levels to permit retreatment by 8 weeks (56 days) from day 1 of the most recent cycle, then the patient will discontinue active treatment.

In patients whose baseline (i.e., before starting protocol therapy) platelet count < 100,000/μL, these dose modifications, if required, would not be applied until Cycle 3.

Autoimmune Hemolytic Anemia or Thrombocytopenic Purpura

Patients on Arm B developing autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (AIT) during fludarabine therapy will be removed from protocol therapy, and treated with alternative agents at the discretion of the local physician. In this event, please consult with the ECOG-ACRIN Study Chair.

Dose Adjustments for Non-Hematologic Toxicity

Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrheal therapy) or any other Grade 4 toxicity (with the exception of hair loss or drug related chills) or any unmanageable Grade 3 toxicity the following actions should be taken:

- For non-hematologic toxicity ≥ grade 2 attributable to fludarabine, reduce fludarabine by 50%.
- For non-hematologic toxicity ≥ grade 2 attributable to cyclophosphamide, reduce cyclophosphamide by 50%.
- If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO).should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.

If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.

Dose modifications are for adverse events attributed to study treatment. Dose modifications are not required for adverse events unrelated to study treatment.

Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO).should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.

If treating provider feels that a dose reduction needs to be made based on first occurrence (e.g. without restarting at original dose level) this must be discussed with study PI who can who can approve this request at their discretion.

Rituximab Infusion Reactions

- Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently in patients with high leukocyte counts and during the first several treatments. Close observation for these potential toxicities should occur. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as meperidine for IV push, oxygen supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and access to crash cart.
- If infusion reactions occur, infusions should be stopped until infusion-related symptoms resolve, and then resumed at a 50% slower rate. Contact the ECOG-ACRIN Study Chair or ECOG-ACRIN Committee chair with any questions.
- If transient bronchospasm occurs, rituximab administration should be interrupted. If these symptoms persist, administration of albuterol (or other B2 agonist) by inhalation and additional hydrocortisone should be administered at the discretion of the treating physician.
- In patients with high leukocyte counts, close observation for potential toxicities should occur. If marked reduction in circulating lymphocytes is noted, close attention to the possibility of acute tumor lysis syndrome should occur.
- As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50x10^9$/L before receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

Dose Modifications for Obese Patients

All drugs were administered according to weight were dosed according to actual body weight. There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing was determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification. Failure to use actual body weight in the calculation of drug dosages was considered a major protocol deviation.

Correlative Laboratory Study Methods

IGVH Mutation Analysis

RNA was isolated by the Trizol method (Life Technologies, Carlsbad, CA) and converted to cDNA using the BioRad iScript cDNA kit (Hercules, CA). 2 µl of cDNA was amplified using the Qiagen HotStarTaq MasterMix kit (Qiagen, Valencia, CA) in a multiplex PCR reaction using 0.5 mM of each of 7 sense primers representing the 7 IGHV families in conjunction with 0.5 mM of antisense primer to either the IgM or JH constant region. Amplified products were electrophoresed and gel purified using the Promega Wizard SV Gel and PCR Cleanup Kit (Madison, WI). Purified products were directly sequenced on an ABI PRISM 3730xl DNA Analyzer (Applied Biosystems/Life Technologies, Grand Island, NY). Resulting sequences were aligned using IMGT/V-Quest software (http://imgt.cines.fr). For samples where the clone was below the threshold of detection with a multiplex reaction, individual PCR reactions were done for each of the 7 sense primers. For each case, immunoglobulin transcript reconstruction, determination of V gene usage, and classification as IGHV mutated (<98%) or unmutated (≥98%) was performed according to our previously-published method.[4,5]

Minimal Residual Disease Analysis

Minimal residual disease analysis was performed in the clinical flow cytometry laboratory at Mayo Clinic in Rochester, Minnesota. Whole blood analysis was performed by initially lysing with ammonium chloride. Cells were then washed and resuspended in PBS with 3% BSA. 1 x 10(6) cells were stained for 15 minutes in the dark with antibodies to CD19, CD20, CD23, CD5, CD38, CD45, and Kappa and lambda light chains (see table for fluorochrome and antibody clone). 500,000 events were acquired on the BD FacsCantos using BD FACS Diva Software (v8.02). MRD gating analysis performed with Beckman Coulter Kaluza software (v2.1). Aggregates, debris, and any acquisition errors were removed using scatter properties and time parameter. Nonaggregated white blood cells were then displayed on a side scatter versus CD45 plot to create a lymphocyte gate. In this lymphocyte gate, B-cells were identified by gating on all CD19 positive cells in the CD19 vs CD5 plot. These CD19 positive B cells were then displayed on a CD20 vs CD5 plot in which four gates were created (20+ 5neg; 20+ and 5+; 20neg 5pos; and 20neg 5neg) to further investigate for clonality and a chronic lymphocytic leukemia immunophenotype. Presence or absence of clonality (or MRD) in each of these gates was based collectively, on expression levels of kappa or lambda light chain, CD23, CD38, as well as considering kappa to lambda ratios. This method has been validated to detect CLL MRD to the level of 0.01% or below, which corresponds to 1 CLL cell in 10,000 total cells analyzed; 20 events were considered the minimum number of events needed to call clonality.

Response Criteria

RESPONSE EVALUATION: The complete response rate at 12-months was determined by central BM review if available or site BM review if no slides available for central review. A total of 355 of 454 patients had slides available for central review while the remaining patients had response classified by site bone marrow analysis without central review. Individuals with an absolute lymphocyte count $\leq$4000/ul, absence of lymphadenopathy hepatomegaly or splenomegaly by physical exam, all nodes $\leq$1.5 cm by CT imaging, a maximal spleen measurement $\leq$13 cm by CT imaging, <30% lymphocytes in the BM

and without nodules and who had also recovered blood counts (Hg>11.0 gm/dl; platelets >100,000/ul; neutrophil count $\geq$ 1500/ul) were considered to have a CR. Individuals who met all of these criteria but who did not have recovered blood counts were considered a CR with incomplete marrow recover (CRi). Individuals meeting all of these criteria but with residual marrow nodules were considered a nodular partial remission (nPR) unless special staining demonstrated the nodules were comprised of T-cells (regenerative nodules) rather than clonal B-cells. Individuals who did not meet the criteria for CR, CRi, or nPR were considered to have a partial response if they experienced a ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value and a ≥ 50% reduction in lymphadenopathy as well as hepatomegaly and splenomegaly by physical exam. To be considered a partial response also required recovery of blood counts in at least one lineage (Hg>11.0 gm/dl or platelets >100,000/ul or neutrophil count $\geq$ 1500/ul) 2 occasions at least 4 weeks apart.

Additional Statistical Methods

The upper boundary for interim efficacy analysis for overall survival was based on a truncated version of the Lan-Demets error spending rate function corresponding to the O'Brien-Fleming shaped boundary. The boundary was truncated to a one-sided nominal significance of 0.0005.

Futility rules for harm and inefficacy were specified in the protocol. At 25% information, the data safety monitoring committee (DSMC) was able to consider stopping the study for harm if the lower 95% confidence boundary for the hazard ratio (IR/FCR) was above 1. Inefficacy monitoring was scheduled to start after approximately 49% of the full information was available with repeated analyses at each semi-annual DSMC meeting.

Since the alternative hypothesis evaluated was that IR was superior to FCR (rather than just different), one-sided p-values (which take into consideration the direction of the difference), were used for analysis, but reported as two-sided in the main paper per journal policy. Small one-sided p-value indicates that IR is significantly better than FCR whereas two sided p-values would indicate the two arms were significantly different but not indicate the direction of effect.

Supplemental Results

A per protocol analysis of PFS and OS for eligible patients who initiated assigned treatment is shown in Supplemental Figures 2-4.

A summary of the basis for progression is shown in Supplemental Table 2. Sub-group analysis of treatment effects are also summarized in Table S3.

Multivariable analysis for PFS is shown in Table S4. After adjusting for age, PS, stage, gender, race, beta-2 micro-globulin, FISH, and IGHV status, patients treated with IR were at decreased risk for progression (HR=0.255; 95% CI: 0.088-0.735). Potential treatment effect heterogeneity is seen in the model by performance status, IGHV mutation status and beta2-microglobulin status.

Causes of death for deceased patients is summarized in Table S5. Eight of the 14 deaths were without documented progression, including 2 of 4 death on the IR arm and 6 of 10 deaths on the FCR arm.

A summary of all grade 3 and above treatment related adverse events is shown in Table S6.

A summary of secondary cancers for patients in each arm are summarized in Table S7.

A comparison of FCR treated patients in the current trial to historical phase 3 German CLL Study Group CLL10 trial is shown in Table S9.

Participating Institutions

Affiliate Institution	N
Abbott-Northwestern Hospital	1
Alegent Health Immanuel Medical Center	1
Allegiance Health	2
AMITA Health Alexian Brothers Medical Center	4
Ascension Saint John Hospital	1
Aspirus Regional Cancer Center	4
Aspirus UW Cancer Center	1
Aurora BayCare Medical Center	4
Aurora Cancer Care-Grafton	1
Aurora Cancer Care-Milwaukee	1
Aurora Cancer Care-Racine	3
Aurora Cancer Care-Waukesha	1
Aurora Saint Luke's Medical Center	1
Avera Cancer Institute	3
Baystate Medical Center	2
Bellin Memorial Hospital	5
Billings Clinic Cancer Center	1
Bozeman Deaconess Hospital	2
California Pacific Medical Center-Pacific Campus	1
Cancer Center of Kansas - Wichita	1
Carle Cancer Center	1

Case Western Reserve University	**4**
Central Illinois Hematology Oncology Center	**1**
CHI Health Saint Francis	**1**
Colorado Blood Cancer Institute	**2**
Columbus Oncology and Hematology Associates Inc	**5**
Comprehensive Ca Ctrs of Nevada - Central Valley	**1**
Cotton O'Neil Cancer Center / Stormont Vail Health	**1**
Covenant Medical Center	**1**
Covenant Medical Center-Lakeside	**2**
CoxHealth South Hospital	**1**
Crossroads Cancer Center	**2**
Danville Hematology Oncology	**1**
Delaware Clinical and Laboratory Physicians PA	**2**
Emory University/Winship Cancer Institute	**7**
Essentia Health Cancer Center	**2**
Fairview Ridges Hospital	**2**
Fairview-Southdale Hospital	**2**
Feather River Cancer Center	**3**
Fred Hutchinson Cancer Research Center	**8**
Freeman Health System	**2**
Froedtert and the Medical College of Wisconsin	**3**
Geisinger Medical Center-Cancer Center Hazleton	**2**
Geisinger Wyoming Valley/Henry Cancer Center	**3**
Good Samaritan Hospital - Dayton	**3**
Grant Medical Center	**1**
Green Bay Oncology at Saint Vincent Hospital	**2**
Green Bay Oncology Limited at Saint Mary's Hosp	**1**
Greenville Health System Cancer Institute-Eastside	**2**

Greenville Health System Cancer Institute-Seneca	**2**
Gundersen Lutheran Medical Center	**4**
Harold Alfond Center for Cancer Care	**3**
Hematology & Onc Assoc of North East Pennsylvania	**1**
Illinois CancerCare-Bloomington	**1**
Illinois CancerCare-Galesburg	**1**
Illinois CancerCare-Peoria	**3**
Illinois CancerCare-Peru	**1**
Jewish Hospital Medical Center Northeast	**2**
John B Amos Cancer Center	**1**
Kaiser Permanente	**5**
Kaiser Permanente Medical Center - Santa Clara	**3**
Kaiser Permanente Moanalua Medical Center	**2**
Kaiser Permanente-Anaheim	**1**
Kaiser Permanente-Baldwin Park	**1**
Kaiser Permanente-Franklin	**2**
Kaiser Permanente-Fresno	**3**
Kaiser Permanente-Irvine	**3**
Kaiser Permanente-Oakland	**1**
Kaiser Permanente-Roseville	**1**
Kaiser Permanente-San Diego Zion	**5**
Kaiser Permanente-San Francisco	**1**
Kaiser Permanente-San Marcos	**2**
Kaiser Permanente-San Rafael	**1**
Kaiser Permanente-Santa Teresa-San Jose	**1**
Kaiser Permanente-Stockton	**2**
Kaiser Permanente-Vallejo	**2**
Kalispell Regional Medical Center	**1**

Katmai Oncology Group	**1**
Lahey Hospital and Medical Center	**2**
Lakeland Regional Health Hollis Cancer Center	**1**
Lakeview Hospital	**1**
Lancaster General Hospital	**4**
Lehigh Valley Hospital-Cedar Crest	**2**
Lewis Ca & Res Pavilion at Saint Joseph's/Candler	**1**
Long Island Jewish Medical Center	**2**
Loyola University Medical Center	**3**
Marshfield Clinic	**1**
Marshfield Clinic Cancer Center at Sacred Heart	**1**
Mayo Clinic	**24**
Mayo Clinic in Arizona	**9**
McFarland Clinic PC - Ames	**5**
Medical Center of Central Georgia	**1**
Medical Oncology and Hem Assoc-West Des Moines	**1**
Medical Oncology Hematology Consultants PA	**3**
Memorial Hospital of South Bend	**1**
Mercy Hospital	**1**
Mercy Medical Center - North Iowa	**1**
Miami Valley Hospital	**1**
Middlesex Hospital	**2**
Mission Hospital Inc-Memorial Campus	**4**
MultiCare Auburn Medical Center	**1**
Multicare Health System	**1**
Nebraska Hematology and Oncology	**2**
New York Oncology Hematology PC -Albany Med Center	**4**
Newark Beth Israel Medical Center	**1**

NorthShore Hematology Oncology-Libertyville	**1**
NorthShore Univ HealthSystem-Evanston Hospital	**5**
NorthShore Univ HealthSystem-Glenbrook Hospital	**1**
Northwell Health/Center for Advanced Medicine	**3**
Northwestern Medicine Cancer Center Warrenville	**1**
Northwestern University	**4**
Ochsner Health Center-Summa	**3**
Ochsner Medical Center Jefferson	**1**
Orange Regional Medical Center	**1**
Pacific Central Coast Health Ctr-San Luis Obispo	**3**
Palo Alto Medical Foundation-Santa Cruz	**1**
Palo Alto Medical Foundation-Sunnyvale	**3**
Paoli Memorial Hospital	**5**
Park Nicollet Clinic - Saint Louis Park	**4**
PeaceHealth Saint Joseph Medical Center	**1**
Penn State Milton S Hershey Medical Center	**1**
Penrose-Saint Francis Healthcare	**1**
Phoebe Putney Memorial Hospital	**4**
Porter Adventist Hospital	**1**
Pottstown Memorial Medical Center	**1**
ProHealth Oconomowoc Memorial Hospital	**2**
ProHealth Waukesha Memorial Hospital	**3**
Providence Hospital	**1**
Providence Newberg Medical Center	**1**
Providence Oncology and Hematology Care Southeast	**1**
Providence Portland Medical Center	**1**
Providence Saint Vincent Medical Center	**3**
Rapid City Regional Hospital	**1**

Reading Hospital	**2**
Regional West Medical Center Cancer Center	**1**
Regions Hospital	**1**
Reid Health	**1**
Rice Memorial Hospital	**1**
Rocky Mountain Cancer Centers-Penrose	**2**
Roswell Park Cancer Institute	**2**
Saint Alphonsus Cancer Care Center-Boise	**2**
Saint Francis Medical Center	**1**
Saint Francis Regional Medical Center	**1**
Saint John's Hospital - Healtheast	**3**
Saint Joseph Mercy Hospital	**6**
Saint Joseph Mercy Oakland	**1**
Saint Louis Cancer and Breast Institute-South City	**1**
Saint Luke's Hospital of Kansas City	**1**
Saint Luke's Mountain States Tumor Inst - Meridian	**1**
Saint Luke's Mountain States Tumor Institute	**1**
Saint Mary Mercy Hospital	**1**
Saint Vincent Hospital Cancer Center Green Bay	**1**
Sanford Bismarck Medical Center	**1**
Sanford Roger Maris Cancer Center	**4**
Sanford USD Medical Center - Sioux Falls	**1**
Siouxland Regional Cancer Center	**2**
Stanford Cancer Center South Bay	**1**
Stanford Cancer Institute Palo Alto	**20**
State Univ of New York Upstate Medical Univ	**1**
SwedishAmerican Regional Cancer Center	**1**
The Don and Sybil Harrington Cancer Center	**1**

The Mark H Zangmeister Center	**2**
Toledo Clinic Cancer Centers-Toledo	**1**
Tufts Medical Center	**1**
UC Irvine Health/Chao Family Comprehensive Ca Ctr	**1**
UF Cancer Center at Orlando Health	**3**
University of Alabama at Birmingham Cancer Center	**3**
University of Arkansas for Medical Sciences	**5**
University of Chicago Comprehensive Cancer Center	**2**
University of Maryland/Greenebaum Cancer Center	**1**
University of Massachusetts Medical School	**5**
University of Nebraska Medical Center	**4**
University of New Mexico Cancer Center	**2**
University of Oklahoma Health Sciences Center	**11**
University of Pennsylvania/Abramson Cancer Center	**16**
University of Pittsburgh Cancer Institute	**9**
University of Rochester	**24**
University of Texas Hlth Science Ctr @ San Antonio	**2**
University of Vermont College of Medicine	**1**
UPMC Susquehanna	**3**
UT Southwestern/Simmons Cancer Center-Dallas	**1**
UW Cancer Center at ProHealth Care	**1**
Veteran Affairs Medical Center	**1**
Veterans Administration New Jersey Hlth Care Sys	**1**
Vidant Oncology-Kinston	**3**
Vince Lombardi Cancer Clinic - Oshkosh	**2**
Vince Lombardi Cancer Clinic-Sheboygan	**2**
Virginia Cancer Institute	**6**
Virginia Commonwealth Univ/Massey Cancer Center	**3**

Wake Forest University Health Sciences	**2**
Washington University School of Medicine	**22**
Wayne State University/Karmanos Cancer Institute	**3**
Wentworth-Douglass Hospital	**1**
West Michigan Cancer Center	**6**
West Virginia University Healthcare	**3**
William Beaumont Hospital-Royal Oak	**6**
Yale University	**5**
Total	**529**

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Supplemental Figures

Figure S1. MRD status by treatment arm at 12-month response evaluation. Earlier time points used for patients who went off treatment early due to reasons other than progression if missing 12-month MRD assessments.

	Ibrutinib-Rituximab	FCR
MRD negative	8.3%	59.2%
Intermediate (MRD positive up to 1%)	26.4%	26.2%
High (>1%)	64.5%	12.6%
Not Interpretable	0.7%	1.9%

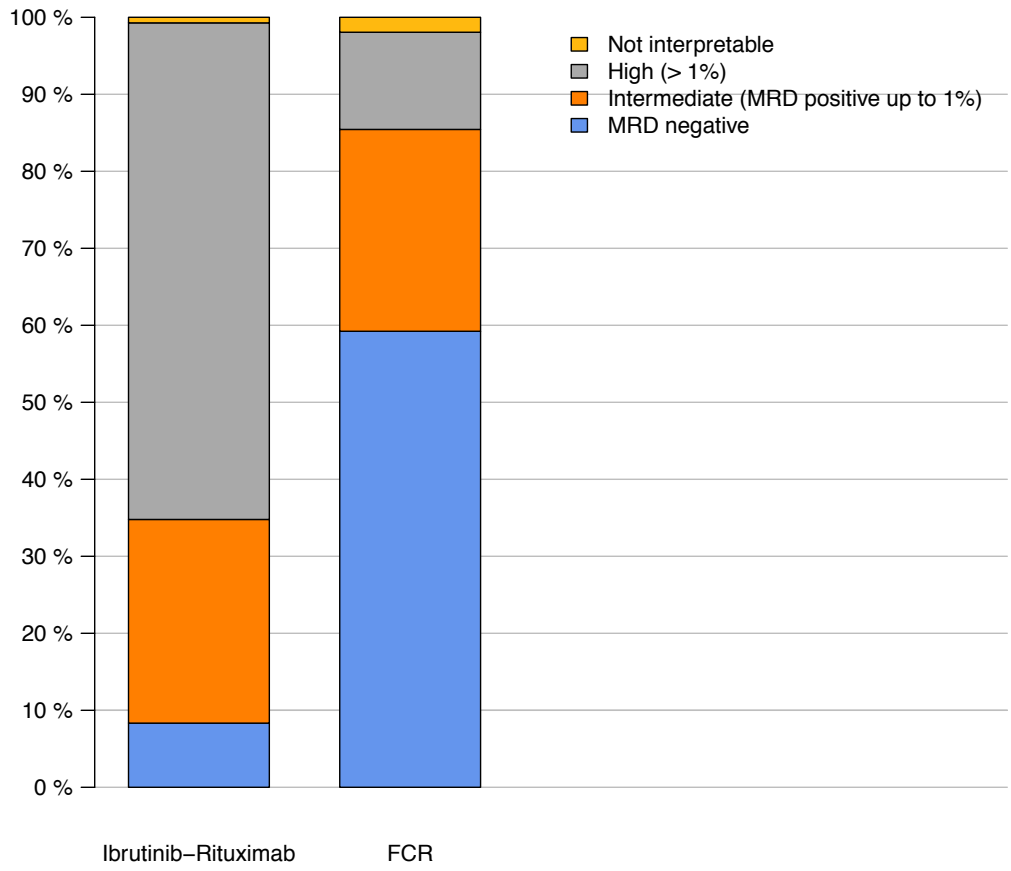


Figure S2. PFS, per-protocol. Includes eligible patients who started assigned protocol treatment.

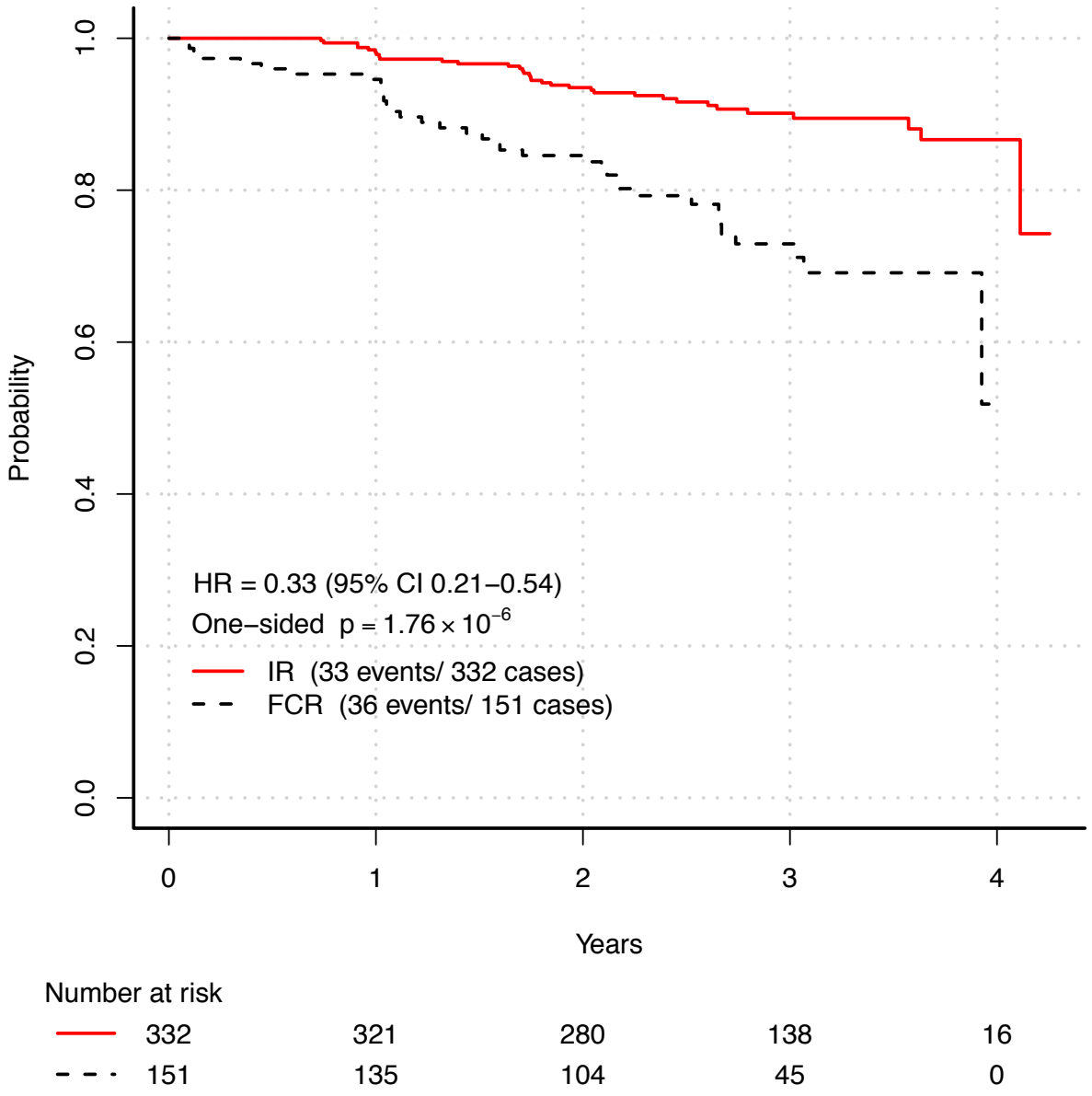


Figure S3A. PFS for IGHV mutated patients, intention-to-treat. Includes all randomized patients with IGHV mutation.

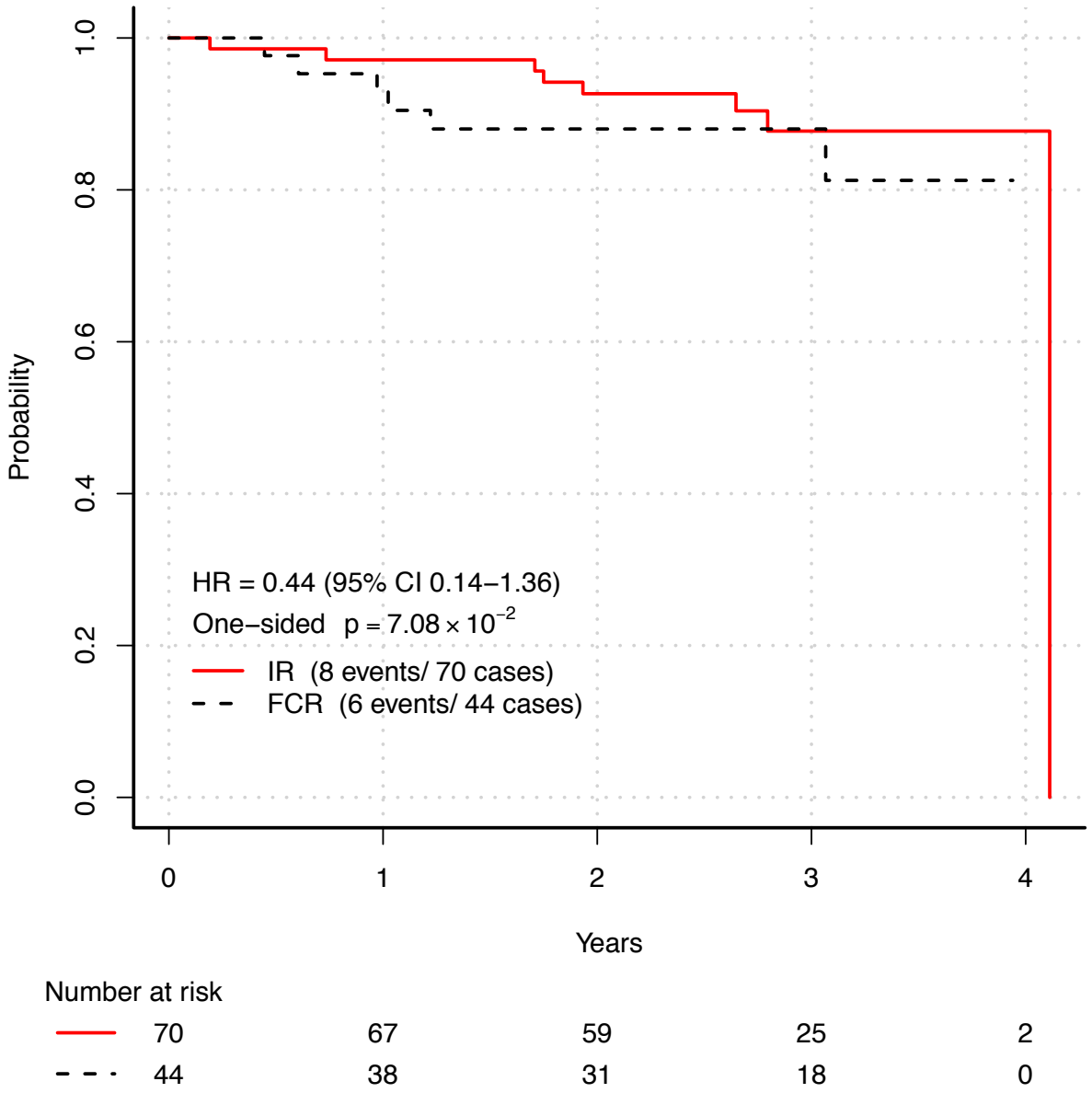


Figure S3B. PFS for IGHV mutated patients, per-protocol. Includes eligible patients with IGHV mutation who started assigned protocol treatment.

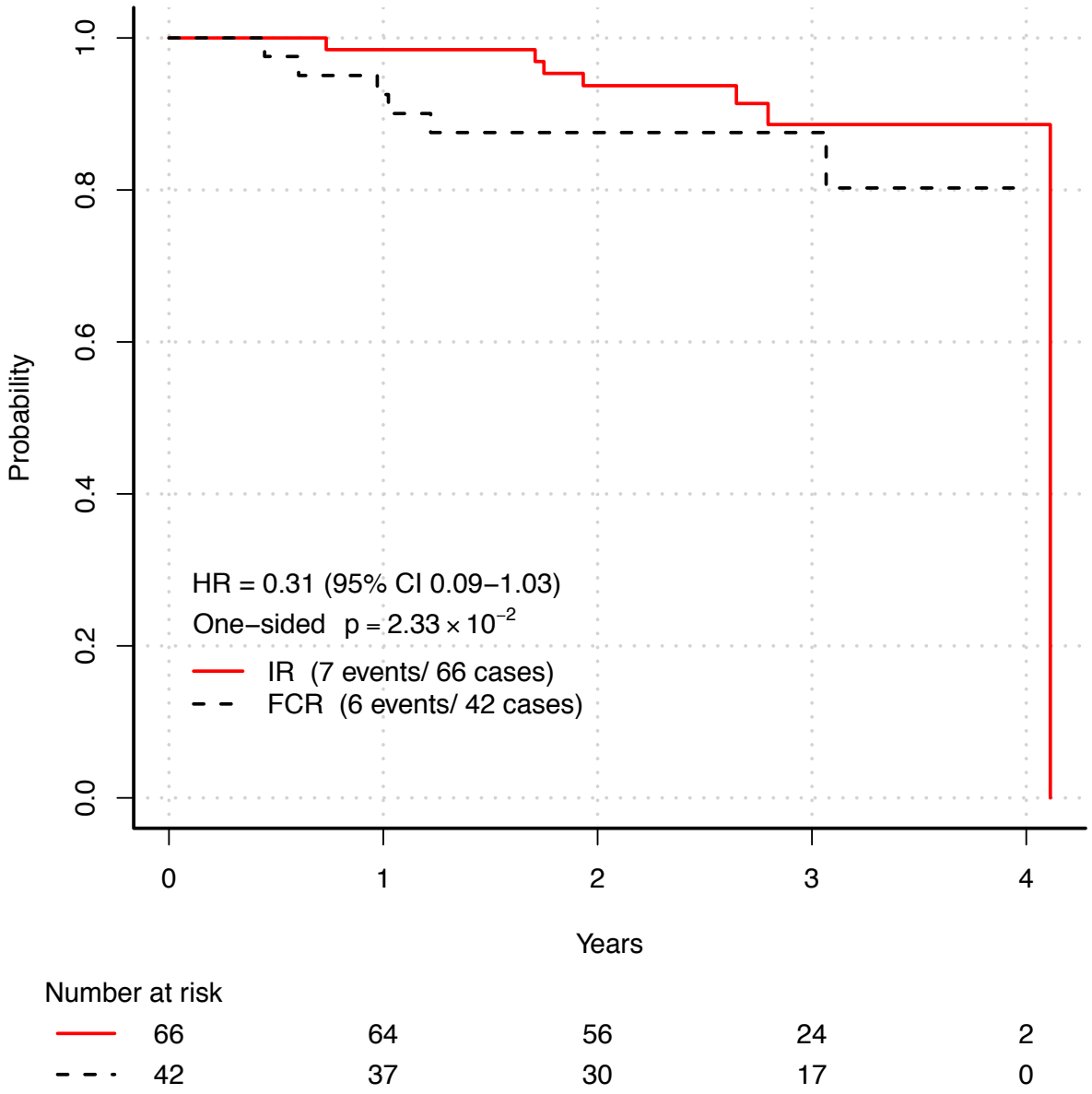


Figure S3C. PFS for IGHV unmutated patients, per-protocol. Includes eligible patients without IGHV mutation who started assigned protocol treatment.

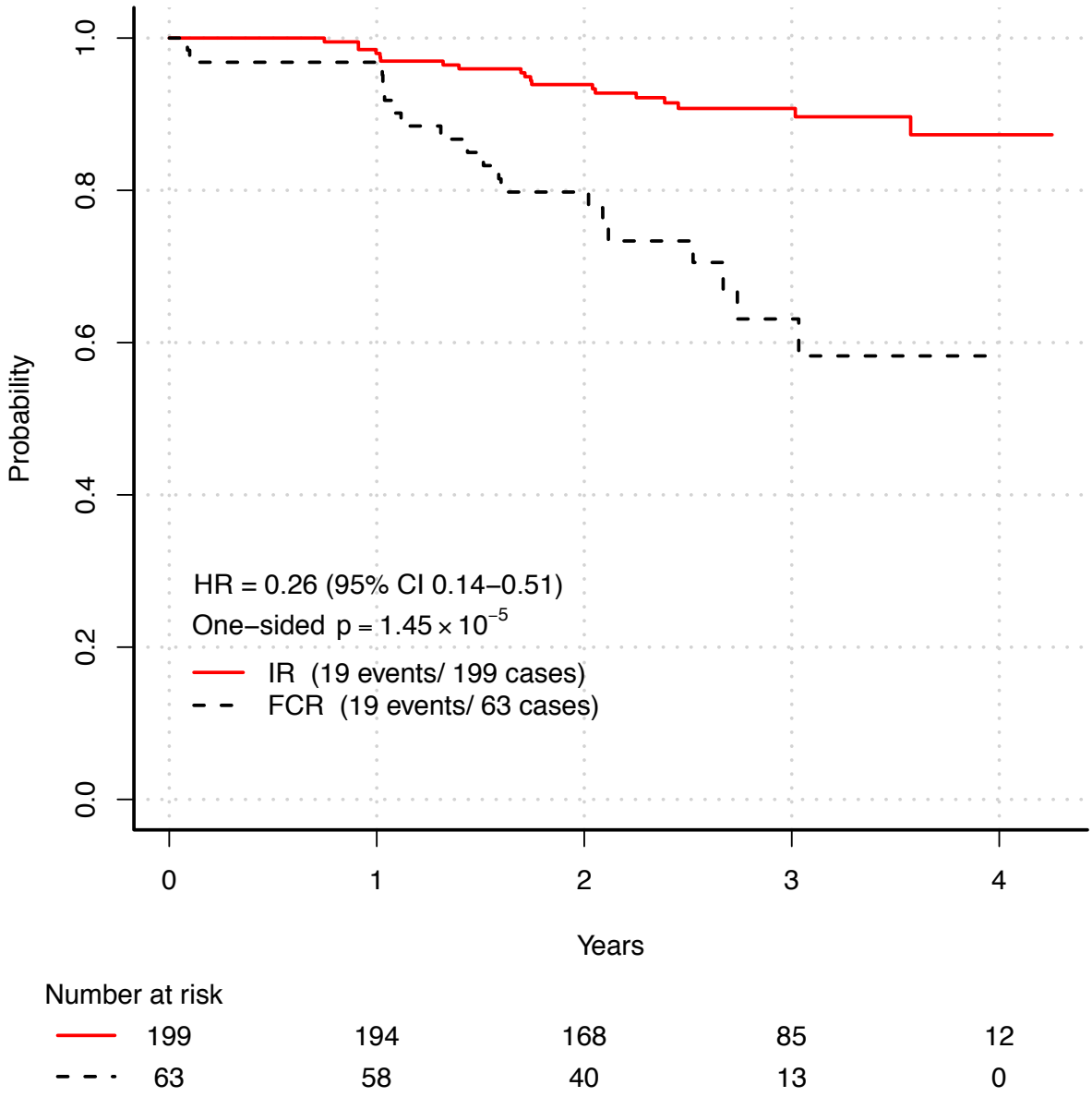
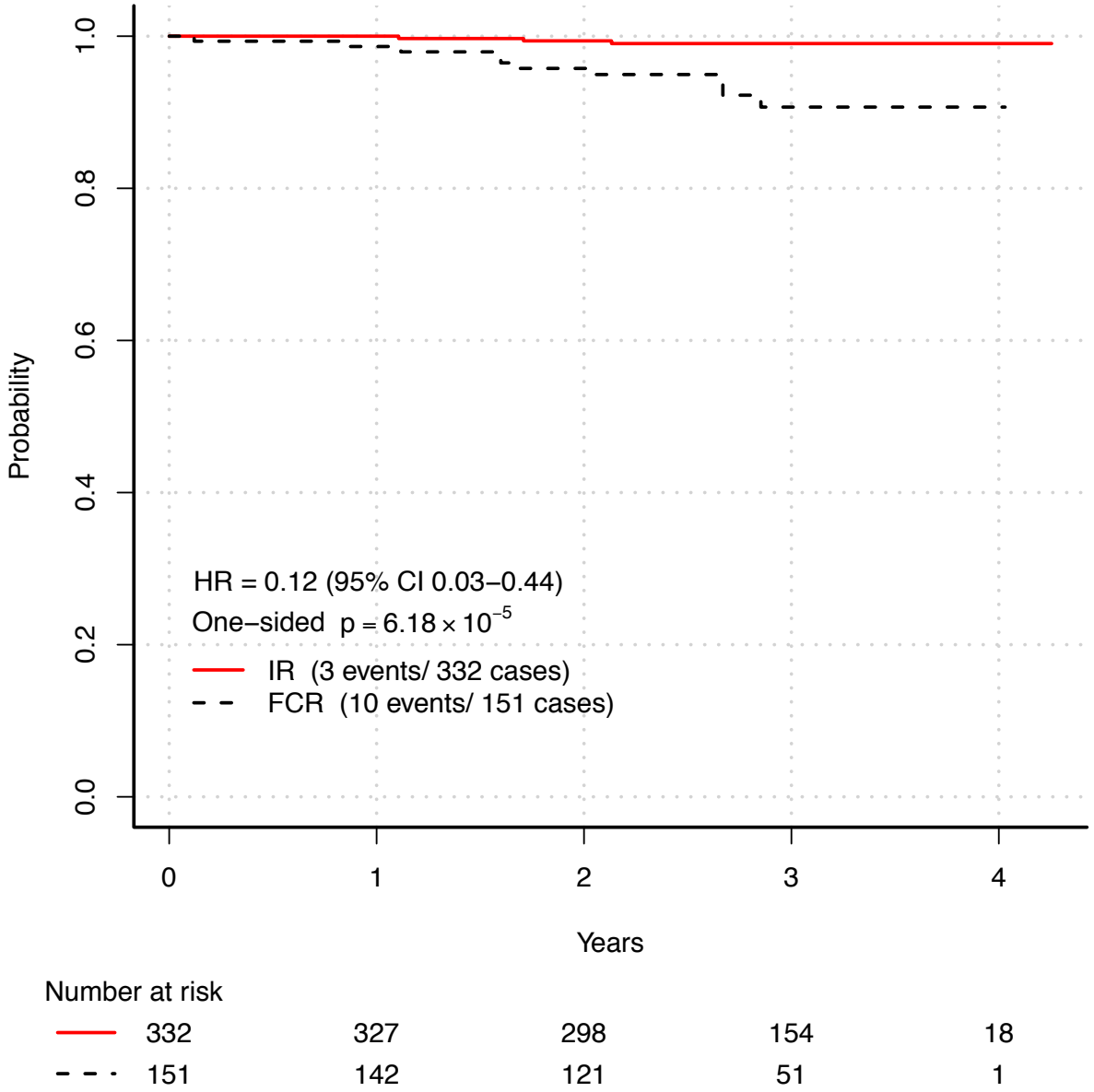


Figure S4. Overall survival, treated per-protocol. Includes eligible patients who started assigned protocol treatment.



Supplemental Tables

Table S1. Baseline characteristics. Includes all randomized patients.

Variable	Category	A (Ibrutinib-rituximab)	B (FCR)	Total
Total[1]		354	175	529
Age	Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing	56.7 (7.5) 58.0 (52.0,62.0) [31.0,70.0] 0	56.7 (7.2) 57.0 (53.0,61.5) [28.0,70.0] 0	56.7 (7.4) 58.0 (52.0,62.0) [28.0,70.0] 0
Age, category	<60 >=60 Unknown/Missing	209 (59.0) 145 (41.0) 0	105 (60.0) 70 (40.0) 0	314 (59.4) 215 (40.6) 0
Gender	Female Male Unknown/Missing	118 (33.3) 236 (66.7) 0	55 (31.4) 120 (68.6) 0	173 (32.7) 356 (67.3) 0
RAI Stage	Low, 0 Intermediate, I-II High, III-IV Unknown/Missing	11 (3.1) 187 (52.8) 156 (44.1) 0	9 (5.1) 94 (53.7) 72 (41.1) 0	20 (3.8) 281 (53.1) 228 (43.1) 0
ECOG PS	0 1 2 Unknown/Missing	226 (63.8) 119 (33.6) 9 (2.5) 0	109 (62.3) 63 (36.0) 3 (1.7) 0	335 (63.3) 182 (34.4) 12 (2.3) 0
Hemoglobin, g/dL	Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing	12.2 (2.2) 12.3 (10.6,13.9) [4.4,17.5] 6	12.1 (2.1) 12.4 (11.0,13.6) [5.5,17.6] 3	12.1 (2.2) 12.4 (10.7,13.8) [4.4,17.6] 9
Platelets, 10^3/uL	Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing	158.3 (71.3) 150.0 (107.0,200.8) [9.6,508.0] 0	157.3 (78.5) 143.0 (102.0,193.5) [13.0,485.0] 0	158.0 (73.7) 148.0 (105.0,200.0) [9.6,508.0] 0
WBC, 10^3/uL	Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing	109.3 (116.5) 73.6 (20.1,157.3) [1.6,617.5] 0	108.9 (110.9) 72.7 (26.5,167.3) [2.3,672.0] 0	109.2 (114.6) 73.3 (22.2,161.3) [1.6,672.0] 0
Beta-2 Microglobulin mg/L	Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing	4.0 (2.1) 3.6 (2.6,4.6) [1.3,14.4] 5	4.0 (1.9) 3.4 (2.7,4.8) [1.0,12.2] 0	4.0 (2.0) 3.6 (2.6,4.7) [1.0,14.4] 5
Beta-2 Microglobulin	Elevated Normal Unknown/Missing	181 (51.9) 168 (48.1) 5	84 (48.0) 91 (52.0) 0	265 (50.6) 259 (49.4) 5
Serum Creatinine	Mean (SD)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)

mg/dL	Median (Q1,Q3) [Min, Max] Freq. of Missing	1.0 (0.8,1.1) [0.5,2.1] 0	1.0 (0.8,1.1) [0.4,1.7] 0	1.0 (0.8,1.1) [0.4,2.1] 0
Creatinine Clearance[2] ml/min	Mean (SD) Median (Q1,Q3) [Min, Max] Freq. of Missing	96.3 (6.8) 94.8 (91.9,98.9) [86.2,123.9] 0	95.8 (5.8) 94.5 (92.2,98.0) [86.8,117.9] 0	96.2 (6.5) 94.8 (91.9,98.5) [86.2,123.9] 0
Coombs Test	Negative Positive Unknown/Missing	316 (92.7) 25 (7.3) 13	157 (92.4) 13 (7.6) 5	473 (92.6) 38 (7.4) 18
Splenomegaly[3]	No Yes Unknown/Missing	212 (59.9) 142 (40.1) 0	99 (56.6) 76 (43.4) 0	311 (58.8) 218 (41.2) 0
Lymphadenopathy[3]	No Yes Unknown/Missing	103 (29.1) 251 (70.9) 0	56 (32.0) 119 (68.0) 0	159 (30.1) 370 (69.9) 0
Del(11q22.3)	Abnormal Normal Unknown/Missing	78 (22.2) 274 (77.8) 2	39 (22.3) 136 (77.7) 0	117 (22.2) 410 (77.8) 2
Dohner Classification	del(17p) del(11q22) trisomy 12 normal del(13q) other Unknown/Missing	2 (0.6) 78 (22.0) 70 (19.8) 69 (19.5) 121 (34.2) 14 (4.0) 0	0 (0.0) 39 (22.3) 27 (15.4) 37 (21.1) 58 (33.1) 14 (8.0) 0	2 (0.4) 117 (22.1) 97 (18.3) 106 (20.0) 179 (33.8) 28 (5.3) 0
IGHV[4]	Mutated Unmutated Unable to sequence Not tested	70 (25.0) 210 (75.0) 24 50	44 (38.3) 71 (61.7) 17 43	114 (28.9) 281 (71.1) 41 93

[1] Including patients with SLL; overall 11.4% of patients had SLL sub-type of CLL (IR: 11.7%; FCR 10.9%)

[2] Determined based on the CKD-EPI formula[6]

[3] As determined by physical exam.

[4] Tested in the 436 (82%) patients who agreed to participate in the correlative study component of the trial and provided a research sample.

Table S2. Antibodies used for MRD analysis:

MRD analysis was performed using an 8 color, single tube flow cytometry based assay as described. The antibodies used are detailed in the table.

Fluorophore	FITC	PE	Percp 5.5	PE-Cy7	APC	APC H7	V450	V500
Antigen	Kappa	Lambda	CD23	CD19	CD5	CD20	CD38	CD45
Clone	Polyclonal	Polyclonal	M-L233	SJ25C1	L17F12	L27	HB7	HI30
Company	Dako	Dako	BD Biosciences	BD Biosciences	BD Biosciences	BD Biosciences	BD Biosciences	BD Biosciences

Abbreviations: BD=Beckman Dickinson

Table S3. Basis of progression.

	IR		FCR	
	n	%	n	%
Absolute lymphocyte count and physical exam	4	10.8	5	12.5
Absolute lymphocyte count only	20	54.1	16	40.0
Physical exam only	11	29.7	12	30.0
Death without documented progression	2	5.4	6	15.0
Biopsy of conglomerate mass in right upper lobe lung	0	0.0	1	2.5
Total	37	100.0	40	100.0

Table S4. Treatment effects in terms of PFS in subgroups. Based on stratified analysis. n=number of patients, e=number of PFS events. HR=hazard ratio (Ibrutinib/FCR). Confidence intervals are 95%. P-values are one-sided.

	n	e	HR	CI.low	CI.high	one-sided pval
All randomized	529	77	0.353	0.223	0.558	1.620e-06
Eligible	498	72	0.319	0.198	0.514	3.744e-07
Female	173	19	0.301	0.118	0.765	3.930e-03
Male	356	58	0.395	0.232	0.673	2.054e-04
White	478	68	0.318	0.194	0.523	9.365e-07
Not-White	38	7	0.809	0.150	4.370	4.028e-01
Age < 60	314	51	0.317	0.180	0.558	1.361e-05
Age >= 60	215	26	0.442	0.201	0.972	1.846e-02
ECOG PS 0	335	46	0.256	0.141	0.466	8.294e-07
ECOG PS 1	182	29	0.653	0.308	1.383	1.311e-01
ECOG PS 0 or 1	517	75	0.359	0.227	0.570	2.862e-06
ECOG PS 1 or 2	194	31	0.609	0.292	1.269	9.046e-02
Rai Stage I-II	281	40	0.305	0.159	0.583	7.313e-05
Rai Stage 0-II	301	41	0.346	0.184	0.651	2.939e-04
Rai Stage III-IV	228	36	0.378	0.194	0.737	1.504e-03
Beta2 Microglobulin Elevated	265	48	0.262	0.144	0.476	1.389e-06
Beta2 Microglobulin Normal	259	29	0.556	0.258	1.199	6.482e-02
Coombs Test Negative	473	68	0.339	0.207	0.555	3.245e-06
Coombs Test Positive	38	6	0.705	0.110	4.530	3.557e-01
Splenomegaly No	311	39	0.364	0.190	0.698	7.672e-04
Splenomegaly Yes	218	38	0.324	0.168	0.628	2.272e-04
Lymphadenopathy No	159	16	0.443	0.138	1.419	8.026e-02
Lymphadenopathy Yes	370	61	0.353	0.210	0.593	2.022e-05
Dohner Del(11q22)	117	22	0.245	0.097	0.617	6.359e-04
Dohner Trisomy 12	97	10	0.733	0.186	2.887	3.277e-01

Dohner Normal	106	18	0.775	0.295	2.040	3.027e-01
Dohner Del(13q)	179	19	0.216	0.078	0.600	6.625e-04
IGHV Mutated	114	14	0.435	0.140	1.355	7.084e-02
IGHV Unmutated	281	41	0.262	0.137	0.498	7.513e-06
IGHV M and not VH 3-21	102	12	0.405	0.123	1.335	6.366e-02
IGHV Unmutated or VH 3-21	293	43	0.271	0.143	0.510	9.389e-06

Table S5. Multivariable Cox proportional hazards model for all randomized patients. Variable selection started with a full model that included the treatment arm, age, ECOG performance status, Rai stage, beta-2 microglobulin (B2M, elevated if > 3.5 mg/L), gender, race, IGHV mutation status, Dohner hierarchical classification, and interaction terms between treatment arm and each of the remaining variables. Backward model selection with ACI was used to arrive at the final model. All main effects were required to remain in the model during model selection. P-values are two-sided.

	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-Value
Arm IR vs FCR	0.255	0.088	0.735	1.143e-02
Age >=60 vs < 60	0.681	0.416	1.116	1.279e-01
PS 1/2 vs 0	0.979	0.491	1.952	9.518e-01
Rai Stage III/IV vs 0/I/II	1.343	0.843	2.142	2.146e-01
B2M Elevated vs Normal	2.794	1.396	5.595	3.719e-03
B2M Unknown vs Normal	0.000	0.000	Inf	9.941e-01
Gender Male vs Female	1.620	0.941	2.790	8.196e-02
Race White vs Other	0.821	0.397	1.698	5.949e-01
IGHV Mutated vs Unmutated	0.401	0.156	1.032	5.826e-02
IGHV Unknown vs Unmutated	0.915	0.434	1.926	8.142e-01
Dohner del(17p) vs del(11q22)	147.547	15.226	1429.799	1.633e-05
Dohner trisomy 12 vs del(11q22)	0.692	0.322	1.490	3.469e-01
Dohner normal vs del(11q22)	1.047	0.547	2.007	8.888e-01
Dohner del(13q) vs del(11q22)	0.595	0.311	1.141	1.184e-01
Dohner other vs del(11q22)	1.209	0.496	2.950	6.759e-01
Arm IR: PS 1/2 vs 0	2.049	0.780	5.383	1.457e-01
Arm IR: B2M Elevated vs Normal	0.441	0.167	1.162	9.770e-02
Arm IR: B2M Unknown vs Normal	NA	NA	NA	NA
Arm IR: IGHV Mutated vs Unmutated	4.313	1.221	15.237	2.319e-02
Arm IR: IGHV Unknown vs Unmutated	1.917	0.642	5.730	2.439e-01

Table S6. Cause of death.

Ibrutinib-Rituximab	On study at time of death	Cause of Death	Baseline Characteristics					Savage therapy received
			Disease stage	11q deletion	Baseline CrCL	IGHV status	Baseline mutations on sequencing	
Patient 1	No	Progressive CLL	III	Yes	96.5	UM	TP53: p.P151S[1]	Rituximab
Patient 2	No	Metastatic lung cancer	IV	No	108.7	UM		Ibrutinib and Rituximab[4]
Patient 3	Yes (last dose before hospitalization and death)	Other cause: acute respiratory failure due to infection	II	No	91.2	M		None.
Patient 4	Yes	Unknown	IV	No	90.6	M		None.
FCR	On study at time of death	Cause of Death	Baseline Characteristics					Savage therapy received
			Disease stage	11q deletion	Baseline CrCL	IGHV status	Baseline mutations on sequencing	
Patient 1	No	Progressive CLL	II	No	91.2	M	No mutation	1.Bendamustine+Rituximab, 2.Rituximab, 3.Venetoclax
Patient 2	Yes	Infection, septic shock	IV	No	94.8			None
Patient 3	No	AML	I	Yes	90.6	UM		None
Patient 4	No	Progressive CLL and infection	II	No	94.5	UM	NOTCH1[2]: p.P2514Rfs4* TBL1XR1: p.V307L	None
Patient 5	No	Progressive CLL	II	No	94.8	UM	ATM: p.K2756* ATM: p.K2317* EGR2[3]: p.E356K	1.Ibrutinib, 2.Methylprednisolone + rituximab 3.Venetoclax 4.Methylprednisolone + Rituximab 5. CHOP
Patient 6	No	AML	II	Yes	94.5	UM		FCR

Patient 7	No	Metastatic colon cancer	II	Yes	95.1	UM		1. Folfox plus Avastin for colon cancer 2. Folfiri and Avastin for colon cancer
Patient 8	No	Drug overdose	III	Yes	92.5	UM		None
Patient 9	No	Lung cancer	I	Yes	95.8	UM		None (lung wedge resection)
Patient 10	No	Progressive CLL	IV	No	97.9	UM	DDX3X[4]: IVS2+2T>C SAMHD1: p.L431F SAMHD1: p.T138A	1. Rituximab 2. Bendamustine (1 cycle)

1. Germline DNA was not available to rule out the non-tumor origin of the variant, however *in silico* analyses strongly suggest its somatic origin and pathogenic effect: a) located in the gene mutational hotspot, b) described over 115 times in multiple cancer types in the Catalog of Somatic Mutations in Cancer (COSMIC), c) damaging functional effect predicted by both, PolyPhen and SIFT tools, and d) not found in any databases analyzing human genetic variation, including The International HapMap Project, the 1000 Genome Project and the NHLBI GO Exome Sequencing Project (ESP).
2. NOTCH1mut was associated with shorter PFS (univariate analysis) and OS (uni and multivariant analysis) in the UK LRF CLL4 trial (**Oscier et al. Blood. 2013;121(3):468-475**). NOTCH1mut is a predictive marker for decreased benefit from the addition of rituximab to FC (**Stilgenbauer et al. Blood. 2014;123(21):3247-3254**)
3. EGR2 activating mutations define a very biologically aggressive subgroup associated with shorter time-to-first-treatment OS in the UK LRF CLL4 trial and CRC cohort (**Young et al. Leukemia (2017) 31, 1547–1554)**
4. DDX3X mutations are associated with worse OS, but the data is in Lenalidomide-treated patients (**Takahashi et al. Blood. 2018;131(16):1820-1832**)
5. Patient went off study after 3 cycles due to missed visits and later received ibrutinib and rituximab off study

Table S7. Grade 3 and above treatment-related adverse events.

Toxicity Type	Treatment Arm					
	Ibrutinib-Rituximab (n=352)			FCR (n=158)		
	Grade			Grade		
	3 n (%)	4 n (%)	5 n (%)	3 n (%)	4 n (%)	5 n (%)
Ear pain	1 (0.3)	-	-	-	-	-
Anemia	9 (2.6)	-	-	13 (8.2)	6 (3.8)	-
Blood and lymphatic system disorders - Other, specify	-	-	-	1 (0.6)	-	-
Febrile neutropenia	8 (2.3)	-	-	21 (13.3)	4 (2.5)	-
Hemolysis	-	-	-	3 (1.9)	1 (0.6)	-
Leukocytosis	34 (9.7)	1 (0.3)	-	1 (0.6)	-	-
Atrial fibrillation	8 (2.3)	2 (0.6)	-	-	-	-
Atrial flutter	3 (0.9)	-	-	-	-	-
Cardiac arrest	-	1 (0.3)	-	-	-	-
Chest pain - cardiac	1 (0.3)	-	-	-	-	-
Heart failure	1 (0.3)	1 (0.3)	-	-	-	-
Pericardial effusion	1 (0.3)	-	-	-	-	-
Sinus bradycardia	1 (0.3)	-	-	-	-	-
Supraventricular tachycardia	1 (0.3)	-	-	-	-	-
Ventricular tachycardia	1 (0.3)	-	-	-	-	-
Chills	1 (0.3)	-	-	1 (0.6)	-	-
Fatigue	7 (2)	-	-	4 (2.5)	-	-
Fever	1 (0.3)	-	-	2 (1.3)	-	-
Multi-organ failure	-	-	1 (0.3)	-	-	-
Pain	2 (0.6)	-	-	-	-	-
Edema limbs	1 (0.3)	-	-	-	-	-
Infusion related reaction	-	1 (0.3)	-	1 (0.6)	-	-

Toxicity Type	Treatment Arm					
	Ibrutinib-Rituximab (n=352)			FCR (n=158)		
	Grade			Grade		
	3	4	5	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Rash maculo-papular	9 (2.6)	-	-	3 (1.9)	-	-
Skin and subcutaneous tissue disorders - Other, specify	2 (0.6)	-	-	1 (0.6)	-	-
Skin ulceration	-	1 (0.3)	-	-	-	-
Abdominal pain	-	-	-	1 (0.6)	-	-
Colitis	1 (0.3)	-	-	1 (0.6)	-	-
Diarrhea	9 (2.6)	-	-	1 (0.6)	-	-
Gastric hemorrhage	1 (0.3)	-	-	-	-	-
Mucositis oral	2 (0.6)	-	-	-	-	-
Nausea	-	-	-	1 (0.6)	-	-
Vomiting	1 (0.3)	-	-	-	-	-
Upper gastrointestinal hemorrhage	1 (0.3)	-	-	-	-	-
Allergic reaction	1 (0.3)	-	-	-	-	-
Immune system disorders - Other, specify	1 (0.3)	-	-	1 (0.6)	-	-
Infections and infestations - Other, specify	5 (1.4)	-	1 (0.3)	1 (0.6)	-	-
Sepsis	-	1 (0.3)	1 (0.3)	-	4 (2.5)	1 (0.6)
Sinusitis	-	-	-	2 (1.3)	-	-
Skin infection	1 (0.3)	-	-	1 (0.6)	-	-
Upper respiratory infection	-	-	-	3 (1.9)	-	-
Urinary tract infection	4 (1.1)	-	-	1 (0.6)	-	-
Enterocolitis infectious	1 (0.3)	-	-	1 (0.6)	-	-
Lung infection	9 (2.6)	-	-	4 (2.5)	-	-
Penile infection	1 (0.3)	-	-	-	-	-
Scrotal infection	1 (0.3)	-	-	-	-	-
Soft tissue infection	2 (0.6)	1 (0.3)	-	-	-	-

Toxicity Type	Treatment Arm					
	Ibrutinib-Rituximab (n=352) Grade			FCR (n=158) Grade		
	3	4	5	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Papulopustular rash	-	1 (0.3)	-	-	-	-
Intraoperative hemorrhage	1 (0.3)	-	-	-	-	-
Alanine aminotransferase increased	5 (1.4)	-	-	-	-	-
Alkaline phosphatase increased	1 (0.3)	-	-	-	-	-
Aspartate aminotransferase increased	5 (1.4)	-	-	1 (0.6)	-	-
Blood bilirubin increased	3 (0.9)	-	-	-	-	-
Creatinine increased	1 (0.3)	-	-	-	-	-
Investigations - Other, specify	1 (0.3)	-	-	-	-	-
Lymphocyte count decreased	6 (1.7)	-	-	42 (26.6)	28 (17.7)	-
Lymphocyte count increased	40 (11.4)	-	-	2 (1.3)	-	-
Neutrophil count decreased	35 (9.9)	45 (12.8)	-	35 (22.2)	34 (21.5)	-
Platelet count decreased	8 (2.3)	2 (0.6)	-	16 (10.1)	6 (3.8)	-
White blood cell decreased	7 (2)	1 (0.3)	-	35 (22.2)	23 (14.6)	-
Anorexia	-	-	-	1 (0.6)	-	-
Dehydration	1 (0.3)	-	-	-	-	-
Hypercalcemia	-	2 (0.6)	-	-	-	-
Hyperglycemia	1 (0.3)	-	-	2 (1.3)	-	-
Hyperkalemia	2 (0.6)	-	-	2 (1.3)	-	-
Hyperuricemia	-	1 (0.3)	-	-	-	-
Hypoalbuminemia	-	-	-	1 (0.6)	-	-
Hyponatremia	1 (0.3)	-	-	-	-	-
Tumor lysis syndrome	2 (0.6)	-	-	2 (1.3)	-	-
Arthralgia	16 (4.5)	-	-	1 (0.6)	-	-
Bone pain	1 (0.3)	-	-	-	-	-
Flank pain	-	-	-	1 (0.6)	-	-
Myalgia	5 (1.4)	-	-	-	-	-

Toxicity Type	Treatment Arm					
	Ibrutinib-Rituximab (n=352) Grade			FCR (n=158) Grade		
	3	4	5	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain in extremity	2 (0.6)	-	-	-	-	-
Generalized muscle weakness	1 (0.3)	-	-	-	-	-
Cognitive disturbance	1 (0.3)	-	-	-	-	-
Dizziness	2 (0.6)	-	-	-	-	-
Encephalopathy	-	-	-	1 (0.6)	-	-
Headache	3 (0.9)	-	-	1 (0.6)	-	-
Peripheral sensory neuropathy	1 (0.3)	-	-	1 (0.6)	-	-
Syncope	1 (0.3)	-	-	-	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	2 (0.6)	-	-	-	-	-
Treatment related secondary malignancy	2 (0.6)	-	-	1 (0.6)	-	-
Depression	1 (0.3)	-	-	-	-	-
Insomnia	-	-	-	1 (0.6)	-	-
Cough	1 (0.3)	-	-	-	-	-
Dyspnea	2 (0.6)	-	-	2 (1.3)	-	-
Hiccups	1 (0.3)	-	-	-	-	-
Pleural effusion	1 (0.3)	-	-	-	-	-
Pneumonitis	-	-	-	1 (0.6)	1 (0.6)	-
Pulmonary edema	-	-	1 (0.3)	-	-	-
Respiratory failure	-	-	1 (0.3)	-	1 (0.6)	-
Respiratory, thoracic and mediastinal disorders - Other, specify	1 (0.3)	-	-	-	-	-
Hematuria	1 (0.3)	-	-	-	-	-
Renal hemorrhage	1 (0.3)	-	-	-	-	-
Urinary tract pain	-	-	-	1 (0.6)	-	-

Toxicity Type	Treatment Arm					
	Ibrutinib-Rituximab (n=352) Grade			FCR (n=158) Grade		
	3	4	5	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Surgical and medical procedures - Other, specify	1 (0.3)	-	-	-	-	-
Hematoma	2 (0.6)	-	-	1 (0.6)	-	-
Hypertension	26 (7.4)	-	-	3 (1.9)	-	-
Hypotension	-	-	-	1 (0.6)	-	-
Thromboembolic event	-	-	-	-	1 (0.6)	-
WORST DEGREE	151 (42.9)	54 (15.3)	2 (0.6)	53 (33.5)	60 (38)	1 (0.6)

Table S8. Second primary cancers.

Site	IR	FCR
	N=354	N=175
Bladder, Urinary Tract	-	1
Brain Tumor	1	-
Breast	3	-
Colon	-	2
Gastric	1	-
Lung Cancer	1	-
Melanoma	6	1
Myelodysplastic Syndrome	-	1
Non-Small Cell Lung	-	1
Other*	1	1
Pancreas	1	-
Prostate	2	1
Skin Cancer Not Melanoma	11	5

* Other, IR: Myeloproliferative disorder – Essential Thrombocytosis. FCR: Pleomorphic rhabdomyosarcoma.

Table S9. Prognostic Characteristics, Response, PFS and OS of FCR Treated Patients in E1912 and German CLL Study Group CLL10 Trial[7]

Characteristic		GCLLSG CLL10[8]	E1912
Prognostic Parameters	B2M>3.5	31%	52%
	IGHV UM	55%	62%
	11q-	24%	22%
Treatment	Mean # cycles	5.27	5.00
	Dose reductions	52%	47.5%
Response	CR	40%[2]	30.3%[3]
MRD negative peripheral blood		49%[4]	61%[5]
Outcome at 36 months	PFS	70%[1]	73%
	OS	90%[1]	92%

[1] Courtesy of Barbara Eichhorst

[2] Response based on abdominal ultrasound or CT, not all patients had CT scan

[3] Response based on CT

[4] At final restaging; MRD results available for 185 of 282 (66%) of patients. MRD results in the peripheral blood at 12 months were negative in 59% of patients however results were only available for 47 of 282 (16.7%) patients

[5] At 12 month response evaluation; MRD results available for 97 of 175 (55%) of patients

Table S10. Treatment discontinuation due to reasons other than progression or death.

	IR	FCR
Started assigned treatment	352	158
Adverse events	40	38
Complication	2	2
Non-protocol therapy	0	1
Second primary	2	0
Withdrawal	7	8
Insurance	2	0
Other	5	0
Total	58	49

Other, IR: wound infection/healing (n=2), missed appointment (n=3).