

Supplemental Table 1: Baseline characteristics. Includes all randomized patients.

Variable	Category	A (IR)	B (FCR)	Total
Total ¹		354	175	529
Age	Mean (SD)	56.7 (7.5)	56.7 (7.2)	56.7 (7.4)
	Median (Q1,Q3)	58.0 (52.0,62.0)	57.0 (53.0,61.5)	58.0 (52.0,62.0)
	[Min, Max]	[31.0,70.0]	[28.0,70.0]	[28.0,70.0]
	Freq. of Missing	0	0	0
Age, category	<60	209 (59.0)	105 (60.0)	314 (59.4)
	>=60	145 (41.0)	70 (40.0)	215 (40.6)
	Unknown/Missing	0	0	0
Gender	Female	118 (33.3)	55 (31.4)	173 (32.7)
	Male	236 (66.7)	120 (68.6)	356 (67.3)
	Unknown/Missing	0	0	0
Rai Stage	Low, 0	11 (3.1)	9 (5.1)	20 (3.8)
	Intermediate, I-II	187 (52.8)	94 (53.7)	281 (53.1)
	High, III-IV	156 (44.1)	72 (41.1)	228 (43.1)
	Unknown/Missing	0	0	0
CIRS	Mean (SD)	2.1 (2.3)	1.9 (1.9)	2.0 (2.2)
	Median (Q1,Q3)	2 (0,3)	1 (0,3)	2 (0,3)
	[Min, Max]	[0,14]	[0,9]	[0,14]
	Freq. of Missing	7	5	12
ECOG PS	0	226 (63.8)	109 (62.3)	335 (63.3)
	1	119 (33.6)	63 (36.0)	182 (34.4)
	2	9 (2.5)	3 (1.7)	12 (2.3)
	Unknown/Missing	0	0	0
Creatinine Clearance (ml/min)	Mean (SD)	96.3 (6.8)	95.8 (5.8)	96.2 (6.5)
	Median (Q1,Q3)	94.8 (91.9,98.9)	94.5 (92.2,98.0)	94.8 (91.9,98.5)
	[Min, Max]	[86.2,123.9]	[86.8,117.9]	[86.2,123.9]
	Freq. of Missing	0	0	0
Hemoglobin g/dL	Mean (SD)	12.2 (2.2)	12.1 (2.1)	12.1 (2.2)
	Median (Q1,Q3)	12.3 (10.6,13.9)	12.4 (11.0,13.6)	12.4 (10.7,13.8)
	[Min, Max]	[4.4,17.5]	[5.5,17.6]	[4.4,17.6]
Platelets 10 ³ /uL	Freq. of Missing	6	3	9
	Mean (SD)	158.3 (71.3)	157.3 (78.5)	158.0 (73.7)
	Median (Q1,Q3)	150.0 (107.0,200.8)	143.0 (102.0,193.5)	148.0 (105.0,200.0)
	[Min, Max]	[9.6,508.0]	[13.0,485.0]	[9.6,508.0]
TUG (seconds)	Freq. of Missing	0	0	0
	Mean (SD)	8.7 (2.6)	8.6 (2.5)	8.6 (2.6)
	Median (Q1,Q3)	9.0 (7.0,10.0)	8.0 (7.0,10.0)	8.0 (7.0,10.0)
	[Min, Max]	[2.0,27.0]	[2.0,20.0]	[2.0,27.0]
Beta-2 Microglobulin	Freq. of Missing	4	5	9
	Mean (SD)	4.0 (2.1)	4.0 (1.9)	4.0 (2.0)
	Median (Q1,Q3)	3.6 (2.6,4.6)	3.4 (2.7,4.8)	3.6 (2.6,4.7)

mg/L	[Min, Max] Freq. of Missing	[1.3,14.4] 5	[1.0,12.2] 0	[1.0,14.4] 5
Beta-2 Microglobulin	Elevated	181 (51.9)	84 (48.0)	265 (50.6)
	Normal	168 (48.1)	91 (52.0)	259 (49.4)
	Unknown/Missing	5	0	5
Lymphadenopathy ²	No	103 (29.1)	56 (32.0)	159 (30.1)
	Yes	251 (70.9)	119 (68.0)	370 (69.9)
	Unknown/Missing	0	0	0
Del(11q22.3)	Abnormal	78 (22.2)	39 (22.3)	117 (22.2)
	Normal	274 (77.8)	136 (77.7)	410 (77.8)
	Unknown/Missing	2	0	2
Dohner Classification based on FISH	del(17p)	2 (0.6)	0 (0.0)	2 (0.4)
	del(11q22)	78 (22.0)	39 (22.3)	117 (22.1)
	trisomy 12	70 (19.8)	27 (15.4)	97 (18.3)
	normal	69 (19.5)	37 (21.1)	106 (20.0)
	del(13q)	121 (34.2)	58 (33.1)	179 (33.8)
	other	14 (4.0)	14 (8.0)	28 (5.3)
	Unknown/Missing	0	0	0
TP53 Mutation by Sequencing ⁴	Present	27 (9.0)	4 (3.0)	31 (7.2)
	Absent	272 (91.0)	130 (97.0)	402 (92.8)
	Unknown/Missing	55	41	96
IGHV ³	Mutated	70 (25.0)	44 (38.3)	114 (28.9)
	Unmutated	210 (75.0)	71 (61.7)	281 (71.1)
	Unable to sequence	24	17	41
	Not tested	50	43	93

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

² As determined by physical exam.

³ Tested in the 436 (82%) patients who agreed to participate in the correlative study component of the trial and provided a research sample.

⁴ 433 patients who agreed to provide samples for research purposes underwent sequencing of TP53.

Supplemental Table 2: Second primary cancers seen in the two arms. Some patients had multiple second primary cancers.

	IR (n=352)	FCR (n=158)
AML	0	1
Bladder	0	1
Brain tumor	4	0
Breast	4	1
Colon	1	2
Diffuse Large B-cell Lymphoma (Richter's transformation)	2	1
Esophagus	1	0
Gastric	1	0
Lung cancer	5	2
Melanoma	9	1
Myelodysplastic syndrome	0	2
Myeloproliferative disorder-essential thrombocythemia	1	0
Pancreas adenocarcinoma/other	1	0
Pleomorphic rhabdomyosarcoma	0	1
Prostate	8	1
Thyroid	2	0
Skin cancer not melanoma	26	6
Total unique patients developing second primary cancers	55	17

Supplemental Table 3a: Causes of Death

Cause of Death	IR (n=354)	FCR (n=175)
AML	0	3
Cardiac	1	1
CLL	5	6
COVID-19	3	0
Other cancer	5	3
Other cause	2	1
Other medical cause	3	2
Sepsis	1	1
Unknown	1	1
Total	21	18

Other cancer: lung cancer (n=2, IR), brain cancer (n=2, IR), esophagus (IR), colon cancer (n=2, FCR), lung cancer (FCR). Other cause: suicide (IR), accident (IR), drug overdose (FCR). Other medical cause: acute respiratory failure (IR), pancreatitis (IR), stroke (IR), tumor lysis from venetoclax (FCR), GVHD (FCR).

Supplemental Table 3b: Salvage therapy for patients who died from CLL or Richter's Transformation.

Patient	Arm	Salvage Therapy
1*	IR	Rituximab
2	IR	1. Bendamustine, 2. Obinutuzumab, 3. Idelalisib, 4. Obinutuzumab, 5. Acalabrutinib
3	IR	1. Obinutuzumab+Venetoclax, 2. BV-CHP, 3. Dexamethasone
4	IR	1. Venetoclax+Rituximab, 2. R-CHOP
5	IR	1. Rituximab, 2. Cyclosporine, 3. Ibrutinib, 4. Ibrutinib+Venetoclax
6*	FCR	1. Bendamustine+Rituximab, 2. Rituximab, 3. Venetoclax
7*	FCR	None
8*	FCR	1. Ibrutinib, 2. Methylprednisolone + Rituximab, 3. Venetoclax 4. Methylprednisolone + Rituximab, 5. CHOP
9*	FCR	1. Rituximab, 2. Bendamustine (1 cycle)
10	FCR	None
11	FCR	1. Ibrutinib, 2. Obinutuzumab-EPOCH

* Reported in Shanafelt et al NEJM 2018.

Supplemental Table 4. Adverse events of all grades regardless of treatment attribution.

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Anemia	69	9	-	-	65	15	4	-
Blood and lymphatic system disorders - Other, specify	10	<1	-	-	3	1	-	-
Febrile neutropenia	-	2	<1	-	-	13	3	-
Hemolysis	<1	1	-	-	-	2	1	-
Leukocytosis	-	18	<1	-	-	9	-	-
Lymph node pain	3	-	-	-	3	-	-	-
Spleen disorder	-	-	-	-	1	-	-	-
Thrombotic thrombocytopenic purpura	<1	-	-	-	-	-	-	-
Bone marrow hypocellular	<1	-	-	-	-	-	-	-
Atrial fibrillation	7	4	1	-	2	1	1	-
Atrial flutter	-	1	-	-	-	-	-	-
Atrioventricular block complete	-	<1	-	-	-	-	-	-
Atrioventricular block first degree	-	-	-	-	1	-	-	-
Cardiac arrest	-	-	1	<1	-	-	-	-
Cardiac disorders - Other, specify	5	<1	-	-	1	-	-	-
Chest pain - cardiac	3	1	-	-	1	-	-	-
Conduction disorder	-	<1	-	-	-	-	-	-
Constrictive pericarditis	-	-	-	-	-	1	-	-
Heart failure	<1	1	<1	-	-	-	-	-
Palpitations	13	-	-	-	3	-	-	-
Pericardial effusion	-	1	-	-	-	-	-	-
Pericarditis	1	-	-	-	-	-	-	-
Sinus bradycardia	6	1	-	-	2	-	-	-
Sinus tachycardia	6	<1	-	-	4	-	-	-
Supraventricular tachycardia	1	1	-	-	-	-	-	-
Ventricular arrhythmia	1	-	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Ventricular tachycardia	<1	<1	-	-	-	-	-	-
Acute coronary syndrome	1	-	-	-	-	1	-	-
Pericardial tamponade	-	-	<1	-	-	-	-	-
Congenital, familial and genetic disorders - Other, specify	<1	-	-	-	-	-	-	-
Ear and labyrinth disorders - Other, specify	4	-	-	-	2	-	-	-
Ear pain	5	<1	-	-	2	-	-	-
Hearing impaired	2	1	-	-	1	-	-	-
Tinnitus	5	-	-	-	3	-	-	-
Vertigo	3	-	-	-	1	-	-	-
Vestibular disorder	<1	-	-	-	-	-	-	-
External ear inflammation	1	-	-	-	-	-	-	-
Middle ear inflammation	1	-	-	-	-	-	-	-
Cushingoid	-	-	-	-	1	-	-	-
Endocrine disorders - Other, specify	3	-	-	-	1	-	-	-
Hyperparathyroidism	1	-	-	-	-	-	-	-
Hyperthyroidism	1	-	-	-	-	-	-	-
Hypothyroidism	3	-	-	-	-	-	-	-
Blurred vision	12	-	-	-	3	-	-	-
Cataract	2	1	-	-	-	-	-	-
Conjunctivitis	5	-	-	-	-	-	-	-
Dry eye	7	-	-	-	-	-	-	-
Eye disorders - Other, specify	9	<1	-	-	1	-	-	-
Eye pain	3	-	-	-	-	-	-	-
Floaters	1	-	-	-	-	-	-	-
Glaucoma	1	-	<1	-	-	-	-	-
Night blindness	<1	-	-	-	-	-	-	-
Photophobia	1	-	-	-	-	-	-	-
Retinal detachment	<1	-	-	-	-	-	-	-
Retinal tear	-	-	<1	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Retinal vascular disorder	<1	-	-	-	-	-	-	-
Retinopathy	<1	-	-	-	1	-	-	-
Uveitis	1	-	-	-	-	-	-	-
Vitreous hemorrhage	1	-	-	-	-	-	-	-
Watering eyes	4	-	-	-	1	-	-	-
Optic nerve disorder	-	<1	-	-	-	-	-	-
Abdominal distension	3	-	-	-	1	-	-	-
Abdominal pain	20	2	-	-	9	1	-	-
Anal fistula	<1	<1	-	-	-	-	-	-
Anal pain	1	-	-	-	-	-	-	-
Ascites	<1	-	-	-	-	1	-	-
Bloating	5	-	-	-	1	-	-	-
Cheilitis	<1	-	-	-	-	-	-	-
Colitis	1	1	-	-	-	1	-	-
Colonic perforation	-	-	<1	-	-	-	-	-
Colonic ulcer	<1	-	-	-	-	-	-	-
Constipation	20	-	-	-	32	-	-	-
Dental caries	1	<1	-	-	-	-	-	-
Diarrhea	53	5	-	-	25	1	-	-
Dry mouth	10	-	-	-	2	-	-	-
Dyspepsia	14	-	-	-	3	-	-	-
Dysphagia	5	<1	-	-	1	-	-	-
Enterocolitis	1	-	-	-	-	-	-	-
Esophageal pain	1	-	-	-	-	-	-	-
Esophageal ulcer	1	-	-	-	-	-	-	-
Esophagitis	2	-	-	-	-	-	-	-
Flatulence	6	-	-	-	1	-	-	-
Gastric hemorrhage	-	<1	-	-	-	-	-	-
Gastric ulcer	<1	-	-	-	1	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Gastritis	3	-	-	-	-	-	-	-
Gastrointestinal disorders - Other, specify	16	<1	-	-	3	-	-	-
Gastrointestinal pain	1	-	-	-	-	-	-	-
Hemorrhoids	5	-	-	-	1	-	-	-
Lip pain	1	-	-	-	1	-	-	-
Mucositis oral	19	1	-	-	7	1	-	-
Nausea	44	1	-	-	63	1	-	-
Oral hemorrhage	2	-	-	-	1	-	-	-
Oral pain	4	-	-	-	4	-	-	-
Pancreatitis	-	<1	-	-	-	-	-	-
Periodontal disease	<1	-	-	-	-	-	-	-
Proctitis	1	-	-	-	-	-	-	-
Rectal fistula	<1	-	-	-	-	-	-	-
Rectal hemorrhage	2	-	-	-	1	-	-	-
Rectal pain	<1	-	-	-	-	-	-	-
Small intestinal obstruction	<1	-	-	-	-	-	-	-
Stomach pain	2	<1	-	-	1	-	-	-
Toothache	2	-	-	-	1	-	-	-
Vomiting	20	3	-	-	28	-	-	-
Lower gastrointestinal hemorrhage	4	-	-	-	1	-	-	-
Oral dysesthesia	1	-	-	-	1	-	-	-
Anal hemorrhage	1	-	-	-	-	-	-	-
Upper gastrointestinal hemorrhage	1	1	-	-	-	-	-	-
Hemorrhoidal hemorrhage	1	-	-	-	-	-	-	-
Small intestinal mucositis	-	-	-	-	1	-	-	-
Gastroesophageal reflux disease	17	-	-	-	7	-	-	-
Chills	13	<1	-	-	16	1	-	-
Death NOS	-	-	-	1	-	-	-	1
Edema face	2	-	-	-	2	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Facial pain	1	-	-	-	-	-	-	-
Fatigue	82	3	-	-	77	3	-	-
Fever	30	1	<1	-	27	1	-	-
Flu like symptoms	10	1	-	-	3	-	-	-
Gait disturbance	1	-	-	-	1	-	-	-
General disorders and administration site conditions - Other, specify	15	<1	-	-	4	-	-	-
Injection site reaction	1	-	-	-	1	-	-	-
Irritability	<1	-	-	-	-	-	-	-
Malaise	4	-	-	-	3	-	-	-
Multi-organ failure	-	-	-	<1	-	-	-	-
Pain	26	2	-	-	8	-	-	-
Edema limbs	33	1	-	-	17	-	-	-
Infusion related reaction	9	-	<1	-	25	1	-	-
Neck edema	-	-	-	-	1	-	-	-
Edema trunk	1	-	-	-	1	-	-	-
Localized edema	9	-	-	-	3	-	-	-
Non-cardiac chest pain	11	<1	-	-	3	1	-	-
Infusion site extravasation	<1	-	-	-	1	-	-	-
Cholecystitis	<1	1	-	-	-	1	-	-
Hepatobiliary disorders - Other, specify	2	-	-	-	-	-	-	-
Bile duct stenosis	<1	-	-	-	-	-	-	-
Allergic reaction	2	<1	-	-	2	-	-	-
Immune system disorders - Other, specify	2	1	-	-	1	1	-	-
Autoimmune disorder	-	-	-	-	1	-	-	-
Appendicitis	-	1	-	-	-	-	-	-
Bladder infection	1	<1	-	-	-	-	-	-
Breast infection	-	-	-	-	1	-	-	-
Catheter related infection	-	<1	-	-	-	-	-	-
Conjunctivitis infective	1	-	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Encephalitis infection	-	-	-	-	-	1	-	-
Eye infection	1	-	-	-	-	-	-	-
Infections and infestations - Other, specify	16	5	1	1	4	1	-	-
Joint infection	1	<1	-	-	-	-	-	-
Kidney infection	-	<1	-	-	-	-	-	-
Otitis externa	1	-	-	-	1	-	-	-
Otitis media	4	-	-	-	1	-	-	-
Paronychia	2	-	-	-	-	-	-	-
Pharyngitis	3	-	-	-	-	-	-	-
Rash pustular	1	-	-	-	-	-	-	-
Salivary gland infection	<1	-	-	-	-	-	-	-
Sepsis	-	-	1	<1	-	-	3	1
Sinusitis	11	<1	-	-	4	1	-	-
Skin infection	14	2	-	-	1	1	-	-
Upper respiratory infection	34	1	<1	-	17	2	-	-
Urinary tract infection	9	2	-	-	2	1	-	-
Vaginal infection	1	-	-	-	1	-	-	-
Wound infection	1	-	-	-	-	-	-	-
Tooth infection	3	1	-	-	1	-	-	-
Prostate infection	1	-	-	-	1	-	-	-
Lymph gland infection	-	1	-	-	-	-	-	-
Bronchial infection	4	-	-	-	1	-	-	-
Phlebitis infective	<1	-	-	-	-	-	-	-
Esophageal infection	<1	-	-	-	-	-	-	-
Enterocolitis infectious	<1	1	-	-	-	1	-	-
Rhinitis infective	1	-	-	-	1	-	-	-
Bone infection	-	<1	-	-	-	-	-	-
Lung infection	10	5	<1	-	3	4	-	-
Nail infection	4	<1	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Penile infection	-	<1	-	-	1	-	-	-
Scrotal infection	-	1	-	-	-	-	-	-
Soft tissue infection	1	1	<1	-	-	-	-	-
Lip infection	1	-	-	-	-	-	-	-
Mucosal infection	1	-	-	-	-	-	-	-
Peripheral nerve infection	<1	-	-	-	-	-	-	-
Papulopustular rash	3	-	<1	-	-	-	-	-
Ankle fracture	1	-	-	-	-	-	-	-
Arterial injury	-	1	-	-	-	-	-	-
Bruising	38	-	-	-	4	-	-	-
Burn	1	-	-	-	-	-	-	-
Fall	4	1	-	-	4	1	-	-
Fracture	4	1	-	-	1	-	-	-
Hip fracture	<1	-	-	-	-	-	-	-
Injury, poisoning and procedural complications - Other, specify	5	<1	-	-	3	-	-	-
Radiation recall reaction (dermatologic)	<1	-	-	-	-	-	-	-
Spinal fracture	<1	<1	-	-	-	-	-	-
Wound dehiscence	-	<1	-	-	-	-	-	-
Wrist fracture	<1	-	-	-	-	-	-	-
Wound complication	1	-	-	-	-	-	-	-
Intraoperative hemorrhage	-	<1	-	-	-	-	-	-
Postoperative hemorrhage	1	-	-	-	-	-	-	-
Dermatitis radiation	<1	-	-	-	-	-	-	-
Urostomy obstruction	-	<1	-	-	-	-	-	-
Activated partial thromboplastin time prolonged	1	-	-	-	1	-	-	-
Alanine aminotransferase increased	22	2	1	-	19	1	-	-
Alkaline phosphatase increased	19	1	-	-	21	-	-	-
Aspartate aminotransferase increased	32	3	1	-	30	1	-	-
Blood bilirubin increased	30	4	<1	-	18	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Blood corticotrophin decreased	<1	-	-	-	-	-	-	-
Cardiac troponin I increased	1	-	-	-	-	-	-	-
CD4 lymphocytes decreased	<1	-	-	-	1	1	-	-
Cholesterol high	5	-	-	-	-	-	-	-
CPK increased	2	-	<1	-	-	-	-	-
Creatinine increased	42	1	<1	-	22	1	-	-
INR increased	<1	-	-	-	-	-	-	-
Investigations - Other, specify	13	1	-	-	3	-	-	-
Lipase increased	1	1	<1	-	-	-	-	-
Lymphocyte count decreased	24	10	2	-	12	36	33	-
Lymphocyte count increased	15	64	-	-	12	51	-	-
Neutrophil count decreased	21	15	20	-	22	22	25	-
Platelet count decreased	59	4	3	-	61	11	7	-
Serum amylase increased	<1	-	<1	-	-	-	-	-
Weight gain	16	2	-	-	5	-	-	-
Weight loss	9	<1	-	-	7	-	-	-
White blood cell decreased	24	7	1	-	37	25	16	-
Ejection fraction decreased	-	1	-	-	-	-	-	-
Hemoglobin increased	1	<1	-	-	1	-	-	-
GGT increased	<1	<1	-	-	-	-	-	-
Alcohol intolerance	-	<1	-	-	-	-	-	-
Anorexia	18	-	-	-	20	1	-	-
Dehydration	3	1	-	-	5	-	-	-
Hypercalcemia	4	-	1	-	3	-	-	-
Hyperglycemia	28	5	1	-	18	6	-	-
Hyperkalemia	16	2	-	-	6	1	-	-
Hypermagnesemia	1	-	-	-	1	-	-	-
Hypernatremia	7	-	-	-	3	-	-	-
Hypertriglyceridemia	3	-	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Hyperuricemia	18	1	1	-	5	-	-	-
Hypoalbuminemia	15	1	-	-	7	1	1	-
Hypocalcemia	26	<1	-	-	22	1	-	-
Hypoglycemia	10	1	-	-	4	-	1	-
Hypokalemia	15	1	-	-	10	1	-	-
Hypomagnesemia	4	-	-	-	3	-	-	-
Hyponatremia	14	5	-	-	10	2	-	-
Hypophosphatemia	5	2	-	-	9	-	-	-
Metabolism and nutrition disorders - Other, specify	6	1	-	-	3	-	-	-
Obesity	-	<1	1	-	1	1	1	-
Tumor lysis syndrome	-	1	-	-	-	1	-	-
Glucose intolerance	2	<1	-	-	1	-	-	-
Arthralgia	39	6	-	-	8	1	-	-
Arthritis	9	-	-	-	1	-	-	-
Back pain	27	2	-	-	10	1	-	-
Bone pain	4	<1	-	-	5	-	-	-
Chest wall pain	2	-	-	-	1	-	-	-
Exostosis	<1	-	-	-	-	-	-	-
Flank pain	4	<1	-	-	-	1	-	-
Joint effusion	1	-	-	-	-	-	-	-
Musculoskeletal and connective tissue disorder - Other, specify	25	1	-	-	4	-	-	-
Myalgia	46	2	-	-	24	1	-	-
Neck pain	7	<1	-	-	3	-	-	-
Osteoporosis	2	-	-	-	1	-	-	-
Pain in extremity	27	2	-	-	6	-	-	-
Buttock pain	1	-	-	-	-	-	-	-
Joint range of motion decreased	1	-	-	-	-	-	-	-
Generalized muscle weakness	7	-	-	-	3	-	-	-
Muscle weakness lower limb	2	-	-	-	1	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Muscle weakness left-sided	<1	-	-	-	-	-	-	-
Muscle weakness right-sided	-	<1	-	-	-	-	-	-
Muscle weakness upper limb	1	-	-	-	-	-	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	13	3	<1	-	2	2	-	-
Leukemia secondary to oncology chemotherapy	-	-	-	-	-	-	-	1
Treatment related secondary malignancy	-	2	-	-	-	1	-	1
Akathisia	-	-	-	-	1	-	-	-
Amnesia	1	-	-	-	-	-	-	-
Ataxia	1	-	-	-	-	-	-	-
Cognitive disturbance	<1	1	-	-	1	-	-	-
Concentration impairment	1	-	-	-	1	-	-	-
Dizziness	23	1	-	-	13	1	-	-
Dysarthria	1	-	-	-	-	-	-	-
Dysgeusia	7	-	-	-	6	-	-	-
Dysphasia	1	<1	-	-	1	-	-	-
Encephalopathy	-	<1	-	-	-	1	-	-
Headache	44	1	-	-	28	1	-	-
Intracranial hemorrhage	-	-	<1	-	-	-	-	-
Lethargy	1	-	-	-	1	-	-	-
Memory impairment	5	-	-	-	3	-	-	-
Movements involuntary	<1	-	-	-	-	-	-	-
Nervous system disorders - Other, specify	4	<1	-	-	1	-	-	-
Neuralgia	1	<1	-	-	-	1	-	-
Paresthesia	7	<1	-	-	4	-	-	-
Peripheral motor neuropathy	2	-	-	-	3	-	-	-
Peripheral sensory neuropathy	21	1	-	-	10	1	-	-
Presyncope	2	-	-	-	2	-	-	-
Seizure	<1	<1	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Sinus pain	1	-	-	-	1	-	-	-
Somnolence	1	-	-	-	1	-	-	-
Spasticity	1	-	-	-	-	-	-	-
Stroke	1	1	-	-	-	1	-	-
Syncope	-	3	-	-	-	2	-	-
Transient ischemic attacks	<1	-	-	-	-	-	-	-
Tremor	2	-	-	-	1	-	-	-
Vasovagal reaction	-	-	-	-	-	1	-	-
Facial muscle weakness	<1	-	-	-	-	-	-	-
Radiculitis	1	-	-	-	-	-	-	-
Dysesthesia	<1	-	-	-	-	-	-	-
Pregnancy, puerperium and perinatal conditions - Other, specify	-	<1	-	-	-	-	-	-
Agitation	1	-	-	-	2	-	-	-
Anxiety	16	1	-	-	11	-	-	-
Confusion	2	1	-	-	1	1	-	-
Depression	14	1	<1	-	6	-	-	-
Hallucinations	-	-	-	-	-	-	1	-
Insomnia	17	1	-	-	18	1	-	-
Libido decreased	1	-	-	-	-	-	-	-
Mania	<1	-	-	-	-	-	-	-
Psychiatric disorders - Other, specify	1	-	-	-	1	-	-	-
Psychosis	-	-	<1	-	-	-	-	-
Restlessness	1	-	-	-	-	-	-	-
Suicidal ideation	-	<1	-	-	-	-	-	-
Suicide attempt	-	-	-	<1	-	-	-	-
Hematuria	18	1	-	-	3	-	-	-
Hemoglobinuria	<1	-	-	-	-	-	-	-
Proteinuria	2	-	-	-	2	-	-	-
Renal and urinary disorders - Other, specify	6	-	-	-	1	-	-	-

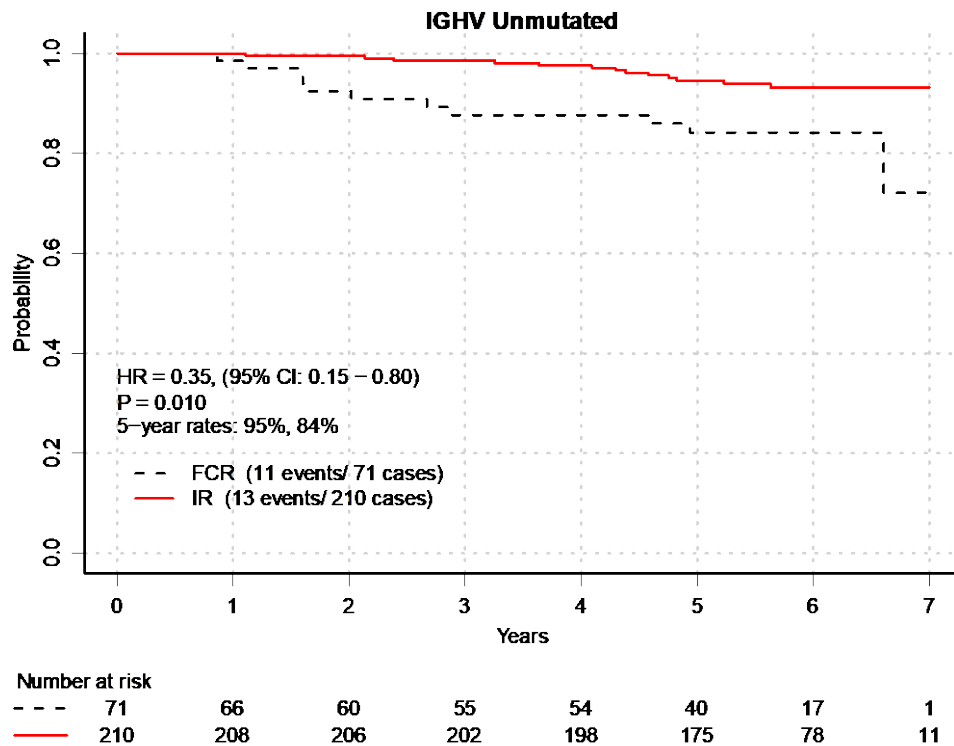
Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Renal calculi	2	2	-	-	-	-	-	-
Renal colic	1	-	-	-	-	-	-	-
Renal hemorrhage	<1	<1	-	-	-	-	-	-
Urinary frequency	7	-	-	-	9	-	-	-
Urinary incontinence	1	-	-	-	1	-	-	-
Urinary retention	2	<1	-	-	-	-	-	-
Urinary urgency	3	-	-	-	1	-	-	-
Urine discoloration	1	-	-	-	-	-	-	-
Bladder spasm	1	-	-	-	-	-	-	-
Urinary tract obstruction	-	<1	-	-	-	-	-	-
Urinary tract pain	2	-	-	-	1	1	-	-
Cystitis noninfective	<1	-	-	-	1	-	-	-
Chronic kidney disease	5	<1	-	-	2	-	-	-
Acute kidney injury	1	<1	-	-	1	1	-	-
Breast pain	1	-	-	-	1	-	-	-
Genital edema	1	-	-	-	-	-	-	-
Gynecomastia	<1	-	-	-	-	-	-	-
Irregular menstruation	1	<1	-	-	-	-	-	-
Menorrhagia	1	-	-	-	1	-	-	-
Pelvic pain	1	<1	-	-	-	-	-	-
Penile pain	<1	-	-	-	-	-	-	-
Prostatic pain	1	-	-	-	-	-	-	-
Reproductive system and breast disorders - Other, specify	3	-	-	-	1	-	-	-
Scrotal pain	1	-	-	-	-	-	-	-
Testicular disorder	1	<1	-	-	-	-	-	-
Testicular pain	1	-	-	-	-	-	-	-
Uterine hemorrhage	<1	-	-	-	-	-	-	-
Vaginal discharge	1	-	-	-	-	-	-	-
Vaginal dryness	1	-	-	-	-	-	-	-

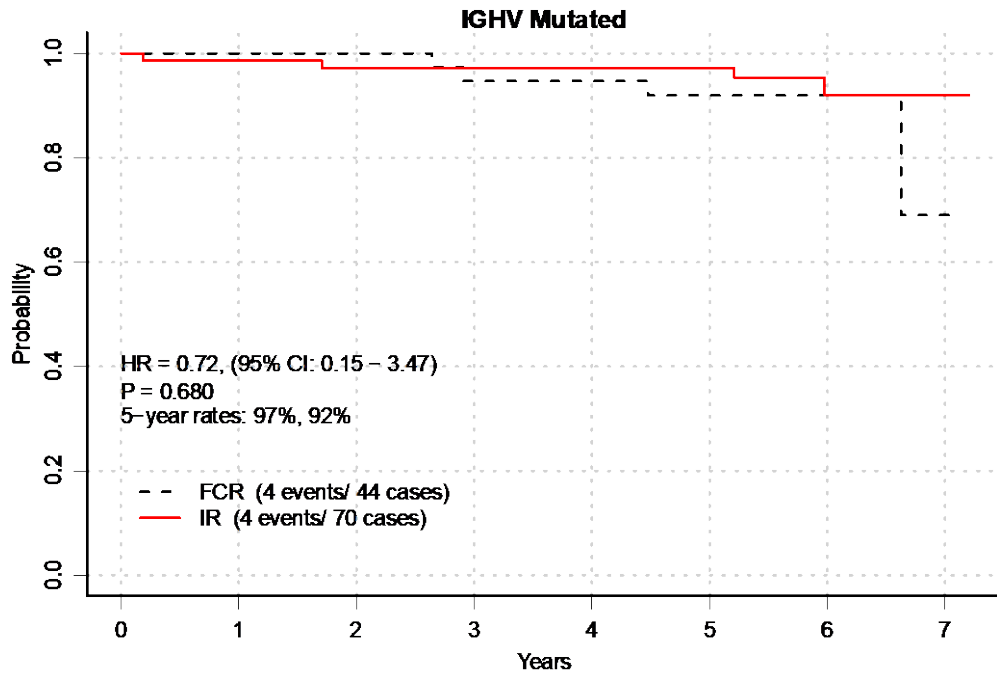
Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Vaginal hemorrhage	1	-	-	-	-	-	-	-
Vaginal inflammation	1	-	-	-	-	-	-	-
Prostatic obstruction	2	-	-	-	-	-	-	-
Erectile dysfunction	2	-	-	-	-	-	-	-
Pelvic floor muscle weakness	<1	-	-	-	-	-	-	-
Spermatic cord hemorrhage	<1	-	-	-	-	-	-	-
Allergic rhinitis	14	-	-	-	3	-	-	-
Apnea	-	-	-	-	-	1	-	-
Aspiration	-	-	-	-	1	-	-	-
Atelectasis	<1	-	-	-	-	-	-	-
Cough	41	<1	-	-	26	-	-	-
Dyspnea	24	3	<1	-	20	1	-	-
Epistaxis	10	-	-	-	1	1	-	-
Hiccups	<1	<1	-	-	3	-	-	-
Hoarseness	3	-	-	-	2	-	-	-
Hypoxia	<1	<1	<1	-	2	-	-	-
Nasal congestion	16	-	-	-	8	-	-	-
Pharyngolaryngeal pain	<1	-	-	-	-	-	-	-
Pleural effusion	2	1	-	-	2	-	-	-
Pleuritic pain	1	-	-	-	1	-	-	-
Pneumonitis	1	-	-	-	1	1	1	-
Postnasal drip	6	-	-	-	3	-	-	-
Productive cough	10	-	-	-	6	-	-	-
Pulmonary edema	-	-	<1	-	-	-	-	-
Pulmonary fibrosis	<1	-	-	-	-	-	-	-
Respiratory failure	-	-	1	<1	-	-	1	-
Respiratory, thoracic and mediastinal disorders - Other, specify	8	1	<1	-	2	-	-	-
Sleep apnea	2	1	-	-	1	-	-	-
Sneezing	1	-	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)	
Sore throat	15	<1	-	-	4	-	-	-
Voice alteration	<1	-	-	-	1	-	-	-
Wheezing	4	-	-	-	4	-	-	-
Sinus disorder	1	-	-	-	1	-	-	-
Laryngeal inflammation	<1	-	-	-	-	-	-	-
Bronchopulmonary hemorrhage	<1	-	-	-	-	-	-	-
Laryngeal hemorrhage	-	-	-	-	1	-	-	-
Pharyngeal mucositis	<1	-	-	-	-	-	-	-
Tracheal mucositis	<1	-	-	-	-	-	-	-
Alopecia	5	-	-	-	3	-	-	-
Bullous dermatitis	1	-	-	-	-	-	-	-
Dry skin	13	<1	-	-	6	-	-	-
Erythema multiforme	2	-	-	-	1	-	-	-
Hirsutism	<1	-	-	-	-	-	-	-
Hyperhidrosis	7	-	-	-	4	-	-	-
Nail discoloration	1	-	-	-	-	-	-	-
Pain of skin	2	-	-	-	1	-	-	-
Photosensitivity	-	-	-	-	1	-	-	-
Pruritus	14	<1	-	-	8	-	-	-
Purpura	4	-	-	-	1	-	-	-
Rash acneiform	6	-	-	-	1	-	-	-
Rash maculo-papular	44	3	-	-	21	5	-	-
Skin and subcutaneous tissue disorders - Other, specify	34	1	-	-	9	1	-	-
Skin hyperpigmentation	1	-	-	-	1	-	-	-
Skin hypopigmentation	<1	-	-	-	-	-	-	-
Skin ulceration	2	<1	<1	-	1	-	-	-
Telangiectasia	<1	-	-	-	-	-	-	-
Urticaria	2	-	-	-	-	-	-	-
Scalp pain	1	-	-	-	-	-	-	-

Toxicity Type	Treatment Arm							
	A (n=352)				B (n=158)			
	Grade				Grade			
	1,2 (%)	3 (%)	4 (%)	5 (%)	1,2 (%)	3 (%)	4 (%)	5 (%)
Nail loss	2	-	-	-	-	-	-	-
Palmar-plantar erythrodysesthesia syndrome	1	-	-	-	1	-	-	-
Periorbital edema	<1	-	-	-	-	-	-	-
Nail ridging	3	-	-	-	-	-	-	-
Surgical and medical procedures - Other, specify	3	3	-	-	-	-	-	-
Flushing	2	-	-	-	3	-	-	-
Hematoma	3	1	-	-	-	1	-	-
Hot flashes	12	-	-	-	13	-	-	-
Hypertension	28	25	1	-	16	8	-	-
Hypotension	4	<1	-	-	9	1	-	-
Lymphedema	1	-	-	-	-	-	-	-
Phlebitis	<1	-	-	-	1	-	-	-
Superficial thrombophlebitis	<1	-	-	-	1	-	-	-
Thromboembolic event	2	1	-	-	1	1	1	-
Vascular disorders - Other, specify	3	<1	-	-	2	-	-	-
Vasculitis	<1	-	-	-	-	-	-	-
WORST DEGREE	5	63	29	3	7	42	49	3

Supplemental Figure 1. Overall survival by IGHV mutation status.





Number at risk		0	1	2	3	4	5	6	7
--	44	44	41	39	35	35	29	16	1
—	70	70	68	67	67	67	59	25	6

Supplemental Figure 2. Progression-free survival (PFS) after discontinuing ibrutinib by time on treatment. Includes patients on IR arm who started protocol therapy and discontinued due to reasons other than progression or death. PFS calculated from date off treatment.

