Supplement to: **Phase 2 Study of Ibrutinib in Classic and Variant Hairy Cell Leukemia**

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Eligibility Criteria

Inclusion Criteria

- Histologically confirmed diagnosis of Hairy Cell Leukemia or variant according to WHO criteria with any of the following indications for therapy:
  - Hemoglobin < 11 g/dL
  - Platelet count < 100,000/µL
  - Absolute neutrophil count < 1,000/µL
  - Progressive or symptomatic splenomegaly or hepatomegaly
  - Enlarging lymphadenopathy ≥ 2 cm
  - Absolute lymphocyte count > 5,000/mL
  - Disease related constitutional symptoms consisting of unexplained weight loss exceeding 10% of body weight over the preceding 6 months, CTEP active version of the CTCAE grade 2 or 3 fatigue, fevers >100.5º F or night sweats for greater than 2 weeks without evidence of infection.
- Patients with Classic Hairy Cell Leukemia may receive therapy under the following conditions:
  - After at least 1 prior purine nucleoside analog-containing regimen, (Fludarabine, Pentostatin, or Cladribine)
  - Or relapsed or de novo disease if deemed medically unfit for therapy with a purine nucleoside analog
- Because there is no recognized standard of care for patients with Variant Hairy Cell Leukemia, both previously treated and previously untreated patients with this diagnosis will be eligible.

- Age >18 years.
- ECOG performance status <2 (Karnofsky >60%).
- Life expectancy of greater than 12 months.
- Patients will be required to meet the following laboratory parameters:
  - Creatinine ≤ 2.0 mg/dL, and/or creatinine clearance (estimated GFR [Cockcroft-Gault]) ≥30 mL/min
  - Total bilirubin ≤ 1.5 x ULN (unless disease related or due to Gilbert's disease)
  - AST ≤ 3.0 x ULN (unless disease related)
  - PT/INR <1.5 × ULN and PTT (aPTT) <1.5 × ULN
- Because patients with HCL are typically pancytopenic at presentation for treatment, patients will be eligible without respect to baseline peripheral blood cell counts if they otherwise meet inclusion criteria.
- The effects of ibrutinib on the developing human fetus are unknown. For this reason, and because tyrosine kinase inhibitors may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry.
- Female patients who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female patients of childbearing potential must have a negative serum pregnancy test upon study entry.
- Male and female patients who agree to use highly effective methods of birth control (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete sexual abstinence, or sterilized partner) during the period of

therapy and for 90 days after the last dose of study drug.

- Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

- Chemotherapy <21 days prior to first administration of study treatment and/or monoclonal antibody <6 weeks prior to first administration of study treatment.
- Patients who are receiving any other investigational agents.
- Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition as ibrutinib.
- Ibrutinib is extensively metabolized by CYP3A4/5. Patients who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or patients who require continuous treatment with a strong CYP3A inhibitor. Therefore, any medications or substances that are strong inhibitors of CYP3A4/5 should be discontinued. Patients unable to change these medications must be excluded from participation.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Recent infections requiring systemic treatment need to have completed therapy >14 days before the first dose of study drug.
- Pregnant women are excluded from this study because ibrutinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects.
- Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ibrutinib, breastfeeding should be discontinued if the mother is treated with ibrutinib.
- HIV-positive patients will be eligible unless they have been previously diagnosed with an AIDS-defining illness.
- Patients who require anticoagulation with warfarin (Coumadin) or who have taken warfarin within 28 days prior to enrollment are not eligible due to a potential increased risk of hemorrhage. Patients who are currently taking vitamin K antagonists are also ineligible for this study.
- Patients requiring daily corticosteroids at a prednisone equivalent of ≥20 mg daily should not be enrolled. If corticosteroids can be discontinued (or reduced to <20 mg per day of prednisone or equivalent), the discontinuation or dose reduction should be done at least 7 days prior to first dose.
- Prior exposure to a BTK inhibitor.
- Major surgery within 4 weeks of first dose of study drug.
- A history of prior malignancy, with the exception of the following:
    - Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to screening, and felt to be at low risk for recurrence by the treating physician.

  - Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
  - Adequately treated cervical carcinoma in situ without current evidence of disease.
- Currently active clinically significant cardiovascular disease such as: uncontrolled arrhythmia, congestive heart failure, or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification or history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to first dose with study drug.
- Patient is unable to swallow capsules, or has disease significantly affecting gastrointestinal function or resection of the stomach or small bowel, or symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) prior to enrollment. (PCR positive patients will be excluded).
- Concurrent systemic immunosuppressant therapy other than corticosteroids (e.g., cyclosporine A, tacrolimus, etc.) within 28 days of the first dose of study drug.
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
- Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 5), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.

- Known bleeding disorders (e.g., von Willebrand’s disease) or hemophilia.
- Unwilling or unable to participate in all required study evaluations and procedures.
- Currently active, clinically significant hepatic impairment (≥ moderate hepatic Impairment according to the NCI/Child Pugh classification).

Institutions Enrolling Patients

Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine

The Ohio State University

Mayo Clinic

MD Anderson Cancer Center

National Institutes of Health

Supplemental Methods

Plasma sample collection and pharmacokinetic (PK) analysis

Ibrutinib was administered at two dose levels 420 and 840mg. Blood samples were collected in heparin tubes at baseline prior to ibrutinib administration and at 30 minutes, 1-, 2-, 4-, 6- and 24-hour post dose on days 1 and 8 of cycle 1. Blood samples were centrifuged at 1,200 rpm for 10 minutes at 4°C, supernatant withdrawn and aliquoted, and then stored at −70°C until analysis. Plasma samples were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Concentration-time data was used to generate ibrutinib pharmacokinetic parameters via non-compartmental methods.

To determine PK parameters (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC], time to reach C_{max} [T_{max}], clearance [CL], volume of distribution [Vd], terminal half-life [$t_{1/2}$]) for each patient, we used ibrutinib concentration-time data and conducted standard non-compartmental analysis in Phoenix WinNonlin Professional v 8.0 (Pharsight, Mountain View, CA). Data from 20 patients were used to conduct non-compartmental analysis and generate plasma-concentration time plots. A two-sided t-test was used for comparisons of C_{max} and AUC_{0-6} values between day 1 and day 8.

Flow Cytometry

Samples of ACDA anticoagulated blood procured via venipuncture at different time points prior to, during, and following treatment were analyzed. All samples were transferred to the Ohio State University clinical flow cytometry laboratory and were

immediately processed upon receipt. Prior to staining all samples were tested for viability using 7AAD method. Only samples with viability of at least 95% were accepted for further analysis. All samples were stained using set of optimally titrated directly conjugated monoclonal antibodies as detailed in the table below. Multiparametric analysis was performed with a gating strategy based on CD45 staining and light side scatter characteristics that allow good separation of lymphocyte, monocyte and myeloid cell populations and immunophenotype characterization according to the table. Detailed characterization of the B lymphocytes was performed using sequential gating and Prism plot utility in a fashion that allows discrimination between cells subsets based on permutations of multiple parameters. After pathologist review, the results were be reported as % of lymphocyte gate and % of total leukocytes analyzed and calculated number of B lymphocytes per microliter of blood.

Fluorochrome		**FITC**	**PE**	**ECD**	**PC5**	**PC7**	**APC 700**	**PACIFIC BLUE**	**KROME ORANGE**
Viability	Marker	CD45		CD19	7AAD		CD2		
	Antibody	BC 20µL		BC 10µL	BC 20µL		BC 5µL		
Tube 1	Marker	CD103	CD11C	CD19	CD25	CD45			
	Antibody	BC 20µL	BC 20µL	BC 10µL	BC 10µL	BC 5µL			
Tube 2	Marker	CD20	CD123	CD19	CD27	CD45			
	Antibody	BC 10µL	BD 20µL	BC 10µL	BC 10µL	BC 5µL			
Tube 3	Marker	KAPPA	LAMBDA	CD19	CD5		CD10	CD20	CD45

	Antibody	Dako 10µL	Dako 10µL	BC 10µL	BC 5µL		BC 5µL	BC 5µL	
BC = Beckman Coulter, BD = Beckton Dickenson.									

Immunohistochemistry

Tissue sections of decalcified bone marrow were cut at a thickness of 4 microns and were then baked in a 65°C oven for 60 minutes. Slides were then placed onto the Leica Bond III (Leica Biosystems, Buffalo Grove, IL) platform for deparaffinization and staining. The slides were deparaffinized online using Leica Bond Dewax and 100% alcohol. The slides were then antigen retrieved using the Leica Bond ER2 (AR9640) for 20 minutes. The tissue was then quenched with hydrogen peroxide for 5 minutes to block any endogenous peroxidase. The tissue was then incubated with PAX5 (clone 1EW Leica Biosytems, Buffalo Grove, IL) at a dilution of 1:100 for 30 minutes. The slides were then treated with Leica Bond Post Primary reagent (part of the Leica Bond Polymer Refine detection DS9800)) for 8 minutes. Leica Bond DAB was then applied and incubated for 10 minutes. Tissue sections were then incubated with pERK (clone Erk1-2, Cell Signaling, Danvers, MA) at a dilution of 1:200 for 15 minutes. Slides were then incubated with Leica Bond Polymer AP (DS9390) for 30 minutes and then incubated with Leica Red Chromogen (Fast Red) for 15 minutes. Slides were then counterstained with Leica Hematoxylin for 5 minutes then dehydrated through graded alcohols and xylene before being cover slipped.

Pictures of immunohistochemical stains were taken with the 40X/0.75 objectives (Olympus UPlan FL N) of an Olympus BX51 microscope equipped with an Olympus

SC100 digital camera, using the AnalySIS getIT software. All immunohistochemistry was done at the Ohio State University.

BTK and PLCG2 Mutation Analysis

BTK and *PLCG2* mutation detection was performed using previously reported methods. Briefly, genomic DNA was extractor using the EZ1 (Qiagen, Chatsworth, CA) from B-cells that were purified by anti-CD19 immunoaffinity using Robo-Sep S (Stem Cell Technologies, Vancouver BC). Using a custom-designed AmpliSeq panel that covered the entire coding regions of *BTK* and *PLCG2*, library preparation and DNA sequencing was performed using the Ion Chef and S5 sequencer (ThermoFisher, San Diego, CA). The mean sequencing depth was 2000-6000 reads per sample, with a validated sensitivity for *BTK/PLCG2* resistance mutations of 0.5%.

Reference: Jones D, Woyach JA, Zhao W, Caruthers S, Tu H, Coleman J, Byrd JC, Johnson AJ, Lozanski G. PLCG2 C2 domain mutations co-occur with BTK and PLCG2 resistance mutations in chronic lymphocytic leukemia undergoing ibrutinib treatment. Leukemia. 2017; 31(7):1645-1647.

BRAF V600E Mutation Detection by ddPCR

Genomic DNA was extracted using the QIAamp DNA Mini Kit (QIAGEN, Germany) and DNA concentrations were measured using Qubit (Thermo Fisher, USA). Determination of the Detection Limit of the ddPCR-Based BRAF V600E Multiplex Assay. The limit of detection is an important performance parameter to be established for

validation of ddPCR measurements, and is defined as the lowest mutant allele fraction (MAF) that can be reliably detected and is distinguishable from the background or negative control. For the determination of the limit of detection of the BRAF V600E multiplex assay, a positive control mutant DNA (A375 Cell line carrying the *BRAF* V600E mutation) was diluted in a background of *BRAF* wild-type DNA (TL-1 Cell line) to obtain a series of standard samples with the desired MAF range (50%, 10%, 1%, 0.1%).

Detection of *BRAF* p.V600E c.1799T>A mutation was performed using QX200 droplet-digital PCR system (Bio-Rad). Each 22.0 µL ddPCR reaction mixture contained: 1X BRAF V600E multiplex assay reagent (Bio-Rad) which includes 900 nM primers and 250 nM each probe (wild-type probe labeled with HEX dye and mutant probe labeled with FAM dye), 1X ddPCR Supermix for probes (no dUTP); (Bio-Rad), and 50ng of DNA template. Volume adjusted to 22.0 µL with DEPC-treated water. 20.0 µL were loaded for droplet generation using QX200 Droplet Generator (Bio-Rad) and moved into a 96-well plate. Amplifications were performed on a C1000 deep-well thermal cycler (Bio-Rad) using the following conditions: 1 cycle of 95 °C for 5 min, 45 cycles of 95 °C for 30 s and 57 °C for 1 min, 1 cycle of 4 °C for 5 min, 1 cycle of 95 °C for 5 min and hold at 12 °C. Fractional abundance and quantitative results for each sample were calculated using QuantaSoft Analysis Pro software version 1.0.5 (Bio-Rad) following the principle of Poisson distribution.

Table S1: *BRAF* V600E Testing

Subject Number	Histology	*BRAF* Status	IHC Stain	Sequencing
1	Classic	Mutated	Yes	No
2	Variant	Unmutated	No	Yes
3	Classic	Mutated	No	Yes*
4	Variant	Unmutated	No	Yes
5	Classic	Unmutated	No	Yes
6	Classic	Mutated	Yes	Yes
7	Classic	Mutated	No	Yes*
8	Classic	Unmutated	Yes	Yes
9	Classic	Unknown	No	No
10	Classic+	Mutated	No	Yes*
11	Classic	Mutated	Yes	No
12	Classic	Mutated	Yes	No
13	Classic	Unmutated	No	Yes
14	Classic	Mutated	No	Yes*
15	Classic	Unmutated	Yes	No
16	Variant	Unmutated	Yes	No
17	Variant	Unmutated	No	Yes
18	Classic	Unmutated	Yes	Yes
19	Variant	Unmutated	Yes	No
20	Variant	Unmutated	Yes	No
21	Classic	Mutated	No	Yes
22	Variant	Unmutated	Yes	No
23	Classic	Mutated	Yes	No
25	Classic	Mutated	Yes	No
26	Classic	Mutated	Yes	No
27	Variant	Unmutated	No	Yes-
28	Variant	Unmutated	Yes	No
29	Classic	Mutated	No	Yes
30	Classic	Mutated	Yes	No

31	Classic	Unmutated	No	Yes
32	Classic	Mutated	Yes	No
33	Classic	Mutated	Yes	No
34	Classic[+]	Mutated	No	Yes
35	Classic	Mutated	Yes	No
36	Classic	Mutated	Yes	No
37	Classic	Mutated	No	Yes
39	Classic	Unmutated	No	Yes

IHC = Immunohistochemistry. Note that there is no subject 24 or 38 due to patients who were found to be ineligible at screening and received a study number but did not start study treatment. [*]Sequenced by ddPCR research assay. [+]Histology was originally entered as variant and confirmed to be classic after review or pathology reports and *BRAF* mutation testing.

Table S2: Prior Treatments for Hairy Cell Leukemia

Subject	Number Prior Treatments	Prior Treatments in Chronological Order
1	10	1. Splenectomy 2. Interferon-alpha 3. Cladribine 4. Cladribine 5. Rituximab 6. Rituximab 7. Local radiation 8. Pentostatin + rituximab 9. Rituximab 10. Bendamustine + rituximab
2	2	1. Cladribine 2. Splenectomy
3	1	1. Cladribine
4	0	
5	4	1. Cladribine 2. BL22 immunotoxin 3. Pentostatin + rituximab 4. Splenectomy
6	4	1. Cladribine 2. Rituximab 3. Rituximab 4. Rituximab
7	4	1. Splenectomy 2. Cladribine 3. Cladribine 4. Cladribine
8	6	1. Cladribine 2. Cladribine 3. Cladribine 4. Pentostatin 5. Moxetumomab pasudotox 6. Cladribine + rituximab
9	3	1. Rituximab 2. Cladribine 3. Cladribine
10	3	1. Cladribine 2. Cladribine 3. Rituximab

11	12	1. Splenectomy 2. Halotestin 3. Prednisone 4. Chlorambucil 5. Chlorambucil 6. Interferon-alpha 7. Rituximab 8. Rituximab 9. Rituximab 10. Rituximab 11. Rituximab 12. Vemurafenib
12	4	1. Cladribine 2. Rituximab 3. Cladribine 4. Moxetumomab pasudotox
13	1	1. Cladribine + rituximab
14	6	1. Interferon 2. Pentostatin 3. Cladribine 4. Fludarabine 5. Rituximab 6. Rituximab
15	1	1. Cladribine
16	2	1. Rituximab 2. Cladribine
17	5	1. Cladribine 2. Splenectomy 3. Rituximab 4. Chlorambucil 5. Moxetumomab pasudotox
18	6	1. Cladribine 2. Cladribine 3. Splenectomy 4. Rituximab 5. Interferon B 6. Pentostatin + rituximab
19	0	
20	8	1. Interferon 2. Cladribine 3. Pentostatin 4. Fludarabine

		5. Chlorambucil 6. Rituximab 7. BL22 8. Splenectomy
21	8	1. Splenectomy 2. Chlorambucil 3. Chlorambucil 4. Interferon B 5. Cladribine 6. Cladribine + rituximab 7. Vemurafenib 8. Vemurafenib
22	6	1. Splenectomy 2. Cladribine 3. Rituximab 4. Bendamustine 5. Cyclophosphamide 6. Bendamustine
23	6	1. Splenectomy 2. Cladribine 3. Cladribine 4. Cladribine + rituximab 5. Pentostatin 6. Rituximab
25	1	1. Cladribine + rituximab
26	2	1. Cladribine 2. Pentostatin
27	7	1. Cladribine 2. Splenectomy 3. Cladribine 4. HiDICE 5. MDMXT/Cytarabine 6. Rituximab 7. HDMTX/Cytarabine
28	5	1. Cladribine 2. Cladribine + rituximab 3. Rituximab 4. Bendamustine + rituximab 5. Pentostatin + rituximab
29*	5	1. Rituximab 2. R-CVP 3. Cladribine 4. Pentostatin + rituximab

		5. Vemurafenib
30	2	1. Cladribine 2. Cladribine
31	6	1. Cladribine 2. Rituximab 3. Pentostatin 4. Pentostatin 5. Bendamustine + rituximab 6. Pentostatin + rituximab
32	5	1. Cladribine 2. Cladribine 3. Cladribine 4. Vemurafenib 5. Moxetumomab pasudotox
33	5	1. Cladribine 2. Cladribine 3. BL22 immunotoxin 4. Rituximab 5. LMB-2
34	2	1. Cladribine 2. Cladribine + rituximab
35	7	1. Interferon 2. Pentostatin 3. Cladribine 4. Cladribine 5. Cladribine + rituximab 6. Cladribine 7. Moxetumomab pasudotox
36	4	1. Cladribine 2. Cladribine 3. Rituximab 4. Rituximab
37	3	1. Cladribine 2. Cladribine 3. Cyclophosphamide + rituximab
39	5	1. Cladribine 2. Rituximab 3. Rituximab 4. Rituximab 5. Cladribine

*Patient had splenectomy for spleen rupture due to trauma and not as a therapy.
Note that there is no subject 24 or 38 due to patients who were found to be ineligible at screening and received a study number but did not start study treatment.

Table S3. Ibrutinib Dose and Exposure

Subject Number	Cycles at 420mg	Cycles at 840mg	Total Cycles
1	22	0	22
2	46	0	46
3	67	0	67
4	12	0	12
5	8	0	8
6	76	0	76
7	73	0	73
8	73	0	73
9	28	0	28
10	7	0	7
11	65	0	65
12	68	0	68
13	62	0	69*
14	15	24	39
15	24	15	39
16	18	28	46
17	58	7	65
18	7	24	31
19	42	22	64
20	0	10	10
21	0	10	10
22	42	19	61
23	0	1	1
25	0	55	55
26	33	24	57
27	0	49	49
28	9	0	9
29	32	0	32
30	49	0	49

31	11	0	11
32	4	0	4
33	40	0	40
34	13	0	13
35	1	0	1
36	28	0	28
37	4	0	6*
39	10	0	10
Total Received	*1,047 (78%)*	*288 (21%)*	*1,344*

Cycle length is 28 days. Data as of 9/9/2019. *Additional cycles were at 140mg. Note that there is no subject 24 or 38 due to patients who were found to be ineligible at screening and received a study number but did not start study treatment.

Table S4. Reason for Study Discontinuation

Subject	Reason for Discontinuation	Days on Study	Days on Treatment
1	Progressive Disease	623	609
2	Progressive Disease	1290	1282
3	Elective withdrawal (no longer able to attend study visits)	1996	1996
4	Progressive Disease	357	336
5	Progressive Disease	252	252
9	Elective withdrawal	2040*	897
10	Adverse Event: Neutropenia	1443	202
11	Progressive Disease	1887	1884
14	Elective withdrawal	1094	1094
15	Adverse Event: palpitations	1099	1092
16	Elective withdrawal	1942*	1282
18	Adverse Event: Colon Cancer	1924*	916
20	Adverse Event: Decreased cardiac function	337	293
21	Death: Pneumonia	287	284
23	Death: Pneumonia	15	15
28	Progressive Disease	352	243
29	Progressive Disease	899	892
31	Progressive Disease	837	281
32	Progressive Disease	213	101
34	Adverse Event: Thrombocytopenia and neutropenia	641	420
35	Adverse Event: Allergy to ibrutinib	203	22
37	Adverse Event: Persistent cytopenias	165	165
*Patient still on follow-up as of 9/9/2019.			

Table S5: Response to Ibrutinib

Response	32-weeks (Cycle 8) (n=37)	48-weeks (Cycle 12) (n=36*)	Best Response Any Cycle (n=37)
Complete Response	1 (2.7%)	4 (11.1%)	7 (18.9%)
Partial Response	8 (21.6%)	9 (25.0%)	13 (35.1%)
Stable Disease	21 (56.8%)	11 (30.6%)	10 (27.0%)
Progressive Disease	3 (8.1%)	6 (16.7%)	3 (8.1%)
Death Before Assessment	1 (2.7%)	2 (5.6%)	1 (2.7%)
No Response, Off Treatment	3 (8.1%)	4 (11.1%)	3 (8.1%)
Overall Response Rate, n (%)	**9/37 (24.3%)**	**13/36 (36.1%)**	**20/37 (54.1%)**
*Patient 39 is on treatment but has not reached the 48-week assessment and is included in the 32-week assessment and best response any cycle totals.			

Table S6: Responses by Histologic Subtype

Assessment	Response	Histology		p
		Classic (n=28*)	**Variant (n=9)**	
32 Weeks (Cycle 8)	Complete Response	1	0	-
	Partial Response	6	2	-
	Overall Response Rate (95% CI)	**7/28, 25.0%** (10.7%-44.9%)	**2/9, 22.2%** (2.8%-60.0%)	**1.0**
48 Weeks (Cycle 12)	Complete Response	4	0	-
	Partial Response	7	2	-
	Overall Response Rate (95% CI)	**11/27, 40.7%** (22.4%-61.2%)	**2/9, 22.2%** (2.8%-60.0%)	**0.44**
Best Response at Any Time	Complete Response	6	1	-
	Partial Response	9	4	-
	Overall Response Rate (95% CI)	**15/28, 53.6%** (33.9%-72.5%)	**5/9, 55.6%** (21.2%-86.3%)	**1.0**

*Patient 39 is on treatment but has not reached the 48-week assessment and is included in the 32-week assessment and best response any cycle totals.

Table S7: Univariate Associations Between Patient Characteristics and Outcome

Variable	Level	Odds ratio for response (95% CI)	PFS hazard ratio (95% CI)
Sex	Male	Ref	Ref
	Female	0.57 (0.11-3.02)	1.20 (0.26-5.67)
Age (continuous)	1-year increase	0.90 (0.84-0.98)	1.05 (0.99-1.12)
Age (binary)	<65 years	Ref	Ref
	65+ years	0.47 (0.13-1.74)	2.26 (0.58-8.75)
Histology	Classic	0.92 (0.20-4.18)	0.90 (0.23-3.49)
	Variant	Ref	Ref
***BRAF* status**	Normal	Ref	Ref
	Mutated	1.22 (0.33-4.57)	0.91 (0.26-3.16)
Splenectomy	No	Ref	Ref
	Yes	0.99 (0.26-3.82)	2.56 (0.72-9.07)
Prior treatments (con.)	1-treatment increase	0.80 (0.61-1.04)	1.11 (0.92-1.35)
Prior treatments	0-1	Ref	Ref
	2+	0.19 (0.02-1.80)	2.28 (0.29-18.03)

Table S8: Frequency of Treatment-Related Adverse Events

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
Abdominal pain	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Alanine aminotransferase increased	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Alkaline phosphatase increased	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	All	4	11%	0	0%	4	11%
Allergic reaction	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Allergic rhinitis	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Alopecia	*840mg*	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	2	5%	0	0%	2	5%
Anemia	*420mg*	*7*	*29%*	*0*	*0%*	*7*	*29%*
	840mg	*1*	*8%*	*1*	*8%*	*2*	*15%*
	All	8	22%	1	3%	9	24%
Anorexia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Arthralgia	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	All	6	16%	0	0%	6	16%
Aspartate aminotransferase increased	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Atrial fibrillation	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	6	16%	0	0%	6	16%
Atrial flutter	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	1	3%	2	5%
Back pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	All	1	3%	0	0%	1	3%
Bladder infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Bloating	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Blood bilirubin increased	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Blurred vision	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Bronchial infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Bruising	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	10	27%	0	0%	10	27%
Bullous dermatitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Cardiac disorders - Other, specify: Chest Heaviness	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Cardiac disorders - Other, specify: “Heart Whooshing”	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Chest pain - cardiac	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Chills	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Confusion	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Constipation	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	All	3	8%	0	0%	3	8%
Cough	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Creatinine increased	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Dehydration	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Diarrhea	*420mg*	*10*	*42%*	*0*	*0%*	*10*	*42%*
	840mg	*5*	*38%*	*0*	*0%*	*5*	*38%*
	All	15	41%	0	0%	15	41%
Dizziness	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	5	14%	0	0%	5	14%
Dry mouth	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	4	11%	0	0%	4	11%
Dry skin	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Dyspepsia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Dyspnea	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Ear pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Edema limbs	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Ejection fraction decreased	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Enterocolitis	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	All	0	0%	1	3%	1	3%
Epistaxis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Erythema multiforme	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Eye disorders - Other, specify: Watery Itchy Eyes	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Eye disorders - Other, specify: Right Eye Redness	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Fall	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Fatigue	*420mg*	*9*	*38%*	*0*	*0%*	*9*	*38%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	11	30%	0	0%	11	30%
Febrile neutropenia	*420mg*	*0*	*0%*	*2*	*8%*	*2*	*8%*
	All	0	0%	2	5%	2	5%
Fever	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Gastroesophageal reflux disease	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	4	11%	0	0%	4	11%
Generalized muscle weakness	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Hair texture abnormal	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Headache	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Heart failure	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	All	0	0%	1	3%	1	3%
Hematuria	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Hyperglycemia	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Hyperhidrosis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Hypertension	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*2*	*15%*	*2*	*15%*	*4*	*31%*
	All	6	16%	2	5%	8	22%
Hyperuricemia	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	5	14%	0	0%	5	14%
Hypoalbuminemia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Hypocalcemia	*840mg*	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	2	5%	0	0%	2	5%
Hypokalemia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Hypophosphatemia	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Infections and infestations - Other, specify: Shingles	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Left ventricular systolic dysfunction	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Leukocytosis	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Lung infection	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	840mg	*0*	*0%*	*1*	*8%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	All	0	0%	2	5%	2	5%
Lymphocyte count decreased	*420mg*	*1*	*4%*	*5*	*21%*	*6*	*25%*
	840mg	*4*	*31%*	*1*	*8%*	*5*	*38%*
	All	5	14%	6	16%	11	30%
Lymphocyte count increased	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Menorrhagia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Mucositis oral	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	7	19%	0	0%	7	19%
Muscle cramp	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Myalgia	*420mg*	*9*	*38%*	*0*	*0%*	*9*	*38%*
	840mg	*5*	*38%*	*0*	*0%*	*5*	*38%*
	All	14	38%	0	0%	14	38%
Nail changes	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Nausea	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	840mg	*7*	*54%*	*0*	*0%*	*7*	*54%*
	All	12	32%	0	0%	12	32%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: basal cell carcinoma of the skin	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: squamous cell carcinoma of the skin	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: polyp	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
Neutrophil count decreased	*420mg*	*0*	*0%*	*6*	*25%*	*6*	*25%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	6	16%	7	19%
Non-cardiac chest pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Oral hemorrhage	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Oral pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Pain	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	All	4	11%	0	0%	4	11%
Pain in extremity	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Palpitations	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	4	11%	0	0%	4	11%
Paresthesia	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	5	14%	0	0%	5	14%
Photosensitivity	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Platelet count decreased	*420mg*	*3*	*13%*	*6*	*25%*	*9*	*38%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	4	11%	6	16%	10	27%
Pruritus	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Rash acneiform	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Rash maculo-papular	*420mg*	*6*	*25%*	*1*	*4%*	*7*	*29%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	10	27%	1	3%	11	30%
Rhinitis infective	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Sepsis	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Shingles	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Sinus bradycardia	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Sinus tachycardia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Sinusitis	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: follicular rash - scalp	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: rosacea	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: panniculitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: blood blister	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: precancerous lesions	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: brittle nails	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	Any	2	6%	0	0%	2	6%
Skin infection	*420mg*	*1*	*4%*	*1*	*4%*	*2*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade 3+		Any	
		n	%	n	%	n	%
	All	1	3%	1	3%	2	5%
Stomach pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Upper respiratory infection	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	1	3%	2	5%
Urinary tract infection	*840mg*	*1*	*8%*	*1*	*8%*	*2*	*15%*
	All	1	3%	1	3%	2	5%
Urinary tract pain	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Urticaria	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Uveitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Ventricular arrhythmia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Vomiting	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Weight gain	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Weight loss	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
White blood cell decreased	*420mg*	*3*	*13%*	*3*	*13%*	*6*	*25%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	5	14%	3	8%	8	22%

Table S9: Frequency of All Adverse Events (n=37 patients)

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Abdominal distension	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Abdominal pain	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	7	19%	0	0%	7	19%
Activated partial thromboplastin time prolonged	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Alanine aminotransferase increased	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	6	16%	0	0%	6	16%
Alkaline phosphatase increased	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	9	24%	0	0%	9	24%
Allergic reaction	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Allergic rhinitis	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	7	19%	0	0%	7	19%
Alopecia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Anemia	*420mg*	*10*	*42%*	*1*	*4%*	*11*	*46%*
	840mg	*4*	*31%*	*1*	*8%*	*5*	*38%*
	All	14	38%	2	5%	16	43%
Anorectal infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Anorexia	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	4	11%	0	0%	4	11%
Anorgasmia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Anxiety	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Aortic valve disease	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Arthralgia	*420mg*	*10*	*42%*	*0*	*0%*	*10*	*42%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	14	38%	0	0%	14	38%
Arthritis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Aspartate aminotransferase increased	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*5*	*38%*	*0*	*0%*	*5*	*38%*
	All	8	22%	0	0%	8	22%
Atrial fibrillation	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	6	16%	0	0%	6	16%
Atrial flutter	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	1	3%	2	5%
Back pain	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*5*	*38%*	*0*	*0%*	*5*	*38%*
	All	11	30%	0	0%	11	30%
Bladder infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Bloating	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	All	4	11%	0	0%	4	11%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Blood and lymphatic system disorders - Other, specify: Iron Deficiency	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Blood bilirubin increased	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	840mg	*2*	*15%*	*1*	*8%*	*3*	*23%*
	All	7	19%	1	3%	8	22%
Blood lactate dehydrogenase increased	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Blurred vision	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Bone pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Bronchial infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Bruising	*420mg*	*10*	*42%*	*0*	*0%*	*10*	*42%*
	840mg	*6*	*46%*	*0*	*0%*	*6*	*46%*
	All	16	43%	0	0%	16	43%
Bullous dermatitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Buttock pain	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Cardiac disorders - Other, specify: Chest Heaviness	840mg	1	8%	0	0%	1	8%
	All	1	3%	0	0%	1	3%
Cardiac disorders - Other, specify: “Heart Whooshing”	840mg	1	8%	0	0%	1	8%
	All	1	3%	0	0%	1	3%
Cataract	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	2	5%	0	0%	2	5%
Chest pain - cardiac	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Chest wall pain	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Chills	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	All	4	11%	0	0%	4	11%
Cholecystitis	*420mg*	*1*	*4%*	*1*	*4%*	*2*	*8%*
	All	1	3%	1	3%	2	5%
Cholesterol high	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	0	0%	3	8%
Colitis	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Confusion	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Conjunctivitis	*840mg*	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	2	5%	0	0%	2	5%
Constipation	*420mg*	*7*	*29%*	*0*	*0%*	*7*	*29%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	9	24%	0	0%	9	24%
Cough	*420mg*	*6*	*25%*	*1*	*4%*	*7*	*29%*
	840mg	*7*	*54%*	*0*	*0%*	*7*	*54%*
	All	13	35%	1	3%	14	38%
Creatinine increased	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	10	27%	0	0%	10	27%
Dehydration	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Depression	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Diarrhea	*420mg*	*14*	*58%*	*0*	*0%*	*14*	*58%*
	840mg	*8*	*62%*	*0*	*0%*	*8*	*62%*
	All	22	59%	0	0%	22	59%
Dizziness	*420mg*	*9*	*38%*	*0*	*0%*	*9*	*38%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	13	35%	0	0%	13	35%
Dry eye	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Dry mouth	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	6	16%	0	0%	6	16%
Dry skin	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	6	16%	0	0%	6	16%
Dysarthria	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Dysgeusia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Dyspepsia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Dysphagia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Dyspnea	*420mg*	*5*	*21%*	*1*	*4%*	*6*	*25%*
	All	5	14%	1	3%	6	16%
Ear pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	2	5%	0	0%	2	5%
Eczema	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Edema face	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Edema limbs	*420mg*	*9*	*38%*	*0*	*0%*	*9*	*38%*
	840mg	*5*	*38%*	*0*	*0%*	*5*	*38%*
	All	14	38%	0	0%	14	38%
Ejection fraction decreased	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Enterocolitis	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Epistaxis	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	5	14%	0	0%	5	14%
Erythema multiforme	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	All	5	14%	0	0%	5	14%
Eye disorders - Other, specify: Style on Right Eye	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Eye disorders - Other, specify: Watery Itchy Eyes	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Eye disorders - Other, specify: Subconjunctival Hemorrhage Right eye	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Eye disorders - Other, specify: Right Eye Redness	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Eyelid function disorder	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Fall	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	7	19%	0	0%	7	19%
Fatigue	*420mg*	*12*	*50%*	*0*	*0%*	*12*	*50%*
	840mg	*8*	*62%*	*0*	*0%*	*8*	*62%*
	All	20	54%	0	0%	20	54%
Febrile neutropenia	*420mg*	*0*	*0%*	*3*	*13%*	*3*	*13%*
	840mg	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	4	11%	4	11%
Fever	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	0	0%	3	8%
Flank pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Flashing lights	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Floaters	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Flu like symptoms	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	5	14%	0	0%	5	14%
Fracture	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Gait disturbance	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Gastritis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Gastroesophageal reflux disease	*420mg*	*7*	*29%*	*0*	*0%*	*7*	*29%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	8	22%	0	0%	8	22%
Generalized muscle weakness	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	3	8%	1	3%	4	11%
Hair texture abnormal	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Headache	*420mg*	*11*	*46%*	*0*	*0%*	*11*	*46%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	15	41%	0	0%	15	41%
Hearing impaired	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Heart failure	*840mg*	*0*	*0%*	*2*	*15%*	*2*	*15%*
	All	0	0%	2	5%	2	5%
Hematoma	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Hematuria	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	0	0%	3	8%
Hoarseness	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Hot flashes	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Hypercalcemia	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Hyperglycemia	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	10	27%	0	0%	10	27%
Hyperhidrosis	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	5	14%	0	0%	5	14%
Hyperkalemia	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Hyperkeratosis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Hypermagnesemia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Hypernatremia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Hyperphosphatemia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Hypertension	*420mg*	*9*	*38%*	*1*	*4%*	*10*	*42%*
	840mg	*3*	*23%*	*3*	*23%*	*6*	*46%*
	All	12	32%	4	11%	16	43%
Hyperuricemia	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*5*	*38%*	*0*	*0%*	*5*	*38%*
	All	11	30%	0	0%	11	30%
Hypoalbuminemia	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	7	19%	0	0%	7	19%
Hypocalcemia	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	7	19%	0	0%	7	19%
Hypokalemia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Hypomagnesemia	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Hyponatremia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Hypophosphatemia	*420mg*	*2*	*8%*	*3*	*13%*	*5*	*21%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	2	5%	3	8%	5	14%
Hypotension	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Hypothyroidism	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Infections and infestations - Other, specify: Shingles	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Infections and infestations - Other, specify: Tooth Abscess	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Infections and infestations - Other, specify: Right Tonsil	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Infections and infestations - Other, specify: Pinworm	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Infections and infestations - Other, specify: Throat Infection	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Injury, poisoning and procedural complications - Other, specify: Wound Left Wrist	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Injury, poisoning and procedural complications - Other, specify: Tick Bite	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Injury, poisoning and procedural complications - Other, specify: Cut on Left Wrist	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Injury, poisoning and procedural complications - Other, specify: Injury Right Toenail	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Insomnia	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	7	19%	0	0%	7	19%
Joint range of motion decreased	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Laryngeal inflammation	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Laryngitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Left ventricular systolic dysfunction	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Lethargy	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Leukocytosis	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Lip infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Localized edema	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Lung infection	*420mg*	*1*	*4%*	*2*	*8%*	*3*	*13%*
	840mg	*0*	*0%*	*4*	*31%*	*4*	*31%*
	All	1	3%	6	16%	7	19%
Lymphocyte count decreased	*420mg*	*1*	*4%*	*5*	*21%*	*6*	*25%*
	840mg	*5*	*38%*	*2*	*15%*	*7*	*54%*
	All	6	16%	7	19%	13	35%
Lymphocyte count increased	*420mg*	*2*	*8%*	*2*	*8%*	*4*	*17%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	2	5%	5	14%
Malaise	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Menorrhagia	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Mucositis oral	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	9	24%	0	0%	9	24%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Muscle cramp	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Musculoskeletal and connective tissue disorder - Other, specify: Plantar Fasciitis Right Foot	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Musculoskeletal and connective tissue disorder - Other, specify: Tenosynovitis Right Middle Finger	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Musculoskeletal and connective tissue disorder - Other, specify: Rotator Cuff Injury	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Musculoskeletal and connective tissue disorder - Other, specify: Right Ankle Sprain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Myalgia	*420mg*	*12*	*50%*	*0*	*0%*	*12*	*50%*
	840mg	*8*	*62%*	*0*	*0%*	*8*	*62%*
	All	20	54%	0	0%	20	54%
Nail changes	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Nail infection	*420mg*	*3*	*13%*	*1*	*4%*	*4*	*17%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	4	11%	1	3%	5	14%
Nasal congestion	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	10	27%	0	0%	10	27%
Nausea	*420mg*	*11*	*46%*	*0*	*0%*	*11*	*46%*
	840mg	*8*	*62%*	*0*	*0%*	*8*	*62%*
	All	19	51%	0	0%	19	51%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: basal cell carcinoma of the skin	*840mg*	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	3	8%	0	0%	3	8%
	420mg	*2*	*9%*	*0*	*0%*	*2*	*9%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: melanoma	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	0	0%	3	8%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: non-invasive high grade urothelial carcinoma	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: bladder polyp	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: benign colon polyp	*420mg*	2	*8%*	*0*	*0%*	*2*	*8%*
	All	2	6%	0	0%	2	6%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: colon cancer	*420mg*	*1*	*4%*	*0*	*0%*	1	*4%*
	All	1	3%	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: lesions	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: squamous cell carcinoma of the skin	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	6%	0	0%	2	6%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify: polyp	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Nervous system disorders - Other, specify: Spinal Cord Compression	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Neutrophil count decreased	*420mg*	*1*	*4%*	*6*	*25%*	*7*	*29%*
	840mg	*4*	*31%*	*2*	*15%*	*6*	*46%*
	All	5	14%	8	22%	13	35%
Non-cardiac chest pain	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	0	0%	3	8%
Oral hemorrhage	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Oral pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	3	8%	0	0%	3	8%
Osteoporosis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Otitis externa	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Otitis media	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Pain	*420mg*	*5*	*21%*	*1*	*4%*	*6*	*25%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	6	16%	1	3%	7	19%
Pain in extremity	*420mg*	*6*	*25%*	*0*	*0%*	*6*	*25%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	8	22%	0	0%	8	22%
Palpitations	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	6	16%	0	0%	6	16%
Paresthesia	*420mg*	*7*	*29%*	*0*	*0%*	*7*	*29%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*
	All	11	30%	0	0%	11	30%
Paronychia	*420mg*	*1*	*4%*	*1*	*4%*	*2*	*8%*
	All	1	3%	1	3%	2	5%
Periodontal disease	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Peripheral motor neuropathy	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Peripheral sensory neuropathy	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Pharyngitis	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Photosensitivity	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Platelet count decreased	*420mg*	*4*	*17%*	*7*	*29%*	*11*	*46%*
	840mg	*3*	*23%*	*1*	*8%*	*4*	*31%*
	All	7	19%	8	22%	15	41%
Pleural effusion	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Pneumonitis	*840mg*	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	0	0%	1	3%	1	3%
Postnasal drip	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Productive cough	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	7	19%	0	0%	7	19%
Prostatic obstruction	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Pruritus	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	3	8%	0	0%	3	8%
Psychosis	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Rash acneiform	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	4	11%	0	0%	4	11%
Rash maculo-papular	*420mg*	*8*	*33%*	*2*	*8%*	*10*	*42%*
	840mg	*4*	*31%*	*0*	*0%*	*4*	*31%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	12	32%	2	5%	14	38%
Renal and urinary disorders - Other, specify: Bladder Polyps	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Renal calculi	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Renal colic	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Reproductive system and breast disorders - Other, specify: Blood in Semen	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Respiratory, thoracic and mediastinal disorders - Other, specify: Shortness of Breath	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Restlessness	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Rhinitis infective	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Sepsis	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Shingles	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Sinus bradycardia	*420mg*	*5*	*21%*	*0*	*0%*	*5*	*21%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	6	16%	0	0%	6	16%
Sinus tachycardia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Sinusitis	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	5	14%	0	0%	5	14%
Skin and subcutaneous tissue disorders - Other, specify: inflamed sebaceous cyst	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: cherry angiomas	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: dermatitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: follicular rash - scalp	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: rosacea	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: panniculitis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: erythematous scaly skin	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: precancerous lesions	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: lesion on penis	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: brittle nails	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	Any	2	6%	0	0%	2	6%
Skin and subcutaneous tissue disorders - Other, specify: lipoma	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	Any	2	6%	0	0%	2	6%
Skin and subcutaneous tissue disorders - Other, specify: blood blister	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
Skin and subcutaneous tissue disorders - Other, specify: seborrheic keratosis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: jock itch	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	Any	1	3%	0	0%	1	3%
Skin and subcutaneous tissue disorders - Other, specify: actinic keratosis	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	Any	2	5%	0	0%	2	5%
Skin atrophy	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Skin hyperpigmentation	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Skin infection	*420mg*	*2*	*8%*	*1*	*4%*	*3*	*13%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	4	11%	1	3%	5	14%
Skin ulceration	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Sleep apnea	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*0*	*0%*	*1*	*8%*	*1*	*8%*
	All	1	3%	1	3%	2	5%
Somnolence	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Sore throat	*420mg*	*4*	*17%*	*0*	*0%*	*4*	*17%*
	840mg	*3*	*23%*	*0*	*0%*	*3*	*23%*
	All	7	19%	0	0%	7	19%
Stomach pain	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	4	11%	0	0%	4	11%
Stroke	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Suicidal ideation	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	1	3%	0	0%	1	3%
Testicular pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Tinnitus	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Tooth infection	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Toothache	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Tracheal mucositis	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Tremor	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Tumor pain	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Upper respiratory infection	*420mg*	*10*	*42%*	*1*	*4%*	*11*	*46%*
	840mg	*5*	*38%*	*1*	*8%*	*6*	*46%*
	All	15	41%	2	5%	17	46%
Urinary frequency	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Urinary incontinence	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Urinary tract infection	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	840mg	*3*	*23%*	*1*	*8%*	*4*	*31%*
	All	5	14%	1	3%	6	16%
Urinary tract obstruction	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Urinary tract pain	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*

Toxicity Type	Dose Level	Grade 1-2		Grade ≥3		Any	
		n	%	n	%	n	%
	All	2	5%	0	0%	2	5%
Urticaria	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Uveitis	*420mg*	*2*	*8%*	*0*	*0%*	*2*	*8%*
	All	2	5%	0	0%	2	5%
Vaginal dryness	*840mg*	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	1	3%	0	0%	1	3%
Vascular disorders - Other, specify: Chronic Venous Insufficiency in the Left Leg	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Vasovagal reaction	*420mg*	*0*	*0%*	*1*	*4%*	*1*	*4%*
	All	0	0%	1	3%	1	3%
Ventricular arrhythmia	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Vertigo	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	2	5%	0	0%	2	5%
Vomiting	*420mg*	*5*	*21%*	*1*	*4%*	*6*	*25%*
	840mg	*1*	*8%*	*0*	*0%*	*1*	*8%*
	All	6	16%	1	3%	7	19%
Watering eyes	*420mg*	*1*	*4%*	*0*	*0%*	*1*	*4%*
	All	1	3%	0	0%	1	3%
Weight gain	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	All	3	8%	0	0%	3	8%
Weight loss	*420mg*	*3*	*13%*	*0*	*0%*	*3*	*13%*
	840mg	*2*	*15%*	*0*	*0%*	*2*	*15%*
	All	5	14%	0	0%	5	14%
White blood cell decreased	*420mg*	*1*	*4%*	*7*	*29%*	*8*	*33%*
	840mg	*4*	*31%*	*1*	*8%*	*5*	*38%*
	All	5	14%	8	22%	13	35%

Table S10: Analysis of Adverse Events by Dose Level

Adverse Event	420mg (n=23)		840mg (n=13)		p
	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	
Arthralgia	6 (26%)	0 (0%)	0 (0%)	0 (0%)	0.07
Atrial fibrillation	2 (9%)	0 (0%)	4 (31%)	0 (0%)	0.16
Bruising	6 (26%)	0 (0%)	3 (23%)	0 (0%)	1.0
Diarrhea	10 (43%)	0 (0%)	5 (38%)	0 (0%)	1.0
Ejection fraction decreased	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0.36
Enterocolitis	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1.0
Fatigue	9 (39%)	0 (0%)	2 (15%)	0 (0%)	0.26
Heart failure	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0.36
Hyperuricemia	2 (9%)	0 (0%)	3 (23%)	0 (0%)	0.33
Hypophosphatemia	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1.0
Left ventricular systolic dysfunction	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0.36
Lung infection	0 (0%)	1 (4%)	0 (0%)	1 (8%)	1.0
Myalgia	9 (39%)	0 (0%)	4 (31%)	0 (0%)	0.73
Nausea	5 (22%)	0 (0%)	7 (54%)	0 (0%)	0.07
Rash maculopapular	6 (26%)	1 (4%)	4 (31%)	0 (0%)	1.0
Sepsis	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1.0
Skin infection	1 (4%)	1 (4%)	0 (0%)	0 (0%)	1.0
Upper respiratory infection	0 (0%)	1 (4%)	1 (8%)	0 (0%)	1.0
Urinary tract infection	0 (0%)	0 (0%)	1 (8%)	1 (8%)	0.12

Adverse events are listed if they occurred in a least 20% of patients within either dose level, or if there were any grade 3 or higher. Only adverse events attributed to study treatment were included. P-values are from Fisher's exact test, comparing proportion of adverse events between dose levels (regardless of grade). Data cuff-off for this analysis is 3/12/2018.

Table S11: Summary of Non-Compartmental Pharmacokinetics Parameters

420 mg	Parent drug							Metabolite	
Patient ID	**T_{max} (h)**	**C_{max} (µg/mL)**	**t½ (h)**	**AUC_{0-24h} (h*µg/mL)**	**$AUC_{0-\infty}$ (h*µg/mL)**	**Vd (L)**	**CL (L/h)**	**C_{max} (µg/mL)**	**AUC_{0-24h} (h*µg/mL)**
1	1.00	33.00	3.86	336.61	341.12	6853.60	1231.24	19.90	170.71
2	1.03	237.00	5.34	704.19	724.07	4469.48	580.05	107.00	933.94
3	1.95	11.40	23.20	130.35	286.96	48978.96	1463.64	25.20	239.46
4	0.58	52.00	24.39	509.56	1157.06	12773.62	362.99	42.70	360.57
5	2.07	461.00	5.13	2336.74	2415.13	1286.08	173.90	128.00	1407.19
6	1.03	92.10	6.16	240.37	253.53	14731.29	1656.60	90.50	518.07
7	1.88	154.00	5.61	669.88	702.47	4834.72	597.89	135.00	1285.10
8	2.00	468.00	7.76	1441.11	1568.76	2997.80	267.73	163.00	1530.82
9	4.00	135.00	3.70	1189.18	1204.24	1862.97	348.77	170.00	2047.80
10	2.05	94.50	6.76	634.35	703.65	5817.81	596.88	120.00	1170.93
11	1.98	83.80	8.45	529.37	614.93	8324.74	683.00	66.20	646.70
13	2.00	312.00	3.51	1809.91	1832.69	1159.85	229.17	136.00	1676.47
29	0.57	215.00	6.22	983.08	1038.79	3626.89	404.32	104.00	1246.90
Summary*	1.70 (0.90)	180.68 (151.99)	8.47 (6.96)	885.75 (649.96)	987.95 (644.59)	9055.22 (12699.20)	661.25 (483.59)	100.58 (49.30)	1018.05 (592.08)
840 mg	**Parent drug**							**Metabolite**	
Patient ID	**T_{max} (h)**	**C_{max} (µg/mL)**	**t½ (h)**	**AUC_{0-24h} (h*µg/mL)**	**$AUC_{0-\infty}$ (h*µg/mL)**	**Vd (L)**	**CL (L/h)**	**C_{max} (µg/mL)**	**AUC_{0-24h} (h*µg/mL)**
14	1.93	220.00	9.59	1722.79	2097.82	5541.31	400.41	97.40	1461.32

15	1.92	77.30	10.61	442.54	555.15	23151.75	1513.10	148.00	1361.60
16	4.00	279.00	8.78	2633.33	3355.54	3171.83	250.33	110.00	1831.32
18	4.00	83.60	5.37	868.06	912.80	7123.91	920.24	83.90	1275.70
19	2.00	163.00	5.94	1040.90	1142.04	6304.47	735.52	195.00	2031.40
21	2.00	328.00	12.49	1487.65	1919.95	7880.73	437.51	121.00	1089.99
22	6.00	165.00	3.85	1949.93	1990.13	2343.72	422.08	235.00	2786.80
Summary*	3.12 (1.59)	187.99 (94.17)	8.09 (3.12)	1449.31 (735.64)	1710.49 (937.42)	7931.10 (7006.53)	668.46 (436.28)	141.47 (55.26)	1691.16 (581.85)

Parameter estimates were obtained using noncompartmental analysis. Parameters reported in the table include maximum plasma drug concentration (C_{max}), time to reach Cmax (T_{max}), t½ (terminal half-life), area under the plasma concentration-time curve from time zero to time of last measurable concentration ($AUC_{0\text{-}24h}$), Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$), volume of distribution (Vd), clearance (CL) (data expressed as mean ± SD).

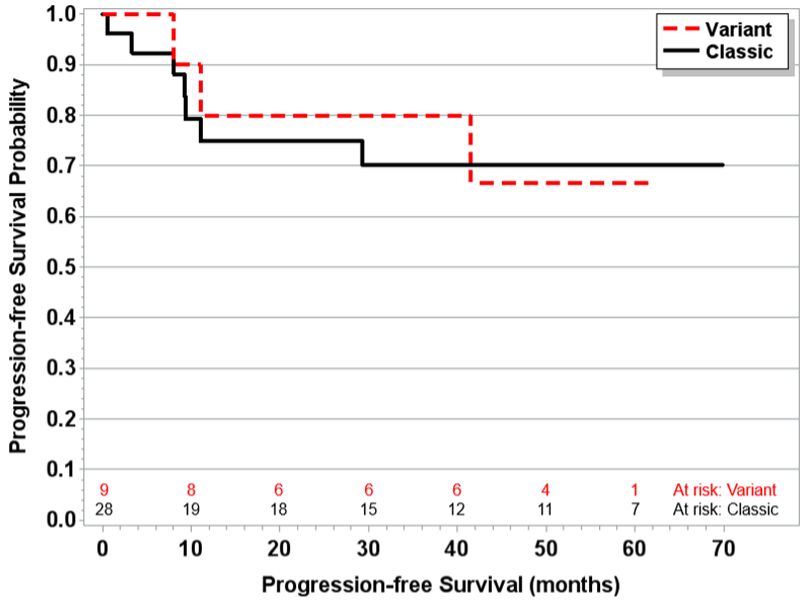
Table S12: Hazard ratios for associations between PK parameters and PFS

Parameter	Unit change	HR (95% CI)	P-value
C_{max} (µg/mL)	100 µg/mL	1.37 (0.76-2.48)	0.29
Dose-normalized C_{max} (µg/mL/mg)	0.1 µg/mL/mg	1.14 (0.90-1.43)	0.28
AUC_{0-24h} (h*µg/mL)	100 h*µg/mL	1.01 (0.90-1.13)	0.89
Dose-normalized AUC_{0-24h} (h*µg/mL/mg)	1 h*µg/mL/mg	1.30 (0.68-2.48)	0.42
$AUC_{0-\infty}$ (h*µg/mL)	100 h*µg/mL	1.02 (0.92-1.12)	0.75
Dose-normalized $AUC_{0-\infty}$ (h*µg/mL/mg)	1 h*µg/mL/mg	1.04 (0.97-1.10)	0.28
CL (L/h)	100 L/h	0.90 (0.71-1.14)	0.39
Statistics are from the Cox proportional hazards model for each PK parameter. The hazard ratios reflect the unit change listed, given that some of the parameters ranged between values in the thousands (i.e. the short-term risk of death or progression was 37% higher for a 100 µg/mL increase in C_{max}). However, none of the parameters were significantly associated with progression-free survival. Martingale residuals were used to assess the linearity assumption of continuous variables in a proportional hazards model. The trends in residuals did not indicate the need for variable transformations in any models.			

Figure S1: Progression-Free and Overall Survival by Histologic Subtype

A. The median progression-free survival was not reached for either histology. B. The median overall survival was similarly not reached for variant, and was 69.1 months for classic. There was no difference in progression-free or overall survival between histologic subtypes (p=0.88 and p=0.76, respectively).

A.



B.

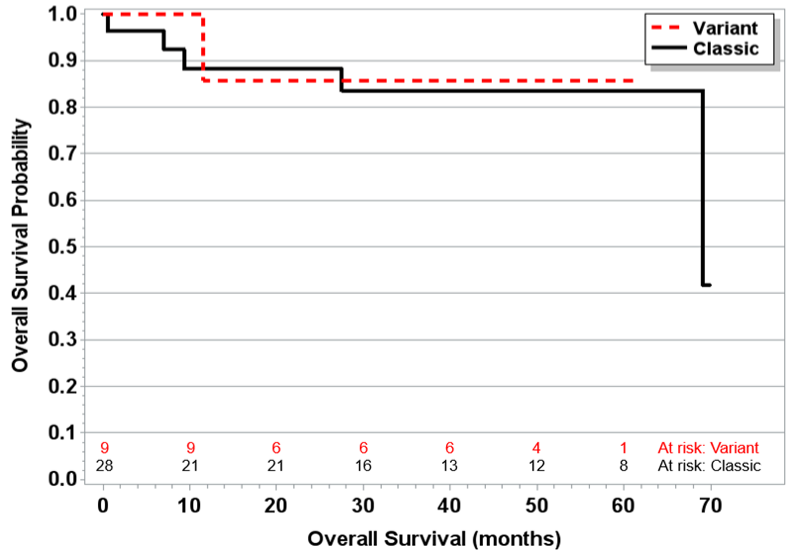


Figure S2: Progression-Free and Overall Survival by Dose Level

A. The median progression-free survival was not reached at either dose level. B. The median overall survival was similarly not reached at either dose level. There was no difference in progression-free or overall survival between dose levels (p=0.19 and p=0.90, respectively).

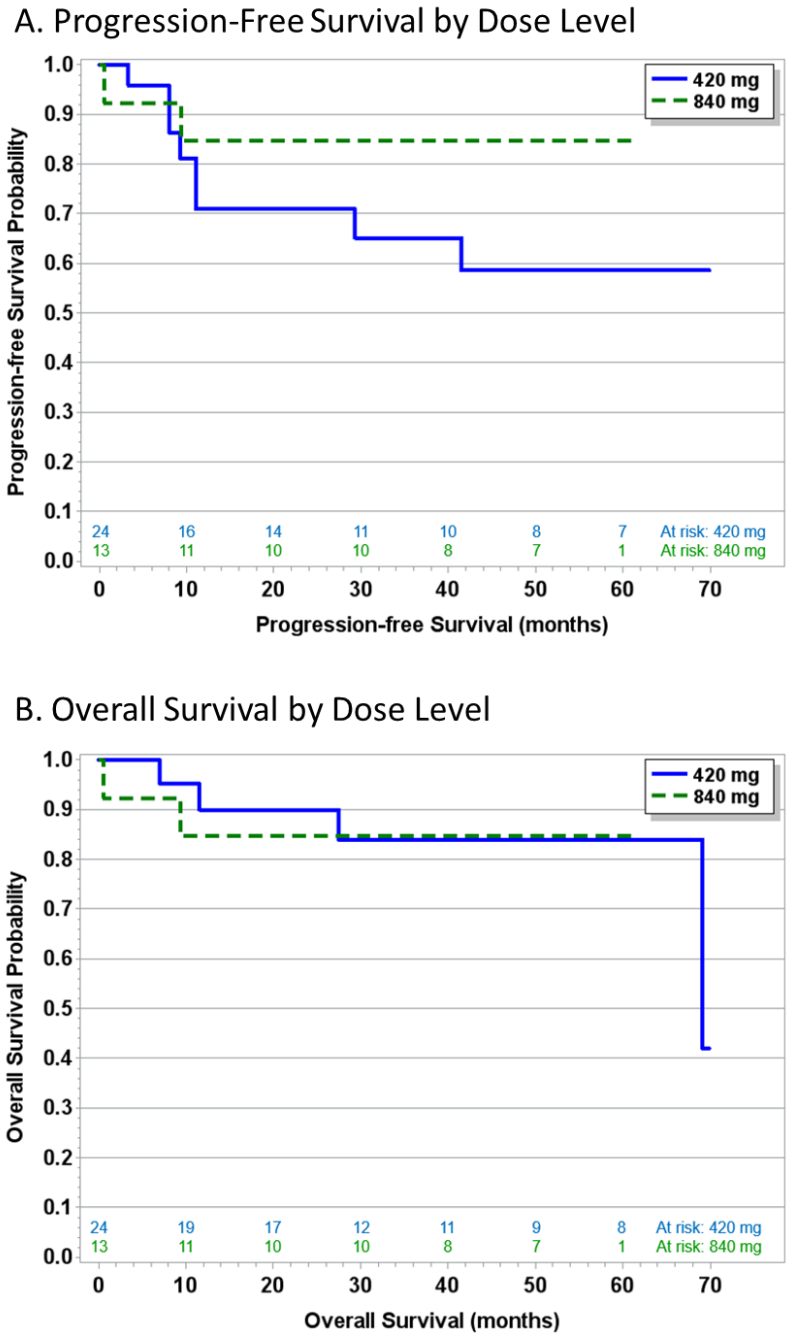


Figure S3: Median Time to Recovery of Peripheral Blood Counts

Probability of recovering peripheral blood counts to above the threshold value for treatment over time. A. Median time to an absolute neutrophil count (ANC) >1,000/µL for patients with a baseline ANC below this level was 2 cycles (95% CI: 1.8-5). B. Median time to a platelet count >100,000/µL for patients with a baseline platelet count below this level was 5 cycles (95% CI: 2-8). C. Median time to a hemoglobin >11 g/dL for patients with a baseline value below this level was 5 cycles (95% CI: 1.3-7).

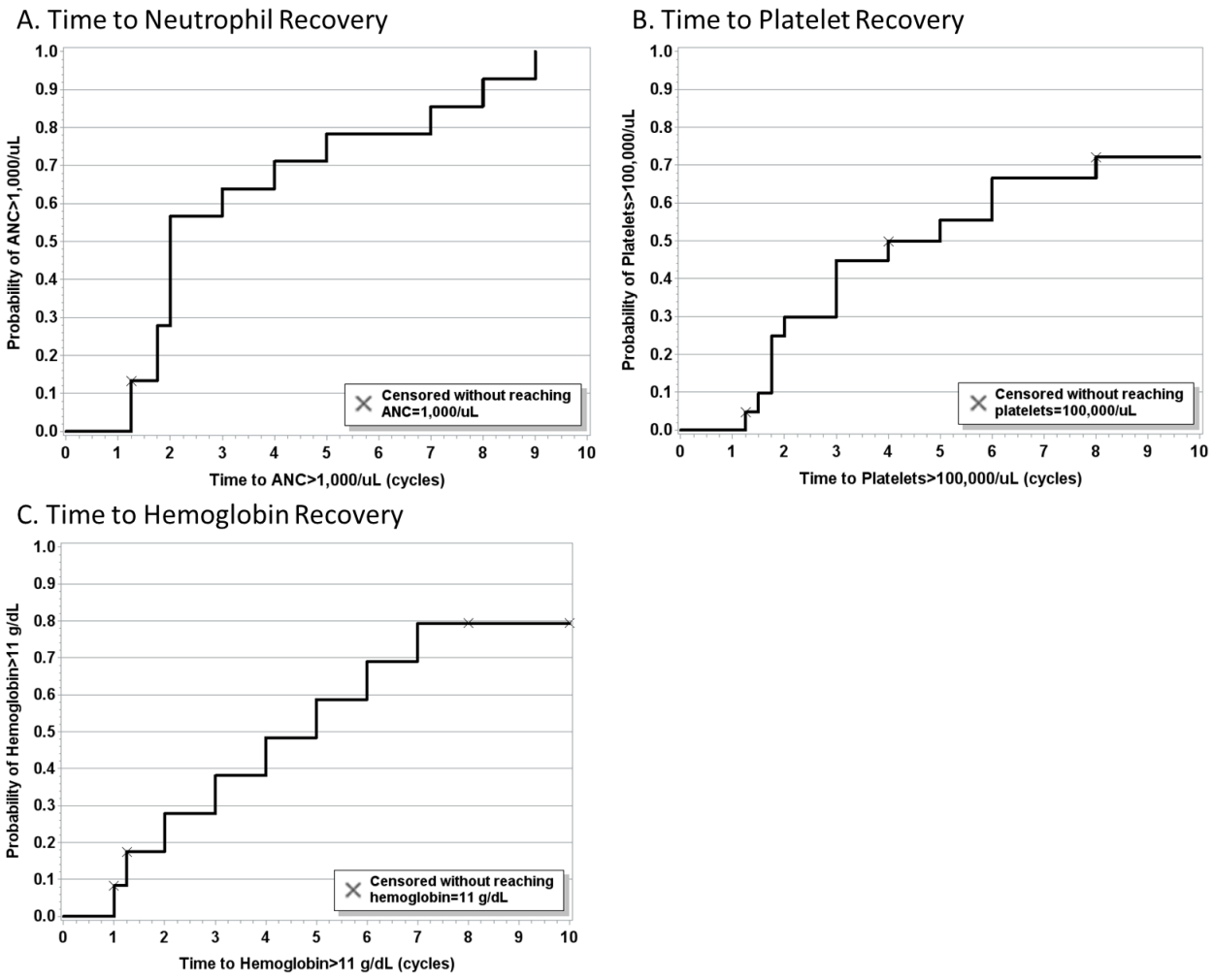


Figure S4: Change in Peripheral Blood Counts During Treatment

The absolute change in blood counts from baseline are shown for absolute neutrophil count (A), absolute lymphocyte count (B), hemoglobin (C), and platelets (D). Color shows the best response achieved by that patient. Complete remission = CR, Partial remission = PR, stable disease = SD, progressive disease = PD, adverse event = AE.

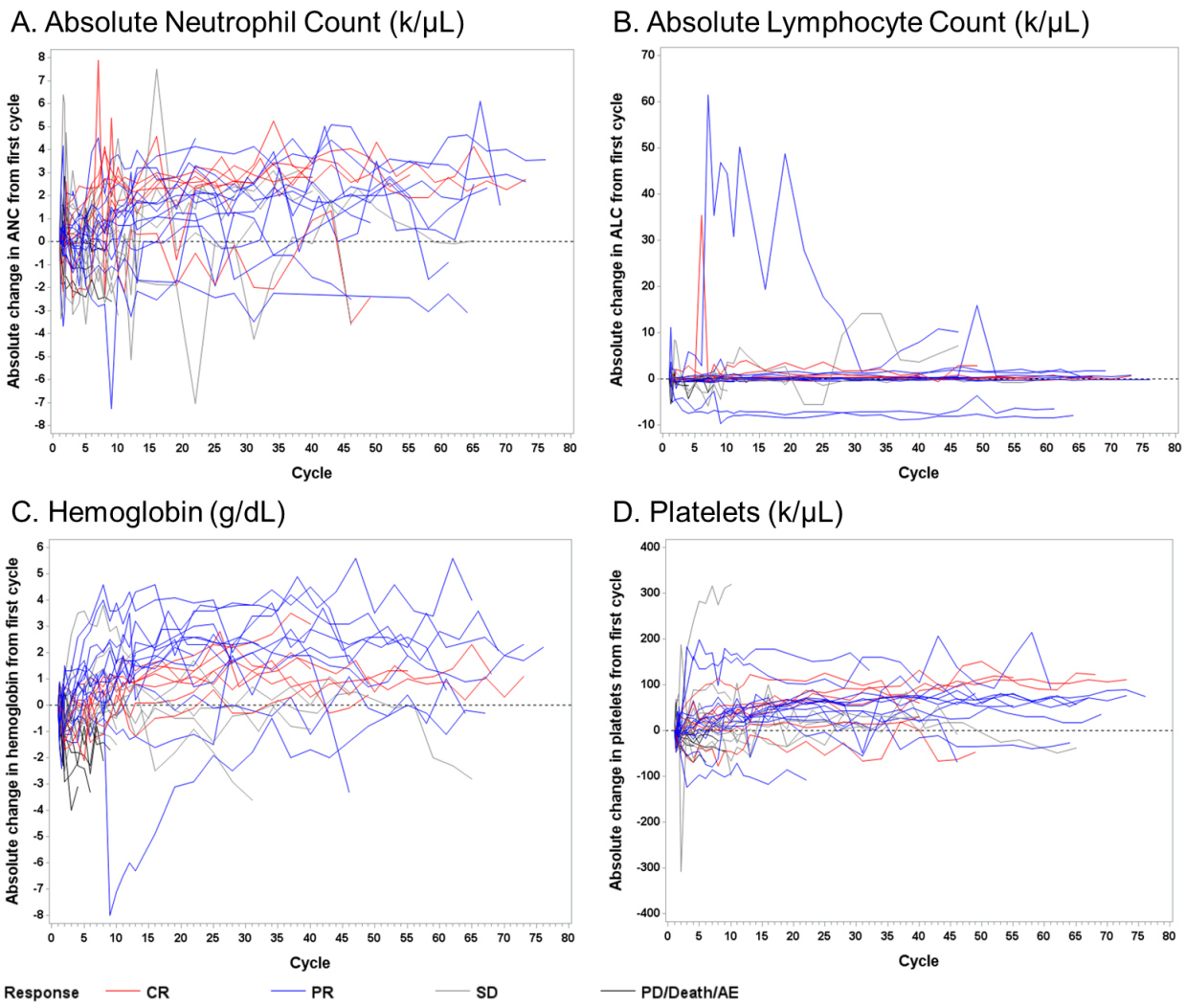
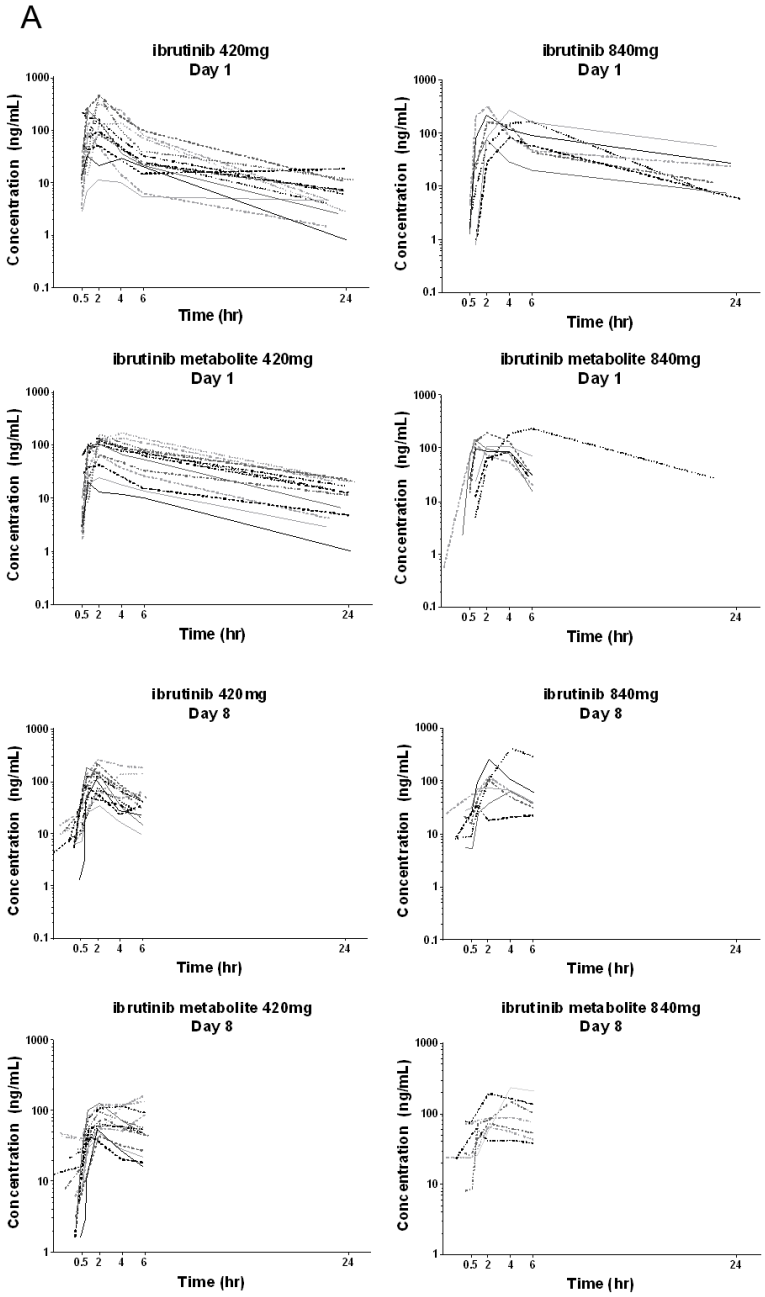


Figure S5: Plasma Concentration of Ibrutinib and Major Metabolite

A. Individual ibrutinib and ibrutinib metabolite (dihydrodiol ibrutinib) plasma concentration versus time data from two dose groups on days 1 and 8. B. Plots of mean ibrutinib and ibrutinib metabolite (dihydrodiol Ibrutinib) plasma concentration versus time data plus individual data points are shown for days 1 and 8.



B

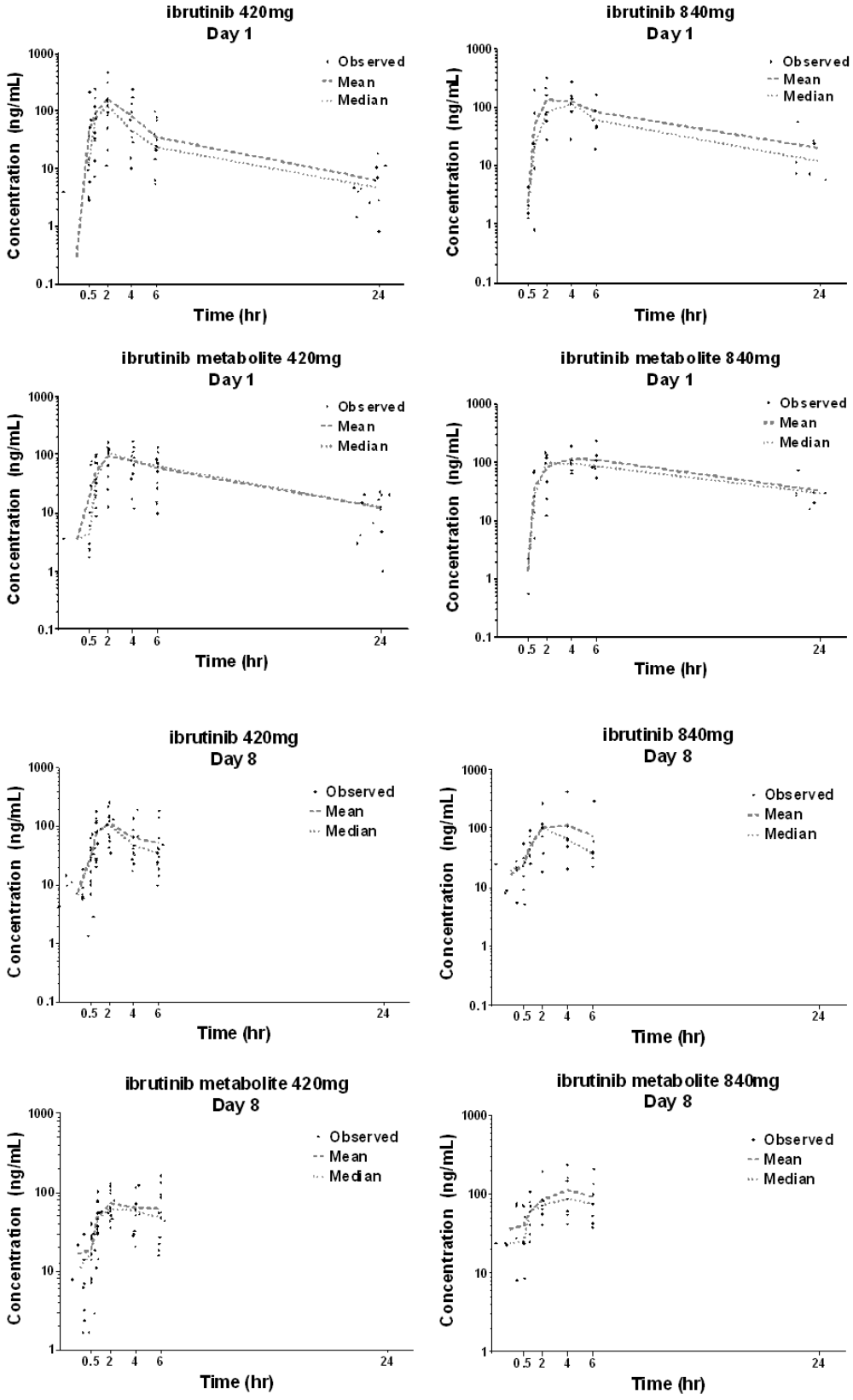

ibrutinib 420mg
Day 1
ibrutinib 840mg
Day 1
ibrutinib metabolite 420mg
Day 1
ibrutinib metabolite 840mg
Day 1
ibrutinib 420mg
Day 8
ibrutinib 840mg
Day 8
ibrutinib metabolite 420mg
Day 8
ibrutinib metabolite 840mg
Day 8
Observed
Mean
Median
Concentration (ng/mL)
Time (hr)
0.1
1
10
100
1000
0.5
2
4
6
24

Figure S6: Association of Pharmacokinetic Parameters and Response to Ibrutinib. Boxplots of PK vs. best response to ibrutinib. Groups were compared using nonparametric test (Kruskal-Wallis test) *, p<0.05.

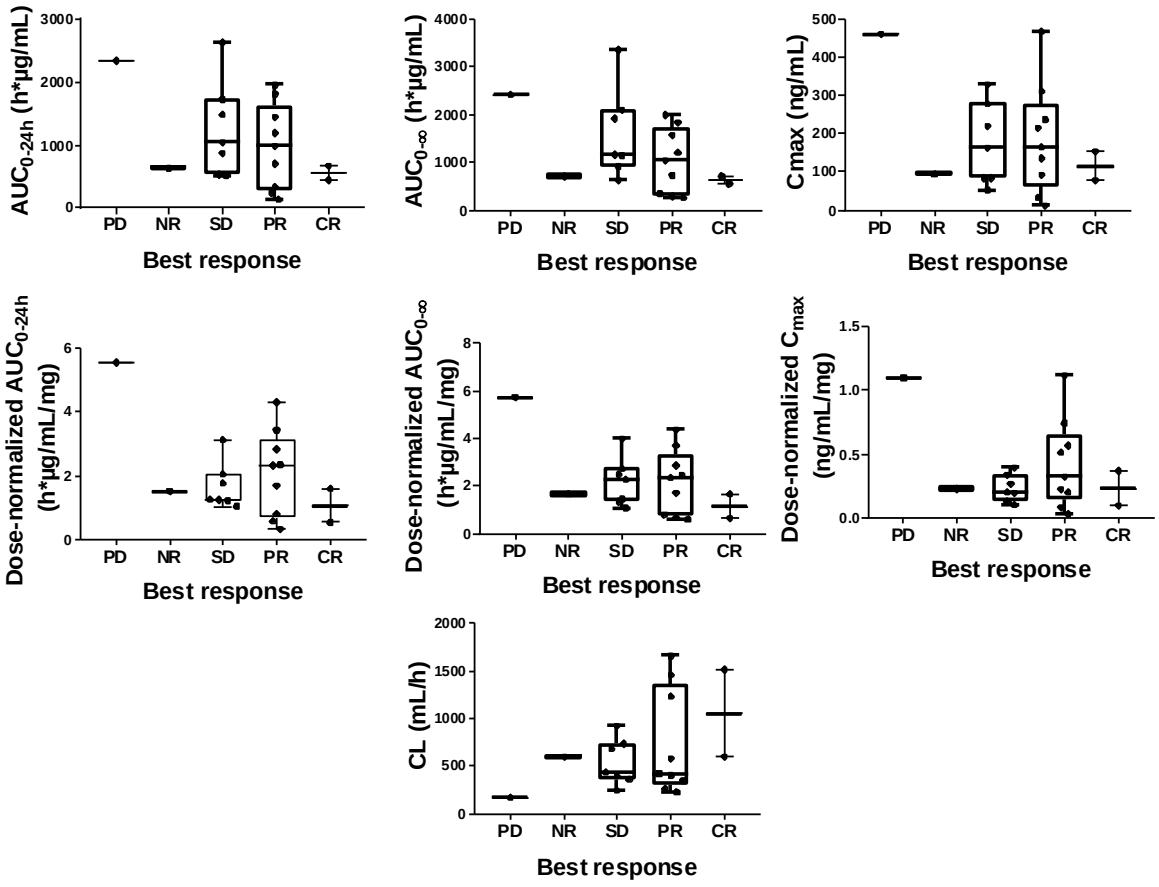
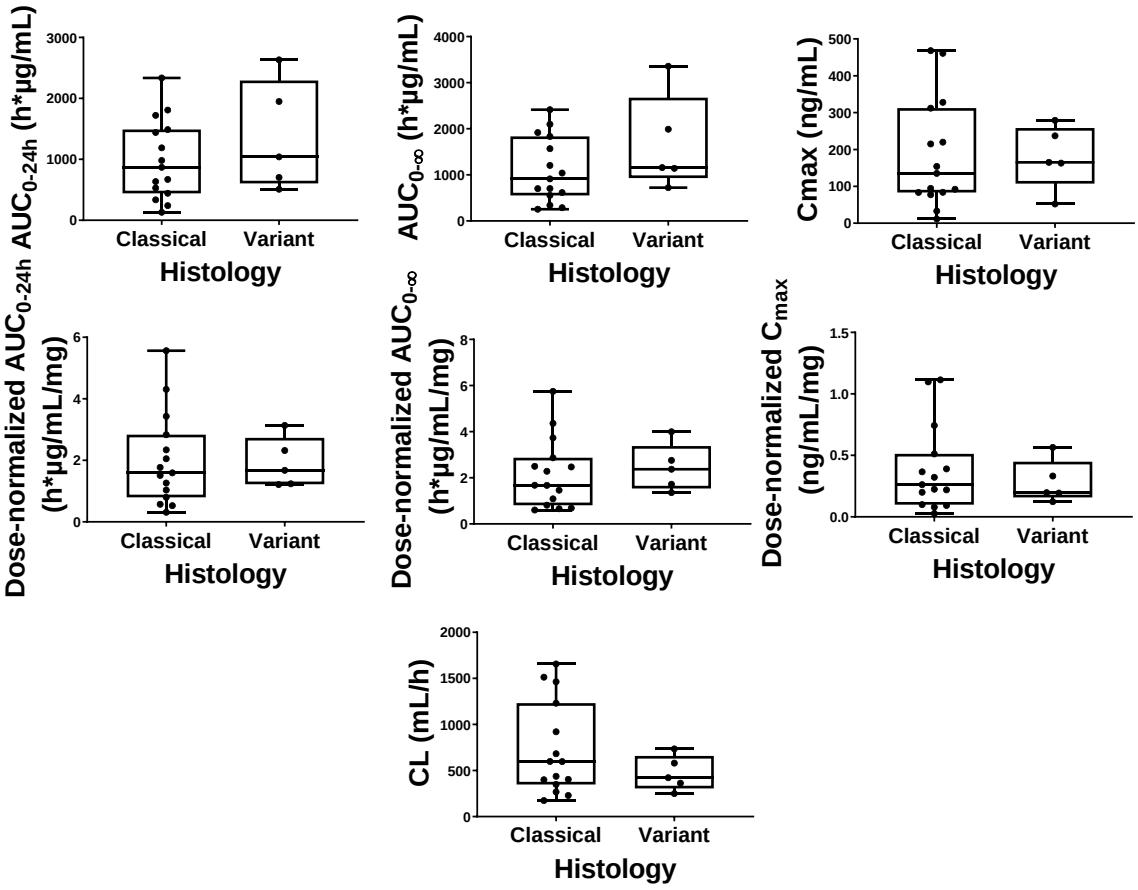


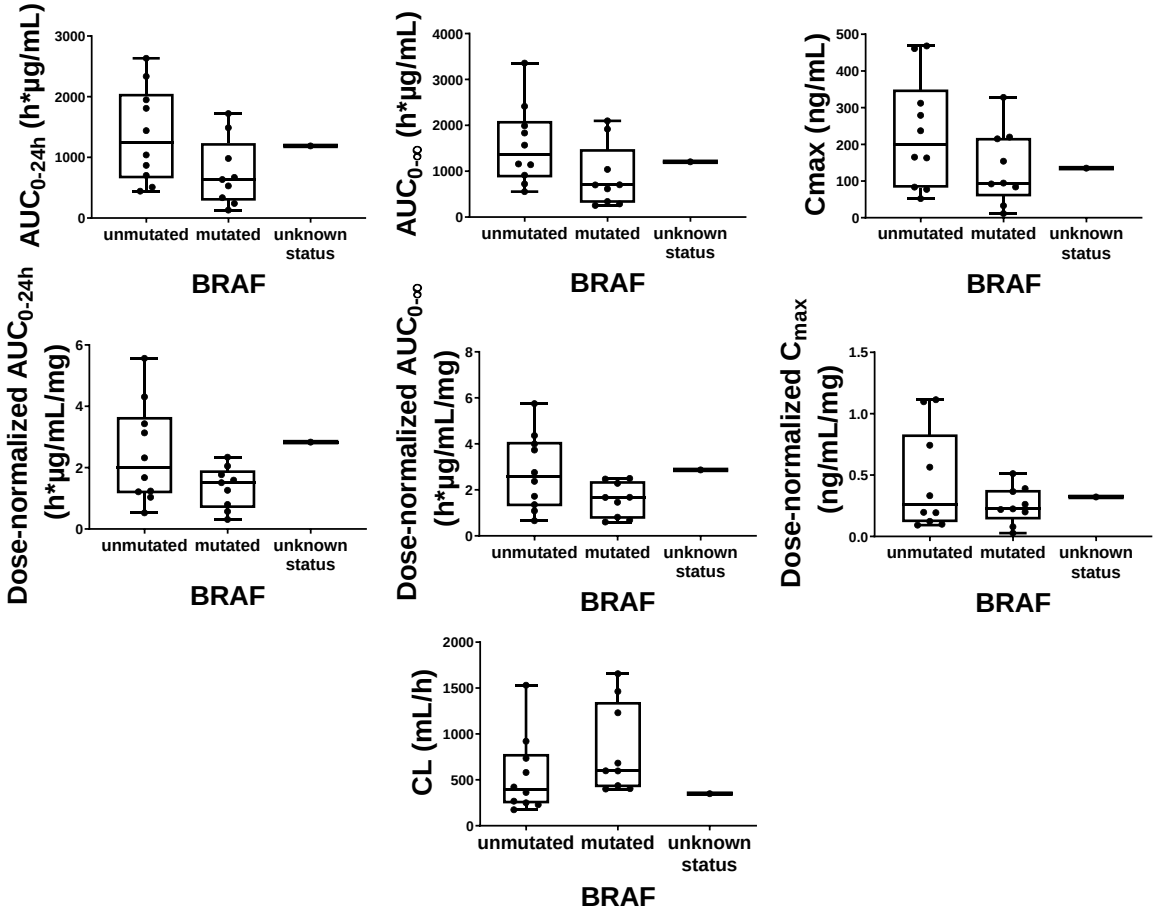
Figure S7: Association of Pharmacokinetic Parameters and Disease Characteristics.

Boxplots of PK vs. disease characteristics (a) disease histology (classical or variant), (b) *BRAF* mutation status, and (c) splenectomy status. Groups were compared using Mann-Whitney test. For the *BRAF* analysis, only unmutated and mutated groups were compared; No comparisons reach significance (p≤0.05).

A



B


AUC0-24h (h*µg/mL)
3000
2000
1000
0
unmutated
mutated
unknown status
BRAF
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
unmutated
mutated
unknown status
BRAF
Cmax (ng/mL)
500
400
300
200
100
0
unmutated
mutated
unknown status
BRAF
Dose-normalized AUC0-24h (h*µg/mL/mg)
6
4
2
0
unmutated
mutated
unknown status
BRAF
Dose-normalized AUC0-∞ (h*µg/mL/mg)
8
6
4
2
0
unmutated
mutated
unknown status
BRAF
Dose-normalized Cmax (ng/mL/mg)
1.5
1.0
0.5
0.0
unmutated
mutated
unknown status
BRAF
CL (mL/h)
2000
1500
1000
500
0
unmutated
mutated
unknown status
BRAF

C

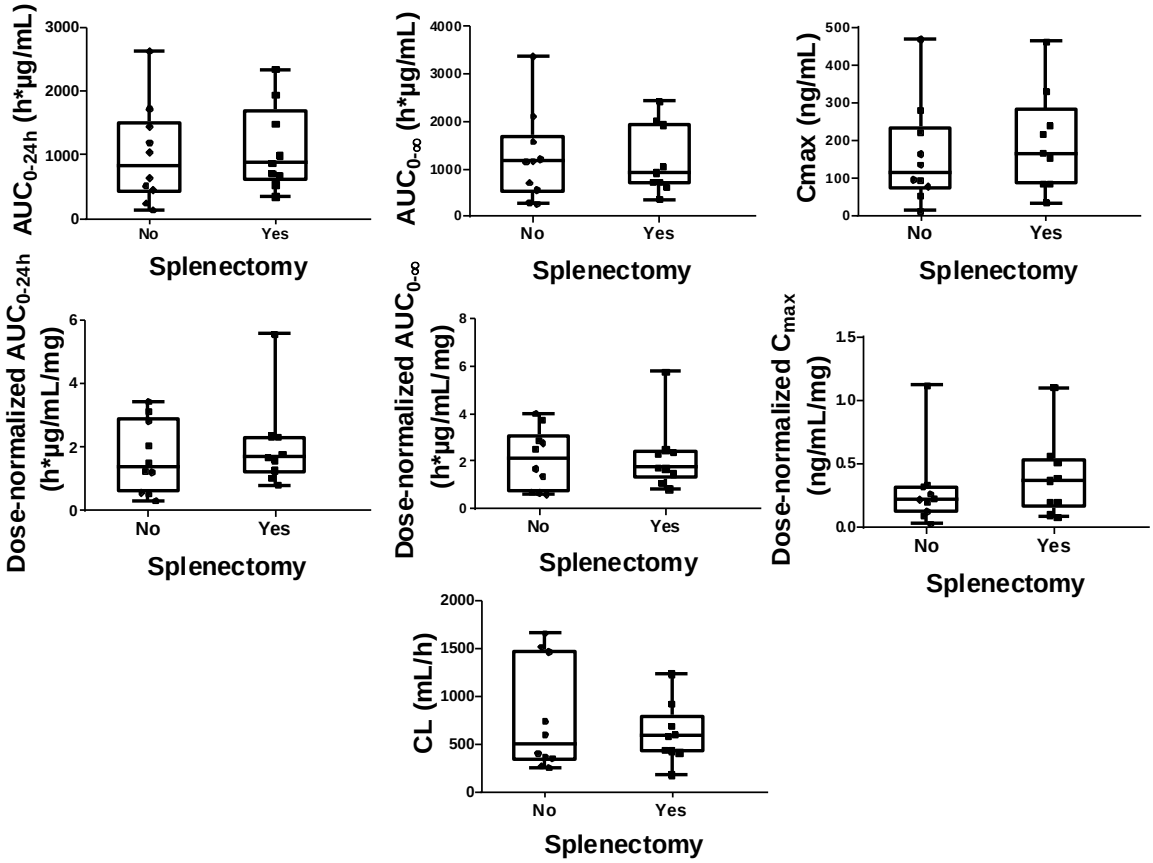
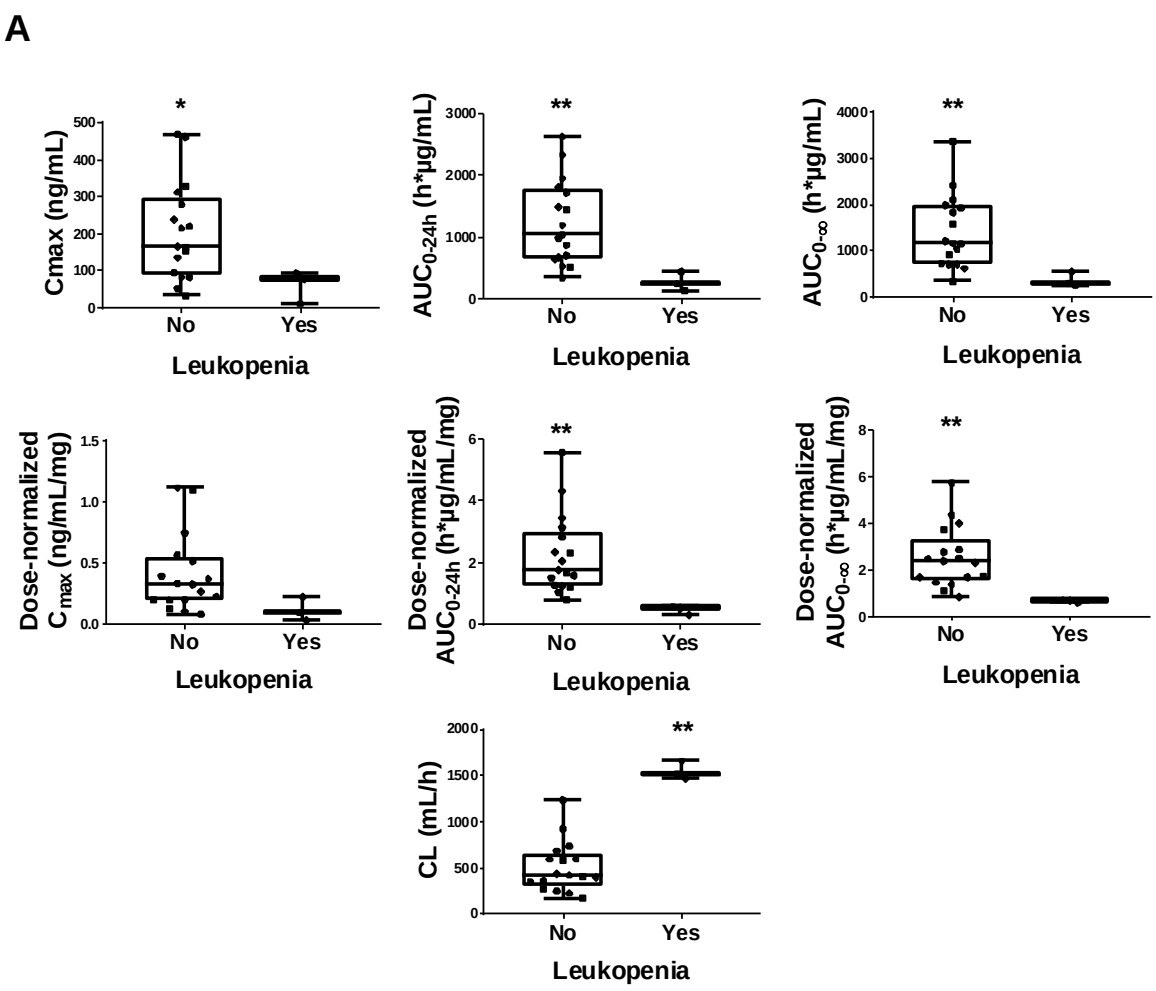
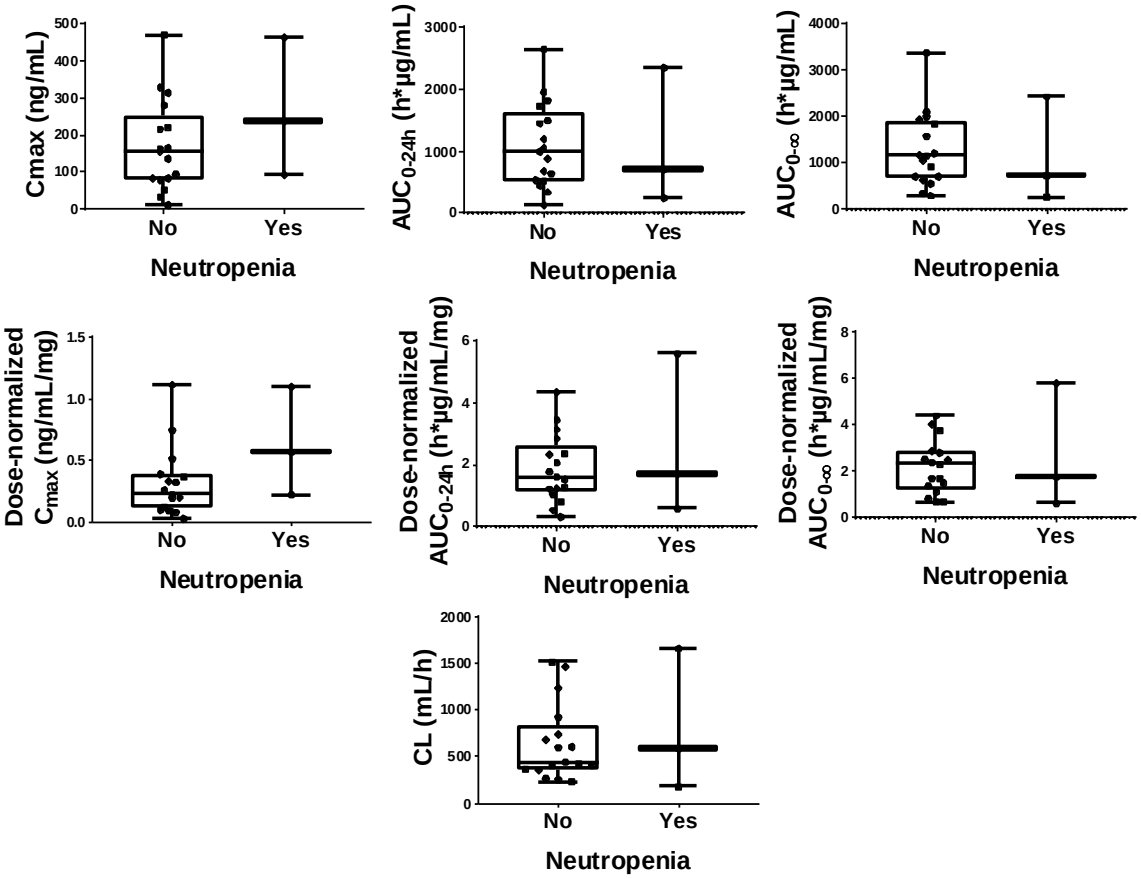

AUC0-24h (h*µg/mL)
3000
2000
1000
0
No
Yes
Splenectomy
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
No
Yes
Splenectomy
Cmax (ng/mL)
500
400
300
200
100
0
No
Yes
Splenectomy
Dose-normalized AUC0-24h (h*µg/mL/mg)
6
4
2
0
No
Yes
Splenectomy
Dose-normalized AUC0-∞ (h*µg/mL/mg)
8
6
4
2
0
No
Yes
Splenectomy
Dose-normalized Cmax (ng/mL/mg)
1.5
1.0
0.5
0.0
No
Yes
Splenectomy
CL (mL/h)
2000
1500
1000
500
0
No
Yes
Splenectomy

Figure S8: Association of Pharmacokinetic Parameters and Adverse Events.

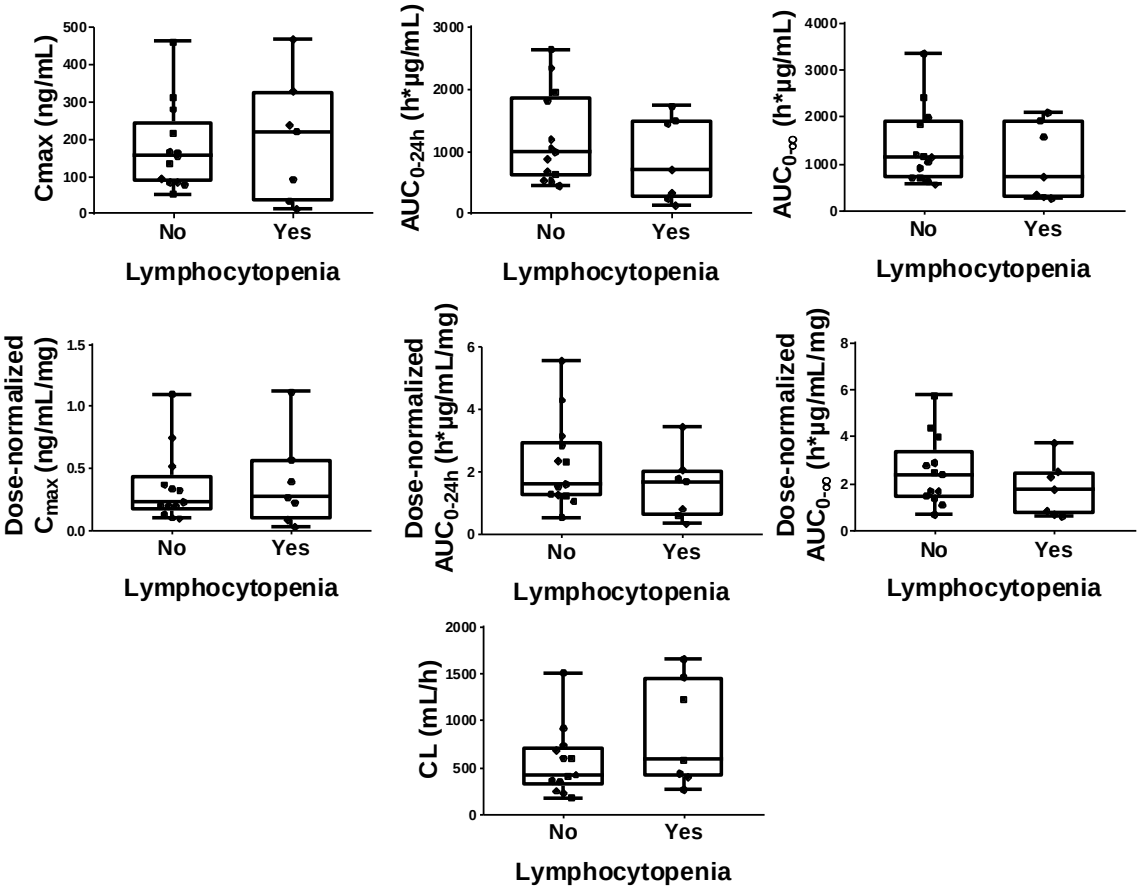
Boxplots of PK parameters with presence of the adverse events of leukopenia (A), neutropenia (B), lymphopenia (C), anemia (D), thrombocytopenia (E), and bruising (F) with ibrutinib. Groups were compared using nonparametric test (Mann-Whitney test) *, p<0.05**; p<0.01.



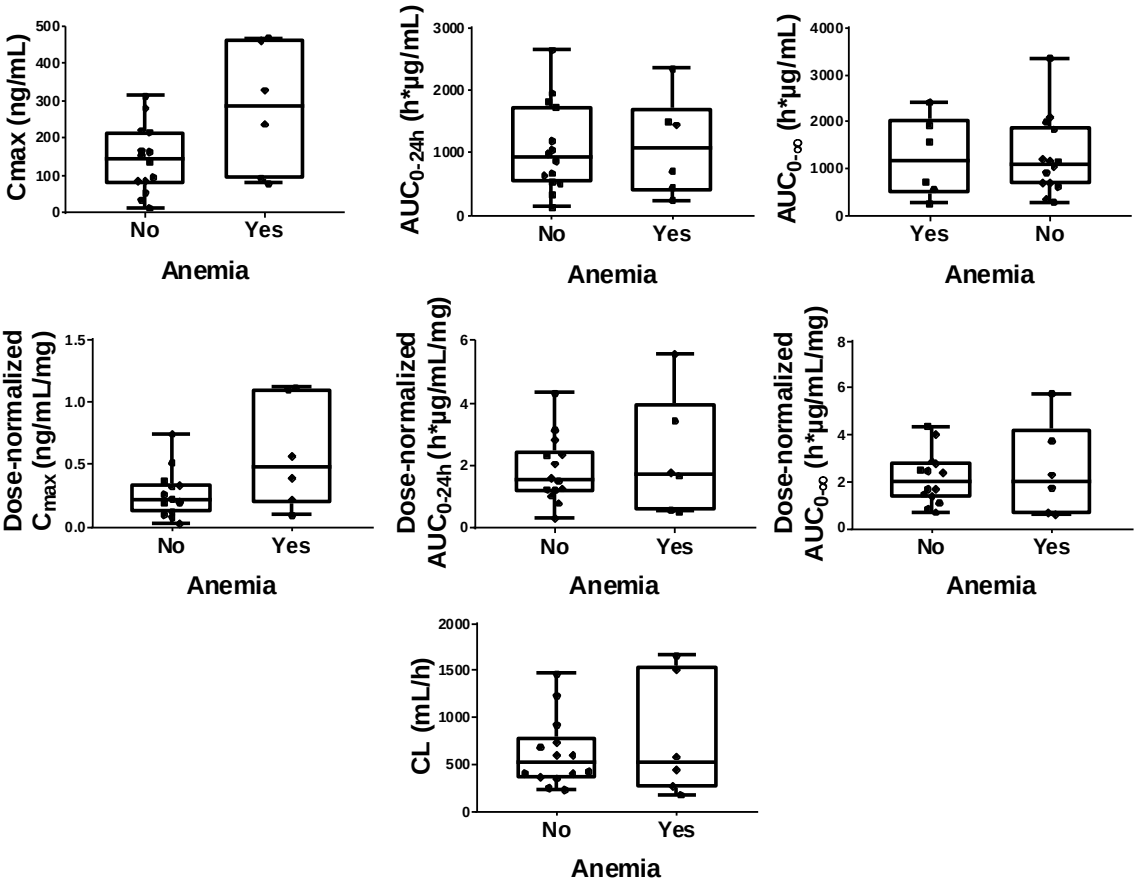
B


Cmax (ng/mL)
500
400
300
200
100
0
No
Yes
Neutropenia
AUC0-24h (h*µg/mL)
3000
2000
1000
0
No
Yes
Neutropenia
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
No
Yes
Neutropenia
Dose-normalized Cmax (ng/mL/mg)
1.5
1.0
0.5
0.0
No
Yes
Neutropenia
Dose-normalized AUC0-24h (h*µg/mL/mg)
6
4
2
0
No
Yes
Neutropenia
Dose-normalized AUC0-∞ (h*µg/mL/mg)
8
6
4
2
0
No
Yes
Neutropenia
CL (mL/h)
2000
1500
1000
500
0
No
Yes
Neutropenia

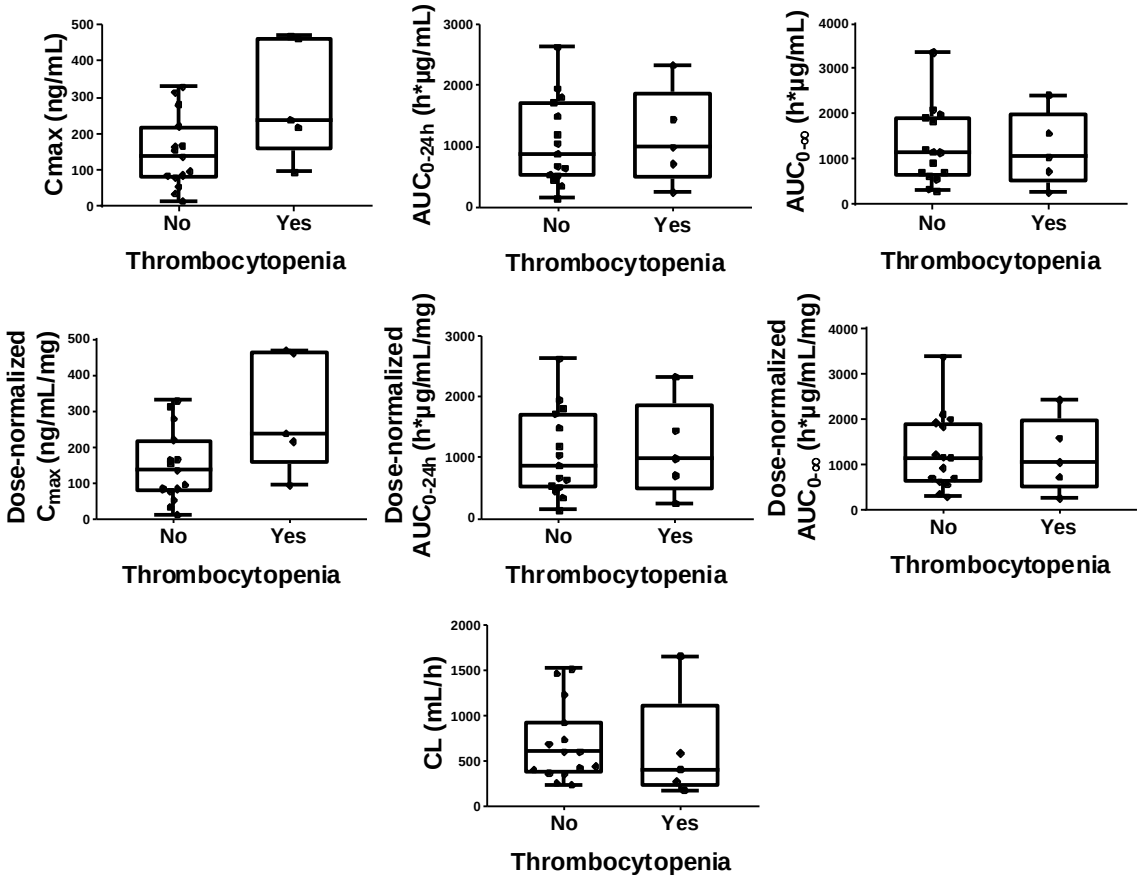
C


Cmax (ng/mL)
500
400
300
200
100
0
No
Yes
Lymphocytopenia
AUC0-24h (h*µg/mL)
3000
2000
1000
0
No
Yes
Lymphocytopenia
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
No
Yes
Lymphocytopenia
Dose-normalized Cmax (ng/mL/mg)
1.5
1.0
0.5
0.0
No
Yes
Lymphocytopenia
Dose-normalized AUC0-24h (h*µg/mL/mg)
6
4
2
0
No
Yes
Lymphocytopenia
Dose-normalized AUC0-∞ (h*µg/mL/mg)
8
6
4
2
0
No
Yes
Lymphocytopenia
CL (mL/h)
2000
1500
1000
500
0
No
Yes
Lymphocytopenia

D


Cmax (ng/mL)
500
400
300
200
100
0
No
Yes
Anemia
AUC0-24h (h*µg/mL)
3000
2000
1000
0
No
Yes
Anemia
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
Yes
No
Anemia
Dose-normalized Cmax (ng/mL/mg)
1.5
1.0
0.5
0.0
No
Yes
Anemia
Dose-normalized AUC0-24h (h*µg/mL/mg)
6
4
2
0
No
Yes
Anemia
Dose-normalized AUC0-∞ (h*µg/mL/mg)
8
6
4
2
0
No
Yes
Anemia
CL (mL/h)
2000
1500
1000
500
0
No
Yes
Anemia

E


Cmax (ng/mL)
500
400
300
200
100
0
No
Yes
Thrombocytopenia
AUC0-24h (h*µg/mL)
3000
2000
1000
0
No
Yes
Thrombocytopenia
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
No
Yes
Thrombocytopenia
Dose-normalized Cmax (ng/mL/mg)
500
400
300
200
100
0
No
Yes
Thrombocytopenia
Dose-normalized AUC0-24h (h*µg/mL/mg)
3000
2000
1000
0
No
Yes
Thrombocytopenia
Dose-normalized AUC0-∞ (h*µg/mL/mg)
4000
3000
2000
1000
0
No
Yes
Thrombocytopenia
CL (mL/h)
2000
1500
1000
500
0
No
Yes
Thrombocytopenia

F

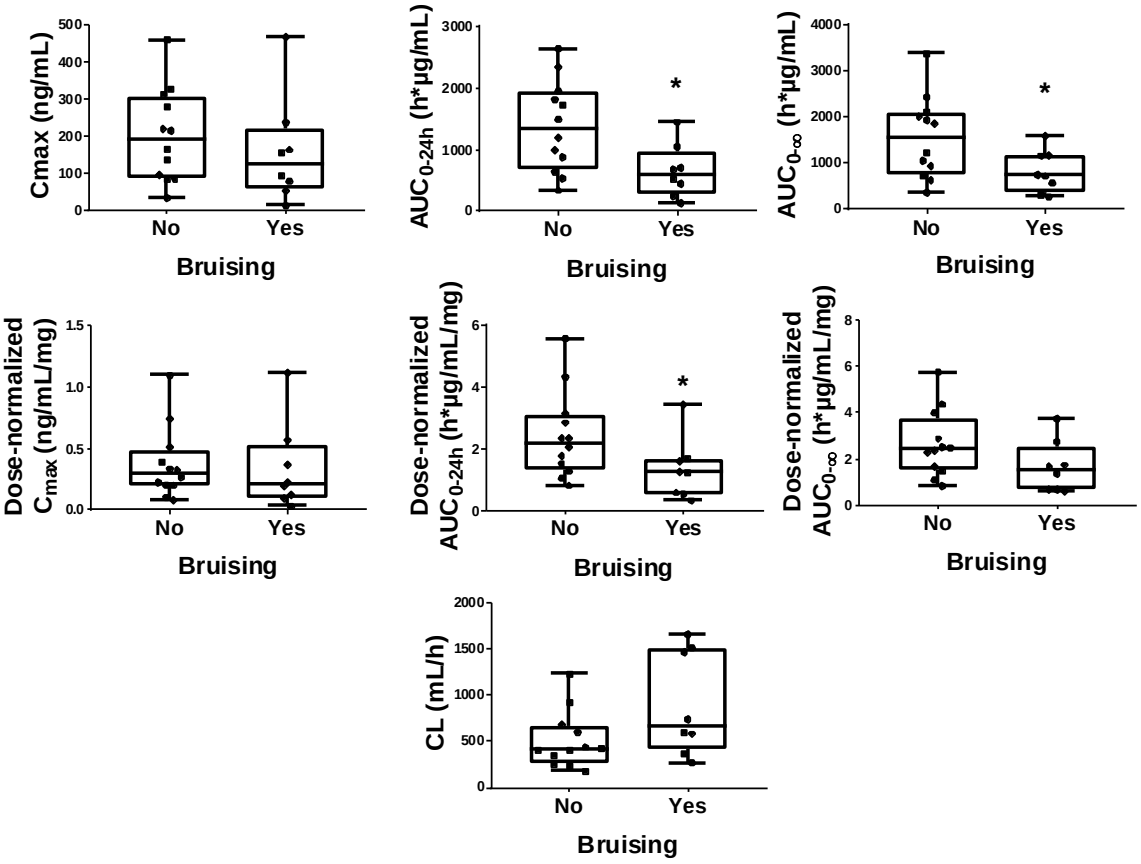

Cmax (ng/mL)
500
400
300
200
100
0
No
Yes
Bruising
AUC0-24h (h*µg/mL)
3000
2000
1000
0
*
No
Yes
Bruising
AUC0-∞ (h*µg/mL)
4000
3000
2000
1000
0
*
No
Yes
Bruising
Dose-normalized Cmax (ng/mL/mg)
1.5
1.0
0.5
0.0
No
Yes
Bruising
Dose-normalized AUC0-24h (h*µg/mL/mg)
6
4
2
0
*
No
Yes
Bruising
Dose-normalized AUC0-∞ (h*µg/mL/mg)
8
6
4
2
0
No
Yes
Bruising
CL (mL/h)
2000
1500
1000
500
0
No
Yes
Bruising

Figure S9: Pharmacodynamic Measures

Absolute circulating CD19+ B-cells are shown over the first 4 weeks of ibrutinib treatment. Of 16 patients examined only 2 patients had a small trend towards increased circulating lymphocytes. Patients are divided into those with counts >500 cells per μL (A) and those without (B) to better observe the trends. C. Serum levels of immune globulins were determined at baseline and at 3, 6, 12, and 18 months after treatment. The percent change from baseline for individual patients are shown. IgG levels were significantly decreased from baseline at every time point (Kruskal-Wallis test, **** p<0.0001). There were no differences in IgM or IgA relative to their baselines.