

Cardiovascular Toxicities Associated With Ibrutinib

Joe-Elie Salem, Ali Manouchehri, Marie Bretagne, Bénédicte Lebrun-Vignes, John D Groarke, Douglas B Johnson, Tao Yang, Nishitha M Reddy, Christian Funck-Brentano, Jennifer R Brown, et al.

► To cite this version:

Joe-Elie Salem, Ali Manouchehri, Marie Bretagne, Bénédicte Lebrun-Vignes, John D Groarke, et al.. Cardiovascular Toxicities Associated With Ibrutinib. Journal of the American College of Cardiology, 2019, 74 (13), pp.1667-1678. 10.1016/j.jacc.2019.07.056 . hal-02309367

HAL Id: hal-02309367 https://hal.sorbonne-universite.fr/hal-02309367

Submitted on 9 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Cardiovascular toxicities and Cardiovascular Fatalities Associated with Ibrutinib

Joe-Elie Salem, MD, PhD^{1,2}; Ali Manouchehri, MD²; Marie Bretagne, MD¹; Bénédicte Lebrun-Vignes, MD¹; John D. Groarke, MBBCh, MPH³, Douglas B. Johnson, MD², Tao Yang, MD, PhD²; Nishitha M. Reddy, MD², Christian Funck-Brentano, MD, PhD¹; Jennifer R. Brown, MD, PhD⁴; Dan M. Roden, MD^{2,5}; Javid J. Moslehi, MD².

¹ Sorbonne Université, INSERM CIC-1421, AP-HP, Regional Pharmacovigilance Center, Pitié-Salpêtrière Hospital, UNICO APHP.6 Cardio-Oncology Program, Department of Pharmacology, F-75013 Paris, France.

² Departments of Medicine and Pharmacology, Cardio-Oncology program, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

³ Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.

⁴ CLL Center, Dana-Farber Cancer Institute; Department of Medicine, Harvard Medical School, USA

⁵ Department of Biomedical informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

Contact Information: Javid Moslehi, M.D. Cardio-Oncology Program, Vanderbilt University Medical Center, 2220 Pierce Avenue, Nashville, TN 37232, Phone: 615-343-9436; Fax: 615-936-1872; Email: javid.moslehi@vumc.org or Joe-Elie Salem, M.D., Ph.D, Centre d'Investigation Clinique Paris-Est, Hôpital Pitié-Salpêtrière, Bâtiment Antonin Gosset, 47-83 Bld de l'hôpital, 75013 Paris, France. Secretariat: +33 1 42 17 85 31, Fax: +33 1 42 17 85 32; Email: joe-elie.salem@aphp.fr.

Abstract: 250 words (Limit: 250) Word Count: 3145; Tables: 2; Figures: 3

Key Words: ibrutinib, oncology, cardiology, cardiac failure, atrial fibrillation, ventricular tachycardia, cardio-oncology

NCT: NCT03530215

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; IC₀₂₅ (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; IC₀₂₅:3.97), central nervous system (CNS) hemorrhagic events (ROR:3.7[3.4-4.1],p<0.0001; IC₀₂₅:1.63), heart failure (HF, ROR:3.5[3.1-3.8],p<0.0001; IC₀₂₅:1.46), ventricular arrhythmias (VA, ROR:4.7[3.7-5.9],p<0.0001; IC₀₂₅:0.96), conduction disorders (CD, ROR:3.5[2.7-4.6],p<0.0001; IC₀₂₅:0.76), CNS ischemic events (ROR:2.2[2.0-2.5],p<0.0001; IC₀₂₅:0.73) and hypertension (ROR:1.7[1.5-1.9],p<0.0001; IC₀₂₅:0.4). 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 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) IC₀₂₅ is the lower end of a 95% credibility interval for the Information Component. A positive IC₀₂₅ 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 Chi², described and used elsewhere (Supplemental Table-2).^(13,18-21) The lower end of ROR 95% confidence interval (CI) \geq 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 (\pm 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

Chi²-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; IC₀₂₅:3.97), central nervous system (CNS) hemorrhagic events (ROR:3.7[3.4-4.1],p<0.0001; IC₀₂₅:1.63), heart failure (HF; ROR:3.5[3.1-3.8],p<0.0001; IC₀₂₅:1.46), ventricular arrhythmias (VA; ROR:4.7[3.7-5.9],p<0.0001; IC₀₂₅:0.96), conduction disorders (CD; ROR:3.5[2.7-4.6],p<0.0001; IC₀₂₅:0.76), CNS ischemic events (ROR:2.2[2.0-2.5],p<0.0001; IC₀₂₅:0.73) and hypertension (ROR:1.7[1.5-1.9],p<0.0001; IC₀₂₅:0.4). 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).

<u>Characteristics of patients</u>

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).

<u>Timing</u>

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 metaanalyses of clinical trials where atrial fibrillation was significantly more commonly observed in ibrutinibtreated 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 betablockers (24%) and less often other types of anti-arrhythmics ($\leq 6\%$, 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-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 Ca2+ 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-} 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 (\leq 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.

Disclosures. JJM has served on advisory boards at Pharmacyclics, Bristol Myers, Pfizer, Novartis, Regeneron, Takeda, Deciphera and Myokardia and has received research funding from Pfizer and Bristol Myers Squibb. DBJ has served on advisory boards for Array Biopharma, BMS, Genoptix, Incyte, Merck, and Novartis, and has received research funding from BMS and Incyte. JRB has served as a consultant for Abbvie, Acerta, Astellas, Beigene, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, Novartis, Pfizer, Pharmacyclics, Redx, Sun, Sunesis, TG Therapeutics, Verastem; received honoraria from Janssen and Teva; received research funding from Gilead, Loxo, Sun and Verastem; and served on data safety monitoring committees for Morphosys and Invectys. NMR has served as a consultant for BMS, Abbvie, KiTe, Genentech, Bayer, TG therapeutics; received research funding from BMS, Celgene. JDG receives research funding from Amgen Pharamaceuticals. The other authors have no conflict of interest to disclose. The supplied data from VigiBase come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the UMC or the World Health Organization.

Funding. The Cancer ITMO of the French National Alliance for Life and Health Sciences (AVIESAN): "Plan Cancer 2014-2019" (JES). Funding sources had no role in study design, collection, analysis or interpretation of the data, neither in the writing of the manuscript nor the decision to submit it for publication. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Bibliography.

- 1. Miklos D, Cutler CS, Arora M et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017;130:2243-2250.
- 2. Byrd JC, Furman RR, Coutre SE et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42.
- 3. Burger JA, Tedeschi A, Barr PM et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 2015;373:2425-37.
- 4. Dreyling M, Jurczak W, Jerkeman M et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet 2016;387:770-8.
- 5. Treon SP, Tripsas CK, Meid K et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med 2015;372:1430-40.
- 6. FDA. Ibrutinib FDA label SUPPL-25. https://wwwaccessdatafdagov/drugsatfda_docs/label/2018/205552s025lblpdf 08/24/2018.
- 7. Brown JR, Moslehi J, O'Brien S et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica 2017;102:1796-1805.
- 8. Brown JR, Hillmen P, O'Brien S et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. Leukemia 2018;32:83-91.
- 9. Leong DP, Caron F, Hillis C et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood 2016;128:138-40.
- 10. Guha A, Derbala MH, Zhao Q et al. Ventricular Arrhythmias Following Ibrutinib Initiation for Lymphoid Malignancies. J Am Coll Cardiol 2018;72:697-698.
- 11. Lampson BL, Yu L, Glynn RJ et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. Blood 2017;129:2581-2584.
- 12. Woyach JA, Ruppert AS, Heerema NA et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med 2018;379:2517-2528.
- 13. Salem JE, Manouchehri A, Moey M et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19:1579-1589.
- 14. Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Information Journal 2008;42:409-419.
- 15. Mertz P, Lebrun-Vignes B, Salem JE, Arnaud L. Characterizing drug-induced capillary leak syndromes using the World Health Organization VigiBase. J Allergy Clin Immunol 2018.
- 16. Bate A, Lindquist M, Edwards IR et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998;54:315-21.
- 17. Noren GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Stat Methods Med Res 2013;22:57-69.
- 18. De Bruin ML, Pettersson M, Meyboom RH, Hoes AW, Leufkens HG. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. Eur Heart J 2005;26:590-7.
- 19. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf 2004;13:519-23.
- 20. Grouthier V, Lebrun-Vignes B, Glazer AM et al. Increased long QT and torsade de pointes reporting on tamoxifen compared with aromatase inhibitors. Heart 2018;104:1859-1863.
- 21. Salem JE, Dureau P, Bachelot A et al. Association of Oral Contraceptives With Drug-Induced QT Interval Prolongation in Healthy Nonmenopausal Women. JAMA Cardiol 2018;3:877-882.

- 22. Lipsky AH, Farooqui MZ, Tian X et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. Haematologica 2015;100:1571-8.
- 23. Busygina K, Jamasbi J, Seiler T et al. Oral Bruton tyrosine kinase inhibitors selectively block atherosclerotic plaque-triggered thrombus formation in humans. Blood 2018;131:2605-2616.
- 24. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost 2017;15:835-847.
- 25. de Jong J, Hellemans P, Jiao JJ et al. Ibrutinib does not prolong the corrected QT interval in healthy subjects: results from a thorough QT study. Cancer Chemother Pharmacol 2017;80:1227-1237.
- 26. O'Brien S, Hillmen P, Coutre S et al. Safety Analysis of Four Randomized Controlled Studies of Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Mantle Cell Lymphoma. Clin Lymphoma Myeloma Leuk 2018;18:648-657 e15.
- 27. Ganatra S, Sharma A, Shah S et al. Ibrutinib-Associated Atrial Fibrillation. JACC: Clinical Electrophysiology 2018;4:1491-1500.
- 28. Wiczer TE, Levine LB, Brumbaugh J et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv 2017;1:1739-1748.
- 29. Thompson PA, Levy V, Tam CS et al. Atrial fibrillation in CLL patients treated with ibrutinib. An international retrospective study. Br J Haematol 2016;175:462-466.
- 30. Salem JE, Dureau P, Funck-Brentano C et al. Effectiveness of heart rate control on hemodynamics in critically ill patients with atrial tachyarrhythmias managed by amiodarone. Pharmacol Res 2017;122:118-126.
- 31. Pretorius L, Du XJ, Woodcock EA et al. Reduced phosphoinositide 3-kinase (p110alpha) activation increases the susceptibility to atrial fibrillation. Am J Pathol 2009;175:998-1009.
- 32. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood 2014;124:3829-30.
- 33. Alexandre J, Moslehi JJ, Bersell KR, Funck-Brentano C, Roden DM, Salem JE. Anticancer druginduced cardiac rhythm disorders: Current knowledge and basic underlying mechanisms. Pharmacol Ther 2018;189:89-103.
- 34. Salem JE, Sabouret P, Funck-Brentano C, Hulot JS. Pharmacology and mechanisms of action of new oral anticoagulants. Fundam Clin Pharmacol 2015;29:10-20.
- 35. Mathur K, Saini A, Ellenbogen KA, Shepard RK. Profound Sinoatrial Arrest Associated with Ibrutinib. Case Rep Oncol Med 2017;2017:7304021.
- 36. Tse G, Chan YW, Keung W, Yan BP. Electrophysiological mechanisms of long and short QT syndromes. Int J Cardiol Heart Vasc 2017;14:8-13.
- 37. Cheng S, Keyes MJ, Larson MG et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA 2009;301:2571-7.
- 38. Park J, Kim TH, Lee JS et al. Prolonged PR interval predicts clinical recurrence of atrial fibrillation after catheter ablation. J Am Heart Assoc 2014;3:e001277.
- 39. Mosley JD, Shoemaker MB, Wells QS et al. Investigating the Genetic Architecture of the PR Interval Using Clinical Phenotypes. Circ Cardiovasc Genet 2017;10.
- 40. Cheng C, Woronow D, Nayernama A, Wroblewski T, Jones SC. Ibrutinib-associated ventricular arrhythmia in the FDA Adverse Event Reporting System. Leuk Lymphoma 2018;59:3016-3017.
- 41. Poglajen G, Fister M, Radovancevic B, Vrtovec B. Short QT interval and atrial fibrillation in patients without structural heart disease. J Am Coll Cardiol 2006;47:1905-7.

- 42. Tomcsanyi J, Nenyei Z, Matrai Z, Bozsik B. Ibrutinib, an Approved Tyrosine Kinase Inhibitor as a Potential Cause of Recurrent Polymorphic Ventricular Tachycardia. JACC Clin Electrophysiol 2016;2:847-849.
- 43. Beyer A, Ganti B, Majkrzak A, Theyyunni N. A Perfect Storm: Tyrosine Kinase Inhibitor-Associated Polymorphic Ventricular Tachycardia. J Emerg Med 2017;52:e123-e127.
- 44. Leenhardt A, Glaser E, Burguera M, Nurnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsade de pointes. A new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. Circulation 1994;89:206-15.
- 45. Fujii Y, Itoh H, Ohno S et al. A type 2 ryanodine receptor variant associated with reduced Ca(2+) release and short-coupled torsades de pointes ventricular arrhythmia. Heart Rhythm 2017;14:98-107.
- 46. Pereira L, Bare DJ, Galice S, Shannon TR, Bers DM. beta-Adrenergic induced SR Ca(2+) leak is mediated by an Epac-NOS pathway. J Mol Cell Cardiol 2017;108:8-16.
- 47. Abehsira G, Bachelot A, Badilini F et al. Complex Influence of Gonadotropins and Sex Steroid Hormones on QT Interval Duration. J Clin Endocrinol Metab 2016;101:2776-84.
- 48. Salem JE, Waintraub X, Courtillot C et al. Hypogonadism as a Reversible Cause of Torsades de Pointes in Men. Circulation 2018;138:110-113.
- 49. Salem JE, Alexandre J, Bachelot A, Funck-Brentano C. Influence of steroid hormones on ventricular repolarization. Pharmacol Ther 2016;167:38-47.
- 50. Wasserstrum Y, Raanani P, Kornowski R, Iakobishvili Z. Concomitant Treatment with Ibrutinib and Amiodarone Causing Reversible Heart Failure Syndrome. Isr Med Assoc J 2016;18:433-434.
- 51. Wallace N, Wong E, Cooper D, Chao H. A case of new-onset cardiomyopathy and ventricular tachycardia in a patient receiving ibrutinib for relapsed mantle cell lymphoma. Clin Case Rep 2016;4:1120-1121.
- 52. Chen J, Kinoshita T, Sukbuntherng J, Chang BY, Elias L. Ibrutinib Inhibits ERBB Receptor Tyrosine Kinases and HER2-Amplified Breast Cancer Cell Growth. Mol Cancer Ther 2016;15:2835-2844.
- 53. Zamorano JL, Lancellotti P, Rodriguez Munoz D et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768-2801.
- 54. Aoyagi T, Matsui T. Phosphoinositide-3 kinase signaling in cardiac hypertrophy and heart failure. Curr Pharm Des 2011;17:1818-24.
- 55. Aguilar C. Ibrutinib-related bleeding: pathogenesis, clinical implications and management. Blood Coagul Fibrinolysis 2018;29:481-487.
- 56. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. N Engl J Med 2016;375:1457-1467.

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. <u>Panel A</u>: Due to diagram limitation, the overlap between VA and CD (n:1), or VA and HF (n:7) groups are not displayed. <u>Panel B</u>: 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. <u>*CNS*</u>: central nervous system

Table 1. Information component (IC) and its 95% credibility interval lower endpoint (IC₀₂₅) 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 IC₀₂₅ 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; 95CI[,]
Total number of ICSRs available	13,572	16,343,451		8,318,890	
	Number of IC	SRs and statistics by (CV-ADR subgr	oups	
Cardiac supra-ventricular		_	<u>U</u>		
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					3.5 [2.7-4.6]
disorders (CD)	50 (0.37%)	26008 (0.16%)	1.19/0.76	8834 (0.11%)	
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				NA	NA
events	108 (0.80%)	134718 (0.82%)	-0.05/-0.34		
Vascular neoplasms	2 (0.01%)	2687 (0.02%)	-0.13/-2.72	NA	NA
Pulmonary hypertension				NA	NA
and cardiac involvements	19 (0.14%)	30718 (0.19%)	-0.42/-1.14		
Hyperglycemia, diabetes	112 (0.83%)	233007 (1.43%)	-0.79/-1.07	NA	NA
Torsade de pointes/QT				NA	NA
prolongation	9 (0.07%)	20938 (0.13%)	-0.91/-2.01		
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 \pm 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 $+ \ge 2$ 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	133/758 (17.6)	10/56 (17.8)	7/43 (16.3)	53/320 (16.5)	34/271 (12.5)	28/229 (12.2)	52/395 (13.2)
>560 mg	9/758 (1.2)	1/56 (1.8)	0/43 (0.0)	0/320 (0.0)	0/295 (0.0)	4/229 (1.7)	5/395 (1.3)
Time to ADR onset (days),	381 (39.7)	39 (55.7)	34 (68.0)	154 (42.4)	21 (7.1)	84 (33.1)	74 (14.7)
Median	74	70	27.5	54	164	51	53.5
[IQR]	[29.5-196.5]	[28.5-152.5]	[1-138.5]	[20.3-142.8]	[20-274]	[17.5-160]	[20.3-183.3]
[min-max]	[1-1299]	[1-1002]	[1-318]	[1 - 929]	[1-806]	[1-902]	[1-741]
Severe ADR*	862 (89.9)	64 (91.4)	45 (90.0)	357 (98.3)	226 (76.6)	248 (97.6)	495 (98.0)
	591/862 (68.6)	64/64 (100.0)	45/45 (100.0)	357/357 (100.0)	226/226 (100)	248/248 (100.0)	495/495 (100)
Outcome	959 (100.0)	70 (100.0)	50 (100.0)	363 (100.0)	295 (100.0)	254 (100.0)	505 (100.0)
Death	103/959 (10.7)	7/70 (10.0)	9/50 (18.0)	76/363 (20.9)	0/295 (0.0)	48/254 (18.9)	90/505 (17.8)
Indications	867 (90.4)	62 (88.6)	47 (94.0)	348 (95.9)	288 (97.6)	237 (93.3)	474 (93.9)
Chronic lymphocytic leukemia	608/867 (70.1)	37/62 (59.7)	29/47 (61.7)	232/348 (66.7)	209/278 (72.6)	177/237 (74.7)	337/474 (71.1)
Lymphoma (all types)	190/867 (21.9)	14/62 (22.6)	9/47 (19.1)	83/348 (23.9)	42/278 (14.6)	41/237 (17.3)	97/474 (20.5)
Waldenstrom's macroglobulinemia	53/867 (6.2)	9/62 (14.5)	2/47 (4.3)	24/348 (6.9)	31/278 (10.7)	15/237 (6.4)	28/474 (5.9)
Myeloma / Myelodysplasia	8/867 (0.9)	1/62 (1.6)	0/47 (0.0)	3/348 (0.9)	0/278 (0.0)	1/237 (0.4)	4/474 (0.8)
Acute lymphoblastic leukemia	3/867 (0.3)	1/62 (1.6)	7/47 (14.9)	3/348 (0.9)	2/278 (0.7)	2/237 (0.8)	5/474 (1.1)
Other	5/867 (0.6)	0/62 (0.0)	0/47 (0.0)	3/348 (0.9)	4/278 (1.4)	1/237 (0.4)	3/474 (0.6)

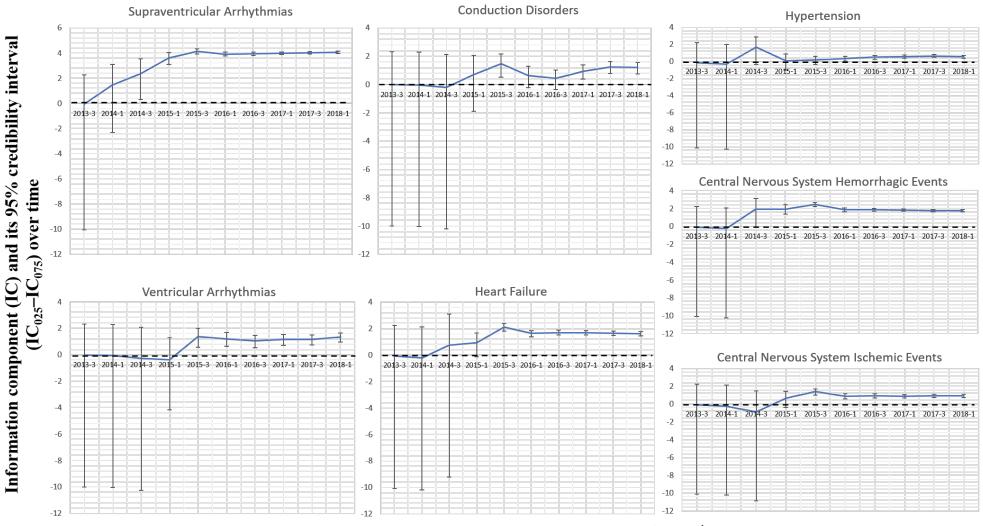
*A severe ADR was defined as such when being life-threatening, leading to persistent or significant disability, birth defect, congenital anomaly, or to any other medically important conditions, requiring hospitalization (initial or prolonged) or when causing death.

[#] 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 IC₀₂₅ 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).



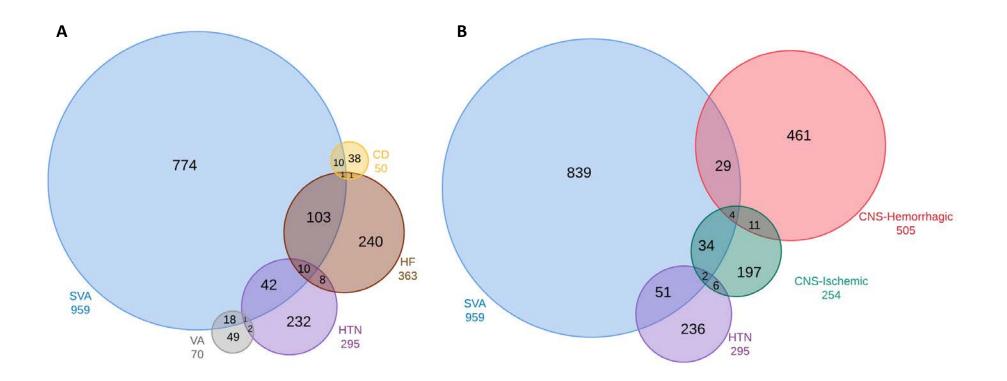
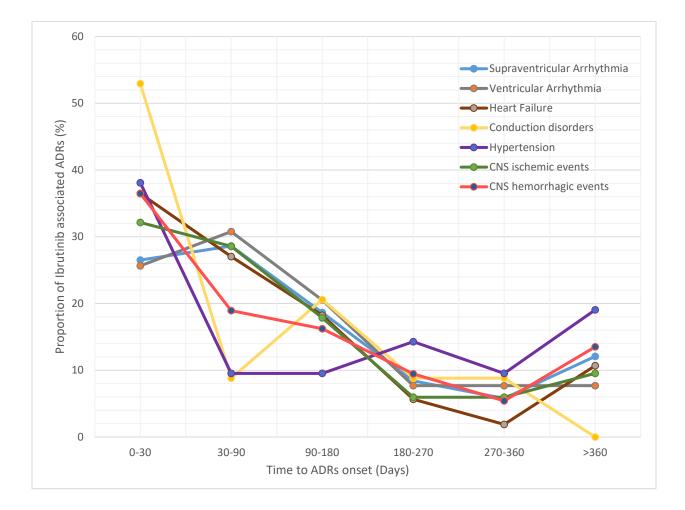


Figure 3



Cardiovascular toxicity of ibrutinib: a pharmacovigilance study.

Joe-Elie Salem, MD, PhD^{1,2}; Ali Manouchehri, MD²; Marie Bretagne, MD¹; Bénédicte Lebrun-Vignes, MD¹; John D. Groarke, MBBCh, MPH³, Douglas B. Johnson, MD², Tao Yang, MD, PhD²; Nishitha M. Reddy, MD², Christian Funck-Brentano, MD, PhD¹; Jennifer R. Brown, MD, PhD⁴; Dan M. Roden, MD^{2,5}; Javid J. Moslehi, MD².

¹ Sorbonne Université, INSERM CIC-1421, AP-HP, Regional Pharmacovigilance Center, Pitié-Salpêtrière Hospital, Department of Pharmacology, F-75013 Paris, France.

² Departments of Medicine and Pharmacology, Cardio-oncology program, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

³ Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.

⁴ CLL Center, Dana-Farber Cancer Institute; Department of Medicine, Harvard Medical School, USA

⁵ Department of Biomedical informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

Contact Information: Javid Moslehi, M.D. Cardio-Oncology Program, Vanderbilt University Medical Center, 2220 Pierce Avenue, Nashville, TN 37232, Phone: 615-343-9436; Fax: 615-936-1872; Email: javid.moslehi@vumc.org or Joe-Elie Salem, M.D., Ph.D, Centre d'Investigation Clinique Paris-Est, Hôpital Pitié-Salpêtrière, Bâtiment Antonin Gosset, 47-83 Bld de l'hôpital, 75013 Paris, France. Secretariat: +33 1 42 17 85 31, Fax: +33 1 42 17 85 32; Email: joe-elie.salem@aphp.fr.

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 \pm 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 \pm acne; digoxin \pm rash).^{3,4}

The statistical formula is as follows,

$$IC = \log 2 \left((N_{observed} + 0.5) / (N_{expected} + 0.5) \right)$$
(1)

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

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

Nobserved: 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

Neffect: the number of case reports for the adverse effect, regardless of drug

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

- 1. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol.* 2018;19(12):1579-1589.
- 2. Mertz P, Lebrun-Vignes B, Salem JE, Arnaud L. Characterizing drug-induced capillary leak syndromes using the World Health Organization VigiBase. *J Allergy Clin Immunol.* 2018.
- 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.
- 4. Noren GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent largescale pattern discovery. *Stat Methods Med Res.* 2013;22(1):57-69.

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	Reports without the suspected
	ADR	ADR
Reports with suspected group of drugs (example: ibrutinib)	A	В
Reports with comparator group of drugs (example: entire database)	С	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).

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

(1)

<u>Abbreviations</u>: 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	Ventricular	Conductive	Heart Failure	Hypertension	CNS ischemic	CNS Hemorrhagic
	Arrhythmia	Tachyarrhythmia	Disorders			Events	Events
Supraventricular		19/959 (2.0%)	11/959 (1.1%)	114/959 (11.9%)	53/959 (5.5%)	40/959 (4.2%)	33/959 (3.4%)
Arrhythmia (n=959)							
Ventricular	19/70 (27.1%)		1/70 (1.4%)	7/70 (10.0%)	3/70 (4.3%)	3/70 (4.3%)	2/70 (2.9%)
Tachyarrhythmia (n=70)							
Conductive Disorders	11/50 (22.0%)	1/50 (2.0%)		2/50 (4.0%)	0/50 (0.0%)	2/50 (4.0%)	0/50 (0.0%)
(n=50)							
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	40/254 (15.7%)	3/254 (1.2%)	2/254 (0.8%)	6/254 (2.4%)	8/254 (3.1%)		15/254 (5.9%)
(n=254)							
CNS Hemorrhagic Events	33/505 (6.5%)	2/505 (0.4%)	0/505 (0.0%)	6/505 (1.2%)	11/505 (2.2%)	15/505 (3.0%)	
(n=505)							

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)
<u>0.4</u>		050 (400.0)
Outcome	102 (10 7)	959 (100.0)
Death Malignant receiver an annual annua	103 (10.7)	050 (100 0)
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)	

<u>Cardiac condition (non-ventricular arrhythmias)</u>	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)
<u>Neurologic condition</u>	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)
	- \/

	I I I I I I I I I I I I I I I I I I I
<u>Gastro-intestinal disorders (any)</u>	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).

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

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)	505 (100.0)
Malignant neoplasm progression	17 (3.4)	505 (100.0)
	17 (3.4)	
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)	

Neurologic condition 138 Brain injury / Contusion 45 Headache 21 Loss of consciousness, Depressed level of consciousness 20 Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention 19	505 (100.0) 6 (36.8) 8 (27.3) (8.9) (4.2) (4.0) (3.8)
Neurologic condition 138 Brain injury / Contusion 45 Headache 21 Loss of consciousness, Depressed level of consciousness 20 Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention 19	8 (27.3) (8.9) (4.2) (4.0) (3.8)
Brain injury / Contusion45Headache21Loss of consciousness, Depressed level of consciousness20Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention19	(8.9) (4.2) (4.0) (3.8)
Brain injury / Contusion45Headache21Loss of consciousness, Depressed level of consciousness20Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention19	(8.9) (4.2) (4.0) (3.8)
Headache21Loss of consciousness, Depressed level of consciousness20Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention19	(4.2) (4.0) (3.8)
Loss of consciousness, Depressed level of consciousness20Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention19	(4.0) (3.8)
Cognitive disorders / Memory impairment / Amnesia/ Hallucination/ Disturbance in attention 19	(3.8)
	(3.8)
	(3.0)
	(3.0)
	(3.0)
Ophthalmological abnormality (visual impairment / Eye movement disorder/Diplopia/ Cataract/	(3.0)
	(2.0)
	(2.0)
	1.8)
	1.6)
	1.4)
	1.4)
	1.0)
Hearing disorders 5 (2	1.0)
Tremor 4 (0	0.8)
	0.8)
Hematologic condition 91	(18.0)
	(13.3)
	(5.5)
	(3.8)
	(4.7)
	0.8)
	0.2)
	0.4)
	0.4)
	0.4)
Tumor lysis syndrome 1 (0	0.4)
	(14.5)
	(6.6)
extrasystoles / Sinus tachycardia)	
Increased blood pressure / Hypertension 11	(2.2)
Myocardial infarction/ Coronary artery disease/Cardiac ischemia 9 (2	1.8)
Thrombosis / embolus (Thrombosis, Deep vein thrombosis, Pulmonary embolism) 6(1	1.2)
	1.2)
	1.0)
	1.0)
	1.2)
	1.2)
	0.4)
	0.4)
Hypotension (Orthostatic hypotension/ Blood pressure decreased) 2(0 Gardia gardia shark (Gardian amount) 2/0	
	0.4)
	0.2)
	0.2)
Peripheral vascular disorder 1 (0	0.2)
Dermatologic and Phaumatologic condition	(14 5)
	(14.5)
	(8.9)
Rash / Blister / Erythema/ Pruritus / Skin atrophy / Skin discoloration/ Skin exfoliation / Skin	()
5	(6.7)
	(3.6)
	(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)
- 1.800.0	- (0.1)
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)
	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), Valproic acid (n: 1), Vitamin D (n: 1), Venlafaxine (n: 1), Voriconazole (n: 1).

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

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]	200 (72.0)
Suspected Drugs *		363 (100.0)
Only Ibrutinib	323 (89.0)	505 (100.0)
Ibrutinib + 1 other drug	32 (8.8)	
Ibrutinib + ≥ 2 other drugs	8 (2.2)	
Ibrutinib Dose :	0 (2.2)	320 (88.2)
140 mg	13 (4.1)	520 (88.2)
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:	0 (0.0)	154 (42.4)
Median delay between treatment and ADR, median [IQR]	54 [20.3 – 142.8]	154 (42.4)
[min-max]	[1-929]	257 (00.2)
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)	5-0 (55.5)
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	5 (0.5)	363 (100.0)
		303 (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)	

Name I donce59 (16.3)50 (15000)Cardiac condition Inner-cardiac fulturel191914Cardiac condition Inner-cardiac fulturel191414Suproventricular arrythmias (Suproventricular tachycardia/Atrial fibrillation/Atrial191414Hypertension / Robot persure increased11414141414Myocardial Infarction/Acute Caronary Syndrome/Caronary artery occlusion/Perpheral Vacular151414Myocardial Infarction/Acute Caronary Syndrome/Caronary artery occlusion/Troponin increase131414Myocardial Infarction/Acute Caronary Syndrome/Caronary artery occlusion/Troponin increase101814Myocardial Caronardia7112161414Indocardia2120 <t< th=""><th>Concurrent associated conditions</th><th></th><th>363 (100.0)</th></t<>	Concurrent associated conditions		363 (100.0)
Cardiac condition (non-cardiac fullure)169 (45.6)Supraventrukular arrhythmis (Supraventrukur tachycardia/Atrial fibrillation/Atrial114 (31.4)Hypertension / Bload pressure increased114 (31.4)Thrombotic event/Superticity15 (4.1)Disease/Deep Vein Thrombosis/super Vena Cava occlusion/Peripheral Vascular15 (4.1)Disease/Deep Vein Thrombosis/super Vena Cava occlusion/Peripheral Vascular13.5.9)Oxycardial Infraction/Acute Coronary Syndrome/Coronary artery occlusion/Troponin incress13.5.9)Cardiomoyopathy10.2.8)Valvular disesse/dysfunction8 (2.2)Ventricular transport10.2.8)Valvular disesse/dysfunction8 (2.2)Ventricular transport20.06Bundle Branch Block20.06Wentrolider Transport77 (2.1)Contaions77 (2.1)Contaions13.6.3)Migraine/Photophobia/Headache10.4.4.1Dizaless10.2.8.1Menal impairment/Definiur/Confusional state/Attered Mental Status11.3.0)Personality change/Aneity/Depression/Hyperupillance/Psychosis/Halucination/Logarrhea61.7.1Gardi disturance/Aneity/Depression/Hyperension/Logarrhea61.7.1Gardi disturance/Aneity/Depression/Hyperension/Acrebal hemorinage/Cocluar hyperension10.2.8.1State discored11.3.0Visual Impairment/Annesia51.4.4Neuropathy (Mypoeshial/Aneita/Attered Mental Status51.4.4Neuropathy (Mypoeshial/Aneita/Attered Mental Status61.7.1Consciouses/Unresponsive to stimuli61.7.1Conscious		50 (16 3)	505 (100.0)
Suppresent/clair arrhythmis (Suppresent/clair facty/ardia/Atrial fibrillation/AtrialI 14 (31.4)Hypertension / Blood pressure increased114 (31.4)Hypertension / Blood pressure increased13 (4.1)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Peripheral Vacuum13 (3.9)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Peripheral Vacuum13 (3.9)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Troponin increase13 (3.9)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Troponin increase13 (3.9)Periodal hermorthage/Periodal efficient13 (3.9)Disease/Optimal disease/dysfunction8 (2.2)Periodal hermorthage/Periodal efficient14 (1.1)Endocarditis2 (0.6)Bandy ardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurologic condition23 (6.3)Contusions23 (6.3)Dizanese14 (3.1)Berodraftis13 (3.0)Personality change/Ansity/Depression/Hyperension/SylFalucinations/Logarther13 (3.0)Berodraftis13 (3.0)Personality change/Ansity/Depression/Hyperension/SylFalucinations/Logarther13 (3.0)Stati disturbance/Stati Sylfand change/Stati Sylfand change/Stati Sylfand13 (3.0)Personality change/Stati Sylfand change/Stati Sylfand change/Stati Sylfand13 (3.0)Personality change/Stati Sylfand change/Stati		55 (10.5)	
Suppresent/clair arrhythmis (Suppresent/clair facty/ardia/Atrial fibrillation/AtrialI 14 (31.4)Hypertension / Blood pressure increased114 (31.4)Hypertension / Blood pressure increased13 (4.1)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Peripheral Vacuum13 (3.9)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Peripheral Vacuum13 (3.9)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Troponin increase13 (3.9)Disease/Deep Vein Thrombois/Suppre Yena Cava occlusion/Troponin increase13 (3.9)Periodal hermorthage/Periodal efficient13 (3.9)Disease/Optimal disease/dysfunction8 (2.2)Periodal hermorthage/Periodal efficient14 (1.1)Endocarditis2 (0.6)Bandy ardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurologic condition23 (6.3)Contusions23 (6.3)Dizanese14 (3.1)Berodraftis13 (3.0)Personality change/Ansity/Depression/Hyperension/SylFalucinations/Logarther13 (3.0)Berodraftis13 (3.0)Personality change/Ansity/Depression/Hyperension/SylFalucinations/Logarther13 (3.0)Stati disturbance/Stati Sylfand change/Stati Sylfand change/Stati Sylfand change/Stati Sylfand change/Stati Sylfand change/Stati Sylfand change/Stati Sylfand change13 (3.0)Personality change/Stati Sylfand change/Sta	Cardiac condition (non-cardiac failure)	160 (46 6)	
flutter/Tachyardia/Heart Rate increase)114 (31.4)Hypertension / Blood pressure increased185.0)Thrombotic events (Ventricular thrombosis/Super Vena Cava occlusion/Peripheral Vascular14.13.0)Bioesay/Deep Veni Thrombosis/Super Vena Cava occlusion/Peripheral Vascular14.13.0)Myocardial Infarction/Acute Coronary Syndrome/Coronary artery occlusion/Tropanin increase14.13.0)Valuar disease/dysfunction8 (2.2)Pericardial Hemorrhage/Pericardial effusion/Ventricular tachycardia)7 (1.9)Cardiomopaly2 (0.6)Bradycardia/Heart Rate decrease3 (0.8)Bradycardia/Heart Rate decrease16 (4.4)Diziness16 (4.3)Bradycardia/Heart Rate/Atter/Atten/Atter/Atten/Atter/Atten/Atter/Atten/Attas/Atter/Atter/Attas/Atter/Attas/Atter/Attas/Atter/Attas/Atter/Attas/Atter/Attas/Atter/Attas/Atter/Attas/Atter/Attas/Attas/Atter/Attas/Attas/Atter/Attas/Atter/Attas/Attas/Atter/Attas/Attas/Atter/Attas/Attas/Atter/Attas/Attas/Attas/Atter/Attas/Attas/Attas/Atter/Attas/Attas/Attas/Atter/Attas/Attas/Atter/Attas/Atta		109 (40.0)	
Hypertension / Blood pressure increased18(30)Trombotic events / Ventricular thrombosis/Super Vena Cava occlusion/Peripheral Vascular15 (4.1)Disease/Deep Vein Thrombosis/15 (4.1)Woycardial Infaction/Acute Coronary Syndrome/Coronary artery occlusion/Troponin increase10 (2.8)Cardiomyopathy10 (2.8)Valvalar disease/dysfunction8 (2.2)Valvalar disease/dysfunction8 (2.2)Ventricular arthythmias (Ventricular fibrillation/Ventricular tachycardia)7 (1.9)Endoardinis2 (0.6)Bradyardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurologic condition21 (3.6)Contusions21 (3.6)Contusions11 (3.0)Neurologic condition12 (3.3)Contusions11 (3.0)Valvalar/Babance disorder11 (3.0)Valvalaring/Notionphobia/Headache12 (3.3)Distriess11 (3.0)Valvalaring/Notionphobia/Headache11 (3.0)Distriess11 (3.0)Valvalaring/Notionphobia/Headache11 (3.0)Distriess5 (1.4)Contusions5 (1.4)Contusions5 (1.4)Valvalaring/Notionphotia/Headache11 (3.0)Distriess5 (1.4)Contusions5 (1.4)Contusions5 (1.4)Contusions5 (1.4)Distriess5 (1.4)Contusions5 (1.4)Contusions5 (1.4)Contusions5 (1.4)Contusions5 (1.4)Contusions<		444 (24 4)	
Trombolic events (Ventricular thrombosis/Super Vena Cava occlusion/Peripheral Vascular Disease/Deep Vern Trombosis) Myocardial Infarction/Acute Coronary Syndrome/Coronary artery occlusion/Troponin increase (ardiomyopathy) 10 [2.8] Syncope / Presyncope 10 [2.8] Valuar disease/dystimution 10 [2.8] Pericardial effusion/Medisatinal effusion 10 [2.8] Pericardial effusion/Medisatinal effusion 10 [2.8] Pericardial hemorrhage/Pericardial effusion/Medisatinal effusion 10 [2.8] Pericardial hemorrhage/Pericardial effusion/Medisatinal effusion 10 [2.8] 10 [2.9] Cardiomopaly Pericardial hemorrhage/Pericardial effusion/Medisatinal effusion 10 [2.8] 10 [2.1] 10 Cardiomopaly 10 [2.6] 10 [2.		. ,	
Disease/Deep Vein Thromobosis)15 (4.1)Worcardial Infaction/Acute Coronary Syndrome/Coronary artery occlusion/Troponin Increas10 (2.8)Cardiomyopathy10 (2.8)Valvular disease/dysfunction8 (2.2)Valvular disease/dysfunction8 (2.2)Ventricular arrhythmias (Ventricular fibrillation/Ventricular tachycardia)7 (1.9)Cardiomegaly2 (0.6)Bardyardia/Heart Rate decrease3 (0.8)Bardyardia/Heart Rate decrease3 (0.8)Bardyardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurologic condition27 (6.1)Contusions21 (6.3)Bradyardia/Heart Rate decrease10 (2.8)Bindre Photophobia/Headache11 (3.0)Dizzhess11 (3.0)Bradyardia/Heart Rate decrease10 (2.8)Steep disorders (Insomini/Steep disturbance/Somolence/Steep apnes)11 (3.0)Menzal Impairment/Delinury/Conjunctional stata/Arter Mental Statas11 (3.0)Personality change/Anaxi/Balance disorder11 (3.0)Visual Impairment/Blury vision/Conjunctional hemorrhage/Docular hyperemia10 (2.8)Erembardiar Bradyardia/Hence Stroke/Transient Ischemic Attack6 (1.7)Memory impairment/Blury vision/Conjunctional hemorrhage/Docular hyperemia10 (2.8)Erembardiar Bradyardia/Hyperotia3 (0.8)Decrebation Bradyardia/Hyperotina3 (0.8)Decrebation Brady Colume Stroke/Transient Ischemic Attack6 (1.7)Memory impairment/Blury vision/Conjunctional hemorrhage/Decrebation/Conormation3 (0.8)Derphala </td <td></td> <td>18(5.0)</td> <td></td>		18(5.0)	
Myocardial infarction/Acute Coronary Syndrome/Coronary artery occlusion/Troponin increase14 [3 9]Cardiamyophy10 [2.8]Syncope / Presyncope10 [2.8]Valual desses/fysionction8 (2.2)Pericardial hemorrhage/Pericardial effusion/Mediastinal effusion8 (2.2)Cardiamopaly11 [3]Cardiamopaly11 [3]Unclusion2 (0.6)Bradycardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurologia (rothobio/Headache16 (4.4)Dizanes12 (3.3)Migraine/Photophobia/Headache12 (3.3)Untal impairment/Delirium/Contisional state/Altered Mental Status11 (3.0)Visual Inpairment/Delirium/Contisional state/Altered Mental Status11 (3.0)Visual Inpairment/Delirium/Contisional state/Altered Mental Status5 (1.4)Less of consciousness/Unresponsive to stimuli6 (1.7)Less of consciousness/Unresponsive to stimuli5 (1.4)Neuropathy (Hypoesthesis/Saraestesis/Sciaica)5 (1.4)Neuropathy (Hypoesthesis/Alaretesis/Saraestesis/Sara			
Cardiomyopathy 102.81 Syncope / Prevyncope 102.81 Valual ruisase/dysfunction 812.21 Pertiardial hemornhage/Periardial effusion/Mediastinal effusion 812.21 Ventricular arthythmias (Ventricular fibrillation/Ventricular tachycardia) 711.91 Cardiomegaly 2006 Bradycardia/Heart Rate decrease 2006 Bradycardia/Heart Rate Rate Rate Rate Rate Rate Rate Rat			
Syncope / Presyncope10 (2.8)Valual ridessed/pfwfunction8 (2.2)Pericardial hemorrhage/Pericardial effusion/Mediastinal effusion8 (2.2)Ventricular arrhythmiss (Ventricular fibrillation/Ventricular tachycardia)7 (1.9)Endocarditis2 (0.6)Endocarditis2 (0.6)Bardycardia/Heart Rate decrease3 (0.8)Bundle Branch Block7 (1.2.2)Contusions25 (6.3)Migraine/Photophobia/Heart Rate decrease3 (6.3)Bundle Branch Block7 (1.2.3)Migraine/Photophobia/Headsche16 (4.4)Dizziness16 (4.4)Sleep disorders (Insomnia/Sleep disturbance/Somnolence/Sleep apnea)13 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrheat11 (3.0)Visual impairment/Blurry vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic Stoke / Subdural hematoma / Cerebral hematoma6 (1.7)Kortoposthesi/Apresthesia/Sciatica)5 (1.4)Cerebral artery embolism/tschemic stroke/Transient Ischemic Attack6 (1.7)Memory impairment/Almesia3 (0.8)Dysphonia2 (0.6)Hematorisky/Propresion/Hypeotopia/Lymphopenia/Lymphopenia/3 (0.8)Dysphonia3 (0.8)Ortypoptina/Lymphopenia/Lymphopenia/Lymphopenia/Lymphopenia/Lymphopenia/Limphopenia/			
Valuar disease/dysfunction8 (2.2)Periardial herminag/Periardial effusion/Mediastinal effusion8 (2.2)Ventricular arrhythmias (Ventricular tachycardia)7 (1.9)Errolardia herminag/Periardial herminag (Ventricular tachycardia)2 (0.6)Bradycardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurologic condition2 3 (6.3)Neurologic condition2 3 (6.3)Siegen disorders (Insomnia/Sleep disturbance/Somonlence/Sleep apnea)12 (3.3)Mertal impairment/Delin/McOnfusional state/Altered Mental Status1 (3.0)Personality change/Anxiety/Depression/Hypererigiance/Psychos/Hallucinations/Logorthea1 (3.0)Valual impairment/Delin/Confusional state/Altered Mental Status1 (3.0)Valual impairment/Delin/McOnfusional state/Altered Mental Status6 (1.7)Gati disturbance/Ataxia/Baince disorder1 (3.0)Valual impairment/Delin/Vicon/junctival hemorthage/Ocular hyperemia1 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma / Cerebral hematoma6 (1.7)Mernory impairment/Annesia5 (1.4)Neuropatity (Hyposthesia/Psirsthesis/Sciatica)5 (1.4)Cerebral artery emblism//schemic stroke/Transient Ischemic Attack6 (1.7)Menning Vis/Spiral abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hermingtis/Hypotonia3 (0.8)Desphonia3 (0.8)Hermingtis/Kippotonia1 (1.3)Cotopathy/UNR Increase/Petchiae/Purpura/Ecchymosi/Increased bruising/Abormal platelef function test5 (1.4)Hermingtis/Spiral abscess/P			
Perciardial hemorrhage/Perciardial effusion/Mediastinal effusion8 (2.2)Ventricular arriythmas (Ventricular fibrillation/Ventricular tachycardia)7 (1.9)Cardiomegaly4 (1.1)Bndocarditis2 (0.6)Bardycardia/Heart Rate decrease3 (0.8)Bundle Branch Block2 (0.6)Neurolaci condition77 (21.2)Contusions25 (6.3)Migraine/Photophobis/Headache16 (4.4)Dizzhees16 (4.4)Sleep disorders (Insomnia/Siepe disturbance/Somolence/Siepe apnea)12 (3.3)Mertal impairment/Oblitur/Octinsional state/Metered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea11 (3.0)Visual impairment/Burry vision/Conjunctival hemorrhage/Octuar hyperemia10 (2.8)Memorrhagic KDS events / hemorrhagic stroke / Subdural hematoma / Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli5 (1.4)Conclusioness/Unresponsive to stimuli3 (0.8)Dysphonia2 (0.6)Hemipareis/Hypotonia3 (0.8)Dysphonia2 (0.6)Hemipareis/Hypotonia13 (3.0)Congulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal patelet function test19 (5.2)Leukocytosis/Unphoetyosis/Monocytosis13 (3.6)Urpupate Mitty Depression/Hypogramaglobulinemia M (Hypogramaglobulinemia M (Hingarease/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal patelet function test19 (5.2)Leukocytosis/Unphoetyosis/Monocytosis13 (3.6)Upmpatengalby/Sple		10 (2.8)	
Ventricular arrhythmis (ventricular tachycardia)7 (1.9)Cardiomegaly2 (0.6)Bradycardia/Heart Rate decrease3 (0.8)Bundle Branch Block20 (0.6)Neurologic condition77 (2.1.2)Contusions23 (6.3)Migraine/Photophobia/Headache16 (4.4)Dizziness16 (4.4)Dizziness12 (3.3)Mental impairment/Deitrium/Contusional state/Attered Mental Status11 (3.0)Gatt disturbance/Ataxia/Balance disorder11 (3.0)Visual impairment/Deitrium/Contusional state/Attered Mental Status11 (3.0)Visual impairment/Deitrium/Contusional state/Attered Mental Status11 (3.0)Visual impairment/Burry vision/Conjunctival hemorthage/Coular hyperenia10 (2.8)Gatt disturbance/Ataxia/Balance disorder11 (3.0)Visual impairment/Burry vision/Conjunctival hemorthage/Coular hyperenia10 (2.8)Less of consclosusess/Unresponsive to stimuli6 (1.7)Less of consclosusess/Unresponsive to stimuli5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)88 (24.2)Cytopenia (Trombocrytopenia/Leukopenia/Pancytopenia/Linghopenia)3 (0.8)Dyshnia2 (0.6)Hematologic condition19 (5.2)Cytopenia (Trombocrytopenia/Leukopenia/Lymphopenia)13 (3.6)Leukorytosis/Unponcytosis13 (3.6)Leukorytosis/Unponcytosis13 (3.6)Leukorytosis/Unponcytosis13 (3.6)Leukorytosis/Unponcytosis13 (3.6)Leukorytosis/Unponcytos	Valvular disease/dysfunction	8 (2.2)	
Cardionegaly Endocarditis4 (1.1) 2 (0.6)Bradycardia/Heart Rate decrease Bundle Branch Block3 (0.8) 2 (0.6)Neurologic condition Contusions2 (0.6)Neurologic condition Contusions23 (6.3)Migraine/Photophobia/Headache Diztiness16 (4.4)Siepe disorders (Insomnia/Sleep disturbance/Somnolence/Sleep apnea)12 (3.3)Mental impairment/Deliritum/Contusional state/Altered Mental Status Personality change/Ansiety/Depression/Hypervigilance/Psychosis/Hailucinations/Logorrhead Gait disturbance/Ataxid/Balance disorder11 (3.0)Gait disturbance/Ataxid/Balance disorder Visual impairment/Burry vision/Conjunctival hemorthage/Ocular hyperemia Loss of consciouness/Unresponsive to stimuli10 (2.8)Hemorthagic CNS events / hemorthagic Stroke / Subdural hematoma /Cerebral hematoma Loss of consciouness/Unresponsive to stimuli5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encophalopathy Mennigtits/Wipothaia3 (0.8)Hemorthagic Condition Cogulectavia (condition Oxphonia3 (0.8)Hemingtits/Hypotonia Dysphonia3 (0.8)Leukocytosis/Unoponytosis/Increase/ bruising/Abnormal platelet function test Leukocytosis/Unophocytosis88 (24.2)Leukocytosis/Unophonytosis/Monocytosis13 (3.6)Sepsis/Septic shock/Bacterennia19 (5.2)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M Hypergammaglobulinemia M5 (1.4)Thrombosis10 (3.3)Turnot visis Syndrome5 (1.4)Thrombosis5 (1.4)Spleine rupture2 (0.6)		8 (2.2)	
Endocardis 2 (0.6) Bardyaradia/Heart Rate decrease Bardyaradia/Heart Rate decrease Bundle Branch Block 2 (0.6) Neurologic condition Contisions 2 (0.6) Neurologic condition Migraine/Photophobia/Headache 16 (4.4) Diziness 16 (4.4) Diziness 16 (4.4) Diziness 16 (4.4) Diziness 11 (2.3) Mental impairment/Delirum/Contusional state/Altered Mental Status 11 (2.3) Mental impairment/Delirum/Contusional state/Altered Mental Status 11 (3.0) Personality change/Anneity/Degression/Hypergingiance/Psychosis/Hallucinations/Logorrhea Gait disturbance/Ataxid/Balance disorder Visual impairment/Delirum/Conjunctival hemorrhage/Ocular hyperenia 10 (2.8) Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma / Cerebral hematoma 6 (1.7) Loss of consciousness/Unresponsive to stimuli 6 (1.7) Encophalopathy (Hypoesthesia/Paresthesia/Statica) 5 (1.4) Neuropathy (Hypoesthesia/Paresthesia/Statica) 5 (1.4) Neuropathy (Hypoesthesia/Paresthesia/Statica) 5 (1.4) Neuropathy (Hypoesthesia/Paresthesia/Statica) 5 (1.4) Neuropathy (Hypoesthesia/Paresthesia/Statica) 5 (0.8) Dysphonia 2 (0.6) Hematologic condition Cytopenia (Hrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia) 4 (1.11) Anemia Dysphonia 19 (5.2) Leukocytosis/(Wphocytosis/Monocytosis Sepsis/Septic shock/Bacteremia Jatelet function test 19 (5.2) Leukocytosis/(Wphocytosis/Monocytosis Sepsis/Septic shock/Bacteremia Lymphadenopathy Humunosuppression/Immune system disorder/Hypogammaglobulinemia M Thrombosis Diarbea / Delydration Statis disorder/Malnutrition 2 (1.4) Specinesse 10 (0.3) Turon Lysis Syndrome 2 (0.6) Diarbea / Delydration Nausea/Vomiting 2 (5.5) Decreased appetite/Feeding disorder/Malnutrition 2 (2.5) Decreased appetite/Feeding disorder/Malnut	Ventricular arrhythmias (Ventricular fibrillation/Ventricular tachycardia)	7 (1.9)	
Bradycardia/Heart Rate decrease Bundle Branch Block 2(0,6) 2(0,6) 2(0,6) 2(1,7) 2(1,2) 2(3,1) Migraine/Photophobia/Headache Dizziness Migraine/Photophobia/Headache Dizziness Mental impairment/Delirum/Confusional stack Steep disorders (Insomnia/Sileep disturbance/Somnolence/Sileep apnea) Mental impairment/Delirum/Confusional stack/Altered Mental Status Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea Gait disturbance/Ataxia/Baiance disorder Visual impairment/Belirum/vision/Conjunctival hemorrhage/Ocular hyperemia 10 (2,8) Hemorrhagic CNS events / hemorrhagis stroke / Subdural hematoma /Cerebral hematoma 6 (1,7) Memory impairment/Amnesia Usus of consciousness/Unresponsive to stimul Memory impairment/Amnesia Sti.1.4) Neuropathy (Hyposethissi/Presthesi/Sciatca) Sti.4) Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack 6 (1,7) Encephalopathy Memory impairment/Amnesia Sti.4) Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack 6 (1,7) Encephalopathy Memingtits/Frain abscess/Progressive Multifocal Leukoencephalopathy Hemiparesis/Hypotonia Dysphonia Psychonia Dispetief function test Leukocytosis/Unphocytosis Sepsis/Septic Shock/Batteremia Mitter Stroke/Batteremia Mitter Stroke/Batteremia Mitter Stroke/Batteremia Mitter Stroke/Batteremia Mitter Stroke/Batteremia Mitter Stroke/Statteremia Mitter Stroke/Statteremia M	Cardiomegaly	4 (1.1)	
Bundle Branch Block2 (0.6)Neurologic condition27 (21.2)Contusions23 (6.3)Migraine//Notophobia/Headache16 (4.4)Dizziness12 (3.3)Mental impairment/Delinum/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorha11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorha6 (1.7)Hemorrhagic Croke Ostor / Homorrhagic Stroke / Subdural hemotoma / Cerebral hemotom6 (1.7)Loss of consciousness/Unresponsive to stimuli5 (1.4)Nemory ingriment/Amensia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral attery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Heminjaresis/Hypotonia2 (0.6)Heminjaresis/Hypotonia2 (0.6)Heminjaresis/Hypotonia88 (4.2)Atemia11 (1.3)Cotypishi11 (1.3)Cotypishi11 (1.3)Menory ingrimetr/Amensia11 (1.3)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)10 (3.0)Dysphonia2 (0.6)Heminjaresis/Hypotonia11 (1.3)Cotypishi10 (3.0)Sepsis/Septic shock/Bacteremia19 (5.2)Leukoptosis/Inmonecytosis16 (4.1)Heminparesis/Information19 (5.2)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M10.3)Hypergarmmaglobulinemia M10.3) <tr<< td=""><td>Endocarditis</td><td>2 (0.6)</td><td></td></tr<<>	Endocarditis	2 (0.6)	
Bundle Branch Block2 (0.6)Neurologic condition27 (21.2)Contusions23 (6.3)Migraine//Notophobia/Headache16 (4.4)Dizziness12 (3.3)Mental impairment/Delinum/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorha11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorha6 (1.7)Hemorrhagic Croke Ostor / Homorrhagic Stroke / Subdural hemotoma / Cerebral hemotom6 (1.7)Loss of consciousness/Unresponsive to stimuli5 (1.4)Nemory ingriment/Amensia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral attery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Heminjaresis/Hypotonia2 (0.6)Heminjaresis/Hypotonia2 (0.6)Heminjaresis/Hypotonia88 (4.2)Atemia11 (1.3)Cotypishi11 (1.3)Cotypishi11 (1.3)Menory ingrimetr/Amensia11 (1.3)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)10 (3.0)Dysphonia2 (0.6)Heminjaresis/Hypotonia11 (1.3)Cotypishi10 (3.0)Sepsis/Septic shock/Bacteremia19 (5.2)Leukoptosis/Inmonecytosis16 (4.1)Heminparesis/Information19 (5.2)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M10.3)Hypergarmmaglobulinemia M10.3) <tr<< td=""><td>Bradycardia/Heart Rate decrease</td><td>3 (0.8)</td><td></td></tr<<>	Bradycardia/Heart Rate decrease	3 (0.8)	
Neurologic condition77 (21.2)Contusions23 (6.3)Migraine/Photophobia/Headache16 (4.4)Diziness16 (4.4)Siep disorders (insomnia/Siep disturbance/Somolence/Seep apnea)12 (3.3)Mental impairment/Delirum/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea11 (3.0)Gatt disturbance/Atxai/Allance disorder11 (3.0)Visual impairment/Blurry vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemotrhagic CNS events / hemorrhagic stroke / subdural hematoma /Cerebral hematoma6 (1.7)Meuropathy (Hyposethisa/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/ischemic stroke / Transient Ischemic Attack6 (1.7)Menory impairment/Ahmesia3 (0.8)Hemingitis/Brain absess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemingitis/Brain absess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemingitis/Brain absess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemingitis/Brain absess/Progressive Multifocal Leukoencephalopathy3 (0.8)Leukocytosis/Lymphocytosis/Monocytosis3 (3.6)Urpmbadenopathy19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis3 (1.4)Coselupathy/INN increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis/Syndrome10 (3.3)Gastroesophaty4 (1.1)Splenomegaly/Splenic rupture10 (3.3)			
Contusions23 (6.3)Migraine/Photophobia/Headache16 (4.4)Dizziness16 (4.4)Steep disorders (Incomnia/Sleep disturbance/Somnolence/Sleep apnea)12 (3.3)Mental imgainem/Delirum/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea10 (2.8)Gait disturbance/Ataxi/Balance disorder11 (3.0)Visual impairment/Delirum/Vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciouses/Unresponsive to stimuli6 (1.7)Memory impairment/Annesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy3 (0.8)Hemingtis/Brian abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Vetopenia (Irrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia2 (0.6)Coggulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic Isodk/Bateremia5 (1.4)Thrombosis3 (1.6)Jyphenomegaly/Splenic rupture2 (0.6)Himuro Leukopenia/Leukopenia/Leukopenia/Lympamaglobulinemia M5 (1.4)Thrombosis13 (3.6)Lymphadenopathy9 (5.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M10.3		()	
Contusions23 (6.3)Migraine/Photophobia/Headache16 (4.4)Dizziness16 (4.4)Steep disorders (Incomnia/Sleep disturbance/Somnolence/Sleep apnea)12 (3.3)Mental imgainem/Delirum/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea10 (2.8)Gait disturbance/Ataxi/Balance disorder11 (3.0)Visual impairment/Delirum/Vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciouses/Unresponsive to stimuli6 (1.7)Memory impairment/Annesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy3 (0.8)Hemingtis/Brian abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Vetopenia (Irrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia2 (0.6)Coggulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic Isodk/Bateremia5 (1.4)Thrombosis3 (1.6)Jyphenomegaly/Splenic rupture2 (0.6)Himuro Leukopenia/Leukopenia/Leukopenia/Lympamaglobulinemia M5 (1.4)Thrombosis13 (3.6)Lymphadenopathy9 (5.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M10.3	Neurologic condition	77 (21.2)	
Migrane/Photophobia/Headache16 (4.4)Dizziness16 (4.4)Dizziness12 (3.3)Mental impairment/Delirium/Confusional state/Altered Mental Status12 (3.3)Personality change/Anxiety/Operssion/Hyperkylgilance/Psychosis/Hallucinations/Logorrhea11 (3.0)Gait disturbance/Ataxia/Balance disorder11 (3.0)Visual impairment/Deliry vision/Conjunctival hemorrhage/Ocular hyperemia01 (2.8)Hemorrhagic CNS events / hemorrhagic Stock / Subdural hematoma / Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli5 (1.4)Memory impairment/Annensia5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemiparesis/Hypotonia2 (0.6)Dysphonia10 (3.0)Cogalupathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal9 (5.2)Jeukotypots/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lumonucouppetsjon/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis10 (3.1)Hyperagramgaloy/Splenic rupture3 (3.6)Lumonucouppetsjon/Immune system disorder/Hypogammaglobulinemia M1 (1.1)Hyperagramgaloy/Splenic rupture3 (3.6)Lumonucouppetsjon/Immune system disorder/Hypogammaglobulinemia M1 (1.1)Hyperagramgaloy/Splenic rupture3 (3.6)Lumonucouppetsjon/Immune system disorder/Hypogammaglobulinemia M1 (1.1)		· · ·	
Display16 (4.4)Sleep disorders (Insomni/Sleep disturbance/Somnolence/Sleep apnea)12 (3.3)Mental impairment/Delirium/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosi/Hallucinations/Logorthea11 (3.0)Sait disturbance/Atxaix/Balance disorder11 (3.0)Visual impairment/Burry vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli6 (1.7)Memory impairment/Burry vision/Conjunctival hemorrhage/Ocular hyperemia5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy3 (0.8)Unrengetis/Hypotonia3 (0.8)Dysphonia2 (0.6) <i>Hematologic condition</i> 88 (24.2)Cytopenia (Ithrombocytopenia/Leukopenia/Lymphopenia)41 (11.3)Anemia19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic bock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Munue system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hippergamaglobulinemia M5 (1.4)Thrombosis Syndrome10 (3.3)Gastro-intestind disorder/Malnutrition2 (0.6)Hippergamaglobulinemia M5 (1.4)Thrombosis Syndrome10 (3.3)Gistro-intestind disorder/Malnutrition2 (0.6) <t< td=""><td></td><td></td><td></td></t<>			
Sleep disorders (Insomnia/Sleep disturbance/Somnolence/Sleep apnea)12 (3.3)Mental impairment/Delirium/Confusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea11 (3.0)Gait disturbance/Ataxia/Balance disorder11 (3.0)Visual impairment/Burry vision/Conjunctival hemorrhage/Ocular hyperemia6 (1.7)Loss of consciousness/Unresponsive to stimuli6 (1.7)Memory impairment/Ammesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/Ischemic stroke / Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Memipariesi/Arisenses/Progressive Multifocal Leukoencephalopathy3 (0.8)Dysphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M Hypergamaglobulinemia M5 (1.4)Splenomegal/V/Splenic rupture2 (0.6)Hi increase10.3)Gatt disorders (any)85 (23.4)Dispensorial Leukocytosis/Increase and the conders (any)Splenomegal/V/Splenic rupture2 (0.5)Dispensorial Leukocytosis/Increase10.3)Gattorintestinal disorder/Malnutrition2 (1.6) <tr< td=""><td></td><td></td><td></td></tr<>			
Mental impairment/Delinium/Contusional state/Altered Mental Status11 (3.0)Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea11 (3.0)Solat disturbance/Atxai/aldalance disorder11 (3.0)Visual impairment/Blurry vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemorrhagic Stos events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli6 (1.7)Memory impairment/Almesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatcia)5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy3 (0.8)Hemingtirs/Brian abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Vertopating (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)40 (11.0)Cogulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test9 (5.2)Leukocytosis/Lymphocytosis/Monocytosis13 (3.6)Lymphadenopathy9 (2.5)Immonsuppression/Immune system disorder/Hypogammaglobulinemia M Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase Immorusuperession/Immune system disorder/Hypogammaglobulinemia M Hypergammaglobulinemia M5 (1.4)Costro-intestinal disorders (ony)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased apetite/Feeding disorder/Malnutrition20 (5.5) <td></td> <td></td> <td></td>			
Personality change/Anxiety/Depression/Hypervigilance/Psychosis/Hallucinations/Logorrhea11 (3.0)Gait disturbance/Ataxia/Balance disorder11 (3.0)Visual impairment/Blurry vision/Conjunctival hemorrhage/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli6 (1.7)Memory impairment/Amnesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy3 (0.8)Hemiparesis/Hypotonia3 (0.8)Dysphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Hrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)40 (1.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M Hypergammaglobulinemia M5 (1.4)Increase1 (0.3)Gastro-intestinal disorders (any)45 (2.34)Diarrhea / Dehydration45 (2.16)Superative Singenia (Histopic Sonres) (Malnutrition17 (4.7)Constipation11 (3.0)Dyspepia/Gastroesophageal Reflux Disease7 (1.9)			
Gait disturbance/Ataxia/Balance disorder11 (3.0)Visual impairment/Blurry vision/Conjunctival hemorhage/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy3 (0.8)Hemingitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Usyphonia2 (0.6)Hematogic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia)41 (1.1)Anemia40 (11.0)Cogulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia (Hypergammaglobulinemia M Hypergammaglobulinemia M Hypergammaglobulinemia M5 (1.4)Thrombosis5 (1.4)Spensorese2 (0.6)Hib increase2 (0.6)Hib increase2 (0.6)Homorbagic condition5 (1.4)Cestor-intestinal disorder/Hypogammaglobulinemia M Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Spenomegaly/Splenic rupture2 (0.6)Hib increase1 (0.3)Cestor-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition20 (5.5)Decreased appetite/Feed		11 (3.0)	
Visual impairment/Blurry vision/Conjunctival hemorrhagic/Ocular hyperemia10 (2.8)Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli5 (1.4)Memory impairment/Amnesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningritis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Dysphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia19 (5.2)Leukocytosis/Monocytosis18 (5.0)Sepsis/Septit shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis2 (0.6)Munosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis5 (1.4)Splenomegaly/Splenic rupture2 (0.6)Hib increase1 (0.3)Gastro-intestinal disorders (any)2 (0.6)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis5 (1.4)Splenomegaly/Splenic rupture2 (0.6)Hib increase1 (0.3)Gastro-intestinal disorders (any)2 (0.5)Diarrhea / Dehydration2 (0.5)Numor Lysis Syndrome2 (5.5)Diarrhea / Dehydration2 (5.5) </td <td></td> <td>11 (2.0)</td> <td></td>		11 (2.0)	
Hemorrhagic CNS events / hemorrhagic stroke / Subdural hematoma /Cerebral hematoma6 (1.7)Loss of consciousness/Unresponsive to stimuli6 (1.7)Memory impairment/Annosaia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Jysphonia3 (0.8)Dysphonia3 (0.8)Codoguic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia9 (2.5)Immonosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hypergammaglobulinemia M5 (1.4)Thrombosis5 (1.4)Spensi/Splein rupture2 (0.6)Hib increase1 (0.3)Costor-intestinal disorders (any)3 (5.3)Lib increase dapetite/Feeding disorder/Malnutrition20 (5.5)Corto-intestinal disorders (any)20 (5.5)Diarrhea / Dehydration20 (5.5)Nausea/Vomiting20 (5.5)Diarrhea / Dehydration11 (3.0)Nausea/Vomiting20 (5.5)Diarrhea / Dehydration11 (3.0)Dyspepsia/Satroesophageal Reflux Disease11 (3.0)Dyspepsia/Gatroesophageal Reflux Disease7 (1.9)			
Loss of consciousness/Unresponsive to stimuli6 (1.7)Memory impairment/Annesia5 (1.4)Neuropathy (Hypoesthesia/Sciatica)5 (1.4)Cerebral artery embolism/lschemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningiti/Striani abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Meningiti/Striani abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Dysponia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy5 (1.4)Hypergesion/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)20 (5.5)Leucacytosis Syndrome20 (5.5)Gastro-intestinal disorder/Malnutrition20 (5.5)Loreace appetite/Feeding disorder/Malnutrition17 (4.7)On Stripation20 (5.5)Decreace appetite/Feeding disorder/Malnutrition11 (3.0)Nussea/Nomiting20 (5.5)Decreace appetite/Feeding disorder/Malnutrition17 (4.7)Onstipation11 (3.0)Nussea/Nomiting11 (3.0)Dispepia/Gastroesphageal Reflux Disease8 (2.2)			
Memory impairment/Amnesia5 (1.4)Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/lschemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemiparesis/Hypotonia3 (0.8)Dysphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coaguopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (5.2)Jelatelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hypergammaglobulinemia M5 (1.4)Thrombosis1 (0.3)Tumor Lysis Syndrom1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition20 (5.5)Decreased appetite/Feeding disorder/Malnutrition20 (5.5)Decreased appetite/Feeding disorder/Malnutrition11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)O hemorrhage7 (1.9)			
Neuropathy (Hypoesthesia/Paresthesia/Sciatica)5 (1.4)Cerebral artery embolism/ischemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemiparesis/Hypotonia3 (0.8)Dysphonia2 (0.6) <i>Hemotologic condition</i> 88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petchiae/Purpura/Ecchymosis/Increased bruising/Abnormal9 (5.2)platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosi1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)20 (5.5)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition20 (5.5)Decreased appetite/Feeding disorder/Malnutrition20 (5.5)Decreased appetite/Feeding disorder/Malnutrition21 (3.0)Diarrhea / Dehydration21 (3.0)Diarrhea / Dehydration </td <td></td> <td></td> <td></td>			
Cerebral artery embolism/lschemic stroke/Transient Ischemic Attack6 (1.7)Encephalopathy4 (1.1)Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Justice Condition3 (0.8)Dysphonia2 (0.6)Hemiapresis/Hypotonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hypergammaglobulinemia M1 (0.3)Tumor Lysis Syndrome1 (0.3)Gostro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition20 (5.5)Decreased appetite/Feeding disorder/Malnutrition11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)(Ghemorrhage11 (3.0)			
Encephalopathy4 (1.1)Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemiparesis/Hypotonia3 (0.8)Dysphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (1.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (5.2)platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bateremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Spenomegaly/Splenic rupture2 (0.6)Hb increase10.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition27 (4.7)Constipation11 (3.0)Dyspepia/Gastroesophageal Reflux Disease8 (2.2)(i hemorrhage11 (3.0)Turon Chage11 (3.0)			
Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy3 (0.8)Hemiparesis/Hypotonia3 (0.8)Dysphonia3 (0.8)Jypsphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (5.2)platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis13 (3.6)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hrhomoosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)Gi hemorrhage7 (1.9)	Cerebral artery embolism/Ischemic stroke/Transient Ischemic Attack	6 (1.7)	
Hemiparesis/Hypotonia3 (0.8) 2 (0.6)Dysphonia2 (0.6)Hematologic condition88 (24.2) 41 (11.3) 40 (11.0)Cogulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2) 18 (5.0)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia Lymphadenopathy13 (3.6) 9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hypergammaglobulinemia M5 (1.4)Hypergammaglobulinemia M10.3)Tumor Lysis Syndrome10.3)Gastro-intestinal disorders (any) Diarrhea / Dehydration85 (23.4)Diarrhea / Dehydration20 (5.5)Perceased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Pyspepsia/Gastroesophageal Reflux Disease82 (2.2)Gl hemorrhage7 (1.9)		4 (1.1)	
Dysphonia2 (0.6)Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis5 (1.4)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)G hemorrhage7 (1.9)	Meningitis/Brain abscess/Progressive Multifocal Leukoencephalopathy	3 (0.8)	
Hematologic condition88 (24.2)Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Thrombosis2 (0.6)Hb increase10 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)Gi hemorrhage7 (1.9)	Hemiparesis/Hypotonia	3 (0.8)	
Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal9 (5.2)platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hypergammaglobulinemia M2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)	Dysphonia	2 (0.6)	
Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)41 (11.3)Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal9 (5.2)platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)Hypergammaglobulinemia M2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Anemia40 (11.0)Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)/Hypergammaglobulinemia M5 (1.4)Thrombosis2 (0.6)Bb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)	Hematologic condition	88 (24.2)	
Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)/Hypergammaglobulinemia M5 (1.4)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)	Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)	41 (11.3)	
platelet function test19 (5.2)Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)/Hypergammaglobulinemia M5 (1.4)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)	Anemia	40 (11.0)	
Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)/Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome85 (23.4)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)	Coagulopathy/INR increase/Petechiae/Purpura/Ecchymosis/Increased bruising/Abnormal		
Leukocytosis/Lymphocytosis/Monocytosis18 (5.0)Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)/Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome85 (23.4)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)		19 (5.2)	
Sepsis/Septic shock/Bacteremia13 (3.6)Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5 (1.4)/Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Lymphadenopathy9 (2.5)Immunosuppression/Immune system disorder/Hypogammaglobulinemia M5/Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Immunosuppression/Immune system disorder/Hypogammaglobulinemia MImmunosuppression/Immune system disorder/Hypogammaglobulinemia M/Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
/Hypergammaglobulinemia M5 (1.4)Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)		- \=/	
Thrombosis4 (1.1)Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)		5 (1.4)	
Splenomegaly/Splenic rupture2 (0.6)Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Hb increase1 (0.3)Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Tumor Lysis Syndrome1 (0.3)Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Gastro-intestinal disorders (any)85 (23.4)Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)		1 (0.5)	
Diarrhea / Dehydration42 (11.6)Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)	Castro intestinal disorders (any)	95 (22 1)	
Nausea/Vomiting20 (5.5)Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Decreased appetite/Feeding disorder/Malnutrition17 (4.7)Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Constipation11 (3.0)Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
Dyspepsia/Gastroesophageal Reflux Disease8 (2.2)GI hemorrhage7 (1.9)			
GI hemorrhage 7 (1.9)			
Gastritis/Gastroenteritis/Colitis/Intestinal Abscess 6 (1.7)			
	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)
Traumatic lung injury	1 (0.3)
	(22.2)
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)
	1 (0.0)
Endocrine-metabolic disorders	49 (13.5)
Pyrexia / Fever	20 (5.5)
Electrolyte abnormalities Thyroid disorder / Hypothyroidism / Euthyroid sick syndrome / Goiter	14 (3.9) E (1.4)
	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)
	- (0.0)
Bleeding and Hemorrhagic conditions	53 (14.6)
	JJ (14.0)

* 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),

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 *	[00.0 00.0]	295 (100.0)
Only Ibrutinib	251 (85.1)	255 (100.0)
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)
	220 (100.0)	
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)	

Consurrent essesiated conditions		205 (100 0)
Concurrent associated conditions	10 (5 4)	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	- (1)	
	4 (1.4)	
pressure) Ventrigular tachyarchythmia (Ventrigular tachycardia, Electrocardiogram OT prolonged)		
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) Dysesthesia (Paranesthesia/ Hypoesthesia/ Hypersensitivity/ Neuropathy peripheral/ Nerve	28 (9.5)	
	26 (0.0)	
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)	
	1 (0.5)	
Hemotologic condition	122 / 41 7	
<u>Hematologic condition</u>	123 (41.7)	
Cytopenia (Thrombocytopenia/Leukopenia/Pancytopenia/Lymphopenia)	70 (33.7)	
Anemia	37 (12.5)	

	1	
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)	
<u>Gastro-intestinal disorders (any)</u>	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)	
Den el ese dittere	10(10.0)	
<u>Renal condition</u>	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)

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	- (0.0)	251 (98.8)
Health Care Professional	115 (45.8)	251 (50.0)
Non-Health Care Professional	136 (54.2)	
Gender	100 (07.2)	249 (98.0)
Male	164 (65.9)	273 (30.0)
Female	85 (34.1)	
	73.9 ± 10.3	194 (76.4)
Age at onset, mean ± SD (years)		194 (76.4)
[min-max]	[41-97]	254 (400.0)
Suspected Drugs *	24.0 (05.2)	254 (100.0)
Only Ibrutinib	219 (86.2)	
Ibrutinib + 1 other drug	21 (8.3)	
lbrutinib + ≥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)	234 (100.0)
	. ,	
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	240 (94.5)	
/Transient ischemic attack /Lacunar infarction / Thalamic infarction		
Motor dysfunction/ Paralysis / Hemiplegia / Hypotonia / Facial paralysis	12 (4.7)	
Encephalopathy (Hypoxic-ischemic/ vascular)	8 (3.1)	
Speech disorder / Aphasia / Dysarthria	8 (3.1)	
	7 (2.8)	

Concurrent associated conditions		254 (100.0)
None (lone)	94 (37.0)	
<u>Cardiac condition</u>	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)	
	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)	
	4 (1.6)	
Fractures / Ligament injury	4 (1.6)	
Skin infection / Cellulitis		
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)	
	14 (5.5)	
Gait disturbance / Balance disturbance / Vertigo / Vestibular disorder	11 (4.3)	
Cognitive disorders / Memory impairment / Amnesia	11 (4.5)	
Ophthalmological abnormality (visual impairment / Eye movement disorder/ Cataract/	10 (2.0)	
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)	
	2 (0.8)	
Nerve injury	2 (0.8)	
Tremor	1 (0.4)	
Headache / Migraine		
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)	
	6 (2.4)	
Hepatitis / Hepatic failure / Gallbladder disorders	6 (2.4)	
Dyspepsia / Flatulence		
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)
	44 (47.2)
<u>Hematologic condition</u>	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)
inappropriate antidiareat normone secretion	- (0.7)

* 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 .)

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

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	1 (1.0)	70 (100.0)
Ventricular tachycardia	31 (44.3)	, 0 (100.0)
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)	70 (100.0)
Cardiac condition (non-ventricular arrhythmias)	36 (51.4)	

Supre-ventricular arrhythmis (Atrial flutter/ Atrial fibrillation/ Supreventricular9 (27.1)Cardiac fallure/ decreased tF/ Pulmonary edem/ Pulmonary Hypertension7 (10.0)Cardiac fallure/ decreased tF/ Pulmonary edem/ Pulmonary Hypertension4 (5.7)Brankyar dia4 (5.7)Brankyar dia5 (3.3)Myocardial Infraction/ Coronary artery disease/Cardiac lachemia3 (4.3)Pericandia effusion3 (4.3)Syncope3 (4.3)Myocardial Infraction/ Coronary artery disease/Cardiac lachemia3 (4.3)Bernesoldius of consciousness7 (1.4)Correlation and the consciousness7 (1.4)Encreased lack of consciousness7 (1.4)Coronarity:7 (2.9)Seture7 (2.9)Seture7 (2.9)Seture7 (2.9)Seture7 (2.9)Seture7 (2.9)Seture5 (3.1)Leukorytos (1.1)(1.4)Leukorytos (1.1)(1	
Cardigeni: shock/ Cardia arreit Cardia failur / Greensed Ef Pulmonary edems/ Pulmonary Hypertension Cardia Toluro / Greensed Ef Pulmonary edems/ Pulmonary Hypertension Badycarda Badycarda Myccardal Infaction/ Coronary artery disease/Cardiac ischemia Pericardial effusion Syncope Syncope Actioventricular block Myccardal Infaction/ Coronary artery disease/Cardiac ischemia Pericardial effusion Myccardial Infaction/ Coronary artery disease/Cardiac ischemia Attioventricular block Myccardial Infaction/ Coronary artery disease/Cardiac ischemia Pericardial effusion Myccardial Infaction/ Coronary artery disease/Cardiac ischemia Attioventricular block Myccardial Infaction/ Coronary artery disease/Cardiac ischemia Decreased level of cansciousness Toto of the Synchysis Status Decreased blocd immunoglobulin (A/G/M) Tota of the Synchysis Tota of Tota of Synchysis Tota of S	Supra- ventricular arrhythmias (Atrial flutter/ Atrial fibrillation/ Supraventricular		
Cardia: failure/ decreased EF Pulmonary edema/ Pulmonary Hypertension7 (100)Bradycardia4(5.7)Bradycardia3(4.3)Hypertension3(4.3)Myocardils Infarction/ Coronary artery disease/Cardiac ischemia3(4.3)Syncope3(4.3)Myocardils1(1.4)Artioventricular block1(1.4)Artioventricular block1(1.4)Mucradiac condition19 (27.1)Decreased level of consciousness7(100)Encephalopathy5(7.1)Cognitive memory impairment / psychosis3(4.3)Ischemic events / Ischemic stroke3(4.3)Peripheral neuropathy5(7.1)Seluce2(2.9)Subdati memory impairment / psychosis2(2.9)Subdati memory impairment / psychosis3(4.3)Ischemic events / Ischemic stroke3(4.3)Peripheral neuropathy5(7.1)Seluce2(2.9)Subdati memotoma2(2.9)Subdati memotoma2(2.9)Decreased level problema, licobacytopenia, licobacytopenia)6(8.6)Increased level problema2(2.9)Seluce (Soluce intersion)2(2.9)Seluce (Soluce intersion)2(2.9			
Cardiomyopathy 4 (5.7) Pradycarda 4 (5.7) Hypertension 3 (4.3) Mycardial infarction/ Coronary artery disease/Cardiac ischemia 3 (4.3) Pericardial effusion 3 (4.3) Syncope 3 (4.3) Mycardial infarction/ Coronary artery disease/Cardiac ischemia 3 (4.3) Mycardial infarction/ Coronary artery disease/Cardiac ischemia 3 (4.3) Artiventricular block 11.4) Artiventricular block 10.00 Decreased level of consciouness 7 (10.00) Encephalopathy 5 (7.1) Cardiominement / psychosis 3 (4.3) Extence events (ischemic ischore) 3 (4.3) Peripheral neuropathy 2 (2.9) Opthalmological abnormality (vision) 2 (2.9) Studuar Hematoma 17 (24.3) Chropenia (pancytopenia, leukocytopenia, thrombocytopenia) 6 (8.6) Cardiopathy 2 (2.9) Decreased blood immunoglobulin (A / G / M) 2 (2.9) Decreased blood immunoglobulin (A / G / M) 2 (2.9) Cardiopath ar/Outs (disease 3 (4.3) Partica / Abnormal liver (incution tests 2 (2.9)			
Bradycardia 4 (5.7) Hypertension 3 (4.3) Mycardilal infarction/ Coronary artery disease/Cardiac ischemia 3 (4.3) Syncope 3 (4.3) Mycardilis 1 (1.4) Atrioventricular block 1 (1.4) Atrioventricular block 1 (1.4) Atrioventricular block 1 (1.4) Atrioventricular block 3 (4.3) Decreased level of consciouness 7 (10.00) Encephalopathy 5 (7.1) Cognitive-memory impairment / psychosis 3 (4.3) Scizure 2 (2.9) Scizure 3 (4.3) Decreased level dum nunoglobulin (A / G / M) 2 (2.9) Decreased level dum scize facthy mobio (Scizy mobio) 2 (2.9) Decreased level dum scize facthy mobio (Scizy mobio) 2 (2.9) Scizor intestinal disoders family 1 (1.4) Bastro dupisia	Cardiac failure/ decreased EF/ Pulmonary edema/ Pulmonary Hypertension	7 (10.0)	
Hypertension3 (4.3)Wycardial frusion3 (4.3)Pericardial effusion3 (4.3)Wycardial frusion3 (4.3)Wycardial frusion1 (1.4)Arrioventricular block1 (1.4)Arrioventricular block1 (1.4)Decreased level of conscioueness7 (10.0)Encephalopathy3 (4.3)Cognitive-memory impairment / psychosis3 (4.3)Ischerin Events / Ischerin Stroke3 (4.3)Seture2 (2.3)Optimal memory impairment / psychosis3 (4.3)Seture2 (2.3)Optimal mological abnormality (vision)2 (2.3)Subduri I hematoma7 (2.4)Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)6 (8.6)Increased tendency to bruske/ techymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Decreased tool munoglobulin (A / G / M)2 (2.9)Castro intestinal disorders (any)1 (2.2.9)Diarthea / Collits / Castroenteritis6 (8.6)Castroenteritis3 (4.3)Hematolagic and promotion (and for M)2 (2.9)Castroenteritis (abnormality (vision)2 (2.9)Castroenteritis (abnormality (vision)1 (1.4)Hematolagi (and final discovers)1 (1.4)Hematolagi (abnormality (vision) <td< td=""><td>Cardiomyopathy</td><td>4 (5.7)</td><td></td></td<>	Cardiomyopathy	4 (5.7)	
Mycardila infarction/ Coronary artery disease/Cardiac ischemia3 (4.3)Pericardial fusction (Coronary artery disease/Cardiac ischemia3 (4.3)Syncope3 (4.3)Mycardilis1 (1.4)Atrioventricular block1 (1.4)Neurologic condition1 (7.1)Decreased level of consciouness7 (10.00)Encephalopathy5 (7.1)Cognitive-menory inpairment/ psychosis3 (4.3)Ischemic events / Ischemic stroke3 (4.3)Periphera Incurry opthy2 (2.9)Seiture2 (2.9)Opthalmological aboranisity (vision)2 (2.9)Subdural hematoma2 (2.9)Cytopania (Annotypenia, Iscukcyropenia, thrombocytopenia)6 (8.6)Increased tendeny to builer (Ectymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukorytosis / Lymphocytosis4 (5.7)Areased tendeny to builer (Ectymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Barton intestinal biodores (am)6 (8.6)Gastro-entestinal biodores (am)1 (1.4)Patros (List / Gastro-entertilis6 (8.6)Gastro-ontestinal biodores (am)1 (1.4)Abdomia pain1 (1.4)Barton intest function tests2 (2.9)Nausa / Vomiting2 (2.9)Bastrointestinal boleng1 (1.4)Premonia1 (1.4)Premonia6 (8.6)Prevatification of the strophy1 (1.4)Prevatification of the strophy3 (4.3)Prevatification of the strophy3 (4.3)Prevatification of the strophy3 (4.3) <td>Bradycardia</td> <td>4 (5.7)</td> <td></td>	Bradycardia	4 (5.7)	
Pericardial effusion3 (4.3)Syncope3 (4.3)Myocardius1 (1.4)Atrioventricular block1 (1.4)Decreased level of consciousness7 (10.0)Encephalogative memory impament / psychosis3 (4.3)Ischemic events / ischemic stroke2 (2.9)Peripheral neuropathy2 (2.9)Seture2 (2.9)Sub of homological abnormality (vision)2 (2.9)	Hypertension	3 (4.3)	
Pericardial effusion3 (4.3)Syncope3 (4.3)Myocardius1 (1.4)Atrioventricular block1 (1.4)Decreased level of consciousness7 (10.0)Encephalogative memory impament / psychosis3 (4.3)Ischemic events / ischemic stroke2 (2.9)Peripheral neuropathy2 (2.9)Seture2 (2.9)Sub of homological abnormality (vision)2 (2.9)			
Syncope3 (4.3)Mycardin's1 (1.4)Atrioventricular block1 (1.4)Incephalopathy1 (1.4)Decreased level of consciousness7 (10.0)Encephalopathy5 (7.1)Cognitive-memory impainment / psychosis3 (4.3)Schemic events / ischemic stroke3 (4.3)Peripheral neuropathy2 (2.9)Schure events / ischemic stroke3 (4.3)Peripheral neuropathy2 (2.9)Ophthalmological abnormality (vision)2 (2.9)Subdural hematoma4 (5.7)Increased tendency to bruise (Exchwnosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Castronitestinal disorders (mu)16 (22.9)Darchas / Obling2 (2.9)Gastronitestinal bleeding1 (1.4)Gastronitestinal bleeding1 (1.4)Gastronitestinal bleeding1 (1.4)Gastronitestinal bleeding1 (1.4)Gastronitestinal bleeding1 (1.4)Gastronitestinal bleeding1 (1.4)Pumouronia2 (2.9)Promotopilon1 (1.4)Strict of yapiasi1 (1.4)Pumouronia2 (2.9)Promotopilonary condition1 (1.4)Putanditis / Strict or phy Costophagel relius (S / Condition2 (2.9)Promotopilonary condition1 (1.4)Putanditis / Strict or phy Costophagelia3 (4.3)Strict of yapiasi1 (1.4)Put			
Myocarditis11.1.4)Atrioventricular block11.4.9)Decreased level of consciousness7 (10.0)Encephalopathy5 (7.1)Cognitive-memory impairment / psychosis3 (4.3)Ischemic events / Ischemic stroke3 (4.3)Peripheral neuropathy2 (2.9)Seizure2 (2.9)Subdural hematoma2 (2.9)Subdural hematoma2 (2.9)Subdural hematoma2 (2.9)Cytopenia (anny toponis)16 (66)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis2 (2.9)Anemia2 (2.9)Decreased biod immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disarders (anz)16 (62.7)Darrhes / Collis / Gastroenteritis6 (6.6)Gastro-intestinal disarders (anz)11.4.9Darrhes / Collis / Gastroenteritis2 (2.9)Gastro-intestinal disarders (anz)11.4.9Darrhes / Collis / Gastroenteritis6 (6.6)Gastro-intestinal disarders (anz)11.4.9Darrhes / Collis / Sciencentritis6 (6.6)Gastrointestinal blocking11.4.9Patting / Monoral liver (nuction tests2 (2.9)Subdural periodoci (and)11.4.9Pumonary condition11.4.9Pumonary condition11.4.9Pumonary condition2 (2.9)Prevenolia2 (2.9)Respiratory failare6 (6.6)Periodoci (and file-unition file-2 (2.9)Pariodoci (and file-unition file-<			
Arioventricular block1 (1.4)Neurologic candition19 (27.1)Decreased level of consciousness7 (100)Encephalopathy5 (7.1)Cognitive memory inpairment / psychosis3 (4.3)Schemic events / tachemic stoke3 (4.3)Peripheral neuropathy2 (2.9)Schur2 (2.9)Ophthalmological abnornality (vision)2 (2.9)Subdural hematoma4 (5.7)Increased tendency to bruise (rectymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)16 (22.9)Darchased blood immunoglobulin (A / G / M)2 (2.9)Certraset ind isorders (any)16 (22.9)Darchas / Collis / Gastroenteritis6 (6.6)Gastro-intestinal bloeding1 (1.4)Adominal pian1 (1.4)Gastro-intestinal bloeding1 (1.4)Gastro-foration1 (1.4)Gastro-intestinal bloeding1 (1.4)Gastro-intestinal bloeding1 (1.4)Gastro-intestinal bloeding1 (1.4)Pumotoplinoary condition1 (1.4)Puller of traition1 (1.4)Puller of traition1 (1.4)Puller of traition2 (2.9)Gastro-intestinal bloeding1 (1.4)Puller of traition1 (1.4)Puller of traition1 (1.4)Strintestinal bloeding1 (1.4)Puller of traition2 (2.9)Puller of traition2 (2.9)Rastro fance (Interne			
ConstructionC 1Decreased level of consciousness7 (10.0)Encephalopathy5 (7.1)Cognitive-memory impairment / psychosis3 (4.3)Ischemic events / Ischemic stroke3 (4.3)Berpheral neuropathy2 (2.9)Seizure2 (2.9)Ophthalmological abnormality (vision)2 (2.9)Subdural hematoma2 (2.9)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased biod immunoglobulin (A / G / M)2 (2.9)Barten A. (Staff Call Scattorentritis6 (6.6)Gastro-intestinal disorders (anu)1 (6 (22.9)Diarrhea / Collis / Gastroenterritis6 (6.6)Gastro-intestinal bleeding1 (1.4)Abdomial pain1 (1.4)Abdomial pain1 (1.4)Abdomial pain1 (1.4)Permotologic and Bheumotologic condition1 (1.4)Pumonary condition1 (1.4)Pumonary condition1 (1.4)Pumonary condition2 (2.9)Broncholinitis / Shart Call Scattorentis6 (6.6)Broncholinitis / Shart Call Scattorentis6 (8.6)Pumonalitier / Lymphocytosis1 (1.4)Pumonary condition1 (1.4)Pumonary condition2 (2.9)Broncholinonary spergillosis1 (1.4)Pumonary condition2 (2.9)Broncholinonary spergillosis2 (2.9)			
Decreased level of consciousness7 (10.0)Cognitive-memory impairment / psychosis3 (4.3)Schemic events / ischemic stroke3 (4.3)Periphera ineuropathy2 (2.9)Seizure2 (2.9)Subdural hematoma2 (2.9)Jentopatopating (pancytopenia, thrombocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis/ S dastroentertis3 (4.3)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests3 (2.9)Gastroitestinal bleeding11 (1.4)Gastroitestinal bleeding11 (1.4)Pulmonary condition11 (1.4)Penumonia9 (12.9)Respiratory failure9 (12.9)Pneumonia2 (2.9)Prochopulmonary aspergillosis11 (4)Dermotologic condition11 (4)Prochopulmonary aspergillosis3 (4.3)Tractures / Liguement injury3 (4.3)Abir / Panicultis / Skin arophy3 (4.3)Ga		1 (1.4)	
Decreased level of consciousness7 (10.0)Cognitive-memory impairment / psychosis3 (4.3)Schemic events / ischemic stroke3 (4.3)Periphera ineuropathy2 (2.9)Seizure2 (2.9)Subdural hematoma2 (2.9)Jentopatopating (pancytopenia, thrombocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis/ S dastroentertis3 (4.3)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests2 (2.9)Gastroescophageal reflux disease3 (4.3)Hepatitis / Abormal liver function tests3 (2.9)Gastroitestinal bleeding11 (1.4)Gastroitestinal bleeding11 (1.4)Pulmonary condition11 (1.4)Penumonia9 (12.9)Respiratory failure9 (12.9)Pneumonia2 (2.9)Prochopulmonary aspergillosis11 (4)Dermotologic condition11 (4)Prochopulmonary aspergillosis3 (4.3)Tractures / Liguement injury3 (4.3)Abir / Panicultis / Skin arophy3 (4.3)Ga	Neurologic condition	19 (27 1)	
Encephiopathy5 (7.1)Cognitive-menony impairment / psychosis3 (4.3)Schemic events / ischemic stroke3 (4.3)Schemic events / ischemic stroke3 (4.3)Peripheral neuropathy2 (2.9)Ophthalmological abnormality (vision)2 (2.9)Schudral hematoma17 (24.3)Cytopenia (pancytopenia, leukocytopenia), thrombocytopenia)6 (8.6)Increased tendency to bruise / Ecohymosis / Hematoma / Hemorrhagic diathesis4 (5.7)Derreased blood immunoglobulin (A / 6 / M)2 (2.9)Decreased blood immunoglobulin (A / 6 / M)16 (22.9)Gastro-intestinal disorders (any)16 (22.9)Diarthea / Colitis / Gastroenteritis6 (8.6)Gastroenteritis2 (2.9)Abdominal pain11.4)Mausea / Vomiting2 (2.9)Gastroenteritis11.4)Gastroenteritis11.4)Gastroenteritis11.4)Schurber / Schult11.4)Pulmonary condition11.4)Pulmonary condition11.4)Pulmonary condition11.4)Pulmonary condition11.4)Pulmonary spergillosis11.4)Derretased blook invertion tests3 (4.3)Pristopain3 (4.3)Pristopain11.4)Pulmonary condition2 (2.9)Pristopain3 (4.3)Pristopain11.4)Pulmonary spergillosis11.4)Pulmonary spergillosis3 (4.3)Picture / Faiture			
Cognitive-memory impairment/ psychois3 (4.3)Peripheral neuropathy2 (2.9)Seizure2 (2.9)Seizure2 (2.9)Subdiral hematoma2 (2.9)Subdiral hematoma2 (2.9)Limmatological abnormality (vision)2 (2.9)Subdiral hematoma17 (24.3)(Cytopenia (panyrotpenia), leukocytopenia, thrombocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)16 (22.9)Gastro-intestinal disorders (any)16 (22.9)Darrhea / Collist / Gastro-entritis6 (8.6)Gastro-intestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastro-intestinal bleeding1 (1.4)Gastro-intestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastro-intestinal bleeding1 (1.4)Abdominal pain1 (1.4)Primonary condition2 (2.9)Preumonia9 (12.9)Respiratory failure6 (8.6)Piezu diffusion2 (2.9)Prochopulmonary aspergillosis1 (1.4)Dernochopulmonary aspergillosis1 (1.4)Principanet injury3 (4.3)Quiga3 (4.3)Piezu diffusion3 (4.3)Piezu diffusion3 (4.3)Piezu diffusion3 (4.3)Piezu diffusion3 (4.3)Piezu diffusion3 (4.3) <trr>Piezu diffusion3 (4.3</trr>			
Ischemic events / Ischemic stroke3 (4.3)Peripheral neuropathy2 (2.9)Seizure2 (2.9)Ophthalmological abnormality (vision)2 (2.9)Subdural hematoma2 (2.9)Hematologic condition17 (24.3)Cytopenia (panyrtopenia, leukocytopenia, hrombocytopenia)6 (8.6)Increased tendency to bruise/ Eachymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Gastro-instrating disorders (any)6 (8.6)Diarrhea / Collitis / Gastroenteritis6 (8.6)Gastroenteritis2 (2.9)Gastroenteritis2 (2.9)Barthea / Collitis / Gastroenteritis2 (2.9)Gastrointestinal disorders (any)16 (22.9)Diarrhea / Collitis / Gastroenteritis2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Pulmony condition2 (2.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Contonditis1 (1.4)Pornocholitis1 (1.4)<			
Peripheral neuropathy2 (2.9)Seiture2 (2.9)Ophthalmological abnormality (vision)2 (2.9)Subdural hematoma2 (2.9)Lematolaci condition17 (24.3)Cytopenia (pancytopenia, lukucytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarhea / Collis / Gastro-netritis6 (8.6)Gastro-intestinal disorders (any)16 (22.9)Diarhea / Collis / Gastro-netritis2 (2.9)Mausea / Vomiting2 (2.9)Gastro-intestinal bleeding1 (1.4)Gastro-intestinal bleeding1 (1.4)Gastro-intestinal obstruction1 (1.4)Gastro-intestinal obstruction1 (1.4)Gastro-intestinal obstruction2 (2.9)Respiratory failure6 (8.6)Pieuronal respiratory failure2 (2.9)Promonal respiratory failure1 (1.4)Pieuronal respiratory failure1 (1.4)Promonal respiratory failure3 (4.3)Promotopulmonary spergillosis1 (1.4)Promotopulmonary spergillosis3 (4.3)Costophateria3 (4.3)Costophateria3 (4.3)Costophateria3 (4.3)Costophateria3 (4.3)Pieuro (abstruction respiratory)3 (4.3)Pieuro (abstruction respiratory)3 (4.3)Pieuro (abstruction respiratory)3 (4.3)<			
Seizure2 (2.9)Ophthalmological abnormality (vision)2 (2.9)Subdural hematoma2 (2.9)Hematologic condition17 (24.3)Cytopenia (pancytopenia, leukocytopenia, hematoma / Hemorrhagic diathesis5 (7.1)Increased tendeny to bruise / Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Ogastro-intestinal disorders (any)16 (22.9)Gastroenteritus6 (8.6)Gastroenteritus2 (2.9)Gastroenteritus2 (2.9)Rastroinestal bleeding1 (1.4)Abdominal pain1 (1.4)Gastroenteritus9 (12.9)Gastroinestal obstruction1 (1.4)Intestial perforation1 (1.4)Gastroinestal obstruction1 (1.4)Pulmonary condition1 (1.4)Pulmonary condition1 (1.4)Pulmonary aspergillosis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Portologic and Rheumatologic condition2 (2.9)Prature Liguer Astenia3 (4.3)Patiguer Astenia3 (4.3)Patiguer Astenia3 (4.3)Patiguer Astenia3 (4.3)Patiguer Astenia6 (8.6)Rastro (Patiguer			
Opthalmological abnormality (vision)2 (2.9)Subdural hematoma17 (24.3)(cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (2.9)Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastro-intestinal disorders (any)16 (2.9)Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastro-intestinal blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal blood inmunoglobulin (A / G / M)1 (1.4)Pleural efficision1 (1.4)Pulmonary condition1 (1.4)Pulmonary condition1 (1.4)Pleural efficision2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Pleural efficision2 (2.9)Pleural efficision2 (2.9)Protopulmonary aspergillosis1 (1.4)Protopulmonary aspergillosis1 (1.4) <t< td=""><td></td><td></td><td></td></t<>			
Subdural hematoma2 (2.9)Hematolanic condition17 (24.3)Cytopenia (pancytopenia, leukocytopenia) increased tendeny to bruise Ecchymosis/ Hematoma / Hemorrhagic diathesis6 (8.6)Increased tendeny to bruise Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blod immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastro-intestinal disorders (any)2 (2.9)Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastro-intestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Pulmonary condition2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Pulmonary sapergillosis1 (1.4)Purmonia6 (8.6)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Particular / Athenia6 (8.6)Pleural effusion3 (4.3)Fractures / Ligament injury3 (4.3)Fractures / Ligament injury3 (4.3)Yaqia2 (2.9)Endocytopina function6 (8.6)Pleural effusion3 (4.3)Fractures / Ligament injury3 (4.3)Yaqia2 (2.9)Endocytopina function6 (8.6)Paratures / Ligament i			
Hematolacic condition17 (24.3)Cytopenia (pancytopenia, leukocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosi? (Jymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)6 (8.6)Gastro-intestinal disorders (any)6 (8.6)Diarrhea / Collis/ Gastroentritis6 (8.6)Gastro-intestinal disorders (any)6 (8.6)Diarrhea / Collis/ Gastroentritis6 (8.6)Gastro-intestinal blooding1 (1.4)Hepatitis / Abnormal liver function tests2 (2.9)Ausea / Vomiting2 (2.9)Gastro-intestinal blooding1 (1.4)Gastro-intestinal blooding1 (1.4)Gastro-intestinal obstruction1 (1.4)Gastro dysplasia1 (1.4)Pulmonary condition1 (1.4)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Dermatologic condition1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Pleural effusion3 (4.3)Fractures / Ligament injury3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Fractures / Ligament injury3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Fractures / Ligament injury3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Yigaja3 (4.3)Yigaja </td <td></td> <td></td> <td></td>			
Cytopenia (pancytopenia, leukocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis (Jymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Collis / Gastroenteritis6 (8.6)Gastro-intestinal disorders (any)16 (22.9)Joarnea / Collis / Gastroenteritis6 (8.6)Gastro-intestinal disorders (any)2 (2.9)Gastrointestinal bleeding1 (1.4)Hepatitis / Abnormal liver function tests2 (2.9)Gastrointestinal obstruction1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Interest (any)9 (12.9)Respiratory failure6 (8.6)Pleumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Broncholitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (1.4)Fractures / Ligament injury3 (4.3)Myalgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders2 (2.9)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Freer1 (1.4)Hypothermia1 (1.4)Hypothermia1 (1.4)	Subdural hematoma	2 (2.9)	
Cytopenia (pancytopenia, leukocytopenia)6 (8.6)Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis5 (7.1)Leukocytosis (Jymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Collis / Gastroenteritis6 (8.6)Gastro-intestinal disorders (any)16 (22.9)Joarnea / Collis / Gastroenteritis6 (8.6)Gastro-intestinal disorders (any)2 (2.9)Gastrointestinal bleeding1 (1.4)Hepatitis / Abnormal liver function tests2 (2.9)Gastrointestinal obstruction1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Interest (any)9 (12.9)Respiratory failure6 (8.6)Pleumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Broncholitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (1.4)Fractures / Ligament injury3 (4.3)Myalgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders2 (2.9)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Freer1 (1.4)Hypothermia1 (1.4)Hypothermia1 (1.4)			
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) Diarrhea / Colitts / Gastroenteritis 6 (8.6) Gastroescrophageal 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) Gastrointestinal obstruction 1 (1.4) Intestinal perforation 1 (1.4) Pulmonary condition 1 (1.4) Pulmonary condition 6 (8.6) Plevral effusion 2 (2.9) Bronchopulmonary aspergillosis 1 (1.4) Dermatologic and Rheumatologic condition 6 (8.6) Rash / Panniculitis / Athrnagia 7 (1.4) Fractures / Ligament injury 3 (4.3) Fractures / Ligament injury 3 (4.3) Myalgia 2 (2.9) Endocrino-metabolic disorders Electrolyte imbalance 1 (1.4) Frever 1 (1.4) Frever 1 (1.4)		17 (24.3)	
Leukorytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Collits / Gastroenteritis6 (8.6)Gastro-ontestinal view function tests2 (2.9)Mausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal perforation1 (1.4)Gastric dysplasia1 (1.4)Pulmanry condition9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchoiltis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (2.17.1)Fattype / Sthenia6 (8.6)Rash / Pannicultis / Sthin atrophy3 (4.3)Costochondritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endacrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Frever1 (1.4)Hypothermia1 (1.4)	Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	6 (8.6)	
Leukorytosis / Lymphocytosis4 (5.7)Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Collits / Gastroenteritis6 (8.6)Gastro-ontestinal view function tests2 (2.9)Mausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal perforation1 (1.4)Gastric dysplasia1 (1.4)Pulmanry condition9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchoiltis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (2.17.1)Fattype / Sthenia6 (8.6)Rash / Pannicultis / Sthin atrophy3 (4.3)Costochondritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endacrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Frever1 (1.4)Hypothermia1 (1.4)	Increased tendency to bruise/ Ecchymosis/ Hematoma / Hemorrhagic diathesis	5 (7.1)	
Anemia2 (2.9)Decreased blood immunoglobulin (A / G / M)2 (2.9)Castroesphaged feltux disease16 (22.9)Diarrhea / Collits / Gastroenteritis6 (8.6)Gastroesphaged reflux disease3 (4.3)Hepatitis / Abnormal liver function tests2 (2.9)Nausea / Voniting2 (2.9)Gastroitestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastroitestinal obstruction1 (1.4)Gastroitestinal obstruction1 (1.4)Gastroitestinal obstruction1 (1.4)Gastroitestinal obstruction1 (1.4)Gastroitestinal obstruction1 (1.4)Pulmonary condition1 (1.4)Pulmonary condition2 (2.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Dermotologic condition1 (1.4)Patigue / Asthenia6 (8.6)Rash / Panniculits / Skin atrophy3 (4.3)Costochondritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic cisonders2 (2.9)Endocrino-metabolic disonders2 (2.9)		4 (5.7)	
Decreased blood immunoglobulin (A / G / M)2 (2.9)Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastroesophageal reflux disease3 (4.3)Hepatitis / Abnormal liver function tests2 (2.9)Nausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Pulmonary condition1 (2.9)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Dermatologic condition2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Dermatologic in A Rhumatologic condition3 (4.3)Costochondritis / arthritis / arthritig / arthritigia3 (4.3)Costochondritis / arthritis / arthritigia3 (4.3)Costochondritis / arthritis / arthritigia3 (4.3)Fradures / Ligament injury3 (4.3)Wyalgia2 (2.9)Endocrino-metabolic disorders2 (2.9			
Gastro-intestinal disorders (any)16 (22.9)Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastroesophageal reflux disease3 (4.3)Hepatitis / Abnormal liver function tests2 (2.9)Gastrointestinal bleeding1 (1.4)Ausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation9 (12.9)Respiratory failure9 (8.6)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Dermotologic condition1 (1.4)Pratigue / Asthenia6 (8.6)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Paratologic and Rheumatologic condition1 (1.4)Paratologic and Rheumatologic condition3 (4.3)Fractures / Ligament injury3 (4.3)Wyalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Ever1 (1.4)Hypothermia1 (1.4)	Decreased blood immunoglobulin (A / G / M)		
Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastroesophageal reflux disease3 (4.3)Hepatitis / Abnormal liver function tests2 (2.9)Nausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal perforation1 (1.4)Gastrointestinal perforation1 (1.4)Gastroi dysplasia1 (1.4)Pulmonary condition1 (1.4)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic condition6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / Arthrelgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fyerer1 (1.4)Hypothermia1 (1.4)		- ()	
Diarrhea / Colitis / Gastroenteritis6 (8.6)Gastroesophageal reflux disease3 (4.3)Hepatitis / Abnormal liver function tests2 (2.9)Nausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal perforation1 (1.4)Gastrointestinal perforation1 (1.4)Gastroi dysplasia1 (1.4)Pulmonary condition1 (1.4)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic condition6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / Arthrelgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fyerer1 (1.4)Hypothermia1 (1.4)	Gastro-intestinal disorders (any)	16 (22.9)	
Gastroesophageal reflux disease3 (4.3)Hepatitis / Abnormal liver function tests2 (2.9)Nausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Bronchory condition9 (12.9)Pleural effusion2 (2.9)Bronchory failure6 (8.6)Pleural effusion2 (2.9)Bronchory aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (1.4)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Ever1 (1.4)Hypothermia1 (1.4)			
Hepatitis / Abnormal liver function tests2 (2.9)Nausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal obstruction1 (1.4)Gastrointestinal operformation1 (1.4)Gastroi dysplasia1 (1.4)Pulmonary condition1 (2.0)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic condition1 (2.17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Nausea / Vomiting2 (2.9)Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal obstruction1 (1.4)Intestinal obstruction1 (1.4)Gastrointestinal obstruction9 (12.9)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (2 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthrits / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Gastrointestinal bleeding1 (1.4)Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastric dysplasia1 (1.4)Pulmonary condition1 (1.4)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Broncholitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition2 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Hypothermia1 (1.4)			
Abdominal pain1 (1.4)Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastric dysplasia1 (1.4)Pulmonary condition1 (1.4)Puemonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 2 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Hypothermia1 (1.4)			
Gastrointestinal obstruction1 (1.4)Intestinal perforation1 (1.4)Gastric dysplasia1 (1.4)Pulmonary condition1 (1.4)Pulmonary condition1 (1.4)Pneumonia14 (20.0)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Broncholltis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (1.4)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / Arthrialgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Hypothermia1 (1.4)			
Intestinal perforation Gastric dysplasia1 (1.4) 1 (1.4)Pulmonary condition Pneumonia Respiratory failure Pleural effusion14 (20.0) 9 (12.9) 6 (8.6) 2 (2.9)Bronchiolitis Bronchiolitis Bronchopulmonary aspergillosis1 (1.4) 1 (1.4) 1 (1.4)Dermatologic and Rheumatologic condition Fatigue / Asthenia Rash / Panniculitis / Skin atrophy Costochondritis / arthritis / Arthralgia Fractures / Ligament injury Myalgia12 (17.1) 6 (8.6) 3 (4.3) 3 (4.3) 2 (2.9)Endocrino-metabolic disorders Electrolyte imbalance Acidosis Fever6 (8.6) 2 (2.9)Indocrino-metabolic disorders Electrolyte imbalance Hypothermia6 (8.6) 2 (2.9)			
Gastric dysplasia1 (1.4)Pulmonary condition14 (20.0)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Hypothermia1 (1.4)			
Pulmonary condition14 (20.0)Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition1 (2 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders Electrolyte imbalance6 (8.6)Acidosis1 (1.4)Hypothermia1 (1.4)			
Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia6 (8.6)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Gastric dysplasia	1 (1.4)	
Pneumonia9 (12.9)Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia6 (8.6)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Respiratory failure6 (8.6)Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia6Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Pulmonary condition	14 (20.0)	
Pleural effusion2 (2.9)Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Bronchiolitis1 (1.4)Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Respiratory failure		
Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Pleural effusion	2 (2.9)	
Bronchopulmonary aspergillosis1 (1.4)Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Bronchiolitis	1 (1.4)	
Dermatologic and Rheumatologic condition12 (17.1)Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Bronchopulmonary aspergillosis		
Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Fatigue / Asthenia6 (8.6)Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Dermatologic and Rheumatologic condition	12 (17.1)	
Rash / Panniculitis / Skin atrophy3 (4.3)Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Costochondritis / arthritis / Arthralgia3 (4.3)Fractures / Ligament injury3 (4.3)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Fractures / Ligament injury3 (4.3) 2 (2.9)Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Myalgia2 (2.9)Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Endocrino-metabolic disorders6 (8.6)Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)			
Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)		2 (2.3)	
Electrolyte imbalance2 (2.9)Acidosis1 (1.4)Fever1 (1.4)Hypothermia1 (1.4)	Endestine metabolis disorders	6 (8 6)	
Acidosis 1 (1.4) Fever 1 (1.4) Hypothermia 1 (1.4)			
Fever 1 (1.4) Hypothermia 1 (1.4)			
Hypothermia 1 (1.4)			
Weight increased 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).

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)	-7 (50)
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)	

1/20)
1 (2.0)
1 (2.0)
ditions 50 (100.0)
9 (18.0)
tricular arrhythmias) 19 (38.0)
nias (Atrial flutter/ Atrial fibrillation/ Supraventricular
les) 11 (22.0)
4 (8.0)
onary artery disease/Cardiac ischemia 3 (8.0)
EF / exersional dyspnea 2 (4.0)
1 (2.0)
1 (2.0)
1 (2.0)
- ()
12 (24.0)
3 (3.0)
ent ischemic attack / Stroke 2 (4.0)
2 (4.0)
nent / Mental status changes / Amnesia 2 (4.0)
1 (2.0)
1 (2.0)
1 (2.0)
1 (2.0)
14 (28.0)
eukocytopenia, thrombocytopenia) 7 (14.0)
se/ Ecchymosis/ Hematoma / Hemorrhagic diathesis 7 (14.0)
5 (10.0)
4 (8.0)
lobulin (A / G / M) 1 (4.0)
(any) 13 (26.0)
2 (4.0)
n 1 (2.0)
8 (16.0)
, , , , , , , , , , , , , , , , , , , ,
1 (2.0)
structive airways disease 1 (2.0)
tologic condition 13 (26.0)
4 (8.0)
1 (2.0)
1 (2.0)
1 (2.0)
ders 7 (14.0)
2 (4.0)
2 (4.0) 2 (4.0)
Interitis /Dehydration 6 (12.0) al discomfort 3 (6.0) pin increased 2 (4.0) n 2 (4.0) n 1 (2.0) atory arrest 8 (16.0) 6 (12.0) 2 (4.0) atory arrest 1 (2.0) structive airways disease 1 (2.0) tologic condition 13 (26.0) ses 5 (10.0) 5 (10.0) 5 (10.0) 5 (10.0) 5 (10.0) 4 (8.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0) 1 (2.0

Hemorrhagic events	5 (10.0)	
<u>Renal condition</u> Renal failure /Acute kidney injury	2 (4.0) 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).