Supplementary Appendix

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

Supplement to: Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med 2018;379:2517-28. DOI: 10.1056/NEJMoa1812836

Contents

Eligibility Criteria

Documentation of Disease:

Patients must be diagnosed with CLL in accordance with IWCLL 2008 criteria[1] that includes all of the following:

- ≥5x10^9 B lymphocytes (5000/µL) in the peripheral blood
- On morphologic review, the leukemic cells must be small mature lymphocytes, and prolymphocytes must not exceed 55% of the blood lymphocytes.
- CLL cells on immunophenotype (performed locally) must reveal a clonal B-cell population, which express the B cell surface markers of CD19 and CD20, as well as the T-cell antigen CD5. Patients with bright surface immunoglobulin expression or lack of CD23 expression in >10% of cells must lack t(11;14) translocation by interphase cytogenetics.

Staging and Indication for Therapy

- Patients must be intermediate or high-risk Rai stage CLL.
    - Intermediate risk (formerly Rai stage I/II) is defined by lymphocytosis plus enlarged lymph nodes at any site, with or without hepatomegaly or splenomegaly
    - High risk (formerly Rai stage III/IV) is defined by lymphocytosis with or without enlarged nodes and spleen plus disease-related anemia (hemoglobin <11 g/dL) or thrombocytopenia (platelet count <100 x 10^9/L) that is not attributable to autoimmune hemolytic anemia or thrombocytopenia
- Patients must meet criteria for treatment as defined by IWCLL 2008 guidelines[1] which includes at least one of the following criteria:
    - Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia)
    - Massive (≥6 cm below the costal margin), progressive or symptomatic splenomegaly
    - Massive nodes (≥10 cm) or progressive or symptomatic lymphadenopathy
    - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy
    - Constitutional symptoms, which include any of the following:
        - Unintentional weight loss of 10% or more within 6 months
        - Significant fatigue
        - Fevers >100.5 degrees F for 2 weeks or more without evidence of infection
        - Night sweats >1 month without evidence of infection

Prior Treatment

- Patients must not have had prior therapy for CLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab or steroids).
- Treatment with rituximab and/or high dose corticosteroids for autoimmune complications of CLL must be complete at least 4 weeks prior to enrollment. Palliative steroids must be at a dose not higher than 20 mg/day of prednisone or equivalent corticosteroid at the time of registration.

Age ≥ 65 years

Eastern Cooperative Oncology Group Performance Status 0-2

Active Hepatitis B

Patients with active hepatitis B defined by hepatitis B surface antigen positivity or core antibody positivity in the presence of hepatitis B DNA are not eligible for this study. Patients with a positive hepatitis B core antibody but with negative hepatitis B DNA may participate, but must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

IVIG can cause a false positive hepatitis B serology. If patients receiving routine IVIG have core antibody or surface antigen positivity without evidence of active viremia (negative hepatitis B DNA) they may still participate in the study, but should have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

Active systemic anticoagulation

Patients must not be receiving active systemic anticoagulation with heparin or warfarin. Patients must be off warfarin therapy for at least 30 days prior to enrollment.

Active intercurrent disease

Patients with Class III or Class IV heart failure by New York Heart Association, those with unstable angina, and those with uncontrolled arrhythmia are not eligible.

Patients who have had a myocardial infarction, intracranial bleed, or stroke within the past 6 months are not eligible.

Patients with known HIV are eligible if their CD4 count is ≥ 350 cells/mm3 and if they are not taking prohibited CYP-interacting medications.

Richter's transformation or prolymphocytic leukemia

Patients must not have any history of Richter's transformation or prolymphocytic leukemia (prolymphocytes in blood > 55%).

Prednisone or equivalent corticosteroid

Patients must not require more than 20 mg prednisone or equivalent corticosteroid daily.

Intravenous antibiotics

Patients must not have uncontrolled active systemic infection requiring intravenous antibiotics.

CYP3A4/5 inhibitor or inducer

Patients must not have continued requirement for therapy with a strong CYP3A4/5 inhibitor or inducer.

Allergy to mannitol

Patients must not have a known allergy to mannitol.

Significant hypersensitivity to rituximab

Patients must not have prior significant hypersensitivity to rituximab (not including infusion reactions).

Prior Surgery

Patients may not have had major surgery within 10 days of enrollment, or minor surgery within 7 days of enrollment. Examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration of a joint. The decision about whether a surgery is major or minor can be made at the discretion of the treating physician.

Initial laboratory values

Patients must meet the following required initial laboratory values:

ANC	≥ 1,000/μL unless due to bone marrow involvement
AST or ALT	≤ 2.5 x upper limits of normal except if due to disease infiltration of the liver
Bilirubin	≤ 1.5 x upper limits of normal (unless due to liver involvement, hemolysis, or Gilbert's disease)
Creatinine Clearance	≥ 40 mL/min*
Platelet count (untransfused)	≥ 30,000/μL

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

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

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, cycle 4 day 1, cycle 9 day 1, cycle 27 day 1, and progression. Bone marrow biopsy was performed at baseline, cycle 9 day 1, cycle 27 day 1, and progression.

Treatment Plan

Arm A: Bendamustine/Rituximab

Treatment on Arm A consists of six 28-day cycles. The day **before** day 1 of cycle 1 (day 0), rituximab is given at 375 mg/m^2 IV, then at 500 mg/m^2 IV on day 1 of cycles 2-6. Bendamustine is given at 90 mg/m^2 IV on days 1 and 2 of each cycle. During cycle 1, at the discretion of the treating investigator, the bendamustine may be given at a dose of 70 mg/m^2 rather than 90. Subsequent cycles should be administered at 90 mg/m^2.

- **Recommended/prohibited ancillary therapy is outlined in the protocol**
- **Premedication:** Premedication per institutional guidelines is permitted, however, recommended premedication is the following:
  - **Bendamustine:** ondansetron 16 mg IV prior to each dose
  - **Rituximab:** acetaminophen 650 mg PO and diphenhydramine (or equivalent antihistamine) 50 mg PO/IV 30 minutes prior to each dose; other premedications may be given per institutional guidelines.
- **Drug administration**

  Full administration guidelines are outlined in the protocol. Bendamustine and rituximab are both administered intravenously. Bendamustine should be administered prior to rituximab on days that they are both given, but the order of administration may be altered per institutional guidelines.
- **Dose modifications/dose delays after cycle 1 are outlined in the protocol**
- Patients enrolled on Arm A bendamustine plus rituximab will be eligible to cross over to single-agent ibrutinib upon documentation of disease progression. These patients will remain on ibrutinib until they experience a second disease progression. The follow-up schedule for those patients who remain on ibrutinib should match those of Arm 2.

Arm B: Ibrutinib

Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each 28-day cycle, until disease progression as defined by IWCLL guidelines.[1] Because of the well-documented lymphocytosis that occurs early with this agent and is not associated with disease progression, progressive lymphocytosis in the absence of other signs of disease progression (e.g. splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) **will not** be considered disease progression.

- **Recommended/prohibited ancillary therapy is outlined in the protocol**
- Premedication is not required.
- **Drug administration**

Full administration guidelines are outlined in the protocol. Ibrutinib is administered by mouth as three capsules daily.

- Patients on ibrutinib should 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. The patient should not take extra capsules to make up the missed dose, and any remaining study drug must be returned at the next scheduled visit.
- Dose modifications/dose delays after cycle 1 are outlined in the protocol

Arm C: Ibrutinib/Rituximab

Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each 28-day cycle, plus rituximab 375 mg/m^2 IV weekly for four weeks starting on cycle 2 day 1 (days 1, 8, 15, and 22), then day 1 of cycles 3 through 6. Ibrutinib will be continued past cycle 6 until disease progression. Because of the well-documented lymphocytosis that occurs early with this agent and is not associated with disease progression, progressive lymphocytosis in the absence of other signs of disease progression (e.g. splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) **will not** be considered disease progression.

- **Recommended/prohibited ancillary therapy is outlined in the protocol**
- **Premedication**

  No premedication is required for ibrutinib. Rituximab premedication per institutional guidelines is permitted. Recommended premedication is acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV (or equivalent antihistamine) 30 minutes prior to each dose
- **Drug administration**

  Full administration guidelines are outlined in the protocol. Ibrutinib is administered orally as three capsules daily, and rituximab is administered intravenously. Ibrutinib should be administered prior to rituximab on days when both agents are given.
- Patients on ibrutinib should 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. The patient should not take extra capsules to make up the missed dose, and any remaining study drug must be returned at the next scheduled visit.
- **Dose modifications/dose delays after cycle 1 are outlined in the protocol**.

Dose Modifications And Management of Toxicity

Dose Modifications for Hematologic Toxicity

G-CSF and GM-CSF may not be used prophylactically to avoid dose reductions, but may be used in cases of prolonged or recurrent neutropenia or in a patient who has had neutropenia with previous cycles. Dose modifications should be made based on day 1 values for each cycle, or the presence of significant bleeding or febrile neutropenia. Hematologic toxicity will be 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)***
1	11%-24%	≥1500 and <2000
2	25%-49%	≥1000 and <1500
3	50%-75%	≥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.

**Hgb levels must be below normal levels for any grade toxicity to be recorded.

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

Arm A

Dose Level	**Bendamustine**	**Rituximab**
1 (starting dose)	90 mg/m^2	500 mg/m^2
-1	50 mg/m^2	500 mg/m^2
-2	30 mg/m^2	500 mg/m^2

- For grade 3 or 4 hematologic toxicity (or significant bleeding), hold therapy until toxicity returns to ≤ grade 1, and then dose reduce by 1 level. If patient experiences grade 3 or 4 toxicity at dose level -2, protocol therapy should be discontinued.
- For febrile neutropenia, hold therapy until fever resolves and ANC is >1000, and then dose reduce by 1 level. If patient experiences febrile neutropenia at dose level -2, protocol therapy should be discontinued.
- Once reduced, dose levels may not be escalated

Arm B

Dose Level	Ibrutinib
1 (starting dose)	420 mg
-1	280 mg
-2	140 mg

- For grade 3 or 4 hematologic toxicity, significant bleeding, or febrile neutropenia, hold therapy until toxicity returns to ≤ grade 1. For the first occurrence, drug may be restarted at the original dose. For the second occurrence and beyond, dose reduce by 1 level.

- Ibrutinib may be held for up to 28 consecutive days for drug-related toxicity. If drug-related toxicity persists, ibrutinib must be discontinued permanently.
- Patients who are dose-reduced and are stable for 3 months may have dose escalated 1 level.
- Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

  A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of toxicity.

Arm C

First 6 months

Dose Level	Ibrutinib	Rituximab
1 (starting dose)	420 mg	375 mg/m2
-1	420 mg	No rituximab
-2	280 mg	No rituximab
-3	140 mg	No rituximab

Subsequent months

Dose Level	Ibrutinib
1 (starting dose)	420 mg
-1	280 mg
-2	140 mg

- For grade 3 or 4 hematologic toxicity, significant bleeding, or febrile neutropenia, hold therapy until toxicity returns to ≤ grade 1. For the first occurrence, drug may be restarted at the original dose. For the second occurrence and beyond, dose reduce by 1 level.
- Ibrutinib may be held for up to 28 consecutive days for drug-related toxicity. If drug-related toxicity persists, ibrutinib must be discontinued permanently.
- Patients who are dose-reduced and are stable for 3 months may have dose escalated 1 level.
- Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated

with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of toxicity.

Dose Adjustments for Non-Hematologic Toxicity

Dose Level	**Bendamustine**	**Ibrutinib**
1 (starting dose)	**90 mg/m^2**	**420 mg**
-1	**50 mg/m^2**	**280 mg**
-2	**30 mg/m^2**	**140 mg**

- For grade 3 or 4 non-hematologic toxicity at possibly, probably, or definitely related to bendamustine, hold bendamustine and rituximab until toxicity returns to ≤ grade 1, and then dose reduce by 1 level. If patient experiences grade 3 or 4 toxicity at dose level -2, bendamustine should be discontinued, but rituximab can continue for total course or can be discontinued at the discretion of the treating physician.
- For grade 3 or 4 non-hematologic toxicity at least possibly, probably, or definitely attributable to ibrutinib, hold ibrutinib until toxicity returns to ≤ grade 1. For a first occurrence, ibrutinib may then be restarted at the same dose. For a second occurrence, once toxicity resolves, dose reduce by 1 dose level. Prior to dose reduction for diarrhea, aggressive supportive care should be instituted. Recommended agents for ibrutinib-induced diarrhea include cholestyramine and diphenoxylate/atropine.
- For infusion reactions attributable to rituximab, supportive care should be provided per institutional protocols. Rituximab can be continued without dose reduction. At the discretion of the treating physician and with study chair approval, rituximab and/or bendamustine can be discontinued for severe infusion reactions.
- Rituximab should be discontinued in the following circumstances: progressive multifocal leukoencephalopathy (PML), significant vesicular or bullous dermatitis, Stevens-Johnsons syndrome, or development of hepatitis B reactivation.
- Patients who require the initiation of systemic anticoagulation should have ibrutinib held and be placed on low molecular weight heparin (concomitant warfarin therapy is prohibited). Treatment with ibrutinib should be held and not be restarted until the patient is clinically stable and has no signs of bleeding. Patients should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.
- For Grade 3 or 4 skin reactions or infusion reaction/anaphylaxis at least possibly, probably or definitely attributable to bendamustine, bendamustine should be permanently discontinued and rituximab may be discontinued as well at the discretion of the treating physician.

- 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.
- Ibrutinib is metabolized in the liver. Please see the Child-Pugh scoring system outlined in Appendix VI to determine whether dose modifications are warranted according to the following instructions. For patients who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Patients who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better and may be re-treated according to resolved hepatic conditions (i.e., 140 mg or 280 mg for moderate or mild impairment, respectively). Monitor patients for signs of toxicity and follow dose modification guidance as needed.
- For Grade 2 toxicity that is causing significant discomfort or functional impairment, dose interruption and modifications may be made using the same guidelines as for Grades 3 and 4 at the discretion of the treating physician and after discussion with the study chair.

Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation

Geriatric Assessment Methods

The geriatric assessment includes validated measures of functional status, comorbidity, psychological status, social activity, cognition, social support, and nutritional status. [2] The feasibility for incorporating this assessment in cooperative group trials has been previously determined.

All patients enrolled on the study were offered the opportunity to participate in a geriatric assessment correlative study. Participants who enrolled on the correlative study, completed a geriatric assessment at three timepoints (pre-treatment, after cycle 6, and at the end of treatment or at 2 years). The geriatric assessment consists of a self-assessment completed by the patient and a questionnaire completed by a healthcare provider. The patient assessment includes validated measures of functional status, comorbidity, psychological status, social activity, social support, and nutritional status. [3,4 5 6 7] The healthcare provider assessment includes an evaluation of the patient's function, cognition, and nutrition. [8-10] A full description of the measures included in the geriatric assessment, as well as the study describing the feasibility of capturing these measures in cooperative group studies has been reported previously. [2] Geriatric assessment measures were scored based on established scoring procedure. Scores were reported as mean ± standard deviation, median and range or frequencies where appropriate.

Correlative Laboratory Study Methods

Central FISH

Central FISH was performed in the clinical cytogenetics laboratory at The Ohio State University. Peripheral blood samples were collected into sodium heparin Vacutainer® tubes and cultured in RPMI media supplemented with FBS, L-glutamine and CpG/PWM/PKM for 72 or 96 hours. Samples were fixed and slides were made following the standard laboratory procedures. FISH was done according to the manufacturer's recommendations, except prior to hybridization, slides were pretreated with pepsin and postfix solution. Co-denaturation of probe and sample was done on HyBrite (Abbot Molecular, Downers Grove, IL) for 5 minutes at 73° C. Hybridization was carried out overnight at 37° C, and slides were washed in 0.4xSSC/0.3% NP-40 for 2 min at 73° C.

For each sample 8 probes were analyzed, CEP 12, D13S319, ATM, TP53, BCL6, MYC, IGH/CCND1-XT) (Abbott Molecular, Downers Grove, IL) and SEC63 (Kreatech Biotechnology, Netherlands). After counterstaining with DAPI, the signals were viewed using a fluorescence microscope (Zeiss Axioscope 40) equipped with appropriate filters and analyzed with Applied Imaging System. At least 200 cells for each probe were counted and scoring was done independently by two technicians. For documentation, 2 images for each probe were captured.

Central Zap 70 Methylation

Central Zap 70 methylation analysis was performed in the clinical molecular pathology laboratory at The Ohio State University. Genomic DNA was extracted using DNA Blood Mini Kit (Qiagen) from peripheral blood sample comprising at least 40% lymphocytic leukemia cells followed by bisulfite treatment of DNA to convert unmethylated cytosines to uracils using EZ DNA Methylation-Gold Kit (Zymogen Research). The bisulfite-treated DNA was amplified by PCR using primers flanking CpG island at +223 of

ZAP70 (5'- tgggagacctggcagaggatgaa, 5'- cctcctgactcccagttaatattctgtctt-3'). [11] The PCR products were analyzed by pyrosequencing on PyroMark Q96 ID Pyrosequencer (Qiagen) with a sequencing primer 5'-atgagtgagaaattttgg -3'. The ratio of methylated "C" versus unmethylated "T" was determined with a cutoff level at 20% validated with clinical correlation. [11]

TP53 Mutation Analysis

TP53 mutation analysis was performed in the Experimental Hematology Laboratory at The Ohio State University. DNA was extracted from peripheral blood mononuclear cells in the standard fashion and sonicated to an average size of 350 nucleotides. Using a KAPA HyperPrep kit (Roche), custom Illumina sequencing adapters with error-correcting unique molecular indices were ligated to the DNA fragments, which were then hybridized to biotinylated oligonucleotide probes (IDT, Skokie, IL) spanning the entire coding sequence of TP53. Captured DNA was amplified and sequenced on a Hiseq 4000 (Illumina, San Diego, CA). Sequencing data were processed according to a modified GATK best-practices [12] workflow, variants present in >1% of human populations were filtered out, and final mutation data were aggregated and reported with Mucor. [13]

IGVH Mutation Analysis

IGVH mutation analysis was performed in the Experimental Hematology Laboratory at The Ohio State University. RNA was extracted from peripheral blood mononuclear cells using the Qiagen (Hilden, Germany) miRNeasy kit. Samples with RNA Integrity Number >= 7 were subjected to library preparation using the Illumina TruSeq stranded mRNA kit, and were sequenced on a Hiseq 2500 instrument targeting 40x10^6 read pairs per sample. 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 Ig-ID method. [14]

Minimal Residual Disease Analysis

Minimal residual disease analysis was performed in the clinical flow cytometry laboratory at The Ohio State University. Cryopreserved Ficoll isolated mononuclear cells were thawed rapidly in a water bath at 37C. Cells were immediately washed with rewarmed to 37% Hanks balanced Salt Solution (HBSS) without phenol red medium supplemented with 5% bovine serum albumin (BSA) and resuspended in 1000 ml of HBSS/BSA medium. Following red cell lysis with Coulter lyse solution (Beckman Coulter) cells were stained for 15 minutes in room temperature in dark (Combination of antibodies listed in Supplemental Table 1). Following staining cells were washed with HBSS/BSA and analyzed using Navios flow cytometry analyzer (Beckman Coulter) using CXP software. Minimum 500,000 events were acquired. Analysis was performed using CXP V2.0 software with prism plot utility (Beckman coulter). Cells were analyzed using CD45 and sides scatter characteristic gating strategy. Viability was assessed using 7ADD dye exclusion method. Gated lymphocytes were interrogated for the presence of B lymphocytes that express immunophenotype c/w chronic lymphocytic leukemia. This method allows reliable and reproducible detection of CLL MRD at the level of 0.01% of all events that corresponds to 1 CLL cell in 10,000 total cells analyzed. Criteria used for CLL MRD status determination for each sample are described in detail in [15] [16]

Statistical Methods

Primary Endpoint. For the primary endpoint of PFS, the overall Type I error for the two main comparisons of interest (BR vs. ibrutinib and BR vs. IR) was pre-specified in the protocol and constrained to 0.05, with each comparison having a one-sided Type I error constrained to 0.025 via Bonferroni correction. Since the comparison of ibrutinib vs. IR was only of interest if both ibrutinib-containing regimens were found to be superior to the BR control arm, the Type I error for this comparison was constrained to 0.05. There were three planned interim analyses for each of the two main comparisons of interest (BR vs. ibrutinib and BR vs. IR) and two planned interim analyses for the comparison of ibrutinib vs. IR. The Lan-DeMets error spending rate function with O'Brien-Fleming boundaries were utilized for tests of superiority and futility boundaries corresponding to a hazard ratio greater than 1.05 and in favor of BR were developed. The interim and final analysis boundaries and characteristics were generated using the East 5 clinical trial software program (version 5.4, Cytel Inc), and are shown below.

Interim and Final Analysis Boundaries for Ibrutinib vs. BR or IR vs. BR					
Analysis Number	Information fraction	Cumulative events	Alpha spent	Beta spent	Truncated boundary
1	0.33	53	0.0001	0.005	3.73
2	0.50	80	0.00153	0.0119	2.96
3	0.75	120	0.00965	0.0356	2.359
4	1.0	159	0.025	0.1	2.014
Interim and Final Analysis Boundaries for IR vs. Ibrutinib					
Analysis Number	Information fraction	Cumulative events	Alpha spent	Beta spent	Boundary
1	0.50	60	0.00557	0.0238	2.538
2	0.75	89	0.0236	0.0712	2.016
3	1.0	119	0.05	0.2	1.72

Secondary Endpoints. Overall survival (OS) was defined from the date of randomization until the date of death from any cause, censoring patients alive at the last date of contact. Response was defined according to the IWCLL 2008 guidelines. Best response was captured across visits that included a CT scan and physical exam, or by physical exam alone when a CT scan was not performed. Best response was defined according to the following hierarchy: complete response (CR) > complete clinical remission (CCR) > nodal partial response (nPR) > partial response (PR) > partial remission with lympocytosis (PR-L) > stable disease (SD) > progressive disease (PD) > not evaluated (NE). Overall response rate was defined as the number of patients with at least PR-L as a best response out of the total number of patients randomized. Best response rates for a particular category were defined as the number of patients achieving that best response out of the total number of patients randomized. Patients who did not have a response assessment were considered failures. Minimal residual disease (MRD) negative rates were

defined as the number of patients with a percentage of MRD cells less than 0.01 in samples with at least 60% viability out of the total number of patients randomized.

Analyses: Chi-square or Fisher's exact tests were used to compare categorical baseline characteristics, patterns of adverse events (AEs), and best response rates among the treatment groups.[1] Kruskal-Wallis tests were used to compare continuous baseline characteristics among the treatment groups.[1] PFS and OS curves were estimated using the method of Kaplan-Meier for the intent-to-treat population and compared between treatment groups using log-rank tests. [2,3] Forest plots were used to illustrate the comparisons between the arms within subgroups defined by the stratification factors. Univariable and multivariable Cox proportional hazards models for the primary end point of PFS were fit (using patients who had complete data on all predictors) to understand the impact of treatment, age, gender, baseline Rai stage, ECOG performance status, white blood cell counts, elevated beta-2 microglobulin, elevated lactate dehydrogenase, splenomegaly, Zap-70 methylation, high-risk FISH abnormalities (del(17p) or del(11q)), TP53 mutations, and complex karyotype on outcome.[2,3] The primary multivariable model was constructed with Rai stage (high vs intermediate), Zap-70 methylation ($\geq$20% vs <20%), and high-risk FISH abnormalities (presence of del(17p) or del(11q) vs absent) as stratification factors and including all other variables with $P < 0.20$ from the univariable models. Due to the strong correlation between TP53 mutations and presence of del(17p) by FISH, as well as the desire to analyze the presence of del(17p) abnormalities separately from del(11q) abnormalities, a second multivariable model was constructed with Rai stage (high vs intermediate) and Zap-70 methylation ($\geq$20% vs <20%) as stratification factors, including Dohner's hierarchical classification (del(17p) vs del(11q) vs other) instead of TP53 mutations, and including all other variables with $P < 0.20$ from the univariable models. The models with main effects from the univariable and multivariable Cox proportional hazards models are presented in Supplemental Tables 4 (primary model results) and 5 (secondary model results). All pairwise interactions between treatment group and variables in the multivariable models for PFS were investigated using a backward elimination approach. Significant interaction effects were illustrated with Kaplan-Meier plots.

Additional analyses were performed within the subset of patients with IGVH mutation results available. Kaplan-Meier plots were used to illustrate the comparisons between treatment arms for subgroups of patients with IGVH mutated and unmutated CLL, respectively.

Per protocol, no adjustment was made for multiple comparisons performed as part of secondary analyses, but tests with $P < 0.05$ were considered significant. All analyses were done using SAS® version 9.4.

Participating Institutions

Abbott-Northwestern Hospital
Allan Blair Cancer Centre
Aria Health-Torresdale Campus
Ascension Saint John Hospital
Asheville Hematology-Oncology Associates
Aurora Cancer Care-Grafton
Aurora Cancer Care-Kenosha South
Aurora Cancer Care-Milwaukee West
Aurora Cancer Care-Racine
Aurora Medical Center in Summit
Aurora Sinai Medical Center
Avera Cancer Institute
Baystate Medical Center

Beebe Medical Center
Boston Medical Center
Bozeman Deaconess Hospital
Bryn Mawr Hospital
CHI Health Saint Francis
CHUM - Centre Hospitalier de l'Universite de Montreal
CSSS Champlain-Charles Le Moyne
California Pacific Medical Center-Pacific Campus
Cancer Care Specialists of Illinois-Swansea
Cancer Center of Kansas - Wichita
Cancer Center of Kansas-Wichita Medical Arts Tower
Cancer Centers of Southwest Oklahoma Research
Capital Region Southwest Campus
Carle Cancer Center
Carle on Vermilion
Case Western Reserve University
Cedars-Sinai Medical Center
Central Care Cancer Center - Great Bend
Central Vermont Medical Center
Champlain Valley Physicians Hospital Medical Center
City of Hope Comprehensive Cancer Center
Cleveland Clinic Cancer Center Mansfield
Cleveland Clinic Cancer Center/Fairview Hospital
Cleveland Clinic Foundation
Cleveland Clinic Wooster Family Health and Surgery Center
Coborn Cancer Center at Saint Cloud Hospital
Columbia University/Herbert Irving Cancer Center
Columbus Oncology and Hematology Associates Inc
Cotton O'Neil Cancer Center / Stormont Vail Health
Covenant Medical Center
CoxHealth South Hospital
Crossroads Cancer Center
Dana-Farber/Harvard Cancer Center
Danbury Hospital
Dartmouth-Hitchcock Medical Center/Norris Cotton Cancer Center
Delaware Clinical and Laboratory Physicians PA
Duke University Medical Center
Eastern Maine Medical Center
Eastern Maine Medical Center Cancer Care
Emory University Hospital/Winship Cancer Institute
Englewood Hospital and Medical Center
Erlanger Medical Center
Fairview-Southdale Hospital
FirstHealth of the Carolinas-Moore Regional Hospital

Fort Wayne Medical Oncology and Hematology Inc-Parkview
Fowler Family Center for Cancer Care
Fox Chase Cancer Center
Geisinger Medical Center
Geisinger Wyoming Valley/Henry Cancer Center
Greenville Health System Cancer Institute-Eastside
Greenville Health System Cancer Institute-Spartanburg
Gundersen Lutheran Medical Center
HSHS Saint Nicholas Hospital
Harold Alfond Center for Cancer Care
Hematology Oncology Associates of Central New York-East Syracuse
Hematology Oncology Associates of Fredericksburg Inc
Hematology and Oncology Associates of North East Pennsylvania
Humber River Regional Hospital
Illinois Cancer Specialists-Hinsdale
Illinois CancerCare-Bloomington
Illinois CancerCare-Galesburg
Illinois CancerCare-Macomb
Illinois CancerCare-Peoria
Illinois CancerCare-Peru
Jewish General Hospital
John Muir Medical Center-Concord
Joliet Oncology-Hematology Associates Limited
Juravinski Cancer Centre at Hamilton Health Sciences
Kaiser Permanente - Panorama City
Kaiser Permanente Los Angeles Medical Center
Kaiser Permanente Medical Center - Santa Clara
Kaiser Permanente Medical Center-Vacaville
Kaiser Permanente Northwest
Kaiser Permanente San Leandro
Kaiser Permanente-Anaheim
Kaiser Permanente-Baldwin Park
Kaiser Permanente-Bellflower
Kaiser Permanente-Franklin
Kaiser Permanente-Fresno
Kaiser Permanente-Irvine
Kaiser Permanente-Modesto
Kaiser Permanente-Oakland
Kaiser Permanente-Richmond
Kaiser Permanente-Riverside
Kaiser Permanente-San Diego Zion
Kaiser Permanente-San Rafael
Kaiser Permanente-Santa Teresa-San Jose
Kaiser Permanente-South Sacramento

Kaiser Permanente-Vallejo
Kaiser Permanente-Walnut Creek
Katmai Oncology Group
Kingston Health Sciences Centre
Kootenai Cancer Center
Lahey Hospital and Medical Center
Lankenau Medical Center
Lawrence Memorial Hospital
Lehigh Valley Hospital - Muhlenberg
Lehigh Valley Hospital-Cedar Crest
Lexington Medical Center
London Regional Cancer Program
Loyola University Medical Center
Maimonides Medical Center
Margaret R Pardee Memorial Hospital
Massachusetts General Hospital Cancer Center
Mayo Clinic
Mayo Clinic in Arizona
McFarland Clinic PC - Ames
McLaren Cancer Institute-Bay City
McLeod Regional Medical Center
MedStar Franklin Square Medical Center/Weinberg Cancer Institute
MedStar Georgetown University Hospital
MedStar Washington Hospital Center
Medical Oncology Hematology Consultants PA
Medical University of South Carolina
Mercy Health Mercy Campus
Mercy Hospital Oklahoma City
Mercy Hospital Springfield
Mercy Medical Center - North Iowa
Miami Valley Hospital
Michael Garron Hospital
Michiana Hematology Oncology PC-Elkhart
Michiana Hematology Oncology PC-Mishawaka
Minneapolis Veterans Medical Center
Mission Hospital Inc-Memorial Campus
Mount Carmel Health Center West
Mount Sinai Medical Center
New Hampshire Oncology Hematology PA-Hooksett
Newark Beth Israel Medical Center
Norris Cotton Cancer Center-Manchester
NorthShore University HealthSystem-Evanston Hospital
NorthShore University HealthSystem-Glenbrook Hospital
Northside Hospital

Northwell Health/Center for Advanced Medicine
Northwestern University
Norwalk Hospital
Odette Cancer Centre- Sunnybrook Health Sciences Centre
Ohio State University Comprehensive Cancer Center
Olathe Medical Center
Orange Regional Medical Center
Ottawa Hospital and Cancer Center-General Campus
Overlook Medical Center
PCR Oncology
Paoli Memorial Hospital
Park Nicollet Clinic - Saint Louis Park
Physicians' Clinic of Iowa PC
Porter Adventist Hospital
Poudre Valley Hospital
Presbyterian Intercommunity Hospital
ProHealth Waukesha Memorial Hospital
Providence Alaska Medical Center
Rapid City Regional Hospital
Reading Hospital
Reid Health
Rocky Mountain Cancer Centers-Penrose
Roswell Park Cancer Institute
Rutgers Cancer Institute of New Jersey
Sacred Heart Hospital
Saint Francis Cancer Center
Saint Joseph Mercy Hospital
Saint Luke's East - Lee's Summit
Saint Luke's Hospital of Duluth
Saint Luke's Hospital of Kansas City
Saint Luke's Mountain States Tumor Institute
Saint Luke's Mountain States Tumor Institute - Meridian
Saint Luke's Mountain States Tumor Institute-Twin Falls
Saint Peter's Community Hospital
Saint Vincent Hospital Cancer Center Green Bay
Saint Vincent Hospital Cancer Center at Oconto Falls
Saint Vincent Hospital Cancer Center at Saint Mary's
Sanford Bismarck Medical Center
Sanford Roger Maris Cancer Center
Shenandoah Oncology PC
Simonds-Sinon Regional Cancer Center
Sinai Hospital of Baltimore
Smilow Cancer Hospital Care Center at Saint Francis
Southeastern Medical Oncology Center-Goldsboro

Spartanburg Medical Center
Stanford Cancer Institute Palo Alto
State University of New York Upstate Medical University
Stony Brook University Medical Center
Stronach Regional Health Centre at Southlake
The Hospital of Central Connecticut
The Mark H Zangmeister Center
The Moncton Hospital
The University of Kansas Cancer Center-Lee's Summit
Thomas Jefferson University Hospital
Tom Baker Cancer Centre
Trinity Cancer Care Center
Tufts Medical Center
UNC Lineberger Comprehensive Cancer Center
UT Southwestern/Simmons Cancer Center-Dallas
United Hospital
University Health Network-Princess Margaret Hospital
University of Arizona Cancer Center-North Campus
University of Chicago Comprehensive Cancer Center
University of Illinois
University of Kansas Cancer Center
University of Kansas Cancer Center-Overland Park
University of Miami Miller School of Medicine-Sylvester Cancer Center
University of New Mexico Cancer Center
University of Pittsburgh Cancer Institute (UPCI)
University of Rochester
University of Texas Health Science Center at San Antonio
University of Virginia Cancer Center
Veterans Administration New Jersey Health Care System
Veterans Affairs Connecticut Healthcare System-West Haven Campus
Virginia Cancer Institute
Virginia Commonwealth University/Massey Cancer Center
Virginia Oncology Associates-Hampton
Wake Forest University Health Sciences
Washington University School of Medicine
Wayne Memorial Hospital
Wayne State University/Karmanos Cancer Institute
WellSpan Health-York Hospital
Wentworth-Douglass Hospital
West Michigan Cancer Center
West Virginia University Healthcare
Western Maryland Regional Medical Center
White River Junction Veteran Administration Medical Center
William Beaumont Hospital - Troy

William Beaumont Hospital-Royal Oak
Yale University
Yale-New Haven Shoreline Medical Center
York Hospital

The following institutional networks have participated in this study:
Avera Cancer Institute, Sioux Falls, SD, Amy Krie; Beaumont NCI Community Oncology Research Program, Royal Oak, MI, John Robertson, UG1CA190002; Cancer Research Consortium of West Michigan NCORP, Grand Rapids, MI, Kathleen Yost, UG1CA189860; Cancer Research for the Ozarks NCORP, Springfield, MO, Jay Carlson, UG1CA189822; Carle Cancer Center NCI Community Oncology Research Program, Urbana, IL, Kendrith Rowland, UG1CA189861; Cedars-Sinai Medical Center, Los Angeles, CA, Armando Giuliano; Coborn Cancer Center at Saint Cloud Hospital, Saint Cloud, MN, Donald Jurgens; Colorado Cancer Research Program NCORP, Denver, CO, Keren Sturtz, UG1CA189805; Columbia University Minority Underserved NCORP, New York, NY, Gary Schwartz, UG1CA189960; Columbus NCI Community Oncology Research Program, Columbus, OH, Timothy Moore, UG1CA189954; Dana-Farber / Partners CancerCare LAPS, Boston, MA, Harold Burstein, U10CA180867; Dartmouth College - Norris Cotton Cancer Center LAPS, Lebanon, NH, Konstantin Dragnev, U10CA180854; Dayton NCI Community Oncology Research Program, Dayton, OH, Howard Gross, UG1CA189957; Delaware/Christiana Care NCI Community Oncology Research Program, Newark, DE, Gregory Masters, UG1CA189819; Duke University - Duke Cancer Institute LAPS, Durham, NC, Jeffrey Crawford, U10CA180857; Eastern Maine Medical Center Cancer Care, Brewer, ME, Thomas Openshaw; Geisinger Cancer Institute NCI Community Oncology Research Program, Danville, PA, Srilatha Hosur, UG1CA189847; Heartland Cancer Research NCORP, Decatur, IL, Bryan Faller, UG1CA189830; Hematology Oncology Associates of Central New York-East Syracuse, East Syracuse, NY, Jeffrey Kirshner; Iowa-Wide Oncology Research Coalition NCORP, Des Moines, IA, Robert Behrens, UG1CA189816; Kansas City NCI Community Oncology Research Program, Prairie Village, KS, Rakesh Gaur, UG1CA189853; Loyola University Medical Center, Maywood, IL, Scott Smith; Main Line Health NCORP, Wynnewood, PA, Paul Gilman, UG1CA189852; Mayo Clinic LAPS, Rochester, MN, Steven Alberts, U10CA180790; MedStar Georgetown University Hospital, Washington, DC, Filipa Lynce; Metro Minnesota Community Oncology Research Consortium, Saint Louis Park, MN, Daniel Anderson, UG1CA189863; Michigan Cancer Research Consortium NCORP, Ann Arbor, MI, Philip Stella , UG1CA189971; Montana Cancer Consortium NCORP, Billings, MT, Benjamin Marchello , UG1CA189872; Mount Sinai Hospital, New York, NY, Lewis Silverman; Mount Sinai Medical Center, Miami Beach, FL, Michael Schwartz; NCORP of the Carolinas (Greenville Health System NCORP), Greenville, SC, Jeffrey Giguere, UG1CA189972; New Hampshire Oncology Hematology PA-Hooksett, Hooksett, NH, Douglas Weckstein; New Mexico Minority Underserved NCORP, Albuquerque, NM, Zoneddy Dayao, UG1CA189856; NorthShore University HealthSystem-Evanston Hospital, Evanston, IL, David Grinblatt; Northern Indiana Cancer Research Consortium, South Bend, IN; Northwell Health NCORP, Lake Success, NY, Daniel Budman, UG1CA189850; The Ohio State University Comprehensive Cancer Center LAPS, Columbus, OH, Claire Verschraegen, U10CA180850; Pacific Cancer Research Consortium NCORP, Seattle, WA, Alison Conlin, UG1CA189953; Porter Adventist Hospital, Denver, CO; Rhode Island Hospital, Providence, RI, Howard Safran; Roswell Park Cancer Institute LAPS, Buffalo, NY, Ellis Levine, U10CA180866; Sanford NCI Community Oncology Research Program of the North Central Plains, Sioux Falls, SD, Preston Steen, UG1CA189825; Sinai Hospital of Baltimore, Baltimore, MD, Marvin Feldman; Southeast Clinical Oncology Research (SCOR) Consortium NCORP, Winston-Salem, NC, James Atkins, UG1CA189858; State University of New York Upstate Medical University, Syracuse, NY, Stephen Graziano; Stony Brook University Medical Center, Stony Brook, NY, Michael Schuster; UCSF Medical Center-Mount Zion, San Francisco, CA, Charalambos Andreadis; UNC Lineberger Comprehensive Cancer

Center LAPS, Chapel Hill, NC, Thomas Shea, U10CA180838; University of Chicago Comprehensive Cancer Center LAPS, Chicago, IL, Hedy Kindler, U10CA180836; University of Illinois, Chicago, IL, John Quigley; University of Iowa/Holden Comprehensive Cancer Center, Iowa City, IA, Umar Farooq; University of Kansas Cancer Center, Kansas City, KS, Jamie Wagner; University of Miami Miller School of Medicine-Sylvester Cancer Center, Miami, FL, Ronald Benveniste; University of Minnesota/Masonic Cancer Center, Minneapolis, MN, Bruce Peterson; University of Oklahoma Health Sciences Center LAPS, Oklahoma City, OK, Adam Asch, U10CA180798; University of Pittsburgh Cancer Institute LAPS, Pittsburgh, PA, Matthew Schuchert, U10CA180844; University of Virginia Cancer Center, Charlottesville, VA, Linda Martin; VCU Massey Cancer Center Minority Underserved NCORP, Richmond, VA, Steven Grossman, UG1CA189869; Wake Forest University Health Sciences, Winston-Salem, NC, Heidi Klepin; Washington University - Siteman Cancer Center LAPS, Saint Louis, MO, Nancy Bartlett, U10CA180833; WellSpan Health-York Cancer Center, York, PA, Dennis Johnson; Wichita NCI Community Oncology Research Program, Wichita, KS, Shaker Dakhil, UG1CA189808; and Wisconsin NCI Community Oncology Research Program, Marshfield, WI, Anthony Jaslowski, UG1CA189956.

Supplemental Results

Intent to Treat Analysis

In an intent to treat analysis of all enrolled patients, PFS was significantly longer with ibrutinib than with BR (hazard ratio = 0.38, 95% CI: 0.25-0.57; one-sided P < 0.001), and significantly longer with IR than with BR (hazard ratio = 0.40, 95% CI: 0.27-0.60; one-sided P < 0.001), but not significantly different between the IR and ibrutinib arms (hazard ratio = 1.06 95% CI: 0.66-1.70; one-sided P = 0.41) (Supplemental Figure 1).

Additional Efficacy Analyses

Prior to the start of this study, advanced Rai stage, high-risk cytogenetic abnormalities including del(17p) or del(11q) and counted as a single group, and unmethylated Zap-70 were deemed as negative prognostic factors that should be controlled for when evaluating the impact of treatment arm and other baseline characteristics on PFS. Stratification on these factors ensured that they were balanced between treatment arms and did not influence comparisons between treatment arms. However, of those three variables, only unmethylated Zap-70 was moderately associated with shortened PFS (Supplemental Table 4). Other baseline characteristics associated with shortened PFS included older age, ECOG performance status of 2, elevated beta-2 microglobulin and lactate dehydrogenase, splenomegaly, and presence of TP53 mutations. When evaluating these variables in the context of one another and after controlling for the stratification factors, only older age, elevated lactate dehydrogenase and presence of TP53 mutations remained significantly associated with inferior PFS. Since del(17p) and del(11q) had been previously grouped together, and del(17p) is known to be associated with presence of TP53 mutations, we also evaluated the association of del(17p) and del(11q) with PFS separately and not in the context of TP53 mutations. In this setting, del(17p) was significantly associated with shortened PFS, but not del(11q) (Supplemental Table 5). While it is not surprising that patients with high genomic risk features such as del(17p) and TP53 mutation have an inferior PFS compared to those without these features, it is surprising that complex karyotype does not portend a higher risk of progression or death, as this has been consistently shown to indicate high risk of relapse, even with ibrutinib, in the setting of previously treated CLL. [4,5] This is the first study that has examined karyotypic complexity in the setting of previously

untreated CLL, and it may be that baseline complexity is not biologically equivalent to acquired abnormalities in the context of therapy. Longer follow-up will be needed to confirm this finding.

In exploratory analyses, the PFS of patients with different cytogenetic abnormalities was shown to strongly depend on the treatment received (P = 0.006). PFS was substantially longer with ibrutinib or IR compared with BR among patients with del(17p) (P < 0.001 for both comparisons; Supplemental Figure 2A); PFS was also longer with ibrutinib or IR compared with BR among patients with del(11q) and among patients without del(17p) or del(11q), although to a lesser extent (P < 0.05 for all comparisons of ibrutinib-containing arms with BR; Supplemental Figures 2B and 2C).

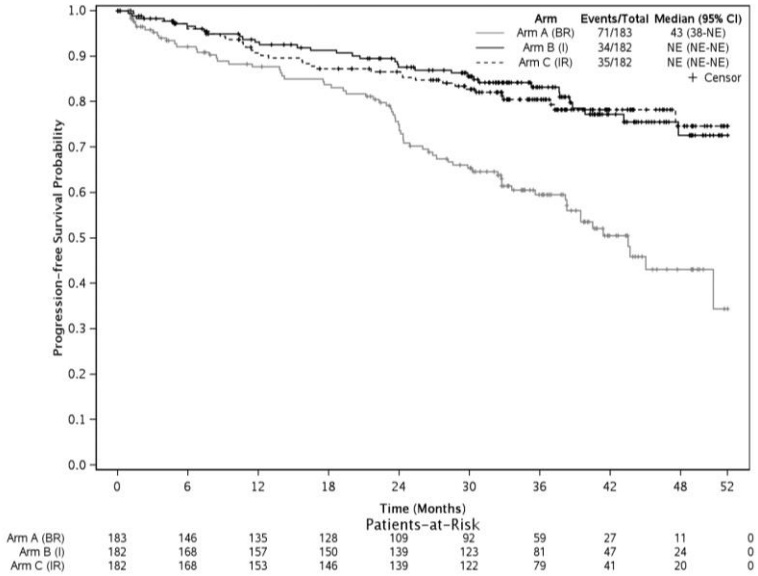
An analysis of PFS was also performed in the subset of 360 patients (66%) who had an IGVH result available. The subset of patients with an IGVH result did tend to differ from patients without an IGVH result; a higher percentage of patients with an IGVH result had high-risk Rai stage (58% versus 48%, P = 0.03) and unmethylated Zap-70 (55% versus 47%, P = 0.08). Further, ECOG performance status of 0 was similar between the groups, but performance status of 1 was more common and performance status of 2 less common in this cohort (P = 0.02). Baseline hemoglobin was lower (P = 0.09), and baseline WBC and LDH were both higher (P = 0.08 and P = 0.07, respectively). In general, this cohort had worse clinical features.

Among the 360 patients, 142 (39%) had IGVH mutated CLL and 218 (61%) had IGVH unmutated CLL. IGVH status was in agreement with Zap-70 methylation status in 76%; of the 142 patients with IGVH mutated CLL 77% were Zap-70 methylated, and of the 218 patients with IGVH unmutated CLL 76% were Zap-70 unmethylated. With respect to PFS, IGVH mutated CLL had longer PFS than IGVH unmutated CLL (hazard ratio = 0.51, 95% CI: 0.32-0.81). IGVH did not significantly modify the effect of treatment arm on PFS (P = 0.45), and ibrutinib appears to prolong PFS in both the IGVH mutated and IGVH unmutated subgroups, albeit emerging later in the IGVH mutated subgroup (Supplemental Figures 3A and 3B). Collectively, the relationship between treatment arm and PFS by IGVH status in the subset patient population was similar to that observed between treatment arm and PFS by Zap-70 methylation status in the intent-to-treat patient population.

Supplemental Figures

Figure S1. Progression-free survival. Progression-free Survival of all enrolled patients, regardless of eligibility. A) all three treatment arms, B) only the BR and ibrutinib arms.

A



B

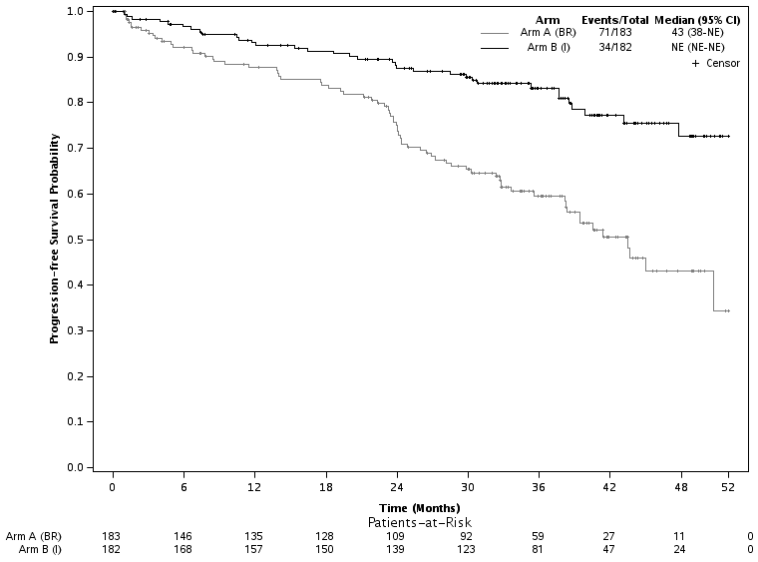
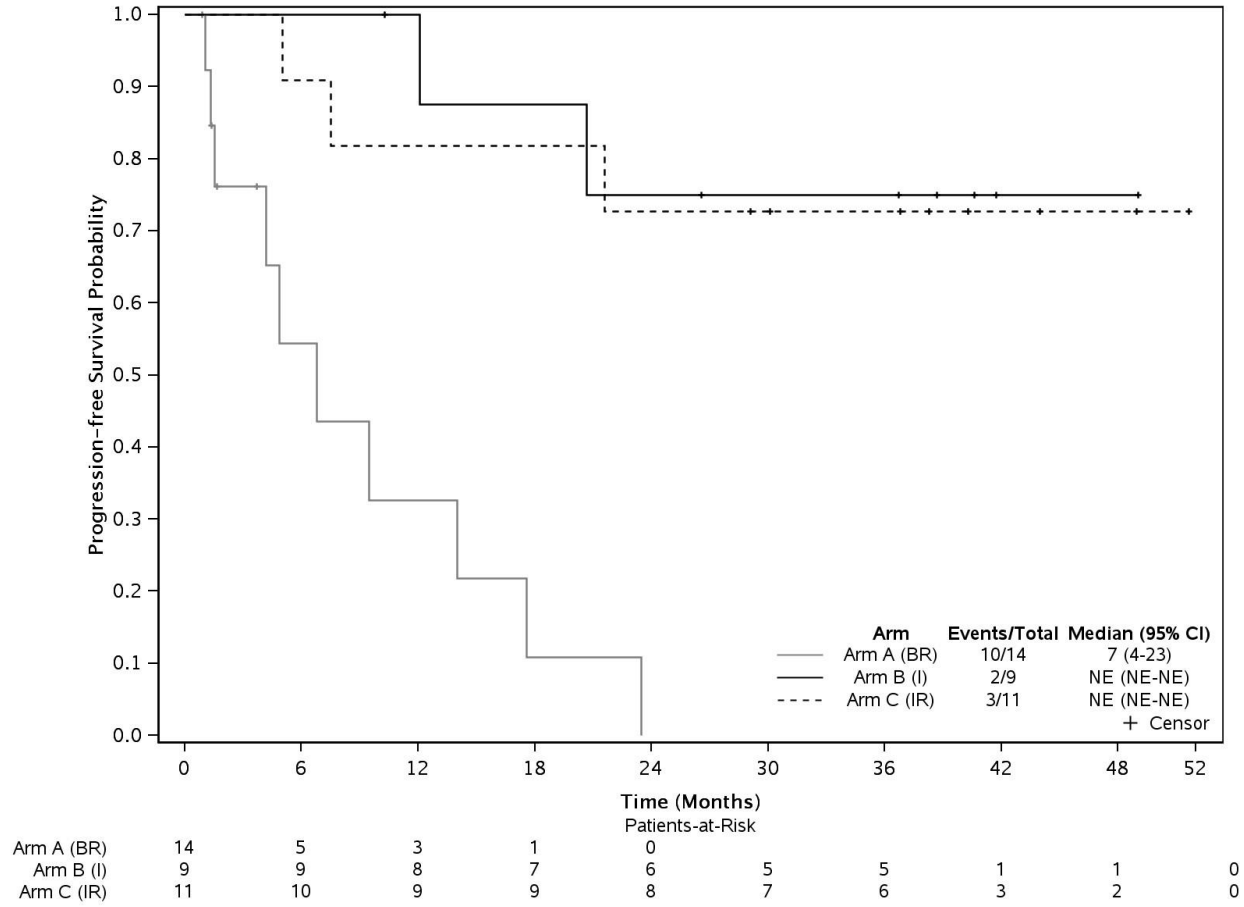
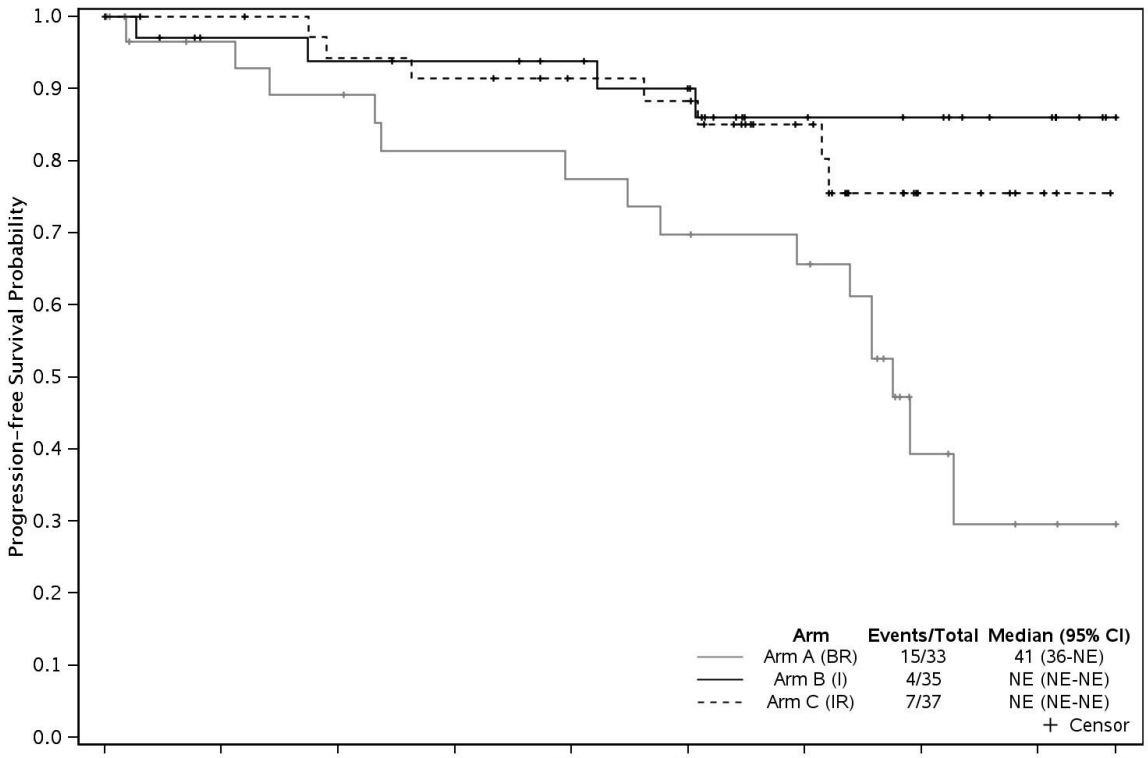


Figure S2: Progression-Free Survival by arm and Dohner's Hierarchy. Progression-Free Survival for A) del(17p); B) del(11q); C) Patients with neither del(17p) nor del(11q)

A



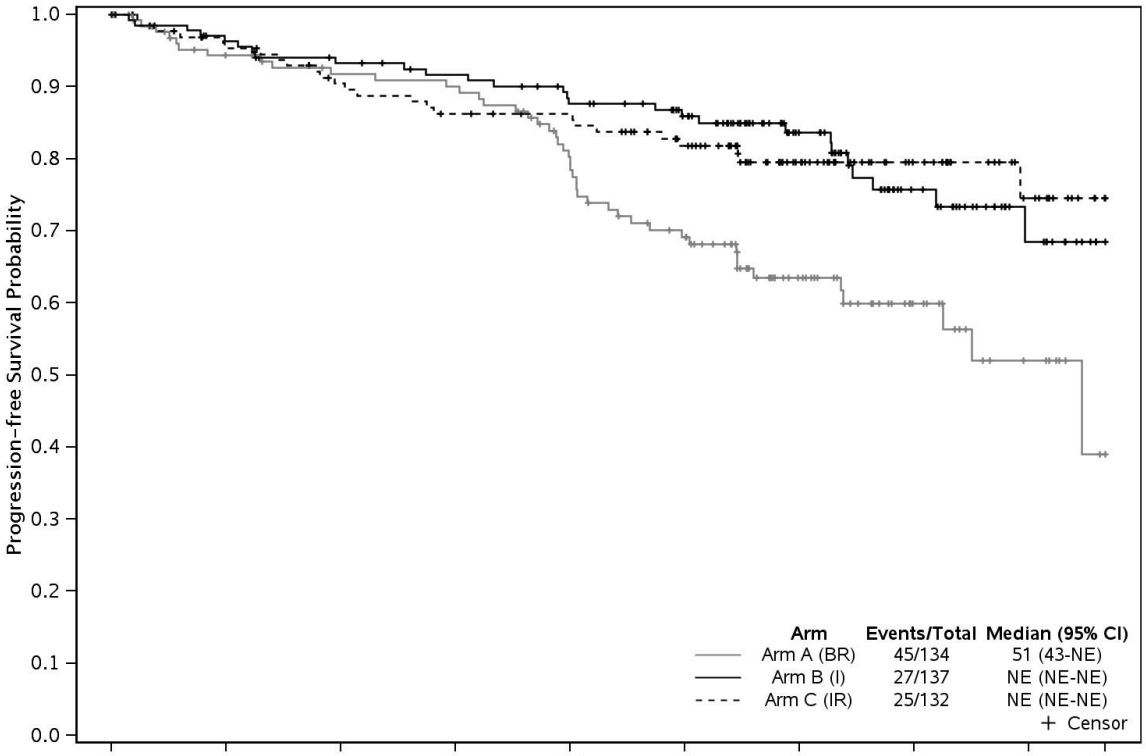
B



Patients-at-Risk

Arm A (BR)	33	26	24	21	20	18	16	5	2	0
Arm B (I)	35	30	29	28	26	23	15	13	9	0
Arm C (IR)	37	36	33	32	29	28	19	6	3	0

C

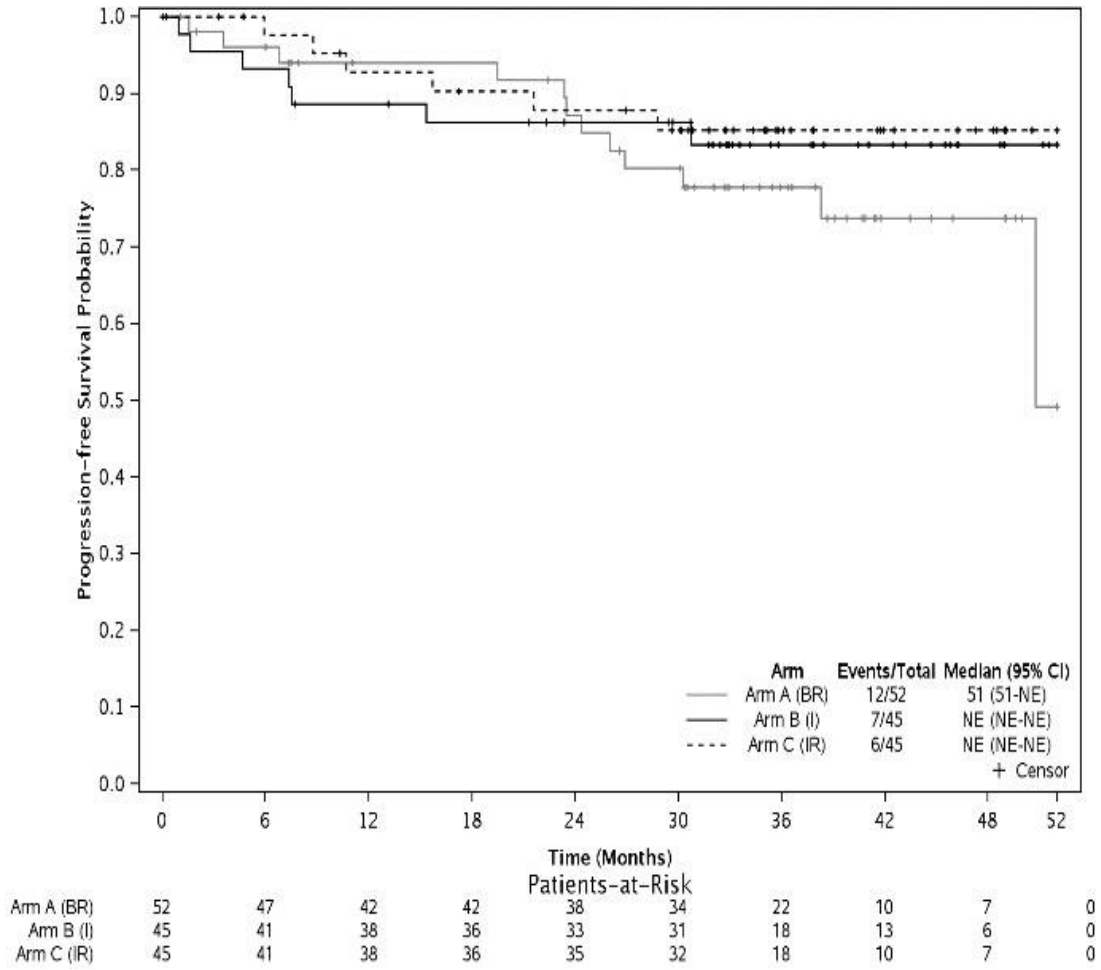


Patients-at-Risk

Arm A (BR)	134	113	106	104	87	72	42	21	9	0
Arm B (I)	137	128	120	115	107	95	61	33	14	0
Arm C (IR)	132	120	109	103	100	85	53	31	14	0

Supplemental Figure 3. Progression free survival by arm and IGHV status. Progression-free Survival for patients with A) Mutated , and B) Unmutated IGHV

A



B

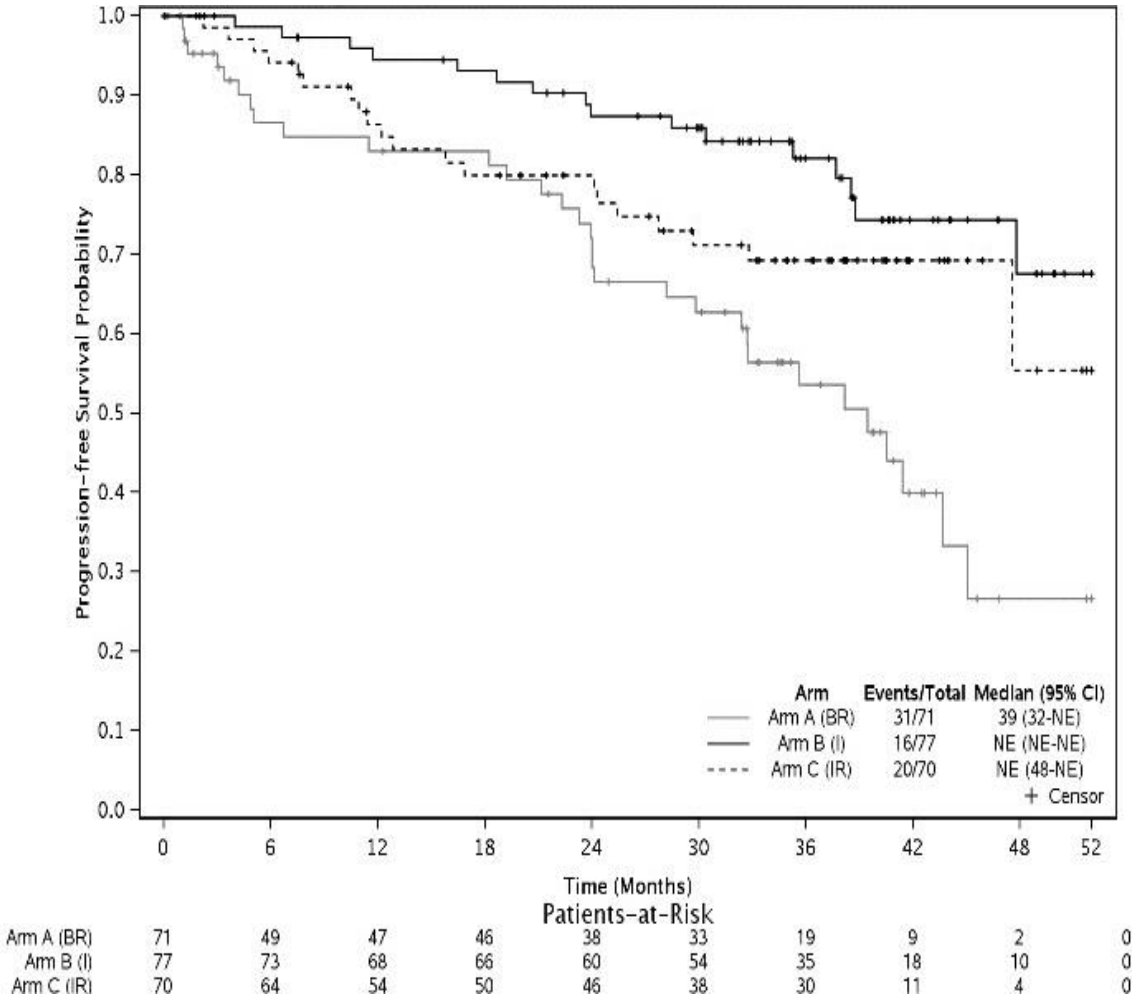
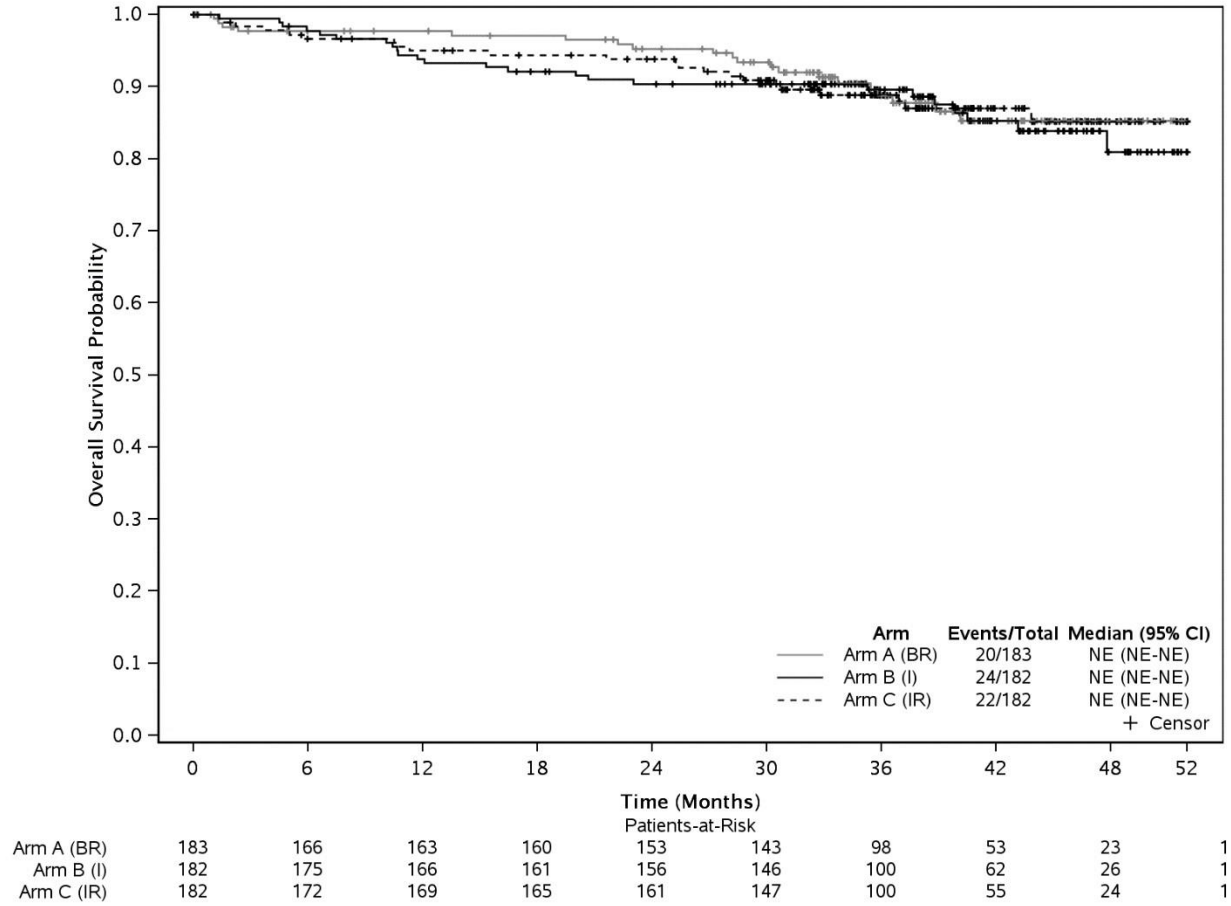

Progression-free Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Arm
Events/Total
Median (95% CI)
Arm A (BR)
31/71
39 (32-NE)
Arm B (I)
16/77
NE (NE-NE)
Arm C (IR)
20/70
NE (48-NE)
Censor
0
6
12
18
24
30
36
42
48
52
Time (Months)
Patients-at-Risk
Arm A (BR) 71 49 47 46 38 33 19 9 2 0
Arm B (I) 77 73 68 66 60 54 35 18 10 0
Arm C (IR) 70 64 54 50 46 38 30 11 4 0

Figure S4: Overall Survival. Overall Survival is shown for the intent to treat patient population.



Supplemental Tables

Table S1. Antibodies used for MRD analysis

Tube number	FITC	PE	ECD	PC5	PC7
1	Dual K/L FITC PE		CD19	CD5	CD45
	10uL Cocktail		10uL	10uL	5uL
	Dakko FR481		BC 6604551	BC B62206	BC IM3548U
2	CD3	CD5616	CD19	CD45	CD13
	20uL Cocktail		10uL	5uL	5uL
	BD 340042		BC 6604551	BC IM2652U	BD 338432
3	CD79b	CD43	CD19	CD5	CD45
	5ul	5ul	10uL	10uL	5uL

	LF MHCD79B01	LF MHCD4304	BC 6604551	BC B62206	BC IM3548U
4	CD22	CD81	CD19	CD5	CD45
	20uL	20uL	10uL	10uL	5uL
	BD 555424	BD 555676	BC 6604551	BC B62206	BC IM3548U
5	CD38	CD20	CD19	CD5	CD45
	20uL	20uL	10uL	10uL	5uL
	BC IM0775U	BD 346581	BC 6604551	BC B62206	BC IM3548U
Viability	CD19/CD2 FITC PE			7AAD	
	10 uL cocktail			20uL	
	BC 6603801			BC A07704	

Abbreviations: BC=Beckman Coulter; LT=Life Technologies

Table S2: Full Baseline Characteristics of Patients

Characteristic*	Total (N=547)	Arm A: BR (N=183)	Arm B: I (N=182)	Arm C: IR (N=182)	P Value †
Age – yr					0.53
N	547	183	182	182	
Median	71	70	71	71	
Range	65-89	65-86	65-89	65-86	
Gender -- no. (%)					0.75
N	547	183	182	182	
Female	180 (33)	64 (35)	59 (32)	57 (31)	
Male	367 (67)	119 (65)	123 (68)	125 (69)	
Rai Stage -- no. (%)					0.99
N	547	183	182	182	
Intermediate	251 (46%)	84 (46%)	83 (46%)	84 (46%)	
High	296 (54%)	99 (54%)	99 (54%)	98 (54%)	
ECOG Performance Status -- no. (%)					0.06
N	547	183	182	182	
0	271 (50)	98 (54)	87 (48)	86 (47)	
1	259 (47)	75 (41)	90 (49)	94 (52)	
2	17 (3)	10 (5)	5 (3)	2 (1)	
Hemoglobin, g/dL					0.47
N	546	182	182	182	
Median	11	11	11	12	
Range	4-17	7-16	4-17	7-17	
Platelets, x10 ^{3} /uL					0.12
N	547	183	182	182	
Median	136	142	130	136	
Range	30-564	30-564	33-327	36-362	
WBC, x10 ^{3} /uL					0.44
N	547	183	182	182	
Median	82	92	79	70	
Range	4-518	7-518	6-438	4-481	
Beta-2 Microglobulin -- no. (%)					0.11
N	547	183	182	182	
Normal	60 (11)	13 (7)	22 (12)	25 (14)	
Elevated	487 (89)	170 (93)	160 (88)	157 (86)	
Lactate Dehydrogenase -- no. (%)					0.33

Characteristic*	Total (N=547)	Arm A: BR (N=183)	Arm B: I (N=182)	Arm C: IR (N=182)	P Value †
N	547	183	182	182	
Normal	316 (58)	100 (55)	103 (57)	113 (62)	
Elevated	231 (42)	83 (45)	79 (43)	69 (38)	
Serum Creatinine -- no. (%)					0.36
N	547	183	182	182	
Normal	449 (82)	156 (85)	148 (81)	145 (80)	
Elevated	98 (18)	27 (15)	34 (19)	37 (20)	
Creatinine Clearance					0.90
N	546	182	182	182	
Median	67	67	69	67	
Range	39-180	40-180	39-158	40-179	
Splenomegaly -- no. (%)					0.67
N	547	183	182	182	
No	360 (66)	120 (66)	116 (64)	124 (68)	
Yes	187 (34)	63 (34)	66 (36)	58 (32)	
del(11q) / del(17p) -- no. (%) ‡					0.91
N	547	183	182	182	
Absent	397 (73)	131 (72)	132 (73)	134 (74)	
Present	150 (27)	52 (28)	50 (27)	48 (26)	
Dohner's Hierarchical Classification -- no. (%) §					0.99
N	542	181	181	180	
del(17p)	34 (6)	14 (8)	9 (5)	11 (6)	
del(11q)	105 (19)	33 (18)	35 (19)	37 (21)	
Trisomy 12	118 (22)	40 (22)	40 (22)	38 (21)	
None	90 (17)	29 (16)	32 (18)	29 (16)	
del(13q)	195 (36)	65 (36)	65 (36)	65 (36)	
TP53 Mutation -- no. (%)					0.60
N	510	174	168	168	
Absent	459 (90)	158 (91)	153 (91)	148 (88)	
Present	51 (10)	16 (9)	15 (9)	20 (12)	
Complex Karyotype -- no. (%) ¶					0.04
N	499	166	165	168	
Absent	356 (71)	122 (73)	126 (76)	108 (64)	
Present	143 (29)	44 (27)	39 (24)	60 (36)	
Zap-70 -- no. (%)					0.99

Characteristic*	Total (N=547)	Arm A: BR (N=183)	Arm B: I (N=182)	Arm C: IR (N=182)	P Value †
N	546	182	182	182	
Unmethylated	287 (53)	95 (52)	96 (53)	96 (53)	
Methylated	259 (47)	87 (48)	86 (47)	86 (47)	
IGVH -- no. (%)					0.69
N	360	123	122	115	
Unmutated	218 (61)	71 (58)	77 (63)	70 (61)	
Mutated	142 (39)	52 (42)	45 (37)	45 (39)	

*Summary statistics are calculated for the number of patients with non-missing data for each characteristic.

†All P values are two-sided. P values for continuous variables were calculated with the use of Kruskal–Wallis tests, and P values for categorical variables were calculated with the use of chi-square or Fisher's exact tests.

‡Presence of del(11)(q22.3) or del(17)(p13.1) was determined by local *Fluorescence In Situ Hybridization* (FISH).

§ Central FISH testing was prioritized according to Dohner's hierarchy.

¶ Complex karyotype was defined as 3 or more unrelated abnormalities, determined by central review.

Table S3: Geriatric Assessment at Baseline for all Consented Enrolled Patients

Domain	Measures	Description		Bendamustine + Rituximab (N=113)	Ibrutinib (N=130)	Ibrutinib + Rituximab (N=126)	Total (N=369)	p value
Functional Status	Activities of Daily Living (Medical Outcomes Study [MOS] subscale)	Measures limitations in physical function activities, ranging from bathing and dressing to running (0-14)	Mean (SD)	13.7 (0.7)	13.6 (1.0)	13.7 (0.7)	13.7 (0.8)	0.68
			Median (Range)	14.0 (9.0-14.0)	14.0 (10.0-14.0)	14.0 (10.5-14.0)	14.0 (9.0-14.0)	
	Instrumental Activities of Daily Living (Older American Resources and Services	Measures ability to complete activities required to maintain independence, ranging from making telephone calls to money management (0-100)	Mean (SD)	79.7 (20.1)	76.9 (22.7)	78.6 (20.9)	78.3 (21.3)	0.69
			Median (Range)	85.0 (20.0-100.0)	85.0 (15.0-100.0)	85.0 (20.0-100.0)	85.0 (15.0-100.0)	
	Karnofsky Performance Status (Self-reported)	Global scale used quantify patient function from "normal" to "severely disabled", as determined by the patient (30-100)	Mean (SD)	88.8 (9.1)	87.5 (10.9)	88.4 (9.1)	88.2 (9.7)	0.80
			Median (Range)	90.0 (60.0-100.0)	90.0 (60.0-100.0)	90.0 (60.0-100.0)	90.0 (60.0-100.0)	
	Karnofsky Performance Status (Physician-reported)	Global scale used quantify patient function from "normal" to "dead", as determined by the physician (0-100)	Mean (SD)	89.9 (8.1)	88.7 (8.0)	89.6 (8.7)	89.4 (8.2)	0.42
			Median (Range)	90.0 (60.0-100.0)	90.0 (60.0-100.0)	90.0 (60.0-100.0)	90.0 (60.0-100.0)	
	Timed "Up and Go" (TUG)	Time it takes for individual to stand up, walk 10 feet, return to chair and sit back down	Mean (SD)	12.2 (11.6)	12.8 (13.3)	13.1 (12.2)	12.7 (12.4)	0.56
			Median (Range)	10.3 (5.0-120.0)	10.0 (0.9-120.0)	10.5 (3.0-120.0)	10.3 (0.9-120.0)	
	Number of Falls in last 6 months	Number of times a fall occurred in the last 6 months	% with 0 falls	102 (90.3%)	112 (86.2%)	108 (85.7%)	322 (87.3%)	0.51
			% with 1+ falls	11 (9.7%)	18 (13.8%)	18 (14.3%)	47 (12.7%)	
Comorbidity	Physician Health Scale (OARS subscale)	Assesses the presence or absence of 14 comorbid conditions and effect of the illness on daily activities. (Number of Comorbidities)	Mean (SD)	2.5 (2.0)	2.6 (2.0)	2.4 (1.8)	2.5 (1.9)	0.93
			Median (Range)	2.0 (0.0-14.0)	2.0 (0.0-12.0)	2.0 (0.0-9.0)	2.0 (0.0-14.0)	
Psychological State	Mental Health Inventory	Evaluates the level of depression and anxiety experienced in the last month (0-100)	Mean (SD)	83.0 (12.4)	82.9 (11.7)	85.1 (11.7)	83.7 (11.9)	0.20
			Median (Range)	87.1 (41.2-100.0)	84.7 (43.5-100.0)	87.1 (31.8-100.0)	85.9 (31.8-100.0)	
Social Activity	MOS Social Activity Survey	Measures the level of physical or emotional interference experienced with social activities (0-100)	Mean (SD)	64.7 (15.8)	61.6 (17.6)	61.7 (18.7)	62.6 (17.5)	0.57
			Median (Range)	66.7 (16.7-100.0)	66.7 (0.0-91.7)	66.7 (0.0-100.0)	66.7 (0.0-100.0)	

Social Support	MOS Social Support: Emotional/Informational subscale	Evaluates the self-reported availability of emotional/informational social support (0-100)	Mean (SD)	86.9 (19.7)	88.8 (18.7)	86.2 (17.1)	87.3 (18.5)	0.07
			Median (Range)	96.9 (0.0-100.0)	100.0 (0.0-100.0)	93.8 (15.6-100.0)	96.9 (0.0-100.0)	
	MOS Social Support: Tangible subscale	Evaluates the self-reported availability of tangible/physical social support (0-100)	Mean (SD)	86.6 (20.8)	87.4 (20.9)	86.5 (20.5)	86.8 (20.7)	0.94
			Median (Range)	100.0 (0.0-100.0)	100.0 (0.0-100.0)	100.0 (12.5-100.0)	100.0 (0.0-100.0)	
Nutrition	BMI	Weight (kg) / Height $(m)^2$	Mean (SD)	27.5 (4.5)	28.1 (4.8)	27.8 (4.5)	27.8 (4.6)	0.73
			Median (Range)	27.4 (19.2-38.8)	27.0 (18.1-51.6)	27.2 (19.3-52.2)	27.2 (18.1-52.2)	
	Percent Unintentional Weight Loss in last 6 months	(Unintentional weight lost in last 6 months / baseline body weight) X 100	% with ≤5% weight loss	86 (76.1%)	98 (75.4%)	102 (81.0%)	286 (77.5%)	0.52
			% with >5% weight loss	27 (23.9%)	32 (24.6%)	24 (19.0%)	83 (22.5%)	
Cognition	Blessed Orientation Memory Concentration Test (BOMC)	Cognitive assessment, score 11 or greater may reveal signs of cognitive impairment (0-28)	% with < 11	107 (94.7%)	128 (98.5%)	120 (95.2%)	355 (96.2%)	0.24
			% with ≥11	6 (5.3%)	2 (1.5%)	6 (4.8%)	14 (3.8%)	

Table S4. Primary Univariable and Multivariable Analysis

Number of Patients N = 467 (120 events)	**Univariable Models***			**Multivariable Model†**		
Modeling the effect of:	**Hazard Ratio**	**95% CI**	**P‡**	**Hazard Ratio**	**95% CI**	**P‡**
Treatment Arm						
I vs BR	0.37	0.24-0.58	<0.001	0.34	0.21-0.54	<0.001
IR vs BR	0.43	0.28-0.66	<0.001	0.42	0.27-0.65	<0.001
Age, 5-year increase	1.33	1.11-1.58	0.002	1.35	1.12-1.63	0.002
Sex (female vs male)	0.86	0.58-1.27	0.44	--	--	--
Rai stage (high vs intermediate)	0.96	0.67-1.38	0.84	--	--	--
ECOG PS						
1 vs 0	1.05	0.73-1.52	0.78	1.10	0.74-1.64	0.64
2 vs 0	2.38	1.03-5.54	0.04	2.12	0.88-5.14	0.10
Log_2(WBC), 2-fold increase	1.01	0.89-1.15	0.89	--	--	--
Elevated B_2M (yes vs no)	1.70	0.83-3.48	0.15	1.45	0.68-3.1	0.34
Elevated LDH (yes vs no)	1.64	1.15-2.36	0.007	1.49	1.03-2.16	0.04
Splenomegaly (yes vs no)	1.36	0.95-1.97	0.10	1.21	0.82-1.8	0.34
High-risk FISH§, (yes vs no)	1.20	0.81-1.76	0.36	--	--	--
TP53 Mutations (yes vs no)	1.86	1.14-3.04	0.01	2.16	1.27-3.68	0.005
Complex Karyotype (yes vs no)	1.01	0.68-1.51	0.95	--	--	--
Zap-70 (methylated vs unmethylated)	0.71	0.49-1.02	0.06	--	--	--

*Univariable Cox models were constructed for each predictor.

† One multivariable Cox model, stratifying on Rai stage, high-risk FISH, and Zap-70 methylation, and containing all predictors with $p < 0.20$ from the univariable models was constructed, with each predictor adjusted for all others in the model.

‡Two-sided Wald χ^2 p-values.

§ High-risk FISH includes patients with del(17p) or del(11q) by local results.

Abbreviations: CI indicates confidence interval; I, ibrutinib; BR, bendamustine with rituximab; IR, ibrutinib with rituximab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBC, white blood cell count; B2M, beta-2 microglobulin; and LDH, lactate dehydrogenase.

Table S5. **Secondary Univariable and Multivariable Analysis**

Number of Patients N = 467 (120 events)	**Univariable Models***			**Multivariable Model†**		
Modeling the effect of:	**Hazard Ratio**	**95% CI**	**P‡**	**Hazard Ratio**	**95% CI**	**P‡**
Treatment Arm						
I vs BR	0.37	0.24-0.58	<0.001	0.33	0.21-0.53	<0.001
IR vs BR	0.43	0.28-0.66	<0.001	0.39	0.25-0.61	<0.001
Age, 5-year increase	1.33	1.11-1.58	0.002	1.34	1.11-1.61	0.002
Sex (female vs male)	0.86	0.58-1.27	0.44	--	--	--
Rai stage (high vs intermediate)	0.96	0.67-1.38	0.84	--	--	--
ECOG PS						
1 vs 0	1.05	0.73-1.52	0.78	1.13	0.77-1.66	0.55
2 vs 0	2.38	1.03-5.54	0.04	2.00	0.84-4.76	0.12
Log_2(WBC), 2-fold increase	1.01	0.89-1.15	0.89	--	--	--
Elevated B_2M (yes vs no)	1.70	0.83-3.48	0.15	1.36	0.65-2.87	0.42
Elevated LDH (yes vs no)	1.64	1.15-2.36	0.007	1.48	1.02-2.14	0.04
Splenomegaly (yes vs no)	1.36	0.95-1.97	0.10	1.14	0.77-1.68	0.51
Hierarchical Classification§						
…del(17p) vs other	2.20	1.2-4.04	0.01	2.61	1.39-4.89	0.003
…del(11q) vs other	0.98	0.62-1.54	0.92	0.91	0.56-1.46	0.69
Complex Karyotype (yes vs no)	1.01	0.68-1.51	0.95	--	--	--
Zap-70 (methylated vs unmethylated)	0.71	0.49-1.02	0.06	--	--	--

*Univariable Cox models were constructed for each predictor.

† One multivariable Cox model, stratifying on Rai stage and Zap-70 methylation, and containing all predictors with p < 0.20 from the univariable models was constructed, with each predictor adjusted for all others in the model.

‡Two-sided Wald χ^2 p-values.

§ Using Dohner's hierarchical model for cytogenetics, patients were classified in the following hierarchical order by central FISH results: del(17p) > del(11q) > other

Abbreviations: CI indicates confidence interval; I, ibrutinib; BR, bendamustine with rituximab; IR, ibrutinib with rituximab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBC, white blood cell count; B2M, beta-2 microglobulin; and LDH, lactate dehydrogenase.

Table S6- Full Description of Maximum Grade 3, 4, or 5 Infections Occurring During First Line Treatment and Observation, Excluding Infections Occurring After Crossover

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
Infections and infestations							
Abdominal infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Appendicitis	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Bladder infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Bone infection	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Bronchial infection	A	1	(1%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	3	(2%)	0	(0%)	0	(0%)
Conjunctivitis	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Encephalitis infection	A	0	(0%)	0	(0%)	1	(1%)
	B	0	(0%)	1	(1%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Enterocolitis infectious	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Hepatitis viral	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Infections and infestations - Other	A	5	(3%)	0	(0%)	0	(0%)
	B	4	(2%)	0	(0%)	0	(0%)
	C	7	(4%)	0	(0%)	0	(0%)

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
Joint infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Lung infection	A	10	(6%)	0	(0%)	0	(0%)
	B	10	(6%)	0	(0%)	1	(1%)
	C	14	(8%)	0	(0%)	0	(0%)
Lymph gland infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Meningitis	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Otitis media	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Scrotal infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Sepsis	A	0	(0%)	6	(3%)	2	(1%)
	B	0	(0%)	5	(3%)	1	(1%)
	C	0	(0%)	7	(4%)	2	(1%)
Skin infection	A	3	(2%)	0	(0%)	0	(0%)
	B	6	(3%)	0	(0%)	0	(0%)
	C	7	(4%)	0	(0%)	0	(0%)
Tooth infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Upper respiratory infection	A	3	(2%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
Urinary tract infection	A	3	(2%)	0	(0%)	0	(0%)
	B	3	(2%)	0	(0%)	0	(0%)
	C	5	(3%)	0	(0%)	0	(0%)
Wound infection	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)

*In Arms A, B, and C there were 176, 180, and 181 patients, respectively, evaluable for AEs.

Table S7. Full Description of Maximum Grade 3, 4, or 5 AE Occurring During First Treatment (Fixed Treatment Schedule of 6 Cycles for Arm A and Indefinite, Continuous Treatment Schedule for Arms B and C) and Up to 30 Days Following the End of First Treatment

	Arm A: BR (N=176)	Arm B: I (N=180)	Arm C: IR (N=181)	P value*
All Hematologic -- no. (%)				**<0.001**
Grade 3	**60 (34%)**	**59 (33%)**	**48 (26%)**	
Grade 4	**42 (24%)**	**15 (8%)**	**21 (12%)**	
Anemia				0.08
Grade 3	21 (12%)	19 (11%)	10 (6%)	
Neutrophil count decreased				<0.001
Grade 3	39 (22%)	15 (8%)	20 (11%)	
Grade 4	27 (15%)	12 (7%)	19 (10%)	
Platelet count decreased				0.008
Grade 3	16 (9%)	7 (4%)	8 (4%)	
Grade 4	9 (5%)	3 (2%)	1 (1%)	
All Non-hematologic -- no. (%)				**<0.001**
Grade 3	**71 (40%)**	**103(57%)**	**104 (57%)**	
Grade 4	**17 (10%)**	**14 (8%)**	**15 (8%)**	
Grade 5	**2 (1%)**	**13 (7%)**	**13 (7%)**	
Bleeding[†]				0.70
Grade 3	0 (0%)	2 (1%)	2 (1%)	
Grade 4	0 (0%)	1 (1%)	1 (1%)	
Grade 5	0 (0%)	0 (0%)	1 (1%)	
Infections[ǂ]				0.007
Grade 3	9 (5%)	29 (16%)	27 (15%)	
Grade 4	5 (3%)	5 (3%)	6 (3%)	
Grade 5	1 (1%)	2 (1%)	0 (0%)	
Febrile neutropenia				<0.001
3	13 (7%)	3 (2%)	1 (1%)	
Atrial fibrillation				0.009
Grade 3	3 (2%)	15 (8%)	9 (5%)	
Grade 4	0 (0%)	2 (1%)	0 (0%)	
Hypertension				<0.001
3	18 (10%)	53 (29%)	60 (33%)	
4	1 (1%)	0 (0%)	1 (1%)	
Secondary malignancies				0.008
Grade 3	1 (1%)	6 (3%)	12 (7%)	

	Arm A: BR (N=176)	Arm B: I (N=180)	Arm C: IR (N=181)	P value*
Grade 4	0 (0%)	1 (1%)	1 (1%)	
Grade 5	0 (0%)	2 (1%)	1 (1%)	
Unknown/Unexplained Death				0.19
Grade 5	1 (1%)	6 (3%)	4 (2%)	

*All P values are two-sided. P values were calculated with the use of Fisher's exact test for differences in the percentage of grade 3 or higher adverse events among treatment arms.

†Bleeding events included 2 patients with epistaxis, 1 with epistaxis and oral hemorrhage, and 4 with intracranial hemorrhage (one grade 5).

‡Infection events included abdominal infections, appendicitis, bone infections, bladder infections, encephalitis infection (one grade 5, Arm A), bronchial infections, hepatitis, joint infections, lung infections (one grade 5, Arm B), meningitis, otitis, scrotal infections, sepsis (one grade 5, Arm B), skin infections, tooth infections, upper respiratory infections, urinary tract infections, wound infections, and other infections specified. Of 84 patients with infections grade 3 or higher, 40 had multiple infections grade 3 or higher (9 Arm A, 12 Arm B, and 19 Arm C). The majority, 29 patients, had 2 different types of infections (9 Arm A, 8 Arm B, 12 Arm C); eight had 3 different types of infections (3 Arm B, 5 Arm C); two had 4 different types of infections (1 Arm B, 1 Arm C); one patient on Arm C had 5 different types of infection. Further details are in Supplemental Table 5.

Table S8. Full Description of Maximum Grade 3, 4, or 5 Adverse Events (AEs) Occurring During First Treatment (Fixed Treatment Schedule of 6 Cycles for Arm A and Indefinite, Continuous Treatment Schedule for Arms B and C) and Up to 30 Days Following the End of First Treatment

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Hematologic Adverse Events							
Blood/Bone Marrow							
Anemia	A	21	*(12%)*	0	*(0%)*	0	*(0%)*
	B	19	*(11%)*	0	*(0%)*	0	*(0%)*
	C	10	*(5%)*	0	*(0%)*	0	*(0%)*
Leukocytosis	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	17	*(9%)*	0	*(0%)*	0	*(0%)*
	C	12	*(7%)*	0	*(0%)*	0	*(0%)*
Lymphocyte count decreased	A	18	*(10%)*	13	*(7%)*	0	*(0%)*
	B	3	*(2%)*	1	*(1%)*	0	*(0%)*
	C	3	*(2%)*	2	*(1%)*	0	*(0%)*
Lymphocyte count increased	A	10	*(6%)*	0	*(0%)*	0	*(0%)*
	B	33	*(18%)*	0	*(0%)*	0	*(0%)*
	C	24	*(13%)*	0	*(0%)*	0	*(0%)*
Myelodysplastic syndrome	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Neutrophil count decreased	A	39	*(22%)*	27	*(15%)*	0	*(0%)*
	B	15	*(8%)*	12	*(7%)*	0	*(0%)*
	C	20	*(11%)*	19	*(10%)*	0	*(0%)*
Platelet count decreased	A	16	*(9%)*	9	*(5%)*	0	*(0%)*
	B	7	*(4%)*	3	*(2%)*	0	*(0%)*
	C	8	*(4%)*	1	*(1%)*	0	*(0%)*
White blood cell decreased	A	7	*(4%)*	1	*(1%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	6	*(3%)*	0	*(0%)*	0	*(0%)*
Non-Hematologic Adverse Events							
Blood and lymphatic sys disorders							
Febrile neutropenia	A	13	*(7%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Cardiac disorders							
Atrial fibrillation	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	15	*(8%)*	2	*(1%)*	0	*(0%)*
	C	9	*(5%)*	0	*(0%)*	0	*(0%)*
Atrioventricular block complete	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Cardiac arrest	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*

	Arm*	Grade of Adverse Event 3-Severe n	(%)	4-LifeThr n	(%)	5-Lethal n	(%)
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Cardiac disorders specified: Cardiac tamponade, LAD stenosis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Chest pain - cardiac	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	3	*(2%)*	0	*(0%)*	0	*(0%)*
Heart failure	A	0	*(0%)*	2	*(1%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	7	*(4%)*	0	*(0%)*	0	*(0%)*
Myocardial infarction	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Pericardial effusion	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	2	*(1%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pericardial tamponade	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pericarditis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Sick sinus syndrome	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Sinus bradycardia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Supraventricular tachycardia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Valvular heart disease	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Ventricular tachycardia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Ear and labyrinth disorders							
Ear and labyrinth disorders specified – Temporary hearing loss	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Hearing impaired	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Eye disorders							
Cataract	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Eye disorders specified – worsening right eye macular pucker (Epiretinal membrane peeling)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Retinopathy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Gastrointestinal disorders							
Abdominal distension	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Abdominal pain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Ascites	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Constipation	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Diarrhea	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	7	*(4%)*	0	*(0%)*	0	*(0%)*
Dysphagia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Gastrointestinal disorders specified – Diverticulitis, Esophageal tear, cecal volvulus, Clostridium difficile	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Mucositis oral	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*

	Arm*	Grade of Adverse Event 3-Severe n	(%)	4-LifeThr n	(%)	5-Lethal n	(%)
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Nausea	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Oral hemorrhage	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pancreatitis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Small intestinal obstruction	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Upper gastrointestinal bleeding	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	2	*(1%)*	0	*(0%)*
	C	1	*(1%)*	1	*(1%)*	0	*(0%)*
Gen disorders and administration site conditions							
Death NOS	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	1	*(1%)*
	C	0	*(0%)*	0	*(0%)*	2	*(1%)*
Edema	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Fatigue	A	6	*(3%)*	0	*(0%)*	0	*(0%)*
	B	9	*(5%)*	0	*(0%)*	0	*(0%)*
	C	8	*(4%)*	0	*(0%)*	0	*(0%)*
Fever	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Flu like symptoms	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
General disorders and administration site conditions specified – Leg cramping	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Multi-organ failure	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	2	*(1%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Non-cardiac chest pain	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Pain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Unknown/Unexplained Death[†]	A	0	*(0%)*	0	*(0%)*	1	*(1%)*
	B	0	*(0%)*	0	*(0%)*	6	*(3%)*
	C	0	*(0%)*	0	*(0%)*	4	*(2%)*
Hepatobiliary disorders							
Gallbladder infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Immune system disorders							
Allergic reaction	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Anaphylaxis	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Immune system disorders specified – Hypogammaglobulinemia, Systemic immune response	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Infections and infestations							
Abdominal infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Appendicitis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Bladder infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Bone infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Bronchial infection	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	3	*(2%)*	0	*(0%)*	0	*(0%)*
Conjunctivitis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Encephalitis infection	A	0	*(0%)*	0	*(0%)*	1	*(1%)*

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hepatitis viral	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Infections and infestations – Others specified	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	4	*(2%)*	0	*(0%)*	0	*(0%)*
	C	6	*(3%)*	0	*(0%)*	0	*(0%)*
Joint infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Lung infection	A	6	*(3%)*	0	*(0%)*	0	*(0%)*
	B	9	*(5%)*	0	*(0%)*	1	*(1%)*
	C	14	*(8%)*	0	*(0%)*	0	*(0%)*
Meningitis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Otitis media	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Papulopustular rash	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Scrotal infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Sepsis	A	0	*(0%)*	5	*(3%)*	0	*(0%)*
	B	0	*(0%)*	4	*(2%)*	1	*(1%)*
	C	0	*(0%)*	6	*(3%)*	0	*(0%)*
Skin infection	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	6	*(3%)*	0	*(0%)*	0	*(0%)*
	C	7	*(4%)*	0	*(0%)*	0	*(0%)*
Tooth infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Upper respiratory infection	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Urinary tract infection	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	4	*(2%)*	0	*(0%)*	0	*(0%)*
Wound infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*

	Arm*	Grade of Adverse Event 3-Severe n	(%)	4-LifeThr n	(%)	5-Lethal n	(%)
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Injury, poising and procedure complications							
Fall	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	3	*(2%)*	0	*(0%)*	0	*(0%)*
Fracture	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Infusion related reaction	A	11	*(6%)*	3	*(2%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Injury, poising and procedure complications specified – Groin bleed, ruptured spleen, bleeding at bone marrow biopsy site	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	1	*(1%)*
Seroma	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Spinal fracture	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Investigations							
Alanine aminotransferase increased	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	2	*(1%)*	1	*(1%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Aspartate aminotransferase increased	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	4	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	1	*(1%)*	0	*(0%)*
Blood bilirubin increased	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
CPK increased	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Creatinine increased	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Ejection fraction decreased	A	0	*(0%)*	0	*(0%)*	0	*(0%)*

	Arm*	Grade of Adverse Event					
		3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Investigations specified – Elevated BNP	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Urine output decreased	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Weight gain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Metabolism and nutrition disorders							
Alkalosis	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Anorexia	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Dehydration	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	1	*(1%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Glucose intolerance	A	4	*(2%)*	0	*(0%)*	0	*(0%)*
	B	6	*(3%)*	0	*(0%)*	0	*(0%)*
	C	5	*(3%)*	0	*(0%)*	0	*(0%)*
Hypercalcemia	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hyperkalemia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	4	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Hypernatremia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Hyperuricemia	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hypoalbuminemia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Hypocalcemia	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*

	Arm*	Grade of Adverse Event 3-Severe n	(%)	4-LifeThr n	(%)	5-Lethal n	(%)
Hypokalemia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Hypomagnesemia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Hyponatremia	A	1	*(1%)*	1	*(1%)*	0	*(0%)*
	B	4	*(2%)*	1	*(1%)*	0	*(0%)*
	C	7	*(4%)*	0	*(0%)*	0	*(0%)*
Hypophosphatemia	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Tumor lysis syndrome	A	3	*(2%)*	2	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Musculoskeletal and connective tissue disorders							
Arthralgia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	3	*(2%)*	0	*(0%)*	0	*(0%)*
Back pain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Bone pain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Generalized muscle weakness	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Joint effusion	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Musculoskeletal, conn tissue disorders specified – Leg cramps, herniated disk, muscle cramps, left knee pain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Myalgia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Neck pain	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Pain in extremity	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Neoplasm benign, malignant and unspecified							
Neoplasms benign, malignant, unspecified – Others specified	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	6	*(3%)*	1	*(1%)*	2	*(1%)*
	C	11	*(6%)*	1	*(1%)*	1	*(1%)*
Treatment related secondary malignancy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Nervous system disorders							
Ataxia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Cognitive disturbance	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Dizziness	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Encephalopathy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Headache	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	4	*(2%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Hydrocephalus	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Intracranial hemorrhage	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	1	*(1%)*
Leukoencephalopathy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	1	*(1%)*
Muscle weakness: left side or right side	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Nervous system disorders specified – Bell's palsy, confusion, cognitive disturbance, pain in feet	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	3	*(2%)*	0	*(0%)*	0	*(0%)*
Neuralgia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Nystagmus	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Peripheral motor neuropathy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Peripheral sensory neuropathy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Seizure	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Stroke	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	1	*(1%)*	0	*(0%)*
Syncope	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	5	*(3%)*	0	*(0%)*	0	*(0%)*
Tremor	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Psychiatric disorders							
Agitation	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Confusion	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	1	*(1%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Delirium	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Depression	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Renal and urinary disorders							

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Acute kidney injury	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Chronic kidney disease	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	1	*(1%)*
Hematuria	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	4	*(2%)*	0	*(0%)*	0	*(0%)*
Renal and urinary disorders specified – Right renal mass, ureterolithiasis, chronic cystitis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Renal calculi	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Urinary incontinence	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Urinary retention	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	3	*(2%)*	0	*(0%)*	0	*(0%)*
Urinary tract obstruction	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Reproductive system and breast disorders							
Prostatic obstruction	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Reproductive system and breast specified –Prostate cancer	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Respiratory, thoracic, mediastinal disorders							
Adult respiratory distress syndrome	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Apnea	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Aspiration	A	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Chylothorax	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Cough	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Dyspnea	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	5	*(3%)*	0	*(0%)*	0	*(0%)*
	C	7	*(4%)*	2	*(1%)*	0	*(0%)*
Epistaxis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Hypoxia	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Pleural effusion	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	6	*(3%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Pneumonitis	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	3	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Pulmonary hypertension	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Respiratory, thoracic, mediastinal disorders specified – Pneumonia, bronchitis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Respiratory failure	A	0	*(0%)*	2	*(1%)*	0	*(0%)*
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	1	*(1%)*
Sleep apnea	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Sore throat	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Skin and subcutaneous tissue disorders							
Pruritus	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Rash maculo-papular	A	12	*(7%)*	0	*(0%)*	0	*(0%)*
	B	7	*(4%)*	0	*(0%)*	0	*(0%)*
	C	7	*(4%)*	0	*(0%)*	0	*(0%)*
Skin and subcutaneous tissue disorders specified – Skin ulceration, erythema multiforme, squamous and basal cell carcinomas	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Skin infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(1%)*	0	*(0%)*	0	*(0%)*
	C	2	*(1%)*	0	*(0%)*	0	*(0%)*
Surgical and medical procedures							
Surgical and medical procedures specified – Spinal stenosis, post-biopsy pyelonephritis, RUQ fluid collection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Vascular disorders							
Hematoma	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	1	*(1%)*	1	*(1%)*
Hot flashes	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*
Hypertension	A	18	*(10%)*	1	*(1%)*	0	*(0%)*
	B	53	*(29%)*	0	*(0%)*	0	*(0%)*
	C	60	*(33%)*	1	*(1%)*	0	*(0%)*
Hypotension	A	8	*(5%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Thromboembolic event	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	1	*(1%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*

*In Arms A, B, and C there were 176, 180, and 182 patients, respectively, evaluable for AEs.

[††]Includes adverse events coded and confirmed as "sudden death" in each arm (BR x2, ibrutinib x5, IR x2) as well as grade 5 adverse events that upon central review were out of hospital unwitnessed death, coded by treating sites as "myocardial infarction" and "heart failure" in ibrutinib arm and "cardiac arrest" and "death, NOS" in IR arm.

Table S9. Full Description of Maximum Grade 3, 4, or 5 Adverse Events (AEs) Occurring More than 30 Days after the End of First Treatment

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Hematologic Adverse Events							
Blood/Bone Marrow							
Anemia	A	4	*(3%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	1	*(2%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Bone marrow hypocellular	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
CD4 lymphocytes decreased	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Leukocytosis	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Lymphocyte count decreased	A	18	*(15%)*	5	*(4%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(2%)*	0	*(0%)*
Lymphocyte count increased	A	6	*(5%)*	0	*(0%)*	0	*(0%)*
	B	2	*(5%)*	0	*(0%)*	0	*(0%)*
	C	2	*(5%)*	0	*(0%)*	0	*(0%)*
Neutrophil count decreased	A	8	*(6%)*	7	*(6%)*	0	*(0%)*
	B	0	*(0%)*	1	*(2%)*	0	*(0%)*
	C	2	*(5%)*	1	*(2%)*	0	*(0%)*
Platelet count decreased	A	4	*(3%)*	1	*(1%)*	0	*(0%)*
	B	2	*(5%)*	1	*(2%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
White blood cell decreased	A	10	*(8%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Non-Hematologic Adverse Events							
Cardiac disorders							
Atrial fibrillation	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Chest pain - cardiac	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Heart failure	A	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Myocardial infarction	A	0	*(0%)*	0	*(0%)*	1	*(1%)*
	B	0	*(0%)*	0	*(0%)*	1	*(2%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Sick sinus syndrome	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Valvular heart disease	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Ear and labyrinth disorders							
Hearing impaired	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Gastrointestinal disorders							
Ascites	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Constipation	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Diarrhea	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Dysphagia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Lower gastrointestinal hemorrhage	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Nausea	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
General disorders and administration site conditions							
Death NOS	A	0	*(0%)*	0	*(0%)*	6	*(5%)*
	B	0	*(0%)*	0	*(0%)*	7	*(17%)*
	C	0	*(0%)*	0	*(0%)*	4	*(9%)*
Fatigue	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Unknown/Unexplained Death[†]	A	0	*(0%)*	0	*(0%)*	1	*(1%)*
	B	0	*(0%)*	0	*(0%)*	1	*(2%)*

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Gen disorders and administration site conditions specified:	A	0	*(0%)*	0	*(0%)*	1	*(1%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hepatobiliary disorders							
Gallbladder infection	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Immune system disorders							
Allergic reaction	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Autoimmune disorder	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Infections and infestations							
Enterocolitis infectious	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Infections and infestations Specified – Pneumonia, viral illness, psoas muscle abscess	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Lung infection	A	4	*(3%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Lymph gland infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Sepsis	A	0	*(0%)*	1	*(1%)*	2	*(2%)*
	B	0	*(0%)*	1	*(2%)*	0	*(0%)*
	C	0	*(0%)*	1	*(2%)*	2	*(5%)*
Skin infection	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Upper respiratory infection	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Urinary tract infection	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Injury, poising and procedure complications							

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Ankle fracture	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Fall	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Fracture	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hip fracture	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Investigations							
INR increased	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Investigations specified - Hypogammaglobulinemia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Metabolic and nutrition disorders							
Glucose intolerance	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(5%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Hypercalcemia	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hyponatremia	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Hypophosphatemia	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Musculoskeletal and connective tissue disorders							
Back pain	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Myalgia	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Neoplasm benign, malignant and unspecified							
Leukemia second to oncology chemo	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Neoplasms benign, mal, unspecified – Others specified	A	5	*(4%)*	0	*(0%)*	1	*(1%)*
	B	0	*(0%)*	0	*(0%)*	2	*(5%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Nervous system disorders							
Encephalopathy	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	1	*(2%)*
Nervous system disorders specified – Carpal tunel	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(2%)*	0	*(0%)*
Stroke	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	1	*(2%)*
Syncope	A	3	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	2	*(5%)*	0	*(0%)*	0	*(0%)*
Psychiatric disorders							
Anxiety	A	1	*(1%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Depression	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Respiratory, thoracic, mediastinal disorders							
Aspiration	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Dyspnea	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	1	*(2%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pleural effusion	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pneumonitis	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Respiratory failure	A	0	*(0%)*	1	*(1%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(2%)*	0	*(0%)*
Epistaxis	A	0	*(0%)*	0	*(0%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Skin and subcutaneous tissue disorders							
Rash maculo-papular	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Skin and subcutaneous tissue disorders specified - Shingles	A	1	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Skin infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Surgical and medical procedures							
Surgical and medical procedures specified – Catheter ablation of AV nodal re-entrant tachycardia, total hip	A	2	*(2%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Vascular disorders							
Hematoma	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	1	*(2%)*
Hypertension	A	13	*(10%)*	0	*(0%)*	0	*(0%)*
	B	2	*(5%)*	0	*(0%)*	0	*(0%)*
	C	1	*(2%)*	0	*(0%)*	0	*(0%)*
Thromboembolic event	A	1	*(1%)*	1	*(1%)*	1	*(1%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*

*In Arms A, B, and C there were 124, 41, and 43 patients, respectively, evaluable for AEs.

[†]Includes adverse events coded and confirmed as “sudden death”.

Table S10. Full Description of Maximum Grade 3, 4, or 5 Adverse Events (AEs) Occurring in Patients after Crossover (CO) from Arm A to Arm B.

		Grade of Adverse Event					
	Arm*	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Hematologic Adverse Events							
Blood/Bone Marrow							
Anemia	B(CO)	6	*(21%)*	0	*(0%)*	0	*(0%)*
Blood and lymph sys disorders specified – Lymphocyte count decreased	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Leukocytosis	B(CO)	2	*(7%)*	0	*(0%)*	0	*(0%)*
Lymphocyte count decreased	B(CO)	3	*(11%)*	1	*(4%)*	0	*(0%)*
Lymphocyte count increased	B(CO)	8	*(29%)*	0	*(0%)*	0	*(0%)*
Neutrophil count decreased	B(CO)	2	*(7%)*	6	*(21%)*	0	*(0%)*
Platelet count decreased	B(CO)	2	*(7%)*	2	*(7%)*	0	*(0%)*
Non-Hematologic Adverse Events							
Blood and lymphatic system disorders							
Febrile neutropenia	B(CO)	2	*(7%)*	0	*(0%)*	0	*(0%)*
Cardiac disorders							
Atrial fibrillation	B(CO)	3	*(11%)*	0	*(0%)*	0	*(0%)*
Heart failure	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Pericardial effusion	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Eye disorders							
Watering eyes	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Gastrointestinal disorders							
Ascites	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Diarrhea	B(CO)	5	*(18%)*	0	*(0%)*	0	*(0%)*
General disorders and administration site conditions							
Death NOS	B(CO)	0	*(0%)*	0	*(0%)*	1	*(4%)*
Pain	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Hepatobiliary disorders							
Hepatobiliary disorders specified – Hepatic encephalopathy	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Infections and infestations							
Infections and infestations specified – Bronchopulmonary infection, pneumonia	B(CO)	1	*(4%)*	1	*(4%)*	0	*(0%)*

		Grade of Adverse Event					
	Arm*	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Lung infection	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Sepsis	B(CO)	0	*(0%)*	1	*(4%)*	0	*(0%)*
Tooth infection	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Upper respiratory infection	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Urinary tract infection	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Injury, poising and procedure complications							
Postoperative hemorrhage	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Metabolic and nutrition disorders							
Hyponatremia	B(CO)	2	*(7%)*	0	*(0%)*	0	*(0%)*
Hypophosphatemia	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Neoplasm benign, mal and unspecified							
Neoplasms benign, malignant, unspecified – Colon cancer, brain metastases, adenocarcinoma of the gastroesophageal junction, adenocarcinoma of the lung	B(CO)	3	*(11%)*	0	*(0%)*	1	*(4%)*
Renal and urinary disorders							
Chronic kidney disease	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Renal and urinary disorders specified – Pyelonephritis	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Respiratory, thoracic, mediastinal disorders							
Pleural effusion	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Sleep apnea	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*
Vascular disorders							
Hypertension	B(CO)	10	*(36%)*	0	*(0%)*	0	*(0%)*
Hypotension	B(CO)	1	*(4%)*	0	*(0%)*	0	*(0%)*

*In the CO cohort, 28 patients were evaluable for AEs.

Table S11. Cause of Death Summarized for All 66 Deaths, by Arm.

Cause of Death	Deaths up to 24 Months			All Deaths		
	Number on Arm A (BR)	Number on Arm B (I)	Number on Arm C (IR)	Number* on Arm A (BR)	Number on Arm B (I)	Number on Arm C (IR)
CLL/Richter's	1	5	0	7	7	1
Secondary Cancer	1	4	1	2	4	3
Unexplained, unwitnessed death†	1	4	3	2	7	4
Sepsis	1	2	1	3	2	3
Myocardial infarction	1	1	0	1	1	0
Suicide				1	0	0
CVA	1	0	1	1	0	2
Death, NOS	0	0	0	1	0	0
Multi-organ failure	0	0	0	0	1	0
Co-morbidities‡	1	1	0	1	1	0
Infection§	1	0	2	1	1	3
Dementia	0	0	0	0	0	1
Encephalopathy	0	0	1	0	0	1
Subdural/intracranial hemorrhage	0	0	1	0	0	3
Surgical complication	0	0	0	0	0	1

*Includes three patients who crossed over to ibrutinib following progression, two with CLL as the cause of death and 1 with secondary cancer prior to 24 months as the cause of death.

†Includes adverse events coded and confirmed as "sudden death" in each arm (BR x2, ibrutinib x5, IR x2) as well as grade 5 adverse events that upon central review were out of hospital unwitnessed death, coded by treating sites as "myocardial infarction" and "heart failure" in ibrutinib arm and "cardiac arrest" and "death, NOS" in IR arm.

‡Includes co-morbidities NOS (ibrutinib), CKD (BR)

§Includes encephalitis (BR), pneumonia (ibrutinib and IR), leukoencephalopathy (IRx2)

Supplemental References

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.
2. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. J Clin Oncol 2011;29:1290-6.
3. Measuring functioning and well-being: the medical outcomes study approach. Durham: Duke University Press; 1992.
4. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. Journal of gerontology 1981;36:428-34.
5. George LK, Fillenbaum GG. OARS methodology. A decade of experience in geriatric assessment. Journal of the American Geriatrics Society 1985;33:607-15.
6. Loprinzi CL, Laurie JA, Wieand HS, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. North Central Cancer Treatment Group. J Clin Oncol 1994;12:601-7.
7. Sherbourne CD, Stewart AL. The MOS social support survey. Social science & medicine 1991;32:705-14.
8. Karnofsky DA, Burchenal JH. The Clinical evaluation of chemotherapeutic agents in Cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949.
9. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Journal of the American Geriatrics Society 1991;39:142-8.
10. Kawas C, Karagiozis H, Resau L, Corrada M, Brookmeyer R. Reliability of the Blessed Telephone Information-Memory-Concentration Test. Journal of geriatric psychiatry and neurology 1995;8:238-42.
11. Claus R, Lucas DM, Ruppert AS, et al. Validation of ZAP-70 methylation and its relative significance in predicting outcome in chronic lymphocytic leukemia. Blood 2014;124:42-8.
12. DePristo MA, Banks E, Poplin R, et al. A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nature genetics 2011;43:491-8.
13. Kroll KW, Eisfeld AK, Lozanski G, Bloomfield CD, Byrd JC, Blachly JS. MuCor: mutation aggregation and correlation. Bioinformatics 2016;32:1557-8.
14. Blachly JS, Ruppert AS, Zhao W, et al. Immunoglobulin transcript sequence and somatic hypermutation computation from unselected RNA-seq reads in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A 2015;112:4322-7.
15. Rawstron AC, Villamor N, Ritgen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia 2007;21:956-64.
16. Rawstron AC, Fazi C, Agathangelidis A, et al. A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. Leukemia 2016;30:929-36.