**Supplementary Information**

Supplementary information for “Bleeding with concomitant ibrutinib and oral anticoagulant therapy: a population-based cohort study” by Neil Dhopeshwarkar1,2\*, Wei Yang1,2, Sean Hennessy1,2, Joanna M. Rhodes3, Adam Cuker4,5, and Charles E. Leonard1,2

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**1. Supplemental Methods**

*1.1 Data source.* Optum’s de-identified Clinformatics® Data Mart includes health insurance data on >80 million commercially-insured and Medicare Advantage beneficiaries of a large US-based health plan. Optum Clinformatics® includes demographic and enrollment information, medical claims for inpatient and outpatient care, and pharmacy claims for drugs dispensed in the outpatient care setting.

*1.2 Incident co-exposure definition.* Individuals entered the cohort by 1) initiating cancer therapy (ibrutinib or BR) during OAC therapy (warfarin, rivaroxaban, apixaban, dabigatran, or edoxaban), i.e., cancer therapy-triggered cohort entry, 2) initiating an OAC during cancer therapy, i.e., OAC-triggered cohort entry, or 3) initiating cancer therapy and an OAC on the same day, i.e., synchronous-triggered cohort entry (Supplementary Figure 1). The date of incident co-exposure served as the index date, and individuals were required to have a preceding 6-month baseline period devoid of 1) ibrutinib dispensing (in ibrutinib users) or bendamustine administration (in BR users) for cancer therapy-triggered cohort entry individuals, 2) OAC dispensing for OAC-triggered cohort entry individuals, or 3) both for synchronous-triggered cohort entry individuals. We allowed rituximab administrations during the baseline period, as rituximab may be used as part of other cancer therapy regimens or for other medical conditions.

*1.3 Inclusion and exclusion criteria.* We included individuals who were diagnosed with CLL (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] 204.1x or ICD-10-CM C91.1x), MCL (ICD-9-CM 200.4x or ICD-10-CM C83.1x), or MZL (ICD-9-CM 200.3x or ICD-10-CM C88.4). For each cancer type, we required at least two any claim-type, any-position diagnosis codes ≥1 day apart preceding the index date. We excluded individuals with: 1) interruption in insurance plan enrollment during the baseline period; 2) age <18 years on the index date; 3) bendamustine administration within 28 days (the duration of one BR cycle) prior to the index date for ibrutinib + OAC-treated individuals; or 4) ibrutinib dispensing within 7 days (the duration of ibrutinib’s antiplatelet effect observed in *in vitro* studies) 1 prior to the index date for BR + OAC-treated individuals (Supplementary Figure 2). We included only the first observation meeting inclusion and exclusion criteria, per individual.

*1.4 Follow-up criteria.* Follow-up began on the index date and continued until the first occurrence of: 1) an outcome (defined below); 2) a >7-day therapy gap for ibrutinib or >56-day gap between BR administrations (allowing for an up to 28-day delay in a treatment cycle); 3) a >7-day therapy gap for the OAC; 4) a dispensing or administration of an alternative anticancer therapy; 5) a dispensing of an alternative OAC; 6) insurance plan disenrollment; 7) the end of the dataset (February 29, 2020); or 8) day 180 (to account for the differing treatment duration between ibrutinib and BR).

*1.5 Exposure ascertainment.* We used National Drug Codes to ascertain ibrutinib and OAC exposure from dispensings in the prescription claims. We used Healthcare Common Procedure Coding System codes and National Drug Codes to ascertain BR exposure from administrations in the inpatient and outpatient medical claims. We chose BR as the active comparator referent as it is a chemoimmunotherapy used in similar settings as ibrutinib in CLL, 2 and is also used in MCL and MZL. 3 We considered but decided against newer therapies (e.g., acalabrutinib) as the referent, given uncommon use of these agents during the study period. We considered an individual exposed to BR if they had a rituximab administration on the same day as or within 7 days before a bendamustine administration. This ensured the capture of individuals who received BR according to the typical administration schedule, 4 and those with slight variations.

*1.6 Outcome ascertainment.* We identified major bleeds in inpatient claims with a bleeding diagnosis code as the principal discharge diagnosis (indicative of reason for admission), or a bleeding diagnosis code as a secondary discharge diagnosis with a principal discharge diagnosis suggestive of a possible bleed (e.g., gastric ulcer) (Supplementary Table 2). We also used the algorithm to exclude bleeding events caused by major trauma. We identified post-hoc outcomes (provider-diagnosed bleeds) in any-setting claims (inpatient, outpatient, and other) with a bleeding diagnosis code in any claim position (i.e., we expanded the primary and secondary outcome definition to include all claim settings and claim positions).

*1.7* *Statistical analysis.* For baseline covariates, we used standardized differences to assess covariate balance in the unweighted and weighted cohorts, with an absolute standardized difference of <0.1 as a threshold for adequate balance. We estimated hazard ratios (HRs) using Cox proportional hazards regression, weighted based on stabilized inverse probability of treatment weight (sIPTW), and used a robust variance estimator to account for weighting. The model also adjusted for calendar year of cohort entry and any covariates that remained imbalanced after sIPTW. We assessed the proportional hazards assumption by including an interaction term of exposure by time since cohort entry in the model.

We conducted a pre-specified subgroup analysis by OAC type (direct oral anticoagulant [DOAC] vs. warfarin). In the DOAC subgroup analysis, we adjusted for dose intensity at cohort entry and included an additional censoring criterion during follow-up in which individuals were censored on the day of a dose intensity change (Supplementary Table 3).

To assess the robustness of our primary findings, we conducted numerous sensitivity analyses including adjustment for cancer type, modification of therapy gaps for ibrutinib, BR, and OACs, and exclusion of individuals with bleeding during the baseline period (Supplementary Table 4). We also calculated the E-value to assess the potential impact of unmeasured confounders, 5 which is the minimum strength of association, on the risk ratio scale, a potential confounder needs to have with both the exposure and outcome to move the outcome result effect estimate to a null value.

We also explored effect modification by use of medications that may affect ibrutinib, BR, or OAC metabolism (e.g., cytochrome P450 3A4 [CYP3A4], CYP1A2, P-glycoprotein inhibitors), and by exposure initiation order at cohort entry. Analyses were conducted using SAS v9.4 (SAS Institute Inc.: Cary, NC).

**2. Supplemental Results**

*2.1 Baseline characteristics.* In the overall cohort, large proportions of individuals had baseline diagnoses of hypertension (78.5%), atrial fibrillation (67.8%), renal dysfunction (35.5%), and thrombocytopenia (29.0%). A modest proportion of individuals had bleeding during the baseline period (8.1%). Most ibrutinib-treated individuals (74.4%) received an average daily dose of 420 mg at cohort entry (Supplementary Table 5).

Among unweighted baseline characteristics, there were differences between ibrutinib + OAC-treated and BR + OAC-treated individuals in CLL diagnosis (89.2% in ibrutinib + OAC vs. 52.4% in BR + OAC), cohort entry year (≥ 2016: 86.7% vs. 71.2%), median age (78 years vs. 73 years), geographic region (East North Central: 17.1% vs. 22.6%; South Atlantic: 28.1% vs. 18.9%), lymphadenopathy (31.5% vs. 55.7%), splenomegaly (12.1% vs. 24.5%), and heparin use (14.8% vs. 32.6%).

*2.2 Concomitant OAC use.* The majority of ibrutinib + OAC-treated individuals (55.2%) entered the cohort by initiating an OAC while on ibrutinib, i.e., OAC-triggered cohort entry, while the majority of BR + OAC-treated individuals (66.5%) entered the cohort by initiating BR while on an OAC, i.e., cancer therapy-triggered cohort entry. Among DOAC-treated individuals, a greater proportion of ibrutinib + OAC-treated individuals were on a low intensity DOAC (23.1%) compared to BR + OAC-treated individuals (8.0%).

*2.3* *Sensitivity analyses and effect modification.* The E-value corresponding to the provider-diagnosed bleeding effect estimate was 4.84 (E-value for the lower bound of the 95% CI: 1.81), indicating that an unmeasured confounder would need a risk ratio association of 4.84 with both the exposure and outcome to move the provider-diagnosed bleeding effect estimate to a null value of 1 (and 1.81 to move the lower bound of the 95% CI to a null value of 1). Results from sensitivity analyses were generally consistent with our provider-diagnosed bleeding findings; the HR ranged from 2.28–2.92 (Supplementary Table 12). There was no evidence of effect modification by use of potentially-interacting medications or exposure initiation order at cohort entry (Supplementary Table 13).

**3. Supplemental Discussion**

*3.1 Major bleeding cumulative incidence.* The cumulative incidence of major bleeding among ibrutinib + OAC-treated individuals in our study (1.88%) was lower than that reported in other studies (13–16%).6,7 This difference may be attributed to: 1) our use of a primarily privately-insured, employed population across the US, and thus a potentially less vulnerable population to bleeding compared to others, 8-10 2) a difference in major bleeding definitions; other studies used the Common Terminology Criteria for Adverse Events, 11 which may have included bleeding events that arose during hospitalization, and 3) a shorter duration of follow-up (median of 38 days) for ibrutinib + OAC-treated individuals in our study compared to others (median of 13 months); 6 previous literature did not report incidence rates of major bleeding which would have accounted for this follow-up time difference. These reasons may have also contributed to the difference in cumulative incidence for broader-defined bleeding outcomes between studies: 17.7% for provider-diagnosed bleeding in our study vs. 53–73% for bleeding of any severity in other studies. 6,12

*3.2 Comparison of bleeding incidence rates in ibrutinib + OAC-treated individuals to those in ibrutinib-treated individuals.* We compared incidence rates of major and clinically-relevant bleeding to our previous work which, using the same data source and methods, investigated these outcomes in ibrutinib-treated individuals with CLL not concomitantly exposed to OACs. 13 Crude incidence rates for major and clinically-relevant bleeding were four times as high for ibrutinib + OAC-treated individuals in this study (major bleeding: 12.5 per 100 p-y; clinically-relevant bleeding: 26.6 per 100 p-y) compared to ibrutinib-treated individuals in the previous study (major bleeding: 3.1 per 100 p-y; clinically-relevant bleeding: 5.8 per 100 p-y). This suggests that, as expected, OACs increase bleeding risk in ibrutinib-treated patients. The notable increase in major and clinically-relevant bleeding rates may have implications for the benefit-harm balance of initiating OAC therapy in patients on ibrutinib.

*3.3 Strengths and additional limitations of this study.* Our study has notable strengths. It directly compared bleeding rates between individuals concomitantly exposed to ibrutinib and an OAC and individuals concomitantly exposed to an alternative cancer therapy and an OAC. Additionally, we identified major bleeding using an algorithm that was validated in a similar claims database and demonstrated an 89% PPV with ICD-9-CM codes. 14 Our study has additional limitations. First, we were unable to ascertain cancer characteristics (e.g., Rai staging for CLL, Lugano staging for MZL) and high-risk genetic features (e.g., deletion 17p or immunoglobulin heavy-chain gene mutation for CLL, TP53 mutation for MCL). However, we included cancer complications that may affect bleeding occurrence (e.g., thrombocytopenia) in the propensity score. Second, international normalized ratio (INR) values were unavailable in Optum Clinformatics®. Third, we used prescription dispensings to identify ibrutinib and OAC exposure, which may not directly reflect ingestion. We conducted sensitivity analyses in which therapy gaps were modified to address this. Fourth, individuals who initiated cancer therapy during OAC therapy may have had a lower risk of bleeding during follow-up compared to those who initiated OAC therapy during cancer therapy due to a possible depletion of susceptibles effect with OACs. 15 To account for this, we examined effect modification by exposure initiation order at cohort entry, although our sample size limited our ability to detect such an effect. Last, we did not account for time-varying confounders (e.g., platelet count on the day that a bleed occurred) during follow-up. Thus, time-varying confounding may have impacted our findings.

# **Supplementary Table 1. Pre-specified baseline covariates.**

|  |  |  |
| --- | --- | --- |
| Demographics | Age | |
| Sex | |
| Geographic region of residence | |
| Race | |
| Education level | |
| Housing | |
| Household income | |
| Total net worth of beneficiary | |
| Cancer complications | Thrombocytopenia | |
| Lymphadenopathy | |
| Splenomegaly | |
| Medical conditions | Hypertension | |
| Renal dysfunction | |
| Liver dysfunction | |
| Stroke | |
| Peptic ulcer | |
| Bleeding\* | |
| Atrial fibrillation | |
| Deep vein thrombosis | |
| Pulmonary embolism | |
| Concomitant medications | Medications associated with bleeding risk | Antiplatelets |
| NSAIDs |
| Heparin |
| Anticancer therapy | Targeted therapy† |
| Chemotherapy |
| Medications that can affect CYP metabolism1,2 | CYP3A4 inhibitors |
| CYP3A4 inducers |
| CYP2D6 inhibitors‡ |
| CYP2D6 inducers§ |
| CYP1A2 inhibitors |
| CYP1A2 inducers |
| P-gp inhibitors |
| P-gp inducers |
| Measure of frailty | Claims-based frailty index3 | |
| BR = bendamustine-rituximab; CYP = cytochrome P450; NSAID = nonsteroidal anti-inflammatory drug; P-gp = p-glycoprotein  See **Supplementary Figure 2** for details on timing of covariate measurement  \* Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim  † Rituximab was excluded from targeted anticancer therapy covariate as it is part of the BR regimen  ‡ Diphenhydramine and hydroxyzine were excluded from CYP2D6 inhibitors covariate as they are used as pre-treatment medications for BR, thus are highly correlated to exposure status but are not confounders  § Dexamethasone was excluded from CYP2D6 inducers covariate as it is used as a pre-treatment medication for BR, thus is highly correlated to exposure status but is not a confounder  1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.  2. Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter). UpToDate®. 2022.  3. Kim DH, et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7. | | |

# **Supplementary Table 2. Diagnosis codes used in primary outcome definition.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Bleed Site** | **ICD-9-CM Code** | **ICD-9-CM Code Description** | **ICD-10-CM Code\*** |
| **Diagnosis Codes Indicating Bleeding**†‡ | | | |
| Gastrointestinal | 531.0x, 531.2x, 531.4x, 531.6x | Gastric ulcer with hemorrhage | K25.0, K25.2, K25.4, K25.6 |
| 532.0x, 532.2x, 532.4x, 532.6x | Duodenal ulcer with hemorrhage | K26.0, K26.2, K26.4, K26.6 |
| 533.0x, 533.2x, 533.4x, 533.6x | Peptic ulcer with hemorrhage | K27.0, K27.2, K27.4, K27.6 |
| 534.0x, 534.2x, 534.4x, 534.6x | Gastrojejunal ulcer with hemorrhage | K28.0, K28.2, K28.4, K28.6 |
| 535.01, 535.11, 525.21, 535.31, 535.41, 535.51, 535.61 | Gastritis, gastroduodenitis, or duodenitis with hemorrhage | K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91 |
| 537.83 | Angiodysplasia of stomach and duodenum with hemorrhage | K31.811 |
| 456.0, 456.20 | Esophageal varices with bleeding | I85.01, I85.11 |
| 530.7, 530.21 | Mallory-Weiss tear (gastroesophageal laceration-hemorrhage syndrome) or ulcer of esophagus with bleeding | K22.11, K22.6 |
| 530.82 | Esophageal hemorrhage | - |
| 578.0 | Hematemesis | K92.0 |
| 455.2, 455.5, 455.8 | Hemorrhoids with other complication | - |
| 562.02, 562.03, 562.12, 562.13 | Diverticulosis or diverticulitis with hemorrhage | K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93 |
| 568.81 | Hemoperitoneum | K66.1 |
| 569.3 | Hemorrhage of rectum and anus | K62.5 |
| 569.85 | Angiodysplasia of intestine with hemorrhage | K55.21 |
| 578.1 | Blood in stool | K92.1 |
| 578.9 | Hemorrhage of gastrointestinal tract, unspecified | K92.2 |
| Genitourinary | 593.81 | Vascular disorders of kidney | N28.0 |
| 599.7x | Hematuria | R31.0, R31.1, R31.21, R31.29, R31.9 |
| 623.8 | Other specified noninflammatory disorders of vagina | N89.8 |
| 626.6 | Metrorrhagia | N92.1 |
| Cerebral | 430 | Subarachnoid hemorrhage | I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.2, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.6, I60.7, I60.8, I60.9 |
| 431 | Intracerebral hemorrhage | I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9 |
| 432.0 | Nontraumatic extradural hemorrhage | I62.1 |
| 432.1 | Subdural hemorrhage | I62.00, I62.01, I62.02, I62.03 |
| 432.9 | Unspecified intracranial hemorrhage | I62.9 |
| Other | 423.0 | Hemopericardium | I31.2 |
| 459.0 | Hemorrhage, unspecified | R58 |
| 568.81 | Hemoperitoneum (nontraumatic) | K66.1 |
| 719.1x | Hemarthrosis | M25.00, M25.011, M25.012, M25.019, M25.021, M25.022, M25.029, M25.031, M25.032, M25.039, M25.041, M25.042, M25.049, M25.051, M25.052, M25.059, M25.061, M25.062, M25.069, M25.071, M25.072, M25.073, M25.074, M25.075, M25.076, M25.08 |
| 784.7 | Epistaxis | R04.0 |
| 784.8 | Hemorrhage from throat | R04.1 |
| 786.3x | Hemoptysis | R04.2, R04.81, R04.89, R04.9 |
| **Diagnosis Codes Suggestive of Possible Bleeding**§ | | | |
| Gastrointestinal | 531.1x, 531.3x, 531.5x, 531.7x, 531.9x | Gastric ulcer without mention of hemorrhage | K25.1, K25.3, K25.5, K25.7, K25.9 |
| 532.1x, 531.3x, 531.5x, 531.7x, 532.9x | Duodenal ulcer without mention of hemorrhage | K26.1, K26.3, K26.5, K26.7, K26.9 |
| 533.1x, 533.3x, 533.5x, 533.7x, 533.9x | Peptic ulcer without mention of hemorrhage | K27.1, K27.3, K27.5, K27.7, K27.9 |
| 534.1x, 534.3x, 534.5x, 534.7x, 534.9x | Gastrojejunal ulcer without mention of hemorrhage | K28.1, K28.3, K28.5, K28.7, K28.9 |
| 535.00, 535.10, 535.20, 535.30, 535.40, 535.50, 535.60 | Gastritis, gastroduodenitis, or duodenitis without mention of hemorrhage | K29.00, K29.20, K29.30, K29.40, K29.50, K29.60, K29.70, K29.80, K29.90 |
| 562.00, 562.01, 562.10, 562.11 | Diverticula or diverticulitis without mention of hemorrhage | K57.00, K57.10, K57.12, K57.20, K57.30, K57.32, K57.40, K57.50, K57.52, K57.80, K57.92 |
| 455.0, 455.1, 455.3, 455.4, 455.6, 455.7, 455.9 | Hemorrhoids | K64.0, K64.1, K64.2, K64.3, K64.4, K64.5, K64.8, K64.9 |
| 530.1x | Esophagitis | K20.0, K20.8, K20.9, K21.0 |
| 530.20 | Ulcer of esophagus without bleeding | K22.10 |
| Unspecified | 285.1 | Acute posthemorrhagic anemia‖ | D62 |
| 280.0 | Anemia due to loss of blood‖ | D50.0 |
| 285.9 | Anemia, unspecified‖ | D64.9 |
| 790.92 | Abnormal coagulation profile‖ | R79.1 |
| 287.49, 287.5 | Thrombocytopenia‖ | D69.59, D69.6 |
| Genitourinary | 626.2 | Excessive/frequent menstruation\*\* | - |
| CM = clinical modification; ICD = International Classification of Diseases  \* ICD-9-CM diagnoses were mapped to ICD-10-CM diagnoses using forward-backwards mapping with general equivalence maps1  † Outcomes were excluded if a major trauma code was recorded on the day prior to admission through the day after admission. See Cunningham et al.2 for list of trauma codes  ‡ Diagnosis code required to be the principal discharge diagnosis  § Diagnosis code required to be the principal discharge diagnosis with either 1) a diagnosis code indicating bleeding as a secondary diagnosis or 2) a revenue code indicating a transfusion  ‖ Diagnosis code required to be the principal discharge diagnosis with a diagnosis code indicating bleeding as a secondary diagnosis (a transfusion revenue code is not sufficient)  \*\* Diagnosis code required to be the principal discharge diagnosis with a diagnosis code of either 1) anemia (ICD-9-CM: 280.0, 285.1, 285.9; ICD-10-CM: D50.0, D62, D64.9) 2), orthostasis (ICD-9-CM: 458.0; ICD-10-CM: I95.1), or 3) syncope (ICD-9-CM: 780.2; ICD-10-CM: R55) as a secondary diagnosis  1. Fung et al. Preparing for the ICD-10-CM transition: Automated methods for translating ICD codes in clinical phenotype definitions. *EGEMS (Wash DC).* 2016;4(1):1211.  2. Cunningham et al. An Automated Database Case Definition for Serious Bleeding Related to Oral Anticoagulant Use. *Pharmacoepidemiol Drug Saf*. 2011:20(6):560-566. | | | |

# **Supplementary Table 3. Direct oral anticoagulant dose categories used for dose intensity adjustment in subgroup analysis.**

|  |  |  |
| --- | --- | --- |
|  | **Average Daily Dose\*** | |
| **DOAC** | **Low Intensity†** | **High Intensity‡** |
| Apixaban | ≤ 5 mg | ≥ 10 mg |
| Rivaroxaban | ≤ 10 mg | ≥ 15 mg |
| Dabigatran | ≤ 220 mg | ≥ 300 mg |
| Edoxaban | ≤ 30 mg | ≥ 60 mg |
| DOAC = direct oral anticoagulant  \* Average Daily Dose = prescription quantity x capsule or tablet strength / prescription days’ supply  † Low intensity includes doses indicated for deep vein thrombosis/pulmonary embolism prophylaxis and deep vein thrombosis/pulmonary embolism treatment in patients with renal dysfunction1  ‡ High intensity includes doses indicated for deep vein thrombosis/pulmonary embolism treatment and stroke/pulmonary embolism prevention in patients with non-valvular atrial fibrillation1  1. Cuker et al. American Society of Hematology 2021 Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19. *Blood Adv.* 2021;5(3):872-888. | | |

# **Supplementary Table 4. Pre-specified and post-hoc sensitivity analyses.**

|  |  |  |
| --- | --- | --- |
| **Type** | **Analysis** | **Rationale** |
| Pre-specified | Depleting days’ supply of ibrutinib dispensings\* during non-outcome hospitalizations | Days of non-outcome hospitalization are subtracted from ibrutinib dispensings, as individuals may use their home supply of ibrutinib during the hospitalization stay, thereby minimizing exposure misclassification. |
| Increasing permissible therapy gap between ibrutinib dispensings from 7 to 14 days | Increases proportion of follow-up time contributed by periods of presumed nonadherence to ibrutinib, thereby minimizing premature censoring of follow-up among poor adherers. |
| Increasing permissible therapy gap between OAC dispensings from 7 to 14 days | Increases proportion of follow-up time contributed by periods of presumed nonadherence to the OAC, thereby minimizing premature censoring of follow-up among poor adherers. |
| Decreasing permissible therapy gap between bendamustine administrations from 56 to 42 days | Decreases proportion of follow-up time contributed by periods of presumed delays in therapy administration, thereby minimizing exposure misclassification. |
| Adjusting for cancer type (CLL, MCL, or MZL) in the Cox proportional hazards regression outcome model | Adjusts for cancer type as a covariate in the outcome model. Cancer type was not included in the propensity score in the primary analysis, as it may be an instrument which can cause bias in the propensity score estimation. |
| Competing risk analysis with disenrollment as competing event | Accounts for a possible competing risk of death that may preclude individuals from developing an outcome. Disenrollment was used as a proxy for death, as death dates were unavailable. |
| Post-hoc | Excluding individuals with bleeding during the baseline period† | Individuals with bleeds diagnosed during the baseline period may experience ‘carry-forward coding’ in which outcomes experienced during follow-up represent historic bleeding events |
| CLL = chronic lymphocytic leukemia, MCL = mantle cell lymphoma, MZL = marginal zone lymphoma; OAC = oral anticoagulant  \* In the primary analysis, days of hospitalization were added to the ibrutinib prescription claim’s days’ supply, as individuals may receive hospital supply of ibrutinib during their hospitalization stay  † Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim | | |

**Supplementary Table 5. Baseline characteristics of ibrutinib + OAC-treated and bendamustine-rituximab + OAC-treated individuals.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Unweighted** | | | **Weighted** |
| **Characteristic, N (%)\*** | **Ibrutinib + OAC**  **N = 480** | **Bendamustine-Rituximab + OAC**  **N = 212** | **Absolute Standardized Difference** | **Absolute Standardized Difference** |
| Average daily ibrutinib dose†‡ |  |  | N/A | N/A |
| <420 mg | 85 (17.7) | N/A |  |  |
| 420 mg | 357 (74.4) | N/A |  |  |
| >420 mg | 38 (7.9) | N/A |  |  |
|  |  |  |  |  |
| Cancer type |  |  |  |  |
| CLL | 428 (89.2) | 111 (52.4) | 0.89 | 0.86 |
| MCL | 40 (8.3) | 73 (34.4) |  |  |
| MZL | 12 (2.5) | 28 (13.2) |  |  |
|  |  |  |  |  |
| **Demographics** |  |  |  |  |
| Cohort entry year§ |  |  | 0.53 | 0.52 |
| 2013 | 2 (0.4) | 7 (3.2) |  |  |
| 2014 | 19 (4.0) | 28 (13.2) |  |  |
| 2015 | 43 (9.0) | 26 (12.3) |  |  |
| 2016 | 64 (13.3) | 26 (12.3) |  |  |
| 2017 | 77 (16.0) | 40 (18.9) |  |  |
| 2018 | 111 (23.1) | 42 (19.8) |  |  |
| 2019 | 134 (27.9) | 40 (18.9) |  |  |
| 2020 | 30 (6.3) | 3 (1.4) |  |  |
|  |  |  |  |  |
| Age in years, median (IQR) | 78 (72 – 84) | 73 (67 – 79) | 0.51 | 0.04 |
|  |  |  |  |  |
| Sex |  |  | 0.06 | 0.04 |
| Female | 166 (34.6) | 67 (31.6) |  |  |
| Male | 314 (65.4) | 145 (68.4) |  |  |
|  |  |  |  |  |
| US geographic region of residence |  |  | 0.38 | 0.08 |
| East North Central | 82 (17.1) | 48 (22.6) |  |  |
| East South Central | 10 (2.1) | 7 (3.3) |  |  |
| Middle Atlantic | 32 (6.7) | 11 (5.2) |  |  |
| Mountain | 53 (11.0) | 33 (15.6) |  |  |
| New England | 15 (3.1) | 12 (5.7) |  |  |
| Pacific | 64 (13.3) | 15 (7.1) |  |  |
| South Atlantic | 135 (28.1) | 40 (18.9) |  |  |
| West North Central | 31 (6.5) | 12 (5.7) |  |  |
| West South Central | 57 (11.9) | 33 (15.6) |  |  |
| Unknown | 1 (0.21) | 1 (0.47) |  |  |
|  |  |  |  |  |
| Race |  |  | 0.12 | 0.07 |
| Asian | 8 (1.7) | 2 (0.9) |  |  |
| Black | 41 (8.5) | 15 (7.1) |  |  |
| Hispanic | 33 (6.9) | 14 (6.6) |  |  |
| White | 345 (71.9) | 160 (75.5) |  |  |
| Unknown | 53 (11.0) | 21 (9.9) |  |  |
|  |  |  |  |  |
| Education level‖ |  |  | 0.12 | 0.04 |
| <12th Grade | 2 (0.4) | 0 (0.0) |  |  |
| High school diploma | 111 (23.1) | 44 (20.7) |  |  |
| <Bachelor degree | 240 (50.0) | 118 (55.7) |  |  |
| Bachelor degree+ | 86 (17.9) | 31 (14.6) |  |  |
| Unknown | 41 (8.6) | 19 (9.0) |  |  |
|  |  |  |  |  |
| Housing‖ |  |  | 0.07 | 0.05 |
| Probable homeowner | 349 (72.7) | 157 (74.1) |  |  |
| Probable renter | 15 (3.1) | 9 (4.3) |  |  |
| Unknown | 116 (24.2) | 46 (21.7) |  |  |
|  |  |  |  |  |
| Household income‖ |  |  | 0.07 | 0.17 |
| <$40K | 114 (23.7) | 48 (22.6) |  |  |
| $40K-$49K | 30 (6.3) | 13 (6.1) |  |  |
| $50K-$59K | 39 (8.1) | 19 (9.0) |  |  |
| $60K-$74K | 45 (9.4) | 19 (9.0) |  |  |
| $75K-$99K | 75 (15.6) | 36 (17.0) |  |  |
| $100K+ | 102 (21.3) | 42 (19.8) |  |  |
| Unknown | 75 (15.6) | 35 (16.5) |  |  |
|  |  |  |  |  |
| Total net worth of beneficiary‖ |  |  | 0.05 | 0.09 |
| <$25K | 74 (15.4) | 30 (14.1) |  |  |
| $25K-$149K | 75 (15.6) | 36 (17.0) |  |  |
| $150K-$249K | 46 (9.6) | 21 (9.9) |  |  |
| $250K-$499K | 72 (15.0) | 32 (15.1) |  |  |
| $500K+ | 138 (28.8) | 58 (27.4) |  |  |
| Unknown | 75 (15.6) | 35 (16.5) |  |  |
|  |  |  |  |  |
| **Cancer complications, present in baseline period** |  |  |  |  |
| Thrombocytopenia | 149 (31.0) | 52 (24.5) | 0.15 | 0.02 |
| Lymphadenopathy | 151 (31.5) | 118 (55.7) | 0.50 | 0.01 |
| Splenomegaly | 58 (12.1) | 52 (24.5) | 0.33 | 0.01 |
|  |  |  |  |  |
| **Medical conditions, present in baseline period** |  |  |  |  |
| Hypertension | 382 (79.6) | 161 (75.9) | 0.09 | <0.01 |
| Renal dysfunction | 164 (34.2) | 82 (38.7) | 0.09 | 0.04 |
| Liver dysfunction | 78 (16.3) | 43 (20.3) | 0.10 | 0.02 |
| Stroke | 54 (11.3) | 18 (8.5) | 0.09 | 0.06 |
| Peptic ulcer | 9 (1.9) | 7 (3.3) | 0.09 | 0.06 |
| Bleeding¶ | 39 (8.1) | 17 (8.0) | 0.004 | 0.07 |
| Atrial fibrillation | 333 (69.4) | 136 (64.2) | 0.11 | 0.03 |
| Deep vein thrombosis | 57 (11.9) | 44 (20.8) | 0.24 | 0.03 |
| Pulmonary embolism | 52 (10.8) | 44 (20.8) | 0.27 | <0.01 |
|  |  |  |  |  |
| **Medications dispensed in the 90 days prior to index date\*\*** |  |  |  |  |
| Antiplatelets | 26 (5.4) | 6 (2.8) | 0.13 | <0.01 |
| NSAIDs | 33 (6.9) | 11 (5.2) | 0.07 | 0.03 |
| Heparin | 71 (14.8) | 69 (32.6) | 0.43 | 0.01 |
| Anticancer therapy – targeted†† | 16 (3.3) | 6 (2.8) | 0.03 | 0.04 |
| Anticancer therapy - chemotherapy†† | 28 (5.8) | 8 (3.8) | 0.10 | 0.07 |
| CYP3A4 inhibitors‡‡ | 64 (13.3) | 38 (17.9) | 0.13 | 0.02 |
| CYP3A4 inducers‡‡ | 10 (2.1) | 4 (1.9) | 0.01 | 0.01 |
| CYP2D6 inhibitors‡‡ | 49 (10.2) | 27 (12.7) | 0.08 | 0.01 |
| CYP2D6 inducers‡‡§§ | 1 (0.2) | 0 (0.0) | 0.06 | 0.07 |
| CYP1A2 inhibitors‡‡ | 20 (4.2) | 16 (7.6) | 0.14 | <0.01 |
| CYP1A2 inducers‡‡ | 88 (18.3) | 37 (17.5) | 0.02 | 0.09 |
| P-gp inhibitors‖‖ | 87 (18.1) | 39 (18.4) | 0.007 | 0.06 |
| P-gp inducers‖‖ | 4 (0.8) | 1 (0.5) | 0.04 | 0.02 |
|  |  |  |  |  |
| **Measure of frailty** |  |  |  |  |
| Claims-based frailty index, median (IQR)¶¶ | 0.173  (0.140 – 0.209) | 0.161  (0.136 – 0.198) | 0.17 | 0.01 |
| CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; IQR = interquartile range; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulant; P-gp = p-glycoprotein  \* Unless otherwise specified  † Average daily dose calculation: prescription quantity × capsule or tablet strength / prescription days’ supply  ‡ Bendamustine-rituximab dose was unavailable in Optum Clinformatics®  § Covariate was not forced into propensity score, but included as a categorical variable in outcome model  ‖ Variable contains group-level information based on census data  ¶ Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim  \*\* Antimicrobial medications were examined within 14 (rather than 90) days prior to index date as these agents are typically prescribed for acute conditions  †† Anticancer therapy was examined within 180 days prior to index date  ‡‡ Medications identified using the Drug Interactions Flockhart TableTM1  §§ Variable not included in propensity score due to low cell counts  ‖‖ Medications identified using UpToDate® list of P-gp inhibitors and inducers2  ¶¶ Claims-based frailty index3 categories: non-frail: <0.10; pre-frail: 0.10 – 0.19; mildly frail: 0.20 – 0.29; moderately frail: 0.30 – 0.39; severely frail: ≥0.40  1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.  2. Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter). UpToDate®. 2022.  3. Kim et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7. | | | | |

# **Supplementary Table 6. Baseline characteristics in the weighted population.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic, N (%)\*** | **Ibrutinib + OAC**  **N = 498** | **Bendamustine-Rituximab + OAC**  **N = 200** | **Absolute Standardized Difference** |
| Cancer type |  |  |  |
| CLL | 442 (88.8) | 109 (54.5) | 0.86 |
| MCL | 43 (8.6) | 56 (28.0) |  |
| MZL | 13 (2.6) | 35 (17.5) |  |
|  |  |  |  |
| **Demographics** |  |  |  |
| Cohort entry year† |  |  | 0.52 |
| 2013 | 8 (1.6) | 6 (3.0) |  |
| 2014 | 19 (3.8) | 29 (14.5) |  |
| 2015 | 51 (10.2) | 26 (13.0) |  |
| 2016 | 75 (15.1) | 21 (10.5) |  |
| 2017 | 72 (14.5) | 41 (20.5) |  |
| 2018 | 105 (21.1) | 38 (19.0) |  |
| 2019 | 138 (27.7) | 37 (18.5) |  |
| 2020 | 30 (6.0) | 2 (1.0) |  |
|  |  |  |  |
| Age in years, median (IQR) | 76 (69 – 83) | 75 (69 – 81) | 0.04 |
|  |  |  |  |
| Sex |  |  | 0.04 |
| Female | 162 (32.5) | 62 (31.0) |  |
| Male | 336 (67.5) | 138 (69.0) |  |
|  |  |  |  |
| Geographic region of residence |  |  | 0.08 |
| East North Central | 95 (19.1) | 38 (19.0) |  |
| East South Central | 11 (2.2) | 5 (2.5) |  |
| Middle Atlantic | 33 (6.6) | 13 (6.5) |  |
| Mountain | 75 (15.1) | 26 (13.0) |  |
| New England | 16 (3.2) | 6 (3.0) |  |
| Pacific | 55 (11.0) | 24 (12.0) |  |
| South Atlantic | 121 (24.3) | 53 (26.5) |  |
| West North Central | 30 (6.0) | 11 (5.5) |  |
| West South Central | 61 (12.3) | 23 (11.5) |  |
| Unknown | 1 (0.20) | 1 (0.5) |  |
|  |  |  |  |
| Race |  |  | 0.07 |
| Asian | 7 (1.4) | 3 (1.5) |  |
| Black | 36 (7.2) | 15 (7.5) |  |
| Hispanic | 33 (6.6) | 13 (6.5) |  |
| White | 369 (74.1) | 150 (75.0) |  |
| Unknown | 53 (10.7) | 19 (9.5) |  |
|  |  |  |  |
| Education level‡ |  |  | 0.04 |
| <12th Grade | 2 (0.4) | 0 (0.0) |  |
| High school diploma | 108 (21.7) | 44 (22.0) |  |
| <Bachelor degree | 263 (52.8) | 105 (52.5) |  |
| Bachelor degree+ | 81 (16.3) | 34 (17.0) |  |
| Unknown | 44 (8.8) | 17 (8.5) |  |
|  |  |  |  |
| Housing‡ |  |  | 0.05 |
| Probable homeowner | 370 (74.3) | 145 (72.5) |  |
| Probable renter | 18 (3.6) | 7 (3.5) |  |
| Unknown | 110 (22.1) | 48 (24.0) |  |
|  |  |  |  |
| Household income‡ |  |  | 0.17 |
| <$40K | 115 (23.1) | 48 (24.0) |  |
| $40K-$49K | 33 (6.6) | 10 (5.0) |  |
| $50K-$59K | 41 (8.2) | 17 (8.5) |  |
| $60K-$74K | 41 (8.2) | 24 (12.0) |  |
| $75K-$99K | 90 (18.1) | 32 (16.0) |  |
| $100K+ | 103 (20.7) | 42 (21.0) |  |
| Unknown | 75 (15.1) | 27 (13.5) |  |
|  |  |  |  |
| Total net worth of beneficiary‡ |  |  | 0.09 |
| <$25K | 74 (14.8) | 29 (14.5) |  |
| $25K-$149K | 82 (16.5) | 37 (18.5) |  |
| $150K-$249K | 45 (9.0) | 19 (9.5) |  |
| $250K-$499K | 69 (13.9) | 26 (13.0) |  |
| $500K+ | 153 (30.7) | 62 (31.0) |  |
| Unknown | 75 (15.1) | 27 (13.5) |  |
|  |  |  |  |
| **Cancer complications, present in baseline period** |  |  |  |
| Thrombocytopenia | 146 (29.3) | 57 (28.5) | 0.02 |
| Lymphadenopathy | 206 (41.4) | 82 (41.0) | 0.01 |
| Splenomegaly | 88 (17.7) | 34 (17.0) | 0.01 |
|  |  |  |  |
| **Medical conditions, present in baseline period** |  |  |  |
| Hypertension | 382 (76.7) | 154 (77.0) | <0.01 |
| Renal dysfunction | 180 (36.1) | 69 (34.5) | 0.04 |
| Liver dysfunction | 87 (17.5) | 37 (18.5) | 0.02 |
| Stroke | 50 (10.0) | 17 (8.5) | 0.06 |
| Peptic ulcer | 10 (2.0) | 6 (3.0) | 0.06 |
| Bleeding§ | 38 (7.6) | 11 (5.5) | 0.07 |
| Atrial fibrillation | 332 (66.7) | 137 (68.5) | 0.03 |
| Deep vein thrombosis | 78 (15.7) | 29 (14.5) | 0.03 |
| Pulmonary embolism | 70 (14.1) | 28 (14.0) | <0.01 |
|  |  |  |  |
| **Medications dispensed in the 90 days prior to index date**‖ |  |  |  |
| Antiplatelets | 22 (4.4) | 9 (4.5) | <0.01 |
| NSAIDs | 29 (5.8) | 10 (5.0) | 0.03 |
| Heparin | 101 (20.2) | 40 (20.0) | 0.01 |
| Anticancer therapy – targeted¶ | 14 (2.8) | 4 (2.0) | 0.04 |
| Anticancer therapy - chemotherapy¶ | 25 (5.0) | 7 (3.5) | 0.07 |
| CYP3A4 inhibitors\*\* | 71 (14.2) | 30 (15.0) | 0.02 |
| CYP3A4 inducers\*\* | 10 (2.0) | 4 (2.0) | 0.01 |
| CYP2D6 inhibitors\*\* | 50 (10.0) | 20 (10.0) | 0.01 |
| CYP2D6 inducers\*\*†† | 1 (0.2) | 0 (0.0) | 0.07 |
| CYP1A2 inhibitors\*\* | 28 (5.6) | 12 (6.0) | <0.01 |
| CYP1A2 inducers\*\* | 85 (17.1) | 41 (20.5) | 0.09 |
| P-gp inhibitors‡‡ | 98 (19.7) | 44 (22.0) | 0.06 |
| P-gp inducers‡‡ | 3 (0.6) | 1 (0.5) | 0.02 |
|  |  |  |  |
| **Measure of frailty** |  |  |  |
| Claims-based frailty index, median (IQR)§§ | 0.169 (0.136 – 0.205) | 0.169 (0.137 – 0.207) | 0.01 |
| CLL = chronic lymphocytic leukemia; CYP = cytochrome P450; IQR = interquartile range; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulant; P-gp = p-glycoprotein  \* Unless otherwise specified  Cancer type was formatted as a categorical variable with a category for each cancer  † Covariate was not forced into propensity score, but included as a categorical variable in outcome model  ‡ Variable contains group-level information based on census data  § Baseline bleeding was identified using the same diagnosis codes as the primary outcome definition, but permitted in any diagnosis position on the claim  ‖ Antimicrobial medications were examined within 14 (rather than 90) days prior to index date as these agents are typically prescribed for acute conditions  ¶ Anticancer therapy was examined within 180 days prior to index date  \*\* Medications identified using the Drug Interactions Flockhart TableTM1  †† Variable not included in propensity score due to low cell counts  ‡‡ Medications identified using UpToDate® list of P-gp inhibitors and inducers2  §§ Claims-based frailty index3 categories: non-frail: <0.10; pre-frail: 0.10 – 0.19; mildly frail: 0.20 – 0.29; moderately frail: 0.30 – 0.39; severely frail: ≥0.40  1. Flockhart DA, et al. The Flockhart Table™. Drug Interactions: Cytochrome P450 drug interaction table. Indiana University School of Medicine. 2020.  2. Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter). UpToDate®. 2022.  3. Kim et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-7. | | | |

**Supplementary Table 7. Characteristics of OAC use in ibrutinib + OAC-treated and bendamustine-rituximab + OAC-treated individuals.**

|  |  |  |
| --- | --- | --- |
| **Characteristic, N (%)** | **Ibrutinib + OAC**  **N = 480** | **Bendamustine-Rituximab + OAC**  **N = 212** |
| Initiation order at cohort entry |  |  |
| Cancer therapy-triggered | 215 (44.8) | 141 (66.5) |
| OAC-triggered | 265 (55.2) | 69 (32.6) |
| Synchronous-triggered | 0 (0.0) | 2 (0.9) |
|  |  |  |
| OAC type |  |  |
| DOAC | 350 (72.9) | 125 (59.0) |
| Warfarin | 130 (27.1) | 87 (41.0) |
|  |  |  |
| **DOAC Subgroup** | **Ibrutinib + OAC**  **N = 350** | **Bendamustine-Rituximab + OAC**  **N = 125** |
| DOAC agent |  |  |
| Rivaroxaban | 100 (28.6) | 53 (42.4) |
| Apixaban | 236 (67.4) | 63 (50.4) |
| Dabigatran | 14 (4.0) | 9 (7.2) |
| Edoxaban | 0 (0.0) | 0 (0.0) |
|  |  |  |
| DOAC dose intensity at cohort entry\* |  |  |
| Low | 81 (23.1) | 10 (8.0) |
| High | 269 (76.9) | 115 (92.0) |
| DOAC = direct oral anticoagulant; OAC = oral anticoagulant  \* See **Supplementary Table 3** for DOAC dose intensity categories | | |

**Supplementary Table 8. Crude incidence rates for major, clinically-relevant, and provider-diagnosed bleeding by individual OAC agent.**

|  |  |  |
| --- | --- | --- |
| **Measure of outcome occurrence\*** | **Crude Incidence Rate, per 100 person-years**  **(95% Confidence Interval)** | |
|  | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** |
| **Major bleeding** |  |  |
| Warfarin | 27.9 (13.2 – 58.7) | 0 (0 – 0) |
| Rivaroxaban | 15.4 (4.3 – 55.0) | 0 (0 – 0) |
| Apixaban | 5.2 (1.4 – 20.2) | 0 (0 – 0) |
| Dabigatran | 0 (0 – 0) | 0 (0 – 0) |
| **Clinically-relevant bleeding** |  |  |
| Warfarin | 39.3 (22.1 – 70.0) | 5.9 (0.9 – 39.6) |
| Rivaroxaban | 47.4 (26.5 – 84.7) | 22.3 (6.6 – 75.7) |
| Apixaban | 15.8 (7.6 – 32.9) | 0 (0 – 0) |
| Dabigatran | 0 (0 – 0) | 0 (0 – 0) |
| **Provider-diagnosed bleeding** |  |  |
| Warfarin | 154.2 (107.5 – 221.2) | 23.8 (10.1 – 56.0) |
| Rivaroxaban | 216.1 (152.7 – 305.7) | 67.3 (42.6 – 106.4) |
| Apixaban | 90.1 (80.8 – 100.5) | 32.6 (14.6 – 72.9) |
| Dabigatran | 11.7 (4.0 – 33.9) | 0 (0 – 0) |
| OAC = oral anticoagulant  \* No individuals in the cohort were co-exposed to edoxaban | | |

# **Supplementary Table 9. Site of bleed for major, clinically-relevant, and provider-diagnosed bleeding.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Major Bleeding** | | | **Clinically-relevant Bleeding** | | | **Provider-diagnosed Bleeding** | | |
| **Site of Bleed, N (%)** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** | **Total** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** | **Total** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** | **Total** |
| Cerebral | 3 (33.3) | 0 (0.0) | 3 (33.3) | 4 (21.1) | 0 (0.0) | 4 (18.2) | 4 (4.7) | 0 (0.0) | 4 (4.1) |
| Gastrointestinal | 3 (33.4) | 0 (0.0) | 3 (33.4) | 6 (31.5) | 1 (33.3) | 7 (31.8) | 18 (21.2) | 4 (28.6) | 22 (22.2) |
| Genitourinary | 1 (11.1) | 0 (0.0) | 1 (11.1) | 4 (21.1) | 2 (66.7) | 6 (27.3) | 27 (31.8) | 8 (57.1) | 35 (35.3) |
| Other\* | 1 (11.1) | 0 (0.0) | 1 (11.1) | 3 (15.8) | 0 (0.0) | 3 (13.6) | 22 (25.8) | 0 (0.0) | 22 (22.2) |
| Unspecified\* | 1 (11.1) | 0 (0.0) | 1 (11.1) | 2 (10.5) | 0 (0.0) | 2 (9.1) | 14 (16.5) | 2 (14.3) | 16 (16.2) |
| Total | 9 (100.0) | 0 (0.0) | 9 (100.0) | 19 (100.0) | 3 (100.0) | 22 (100.0) | 85 (100.0) | 14 (100.0) | 99 (100.0) |
| OAC = oral anticoagulant  \* See **Supplementary Table 2** for bleed types in Other and Unspecified sites of bleed | | | | | | | | | |

**Supplementary Table 10. Site of bleed by individual OAC agent for major, clinically-relevant, and provider-diagnosed bleeding.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Major Bleeding** | | | **Clinically-relevant Bleeding** | | | **Provider-diagnosed Bleeding** | | |
| **Site of Bleed, N (%)\*** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** | **Total** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** | **Total** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** | **Total** |
| **Warfarin** |  |  |  |  |  |  |  |  |  |
| Cerebral | 2 (40.0) | 0 (0.0) | 2 (40.0) | 2 (28.6) | 0 (0.0) | 2 (25.0) | 2 (8.0) | 0 (0.0) | 2 (6.9) |
| Gastrointestinal | 1 (20.0) | 0 (0.0) | 1 (20.0) | 2 (28.6) | 0 (0.0) | 2 (25.0) | 5 (20.0) | 0 (0.0) | 5 (17.2) |
| Genitourinary | 1 (20.0) | 0 (0.0) | 1 (20.0) | 2 (28.6) | 1 (100.0) | 3 (37.5) | 6 (24.0) | 3 (75.0) | 9 (31.1) |
| Other† | 1 (20.0) | 0 (0.0) | 1 (20.0) | 1 (14.2) | 0 (0.0) | 1 (12.5) | 8 (32.0) | 0 (0.0) | 8 (27.6) |
| Unspecified† | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (16.0) | 1 (25.0) | 5 (17.2) |
| Total | 5 (100.0) | 0 (0.0) | 5 (100.0) | 7 (100.0) | 1 (100.0) | 8 (100.0) | 25 (100.0) | 4 (100.0) | 29 (100.0) |
| **Rivaroxaban** |  |  |  |  |  |  |  |  |  |
| Cerebral | 1 (50.0) | 0 (0.0) | 1 (50.0) | 1 (16.7) | 0 (0.0) | 1 (12.5) | 1 (4.0) | 0 (0.0) | 1 (3.2) |
| Gastrointestinal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (12.5) | 3 (12.0) | 4 (66.6) | 7 (22.6) |
| Genitourinary | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (33.3) | 1 (50.0) | 3 (37.5) | 10 (40.0) | 1 (16.7) | 11 (35.5) |
| Other† | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) | 0 (0.0) | 1 (12.5) | 5 (20.0) | 0 (0.0) | 5 (16.1) |
| Unspecified† | 1 (50.0) | 0 (0.0) | 1 (50.0) | 2 (33.3) | 0 (0.0) | 2 (25.0) | 6 (24.0) | 1 (16.7) | 7 (22.6) |
| Total | 2 (100.0) | 0 (0.0) | 2 (100.0) | 6 (100.0) | 2 (100.0) | 8 (100.0) | 25 (100.0) | 6 (100.0) | 31 (100.0) |
| **Apixaban** |  |  |  |  |  |  |  |  |  |
| Cerebral | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) | 0 (0.0) | 1 (16.7) | 1 (3.1) | 0 (0.0) | 1 (2.8) |
| Gastrointestinal | 2 (100.0) | 0 (0.0) | 2 (100.0) | 4 (66.6) | 0 (0.0) | 4 (66.6) | 10 (31.2) | 0 (0.0) | 10 (27.8) |
| Genitourinary | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 10 (31.2) | 4 (100.0) | 14 (38.9) |
| Other† | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) | 0 (0.0) | 1 (16.7) | 9 (28.2) | 0 (0.0) | 9 (25.0) |
| Unspecified† | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.3) | 0 (0.0) | 2 (5.5) |
| Total | 2 (100.0) | 0 (0.0) | 2 (100.0) | 6 (100.0) | 0 (0.0) | 6 (100.0) | 32 (100.0) | 4 (100.0) | 36 (100.0) |
| **Dabigatran** |  |  |  |  |  |  |  |  |  |
| Cerebral | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Gastrointestinal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Genitourinary | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) |
| Other† | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Unspecified† | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 2 (66.7) |
| Total | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (100.0) | 0 (100.0) | 3 (100.0) |
| OAC = oral anticoagulant  \* No individuals in the cohort were co-exposed to edoxaban  † See **Supplementary Table 2** for bleed types in Other and Unspecified sites of bleed | | | | | | | | | |

**Supplementary Table 11. Bleed types for provider-diagnosed bleeds of other and unspecified bleed sites.**

|  |  |  |
| --- | --- | --- |
| **Bleed type\*, N (%)** | **Ibrutinib + OAC** | **Bendamustine-Rituximab + OAC** |
| **Other** |  |  |
| Epistaxis | 10 (45.5) | 0 (0.0) |
| Hemarthrosis | 2 (9.0) | 0 (0.0) |
| Hemoptysis | 10 (45.5) | 0 (0.0) |
| Total | 22 (100.0) | 0 (0.0) |
| **Unspecified** |  |  |
| Acute posthemorrhagic anemia | 6 (42.9) | 2 (100.0) |
| Hemorrhage, not elsewhere classified | 8 (57.1) | 0 (0.0) |
| Total | 14 (100.0) | 2 (100.0) |
| CM = clinical modification; ICD = International Classification of Diseases; OAC = oral anticoagulant  \* Bleed type based on ICD-10-CM diagnosis code descriptions | | |

# **Supplementary Table 12. Results from sensitivity analyses.**

|  |  |  |
| --- | --- | --- |
|  | **Number of Provider-diagnosed Bleeding Events** | **Hazard Ratio (95% Confidence Interval)\*** |
| Depleting days’ supply of ibrutinib dispensings during hospitalizations | 99 | 2.75 (1.28 – 5.94) |
| Increasing permissible therapy gap of ibrutinib dispensings from 7 to 14 days | 104 | 2.63 (1.22 – 5.67) |
| Decreasing permissible therapy gap between bendamustine administrations from 56 to 42 days | 97 | 2.79 (1.26 – 6.20) |
| Increasing permissible therapy gap between OAC dispensings from 7 to 14 days | 107 | 2.82 (1.39 – 5.69) |
| Adjusting for cancer type (CLL, MCL, or MZL) in the Cox proportional hazards regression outcome model | 99 | 2.92 (1.39 – 6.15) |
| Competing risk analysis with disenrollment as competing event | 99 | 2.70 (1.25 – 5.82) |
| Excluding individuals with bleeding during the baseline period | 83 | 2.28 (1.03 – 5.03) |
| CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; OAC = oral anticoagulant  \* Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year and household income | | |

# **Supplementary Table 13. Results from effect modification analyses.**

|  |  |  |
| --- | --- | --- |
|  | **P-value** | **Hazard Ratio (95% Confidence Interval)** |
| CYP3A4 inhibitors | 0.55 | Not displayed because p-value is not significant |
| CYP3A4 inducers | <0.01 | Not displayed because of unstable hazard ratio estimate\* |
| CYP2D6 inhibitors | 0.11 | Not displayed because p-value is not significant |
| CYP2D6 inducers | - | Not displayed because interaction term could not be included in model† |
| CYP1A2 inhibitors | 0.82 | Not displayed because p-value is not significant |
| CYP1A2 inducers | 0.23 |
| P-gp inhibitors | 0.31 |
| P-gp inducers | 0.58 |
| Exposure initiation order at cohort entry | 0.60 |
| CYP = cytochrome P450; P-gp = p-glycoprotein  \* There was only 1 outcome among the 14 individuals who had CYP3A4 inducer use during the baseline period, thus the hazard ratio estimate was unstable  † There was only 1 individual in the cohort who had CYP2D6 inhibitor use during the baseline period, thus the interaction term could not be included | | |

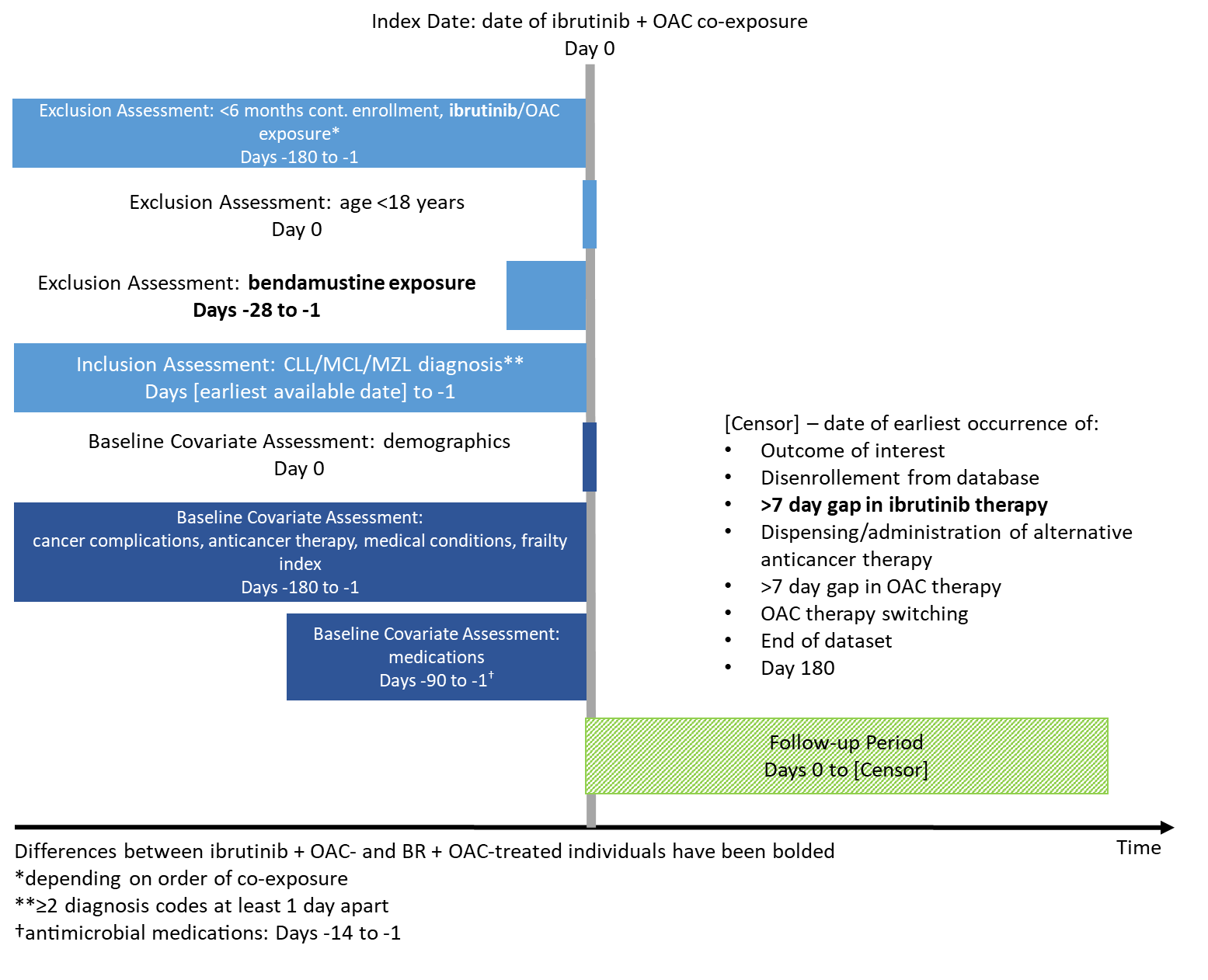
**Supplementary Figure 1. Incident co-exposure definition for individuals with A) cancer therapy-triggered, B) OAC therapy-triggered, and C) synchronous-triggered cohort entry.** For A) and C), the 6 months preceding the index date needed to be devoid of ibrutinib dispensing for ibrutinib + OAC-treated individuals and bendamustine for BR + OAC-treated individuals. BR = bendamustine-rituximab; OAC = oral anticoagulant.

Graphical user interface, website

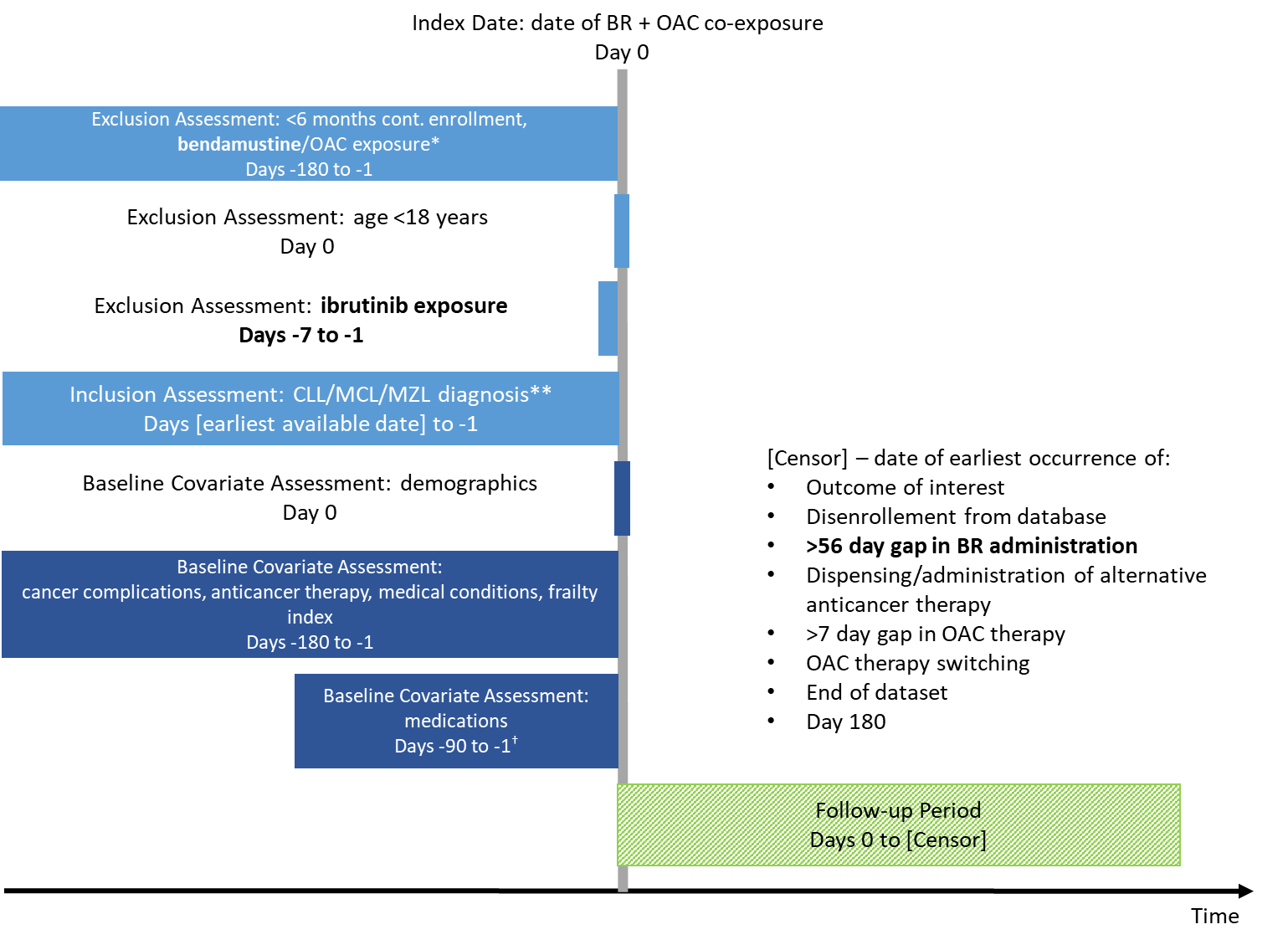
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# **Supplementary Figure 2. Study design depiction for A) ibrutinib + OAC-treated individuals and B) bendamustine-rituximab + OAC-treated individuals.**

**A)**



**B)**



# **Supplementary Figure 3. Study cohort flowchart.**



# **Supplementary Figure 4. Propensity score distribution in unweighted population.**

Chart, bar chart

Description automatically generated

**Supplementary Figure 5.** **Kaplan-Meier curve for provider-diagnosed bleeding in the weighted population based on stabilized inverse probability of treatment weighting.** The number of individuals remaining in the risk set at each time point is displayed below the graph legend. BR = bendamustine-rituximab; OAC = oral anticoagulant.

Chart, line chart

Description automatically generated

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