# Supplementary Appendix

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

Supplement to: Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42. DOI: 10.1056/NEJMoa1215637

## SUPPLEMENTARY APPENDIX

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**Figure S1:** **Mean plasma concentration-time profile of ibrutinib after once daily oral administration of ibrutinib on day 8 of cycle 1.**

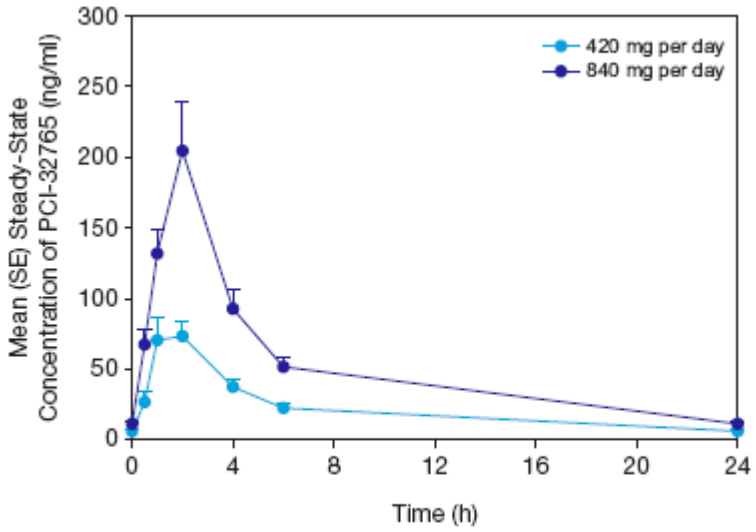
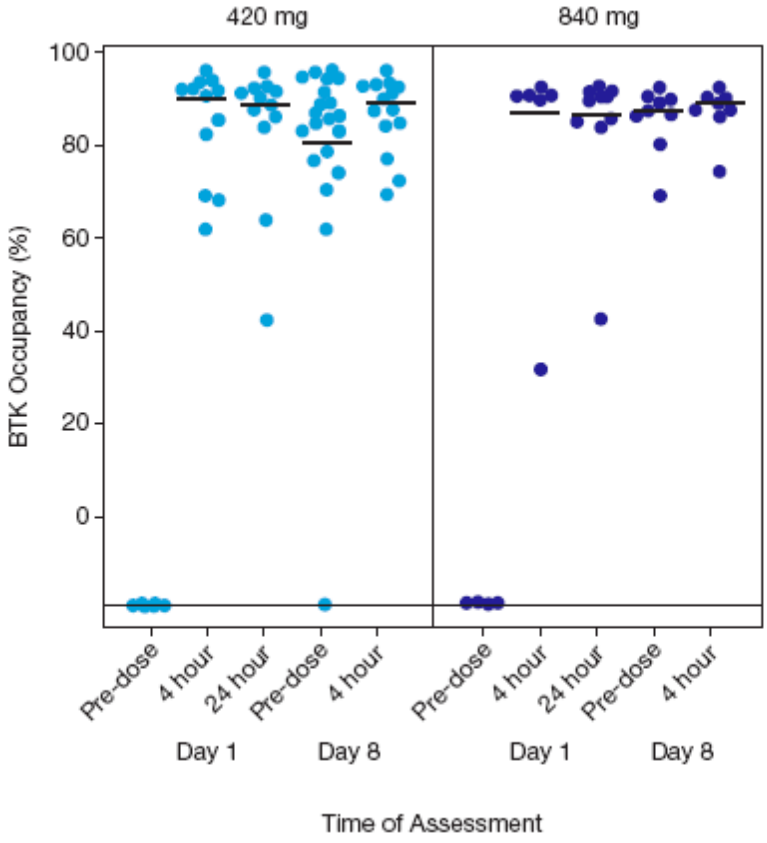
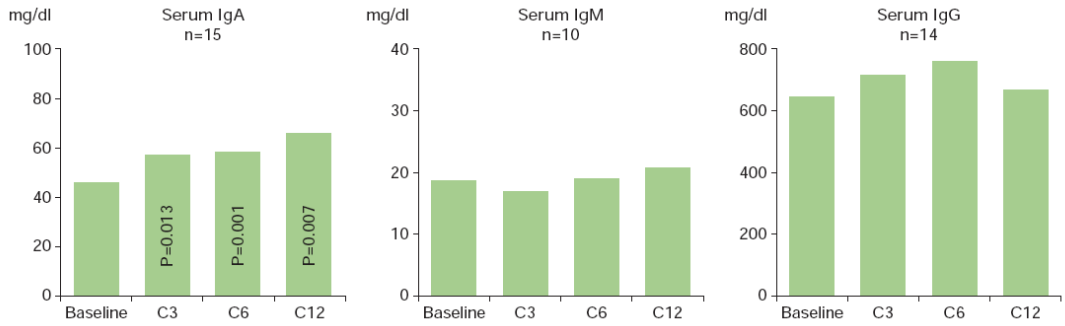


**Figure S2:** **BTK Occupancy. Percent of BTK bound by ibrutinib before, 4- and 24-hours after dosing on Days 1 and 8 of treatment. The mean percent for each time period is shown by a horizontal line.**



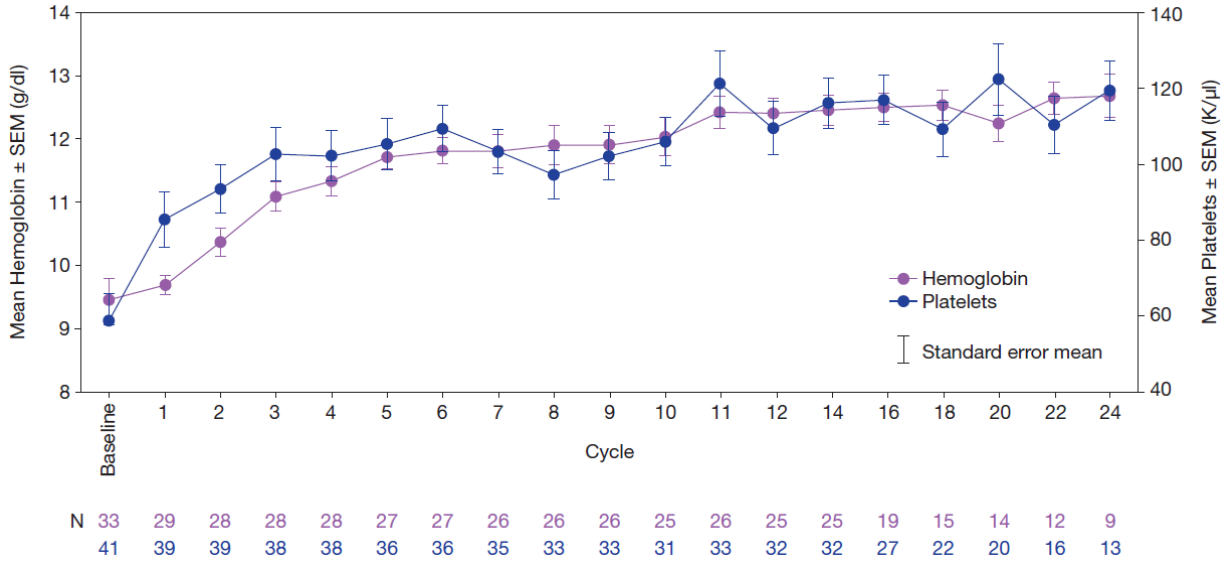

The laboratory measurement of percent bound BTK on Day 8 of Cycle 1 is not a significant predictor of best objective response in an ordinal logistic regression model, indicating that for these data there is no association between these variables. The range of observed BTK binding was limited and the best objective response was overwhelmingly PR, thus an association could exist that these data cannot detect. Similarly, percent bound BTK and change from baseline Absolute Lymphocyte Count at Day 8 of Cycle1 are not correlated using these data, though the broader range of observed BTK binding could yield a different result.

**Figure S3: Median serum Immunoglobulin (Ig) levels in relapsed or refractory and high-risk patients during ibrutinib treatment.**




The p-values are from Wilcoxon Signed Rank test. Multiplicity was not adjusted. Patients on intravenous immunoglobulin and those without assessments at each follow-up time-point were excluded. Analysis was limited to patients who did not receive intravenous gammaglobulin (n=41) during study follow-up. 13 patients discontinued IVIG during the course of follow-up.

**Figure S4: Ibrutinib improves hemoglobin and platelet counts in relapsed or refractory patients with cytopenias at baseline.**




78% of 41 patients with baseline thrombocytopenia experienced sustained improvement of platelet counts.
82% of 33 patients with baseline anemia experienced sustained improvement of hemoglobin.
77% of 31 patients with baseline neutropenia experienced sustained improvement of neutrophil count

**Table S1: Protocol Criteria for Response based on the criteria from the International Workshop on Chronic Lymphocytic Leukemia 2008**

| Parameter | CR | PR | PD |
|---|---|---|---|
| **Group A** | | | |
| Lymphadenopathy[a] | None; ≤1.5cm | Decrease ≥50% | increase ≥50% or any new lesion >1.5 cm |
| Hepatomegaly | None | Decrease ≥50% | increase ≥50% or new hepatomegaly |
| Splenomegaly | None | Decrease ≥50% | increase ≥50% or new splenomegaly |
| Blood lymphocytes | <4000/μL | Decrease ≥50% from baseline | increase ≥50% over baseline[c] or > 5000/μL |
| Marrow[b] | Normocellular, <30% lymphocytes, no B lymphoid[d] nodules, no clonal infiltrate. Hypocellular defines Cri | | |
| **Group B** | | | |
| Platelet count | >100,000/μL | >100,000/μL or increase ≥50% over baseline | Decrease of ≥50% from baseline secondary to CLL |
| Hemoglobin | >11 g/dL | >11g/dL or increase ≥50% over baseline | Decrease of >2g/dL from baseline secondary to CLL |
| Neutrophils | >1500/μL | >1500/μL or increase ≥50% over baseline | N/A |

[a]Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node; [b]This parameter is not relevant for the PD category unless confirming cytopenic progression.; [c]Patients with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease. ; [d]Patients meeting all criteria for a CR with B-lymphocyte nodules on bone marrow exam will be considered nodular partial response (nPR)

Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system

CR: all of the criteria need to be met and patients have to lack disease related constitutional symptoms. Bone marrow and aspirate is required to confirm CR.

CRi: Defined as CR with incomplete hematopoietic recovery PR: Requires two criteria from Group A, if abnormal at baseline to respond plus 1 of the criteria from Group B must be met. Improvement in Group B criteria must be in absence of growth factor or transfusion support. If all group B criteria normal at baseline, criteria must continue to remain within these limits. Note if all PR criteria with the exception of ALC are met this is consistent with a PR with lymphocytosis.

SD: the absence of PD and the failure to achieve a CR,CRi, nPR, PR, or PR with lymphocytosis.

PD: at least 1 of the above criteria from Group A or B are met or development of transformation to a more aggressive histology

Cross reference: 1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56. 2. Hallek M, Cheson BD, Catovsky D, et al. Response Assessment in Chronic Lymphocytic Leukemia Treated with Novel Agents Causing an Increase of Peripheral Blood Lymphocytes. Blood 2012;eUpdate June 4, 2012. http://bloodjournal.hematologylibrary.org/content/111/12/5446.full/reply#bloodjournal_el_6920.

**Table S2: Demographics and baseline disease characteristics.**

| | 420 mg Cohort (n=51) | 840 mg Cohort (n=34) |
|---|---|---|
| Median age (range) − years | 68 (37-82) | 64 (44-80) |
| Patients ≥70 years − No. (%) | 20 (39) | 10 (29) |
| Sex − No. (%) | | |
| Male | 37 (73) | 28 (82) |
| Female | 14 (27) | 6 (18) |
| Diagnosis − No. (%) | | |
| CLL | 49 (96) | 33 (97) |
| SLL | 2 (4) | 1 (3) |
| Time from Initial Diagnosis to Enrollment (months, range) | 79 (14-283) | 99 (27-232) |
| Time from Most Recent Systemic Cancer-Related Therapy (months, range) | 4 (1-98) | 2 (1-60) |
| Rai Stage at treatment − No. (%) | | |
| 0/I/II (low/intermediate risk) | 21 (41) | 8 (24) |
| III/IV (high risk) | 30 (59) | 25 (74) |
| Missing data | 0 | 1 (3) |
| ECOG Performance Status − No. (%) | | |
| 0 | 19 (37) | 16 (47) |
| 1 | 32 (63) | 16 (47) |
| 2 | 0 | 2 (6) |
| Prior therapies − median No. (range) | 3 (1-11) | 5 (1-12) |
| Types of therapy − No. (%) | | |
| Nucleoside analog | 47 (92) | 34 (100) |
| Rituximab | 50 (98) | 33 (97) |
| Alkylator | 44 (86) | 32 (94) |
| Alemtuzumab | 11 (22) | 7 (21) |
| Bendamustine | 20 (39) | 13 (38) |
| Ofatumumab | 10 (20) | 12 (35) |

**Table S2: Demographics and baseline disease characteristics.**

| | 420 mg Cohort (n=51) | 840 mg Cohort (n=34) |
|---|---|---|
| Bulky nodes − No (%) | | |
| ≥ 5 cm | 24 (47) | 20 (59) |
| ≥10 cm | 4 (8) | 9 (26) |
| Missing | 2 (4) | 1 (3) |
| IGHV, unmutated − No (%) | 41 (80) | 28 (82) |
| Missing | 2 (4) | 2 (6) |
| Interphase cytogenetics+ − No (%)[a] | | |
| Del(17p13.1) | 17 (33) | 11 (32) |
| Del(11q22.3) | 16 (31) | 15 (44) |
| Del(13q) 0 copies | 9 (18) | 7 (21) |
| Del(13q) 1 copy | 20 (39) | 14 (41) |
| Missing | 3 (6) | 2 (6) |
| $\beta_2$M – No. (%) | | |
| >3 mg/L | 18 (35) | 21 (62) |
| Missing | 3 (6) | 2 (6) |
| Cytopenia | | |
| ANC< 1500/μL | 14 (27%) | 17 (50%) |
| HGB< 11g/dL | 15 (29%) | 18 (53%) |
| PLT< 100,000/μL | 18 (35%) | 23 (68%) |
| Disease Resistant to Purine Analog[b] | 22 (43%) | 19 (56%) |

$\beta_2$M = Beta2 microglobulin; CLL=chronic lymphocytic leukemia; del=deletion;
IGHV= immunoglobulin variable heavy chain; SLL=small lymphocytic lymphoma
[a]Cut offs were defined per the assay specifications as performed in the central laboratory
[b]Resistant to purine analog is defined as treatment failure (SD or PD) or progression within 12 months of receipt of a purine analog containing regimen.

**Table S3: Disposition of patients who discontinued study treatment**

| | **Relapsed/refractory + high-risk patients (n=85)** |
|---|---|
| Median Time on Treatment, months | 21.0 R/R |
| Range | 0.3 – 26.7 |
| Subjects Still on Treatment, # (%) | 54 (64) |
| Treatment discontinuation secondary to Disease Progression | 11 (13) |
| Non-PD Reasons for Treatment Discontinuation, # (%) | 20 (24) |
| Adverse Event (includes death)[1] | 7 (8) |
| Stem cell transplant (while in response)[2] | 5 (6) |
| Subject decision[3] | 5 (6) |
| Investigator decision – not stem cell transplant[4] | 3 (4) |

1. 7 patients discontinued for Adverse Events and died during survival follow-up including 3 pneumonias, 2 sepsis, and one each bacteremia and GI hemorrhage (in a patient with a pretreatment bleeding diathesis died 292 days after ibrutinib discontinuation).
2. 4 patients who received SCT were known to be alive at last contact while one died of GVHD.
3. 4 patients withdrew consent for follow-up including one additional patient who decided to pursue SCT outside of study center, the remaining 1 patient was known to be alive at last contact.
4. All 3 patients who discontinued for investigator decision (non-SCT) were alive at last contact, one patient had squamous cell carcinoma (lung ca) present on baseline CT (confirmed on D2 of treatment) and one patient investigator assessed as having maximal treatment benefit and elected new anti-cancer therapy (bendamustine).

**Table S4: Serious Adverse Events**

| | ≤Grade 3 | ≥Grade 4 N (%) | Total |
|---|---|---|---|
| Pneumonia | 9 (10) | 1 (1) | 10 (12) |
| Bacteremia | 3 (4) | 1 (1) | 4 (5) |
| Cellulitis | 4 (5) | 0 (0) | 4 (5) |
| Sinusitis | 4 (5) | 0 (0) | 4 (5) |
| Atrial fibrillation | 3 (4) | 0 (0) | 3 (4) |
| Febrile neutropenia | 2 (2) | 1 (1) | 3 (4) |
| Abdominal pain | 2 (2) | 0 (0) | 2 (2) |
| Clostridial infection | 2 (2) | 0 (0) | 2 (2) |
| Dehydration | 2 (2) | 0 (0) | 2 (2) |
| Sepsis | 0 (0) | 2 (2) | 2 (2) |
| Subdural hematoma | 2 (2) | 0 (0) | 2 (2) |
| Asthenia | 1 (1) | 0 (0) | 1 (1) |
| Back pain | 1 (1) | 0 (0) | 1 (1) |
| Bone lesion | 1 (1) | 0 (0) | 1 (1) |
| Bronchitis viral | 0 (0) | 1 (1) | 1 (1) |
| Bursitis | 1 (1) | 0 (0) | 1 (1) |
| Chest pain | 1 (1) | 0 (0) | 1 (1) |
| Chronic lymphocytic leukemia | 0 (0) | 1 (1) | 1 (1) |
| Cystitis | 1 (1) | 0 (0) | 1 (1) |
| Decreased appetite | 1 (1) | 0 (0) | 1 (1) |
| Diarrhea | 1 (1) | 0 (0) | 1 (1) |
| Dizziness | 1 (1) | 0 (0) | 1 (1) |
| Gastroenteritis | 1 (1) | 0 (0) | 1 (1) |
| Herpes zoster disseminated | 1 (1) | 0 (0) | 1 (1) |
| Hypercalcemia | 0 (0) | 1 (1) | 1 (1) |
| Hyperglycemia | 0 (0) | 1 (1) | 1 (1) |
| Hypoxia | 1 (1) | 0 (0) | 1 (1) |
| Ileus | 1 (1) | 0 (0) | 1 (1) |
| Joint abscess | 1 (1) | 0 (0) | 1 (1) |
| Laceration | 1 (1) | 0 (0) | 1 (1) |
| Left ventricular dysfunction | 1 (1) | 0 (0) | 1 (1) |
| Leukostasis | 0 (0) | 1 (1) | 1 (1) |
| Malignant melanoma | 1 (1) | 0 (0) | 1 (1) |
| Nausea | 1 (1) | 0 (0) | 1 (1) |
| Orthostatic hypotension | 1 (1) | 0 (0) | 1 (1) |

**Table S4: Serious Adverse Events**

| | ≤Grade 3 | ≥Grade 4 | Total |
|---|---|---|---|
| | | N (%) | |
| Pleuritic pain | 1 (1) | 0 (0) | 1 (1) |
| Prostate cancer | 1 (1) | 0 (0) | 1 (1) |
| Pyrexia | 1 (1) | 0 (0) | 1 (1) |
| Rhinovirus infection | 1 (1) | 0 (0) | 1 (1) |
| Richter's syndrome | 0 (0) | 1 (1) | 1 (1) |
| Sarcoma | 0 (0) | 1 (1) | 1 (1) |
| Splenomegaly | 1 (1) | 0 (0) | 1 (1) |
| Squamous cell carcinoma | 1 (1) | 0 (0) | 1 (1) |
| Supraventricular tachycardia | 0 (0) | 1 (1) | 1 (1) |
| Tumour lysis syndrome | 0 (0) | 1 (1) | 1 (1) |
| Upper respiratory tract infection | 1 (1) | 0 (0) | 1 (1) |
| Urinary retention | 1 (1) | 0 (0) | 1 (1) |
| Urinary tract infection | 1 (1) | 0 (0) | 1 (1) |
| Varicella | 1 (1) | 0 (0) | 1 (1) |
| Vestibular neuronitis | 1 (1) | 0 (0) | 1 (1) |
| Vomiting | 1 (1) | 0 (0) | 1 (1) |

**Table S5: Rate of Severe Infections (≥Grade 3)**

| Exposure adjusted Event Rate of ≥Grade 3 infections (per 100 patient month) | | |
|---|---|---|
| | First 6 months | ≥7 months |
| All (N=85) | 7.1 | 2.6 |
| | | |
| Subgroup by Exposure duration | | |
| ≤6 month (N=15) | 23.3 | - |
| >6 month (N=70) | 5.5 | 2.6 |
| | | |
| ≤12 month (N= 22) | 17.7 | 4.1 |
| >12 month (N=63) | 4.8 | 2.6 |
| | | |
| ≥18 month (N=38) | 4.8 | 2 |

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