Cardiovascular Toxicities Associated With Ibrutinib

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Cardiovascular toxicities and Cardiovascular Fatalities Associated with Ibrutinib

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Abstract.

Background: Ibrutinib has revolutionized treatment for several B-cell malignancies. However, a recent clinical trial where ibrutinib was used in front-line setting showed increased mortality during treatment compared to conventional chemotherapy. Cardiovascular toxicities were suspected as the culprit but not directed assessed in the study.

Objective: We aimed to identify and characterize cardiovascular adverse drug reactions (CV-ADR) associated with ibrutinib.

Methods: We utilized VigiBase (International pharmacovigilance database) and performed a disproportionality analysis using reporting odds-ratios (ROR) and information component (IC) to determine whether CV-ADR and CV-ADR deaths were associated with ibrutinib. IC compares observed and expected values to find associations between drugs and ADR using disproportionate Bayesian-reporting; IC_{025} (lower end of the IC 95% credibility interval)> 0 is significant.

Results: We identified 303 ibrutinib-associated cardiovascular deaths. Ibrutinib was associated with higher reporting of Supraventricular Arrhythmias (SVA, ROR:23.1 [21.6-24.7],p<0.0001; IC_{025}:3.97), central nervous system (CNS) hemorrhagic events (ROR:3.7[3.4-4.1],p<0.0001; IC_{025}:1.63), heart failure (HF, ROR:3.5[3.1-3.8],p<0.0001; IC_{025}:1.46), ventricular arrhythmias (VA, ROR:4.7[3.7-5.9],p<0.0001; IC_{025}:0.96), conduction disorders (CD, ROR:3.5[2.7-4.6],p<0.0001; IC_{025}:0.76), CNS ischemic events (ROR:2.2[2.0-2.5],p<0.0001; IC_{025}:0.73) and hypertension (ROR:1.7[1.5-1.9],p<0.0001; IC_{025}:0.4). CV-ADR often occurred early after ibrutinib administration. Importantly, CV-ADR were associated with fatalities, that ranged from ~10% (SVA and VA) to ~20% (CNS events, HF and CD). Ibrutinib-associated SVA portends poor prognosis when CNS events occur concomitantly with 28.8% deaths (15/52 cases).

Conclusion: Severe and occasionally fatal cardiac events occur in patients exposed to ibrutinib. These events should be considered in patient care and in clinical trial designs.

Condensed abstract.

Ibrutinib has revolutionized treatment for several B-cell malignancies but induced cardiovascular adverse drug reactions (CV-ADR) represent a clinical challenge. We utilized VigiBase and performed a Bayesian-reporting disproportionality analysis using information component (IC) to find associations between drugs and ADR; IC_{025} ($IC_{95\%}$ credibility interval lower end)> 0 is significant. Ibrutinib was associated with higher reporting of supraventricular arrhythmias (IC_{025}:3.97), central nervous system (CNS) hemorrhagic events (IC_{025}:1.63), heart failure (IC_{025}:1.46), ventricular arrhythmias (IC_{025}:0.96), conduction disorders (IC_{025}:0.76), CNS ischemic events (IC_{025}:0.73) and hypertension (IC_{025}:0.4). CV-ADR often occurred early after ibrutinib administration. CV-ADR were associated with fatalities that ranged up to ~30%.

Abbreviations:

BTK : Bruton tyrosine kinase

CD: conduction disorders

CNS: central nervous system

CV-ADR: cardiovascular adverse drug reactions

HF: heart failure

$IC_{(025)}$: information component (and its 95% credibility interval lower end)

ICSRs : individual case safety reports

ROR: reporting odds-ratios

SVA: supraventricular arrhythmias

VA: ventricular arrhythmias

Introduction.

Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, is an effective treatment for hematological malignancies including chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, mantle cell lymphoma, marginal zone lymphoma, and chronic graft versus host disease.(1-8) However, early data suggested ibrutinib was associated with atrial fibrillation and bleeding.(1-9) More recently, reports of supra-ventricular arrhythmias (SVA) and life threatening ventricular arrhythmias (VA) associated with ibrutinib have emerged.(10,11) As ibrutinib is being tested in a front line setting, it is important to assess its overall adverse risks on the CV system. A recent randomized trial with two ibrutinib-containing arms in the front-line setting reported death rates of 7% in each ibrutinib arm, compared to 1% in the control arm, with many of these deaths “unexplained/unwitnessed death” or cardiac in nature.(12) Whether ibrutinib is associated with other cardiovascular adverse drug reactions (CV-ADR) and the extent of cardiovascular toxicities in a “real world” population is also unclear, as are the characteristics, timing, and outcomes of ibrutinib-associated CV-ADR. Defining these ibrutinib-associated toxicities is critical, especially since ibrutinib is increasingly used in front-line setting and combined with other agents. Here, we used VigiBase, the World Health Organization’s (WHO) global database of individual case safety reports (ICSRs) to further characterize these CV-ADR.(13)

Material and Methods.

Study design and data sources

The study is a disproportionality analysis based on adverse drug reactions (ADR) reported within VigiBase, the WHO global deduplicated database of individual case safety reports (ICSRs), originating from more than 130 countries.[14] VigiBase is managed by UMC (Uppsula Monitoring Center) and contains more than 16 million ICSRs of suspected medication ADR (as of January 2018) submitted by national pharmacovigilance centers since 1967. These reports originate from different sources such as physicians or other healthcare professionals, pharmaceutical companies, and patients, and generally occur post-marketing. The use of confidential electronically processed patient data was approved by the Vanderbilt University Medical Center institutional review board (#181337).

Procedures

This observational retrospective study included all CV-ADR classified by group queries according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) (Supplementary Table-1), between inception in November 14, 1967 and January 02, 2018. CV-ADR specifically considered in the analysis were suspected to be induced by ibrutinib. Each report contains general administrative information (reporter qualification, date of reporting, country of origin), patient characteristics (age, sex), drugs (indication for the drug, dosage regimen, start and end dates, route of administration), reactions/events (reported terms, MedDRA classification terms, onset date, end date, seriousness, final outcome).

Statistical analysis

VigiBase allows for case/non-case analysis (disproportionality analysis), which we utilized to study if suspected drug-induced CV events were differentially reported with ibrutinib compared to CV events reported in the entire database. Disproportionality analysis compares the proportion of selected specific ADR reported for a single or a group of drugs (e.g., ibrutinib) with the proportion of the same ADR for a control group of drugs (e.g., entire database). The denominator in these analyses is the overall ADR reported for each group of drugs. If the proportion of an ADR is greater in patients exposed to a group of drug (cases) than in patients not exposed to this drug (non-cases), this suggests an association between the specific drug and the reaction and is a potential signal for safety. Disproportionality can be either calculated by the information component (IC) or reporting odds-ratio (ROR) when using entire database as comparator.

Calculation of the IC (details in Appendix 1), using a Bayesian confidence propagation neural network, was specifically developed and validated by UMC as an automated, flexible indicator value for disproportionate reporting that compares expected and observed drug-ADR associations to find new drug-ADR signals with identification of probability difference from the background data (entire database since inception).(13,15,16) IC_{025} is the lower end of a 95% credibility interval for the Information Component. A positive IC_{025} value (>0) is the traditional threshold used in statistical signal detection at UMC.[16,17] As compared to Bayesian statistics, disproportionality in VigiBase can also be assessed using a more classical frequentist approach by calculating the ROR Chi^2, described and used elsewhere (Supplemental Table-2).[13,18-21] The lower end of ROR 95% confidence interval (CI)≥1 is the threshold deemed significant. ROR was calculated taking as comparator the entire database since 2013 to provide a contemporary control group for ibrutinib (first ICSR in VigiBase in 2013, the year of its first FDA approval).(6)

Characteristics of cases were described in terms of means (± standard-deviation) or medians (with interquartile range) for quantitative variables, and in terms of effective and proportion for qualitative ones. Comparison of qualitative and quantitative variables (non-normally distributed) were performed by

Chi^2-test and Kruskal-Wallis with Dunn's post-tests, respectively (Graphpad Prism-7). P-value <0.05 was deemed significant.

Results.

CV-ADR signal detected using WHO's global database of ICSRs

Given the considerable overlap of symptoms for various CV disease etiologies as well as redundancies in reporting cardiac complications associated with oncologic therapies, we broadly categorized cardio-vascular disease entities in the MedDRA Classification (Version 20.1) based on underlying pathophysiology (Supplemental Table-1). The total ADR (rate) in the ibrutinib subgroup (n: 13,572) versus the entire database (n:16,343,451 since inception; n:8,318,890 since 2013 – date of the first ICSR with ibrutinib) was compared. Details concerning number of CV-ADR by CV grouping categories are available in Table 1.

Using this approach, we identified seven broad CV entities where CV reporting was significantly increased in ibrutinib as compared to the entire database. Ibrutinib was associated with higher reporting of supraventricular arrhythmias (SVA; ROR:23.1[21.6-24.7],p<0.0001; IC_{025}:3.97), central nervous system (CNS) hemorrhagic events (ROR:3.7[3.4-4.1],p<0.0001; IC_{025}:1.63), heart failure (HF; ROR:3.5[3.1-3.8],p<0.0001; IC_{025}:1.46), ventricular arrhythmias (VA; ROR:4.7[3.7-5.9],p<0.0001; IC_{025}:0.96), conduction disorders (CD; ROR:3.5[2.7-4.6],p<0.0001; IC_{025}:0.76), CNS ischemic events (ROR:2.2[2.0-2.5],p<0.0001; IC_{025}:0.73) and hypertension (ROR:1.7[1.5-1.9],p<0.0001; IC_{025}:0.4). IC values and their 95% credibility interval over time are in Figure 1. Other cardiovascular disease conditions, including cardiac ischemia, myocarditis, venous thromboembolic events, QT prolongation and valvular disorders were not over-reported in this population (Table 1).

Characteristics of patients

Given that ibrutinib-associated CV toxicities are novel clinical entities and represent new challenges for the clinician, we extracted additional data to better characterize clinical features of ibrutinib-associated CV-ADR in 2093 patients. A total of 90.6% (1896/2093) were reported from "real-world" settings compared to 9.4% (197/2093) from clinical trials. CV-ADR included SVA (n:959; of which 900/959, 93.8% were atrial fibrillation, Supplemental Table 3), CNS hemorrhagic events (n:505; of which 275/505, 54.5% were intra-cerebral hemorrhage and 156/505, 30.9% were extra-cerebral hemorrhage,

Supplemental Table 4), HF (n:363; Supplemental Table 5), hypertension (n:295; Supplemental Table 6), CNS ischemic events (n:254; Supplemental Table 7), VA (n:70; of which 31/70, 44.3% were ventricular tachycardia and 20/70, 28.6% were ventricular fibrillation, Supplemental Table 8), and CD (n:50; of which 33/50, 64% were atrioventricular block and 14/50, 28.0% were bundle branch block, Supplemental Table 9). Overlap among these conditions is shown in Figure 2 and Supplemental Table 3. Main clinical and demographical characteristics, concurrent conditions, concomitant drugs (including anti-arrhythmics) and CV-ADR diagnosis details (i.e., type of SVA, VA, CNS events or CD) are displayed in Table 2 and Supplemental Tables 4-9. Diagnosis of each was reported worldwide with an increasing rate over time with most of the cases reported in 2017. CV-ADR affected mostly men (58-73%), with a wide age range (8-97 years), but generally older than 70 years. All cancer types where ibrutinib have been utilized were affected, with chronic lymphocytic leukemia (60-76%), lymphomas (20-24%) and Waldenstrom's macroglobulinemia (4-15%) being the most common (Table 2). The indication of ibrutinib for Waldenstrom's macroglobulinemia was more frequent among VA cases vs. SVA cases (9/62, 14.5% vs. 53/867, 6.2%; p:0.01).

Timing

CV-ADR occurred early after ibrutinib administration (Figure 3), as soon as after the first dose, with a shorter median time to onset of 27.5days (IQR:1-138.5days) for CD ($p<0.01$, Kruskal-Wallis), as compared to CNS ischemic events (51days; IQR:17.5-160days, p:0.05 vs. CD), CNS hemorrhagic events (53.5days; IQR:20.3-183.3days, p:0.03 vs. CD), HF (54days; IQR:20.3-142.8days, p:0.05 vs. CD), VA (70days; IQR: 28.5-152.5days, p:0.03 vs. CD), SVA (74days; (IQR:29.5-196.5days, p:0.0004 vs. CD) and hypertension (164days; IQR:20-274days, p:0.04 vs. CD).

Outcomes

CV-ADR were almost always considered severe (77-98%) and were associated with fatalities ranging from ~10% (SVA and VA) to ~20% (CNS events, HF and CD) with the exception of ibrutinib associated hypertension being non-fatal (Table 2). SVA were associated with HF in 11.9% of SVA cases (114/959), with CNS ischemic events in 4.2% (40/959) and with CNS hemorrhagic events in 3.4% (33/959). There

were more deaths when SVA cases were associated with CNS hemorrhagic and/or ischemic events compared to their absence (15/52, 28.8% vs. 88/907, 9.7%, $p<0.0001$, respectively). HF cases were frequently associated with concurrent contributing conditions (Figure 2), such as SVA (114/363, 31.4%) and more rarely hypertension (18/363, 5%). CD were often associated with SVA (11/50, 22%).

Discussion.

We report the largest and most extensive clinical characterization of CV-ADR associated with ibrutinib through analysis of individualized reportable events from the WHO pharmacovigilance database. The results show significant incidence of SVA, VA, CD, HF, hypertension, CNS ischemic and hemorrhagic events with ibrutinib, with numbers high enough to suggest that some of these CV-ADR may be underrepresented in the published literature. SVA, VA, hemorrhage and hypertension induced by ibrutinib have already been demonstrated and are listed in US Food and Drug Administration label and represent positive control for our analysis strategy;(6) however, our findings of association with HF and CD (mainly high grade atrioventricular block) are new findings. Importantly, a number of other CV-ADR including cardiac ischemia and QT prolongation were not over-reported with ibrutinib, which is consistent with the anti-platelet effects of ibrutinib and studies showing no QT prolonging effects of ibrutinib.(22-25) The lack of association with these and other CV-ADR serve as negative controls for our analysis. Moreover, our study describes the differential spectrum of time to onset with each CV-ADR. In our study, the median time from initiation of treatment with ibrutinib to onset for SVA was ~2-3 months and for hypertension was ~4-5 months. On the other hand, CD occurred mainly within the first month of ibrutinib start, contrasting with CNS events, HF and VA occurring around ~2-3 months (Figure 3).(26)

The association of SVA (and specifically atrial fibrillation) with ibrutinib was identified early in human studies with ibrutinib and emerged in our analysis as the first CV-ADR significantly over-reported in VigiBase since 2014 (the year after U.S approval, Figure 1).(1-6,9) This signal is consistent with meta-analyses of clinical trials where atrial fibrillation was significantly more commonly observed in ibrutinib-treated arms (4-16%) compared to control arms leading to increased vigilance by clinicians and regulatory authorities.(1-6,27) In these studies, risk factors for developing SVA on ibrutinib included older age, male sex, a history of SVA, hypertension and pre-existing cardiac diseases.(7,28) Our study reports the data on almost 1000 cases of SVA suspected to be induced by ibrutinib with most of these occurring in the “real world” population, which is by far the largest case-series reported to date (<100

cases by other groups, mostly from clinical trials).(7,9,27-29) We show that SVA cases occurred mainly in men, in patients > 70 years old and frequently associated with other CV complications, including HF (11.9%) and CNS events (5.4%). Patients with ibrutinib-associated SVA were mainly taking beta-blockers (24%) and less often other types of anti-arrhythmics (≤6%, Table 1), which is consistent with current proposed management by experts favoring lenient rate control (rather than rhythm control) with drugs at lower risk of interaction with ibrutinib metabolism (i.e. beta-blockers favored over amiodarone, digoxin, verapamil and diltiazem).(27,30) Due to the frequent need for co-prescriptions of drugs for rate control, anticoagulant stroke prophylaxis and bleeding risk complicated by multiple drug interactions (Ibrutinib being a cytochrome 3A4 substrate and a P-glycoprotein inhibitor), there is a clear and pressing need to improve management of these patients, requiring a better understanding of pathophysiology of SVA induced by ibrutinib.(27) Current data are emerging and suggest that a drug-induced blockade of phosphoinositide 3-kinase-protein kinase B (PI3K–AKT) pathway, leading to activation of the late sodium current ($I_{Na\text{-}L}$) in atrial cells may play a role.(27,31-33) For patients with thromboembolic risks outwaiting hemorrhagic risks, possible choices for long-term anticoagulation include vitamin K antagonists, heparins and factor Xa inhibitors based on individual patient profile and preference, as recently summarized.(27,34)

Our report identified CD as a new complication with ibrutinib, which carries a high mortality, 18% (9/50) cases of atrioventricular block in VigiBase. Only a single case-report was found by a PubMed/Embase literature review, in contrast with the 50 ICSRs documented in VigiBase.(35) Ibrutinib prolongs PR in a concentration-dependent manner (<5msec at therapeutic concentration) in healthy volunteers, in patients with B-cell malignancies, and in dogs.(36) Ibrutinib-associated CD occurred early after initiation of ibrutinib and prior to other CV-ADRs. CD were often associated with SVA, suggesting a possible interplay between CD and SVA on ibrutinib, consistent with other data where PR prolongation is associated with increased risk of atrial fibrillation.(37-39)

VA on ibrutinib (and not long QT) have been increasingly recognized as an emerging concern.(6,10,11,40) Our pharmacovigilance query has captured this increasing trend for VA reporting

over time in VigiBase (Figure 1). This is unlikely mediated by QT prolongation, given that ibrutinib has been shown to reduce QT duration (corrected for heart rate) in multiple settings including preclinical data in dogs, in clinical trials and in a thorough-QT study in healthy volunteers.(36) Notably, an extreme shortening of QTc can be a risk factor for VA and SVA.(36,41) Interestingly, three independent groups published several case reports of polymorphic ventricular tachycardia induced by ibrutinib with normal QTc interval, and no short-long-short coupling pattern before the VA.(11,42,43) This ECG description corresponds to the rare short-coupled variant of polymorphic ventricular tachycardia.(44) This peculiar form of VA has a specific pathophysiology thought to involve alteration in cardiac sarcoplasmic reticulum Ca^{2+} homeostasis associated with cardiac ryanodine receptor (RyR2)-Calmodulin-dependent protein kinase (CaMKII) pathways.(45) CaMKII-RyR2 and PI3K-AKT signaling cascades have been shown to crosstalk,(46) and cardiac PI3K-AKT signaling is inhibited by ibrutinib leading to increased $I_{Na\text{-}L}$, a trigger of VA.(32,33) The exact mechanism of this observed association between ibrutinib and VA needs further investigation. Specifically, prospective studies of patients on ibrutinib with detailed electrophysiological studies may elucidate new mechanisms involved in VA in general. Clinical risk factors for developing VA on ibrutinib appear to be a history of SVA and male sex from one small retrospective study.(10) Notably, our study reveals a significant overlap between SVA and VA reports among VA cases (~30%) with most cases occurring in male patients (~75%, Table 2). Men are associated with shorter QTc than women(47-49) and this may contribute to sex dimorphism in ibrutinib induced VA.

An association between HF and ibrutinib has been described in case reports.(50,51) However, our study reports 363 cases of ibrutinib-associated AF. Even though SVA, HTN and VA are risk factors for HF, most cases (66%) occurred without these concurrent conditions, suggesting a possible direct role for ibrutinib. This might be explained by the multiple off-target kinases blocked by ibrutinib at clinically relevant concentrations, including HER2 (Erb-B2 receptor tyrosine kinase 2) and/or PI3K-AKT pathways, which are critical for cardiac myocyte homeostasis and may lead to HF.(31,32,52-54)

CNS hemorrhagic events signal over reporting is concordant with ibrutinib's inhibition of platelet function resulting in hemorrhagic risk in a subset of patients. As with other CV-ADR signals, it remains

to be seen whether this is due to on-target inhibition of BTK or off target effects (from effects on other kinase targets). Antiplatelet effects of ibrutinib are thought to be mediated by targeting platelets' von Willebrand factor-glycoprotein (GP)Ib and collagen-GPVI signals transduction.(22-24,55) This phenomenon is more frequently observed early on ibrutinib therapy start and it appeared to decrease beyond 6 months,(22) compatible with the observation we have seen in VigiBase that most CNS hemorrhagic events were observed within 3 months of ibrutinib initiation (Table 2). In published clinical trials, subdural (extra-cerebral) hematoma was the most commonly reported form of CNS bleeding and occurred in 1-2% of ibrutinib treated patients, and, although hemorrhagic conversion of ischemic stroke, subarachnoid hemorrhage after a fall and vitreous hemorrhage have also been reported.(6,24) Interestingly, in our series, we identified that most CNS hemorrhage reported were intra-cranial, in contrast with clinical trial findings. Overlap between ischemic stroke and hemorrhage was modest (≤5%) in VigiBase. Considering the expected antiplatelet effects of ibrutinib and its propensity to induce SVA, the CNS ischemic over-reporting signal might be more driven by embolic events secondary to thromboembolism rather than by atherothrombosis.(27) In the current series, ~20% of stroke had a coreported SVA event but data concerning differential temporality of onset were rarely available in the same case.

While the incidence of ibrutinib-associated CV-ADR events cannot be determined using VigiBase, the following data have been published previously.(1-6) U.S FDA labels and meta-analyses issued from randomized clinical trials evaluation of ibrutinib efficacy estimate rate of any grade SVA ~5-6% after 18 months on therapy and up to 16% with longer follow-up (3-12% grade 3-4 CTCAE, Common Terminology Criteria for Adverse Events). Any grade hypertension occurred ~11-29% (4-13% grade 3-4) and VA occurred ~0.2% for grade≥3, depending on hematological indications and total duration of ibrutinib exposure.(1-6) Other CV-ADR identified in this work have been sporadically reported and thus the incidence is essentially unknown.

Limitations.

Several limitations need to be recognized for VigiBase analysis. Some cases of suspected drug-induced CV-ADR are likely not reported to the national drug authorities, and therefore not submitted to VigiBase. However, a major strength is that VigiBase aggregates ICSRs collected from over 130 countries, which enables better identification of rare ADR and broader generalization of our findings. Importantly, another limitation of VigiBase is that sources of reports are non-homogeneous, and there is limited possibility of verification of the clinical, laboratory tests or radiological findings justifying the reported diagnosis, nor completeness of reporting for age, drug dosing, time to onset, comorbid conditions and concomitant drugs. The exact denominator of patients exposed to ibrutinib cannot be evaluated. Instead, the total number of ICSRs for each drug is used as a denominator for this kind of disproportionality analysis in pharmacovigilance databases for signal detection.(18,19) The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors such as competition bias. The value of disproportionality reporting (as the ROR) for several CV-ADR and culprit anticancer or endocrine drugs has already been demonstrated in various settings;(13,20,21,48) nevertheless, there is still a risk that comparisons of disproportionality between medicinal products in pharmacovigilance databases may be misleading. Hypothesis generated require validation by prospective studies.

Clinical trials are mandatory to establish efficacy but may not allow definitive conclusions on drug safety in part due to selected populations and limited power to detect imbalances in rare ADR. However, clinical trials in oncology, often do not reflect “real world” population which often have a higher prevalence of CV diseases and risk factors.(56) Spontaneous notifications remain the cornerstone for ADR evaluation despite their limitations. Disproportionality analysis in pharmacovigilance databases is an important method to detect signals in drug safety research and post-marketing surveillance. Herein, we used this analysis to identify several new cardiovascular complications with ibrutinib.

Conclusions.

Severe and occasionally fatal cardiac events related to cardiac SVA, VA, CD, HF, hypertension, CNS hemorrhagic and ischemic events occur in patients exposed to ibrutinib. These events should be considered in patient care and in clinical trial designs.

Clinical Perspectives.

- Ibrutinib has revolutionized treatment for several B-cell malignancies. However, a recent clinical trial where ibrutinib was used in front-line setting showed increased mortality during treatment compared to conventional chemotherapy. Cardiovascular toxicities were suspected as the culprit but not directly assessed in the study.
- We identified using the international pharmacovigilance database that severe and occasionally fatal cardiac events related to cardiac supraventricular and ventricular arrhythmias, conduction disorders, heart failure, hypertension, central nervous system hemorrhagic and ischemic events occur in patients exposed to ibrutinib. These events should be considered in patient care and in clinical trial designs.

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Figure Legends

Figure 1 – Central Illustration- Information component (IC) and its 95% credibility interval over time for supraventricular arrhythmias (SVA), ventricular arrhythmias (VA), conduction disorders (CD), heart failure (HF), hypertension, and central nervous system (CNS) hemorrhagic and ischemic events. The error bars show the 95% credibility interval of the information component (IC_{025}–IC_{075}). An IC_{025} value of more than zero is deemed significant (dotted line). Data are shown for 1st and 3rd trimester of each year (year-1; year-3).

Figure 2 - Overlap of cardiovascular adverse drug reactions CV-ADR associated with Ibrutinib in VigiBase. Panel A displays overlap between supraventricular arrhythmias (SVA), ventricular arrhythmias (VA), conduction disorders (CD), heart failure (HF) and hypertension (HTN). Panel B displays overlap between SVA, HTN and central nervous system (CNS) ischemic and hemorrhagic events. *Panel A*: Due to diagram limitation, the overlap between VA and CD (n:1), or VA and HF (n:7) groups are not displayed. *Panel B*: Due to diagram limitation, the overlap between HTN and CNS-Hemorrhagic (n:11) groups is not displayed.

Figure 3 - Time to adverse drug reactions (ADR) onset associated with Ibrutinib. *CNS*: central nervous system

Table 1. Information component (IC) and its 95% credibility interval lower endpoint (IC_{025}) comparing cardiovascular adverse drug reactions (CV-ADR) associated with ibrutinib vs. entire database in VigiBase (from inception in 11/14/1967 to 02/01/2018). A positive IC_{025} value (>0) is the traditional threshold used for statistical signal detection (in bold). For significant signals, reporting odds-ratio (ROR) and its 95% confidence ($_{95}$CI) interval were also calculated using entire database from 01/01/2013 to 02/01/2018 as comparator (contemporary control group for ibrutinib, first ibrutinib report in 2013).

	Ibrutinib	Entire database (since inception)	IC / IC_{025}	Entire database (since 2013)	ROR; $_{95}$CI[,]
Total number of ICSRs available	13,572	16,343,451		8,318,890	
Number of ICSRs and statistics by CV-ADR subgroups					
Cardiac supra-ventricular arrhythmias (SVA)	**959 (7.07%)**	**68597 (0.42%)**	**4.06/3.97**	**28242 (0.34%)**	**23.1 [21.6-24.7]**
CNS Hemorrhagic Events	**505 (3.72%)**	**179621 (1.10%)**	**1.76/1.63**	**85402 (1.03%)**	**3.7 [3.4-4.1]**
Heart failure (HF)	**363 (2.67%)**	**142502 (0.87%)**	**1.61/1.46**	**65680 (0.79%)**	**3.5 [3.1-3.8]**
Cardiac ventricular arrhythmias (VA)	**70 (0.52%)**	**33504 (0.20%)**	**1.32/0.96**	**9220 (0.11%)**	**4.7 [3.7-5.9]**
Cardiac conduction disorders (CD)	**50 (0.37%)**	**26008 (0.16%)**	**1.19/0.76**	**8834 (0.11%)**	**3.5 [2.7-4.6]**
CNS ischemic Events	**254 (1.87%)**	**161618 (0.99%)**	**0.92/0.73**	**70529 (0.85%)**	**2.2 [2.0-2.5]**
Hypertension and related end-organ damages	**295 (2.17%)**	**239232 (1.46%)**	**0.57/0.40**	**109148 (1.31%)**	**1.7 [1.5-1.9]**
Cardiac valve disorders	30 (0.22%)	25500 (0.16%)	0.49/-0.07	NA	NA
Myocardial infarction	149 (1.10%)	163908 (1.00%)	0.13/-0.11	NA	NA
Cardiac death or shock	131 (0.97%)	144825 (0.89%)	0.12/-0.13	NA	NA
Venous thrombo-embolic events	108 (0.80%)	134718 (0.82%)	-0.05/-0.34	NA	NA
Vascular neoplasms	2 (0.01%)	2687 (0.02%)	-0.13/-2.72	NA	NA
Pulmonary hypertension and cardiac involvements	19 (0.14%)	30718 (0.19%)	-0.42/-1.14	NA	NA
Hyperglycemia, diabetes	112 (0.83%)	233007 (1.43%)	-0.79/-1.07	NA	NA
Torsade de pointes/QT prolongation	9 (0.07%)	20938 (0.13%)	-0.91/-2.01	NA	NA
Myocarditis	2 (0.01%)	5515 (0.03%)	-1.02/-3.61	NA	NA
Dyslipidemia	14 (0.10%)	64555 (0.39%)	-1.90/-2.75	NA	NA

ADRs: adverse drug reactions; CNS: central nervous system, NA: Not applicable

Table 2. Characteristics of reported individual case safety reports (ICSRs) with cardiovascular adverse drug reactions (ADR) associated with Ibrutinib in VigiBase (last accessed: 02/01/2018). Availability of data is mentioned in bold and top rows.

Characteristics	Supra-ventricular arrhythmias [#]	Ventricular arrhythmias	Conduction disorders	Heart failure	Hypertension	CNS ischemic events	CNS hemorrhagic events [##]
Region reporting, n (%)	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
Americas	629/959 (65.7)	48/70 (68.6)	36/50 (72.0)	307/363 (84.6)	254/295 (86.1)	209/254 (82.3)	395/505 (78.2)
Europe	317/959 (33.0)	19/70 (27.1)	14/50 (28.0)	54/363 (14.8)	39/295 (13.2)	42/254 (16.5)	100/505 (19.8)
Australia	12/959 (1.2)	2/70 (2.9)	0/50 (0.0)	1/363 (0.3)	2/295 (0.7)	2/254 (0.8)	4/505 (0.8)
Asia	1/959 (0.1)	1/70 (1.4)	0/50 (0.0)	1/363 (0.3)	0/295 (0.0)	1/254 (0.4)	6/505 (1.2)
Africa	0/959 (0.0)	0/70 (0.0)	0/50 (0.0)	0/363 (0.0)	0/295 (0.0)	0/254 (0.0)	0/505 (0.0)
Clinical trial reporting, n (%)	129/959 (13.5)	6/70 (8.6)	1/50 (2.0)	29/363 (8.0)	36/295 (12.2)	19/254 (7.5)	43/505 (8.5)
Reporting Year	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
2018 (*thru February 2018*)	27/959 (2.8)	2/70 (2.9)	3/50 (6.0)	2/363 (0.6)	3/295 (1.0)	4/254 (1.6)	10/505 (2.0)
2017	394/959 (41.1)	34/70 (48.6)	25/50 (50.0)	124/363 (34.1)	128/295 (43.4)	100/254 (39.4)	177/505 (35.0)
2016	300/959 (31.3)	15/70 (21.4)	10/50 (20.0)	118/363 (32.5)	122/295 (41.4)	66/254 (25.9)	125/505 (24.8)
2015	231/959 (24.1)	19/70 (27.1)	11/50 (22.0)	114/363 (31.4)	39/295 (13.2)	82/254 (32.3)	182/505 (36.0)
2014	7/959 (0.7)	0/70 (0.0)	1/50 (2.0)	5/363 (1.4)	3/295 (1.0)	2/254 (0.8)	11/505 (2.2)
Reporter	**942 (98.2)**	**67 (95.7)**	**50 (100.0)**	**361 (99.4)**	**289 (98.0)**	**251 (98.8)**	**481 (95.2)**
Health Care Professional	609/942 (64.6)	49/67 (73.1)	39/50 (78.0)	174/361 (48.2)	116/289 (40.1)	115/251 (45.8)	263/481 (54.7)
Non-Health Care Professional	333/942 (35.4)	18/67 (26.9)	11/50 (22.0)	187/361 (51.8)	173/289 (59.9)	136/251 (54.2)	218/481 (45.3)
Gender	**904 (94.7)**	**67 (95.7)**	**49 (98.0)**	**354 (97.5)**	**288 (97.6)**	**249 (98.0)**	**475 (94.1)**
Male	631/904 (69.8)	49/67 (73.1)	32/49 (65.3)	236/354 (66.7)	166/288 (57.6)	164/249 (65.9)	306/475 (64.4)
Female	273/904 (30.2)	18/67 (26.9)	17/49 (34.7)	118/354 (33.3)	122/288 (42.4)	85/249 (34.1)	169/475 (35.6)
Age at onset,	**731 (76.2)**	**54 (77.1)**	**35 (70.0)**	**263 (72.5)**	**236 (80.0)**	**194 (76.4)**	**378 (74.9)**
mean ± SD (years)	70.1 ± 9.1	65.3 ± 12.4	72.7 ± 13.6	75.45 ± 9.8	71.6 ± 29.8	73.9 ± 10.3	73.1 ± 32.8
[min-max]	[23-94]	[8-85]	[9-91]	[45-97]	[35-93]	[41-97]	[46-94]
Suspected Drugs	**959 (100.0)**	**70 (100.0)**	**50 (100.0)**	**363 (100.0)**	**295 (100.0)**	**254 (100.0)**	**505 (100.0)**
Only Ibrutinib	817/959 (85.2)	57/70 (81.4)	45/50 (90.0)	323/363 (89.0)	251/295 (85.1)	219/254 (86.2)	415/505 (82.2)
Ibrutinib + 1 other drug	100/959 (10.4)	7/70 (10.0)	2/50 (4.0)	32/363 (8.8)	27/295 (9.1)	21/254 (8.3)	69/505 (13.7)
Ibrutinib + ≥2 other drugs	42/959 (4.4)	6/70 (8.6)	3/50 (6.0)	8/363 (2.2)	17/295 (5.8)	14/254 (5.5)	21/505 (4.1)
Ibrutinib Dose, per day, oral:	**758 (79.0)**	**56 (80.0)**	**43 (86.0)**	**320 (88.2)**	**271 (91.9)**	**229 (90.2)**	**395 (78.2)**
140 mg	31/758 (4.1)	2/56 (3.6)	5/43 (11.6)	13/320 (4.1)	7/271 (2.6)	11/229 (4.8)	31/395 (7.8)
280 mg	51/758 (6.7)	3/56 (5.4)	6/43 (14.0)	23/320 (7.2)	13/271 (4.8)	23/229 (10.1)	34/395 (8.6)
420 mg	534/758 (70.4)	40/56 (71.4)	25/43 (58.1)	231/320 (72.2)	217/271 (80.1)	163/229 (71.2)	273/395 (69.1)

560 mg **>560 mg**	133/758 (17.6) 9/758 (1.2)	10/56 (17.8) 1/56 (1.8)	7/43 (16.3) 0/43 (0.0)	53/320 (16.5) 0/320 (0.0)	34/271 (12.5) 0/295 (0.0)	28/229 (12.2) 4/229 (1.7)	52/395 (13.2) 5/395 (1.3)
Time to ADR onset (days), Median [IQR] [min-max]	**381 (39.7)** 74 [29.5-196.5] [1-1299]	**39 (55.7)** 70 [28.5-152.5] [1-1002]	**34 (68.0)** 27.5 [1-138.5] [1-318]	**154 (42.4)** 54 [20.3-142.8] [1 - 929]	**21 (7.1)** 164 [20-274] [1-806]	**84 (33.1)** 51 [17.5-160] [1-902]	**74 (14.7)** 53.5 [20.3-183.3] [1-741]
Severe ADR*	**862 (89.9)** 591/862 (68.6)	**64 (91.4)** 64/64 (100.0)	**45 (90.0)** 45/45 (100.0)	**357 (98.3)** 357/357 (100.0)	**226 (76.6)** 226/226 (100)	**248 (97.6)** 248/248 (100.0)	**495 (98.0)** 495/495 (100)
Outcome Death	**959 (100.0)** 103/959 (10.7)	**70 (100.0)** 7/70 (10.0)	**50 (100.0)** 9/50 (18.0)	**363 (100.0)** 76/363 (20.9)	**295 (100.0)** 0/295 (0.0)	**254 (100.0)** 48/254 (18.9)	**505 (100.0)** 90/505 (17.8)
Indications Chronic lymphocytic leukemia Lymphoma (all types) Waldenstrom's macroglobulinemia Myeloma / Myelodysplasia Acute lymphoblastic leukemia Other	**867 (90.4)** 608/867 (70.1) 190/867 (21.9) 53/867 (6.2) 8/867 (0.9) 3/867 (0.3) 5/867 (0.6)	**62 (88.6)** 37/62 (59.7) 14/62 (22.6) 9/62 (14.5) 1/62 (1.6) 1/62 (1.6) 0/62 (0.0)	**47 (94.0)** 29/47 (61.7) 9/47 (19.1) 2/47 (4.3) 0/47 (0.0) 7/47 (14.9) 0/47 (0.0)	**348 (95.9)** 232/348 (66.7) 83/348 (23.9) 24/348 (6.9) 3/348 (0.9) 3/348 (0.9) 3/348 (0.9)	**288 (97.6)** 209/278 (72.6) 42/278 (14.6) 31/278 (10.7) 0/278 (0.0) 2/278 (0.7) 4/278 (1.4)	**237 (93.3)** 177/237 (74.7) 41/237 (17.3) 15/237 (6.4) 1/237 (0.4) 2/237 (0.8) 1/237 (0.4)	**474 (93.9)** 337/474 (71.1) 97/474 (20.5) 28/474 (5.9) 4/474 (0.8) 5/474 (1.1) 3/474 (0.6)

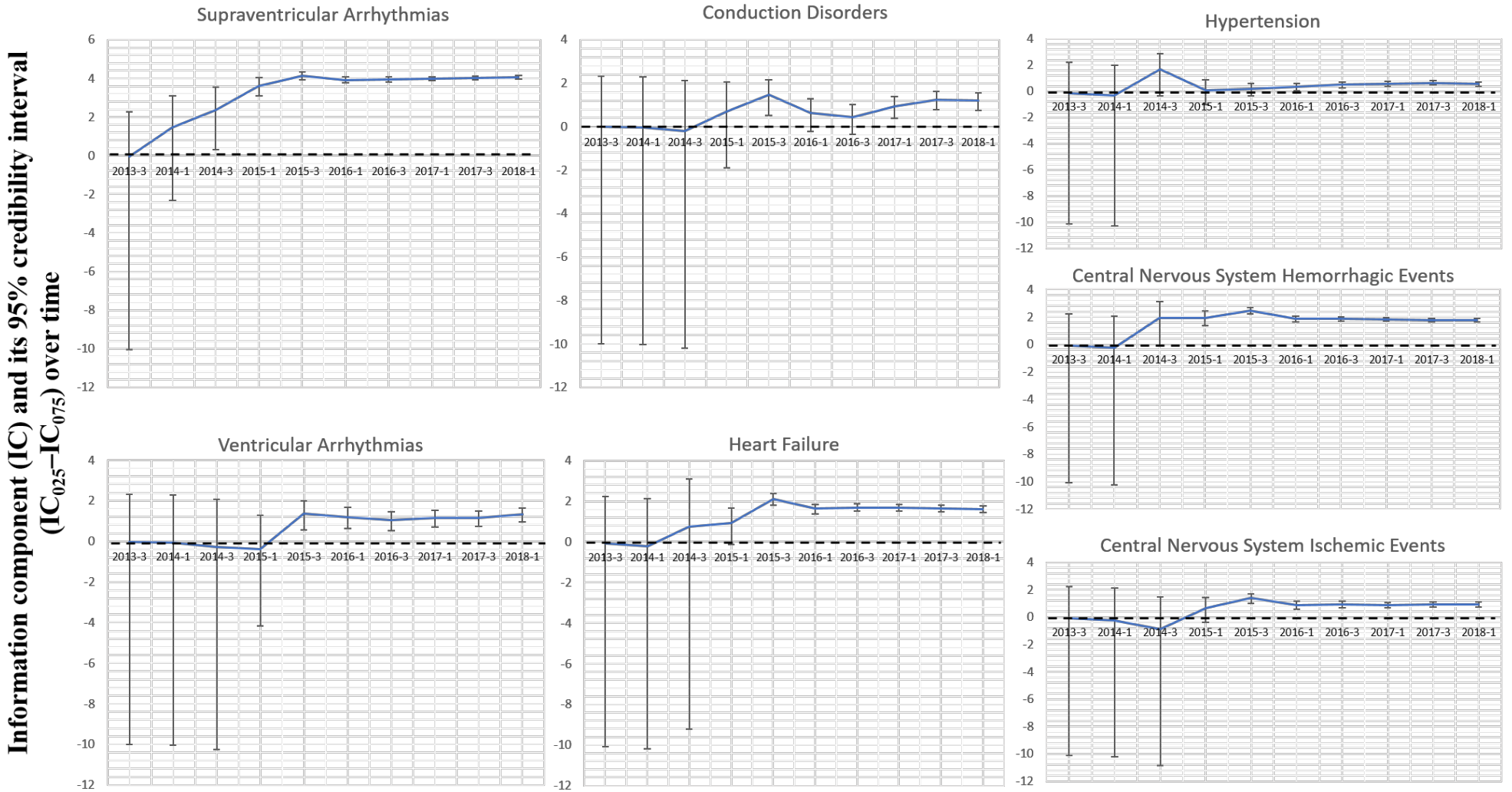
*A severe ADR was defined as such when being life-threatening, leading to persistent or significant disability, birth defect, congenital anomaly, or to any other medically important conditions, requiring hospitalization (initial or prolonged) or when causing death.

SVA cases were reported on class I: 24/959 (2.5%), class II: 230/959 (24%), class III: 58/959 (6%), class IV: 42/959 (4.4%), other class: 9/959 (3%) reported anti-arrhythmic drugs according to Vaughan-Williams classification.

CNS hemorrhagic events were reported on antiplatelets: 69/505 (13.7%), vitamin K antagonists: 38/505 (7.5%), heparins: 6/505 (1.2%), direct factor Xa: 24/505 (4.8%), and factor IIa: 4/505 (0.8%) inhibitors.

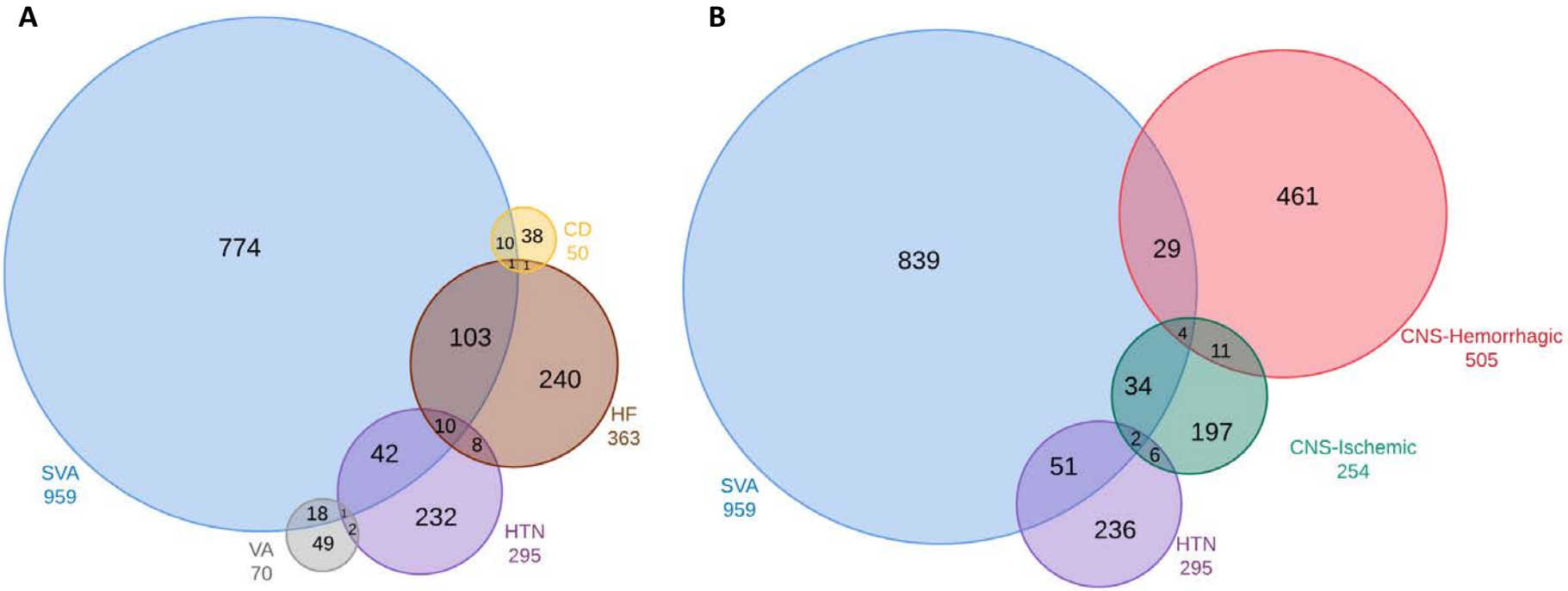
ADR: adverse drug reactions; [min-max]: minimum-maximum; SD: standard deviation; CNS: central nervous system.

Figure 1 – Central Illustration



An IC_{025} value of more than zero is deemed significant (dotted line). Data are shown for 1st and 3rd trimester of each year (year-1; year-3).

Figure 2


A
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10
38
CD
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HF
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SVA
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VA
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HTN
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839
29
461
CNS-Hemorrhagic
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CNS-Ischemic
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SVA
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HTN
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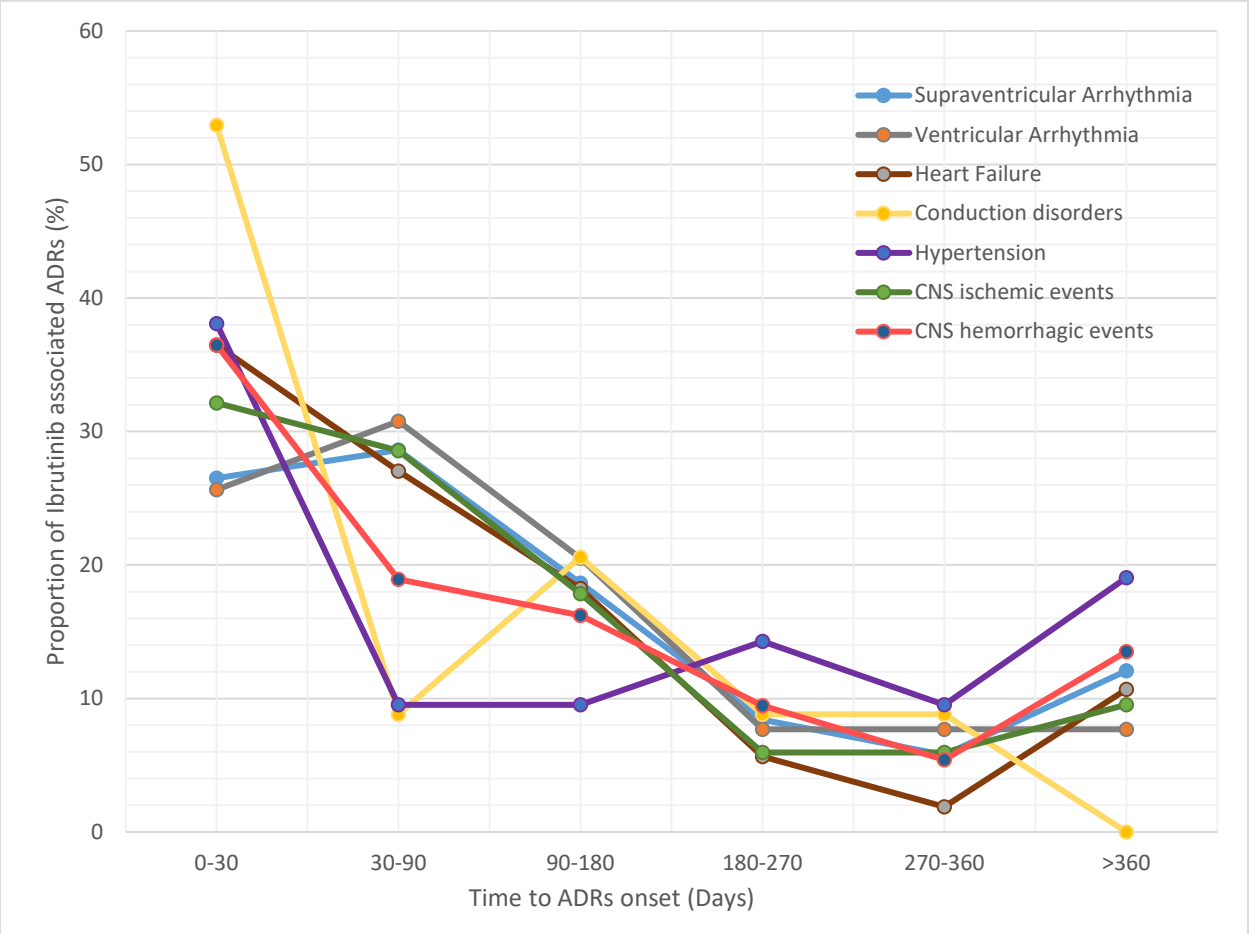
Figure 3


60
50
40
30
20
10
0
Proportion of Ibrutinib associated ADRs (%)
0-30
30-90
90-180
180-270
270-360
>360
Time to ADRs onset (Days)
Supraventricular Arrhythmia
Ventricular Arrhythmia
Heart Failure
Conduction disorders
Hypertension
CNS ischemic events
CNS hemorrhagic events

Cardiovascular toxicity of ibrutinib: a pharmacovigilance study.

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Supplementary Data.

Appendix 1. Details concerning information component (IC) calculation

Calculation of the IC, using a Bayesian confidence propagation neural network, was specifically developed and validated by UMC as an automated, flexible indicator value for disproportionate reporting that compares expected and observed drug-ADR associations to find new drug-ADR signals with identification of probability difference from the background data (entire database).[1-3] Probabilistic reasoning in intelligent systems (information theory) has been proven effective to manage large data sets, is robust in handling incomplete data, and may be used with complex variables. Information theory tool is ideal for finding drug-ADR combinations with other variables, which are highly associated compared to the generality of the stored data.[3] Several examples with IC have been first validated showing the power of the technique to find signals very early after drug approval (e.g. captopril ± coughing) and to avoid false positives where a common drug and a common AE association occur in the database, only because the drug is widely used and the AE frequently reported (e.g. digoxin ± acne; digoxin ± rash).[3,4]

The statistical formula is as follows,

$$IC = \log2 ((N_{observed}+0{\cdot}5)/(N_{expected}+0{\cdot}5) \quad (1)$$

$$\text{where } N_{expected} = (N_{drug}*N_{effect}) / N_{total} \quad (2)$$

$N_{expected}$: the number of case reports expected for the drug-adverse effect combination

$N_{observed}$: the actual number of case reports for the drug- adverse effect combination

N_{drug}: the number of case reports for the drug, regardless of adverse effects

N_{effect}: the number of case reports for the adverse effect, regardless of drug

N_{total}: the total number of case reports in the database

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3. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol.* 1998;54(4):315-321.
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Supplementary Table 1. Cardiovascular adverse events grouping as a function of Medical Dictionary for Regulatory Activities (MedDRA) Classification Version 20.1.

Groups	MedDRA Terms used
Cardiac supra-ventricular arrhythmias	Supraventricular tachyarrhythmias (SMQ narrow)
CNS Hemorrhagic Events	Haemorrhagic central nervous system vascular conditions (SMQ narrow)
Heart failure	Cardiac Failure (SMQ narrow)
Cardiac ventricular arrhythmias	Ventricular tachyarrhythmias (SMQ narrow)
Cardiac conductive disorders	Cardiac conduction disorders (HLT)
CNS ischemic Events	Ischaemic central nervous system vascular conditions (SMQ narrow)
Hypertension and related end-organ damages	Hypertension (SMQ narrow)
Cardiac valve disorders	Cardiac valve disorders (HLGT narrow)
Myocardial infarction	Myocardial infarction (SMQ narrow)
Cardiac death or shock	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ narrow)
Venous thrombo-embolic events	Embolic and thrombotic events, venous (SMQ narrow)
Vascular neoplasms	Vascular neoplasm (HLT)
Pulmonary hypertension and cardiac involvements	Pulmonary hypertension (SMQ narrow)
Hyperglycemia, diabetes	Hyperglycaemia/new onset diabetes mellitus (SMQ narrow)
Torsade de pointes/QT prolongation	Torsade de pointes (PT) and/or Electrocardiogram QT prolonged (PT) and/or Long QT syndrome (PT)
Myocarditis	Noninfectious myocarditis (HLT)
Dyslipidemia	Dyslipidaemia (SMQ narrow)

Abbreviations: CNS: central nervous system, HL(G)T: High Level (Group) Term; NEC: Not elsewhere classified; PT: Preferred Term; SMQ: Standardized MedDRA Query

Supplementary Table 2. Calculation of the reporting Odds-Ratios (ROR).

	Reports with the suspected ADR	**Reports without the suspected ADR**
Reports with suspected group of drugs (example: ibrutinib)	A	B
Reports with comparator group of drugs (example: entire database)	C	D

A: Number of reports of drug-induced ADR of interest (e.g; heart failure) associated with the given group of drugs (ibrutinib).

B: Number of reports of other ADR (e.g; all ADR excluding heart failure) associated with the given group of drugs (ibrutinib).

C: Number of reports of ADR of interest (e.g; heart failure) associated with a comparator group of drugs (entire database).

D: Number of reports of other ADR (e.g; all ADR excluding heart failure) associated with a comparator group of drugs (entire database).

$$ROR = (A/C)/(B/D) = AD/BC. \quad (1)$$

Abbreviations: ADR, adverse drug reaction; ROR: Reporting Odds-Ratio

Supplementary Table 3. Overlap of adverse drug reactions (ADR) associated with Ibrutinib. In bold, when overlap is >10%.

	Supraventricular Arrhythmia	Ventricular Tachyarrhythmia	Conductive Disorders	Heart Failure	Hypertension	CNS ischemic Events	CNS Hemorrhagic Events
Supraventricular Arrhythmia (n=959)		19/959 (2.0%)	11/959 (1.1%)	**114/959 (11.9%)**	53/959 (5.5%)	40/959 (4.2%)	33/959 (3.4%)
Ventricular Tachyarrhythmia (n=70)	**19/70 (27.1%)**		1/70 (1.4%)	**7/70 (10.0%)**	3/70 (4.3%)	3/70 (4.3%)	2/70 (2.9%)
Conductive Disorders (n=50)	**11/50 (22.0%)**	1/50 (2.0%)		2/50 (4.0%)	0/50 (0.0%)	2/50 (4.0%)	0/50 (0.0%)
Heart Failure (n=363)	**114/363 (31.4%)**	7/363 (1.9%)	2/363 (0.6%)		18/363 (5.0%)	6/363 (1.7%)	6/363 (1.7%)
Hypertension (n=295)	**53/295 (18.0%)**	3/295 (1.0%)	0/295 (0.0%)	18/295 (6.1%)		8/295 (2.7%)	11/295 (3.7%)
CNS ischemic Events (n=254)	**40/254 (15.7%)**	3/254 (1.2%)	2/254 (0.8%)	6/254 (2.4%)	8/254 (3.1%)		15/254 (5.9%)
CNS Hemorrhagic Events (n=505)	33/505 (6.5%)	2/505 (0.4%)	0/505 (0.0%)	6/505 (1.2%)	11/505 (2.2%)	15/505 (3.0%)	

CNS: central nervous system

Supp. Table 3. Clinical characteristics of patients with ibrutinib-associated cardiac supra-ventricular arrhythmias collected from VigiBase (through Jan 2, 2018)

Characteristics	**N (%)**	**Data availability, n (%)**
Region reporting, n (%)		959 (100.0)
Americas:	629 (65.7)	
Europe	317 (33.0)	
Australia	12 (1.2)	
Asia	1 (0.1)	
Africa	0 (0.0)	
Reporting Year		959 (100.0)
2018 (*thru January 2018*)	27 (2.8)	
2017	394 (41.1)	
2016	300 (31.3)	
2015	231 (24.1)	
2014	7 (0.7)	
Reporter		942 (98.2)
Health Care Professional	609 (64.6)	
Non-Health Care Professional	333 (35.4)	
Gender		904 (94.7)
Male	631 (69.8)	
Female	273 (30.2)	
Age at onset, mean ± SD (years)	70.1 ± 9.1	731 (76.2)
[min-max]	[23-94]	
Suspected Drugs *		959 (100.0)
Only Ibrutinib	817 (85.2)	
Ibrutinib + 1 other drug	100 (10.4)	
Ibrutinib + ≥2 other drugs	42 (4.4)	
Ibrutinib Dose :		758 (79.0)
140 mg	31 (4.1)	
280 mg	51 (6.7)	
420 mg	534 (70.4)	
560 mg	133 (17.6)	
>560 mg (700 mg)	9 (1.2)	
Time to ADR onset, days**:**		381 (39.7)
Median delay between treatment and irAE, median [IQR]	74 [29.5- 196.5]	
[min-max]	[1-1299]	
Severe AE	591 (68.6)	862 (89.9)
Outcome		959 (100.0)
Death	103 (10.7)	
Malignant neoplasm progression	39 (4.1)	959 (100.0)
Indications		867 (90.4)
Chronic lymphocytic leukemia	608 (70.1)	
Lymphoma (all variants)	190 (21.9)	
Waldenstrom's macroglobulinemia	53 (6.2)	
Plasma cell myeloma	8 (0.9)	
Acute lymphoblastic leukemia	3 (0.3)	
Other	5 (0.6)	
Reported cardiac supra-ventricular arrhythmias		959 (100.0)
Atrial fibrillation	900 (93.8)	
Atrial flutter	33 (3.5)	
Supraventricular tachycardia and extra-systoles	22 (2.3)	
Sinus Tachycardia	4 (0.4)	
Concurrent associated conditions		959 (100.0)
None (lone)	304 (31.7)	

Cardiac condition (non-ventricular arrhythmias)	312 (32.5)	
Cardiac failure/ decreased EF/ Pulmonary edema/ Pulmonary Hypertension / Dyspnea exertional	114 (11.9)	
Hypertension / Blood pressure increased	53 (5.5)	
Pericardial disorder/ Pericarditis /Pericardial effusion / Cardiac Tamponade	37 (3.9)	
Hypotension / Blood pressure decreased	28 (2.9)	
Myocardial infarction/ Coronary artery disease/Cardiac ischemia / Unstable Angina	28 (2.9)	
Bradycardia	22 (2.3)	
Syncope / Presyncope	19 (2.0)	
Chest pain / Chest discomfort	18 (1.9)	
Palpitations	18 (1.9)	
Cardiomyopathy	13 (1.4)	
Cardiomegaly / Cardiac hypertrophy	11 (1.1)	
Cardiogenic shock/ Cardiac arrest	10 (1.0)	
Thrombotic events (Thrombosis, Deep vein thrombosis, Pulmonary thromboembolism)	10 (1.0)	
Cardiac valvular disorders	7 (0.7)	
Bundle Branch Block	6 (0.6)	
Arterial disorders /Aortic stenosis/ Aortic aneurysm / Arterial stenosis	5 (0.5)	
Atrioventricular block	5 (0.5)	
Endocarditis	1 (0.1)	
Neurologic condition	265 (27.6)	
Decreased level of consciousness	65 (6.8)	
Contusion	53 (5.5)	
Dysphonia	46 (4.8)	
Cerebrovascular accident / Ischemic stroke / Cerebral ischemia / Cerebral infarction	40 (4.2)	
CNS hemorrhagic events	33 (3.4)	
Ophthalmological abnormality (vision problems)	28 (2.9)	
Cognitive-memory impairment / Delirium / Memory impairment	23 (2.4)	
Sleep disorders / Insomnia / Somnolence / Abnormal dreams	23 (2.4)	
Balance disorder/ Vertigo /Gait disturbance	19 (2.0)	
Headache / Migraine	18 (1.9)	
Encephalopathy	15 (1.6)	
Peripheral neuropathy / Paresthesia / Hypoesthesia / Hemiparesis / Neuralgia	15 (1.6)	
Psychologic disorders / Anxiety / Depression/ Mood disorder / Impulsive behavior	14 (1.5)	
Hearing impairments / Ear problems	12 (1.3)	
Dysarthria / Aphasia / Speech disorder	6 (0.6)	
Tremor	6 (0.6)	
Meningitis / Encephalitis / Brain abscess	4 (0.4)	
Motor dysfunction/ Paralysis / Facial paralysis	4 (0.4)	
Seizure	3 (0.3)	
Carotid artery diseases / Carotid artery aneurysm / Carotid artery stenosis	1 (0.1)	
Withdrawal syndrome	1 (0.1)	
Pulmonary condition	278 (29.0)	
Pneumonia/ Lung infection / Pneumonitis/ Pneumocystis jirovecii pneumonia /Bronchopulmonary aspergillosis/ Empyema	116 (12.1)	
Dyspnea/ Hypoxia	76 (7.9)	
Pleural disorders /Pleural effusion/ Pleural thickening / Chylothorax / Hemothorax / Pneumothorax	54 (5.6)	
Upper respiratory tract infection/ Sinusitis/ Nasopharyngitis / Influenza	48 (5.0)	
Cough	40 (4.2)	
Respiratory failure / Acute respiratory distress syndrome	28 (2.9)	
Bronchiectasis / Chronic obstructive pulmonary disease	11 (1.1)	
Bronchitis	10 (1.0)	
Acne	7 (0.7)	
Hemoptysis	6 (0.6)	
Sleep apnea syndrome	4 (0.4)	
Asthma /Asthmatic crisis	2 (0.2)	
Interstitial lung disease	2 (0.2)	
Atelectasis	1 (0.1)	

Gastro-intestinal disorders (any)	248 (25.9)	
Diarrhea / Colitis / Gastroenteritis / Dehydration	99 (10.3)	
Feeding disorder / Malnutrition / Weight disturbance	56 (5.8)	
Abdominal pain / Dyspepsia / Abdominal discomfort/ hernia	44 (4.6)	
Nausea / Vomiting	42 (4.4)	
Gastrointestinal bleeding	36 (3.8)	
Oropharyngeal discomfort or pain/ Dysphasia/ Stomatitis / Oral herpes /Oral candidiasis	27 (2.8)	
Liver disorders/ Hepatitis / Abnormal liver function tests/ Hypoalbuminemia	21 (2.2)	
Constipation	15 (1.6)	
Gastroesophageal reflux disease / Esophagitis /Gastritis / Hiatus hernia	13 (1.4)	
Biliary trach disorders / Cholecystitis/ Cholelithiasis / Cholestasis/ Hyperbilirubinemia	10 (1.0)	
Diverticulitis	4 (0.4)	
Gastrointestinal obstruction	3 (0.3)	
Abdominal abscess	3 (0.3)	
Intestinal perforation	3 (0.3)	
Peritonitis	2 (0.2)	
Dermatologic and Rheumatologic condition	245 (25.5)	
Fatigue / Asthenia / Malaise / Muscular weakness	128 (13.3)	
Rash / Erythema/ Pruritus / Dermatitis / Skin reaction / Hypersensitivity /Skin lesion	79 (8.2)	
Myalgia / Muscular disorders / Muscular spasm / Musculoskeletal pain / Tendinitis	63 (6.6)	
Arthorpathy/ Arthritis / Arthralgia / Costochondritis	43 (4.5)	
Cellulitis / Folliculitis / Erysipelas / Pyoderma gangrenosum	19 (2.0)	
Fractures/ Ligament injury	14 (1.5)	
Alopecia	3 (0.3)	
Stevens-Johnson syndrome	2 (0.2)	
Gout	1 (0.1)	
Lumbar radiculopathy	1 (0.1)	
Onychoclasis	1 (0.1)	
Osteomyelitis	1 (0.1)	
Osteonecrosis	1 (0.1)	
Plantar fasciitis	1 (0.1)	
Sjogren's syndrome	1 (0.1)	
Hematologic condition	201 (21.0)	
Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	96 (10.0)	
Anemia / Hemoglobin decreased	65 (6.8)	
Leukocytosis / Lymphocytosis	47 (4.9)	
Coagulopathy / Bleeding time prolonged / Petechia / Purpura / Tendency to bruise	29 (3.0)	
Lymphadenopathy	13 (1.4)	
Abnormal blood immunoglobulin (A / G / M) / Immune system disorder	10 (1.0)	
Tumor lysis syndrome	4 (0.4)	
Hemoglobin increased / Hematocrit increased / Red blood cell count increased	3 (0.3)	
Disseminated intravascular coagulation / Thrombotic thrombocytopenic	3 (0.3)	
Splenomegaly	2 (0.2)	
Renal condition	133 (13.9)	
Renal failure /Acute kidney injury / Blood creatinine increased / Renal tubular necrosis	75 (7.8)	
Edema (peripheral, general, peri-orbital)	34 (3.5)	
Urinary tract infections	31 (3.2)	
Hematuria / Renal hemorrhage	10 (1.0)	
Nephrolithiasis	2 (0.2)	
Chronic kidney disease	1 (0.1)	
Bleeding and Hemorrhagic events (CNS, GI, Pulmonary, ...)	132 (13.8)	
Gastrointestinal system	36 (3.8)	
Central nervous system	33 (3.4)	
Hematoma / Ecchymosis / Bruise /purpura / Skin hemorrhage	28 (2.9)	
Ear and Nose	27 (2.8)	
Unspecified	19 (2.0)	

Genitourinary system	10 (1.0)	
Respiratory system	8 (0.8)	
Cardiovascular (pericardial)	5 (0.5)	
Splenic	2 (0.2)	
Endocrine-metabolic disorders	35 (3.6)	
Electrolyte imbalance	17 (1.8)	
Fever / pyrexia	11 (1.1)	
Thyroid disorder	4 (0.4)	
Hyperglycemia / Diabetes mellitus	4 (0.4)	
Acid-Base disturbance	2 (0.2)	
Adrenal insufficiency	2 (0.2)	
Parathyroid disorder	1 (0.1)	
Cold intolerance	1 (0.1)	
Hyperlipidemia	1 (0.1)	

* Other concomitant reported suspected medications were Rituximab (n: 5), Dexamethasone (n: 2), Doxorubicin (n: 2), Azithromycin (n: 1), Carfilzomib (n: 1), Cetirizine (n: 1), Cyclophosphamide (n: 1), Cytarabine (n: 1), Deferasirox (n: 1), Epinephrine (n:1), Etoposide (n:1), Lenalidomide (n: 1), Pegfilgrastim (n:1), Prednisone (n: 1), Sunitinib (n: 1), Temozolomide (n: 1), Ticlopidine (n: 1), Valaciclovir (n: 1), and Vincristine (n: 1).

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation; CNS, central nervous system.

Supp. Table 4. Clinical characteristics of patients with ibrutinib-associated central nervous system (CNS) hemorrhagic events collected from VigiBase (through Jan 2, 2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		505 (100.0)
Americas	395 (78.2)	
Europe	100 (19.8)	
Australia	4 (0.8)	
Asia	6 (1.2)	
Africa	0 (0.0)	
Reporting Year		505 (100.0)
2018 (*thru January 2018*)	10 (2.0)	
2017	177 (35.0)	
2016	125 (24.8)	
2015	182 (36.0)	
2014	11 (2.2)	
Reporter		481 (95.2)
Health Care Professional	263 (54.7)	
Non-Health Care Professional	218 (45.3)	
Gender		475 (94.1)
Male	306 (64.4)	
Female	169 (35.6)	
Age at onset, mean ± SD (years)	73.1 ± 32.8	378 (74.9)
[min-max]	[46-94]	
Suspected Drugs *		505 (100.0)
Only Ibrutinib	415 (82.2)	
Ibrutinib + 1 other drug	69 (13.7)	
Ibrutinib + ≥2 other drugs	21 (4.1)	
Ibrutinib Dose:		395 (78.2)
140 mg	31 (7.8)	
280 mg	34 (8.6)	
420 mg	273 (69.1)	
560 mg	52 (13.2)	
>560 mg (640 mg-700 mg -960 mg-1260 mg)	5 (1.3)	
Time to ADR onset, days**:**		74 (14.7)
Median delay between treatment and ADR, median [IQR]	53.5 [20.3-183.3]	
[min-max]	[1-741]	
Severe ADR	495 (100)	495 (98.0)
Outcome		505 (100.0)
Death	90 (17.8)	
Malignant neoplasm progression	17 (3.4)	505 (100.0)
Indications		474 (93.9)
Chronic lymphocytic leukemia	337 (71.1)	
Lymphoma (all variants)	97 (20.5)	
Waldenstrom's macroglobulinemia	28 (5.9)	
Acute lymphoblastic leukemia	5 (1.1)	
Plasma cell myeloma	4 (0.8)	
Other	3 (0.6)	
Reported CNS hemorrhagic events		505 (100.0)
Intra cerebral hemorrhage	275 (54.5)	
Extra cerebral hemorrhage	156 (30.9)	
Intracranial hemorrhage	54 (10.7)	
Subarachnoid hemorrhage	27 (5.35)	
Spinal cord hemorrhage	5 (1.0)	
Cerebellar hemorrhage	3 (0.6)	
Cerebrovascular disorder	2 (0.4)	

Concurrent associated conditions		505 (100.0)
None (lone)	186 (36.8)	
Neurologic condition	138 (27.3)	
Brain injury / Contusion	45 (8.9)	
Headache	21 (4.2)	
Loss of consciousness, Depressed level of consciousness	20 (4.0)	
Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention	19 (3.8)	
Gait disturbance / Balance disturbance /Vertigo / Vestibular disorder	19 (3.8)	
Hemiplegia/ Paralysis/ Motor dysfunction/ Hemiparesis/ Facial paralysis/ Monoplegia	15 (3.0)	
Speech disorder/ Aphasia/ Dysphonia	15 (3.0)	
Cerebral ischemia/ Transient ischemic attack/ Ischemic stroke/ Cerebral infarction	15 (3.0)	
Ophthalmological abnormality (visual impairment / Eye movement disorder/Diplopia/ Cataract/ Blepharitis/ Dry eye/ Retinal artery occlusion/ Hemorrhage)	10 (2.0)	
Peripheral neuropathy /Guillain-Barre / Dysesthesia/ Paresthesia / Hypoesthesia	10 (2.0)	
CNS lesions / Hydrocephalus/ Pneumocephalus/ Brain edema/ Intracranial pressure increased	9 (1.8)	
Seizure / Epilepsy	8 (1.6)	
Sleep disorder/ Insomnia/ Hypersomnia/ Sleep apnea syndrome	7 (1.4)	
Psychologic disorders / Anxiety / Depression/ Psychosis / Impulsive behavior / Bradyphrenia	7 (1.4)	
Encephalopathy	5 (1.0)	
Hearing disorders	5 (1.0)	
Tremor	4 (0.8)	
Encephalitis /meningitis / CNS infection	4 (0.8)	
Hematologic condition	91 (18.0)	
Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	67 (13.3)	
Anemia	28 (5.5)	
Coagulopathy / Bleeding time prolonged / Petechia /Purpura/ Tendency to bruise	19 (3.8)	
Leukocytosis	12 (4.7)	
Splenomegaly	4 (0.8)	
Hypogammaglobulinemia / Immune system disorder	1 (0.2)	
Hemoglobin increased	1 (0.4)	
Lymphadenopathy	1 (0.4)	
Systemic inflammatory response syndrome	1 (0.4)	
Tumor lysis syndrome	1 (0.4)	
Cardiac condition	73 (14.5)	
Supraventricular arrhythmias (Atrial flutter/ Atrial fibrillation/ Supraventricular tachycardia / extrasystoles / Sinus tachycardia)	33 (6.6)	
Increased blood pressure / Hypertension	11 (2.2)	
Myocardial infarction/ Coronary artery disease/Cardiac ischemia	9 (1.8)	
Thrombosis / embolus (Thrombosis, Deep vein thrombosis, Pulmonary embolism)	6(1.2)	
Cardiac failure/ decreased EF/ Pulmonary edema/ Pulmonary Hypertension	6 (1.2)	
Chest pain (Chest pain, Chest discomfort)	5 (1.0)	
Syncope/ Presyncope	5 (1.0)	
Arterial disorders (Aortic stenosis, Aneurysm, Aortic aneurysm rupture)	3 (1.2)	
Palpitation	3 (1.2)	
Bradycardia	2 (0.4)	
Ventricular arrhythmias (Long QT, Ventricular arrhythmias, Torsade de pointes)	2 (0.4)	
Hypotension (Orthostatic hypotension/ Blood pressure decreased)	2(0.4)	
Cardiogenic shock/ Cardiac arrest	2 (0.4)	
Cardiomegaly and cardiac hypertrophy	1 (0.2)	
Pericardial disorder/ effusion	1 (0.2)	
Peripheral vascular disorder	1 (0.2)	
Dermatologic and Rheumatologic condition	73 (14.5)	
Asthenia/ Fatigue/ Malaise/ Lethargy	45 (8.9)	
Rash / Blister / Erythema/ Pruritus / Skin atrophy / Skin discoloration/ Skin exfoliation / Skin hemorrhage	34 (6.7)	
Myalgia /Muscle weakness / Muscle hemorrhage / Tendonitis	18 (3.6)	
Arthritis / Arthralgia / Costochondritis / Chondropathy	15 (3.0)	
Fractures / Ligament injury	11 (2.2)	

Skin infection / Cellulitis	5 (1.0)	
Nail infection / Onycholysis / Nail growth abnormal/ Panniculitis	3 (0.6)	
Drug hypersensitivity/ Allergy to chemicals	1 (0.2)	
Carpal tunnel syndrome	1 (0.2)	
Gastro-intestinal disorders (any)	68 (13.5)	
Diarrhea / Colitis / Gastroenteritis/ Enteritis/ Dehydration	26 (5.1)	
Appetite / Weight disorders	21 (4.2)	
Stomatitis / Dry mouth / Oral pain	11 (2.2)	
Abdominal pain/ discomfort/ irritation	10 (2.0)	
Nausea / Vomiting	10 (2.0)	
Gastroesophageal reflux disease /Dyspepsia	8 (1.6)	
Hepatitis / Hepatic failure / Biliary system and Gallbladder disorders	7 (1.4)	
Dysphagia	6 (1.2)	
Constipation	3 (0.6)	
Dysgeusia	2 (0.2)	
Pulmonary condition	52 (10.3)	
Lung infection/Pneumonia/ Pneumonitis,	34 (6.7)	
Upper respiratory infection/ Rhinitis /Cough	16 (3.2)	
Respiratory failure	10 (2.0)	
Pleural effusion / Pleural disorders	7 (2.8)	
Pulmonary hemorrhage / Hemoptysis	4 (0.8)	
Chronic obstructive pulmonary disease / Emphysema	2 (0.4)	
Bronchitis	2 (0.4)	
Atelectasis	1 (0.2)	
Non-CNS Bleeding and Hemorrhagic events (GI, Pulmonary, ...)	41 (8.1)	
Urinary system conditions	33 (6.5)	
Acute kidney injury / Nephropathy / Renal Failure / Blood Uric Acid or Creatinine increased	18 (3.6)	
Urinary tract infection	10 (2.0)	
Urinary incontinence / Urinary retention	6 (1.2)	
Hematuria / Hemorrhage urinary tract	5 (1.0)	
Cystitis	1 (0.4)	
Nephrolithiasis	1 (0.2)	
Endocrine-metabolic disorders	33 (6.5)	
Fever / Pyrexia/ Chills	18 (3.6)	
Electrolyte imbalance	7 (2.8)	
Glycosylated hemoglobin increased / Blood glucose increased	5 (1.0)	
Hyperlipidemia	2 (0.4)	
Thyroid disorders	2 (0.4)	
Night sweats (Night sweats)	1 (0.2)	

* Other concomitant reported suspected medications were Warfarin (n: 18), Rivaroxaban (n: 13), Rituximab (n: 11), Acetylsalicylic acid (n: 10), Apixaban (n: 6), Clopidogrel (n: 4), Bendamustine (n: 3), Cytarabine (n: 3), Dabigatran (n: 3), Methotrexate (n: 3), Obinutuzumab (n: 3), Pantoprazole (n: 3), Dexamethasone (n: 2), Enoxaparin (n: 2), Glyceryl trinitrate (n: 2), Potassium bicarbonate/ Potassium citrate (n: 2), Pregabalin (n: 2), Venetoclax (n: 2), Acenocoumarol (n: 1), Acetylsalicylic acid (n: 1), Allopurinol (n: 1), Amiodarone (n: 1), Amitriptyline (n: 1), Ampicillin (n: 1), Antineoplastic agents (n: 1), Atenolol (n: 1), Azacitidine (n: 1), Bortezomib (n: 1), Carfilzomib (n: 1), Carisoprodol (n: 1), Cefaclor (n: 1), Cefadroxil (n: 1), Dalteparin (n: 1), Diltiazem (n: 1), Drug name/s under assessment for who-dd (n: 1), Eltrombopag (n: 1), Escitalopram (n: 1), Etoricoxib (n: 1), Fluconazole (n: 1), Heparin (n: 1), Hydrocodone-Paracetamol (n: 1), Hydrocortisone (n: 1), Ibuprofen (n: 1), Iron (n: 1), Lamivudine (n: 1), Losartan (n: 1), Magnesium (n: 1), Metoprolol (n: 1), Naproxen (n: 1), Prednisone (n: 1) Propafenone (n: 1), Valaciclovir (n: 1), Valproic acid (n: 1), Vitamin D (n: 1), Venlafaxine (n: 1), Voriconazole (n: 1).

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation; CNS, central nervous system.

Supp. Table 5. Clinical characteristics of patients with ibrutinib-associated heart failure collected from VigiBase (through Jan 2, 2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		363 (100.0)
Americas:	307 (84.6)	
Europe	54 (14.8)	
Australia	1 (0.3)	
Asia	1 (0.3)	
Africa	0 (0.0)	
Reporting Year		363 (100.0)
2018 (*thru January 2018*)	2 (0.6)	
2017	124 (34.1)	
2016	118 (32.5)	
2015	114 (31.4)	
2014	5 (1.4)	
Reporter		361 (99.4)
Health Care Professional	174 (48.2)	
Non-Health Care Professional	187 (51.8)	
Gender		354 (97.5)
Male	236 (66.7)	
Female	118 (33.3)	
Age at onset, mean ± SD (years)	75.45 ± 9.8	263 (72.5)
[min-max]	[45-97]	
Suspected Drugs *		363 (100.0)
Only Ibrutinib	323 (89.0)	
Ibrutinib + 1 other drug	32 (8.8)	
Ibrutinib + ≥2 other drugs	8 (2.2)	
Ibrutinib Dose :		320 (88.2)
140 mg	13 (4.1)	
280 mg	23 (7.2)	
420 mg	231 (72.2)	
560 mg	53 (16.5)	
>560 mg (700 mg)	0 (0.0)	
Time to ADR onset, days**:**		154 (42.4)
Median delay between treatment and ADR, median [IQR]	54 [20.3 – 142.8]	
[min-max]	[1- 929]	
Severe ADR	357 (100.0)	357 (98.3)
Outcome		363 (100.0)
Death	76 (20.9)	
Malignant neoplasm progression	17 (4.7)	363 (100.0)
Indications		348 (95.9)
Chronic lymphocytic leukemia	232 (66.7)	
Lymphoma (all variants)	83 (23.9)	
Waldenstrom's macroglobulinemia	24 (6.9)	
Plasma cell myeloma	3 (0.9)	
Acute lymphoblastic leukemia	3 (0.9)	
Oher	3 (0.9)	
Reported cardiac failure events		363 (100.0)
Cardiac failure (congestive/ Cardiopulmonary failure / Ejection fraction decreased/ Left ventricular failure/dysfunction)	275 (75.7)	
Pulmonary edema/ Pulmonary congestion/ Pulmonary Hypertension	80 (22.0)	
Cardiogenic shock	6 (1.7)	
Diastolic dysfunction	1 (0.3)	
Right ventricular failure/dysfunction	1 (0.3)	

Concurrent associated conditions		363 (100.0)
None (lone)	59 (16.3)	
Cardiac condition (non-cardiac failure)	169 (46.6)	
Supraventricular arrhythmias (Supraventricular tachycardia/Atrial fibrillation/Atrial flutter/Tachycardia/Heart Rate increase)	114 (31.4)	
Hypertension / Blood pressure increased	18(5.0)	
Thrombotic events (Ventricular thrombosis/Super Vena Cava occlusion/Peripheral Vascular Disease/Deep Vein Thrombosis)	15 (4.1)	
Myocardial Infarction/Acute Coronary Syndrome/Coronary artery occlusion/Troponin increase	14 (3.9)	
Cardiomyopathy	10 (2.8)	
Syncope / Presyncope	10 (2.8)	
Valvular disease/dysfunction	8 (2.2)	
Pericardial hemorrhage/Pericardial effusion/Mediastinal effusion	8 (2.2)	
Ventricular arrhythmias (Ventricular fibrillation/Ventricular tachycardia)	7 (1.9)	
Cardiomegaly	4 (1.1)	
Endocarditis	2 (0.6)	
Bradycardia/Heart Rate decrease	3 (0.8)	
Bundle Branch Block	2 (0.6)	
Neurologic condition	77 (21.2)	
Contusions	23 (6.3)	
Migraine/Photophobia/Headache	16 (4.4)	
Dizziness	16 (4.4)	
Sleep disorders (Insomnia/Sleep disturbance/Somnolence/Sleep apnea)	12 (3.3)	
Mental impairment/Delirium/Confusional state/Altered Mental Status	11 (3.0)	
Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea		
Gait disturbance/Ataxia/Balance disorder	11 (3.0)	
Visual impairment/Blurry vision/Conjunctival hemorrhage/Ocular hyperemia	10 (2.8)	
Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma	6 (1.7)	
Loss of consciousness/Unresponsive to stimuli	6 (1.7)	
Memory impairment/Amnesia	5 (1.4)	
Neuropathy (Hypoesthesia/Paresthesia/Sciatica)	5 (1.4)	
Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack	6 (1.7)	
Encephalopathy	4 (1.1)	
Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy	3 (0.8)	
Hemiparesis/Hypotonia	3 (0.8)	
Dysphonia	2 (0.6)	
Hematologic condition	88 (24.2)	
Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)	41 (11.3)	
Anemia	40 (11.0)	
Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test	19 (5.2)	
Leukocytosis/Lymphocytosis/Monocytosis	18 (5.0)	
Sepsis/Septic shock/Bacteremia	13 (3.6)	
Lymphadenopathy	9 (2.5)	
Immunosuppression/Immune system disorder/Hypogammaglobulinemia M /Hypergammaglobulinemia M	5 (1.4)	
Thrombosis	4 (1.1)	
Splenomegaly/Splenic rupture	2 (0.6)	
Hb increase	1 (0.3)	
Tumor Lysis Syndrome	1 (0.3)	
Gastro-intestinal disorders (any)	85 (23.4)	
Diarrhea / Dehydration	42 (11.6)	
Nausea/Vomiting	20 (5.5)	
Decreased appetite/Feeding disorder/Malnutrition	17 (4.7)	
Constipation	11 (3.0)	
Dyspepsia/Gastroesophageal Reflux Disease	8 (2.2)	
GI hemorrhage	7 (1.9)	
Gastritis/Gastroenteritis/Colitis/Intestinal Abscess	6 (1.7)	

Transaminase increase/Liver disorder/Hyperbilirubinemia	6 (1.7)	
Abdominal distention	4 (1.1)	
Cholecystitis/Cholelithiasis/Gallbladder disorder	3 (0.8)	
Diverticulitis/Diverticular perforation	2 (0.6)	
Dysphagia	2 (0.6)	
Large intestine perforation/obstruction	2 (0.6)	
Bowel movement irregularity	1 (0.3)	
Duodenal ulcer	1 (0.3)	
Pancreatitis	1 (0.3)	
Pulmonary condition	111 (30.6)	
Pneumonia / Bronchopulmonary aspergillosis / Lung infection / Pneumonitis / Respiratory tract infection / Pulmonary sepsis	73 (20.1)	
Pleural effusion / Pleural calcification	35 (9.6)	
Acute Respiratory Distress Syndrome / Respiratory failure	17 (4.7)	
Pulmonary hemorrhage / Hemoptysis	8 (2.2)	
Chronic Obstructive Pulmonary Disease / Emphysema / Bronchiectasis	7 (1.9)	
Pulmonary embolism	5 (1.4)	
Wheezing / Rales / Asthma	5 (1.4)	
Exertional Dyspnea	4 (1.1)	
Tachypnea / Abnormal respiration / Diaphragmatic paralysis	3 (0.8)	
Bronchitis	2 (0.6)	
Traumatic lung injury	1 (0.3)	
Dermatologic and Rheumatologic condition	108 (29.8)	
Asthenia/Fatigue/Malaise	74 (20.4)	
Rash / Acne / Skin fissures / Skin lesions / Erythema / Eczema / Blister / Pruritus/Alopecia	32 (8.8)	
Arthritis / Arthropathy / Arthralgia / Joint lock / Joint swelling / Gout	27 (7.4)	
Muscle weakness / Myalgia / Myositis / Muscle spasms	24 (6.6)	
Cellulitis / Herpes dermatitis / Erysipelas / Skin infection	7 (1.9)	
Fracture / Osteopenia	5 (1.4)	
Vasculitis / Henoch Schonlein Purpura / Sjogren's	3 (0.8)	
Immune Thrombocytopenic Purpura	1 (0.3)	
Ligament Sprain	1 (0.3)	
Melanocytic nevus	1 (0.3)	
Tendonitis	1 (0.3)	
Endocrine-metabolic disorders	49 (13.5)	
Pyrexia / Fever	20 (5.5)	
Electrolyte abnormalities	14 (3.9)	
Thyroid disorder / Hypothyroidism / Euthyroid sick syndrome / Goiter	5 (1.4)	
DM/Blood glucose increase / Hyperglycemia	4 (1.1)	
Acid-base imbalance	3 (0.8)	
Adrenal insufficiency	2 (0.6)	
Failure to thrive	2 (0.6)	
Temperature intolerance	2 (0.6)	
Hyperlipidemia	1 (0.3)	
Parathyroid disorder	1 (0.3)	
Renal condition	47 (12.9)	
Renal impairment (Acute Kidney Injury / Chronic Kidney Disease / Anuria / End Stage Renal Disease / Hyperuricemia / Blood Cr increase)	37 (10.2)	
Hematuria	9 (2.5)	
Nocturia / Micturation urgency / Urinary retention	6 (1.7)	
Pyelonephritis	1 (0.3)	
Bleeding and Hemorrhagic conditions	53 (14.6)	

* Other concomitant reported suspected medications were Rituximab (n: 11), Cyclophosphamide (n: 7), Fludarabine (n: 5), Amiodarone (n: 4), Bendamustine (n: 4), Dexamethasone (n: 4), Doxorubicine (n: 4), Obinutuzumab (n: 3), Warfarin (n: 3), Acetylsalicylic acid (n:2), Alemtuzumab (n: 2), Allopurinol (n: 2), Apixaban (n: 2), Carfilzomib (n: 2), Heparin (n: 2), Idelalisib (n: 2), Vincristine (n: 2), Atorvastatin (n: 1), Carvedilol (n: 1), Chlorambucil (n: 1), Cisplatin (n: 1), Clopidogrel (n: 1), Cytarabine (n: 1), Dabigatran (n: 1), Immunoglobulins nos (n: 1), Lenalidomide (n: 1), Linsinopril (n: 1), Metoprolol (n: 1), Mitoxantrone (n: 1), Nitrofurantoin (n: 1), Oxaliplatin (n: 1), Palbociclib (n: 1), Prednisolone (n: 1), Prednisone (n: 1), Pregabalin (n: 1), Rivaroxaban (n: 1), Vancomycin (n: 1), Verapamil (n: 1), Voriconazole (n: 1),

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation

Supp. Table 6. Clinical characteristics of patients with ibrutinib-associated hypertension collected from VigiBase (through Jan 2, 2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		295 (100.0)
Americas:	254 (86.1)	
Europe	39 (13.2)	
Australia	2 (0.7)	
Asia	0 (0.0)	
Africa	0 (0.0)	
Reporting Year		295 (100.0)
2018 (*thru January 2018*)	3 (1.0)	
2017	128 (43.4)	
2016	122 (41.4)	
2015	39 (13.2)	
2014	3 (1.0)	
Reporter		289 (98.0)
Health Care Professional	116 (40.1)	
Non-Health Care Professional	173 (59.9)	
Gender		251 (85.1)
Male	166 (57.6)	
Female	122 (42.4)	
Age at onset, mean ± SD (years)	71.6±29.8	236 (80.0)
[min-max]	[35.0-93.0]	
Suspected Drugs *		295 (100.0)
Only Ibrutinib	251 (85.1)	
Ibrutinib + 1 other drug	27 (9.2)	
Ibrutinib + ≥2 other drugs	17 (5.8)	
Ibrutinib Dose :		271 (91.9)
140 mg	7 (2.6)	
280 mg	13 (4.8)	
420 mg	217 (80.1)	
560 mg	34 (12.5)	
>560 mg (700 mg)	0 (0.0)	
Time to ADR onset, days**:**		21 (7.1)
Median delay between treatment and ADR, median [IQR]	164.0 [20.0-274.0]	
[min-max]	[0.0-806.0]	
Severe ADR	226 (100.0)	226 (76.6)
Outcome		295 (100.0)
Death	0 (0.0)	
Malignant neoplasm progression	12 (4.1)	226 (76.6)
Indications		288 (97.6)
Chronic lymphocytic leukemia	209 (72.6)	
Lymphoma (all variants)	42 (14.6)	
Waldenstrom's macroglobulinemia	31 (10.7)	
Acute lymphoblastic leukemia	2 (0.7)	
Other	4 (1.4)	
Reported hypertension events		295 (100.0)
Hypertension	283 (95.9)	
Hypertensive crisis	7 (2.4)	
Blood pressure diastolic increased	2 (0.7)	
Hypertensive emergency	1 (0.3)	
Labile hypertension	1 (0.3)	
Orthostatic hypertension	1 (0.3)	

Concurrent associated conditions		295 (100.0)
None (lone)	19 (6.4)	
Cardiac condition	167 (56.6)	
Supraventricular arrhythmias (Supraventricular tachycardia/Atrial fibrillation/Atrial flutter/Tachycardia/Heart Rate increase)	53 (18.0)	
Cardiac failure / Ejection fraction decreased/ Pulmonary hypertension/ Pulmonary edema	18 (6.1)	
Palpitation	16 (5.4)	
Chest pain (Chest pain, Chest discomfort)	13 (4.4)	
Hypotension / Blood pressure decreased / Orthostatic hypotension	13 (4.4)	
Bradycardia / Heart rate decrease	9 (3.1)	
Cardiomegaly / Cardiac hypertrophy	6 (2.0)	
Syncope / Presyncope	6 (2.0)	
Myocardial infarction/ Acute coronary syndrome/ Angina pectoris/ Coronary artery occlusion	5 (1.7)	
Pericardial disorder (Pericardial effusion, Pericarditis)	4 (1.4)	
Thromboembolic events	4 (1.4)	
Blood pressure abnormal (Blood pressure fluctuation, Blood pressure abnormal, Labile blood pressure)	4 (1.4)	
Ventricular tachyarrhythmia (Ventricular tachycardia, Electrocardiogram QT prolonged)	3 (1)	
Arterial disorders (Hepatic artery aneurysm, Aortic rupture, Carotid artery stenosis)	3 (1)	
Valvular disorders	2 (0.7)	
Cardiomyopathy	1 (0.3)	
Cardiac arrest	1 (0.3)	
Dermatologic and Rheumatologic condition	162 (54.9)	
Asthenia/Fatigue/Malaise	96 (32.5)	
Rash / Acne / Skin fissures / Skin lesions / Erythema / Eczema / Blister / Pruritus	67 (22.7)	
Arthritis / Arthropathy / Arthralgia / Joint lock / Joint swelling / Gout	54 (18.3)	
Muscle weakness / Myalgia / Myositis / Muscle spasms	47 (15.9)	
Fracture / Osteopenia	22 (7.5)	
Nail and hair disorders	19 (6.4)	
Cellulitis / Herpes dermatitis / Erysipelas / Skin infection	10 (3.4)	
Allergy (Drug hypersensitivity, Allergy to arthropod bite)	3 (1.0)	
Scleroderma (Scleroderma)	1 (0.3)	
Neurologic condition	126 (42.7)	
Loss of consciousness	47 (15.9)	
Contusion/ Head injury	44 (14.9)	
Headache	34 (11.5)	
Eye disorder	28 (9.5)	
Sleep disorder (Insomnia/ Somnolence /Sleep apnea syndrome/ Hypersomnia)	28 (9.5)	
Dysesthesia (Paranesthesia/ Hypoesthesia/ Hypersensitivity/ Neuropathy peripheral/ Nerve injury/ Neuralgia/ Burning sensation/ Diabetic neuropathy/ Nerve compression)	26 (8.8)	
Cognitive disorder /Memory impairment/ Amnesia/ Hallucination/ Agitation	21 (7.1)	
Psychiatric disorder (Depression/ Anxiety/ Irritability/ Nervousness/ Depressed mood/Psychiatric symptom/ Bipolar disorder/ Post-traumatic stress disorder)	20 (6.8)	
Ear and hearing disorders	19 (6.4)	
Vertigo / Balance disturbance / Gait disturbance	11 (3.7)	
CNS hemorrhagic events / Subarachnoid hemorrhage/ Subdural hematoma/ Hemorrhage intracranial/ Cerebral hemorrhage/ Intracranial hematoma	11 (3.7)	
Cerebral ischemia / Transient ischemic attack/ Cerebral infarction	8 (2.7)	
Speech disorder/ Dysphonia/ Aphasia	7 (2.4)	
Tremor	5 (1.7)	
Cerebral cyst, Brain abscess, Central nervous system lesion/ Brain edema	4 (1.4)	
Seizure (Seizure)	2 (0.7)	
Paralysis / Peroneal nerve palsy/ Facial paralysis	2 (0.7)	
Encephalopathy	2 (0.7)	
CNS infection / Meningitis	1 (0.3)	
Hematologic condition	123 (41.7)	
Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)	70 (33.7)	
Anemia	37 (12.5)	

Leukocytosis/Lymphocytosis/Monocytosis	28 (9.5)	
Immunosuppression/Immune system disorder/Hypogammaglobulinemia M /Hypergammaglobulinemia M	9 (3.1)	
Lymphadenopathy	8 (2.7)	
Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising	7 (2.4)	
Hb increase	4 (1.4)	
Splenomegaly/Splenomegaly	3 (1)	
Tumor Lysis Syndrome	2 (0.7)	
Gastro-intestinal disorders (any)	121 (41.0)	
Diarrhea / Dehydration	55 (18.6)	
Nausea/Vomiting	50 (16.9)	
Appetite and Weight disorder	40 (13.6)	
Abdominal pain, Abdominal discomfort	32 (10.8)	
Dyspepsia/Gastroesophageal Reflux Disease/ Peptic ulcer	29 (9.8)	
Constipation	16 (5.4)	
Hepatic, biliary and pancreatic disorders	13 (4.4)	
GI hemorrhage	9 (3.1)	
Gastro-intestinal Obstruction	3 (1)	
Esophageal disorders / Dysphagia	3 (1)	
Pulmonary condition	85 (28.8)	
Upper respiratory infection/ Rhinitis /Cough	44 (14.9)	
Pneumonia / Bronchopulmonary aspergillosis / Lung infection / Pneumonitis / Respiratory tract infection / Pulmonary sepsis	32 (10.8)	
Dyspnea/ Tachypnea / Abnormal respiration	27 (9.2)	
Bronchitis	8 (2.7)	
Pleural effusion / Pleural calcification/ Pneumothorax/ Pleural thickening	6 (2)	
Acute Respiratory Distress Syndrome / Respiratory failure	5 (1.7)	
Wheezing / Rales / Asthma	4 (1.4)	
Chronic obstructive pulmonary disease/ Emphysema / Bronchiectasis	3 (1)	
Atelectasis	2 (0.7)	
Bleeding and Hemorrhagic conditions	76 (25.8)	
Endocrino-metabolic disorders	72 (24.4)	
Pyrexia / Fever	35 (11.9)	
Electrolyte abnormalities	22 (7.5)	
DM/Blood glucose increase / Hyperglycemia	14 (4.7)	
Hyperlipidemia	3 (1)	
Thyroid disorder / Hypothyroidism / Euthyroid sick syndrome / Goiter	2 (0.7)	
Renal condition	49(16.6)	
Renal impairment (Acute Kidney Injury / Chronic Kidney Disease /Hyperuricemia / Blood Creatinine increase)	25 (8.5)	
Hematuria		
Nocturia / Micturition urgency / Urinary retention / Dysuria	16 (5.4)	
Urinary tract infection / Pyelonephritis	15 (5.1)	
Nephrolithiasis	2 (0.7)	

* Other concomitant reported suspected medications were Rituximab (9), Prednisone (5), Amlodipine (4), Bendamustine (3), Diltiazem (3), Obinutuzumab (3), Cyclophosphamide (2), Lenalidomide (2), Lisinopril (2), Methylprednisolone (2), Metoprolol (2), Allopurinol (1), Amiodarone (1), Amphotericin b (1), Benzylpenicillin (1), Cefaclor (1), Cefadroxil (1), Cetirizine (1), Chlorambucil (1), Curcuma longa (1), Cyanocobalamin (1), Docetaxel (1), Doxorubicin (1), Duloxetine (1), Fluconazole (1), Flucytosine (1), Fludarabine (1), Hydrocodone;Paracetamol (1), Hydroxyzine (1), Idelalisib (1), Letrozole (1), Levofloxacin (1), Losartan (1), MOR208 (1), Morphine (1), Ofatumumab (1), Oxycodone (1), Pegfilgrastim (1), Prednisolone (1), Ublituximab (1), Venetoclax (1), Vincristine (1)

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation

Supp. Table 7. Clinical characteristics of patients with ibrutinib-associated central nervous system (CNS) ischemic events collected from VigiBase (through Jan 2, 2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		254 (100.0)
Americas	209 (82.3)	
Europe	42 (16.5)	
Australia	2 (0.8)	
Asia	1 (0.4)	
Africa	0 (0.0)	
Reporting Year		254 (100.0)
2018 (*thru January 2018*)	4(1.6)	
2017	100 (39.4)	
2016	66 (25.9)	
2015	82 (32.3)	
2014	2 (0.8)	
Reporter		251 (98.8)
Health Care Professional	115 (45.8)	
Non-Health Care Professional	136 (54.2)	
Gender		249 (98.0)
Male	164 (65.9)	
Female	85 (34.1)	
Age at onset, mean ± SD (years)	73.9 ± 10.3	194 (76.4)
[min-max]	[41-97]	
Suspected Drugs *		254 (100.0)
Only Ibrutinib	219 (86.2)	
Ibrutinib + 1 other drug	21 (8.3)	
Ibrutinib + ≥2 other drugs	14 (5.5)	
Ibrutinib Dose :		229 (90.2)
140 mg	11 (4.8)	
280 mg	23 (10.1)	
420 mg	163 (71.2)	
560 mg	28 (12.2)	
>560 mg (640 mg-700 mg -960 mg-1260 mg)	4 (1.7)	
Time to ADR onset, days**:**		84 (33.1)
Median delay between treatment and ADR, median [IQR]	51 [17.5-160]	
[min-max]	[1-902]	
Severe ADR	248 (100.0)	248 (97.6)
Outcome		254 (100.0)
Death	48 (18.9)	
Malignant neoplasm progression	9 (3.5)	254 (100.0)
Indications		237 (93.3)
Chronic lymphocytic leukemia	177 (74.7)	
Lymphoma (all variants)	41 (17.3)	
Waldenstrom's macroglobulinemia	15 (6.4)	
Acute lymphoblastic leukemia	2 (0.8)	
Plasma cell myeloma	1 (0.4)	
Other	1 (0.4)	
Reported CNS ischemic events		254 (100.0)
Cerebrovascular accident / Ischemic stroke / Cerebral ischemia – thrombosis - infarction /Transient ischemic attack /Lacunar infarction / Thalamic infarction	240 (94.5)	
Motor dysfunction/ Paralysis / Hemiplegia / Hypotonia / Facial paralysis	12 (4.7)	
Encephalopathy (Hypoxic-ischemic/ vascular)	8 (3.1)	
Speech disorder / Aphasia / Dysarthria	8 (3.1)	
Carotid artery diseases/ occlusion (embolic, thrombotic, stenosis)/ aneurysm	7 (2.8)	

Concurrent associated conditions		254 (100.0)
None (lone)	94 (37.0)	
Cardiac condition	67 (26.4)	
Supraventricular arrhythmias (Atrial flutter/ Atrial fibrillation/ Supraventricular tachycardia / extrasystoles / Sinus tachycardia)	40 (15.7)	
Myocardial infarction/ Coronary artery disease/Cardiac ischemia	13 (5.1)	
Increased blood pressure / Hypertension	8 (3.1)	
Cardiac failure/ decreased EF/ Pulmonary edema/ Pulmonary Hypertension	6 (2.4)	
Cardiogenic shock/ Cardiac arrest	5 (2.0)	
Syncope	3 (1.2)	
Ventricular arrhythmias (Long QT, Ventricular arrhythmias, Torsade de pointes)	3 (1.2)	
Valvular diseases	3 (1.2)	
Bradycardia / Bradyarrhythmia	3 (1.2)	
Conduction disorder (Atrioventricular block / Bundle branch block / Brugada syndrome)	2 (0.8)	
Pericardial effusion/ Tamponade/ Pericarditis /Pericardial hemorrhage	2 (0.8)	
Peripheral vascular disorder	1 (0.4)	
Endocarditis	1 (0.4)	
Dermatologic and Rheumatologic condition	56 (22.1)	
Myalgia /Muscle weakness / Asthenia / Muscle hemorrhage / Tendonitis	30 (11.8)	
Rash / Blister / Erythema/ Pruritus / Skin atrophy / Skin discoloration/ Skin exfoliation / Skin hemorrhage	22 (8.7)	
Arthritis / Arthralgia / Costochondritis / Chondropathy	20 (7.9)	
Fractures / Ligament injury	4 (1.6)	
Skin infection / Cellulitis	4 (1.6)	
Nail infection / Onycholysis / Nail growth abnormal	3 (1.2)	
Gout	1 (0.4)	
Osteomyelitis	1 (0.4)	
Alopecia	1 (0.4)	
Neurologic condition	54 (21.3)	
Brain injury / Contusion	18 (7.1)	
Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma	15 (5.9)	
Gait disturbance / Balance disturbance /Vertigo / Vestibular disorder	14 (5.5)	
Cognitive disorders / Memory impairment / Amnesia	11 (4.3)	
Ophthalmological abnormality (visual impairment / Eye movement disorder/ Cataract/ Blepharitis/ Dry eye/ Retinal artery occlusion/ Hemorrhage)	10 (3.9)	
Psychologic disorders / Anxiety / Depression/ Psychosis / Impulsive behavior / Bradyphrenia	5 (2.0)	
Decreased level of consciousness	3 (1.2)	
Insomnia	3 (1.2)	
Seizure / Epilepsy	3 (1.2)	
Peripheral neuropathy /Guillain-Barre / Paresthesia / Hypoesthesia	3 (1.2)	
Encephalitis /meningitis / CNS infection	2 (0.8)	
Nerve injury	2 (0.8)	
Tremor	2 (0.8)	
Headache / Migraine	1 (0.4)	
Urinary incontinence	1 (0.4)	
Withdrawal syndrome	1 (0.4)	
Gastro-intestinal disorders (any)	54 (21.3)	
Diarrhea / Colitis / Gastroenteritis/ Enteritis/ Dehydration	25 (9.8)	
Nausea / Vomiting	9 (3.5)	
Gastrointestinal bleeding	8 (3.1)	
Hepatitis / Hepatic failure / Gallbladder disorders	6 (2.4)	
Dyspepsia / Flatulence	6 (2.4)	
Stomatitis / Dry mouth	6 (2.4)	
Constipation	6 (2.4)	
Dysphagia	5 (2.0)	
Abdominal pain	3 (1.2)	
Gastroesophageal reflux disease	3 (1.2)	

Gastrointestinal obstruction	1 (0.4)	
Diverticulitis	1 (0.4)	
Irritable bowel syndrome	1 (0.4)	
Hematologic condition	44 (17.3)	
Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	19 (7.5)	
Coagulopathy / Bleeding time prolonged / Petechia / Tendency to bruise	13 (5.1)	
Leukocytosis	12 (4.7)	
Anemia	12 (4.7)	
Hypogammaglobulinemia / Immune system disorder	4 (1.6)	
Lymphadenopathy	3 (1.2)	
Splenomegaly	1 (0.4)	
Tumor lysis syndrome	1 (0.4)	
Pulmonary condition	37 (14.6)	
Pneumonia/ Pneumonitis	28 (11.0)	
Respiratory failure	7 (2.8)	
Pleural effusion / Pleural disorders	5 (2.0)	
Chronic obstructive pulmonary disease / Emphysema	4 (1.6)	
Pulmonary hemorrhage	2 (0.8)	
Hemoptysis	2 (0.8)	
Atelectasis	2 (0.8)	
Bronchitis	1 (0.4)	
Bleeding and Hemorrhagic events (CNS, GI, Pulmonary, ...)	31 (12.2)	
Urinary system conditions	27 (10.6)	
Acute kidney injury / Nephropathy / Renal Failure / Blood Uric Acid or Creatinine increased	10 (3.9)	
Urinary tract infection	10 (3.9)	
Urinary incontinence / Urinary retention	2 (0.8)	
Hematuria	1 (0.4)	
Cystitis	1 (0.4)	
Nephrolithiasis	1 (0.4)	
Renal artery occlusion	1 (0.4)	
Renal hemorrhage	1 (0.4)	
Endocrine-metabolic disorders	24 (9.4)	
Fever	8 (3.1)	
Electrolyte imbalance	7 (2.8)	
Glycosylated hemoglobin increased / Blood glucose increased	4 (1.6)	
Hyperlipidemia	2 (0.8)	
Feeling cold / Cold intolerance	1 (0.4)	
Hypothyroidism	1 (0.4)	
Inappropriate antidiuretic hormone secretion	1 (0.4)	

* Other concomitant reported suspected medications were Rituximab (n: 8), Rivaroxaban (n: 5), Bendamustine (n: 5), Cytarabine (n: 2), Dexamethasone (n: 2), Lenalidomide (n: 2), Methotrexate (n: 2), Ampicillin (n: 1), Azithromycin (n: 1), Bortezomib (n: 1), Buparlisib (n: 1), Carfilzomib (n: 1), Cefaclor (n: 1), Cefadroxil (n: 1), Cetirizine (n: 1), Cyclophosphamide (n: 1), Diltiazem (n: 1), Doxorubicin (n: 1), Epinephrine (n: 1), Etoposide (n: 1), Fish oil (n: 1), Flecainide (n: 1), Hydrocodone-Paracetamol (n: 1), Hydrocortisone (n: 1), Iron (n: 1), Obinutuzumab (n: 1), Ofatumumab (n: 1), Palbociclib (n: 1), Prednisone (n: 1), Pregabalin (n: 1), Temozolomide (n: 1), Ticlopidine (n: 1), Venetoclax (n: 1), Vitamin b complex (n: 1), Vitamin d nos (n: 1), and Voriconazole (n: 1).(2 Drugs were under assessment for who-dd .)

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation; CNS, central nervous system.

Supp. Table 8. Clinical characteristics of patients with ibrutinib-associated cardiac ventricular arrhythmias collected from VigiBase (through Jan 2, 2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		70 (100.0)
Americas:	48 (68.6)	
Europe	19 (27.1)	
Australia	2 (2.9)	
Asia	1 (1.4)	
Africa	0 (0.0)	
Reporting Year		70 (100.0)
2018 (*thru January 2018*)	2 (2.9)	
2017	34 (48.6)	
2016	15 (21.4)	
2015	19 (27.1)	
Reporter		67 (95.7)
Health Care Professional	49 (73.1)	
Non-Health Care Professional	18 (26.9)	
Gender		67 (95.7)
Male	49 (73.1)	
Female	18 (26.9)	
Age at onset, mean ± SD (years)	65.3 ± 12.4	54 (77.1)
[min-max]	[8-85]	
Suspected Drugs *		70 (100.0)
Only Ibrutinib	57 (81.4)	
Ibrutinib + 1 other drug	7 (10.0)	
Ibrutinib + ≥2 other drugs	6 (8.6)	
Ibrutinib Dose :		56 (80.0)
140 mg	2 (3.6)	
280 mg	3 (5.4)	
420 mg	40 (71.4)	
560 mg	10 (17.8)	
>560 mg (700 mg)	1 (1.8)	
Time to ADR onset, days**:**		39(55.7)
Median delay between treatment and ADR, median [IQR]	70 [28.5-152.5]	
[min-max]	[1-1002]	
Severe ADR	64 (100.0)	64(91.4)
Outcome		70 (100.0)
Death	7 (10.0)	
Malignant neoplasm progression	2 (2.9)	70 (100.0)
Indications		62 (88.6)
Chronic lymphocytic leukemia	37 (59.7)	
Lymphoma (all variants)	14 (22.6)	
Waldenstrom's macroglobulinemia	9 (14.5)	
Plasma cell myeloma	1 (1.6)	
Acute lymphoblastic leukemia	1 (1.6)	
Reported cardiac ventricular arrhythmias		70 (100.0)
Ventricular tachycardia	31 (44.3)	
Ventricular fibrillation	20 (28.6)	
Ventricular arrhythmia (unspecified)	9 (12.8)	
Ventricular extrasystoles	8 (11.4)	
Torsade de pointes	2 (2.9)	
Concurrent associated conditions		70 (100.0)
None (lone)	19 (27.1)	
Cardiac condition (non-ventricular arrhythmias)	36 (51.4)	

Supra- ventricular arrhythmias (Atrial flutter/ Atrial fibrillation/ Supraventricular tachycardia and extrasystoles)	19 (27.1)	
Cardiogenic shock/ Cardiac arrest	9 (12.9)	
Cardiac failure/ decreased EF/ Pulmonary edema/ Pulmonary Hypertension	7 (10.0)	
Cardiomyopathy	4 (5.7)	
Bradycardia	4 (5.7)	
Hypertension	3 (4.3)	
Myocardial infarction/ Coronary artery disease/Cardiac ischemia	3 (4.3)	
Pericardial effusion	3 (4.3)	
Syncope	3 (4.3)	
Myocarditis	1 (1.4)	
Atrioventricular block	1 (1.4)	
Neurologic condition	19 (27.1)	
Decreased level of consciousness	7 (10.0)	
Encephalopathy	5 (7.1)	
Cognitive-memory impairment / psychosis	3 (4.3)	
Ischemic events / Ischemic stroke	3 (4.3)	
Peripheral neuropathy	2 (2.9)	
Seizure	2 (2.9)	
Ophthalmological abnormality (vision)	2 (2.9)	
Subdural hematoma	2 (2.9)	
Hematologic condition	17 (24.3)	
Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	6 (8.6)	
Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis	5 (7.1)	
Leukocytosis / Lymphocytosis	4 (5.7)	
Anemia	2 (2.9)	
Decreased blood immunoglobulin (A / G / M)	2 (2.9)	
Gastro-intestinal disorders (any)	16 (22.9)	
Diarrhea / Colitis / Gastroenteritis	6 (8.6)	
Gastroesophageal reflux disease	3 (4.3)	
Hepatitis / Abnormal liver function tests	2 (2.9)	
Nausea / Vomiting	2 (2.9)	
Gastrointestinal bleeding	1 (1.4)	
Abdominal pain	1 (1.4)	
Gastrointestinal obstruction	1 (1.4)	
Intestinal perforation	1 (1.4)	
Gastric dysplasia	1 (1.4)	
Pulmonary condition	14 (20.0)	
Pneumonia	9 (12.9)	
Respiratory failure	6 (8.6)	
Pleural effusion	2 (2.9)	
Bronchiolitis	1 (1.4)	
Bronchopulmonary aspergillosis	1 (1.4)	
Dermatologic and Rheumatologic condition	12 (17.1)	
Fatigue / Asthenia	6 (8.6)	
Rash / Panniculitis / Skin atrophy	3 (4.3)	
Costochondritis / arthritis / Arthralgia	3 (4.3)	
Fractures / Ligament injury	3 (4.3)	
Myalgia	2 (2.9)	
Endocrino-metabolic disorders	6 (8.6)	
Electrolyte imbalance	2 (2.9)	
Acidosis	1 (1.4)	
Fever	1 (1.4)	
Hypothermia	1 (1.4)	
Weight increased	1 (1.4)	

Hemorrhagic events	6 (8.6)	
Renal condition	5 (7.1)	
Renal failure /Acute kidney injury	5 (7.1)	

* Other concomitant reported suspected medications were Rituximab (n: 5), Dexamethasone (n: 2), Doxorubicin (n: 2), Azithromycin (n: 1), Carfilzomib (n: 1), Cetirizine (n: 1), Cyclophosphamide (n: 1), Cytarabine (n: 1), Deferasirox (n: 1), Epinephrine (n:1), Etoposide (n:1), Lenalidomide (n: 1), Pegfilgrastim (n:1), Prednisone (n: 1), Sunitinib (n: 1), Temozolomide (n: 1), Ticlopidine (n: 1), Valaciclovir (n: 1), and Vincristine (n: 1).

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation

Supp. Table 9. Clinical characteristics of patients with ibrutinib-associated cardiac conduction disorders collected from VigiBase (through Jan 2, 2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		50(100.0)
Americas:	36 (72.0)	
Europe	14 (28.0)	
Australia	0 (0.0)	
Asia	0 (0.0)	
Africa	0 (0.0)	
Reporting Year		50 (100.0)
2018 (*thru January 2018*)	3 (6.0)	
2017	25 (50.0)	
2016	10 (20.0)	
2015	11 (22.0)	
2014	1 (2.0)	
Reporter		50 (100.0)
Health Care Professional	39 (78.0)	
Non-Health Care Professional	11 (22.0)	
Gender		49 (98.0)
Male	32 (65.3)	
Female	17 (34.7)	
Age at onset, mean ± SD (years)	72.7 ± 13.6	35 (70.0)
[min-max]	[9-91]	
Suspected Drugs *		50 (100.0)
Only Ibrutinib	45 (90.0)	
Ibrutinib + 1 other drug	2 (4.0)	
Ibrutinib + ≥2 other drugs	3 (6.0)	
Ibrutinib Dose :		43 (86.0)
140 mg	5 (11.6)	
280 mg	6 (14.0)	
420 mg	25 (58.1)	
560 mg	7 (16.3)	
>560 mg (700 mg)	0 (0.0)	
Time to ADR onset, days**:**		34 (68.0)
Median delay between treatment and ADR, median [IQR]	27.5 [[1-138.5]	
[min-max]	[1-318]	
Severe ADR	45 (100.0)	45 (90.0)
Outcome		50 (100.0)
Death	9 (18.0)	
Malignant neoplasm progression	3 (6.0)	50 (100.0)
Indications		47 (94.0)
Chronic lymphocytic leukemia	29 (61.7)	
Lymphoma (all variants)	9 (19.1)	
Acute lymphoblastic leukemia	7 (14.9)	
Waldenstrom's macroglobulinemia	2 (4.3)	
Plasma cell myeloma	0 (0.0)	
Reported cardiac conductive disorders		50 (100.0)
Atrioventricular block complete	15 (30.0)	
Bundle branch block right	8 (16.0)	
Atrioventricular block second degree	6 (12.0)	
Atrioventricular block (unspecified)	6 (12.0)	
Atrioventricular block first degree	5 (10.0)	
Bundle branch block left	5 (10.0)	
Conduction disorder (unspecified)	2 (4.0)	
Brugada syndrome	1 (2.0)	

Bifascicular block	1 (2.0)	
Sinoatrial block	1 (2.0)	
Concurrent associated conditions		50 (100.0)
None (lone)	9 (18.0)	
Cardiac condition (non-ventricular arrhythmias)	19 (38.0)	
Supra- ventricular arrhythmias (Atrial flutter/ Atrial fibrillation/ Supraventricular tachycardia and extrasystoles)	11 (22.0)	
Syncope	4 (8.0)	
Myocardial infarction/ Coronary artery disease/Cardiac ischemia	3 (8.0)	
Cardiac failure/ decreased EF / exersional dyspnea	2 (4.0)	
Cardiomyopathy	1 (2.0)	
Torsade de pointes	1 (2.0)	
Valvular diseases	1 (2.0)	
Neurologic condition	12 (24.0)	
Peripheral neuropathy	3 (3.0)	
Cerebral ischemia / Transient ischemic attack / Stroke	2 (4.0)	
Insomnia	2 (4.0)	
Cognitive-memory impairment / Mental status changes / Amnesia	2 (4.0)	
Encephalopathy	1 (2.0)	
Seizure	1 (2.0)	
Vertigo	1 (2.0)	
Speech disorder	1 (2.0)	
Hematologic condition	14 (28.0)	
Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	7 (14.0)	
Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis	7 (14.0)	
Leukocytosis / Lymphocytosis	5 (10.0)	
Anemia	4 (8.0)	
Decreased blood immunoglobulin (A / G / M)	1 (4.0)	
Gastro-intestinal disorders (any)	13 (26.0)	
Diarrhea / Colitis / Gastroenteritis /Dehydration	6 (12.0)	
Abdominal pain / Abdominal discomfort	3 (6.0)	
Cholecystitis / Blood bilirubin increased	2 (4.0)	
Nausea / Vomiting	2 (4.0)	
constipation	2 (4.0)	
Gastrointestinal obstruction	1 (2.0)	
Pulmonary condition	8 (16.0)	
Pneumonia / Pneumonitis	6 (12.0)	
Respiratory failure / Respiratory arrest	2 (4.0)	
Pulmonary fibrosis	1 (2.0)	
Atelectasis	1 (2.0)	
Pleural effusion	1 (2.0)	
Exacerbation of chronic obstructive airways disease	1 (2.0)	
Dermatologic and Rheumatologic condition	13 (26.0)	
Asthenia / Muscular weakness	5 (10.0)	
Rash / Urticaria / Pruritus	5 (10.0)	
Arthritis / Arthralgia	5 (10.0)	
Myalgia / Muscle spasms	4 (8.0)	
Hair texture abnormal	1 (2.0)	
Collagen disorder	1 (2.0)	
Soft tissue infection	1 (2.0)	
Endocrino-metabolic disorders	7 (14.0)	
Electrolyte imbalance	3 (6.0)	
Fever	2 (4.0)	
Blood glucose increased	2 (4.0)	
Inappropriate antidiuretic hormone secretion	1 (2.0)	

Hemorrhagic events	5 (10.0)	
Renal condition	2 (4.0)	
Renal failure /Acute kidney injury	2 (4.0)	

* Other concomitant reported suspected medications were Acebutolol (n: 1), Apixaban (n: 1), Diltiazem (n: 1), Filgrastim (n: 1), Flecainide (n: 1), Lenalidomide (n: 1), Ofatumumab (n: 1), Oseltamivir (n: 1), Pegfilgrastim (n: 1), Prednisone (n:1), Etoposide (n:1), Rituximab (n: 1), Rivaroxaban (n: 1) ,and Valaciclovir (n: 1).

Abbreviations: ADR, adverse drug reactions; [min-max], minimum-maximum; SD, standard deviation