Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study

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ABSTRACT

Aims. With the explosion of anticancer drugs, an emerging concern is the risk for drug-induced sudden-death (SD) via ventricular arrhythmias (VA).

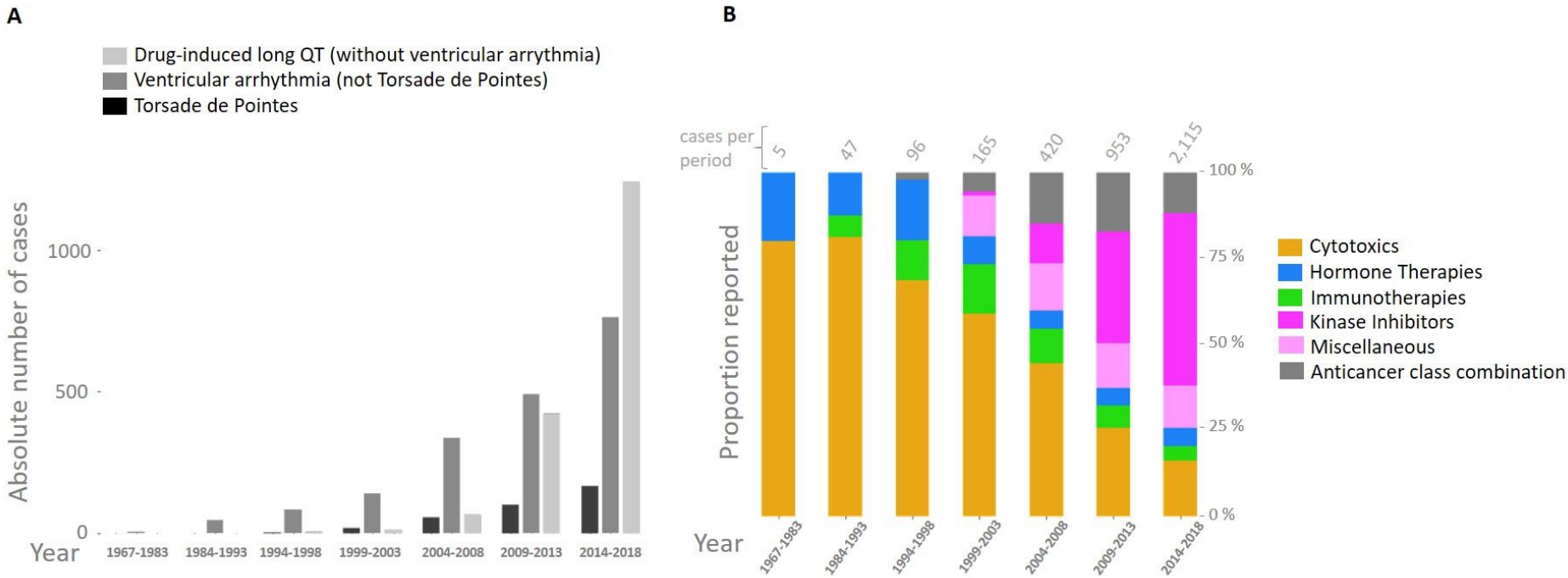
Methods. We used the international pharmacovigilance database VigiBase (n=18,441,659 reports) to compare drug-induced long-QT (diLQT, n=18,123) and VA (n=29,193) (including torsade-de-pointes (TdP, n=8,163) reporting for 663 anticancer drugs versus all other drugs until 01/01/2019. The analysis used the 95% lower-end credibility interval of the information-component (IC_{025}), an indicator for disproportionate Bayesian reporting; significant when IC_{025} >0.

Results. There were 2301 reports (13.8% fatal) for 40 anticancer drugs significantly associated with diLQT (with 27 also associated with VA or SD), and 9 drugs associated with VA without diLQT. Half of these (46·9%, 23/49) were associated with SD. Most (41%, 20/49) were kinase inhibitors, 8% (4/49) were hormonal therapies, 6% (3/49) were immunotherapies, 24% (12/49) were cytotoxics, and 20% (10/49) were miscellaneous. In VigiBase, reports of diLQT, TdP or VA increased from 580 in the period 1967-1983 to 15,070 in 2014-2018 with the proportion related to anticancer drugs increasing from 0.9% (5/580) to 14.0% (2115/15,070) ($p<0.0001$). Concordance between these VigiBase signals and data concerning diLQT and VA/TdP identified in CredibleMeds or US FDA labels were moderate ($\kappa=0.47$ and 0.40, $p<0.0001$). Twenty-three drugs represent new signals, while 24 flagged by CredibleMeds or FDA had no signal in VigiBase. A three-level SD risk stratification relying on isolated long QT (low-risk), associated with VA without SD (moderate-risk) and VA with SD (high-risk) is proposed.

Conclusion. This list of liable anticancer drugs may prove useful for physicians and regulatory authorities to reevaluate cardiac monitoring requirements.

Keywords. Disproportionality analysis, anticancer drugs, long QT, ventricular arrhythmias, pharmacovigilance, torsade de pointes

Graphical Abstract. Evolution of reporting for drug-induced long QT, ventricular arrhythmias and torsade de pointes associated with anticancer drugs (A) as a function of their classes (B) in VigiBase from inception (1967) to January 2019.



Introduction.

The development of cancer therapeutics has resulted in a better prognosis and long-term survival for patients with many malignancies.[1] Anticancer drugs may also lead to severe cardiovascular adverse drug reactions (ADR) carrying a high morbidity burden, and can be fatal.[2] This interplay between cancer and heart conditions is the subject of the booming field of cardio-oncology. Cardiac ADR of cytotoxic anticancer drugs have been identified for decades, such as anthracycline-induced heart failure or acute myocardial infarction with anti-metabolites.[2, 3] With the exponential development of new classes of anticancer drugs (including immunotherapy and kinase inhibitors, KI), other heart-related ADR have emerged and represent an important concern for regulatory agencies, companies, and patients care providers. A striking example is the increased reporting of myocarditis (fatality rate ~30-50%) occasionally induced by immune checkpoint inhibitors, which are breakthrough therapeutics approved in a wide variety of cancers.[4, 5] Cardiac arrhythmias are another emerging and poorly characterized concern of anticancer drugs with an increasing number of targeted therapies such as KI and anti-hormonal agents prolonging QT interval, a well-recognized marker of increased risk for cardiac arrhythmias and sudden death (SD).[6, 7]

The QT interval on the electrocardiogram (ECG), corrected for heart rate (QTc), is a measure of the duration of ventricular repolarization and is a widely used proxy of the drug-induced ventricular arrhythmia risk.[8] It remains the recommended standard surrogate used in human studies despite its well-recognized limitations.[9] Many drugs slightly prolong the QT interval, but in some patients, this prolongation can be exaggerated and provoke the morphologically distinctive polymorphic ventricular arrhythmia (VA) torsade de pointes (TdP). Symptoms associated with TdP include syncope and SD if the arrhythmia is prolonged or degenerates into ventricular fibrillation. More recently, it has been reported that some anticancer drugs, such as ibrutinib (a Bruton KI) can also lead to fatal VA without prolonging QT.[10]

Using VigiBase, the World Health Organization's (WHO) global pharmacovigilance database, we aimed to better define and risk stratify these severe cardiac arrhythmia ADR to improve patient safety and facilitate monitoring guidelines after administration of anticancer drugs. We also sought to identify new drugs with signals for VA, long QT and TdP which were not previously identified during clinical trials.

Methods.

Study design and data sources

This observational, retrospective, pharmacovigilance study is a disproportionality analysis based on ADR reported in VigiBase, the WHO deduplicated database of individual case safety reports (i.e., reports thereafter).[11] VigiBase is managed by the Uppsala Monitoring Centre (UMC, Uppsala, Sweden) and contains approximatively 19 million reports (through January 2019) submitted by national pharmacovigilance centers since 1967. The use of confidential, electronically processed patient data was approved by the Vanderbilt University Medical Center institutional review board (#181337, USA).

Procedures

This study included all drug-induced long QT (diLQT), TdP or VA classified by group queries according to the Medical Dictionary for Regulatory Activities (MedDRA, **Supplementary Table 1**), between inception on November 14, 1967, and January 1, 2019. DiLQT, TdP or VA specifically assessed in the analysis were those reported as suspected to be caused by a drug (versus concomitant use). Each report contains general administrative information (country of origin, date of reporting, and reporter qualification), patient characteristics (sex, age), drugs (indication, start and end dates of administration, dosage regimen, and route of administration), and reactions or events (reported terms, onset and end date, seriousness, and final outcome). A severe ADR was defined as causing death; being life-threatening; requiring hospital stay (initial or prolonged); or leading to persistent or clinically significant disability, congenital anomaly, birth defect, or any other medically important conditions.

Statistical analysis

VigiBase allows disproportionality analysis (also known as case–non-case analysis), which we used to assess whether suspected diLQT, TdP and VA were differentially reported with each drug (663 individual molecules pertaining to the anticancer drugs) *vs.* the full database of 20,222 drugs (**Supplementary Figure 1** for the flow-chart). Disproportionality analyses compare the proportion of a

selected specific ADR reported for a single drug with the proportion of the same ADR for a control group of drugs (i.e., full database with all drugs). The denominator in these analyses is the total number of ADR reported for each group of drugs. If the proportion of cases associated with a specific drug is greater than in patients without this ADR (non-cases), there is a disproportional association (signal identification) between the ADR and the drug.[12] We calculated a Bayesian disproportionality estimate suitable when taking the full database as comparator, i.e. the information component (IC). IC compares observed and expected number of reports for drug-ADR pairs. The IC_{025} is the lower-end of the 95% credibility interval for the IC so a positive value of the IC_{025} is deemed significant. More information concerning calculation of the IC/IC_{025} is provided in **Supplementary Methods** and these methods have been recently used in similar settings and detailed elsewhere.[10, 12-14] Since this work focused on identifying culprit anticancer drugs, we further performed a sensitivity analysis and estimated the frequentist disproportionality association (reporting odds ratio, ROR) with diLQT, TdP, VA and SD for each anticancer drug already flagged with positive $IC_{025,}$ restricting the background database to reports associated with at least one anticancer drugs (defined as drugs pertaining to the anatomical therapeutic classification L: Antineoplastic and immunomodulating agents). ROR was calculated by Chi^2 test, and the 95% confidence interval ($CI_{95\%}$) was estimated, as previously described.[12, 15] A lower end of the ROR $CI_{95\%}$ $\geq$1 is considered significant.

Characteristics of reports in VigiBase were described in terms of means ± standard-deviation or medians and interquartile range [IQR] for quantitative variables, and in terms of numbers and proportion for qualitative ones. Comparisons were performed by Chi2 test, Wilcoxon test with Dunn's post-tests, as appropriate. $P<0.05$ was deemed significant.

Concordance (agreement) between the data describing liability of anticancer drugs to induce cardiac arrhythmias according to VigiBase vs. US Food and Drug Administration (FDA) labels

(accessible at https://www.accessdata.fda.gov/scripts/cder/daf/) and CredibleMeds® (accessible at www.crediblemeds.org) was computed using the Cohen kappa coefficient.

Results.

Trends in anticancer drug-associated cardiac arrhythmia reporting over decades

The study included 42,462 reports of diLQT, TdP or VA from VigiBase inception, through January 1st, 2019. The number increased from 580 in the period 1967-1983 to 15,070 for 2014-2018 (**Supplementary Figure 2**). The corresponding proportion related to anticancer drugs increased from 0·9% (5/580) to 14·0% (2115/15,070) ($p<0.00001$). Anticancer drugs were divided into five subgroups: cytotoxic treatments (CT, including antimetabolites and anthracyclines), hormone therapies (HT), immunotherapies (IT, including immune-related cell therapies), KI (including any drug interacting directly with a kinase protein or its ligands) and other therapies (miscellaneous, Misc). The majority of this increase in reporting over years was in the KI group (**graphical abstract**) representing 51·6%, (1091/2115) of these cardiac arrhythmia reports associated with anticancer drugs within the 2014-2018 period versus 14·7% (311/2115) with CT, 5·9% (124/2115) with HT, 2·5% (52/2115) with IT, and 12·5% (265/2115) with a combination of any of these anticancer classes (Combo; i.e one drug or more pertaining to at least two of these classes: CT, HT, IT, KI, Misc) ($p<0·00001$).

Anticancer drugs associated with long QT, VA including TdP and SD

Forty anticancer drugs were significantly associated with diLQT (including 27 also associated with VA or SD), and 9 with VA without diLQT when taking as background either the full database (n=18,441,659; $IC_{025}>0$) or when restricting the database to cases involving at least one anticancer drug used (n=4,197,602; ROR $CI_{95\%} \geq 1$) (**Table 1**). Most (41%, 20/49) were KI, 24% (12/49) were CT, 8% (4/49) were HT, 6% (3/49) were IT, and 20% (10/49) were Misc. Details regarding the magnitude of the association by drug and per subtype of arrythmia (diLQT, VA and TdP) and signals for SD are shown in **Table 1**. Details concerning the year for which these anticancer drugs were first significantly associated with any of these cardiac arrhythmias are shown in **Supplementary Figure 2**. Details concerning number of reports per year of these cardiac arrhythmias are shown in **Figure 1**. To further evaluate the seriousness

of these cardiac events (diLQT, VA including TdP), we stratified the 49 drugs of interest as a function of the presence or not of a significant association with drug-induced SD (**Table 2**). Half of these anticancer drugs (46·9%, 23/49) were associated with SD. We generated a three-level SD risk stratification (**Figure 2**) constituted of drugs associated with only isolated diLQT without VA nor SD (low-risk, n=13), drugs associated with VA without SD (moderate-risk, n=13) and drugs associated with VA and SD (high-risk, n=23). Among anticancer drugs with moderate and high-risk for SD, most were also associated with diLQT (75%, 27/36) but not all (25%, 9/36). The top three drugs with the highest disproportional association (**Table 1**, **Supplementary Figure 3**, using IC_{025}) with diLQT were vandetanib (KI, n=97, IC_{025}=5.8, year of FDA approval 2011), arsenic trioxide (Misc, n=115, IC_{025}=5.5, year of FDA approval 2000) and ribociclib (KI, n=105, IC_{025}=5.3, year of FDA approval 2017). This was concordant with arsenic trioxide (n=14, IC_{025}=2.7), vandetanib (n=10, IC_{025}=2.5) and vorinostat (Misc, n=6, IC_{025}=1.2, year of FDA approval 2006) carrying the highest association with TdP. The top three drugs associated with VA were amsacrine (CT, n=14, IC_{025}=3.1), arsenic trioxide (n=25, IC_{025}=2.4) and daunorubicin (CT, n=52, IC_{025}=1.8, year of FDA approval 1979). The top drugs in terms of absolute number of reports were respectively nilotinib for diLQT (KI, n=369, IC_{025}=0.4, year of FDA approval 2007) and TdP (n=18, IC_{025}=0.4), and capecitabine for VA (CT, n=161, IC_{025}=0.8, year of FDA approval 1998) (**Table 1**, **Figure 1**). The major mechanisms of action of these drugs are detailed in **Table 2**.

Of note, we further validated this disproportionality method using positive and negative controls in terms of drugs at known risk of diLQT and TdP (dofetilide, sotalol, ibutilide with IC_{025} values among the highest (4.9 to 5·82)) vs. protective for diLQT and TdP (progesterone, levonorgestrel and testosterone carrying among the lowest IC_{025} values).[7, 9, 16] These data are shown in **Supplementary Figure 3** and the top 25 highest and lowest IC_{025} values for diLQT among all drugs available in VigiBase are shown in **Supplementary Table 2** and **Supplementary Table 3**.

Clinical features of cardiac arrhythmias associated with anticancer drugs in VigiBase

Clinical characteristics derived from the 2301 reports (diLQT without TdP, n=1406; TdP, n=196, and VA without TdP, n=699) associated with the 49 anticancer drugs of interest are displayed in **Table 3** and in **Supplementary Table 4**. Overlap between culprit anticancer drug classes within these reports is represented in **Figure 3**. Median age was 63 years (IQR 51-71). Male predominance was found in VA reports excluding TdP (64·9%, 431/664), contrasting with female predominance in diLQT and TdP reports (51·4%, 698/1359, p<0.0001). Most reports were in the last 5 years (1434/2301, 62%) and were by health-care professionals (1701/1943, 88%) in America (1038/2301, 45%) or Europe (762/2301, 33%). Most reports involved at least one culprit KI (64%, 1477/2301). A majority of reports were considered serious (94%, 1946/2078). All-cause fatality was 13·8% (317/2301) and 10% reported SD (228/2301, **Table 3**). The final outcome after stopping the culprit anticancer drug was available for 397 reports, of which 326/397 (82%) resolved. Most patients (49%, 766/1555) had hematologic diseases, particularly chronic myeloid leukemia (23%, 363/1555) or other leukemia (17%, 272/1555). Among solid tumors, the most represented were colorectal, lung, breast, and kidney cancers (8·1%, 126/1555; 7·3%, 114/1555; 6·7%, 104/1555 and 6·1%, 95/1555; respectively).

Details concerning concurrent drugs and conditions favoring QT prolongation, TdP and VA are shown in **Table 3**. Most reports 1381/1602 (86%) had no concomitant drugs at known risk of TdP on top of the culprit anticancer drug in the diLQT and/or TdP patients. Among these 1602 reports, the most reported drug classes with molecules concomitantly used at known risk of TdP were proton pomp inhibitors (8.6%; n=137), antiemetics (7.4%, n=119), anti-infectious agents (7.1%, n=114) and antidepressants (6%, n= 96). Reports of concurrent conditions favoring diLQT and VA were frequent with 12% (275/2301) of infection, or cardiac conditions including 10% (239/2301) of heart failure, and 8% (183/2301) of cardiac ischemia (**Table 3**).

Median time to onset (in days) was not significantly different between patients with diLQT without TdP, TdP and non-TdP VA (21 [IQR 7-91] *vs*. 23 [IQR 5·5-139] *vs*. 24 [IQR 4-120] days,

respectively; p=0·93) (**Figure 3**). When comparing different drug classes, median time to onset were variable ranging from 9 days [IQR 3-23] for IT, 9 [IQR 3-34] for CT, 12 [IQR 3-38] for Misc treatments, 31 [IQR 11-140] for KI, to 142 [IQR 25-409] for HT (p<0.0001). The differences between anticancer drug classes are displayed in **Figure 3**. The differences between anticancer drug molecules are displayed in **Supplementary Table 4**.

Concordance of cardiac arrhythmia risk evaluations between VigiBase, CredibleMeds and FDA

A total of 663 anticancer drugs were referenced in VigiBase (through July 1st 2019), of which 199 were FDA approved at least once and 195 currently approved (through July 1st 2019). Concordance between VigiBase results and data concerning diLQT, TdP and/or VA available in CredibleMeds database (which aggregates all known drugs prolonging QT) or US FDA labels were moderate (κ=0·47 [0.34-0.6], p<0·0001 and 0·40 [0.27-0.54]], p<0·0001, respectively, **Supplementary Figure 4**). Corresponding concordance between CredibleMeds and VigiBase was high (κ=0·74 [0.62-0.85], p<0·0001). Twenty-three drugs (16 for diLQT or TdP, and 14 for VA) were not described in CredibleMeds and/or FDA databases. In contrast, CredibleMeds and/or FDA databases described 24 drugs associated with these ADR which yielded no significant association in VigiBase. Details concerning the concordance per drug and specific type of cardiac arrhythmia (diLQT, TdP, VA) between these databases are presented in **Table 4**. Analyses of concordance restricted to the 199 FDA approved drugs showed similar results (**Supplementary Figure 4**). The most relevant new signals were those carrying a very high proportion of single suspect culprit drug (SSCD) in the reports (not confounded by the concurrent intake of other liable anticancer drugs) (**Supplementray Table 4**). Within FDA approved drugs, these latter were carfilzomib (n=19, SSCD=100%, proteasome inhibitor), imatinib (n=64, SSCD=73%, KI), alectinib (n=5, SSCD=100%, KI), axicabtagene-ciloleucel (n=4, SSCD=100%, CAR-T anti-CD19), mogamulizumab (n=5, SSCD=100%, C-C chemokine receptor type 4 inhibitor), and bicalutamide (n=30, SSCD=93%, androgen receptor antagonist). Interestingly, four drugs were flagged

before any FDA approval (amsacrine [CT], combretastatin a4 [CT], chidamide [histone deacetylase inhibitor] and enzastaurin [KI]).

Discussion.

In this worldwide pharmacovigilance study which included almost 19 million reports, disproportionality analyses yielded significant association between 49 anticancer drugs and cardiac arrhythmias including diLQT, TdP, and VA. This detailed report summarizes all available data addressing drug-induced cardiac arrhythmias extracted from US FDA labels, CredibleMeds and VigiBase. We believe our data can serve as a compendium for all clinicians using anticancer drugs and considering their potential arrhythmic risk (**Table 4**). FDA labels mainly summarize data systematically gathered and analyzed during drug development (thorough and concentration QT studies, clinical trials), and in some cases updates arising from post-marketing evaluation. Consensus achieved by experts from academia of these available data is found in the widely-recognized CredibleMeds website for TdP risk. VigiBase is a complementary source which assembles data from real-life surveillance with spontaneous post-marketing reporting mainly arising from healthcare professionals. VigiBase has previously been utilized to describe other cardiovascular sequelae from anticancer therapies and has allowed a better appreciation of the magnitude of these toxicities.[5, 7, 10] Interestingly, in our work, 23 drugs represented new signals, while 24 flagged by Crediblemeds or FDA had no signal in VigiBase. These findings may guide clinicians and regulatory institutions to conduct further research to reevaluate cardiac monitoring requirements focusing on these specific drugs. Moreover, information generally contained in FDA labels focus on magnitude of QT prolongation identified in QT studies, but does not provide information concerning VA and TdP risk as such, because these events are often too rare and not adjudicated in cancer-focused clinical trials. CredibleMeds website only assess TdP risk in context of QTc prolongation. Herein, we were able to identify three levels of SD risk profile with anticancer drugs only associated with isolated long QT (low-risk), associated with VA without SD (moderate-risk) and VA with SD (high-risk). This SD risk stratification may prove useful to clinicians when confronted to difficulties in the risk/benefit assessment of pursuing a liable anticancer drug with a possible overall benefit for the patient.

Importantly, we have identified a novel group that has not been particularly well flagged previously: drugs associated with potentially fatal VA but not mediated by QTc prolongation. This group is important to recognize in clinical situations where arrhythmias are suspected with a normal QTc on ECG. Lastly, this work provides a quantitative magnitude of disproportional association of 663 anticancer drugs with diLQT, TdP and VA. These data may prove useful for translational cardio-oncology researches seeking at identifying new pathways involved in arrhythmias, as we recently showed with ibrutinib and identification of kinase-dependent off-target inhibition leading to atrial fibrillation.[17]

To date, this study is the most extensive, analyzing over 42,000 suspected drug-induced cardiac arrhythmia events internationally reported from healthcare professionals. The evolution of reporting in VigiBase has been marked in the last decade by the introduction of new drug classes, KI, and IT; they currently represent the majority of reported drug-induced cardiac arrhythmias. As expected, CT have been associated with these ADR for far longer. In VigiBase, the first treatment to yield a significant association with cardiac arrhythmias was an anthracycline, idarubicin, in 1995. Of note, an average QTc >500 ms (normal <450 ms for men and <460 ms for women) or a >60 ms QTc change from baseline is considered as of particular concern (grade 3) according to the Common Terminology Criteria for Adverse Events, the grading mostly used in oncology trials. Anthracycline-related increase in QTc >60 ms vs. baseline has been reported with an incidence up to 14% with doxorubicin, and relates to their propensity to induce cardiomyocyte injury via overproduction of free radicals and alteration of cardiac ion currents, notably via I_{Ks} channel blockade and intra-cellular calcium dysregulation.[3, 6, 18] Our study also supports multiple observations previously reported in the literature, highlighting the robustness of the methodology with positive controls (e.g. arsenic trioxide, nilotinib, vandetanib, vorinostat, ribociclib).[6, 18-20] The anticancer drug most reported with long QT in VigiBase was arsenic trioxide, a drug used against some leukemia, and significantly associated with long QT/TdP since 2002 in VigiBase. The most comprehensive QT study included 99 patients with advanced malignancies who received 170 courses of

arsenic trioxide. Of them, 35/99 (35.4%) developed increase in QTc >60 ms vs. baseline, and one developed asymptomatic TdP.[19] Nilotinib, a second-generation BCR-ABL inhibitor, has been previously linked to moderate increase in QTc (average QTc prolongation of 5 to 15 ms).[6] In studies, 2.5% to 4% of patients exhibited QTc prolongation >60 ms on nilotinib, and in one study, 1.2% of patients showed QTc >500 ms.[6, 18, 21] Similarly, vandetanib, a vascular endothelial growth factor receptor inhibitor, has been associated with long QT in a meta-analysis including nine phase II-III trials, which found a significant risk of QTc prolongation (all-grade according to the National Cancer Institute Common Toxicity Criteria v.2.0 or 3.0), 123/2552 (4.82%) in treated patients vs. 6/2204 (0.27%) in control groups (relative-risk 7.90, $_{95\%CI}$ [4.03-15.50]).[22] Vorinostat, a histone deacetylase inhibitor used in the treatment of cutaneous T-cell lymphoma, was associated with QTc prolongation (>470 ms or delta >60 ms from baseline) in 5/116 (4.3%) patients in a retrospective review including phase I-II trials.[23] Ribociclib, a CDK 4/6 inhibitor used in breast cancer, was associated with QTc prolongation (>480 ms) in 11/334 (3.3%) of ribociclib-treated patients vs. 1/334 (0.3%) in the placebo arm, in its landmark randomized controlled trial.[24]

Distinct from drugs prolonging QT, several drugs were associated with VA without long QT. They included ibrutinib, and CAR-T. Indeed, although ibrutinib has not been associated with long QT (studies reported concentration-dependent QTc shortening),[25] it has been associated with atrial and ventricular arrhythmias and SD.[10, 26] As described previously, it may correspond to a short-coupled variant of polymorphic ventricular tachycardia, which is thought to involve alteration in cardiac sarcoplasmic reticulum Ca^{2+} homeostasis associated with cardiac ryanodine receptor-calmodulin-dependent protein kinase pathways.[10, 26] In our study, which found a few cases of CAR-T (axicabtagene-ciloleucel) related VA, there was also a signal towards association with VA but not long QT. In a retrospective study, 54% of tested patients who received CAR-T showed myocardial injury with troponin elevation and 12% developed a cardiac ADR (including heart failure, arrhythmias, and cardiac deaths).[27]

Our study also yielded new signals requiring further investigations to confirm the causality of the association, its magnitude and mechanisms at play. Alectinib, an ALK inhibitor, was not previously associated with VA nor QT modification, but it was associated with mild sinus bradycardia.[28] Carfilzomib, a proteasome inhibitor approved for the treatment of multiple myeloma, was known for its risk of cardiac failure, but not long QT and SD.[29] We also found imatinib associated with long QT, while imatinib was considered so far as relatively safe from a cardiovascular standpoint, as compared to other BCR-ABL inhibitors including nilotinib, ponatinib and dasatinib.[6, 18, 30] In our study, a key element strengthening the association between these drugs and cardiac arrhythmias is the fact that in most reports alectinib (100%), carfilzomib (100%) and imatinib (73.4%) was the only anticancer drug suspect involved in the appearance of these cardiac ADR. Notably, we also observed hormone therapies blocking testosterone association with long QT and TdP, such as bicalutamide, an androgen receptor antagonist used in prostate cancer. In a translational study combining pharmacoepidemiologic and mechanistic studies using iPSC cardiomyocytes, we recently confirmed the causal association between androgen deprivation and long QT and TdP.[7] Interestingly, our analysis showed that in four instances, signals of association between an incriminated drug under development and long QT, VA and TdP, in VigiBase, appeared prior to FDA approval of those drugs (namely, amsacrine, chidamide, combrestatin-a4 and enzastaurin). In the specific field of drug-induced QT prolongation and cardiac arrhythmias, the agreement between the FDA labels, CredibleMeds and VigiBase remains modest at best, and emphasizes the complementarity of a multimodal approach to apprehend the toxicity of a specific drug.

The variety of anticancer drug classes associated with long QT highlights the heterogeneity of the mechanisms which may underly cardiac arrhythmias related to these agents. The generally accepted common mechanism whereby drugs prolong QT is block of a key cardiac repolarizing potassium current, IKr.[8] While some anticancer drugs associated with diLQT and TdP have been shown to inhibit IKr, recent works focusing on anticancer drugs prolonging QT identified new pathways.[8] The *in-vitro* effects of

some KI to prolong cardiac action potentials (the cellular correlate of QT) can be rescued by intracellular phosphatidylinositol 3,4,5-trisphosphate, the downstream effector of phosphoinositide-3-kinase. This finding supports a role for inhibition of this enzyme, either directly or by inhibition of upstream kinases, to prolong QTc through mechanisms that are being investigated, but include enhanced inward 'late' sodium current (INaL) activation during the plateau of the action potential.[8] These observations emphasize the need to better explore the kinome in general, and in particular, the effects of kinases located up- and downstream to that of phosphoinositide-3-kinase, to better understand their influence on cardiac electrophysiology.[31]

We acknowledge several inherent limitations to our results related to pharmacovigilance studies.[13] First, the exact denominator of patients exposed to anticancer drugs cannot be evaluated, hence the true incidence of the events cannot be computed, and all values are expressed as relative to each other, with the basis that VigiBase aggregates millions of reports, hence may allow for a generalization of the findings. The second bias stems from the observational and declarative nature of the reports with variable degree of exhaustivity. Third, the number 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 bias.[13] Fourth, some drugs specifically annotated in **Supplementary Table 4** (low SSCD) were systematically used in association, which require cautious interpretation of the results when one of these were known to be associated with cardiac arrhythmias. Finally, in the specific context of anticancer drugs, the added risk due to these drugs is difficult to assess, as end-stage cancers may be associated with cardiac arrhythmias; however, this have been partially mitigated by our sensitivity disproportionality analysis restricted to patients on anticancer drugs. While these limitations are numerous, the added value of pharmacovigilance studies have already been demonstrated in various settings.[10, 12, 15, 16] Nevertheless, they are only to be taken as signal-generating studies and all hypotheses generated require validation by translational mechanistic or prospective studies.[7, 10] Indeed, while they are mandatory to establish efficacy, their power

to detect ADR may be lower, due to the rarer incidence in these events and the fact that “real-world population” may differ from included patients in the said clinical trial. Translational experimental studies specifically designed to answer a question of cardiotoxicity in oncology remain the most comprehensive design available, yet.[7]

Contributors. J-ES and PG were involved in study design. PG did the literature search. PG and J-ES made the figures. PG, J-ES, BL-V were involved in data collection. PG and J-ES analyzed the data. PG, LSN and J-ES were involved in data interpretation. PG, LSN, J-ES, JJM, CF-B, SE, AC, DR, and BL-V were involved in the writing of the manuscript. All authors edited the manuscript.

Declaration of interests. JES had paied lectures from AstraZeneca and BMS, unrelated to this work and have patents pending and issued related to methods for detecting risk of Torsade-de-Pointes. JJM had consultancy fees from BMS, AstraZeneca, Deciphera, Janssen, Takeda, Cytokinetics, Audentes, Boston Biomedical, and Myovant unrelated to this work. All other authors have nothing to disclose.

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Tables and Figures.

Table 1.

Anticancer drugs associated with at least one of the following adverse drug reactions: drug-induced long QT syndrome (diLQT), torsade de pointes (TdP), and ventricular arrhythmias (VA) based on disproportionality analysis in VigiBase (through 01/01/2019). Associations were deemed significant when the lower end of the 95% credibility interval was positive (IC_{025} >0) for analysis vs. full database (n=18,441,659); or when the lower end of the 95% confidence interval of the reporting odds ratio was >1 (rOR_{025} >1) for analysis restricted to reports with anticancer drugs as background (n= 4,197,602). Non-significant associations are not represented. Results with sudden death (SD) are also represented for these latter drugs.

			diLQT (N_{effect}†=3,036)			**TdP*** (N_{effect}†=761)			**VA** (N_{effect}†=3,748)			**SD** (N_{effect}†=13,288)		
drug	class	N_{drug}	N_{obs}	IC_{025}	rOR [$CI_{95\%}$]	N_{obs}	IC_{025}	rOR [$CI_{95\%}$]	N_{obs}	IC_{025}	rOR [$CI_{95\%}$]	N_{obs}	IC_{025}	rOR [$CI_{95\%}$]
amsacrine$^{€}$	CT	287	5	1·3	25 [10-59]	3	0·4	58 [19-183]	14	3·1	58 [34-99]	10	1·5	11·4 [6·1-21·4]
capecitabine$^{\$,€}$	CT	49174							161	0·8	3·8 [3·2-4·4]	319	0·3	2·1 [1·9-2·3]
clofarabine$^{\$,€}$	CT	2216	5		3·1 [1·3-7·5]	2		5 [1·2-20]	11	0·5	5·6 [3·1-10]	57	2·0	8·3 [6·4-10·9]
combretastatin a4	CT	25	3	0·7	189 [56-630]	1		230 [31-1703]	1		47 [6·3-345]			
cytarabine$^{\$,€}$	CT	26300	52	0·6	2·8 [2·1-3·6]	14		3 [1·8-5]	89	0·8	3·9 [3·1-4·8]	358	1·4	4·4 [4-4·9]
daunorubicin$^{\$,€}$	CT	6655	28	1·4	5·9 [4·1-8·5]	9	0·4	7·5 [3·9-15]	52	1·8	8·9 [6·8-12]	149	2·0	7·3 [6·2-8·6]
decitabine$^{\$,€}$	CT	2894	10	0·6	4·8 [2·6-8·9]							22		2·4 [1·6-3·7]
fluorouracil$^{\$,€}$	CT	65547							138	0·2	2·4 [2-2·9]	383	0·2	1·9 [1·7-2·1]
idarubicin$^{\$,€}$	CT	3539	12	0·7	4·7 [2·7-8·3]	5		7·8 [3·3-19]	18	0·9	5·7 [3·6-9·1]	42	0·9	3·8 [2·8-5·1]
mitoxantrone$^{\$,€}$	CT	4847	12	0·3	3·4 [1·9-6·1]	9	0·8	10 [5·4-20]	28	1·2	6·5 [4·5-9·5]	60	1·0	4 [3·1-5·1]
nelarabine$^{\$,€}$	CT	370							4	0·3	12 [4·6-33]			
pegaspargase$^{\$,€}$	CT	4481							22	0·9	5·5 [3·6-8·4]	146	2·5	10·7 [9·1-12·6]
bicalutamide$^{\$,€}$	HT	4802	13	0·5	3·8 [2·2-6·5]	10	1·0	12 [6·2-22]	23	0·9	5·4 [3·6-8·2]	24		1·6 [1·1-2·4]
letrozole$^{\$,€}$	HT	15564	25	0·1	2·2 [1·5-3·3]									
tamoxifen$^{\$,€}$	HT	18567	28	0·0	2·1 [1·4-3]	8		2·4 [1·2-4·8]						
toremifene$^{\$,€}$	HT	258	2		11 [2·7-43]	1		21 [3-153]	4	0·6	18 [6·6-47]	8	1·2	10·1 [5-20·4]
aldesleukin$^{\$,€}$	IT	1553							15	1·6	11 [6·6-18]	29	1·4	6 [4·2-8·7]
axicabtagene ciloleucel$^{\$,€}$	IT	117							4	1·0	40 [15-108]	3		8·3 [2·6-26·1]
interferon alfacon-1$^{\#}$	IT	742							5	0·2	7·6 [3·2-18]			
alectinib$^{\$,€}$	KI	1346	5	0·1	5·2 [2·1-12]									
bosutinib$^{\$,€}$	KI	2927	9	0·4	4·3 [2·2-8·2]									
ceritinib$^{\$,€}$	KI	1747	21	2·6	17 [11-26]	2		6·3 [1·6-25]						

cobimetinib[$,€]	KI	1496	20	2·7	19 [12-29]										
crizotinib[$,€]	KI	7614	102	3·4	19 [16-24]	9	0·2	6·6 [3·4-13]							
dabrafenib[$,€]	KI	7612	27	1·2	5 [3·4-7·2]										
dasatinib[$,€]	KI	19654	94	1·9	6·8 [5·6-8·4]										
enzastaurin	KI	138	1		10 [1·4-72]				3	0·2	25 [7·9-78]	2			4·6 [1·1-18·7]
ibrutinib[$,€]	KI	21110							99	1·3	5·4 [4·4-6·6]	126	0·1		1·9 [1·6-2·3]
imatinib[$,€]	KI	44671	64	0·2	2 [1·6-2·6]										
lenvatinib[$,€]	KI	2555	11	1	6 [3·3-11]										
midostaurin[$,€]	KI	1001	34	4	49 [35-69]	2		11 [2·8-44]	4		4·5 [1·7-12]				
nilotinib[$,€]	KI	17471	369	4·2	34 [30-38]	18	0·4	5·8 [3·6-9·3]	46	0·3	3 [2·2-4]	92			1·7 [1·4-2·1]
osimertinib[$,€]	KI	2423	37	3·2	22 [16-30]	4		9·2 [3·4-24]							
pazopanib[$,€]	KI	19816	40	0·5	2·8 [2·1-3·9]	14		4 [2·3-6·7]							
ribociclib[$,€]	KI	1738	105	5·3	92 [75-112]	4	0·1	13 [4·8-34]							
sunitinib[$,€]	KI	29774	71	0·9	3·4 [2·7-4·2]	12		2·2 [1·3-4]				130			1·4 [1·2-1·6]
trametinib[$,€]	KI	7538	26	1·1	4·8 [3·3-7·1]										
vandetanib[$,€]	KI	971	97	5·8	158 [128-196]	10	2·5	58 [31-109]	10	1·3	12 [6·3-22]				
vemurafenib[$,€]	KI	8322	106	3·3	18 [15-22]										
arsenic trioxide[$,€]	Misc	1642	115	5·5	108 [89-131]	14	2·7	48 [28-82]	25	2·4	17 [12-26]	20	0·6		3·9 [2·5-6]
belinostat[$,€]	Misc	61	3	0·6	72 [22-228]										
carfilzomib[$,€]	Misc	8109	19	0·5	3·3 [2·1-5·1]				18		2·5 [1·6-4]	59	0·3		2·3 [1·8-3]
chidamide	Misc	238	7	2·1	42 [20-89]										
gemtuzumab ozogamicin[$,€]	Misc	1729	9	1	7·2 [3·8-14]	3		9·6 [3·1-30]	8	0·2	5·2 [2·6-10]	34	1·5		6·3 [4·5-8·9]
mogamulizumab[$,€]	Misc	497							5	0·6	11 [4·7-27]				
panobinostat[$,€]	Misc	1483	24	3	23 [15-34]										
romidepsin[$]	Misc	462	11	2·6	34 [19-62]	2		24 [6-97]	4	0·1	9·8 [3·7-26]	4			2·8 [1-7·4]
tretinoin[$,€]	Misc	5250	14	0·4	3·7 [2·2-6·3]	3		3·2 [1-9·8]							
vorinostat[$,€]	Misc	1378	23	3	24 [16-36]	6	1·2	24 [11-54]	7	0·2	5·7 [2·7-12]	24	1·2		5·6 [3·7-8·4]

$CI_{95\%}$: 95% confidence interval; CT: chemotherapy; HT: hormonotherapy; IT immunotherapy; KI: kinase inhibitor; Misc: miscellaneous; N_{drug}: number of reports for the drug; N_{obs}: number of reports observed for the ADR with the drug of interest

*Data of disproportionality for TdP breakdown (vs. VA) was considered only for drugs with a positive signal for diLQT

[#] Withdrawn from US market, [$] available on the US market, [€] available on the European market

[†] N_{effect} refers to the number of reports for the ADR of interest in the anticancer group. The N_{effect} in the full database background is 18,123 for diLQT; 8,163 for TdP; 29,193 for VA; and 85,350 for SD.

Table 2. Classification of the 49 anticancer drugs as a function of the signals identified in VigiBase for drug-induced long QT syndrome (diLQT), ventricular arrhythmias (VA) including torsade de pointes (TdP), and sudden death (SD).

	drug	class	subclass	target / mechanism
diLQT	**VA or TdP and sudden death**			
	amsacrine	CT	anthracycline and derivatives	topoisomerase II
	daunorubicin	CT	anthracycline and derivatives	topoisomerase II
	idarubicin	CT	anthracycline and derivatives	topoisomerase II
	mitoxantrone	CT	anthracycline and derivatives	topoisomerase II
	clofarabine	CT	antimetabolite	purine analog
	cytarabine	CT	antimetabolite	cytidine analog
	decitabine*	CT	antimetabolite	hypomethylating agent / cytidine analog
	bicalutamide	HT	antiandrogen	androgen receptor
	toremifene	HT	SERM	estrogen receptor
	enzastaurin	KI	kinase inhibitor	PKCβ, AuroraA/B, Chk1/2, URACα, and PI3Kα
	nilotinib	KI	kinase inhibitor	BCR-ABL, PDGFR, KIT, CSF-1R, and DDR1
	sunitinib	KI	kinase inhibitor	VEGFR1/2/3, PDGFRα/β, KIT, FLT3, CSF-1R, and RET
	arsenic trioxide	Misc	other small molecule	PML/RAR-alpha
	carfilzomib	Misc	other small molecule	proteasome inhibitors
	romidepsin	Misc	epigenetic inhibitor	histone deacetylase
	vorinostat	Misc	epigenetic inhibitor	histone deacetylase
	gemtuzumab ozogamicin	Misc	antibody drug conjugate	CD33
	VA or TdP without sudden death			
	combretastatin a4	CT	vascular disruptive agent	vascular endothelial cells
	tamoxifen	HT	SERM	estrogen receptor
	ceritinib	KI	kinase inhibitor	ALK, IGF-1R, InsR, and ROS1
	crizotinib	KI	kinase inhibitor	ALK, ROS1, Met, RON
	midostaurin	KI	kinase inhibitor	FLT3, KIT ,PDGFRα/β, VEGFR2, and PKC
	osimertinib	KI	kinase inhibitor	EGFRm (19 indel, L858R, T790M)
	pazopanib	KI	kinase inhibitor	VEGFR1/2/3, PDGFRα/β, KIT,FGFR1/3,ITK,LCK,FMS
	ribociclib	KI	kinase inhibitor	CDK4/6
	vandetanib	KI	kinase inhibitor	EGFR,VEGFR, RET, BRK, TIE2, EPHR, and SRC
	tretinoin	Misc	other small molecule	PML/RAR-alpha
	No VA, TdP nor sudden death			
	letrozole	HT	aromatase inhibitor	estrogen receptor
	alectinib	KI	kinase inhibitor	ALK and RET
	bosutinib	KI	kinase inhibitor	BCR-ABL, Src, Lyn, and Hck
	cobimetinib	KI	kinase inhibitor	MEK1, MEK2
	dabrafenib	KI	kinase inhibitor	BRAF V600/wt, CRAF, SIK1, NEK11, and LIMK1
	dasatinib	KI	kinase inhibitor	BCR-ABL, SRC, LCK, YES, FYN, c-KIT, EPHA2, and PDGFRβ
	imatinib	KI	kinase inhibitor	BCR-ABL,PDGFR, SCF, and KIT
	lenvatinib	KI	kinase inhibitor	VEGFR1/2/3, PDGFRα, KIT, FGFR1/2/3/4, and RET

	drug	class	subclass	target / mechanism
	trametinib	KI	kinase inhibitor	MEK1, MEK2
	vemurafenib	KI	kinase inhibitor	BRAF, CRAF, ARAF, SRMS, ACK1, MAP4K5, and FGR
	belinostat	Misc	epigenetic inhibitor	histone deacetylase
	chidamide	Misc	epigenetic inhibitor	histone deacetylase
	panobinostat	Misc	epigenetic inhibitor	histone deacetylase
no diLQT	**VA with sudden death**			
	capecitabine	CT	antimetabolite	uracil analogue
	fluorouracil	CT	antimetabolite	uracil analogue
	pegaspargase	CT	other protein-based therapies	L-asparagine
	aldesleukin	IT	cytokine	interleukin-2
	axicabtagene ciloleucel	IT	CAR T-cell	CD19
	ibrutinib	KI	kinase inhibitor	BTK
	VA without sudden death			
	nelarabine	CT	antimetabolite	guanosine analogue
	interferon alfacon-1	IT	cytokine	interferon
	mogamulizumab	Misc	chemokine receptor inhibitor	CCR4

CAR: chimeric antigen receptor; CT: chemotherapy; HT: hormonotherapy; IT immunotherapy; KI: kinase inhibitor; MAB: monoclonal antibody; Misc: Miscellaneous; SERM: selective estrogen receptor modulator

* decitabine was significantly associated with diLQT and SD, but not with TdP nor VA

Table 3. Characteristics of patients receiving at least one of the 49 anticancer drugs associated significantly with diLQT, TdP or VA through 01/01/2019, in VigiBase.

	Total N= **2301**
Age at Onset**, years; median [IQR]**	63; [51-71] N=1609 available
Time to Onset**, days; median [IQR]**	25; [7-97] N=776 available
Reporting Year	
1973-1993	22/2301 (1·0%)
1994-1998	34/2301 (1·5%)
1999-2003	67/2301 (2·9%)
2004-2008	191/2301 (8·3%)
2009-2013	553/2301 (24%)
2014-2018	1434/2301 (62·3%)
Notifier	
Healthcare professionals	1701/1943 (88%)
Non-healthcare professionals	242/1943 (12%)
Country of reporting	
Africa	1/2301 (0·1%)
Americas	1038/2301 (45·1%)
Asia	423/2301 (18·4%)
Europe	762/2301 (33·1%)
Oceania	77/2301 (3·3%)
Sex	
Female	931/2023 (46%)
Male	1092/2023 (54%)
Type of report	
diLQT without TdP; % including SD	1406/2301 (61%); 0/1406 (0%)
TdP; % including SD	196/2301 (9%); 44/196 (29%)
VA (not TdP); % including SD	699/2301 (30%); 184/699 (26%)
Seriousness	
Serious	1946/2078 (94%)
Death	317/2301 (14%)
Sudden death	228/2301 (10%)
Number of anticancer drug suspected/interacting	
1	1793/2301 (78%)
2	313/2301 (14%)
≥3	195/2301 (8%)
Type of anticancer drugs suspected/ interacting	
At least one cytotoxic	621/2301 (27%)
At least one hormonotherapy	138/2301 (6%)
At least one immunotherapy	33/2301 (1·4%)
At least one kinase inhibitor	1477/2301 (64·2%)
At least one miscellaneous drug	300/2301 (13%)
2 types or more combined	258/2301 (11·2%)

	Total N= **2301**
Indications	
chronic myeloid leukemia (CML)	363/1555 (23%)
leukemia other than CML	272/1555 (17%)
colorectal cancer	126/1555 (8·1%)
lung cancer	114/1555 (7·3%)
breast cancer	104/1555 (6·7%)
kidney cancer	95/1555 (6·1%)
melanoma	90/1555 (5·8%)
thyroid cancer	76/1555 (4·9%)
myeloma	50/1555 (3·2%)
lymphoma	47/1555 (3%)
prostate cancer	24/1555 (1·5%)
cancer other	90/1555 (5·8%)
cancer no precision	52/1555 (3·3%)
other hematological diseases or malignancies	34/1555 (2·2%)
indication other than malignancy (inflammatory or autoimmune diseases)	18/1555 (1·2%)
Concurrent reported drugs at known risk of TdP (in the diLQT and/or TdP reports, n= 1602)	
0	1381/1602 (86·2%)
1	192/1602 (12%)
2	18/1602 (1·1%)
≥3	11/1602 (0·7%)
Concurrent reported drugs at conditional, possible or known risk of TdP [32] (in the diLQT and/or TdP reports, n= 1602)	
0	1157/1602 (72·2%)
1	244/1602 (15·2%)
2	103/1602 (6·4%)
≥3	98/1602 (6·1%)
Classes of concurrently reported drugs at conditional, possible or known risk of TdP[32] (in the diLQT and/or TdP reports, n= 1602)	
anti-alpha1-adrenergics	3/1602 (0·2%)
antiarrhythmic	41/1602 (2·6%)
antidepressant	96/1602 (6·0%)
antiemetic	119/1602 (7·4%)
antihistamine	36/1602 (2·2%)
anti-infectious	114/1602 (7·1%)
antipsychotic	23/1602 (1·4%)
diuretic-potassium lowering agents	96/1602 (6·0%)
opioid	73/1602 (4·6%)
proton pump inhibitor	137/1602 (8·6%)
Other cardiovascular drugs	2/1602 (0·1%)
Other	13/1602 (0·8%)
Concurrent reported condition favoring LQT/TdP or VA	
none	1216/2301 (53%)
hypokalemia	107/2301 (4·7%)
hypocalcemia	65/2301 (2·8%)

	Total N= **2301**
hypomagnesemia	33/2301 (1·4%)
diabetes mellitus	39/2301 (1·7%)
uncontrolled hypertension	92/2301 (4%)
pericarditis or pericardia effusion	25/2301 (1·1%)
cardiac ischemia	183/2301 (8%)
heart failure	239/2301 (10%)
bradycardia	94/2301 (4·1%)
tachycardia	113/2301 (4·9%)
conductive disorders	174/2301 (7·6%)
atrial fibrillation	126/2301 (5·5%)
hypotension or shock	134/2301 (5·8%)
ischemia or thrombosis (not cardiac nor cerebral)	75/2301 (3·3%)
acute kidney injury	133/2301 (5·8%)
acute hepatic injury	139/2301 (6%)
acute stroke	43/2301 (1·9%)
epilepsy	43/2301 (1·9%)
infection (virus, bacteria, fungus, or parasite)	275/2301 (12%)
inflammation	160/2301 (7%)
other cardiovascular disorders	132/2301 (5·7%)

diLQT: drug-induced long QT syndrome; VA: ventricular arrhythmia; SD: sudden death; TdP: torsade de pointes

Table 4.

Comparison of VigiBase signals (IC_{025} >0 vs. full database; or rOR_{025} >1 vs. anticancer drug background) for drug-induced long QT (diLQT), torsade de pointes (TdP), and ventricular arrhythmias (VA) with information retrieved in CredibleMeds® website and US FDA labels (through July 1st, 2019). Among the 663 anticancer drugs screened (full list in **Supplementary Table 3**), only those with evidence of association with diLQT, TdP, VA mentioned in one of these three reference sources are shown. For these latter drugs, information concerning sudden death (SD) is also represented.

	Signal in VigiBase				Credible Meds *	Signal in FDA label				
Drug	diLQT	TdP	VA	SD	TdP risk	diLQT	TdP	VA	SD	new signal
abarelix					possible	in text				
aldesleukin			Yes	Yes				BW		
alectinib	Yes									Yes
amsacrine	Yes	Yes	Yes	Yes		NA	NA	NA	NA	Yes
apalutamide					possible	in text				
arsenic trioxide	Yes	Yes	Yes	Yes	known	BW	BW	BW	BW	
axicabtagene ciloleucel			Yes	Yes						Yes
belinostat	Yes									Yes
bendamustine					possible					
bicalutamide	Yes	Yes	Yes							Yes
bortezomib				Yes	possible	in text				
bosutinib	Yes				possible					
cabozantinib					possible					
capecitabine			Yes	Yes	possible					
carfilzomib	Yes		Yes	Yes						Yes
ceritinib	Yes	Yes			possible	warning	in text	in text	in text	
chidamide	Yes					NA	NA	NA	NA	Yes
clofarabine	Yes	Yes	Yes	Yes						Yes
cobimetinib	Yes				possible					
combretastatin a4	Yes	Yes	Yes			NA	NA	NA	NA	Yes
crizotinib	Yes	Yes			possible	warning				
cyclophosphamide				Yes				in text		
cytarabine	Yes	Yes	Yes	Yes						Yes
dabrafenib	Yes				possible					
dasatinib	Yes				possible	warning				
daunorubicin	Yes	Yes	Yes	Yes						Yes
decitabine	Yes			Yes						Yes
degarelix					possible	warning				
encorafenib					possible	warning				
enzastaurin	Yes		Yes	Yes		NA	NA	NA	NA	Yes
epirubicin					possible					
eribulin					possible	warning				
fluorouracil			Yes	Yes	possible					
gemtuzumab ozogamicin	Yes	Yes	Yes	Yes		in text				Yes
gilteritinib					possible	warning				
glasdegib					possible	warning		in text		
goserelin						warning				

Drug	Signal in VigiBase				Credible Meds * TdP risk	Signal in FDA label				new signal
	diLQT	TdP	VA	SD		diLQT	TdP	VA	SD	
histrelin						warning		in text	warning	
ibrutinib			Yes	Yes				warning		
idarubicin	Yes	Yes	Yes	Yes						Yes
ifosfamide								warning		
imatinib	Yes									Yes
inotuzumab					possible	warning				
interferon alfacon-1			Yes					in text		
ivosidenib					possible	warning		in text		
lapatinib					possible	warning		in text		
lenvatinib	Yes				possible	warning				
letrozole	Yes									Yes
leuprorelin					possible	warning			warning	
midostaurin	Yes	Yes	Yes		possible	in text				
mitoxantrone	Yes	Yes	Yes	Yes						Yes
mogamulizumab			Yes							Yes
necitumumab					possible					
nelarabine			Yes							Yes
nilotinib	Yes	Yes	Yes	Yes	possible	BW			BW	
osimertinib	Yes	Yes			possible	warning				
oxaliplatin				Yes	known	in text	in text	in text		
panobinostat	Yes				possible	warning				
pazopanib	Yes	Yes			possible	warning	warning		in text	
pegaspargase			Yes	Yes						Yes
ribociclib	Yes	Yes			possible	warning				
romidepsin	Yes	Yes	Yes	Yes	possible	warning				
sorafenib					possible	warning		in text		
sunitinib	Yes	Yes		Yes	possible	warning	warning	in text		
tamoxifen	Yes	Yes			possible					
tipiracil- trifluridine					possible					
toremifene	Yes	Yes	Yes	Yes	possible	BW	BW	BW		
trametinib	Yes									Yes
tretinoin	Yes	Yes								Yes
triptorelin						warning			warning	
vandetanib	Yes	Yes	Yes		known	BW	BW	in text	BW	
vemurafenib	Yes				possible	warning	in text	in text		
vorinostat	Yes	Yes	Yes	Yes	possible					

* Signals accounted when drugs were flagged at possible or known risk for TdP (conditional risk not accounted);
BW: box warning; CT: cytotoxic therapy; FDA: Food and Drug Administration; HT: hormone therapy; IT: immunotherapy; KI: kinase inhibitor; Misc: Miscellaneous; NA: Not available

Figure Legends.

Figure 1. Evolution of the absolute number of long QT syndrome and/or ventricular arrhythmias including torsade de pointe reports over time for each of the 49 culprit anticancer drugs identified using VigiBase (see **Table 1**). For each drug, the year of FDA approval was added when available (otherwise, NA stands for not available).

Figure 2. Three-level sudden death (SD) risk stratification for the 49 liable anticancer drugs associated with isolated diLQT (low-risk), ventricular arrhythmias (VA) without SD (moderate-risk) and VA with SD (high-risk) identified in VigiBase (through Jan 1, 2019). Absolute number of VA (N_{VA}) including torsade de pointes (TdP) associated ($N_{LQT+}N_{VA}$) or not with diLQT reports by drug and SD risk level is displayed in panels A and B, respectively. The corresponding proportion of such cases (N_{VA} or $N_{LQT+}N_{VA}$) over the total number of overall adverse drug reactions per drug (N_{drug}) are displayed in panels C and D, respectively.

Figure 3. Overlap and overall fatality rate of drug-induced long QT syndrome (diLQT), torsade de pointe (TdP), and ventricular arrhythmia (VA) reports associated with the 49 drugs identified in VigiBase (A) with their respective time to onset (B). Overlap in VigiBase for reports of diLQT and VA including TdP for these 49 drugs as a function of the underlying drug classes (C) with their corresponding time to onset (D). Differences in median time to onset by groups were compared by Wilcoxon tests and Dunn's post-test. * and ** stands for $p \leq 0.05$ and ≤ 0.0001, respectively.

Abbreviations: combo: reports containing at least one culprit anticancer drugs from at last 2 different anticancer drug classes; CT: cytotoxic therapy; HT: hormone therapy; IT: immunotherapy; KI: kinase inhibitor; Misc: Miscellaneous

Figure 1.

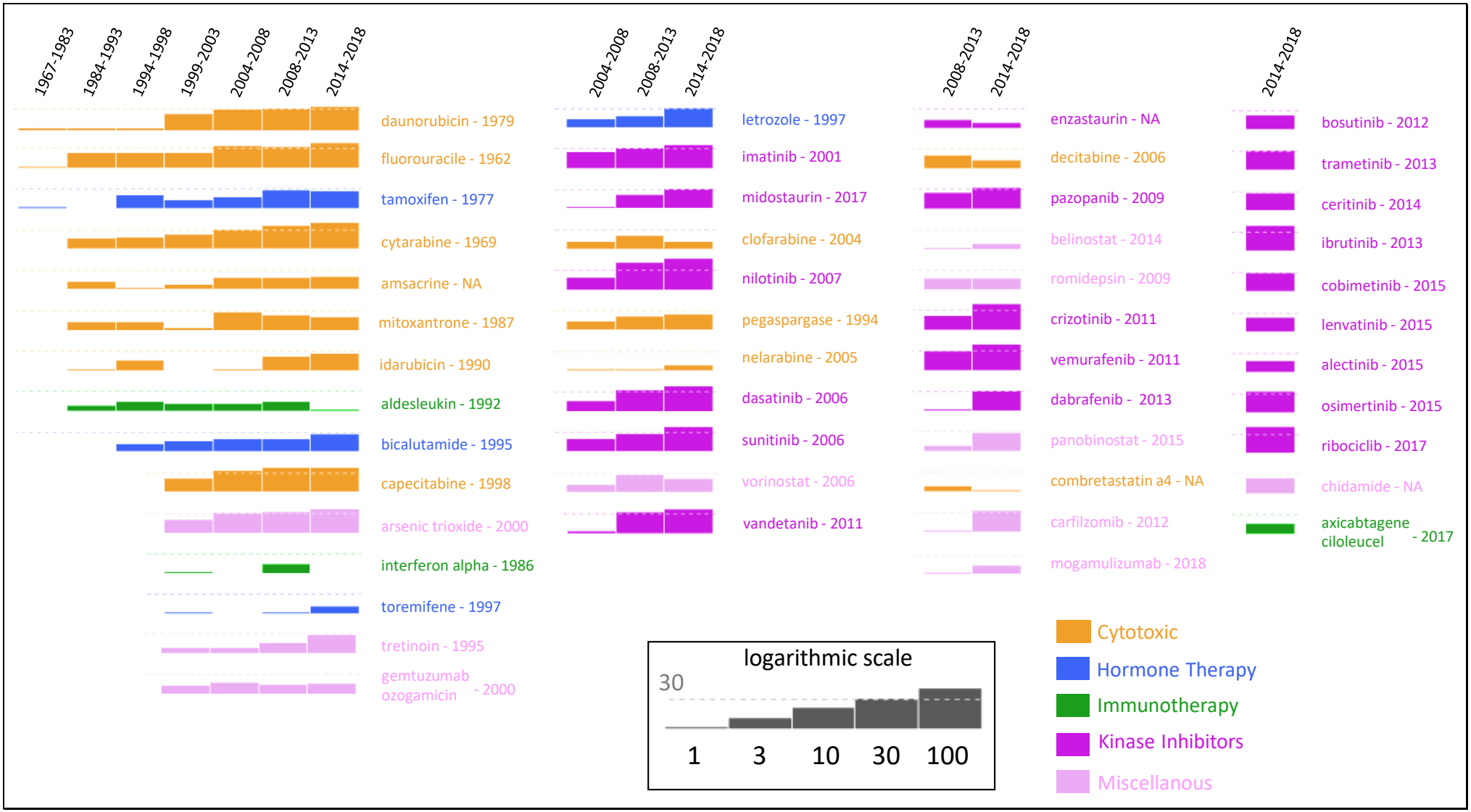

1967-1983
1984-1993
1994-1998
1999-2003
2004-2008
2008-2013
2014-2018
daunorubicin - 1979
fluorouracile - 1962
tamoxifen - 1977
cytarabine - 1969
amsacrine - NA
mitoxantrone - 1987
idarubicin - 1990
aldesleukin - 1992
bicalutamide - 1995
capecitabine - 1998
arsenic trioxide - 2000
interferon alpha - 1986
toremifene - 1997
tretinoin - 1995
gemtuzumab ozogamicin - 2000
2004-2008
2008-2013
2014-2018
letrozole - 1997
imatinib - 2001
midostaurin - 2017
clofarabine - 2004
nilotinib - 2007
pegaspargase - 1994
nelarabine - 2005
dasatinib - 2006
sunitinib - 2006
vorinostat - 2006
vandetanib - 2011
2008-2013
2014-2018
enzastaurin - NA
decitabine - 2006
pazopanib - 2009
belinostat - 2014
romidepsin - 2009
crizotinib - 2011
vemurafenib - 2011
dabrafenib - 2013
panobinostat - 2015
combretastatin a4 - NA
carfilzomib - 2012
mogamulizumab - 2018
2014-2018
bosutinib - 2012
trametinib - 2013
ceritinib - 2014
ibrutinib - 2013
cobimetinib - 2015
lenvatinib - 2015
alectinib - 2015
osimertinib - 2015
ribociclib - 2017
chidamide - NA
axicabtagene ciloleucel - 2017
logarithmic scale
30
1
3
10
30
100
Cytotoxic
Hormone Therapy
Immunotherapy
Kinase Inhibitors
Miscellanous

Figure 2.

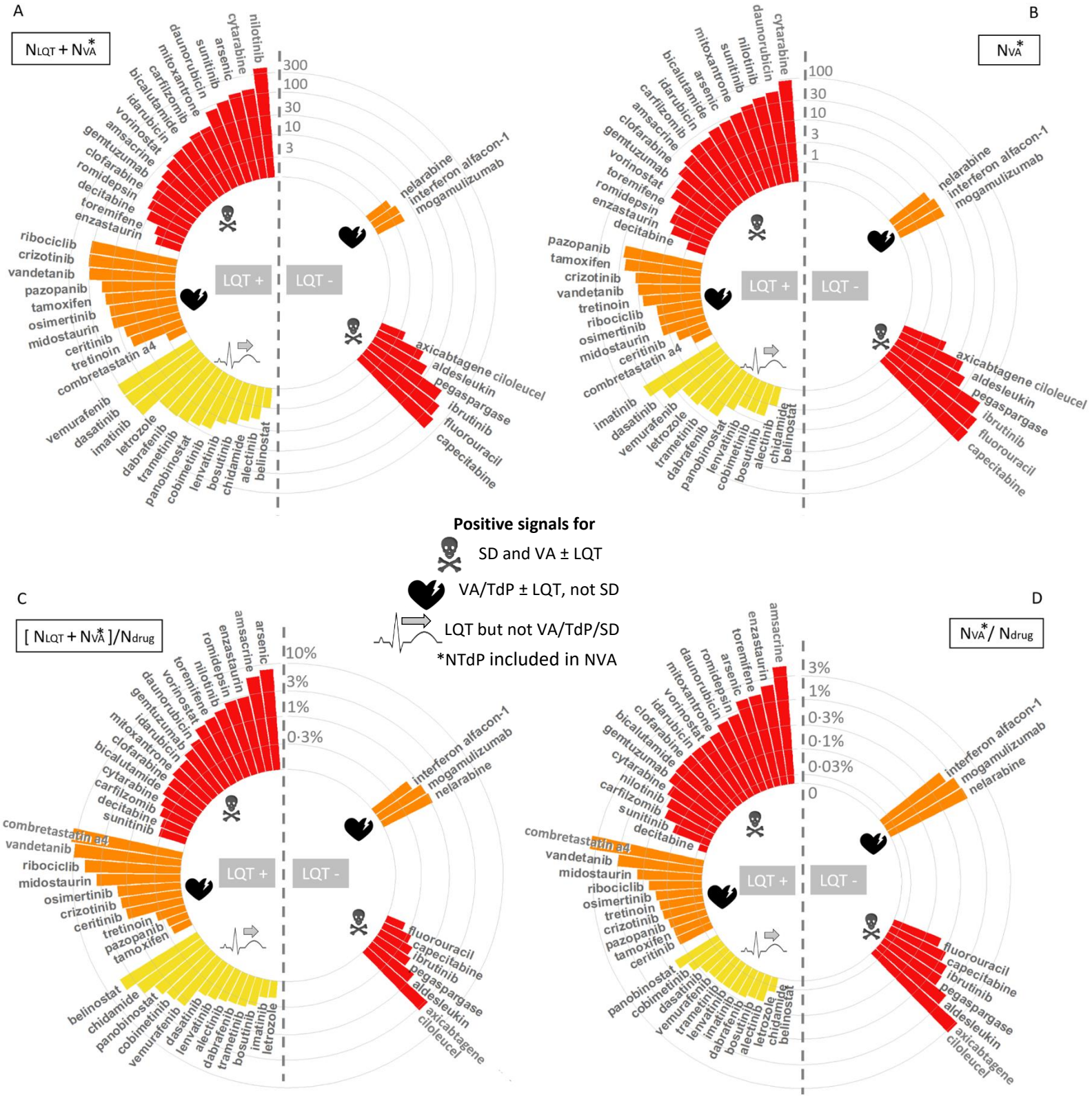
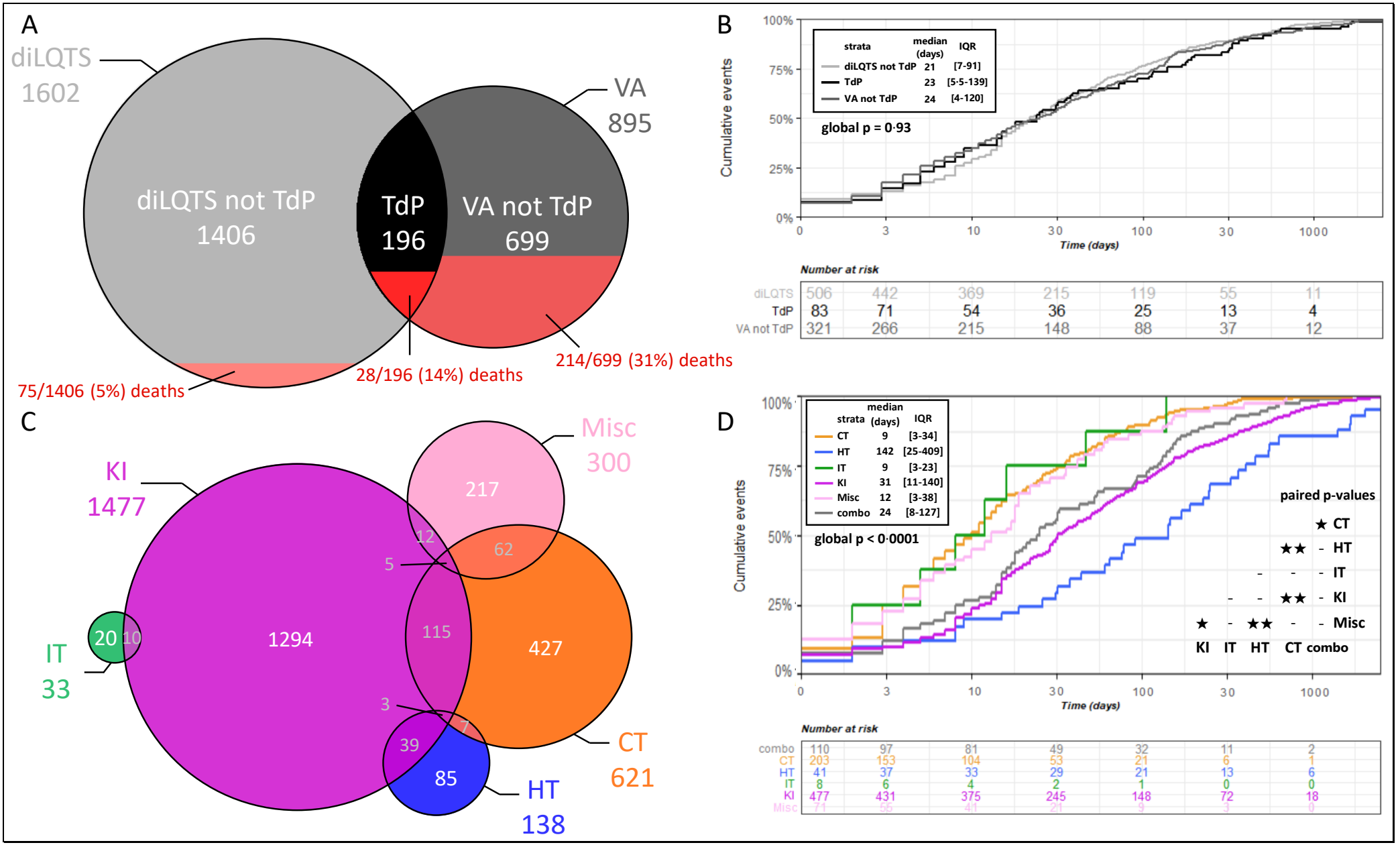

A
NLQT + NVA*
300
100
30
10
3
nilotinib
cytarabine
arsenic
sunitinib
daunorubicin
mitoxantrone
carfilzomib
bicalutamide
idarubicin
vorinostat
amsacrine
gemtuzumab
clofarabine
romidepsin
decitabine
toremifene
enzastaurin
ribociclib
crizotinib
vandetanib
pazopanib
tamoxifen
osimertinib
midostaurin
ceritinib
tretinoin
combretastatin a4
vemurafenib
dasatinib
imatinib
letrozole
dabrafenib
trametinib
panobinostat
cobimetinib
lenvatinib
bosutinib
chidamide
alectinib
belinostat
LQT +
LQT -
nelarabine
interferon alfacon-1
mogamulizumab
axicabtagene ciloleucel
aldesleukin
pegaspargase
ibrutinib
fluorouracil
capecitabine
B
NVA*
100
30
10
3
1
daunorubicin
cytarabine
mitoxantrone
arsenic
sunitinib
nilotinib
bicalutamide
idarubicin
carfilzomib
amsacrine
clofarabine
gemtuzumab
vorinostat
toremifene
romidepsin
enzastaurin
decitabine
pazopanib
tamoxifen
crizotinib
vandetanib
tretinoin
ribociclib
osimertinib
midostaurin
ceritinib
combretastatin a4
imatinib
dasatinib
vemurafenib
letrozole
trametinib
dabrafenib
panobinostat
lenvatinib
cobimetinib
bosutinib
alectinib
chidamide
belinostat
LQT +
LQT -
nelarabine
interferon alfacon-1
mogamulizumab
axicabtagene ciloleucel
aldesleukin
pegaspargase
ibrutinib
fluorouracil
capecitabine
Positive signals for
SD and VA ± LQT
VA/TdP ± LQT, not SD
LQT but not VA/TdP/SD
*NTdP included in NVA
C
[NLQT + NVA*]/Ndrug
10%
3%
1%
0·3%
arsenic
amsacrine
enzastaurin
romidepsin
nilotinib
toremifene
vorinostat
daunorubicin
gemtuzumab
idarubicin
mitoxantrone
clofarabine
bicalutamide
cytarabine
carfilzomib
decitabine
sunitinib
combretastatin a4
vandetanib
ribociclib
midostaurin
osimertinib
crizotinib
ceritinib
tretinoin
pazopanib
tamoxifen
belinostat
chidamide
panobinostat
cobimetinib
vemurafenib
dasatinib
lenvatinib
alectinib
dabrafenib
trametinib
bosutinib
imatinib
letrozole
LQT +
LQT -
interferon alfacon-1
mogamulizumab
nelarabine
fluorouracil
capecitabine
ibrutinib
pegaspargase
aldesleukin
axicabtagene ciloleucel
D
NVA*/ Ndrug
3%
1%
0·3%
0·1%
0·03%
0
amsacrine
enzastaurin
toremifene
arsenic
romidepsin
daunorubicin
mitoxantrone
vorinostat
idarubicin
clofarabine
bicalutamide
gemtuzumab
cytarabine
nilotinib
carfilzomib
sunitinib
decitabine
combretastatin a4
vandetanib
midostaurin
ribociclib
osimertinib
tretinoin
crizotinib
pazopanib
tamoxifen
ceritinib
panobinostat
cobimetinib
dasatinib
vemurafenib
trametinib
lenvatinib
imatinib
dabrafenib
bosutinib
alectinib
letrozole
chidamide
belinostat
LQT +
LQT -
interferon alfacon-1
mogamulizumab
nelarabine
fluorouracil
capecitabine
ibrutinib
pegaspargase
aldesleukin
axicabtagene ciloleucel

Figure 3.


A
diLQTS
1602
VA
895
diLQTS not TdP
1406
TdP
196
VA not TdP
699
75/1406 (5%) deaths
28/196 (14%) deaths
214/699 (31%) deaths
B
Cumulative events
100%
75%
50%
25%
0%
strata
median (days)
IQR
diLQTS not TdP 21 [7-91]
TdP 23 [5·5-139]
VA not TdP 24 [4-120]
global p = 0·93
0 3 10 30 100 30 1000
Time (days)
Number at risk
diLQTS 506 442 369 215 119 55 11
TdP 83 71 54 36 25 13 4
VA not TdP 321 266 215 148 88 37 12
C
KI
1477
Misc
300
IT
33
CT
621
HT
138
217
12
62
5
20
10
1294
115
427
3
7
39
85
D
Cumulative events
100%
75%
50%
25%
0%
strata
median (days)
IQR
CT 9 [3-34]
HT 142 [25-409]
IT 9 [3-23]
KI 31 [11-140]
Misc 12 [3-38]
combo 24 [8-127]
global p < 0·0001
paired p-values
★ CT
★★ - HT
- - - IT
- - ★★ - KI
★ - ★★ - - Misc
KI IT HT CT combo
0 3 10 30 100 30 1000
Time (days)
Number at risk
combo 110 97 81 49 32 11 2
CT 203 153 104 53 21 6 1
HT 41 37 33 29 21 13 6
IT 8 6 4 2 1 0 0
KI 477 431 375 245 148 72 18
Misc 71 56 41 21 9 3 0

Supplementary Data.

Spectrum of anticancer drug-induced Long QT, Torsade-de-Pointes, and ventricular arrhythmias – a WHO pharmacovigilance study

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Supplementary methods.

Disproportionality analysis compares the proportion of selected specific adverse drug reaction (ADR) reported for a single drug (e.g., each anticancer drugs) vs. the proportion of the same ADR for a control group of drugs (e.g., full database). The denominator in these analyses is the total number of ADR reported for each group of drugs. If the proportion of ADR is greater in cases exposed to a specific drug (cases) than in cases not exposed to this drug (non-cases), then an association can be made between the specific drug and the reaction and is deemed a potential safety concern. Disproportionality can be calculated by the information component (IC, Bayesian approach) or the reporting odds ratio (ROR, frequentist approach).[10,33] Calculation of the IC using a Bayesian confidence propagation neural network was developed and validated by the Uppsala Monitoring Center as a flexible, automated indicator value for disproportionate reporting that compares observed and expected drug–ADR associations to find new drug–ADR signals with identification of probability difference from the background data (full database). Probabilistic reasoning in intelligent systems (information theory) has proved to be effective for the management of large datasets, is robust in handling incomplete data, and can be used with complex variables. The information theory tool is ideal for finding drug–ADR combinations that are highly associated compared with the generality of the stored data. Several examples of validation with the IC exist, showing the power of the technique to find signals soon after drug approval by a regulatory agency (e.g., an association between immune-checkpoint inhibitors and myocarditis),[10,33] and to avoid false positives, whereby an association between a common drug and a common ADR occurs in the database only because the drug is widely used and the ADR is frequently reported (e.g., between bevacizumab and acne, and between bevacizumab and rash). The statistical formula is as follows:

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

with $N_{expected}$ being the number of reports expected for the drug–ADR combination and

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

- $N_{observed}$ (N_{obs}) being the actual number of reports observed for the drug–ADR combination

- N_{drug} being the number of reports for the drug, regardless of ADR

- N_{effect} being the number of reports for the ADR, regardless of the drug.

- N_{total} being the total number of reports in the database.

IC_{025} is the lower end of a 95% credibility interval for the IC. A positive IC_{025} value (>0) is the traditional threshold used in statistical signal detection at the UMC. IC_{025} values have only been validated for comparison of drug-specific ADR vs. the full database and cannot be used to compare disproportionate reporting with a subgroup background. Since the focus of this work concerned identification of culprit anticancer drugs, we further performed a sensitivity analysis and estimated the frequentist disproportionality association (ROR) with LQT, TdP, VA and SD for anticancer drugs already flagged as signal with IC_{025} filtering, restricting the background database to reports associated with at least one anticancer drugs (defined as drugs pertaining to the anatomical therapeutic classification L: Antineoplastic and immunomodulating agents). ROR was calculated by Chi^2-test, and the 95% confidence interval ($CI_{95\%}$) was estimated, as recently described elsewhere [Grouthier V et al. , Heart 2018]. A lower end of the ROR $CI_{95\%} \geq 1$ was deemed significant.

Supplementary Figure 1. Flow chart of drugs analyzed in VigiBase. There were 663 anticancer drugs in total, of which 199 had an FDA approval (195 still active).

Supplementary Figure 2. Cumulative number of individual case safety reports in VigiBase for drug-induced long-QT syndrome (diLQT), or ventricular arrhythmias (VA) including Torsade-de-pointes (TdP) over years for all drugs with the subset of anticancer drugs per classes in VigiBase (A). The year for which the disproportional reporting became significant (IC_{025}>0 vs. full database, see **Supplementary methods**) for each of the 49 identified liable anticancer drugs significantly associated with either diLQT, or VA including TdP is in bracket (B).

Supplementary Figure 3A. Information component (IC) and its 95% lower-end credibility interval (IC_{025}>0, see **methods**) for all drugs significantly associated with drug-induced long-QT syndrome (diLQT), Torsade-de-pointes (TdP) or ventricular arrhythmias (VA) in VigiBase thru Jan 1, 2019. Anticancer drugs are flagged by their name and different colors depending on their classes: cytotoxic chemotherapy (CT); hormone therapy (HT); immunotherapy (IT); kinase inhibitor (KI) and Miscellaneous (Misc). See **Supplementary-Figure-3B** and **Supplementary-Table-2** for more details for top associations with diLQT and TdP of non-anticancer drugs including positive controls at know risk of diLQT and TdP (ibutilide, dofetilide, sotalol),[15,16] and negative controls (testosterone, progesterone, and levonorgestrel).[5,17]

Supplementary Figure 3B. Information Component (IC, a Bayesian disproportionality estimate) and its 95% lower end credibility interval (IC_{025}>0 is deemed significant) for diLQT (drug-induced Long-QT syndrome) and TdP (Torsade-de-Pointes) associated with all drugs with at least one report available in VigiBase(n=330/1,498 significant for diLQT and all drugs in VigiBase of which 37/164 anticancer molecules, and n=239/1,134 significant for TdP and all drugs in VigiBase of which 10/105 anticancer drugs). Each bar represents one drug including the anticancer drugs (AntiK) which are displayed in red or pink if the association is significant or not, respectively. Drugs known to prolong QT and to induce TdP, such as sotalol, ibutilide, and dofetilide are used as positive controls (blue).[15,16] Drugs known to protect against drug-induced QT-prolongation and eventually TdP, such as progesterone, testosterone, and levonorgestrel were used as negative controls.[5,17]

Supplementary Figure 4. Concordance (Cohen's kappa coefficient) of signals in VigiBase and information retrieved in crediblemeds[13] and US FDA (Food and Drug Administration) labels[14] for drug-induced long-QT syndrome (diLQT) and/or ventricular arrhythmias (VA) including Torsade-de-pointes (TdP) for anticancer drugs (See **supplementary-Table-3** for the full list of 663 screened anticancer drugs). Drugs were considered at risk of diLQT and/or VA (including TdP) cardiac pro-arrhythmias in VigiBase if there was any significant association with diLQT, VA or TdP (IC_{025}>0; vs. full database); in CredibleMeds (queried July 1st,2019) if the drugs were flagged at possible or known risk for TdP (conditional risk not accounted); and in USA FDA labels (queried July 1st,2019) if the last available drug label mentioned a risk for diLQT, VA or TdP as a warning (boxed or not) or a clear mention in the text (**Table-4**). Panel A shows the results when considering the 663 VigiBase referenced anticancer drugs and panel B when restricting the analysis to FDA approved drugs (199, of which 195 with still an active approval).

Supplementary Table 1. Cardiac phenotypes grouping used in our VigiBase analysis as a function of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) levels Classification Version 21.1.

Supplementary Table 2. Number of reports observed (N_{obs}) for a given drug and an adverse drug reaction (ADR); and disproportionality association evaluated by the IC_{025} (lower-end of the 95% credibility interval, >0 is significant) for the top 25 drugs (highest and lowest IC_{025}) with drug-induced Long-QT Syndrome (diLQT) in VigiBase thru Jan 1, 2019 (using full database as background). Association with ventricular arrhythmias (VA), Torsade-de-Pointes (TdP) and sudden-death (SD) are also displayed for these latter drugs. Positive control drugs are in blue (sotalol, ibutilide, and dofetilide),[15,16] negative control drugs are in green (progesterone, testosterone, and levonorgestrel),[5,17] and anticancer drugs are in red. (-) stands for the absence of reports and the possibility for IC_{025} evaluation.

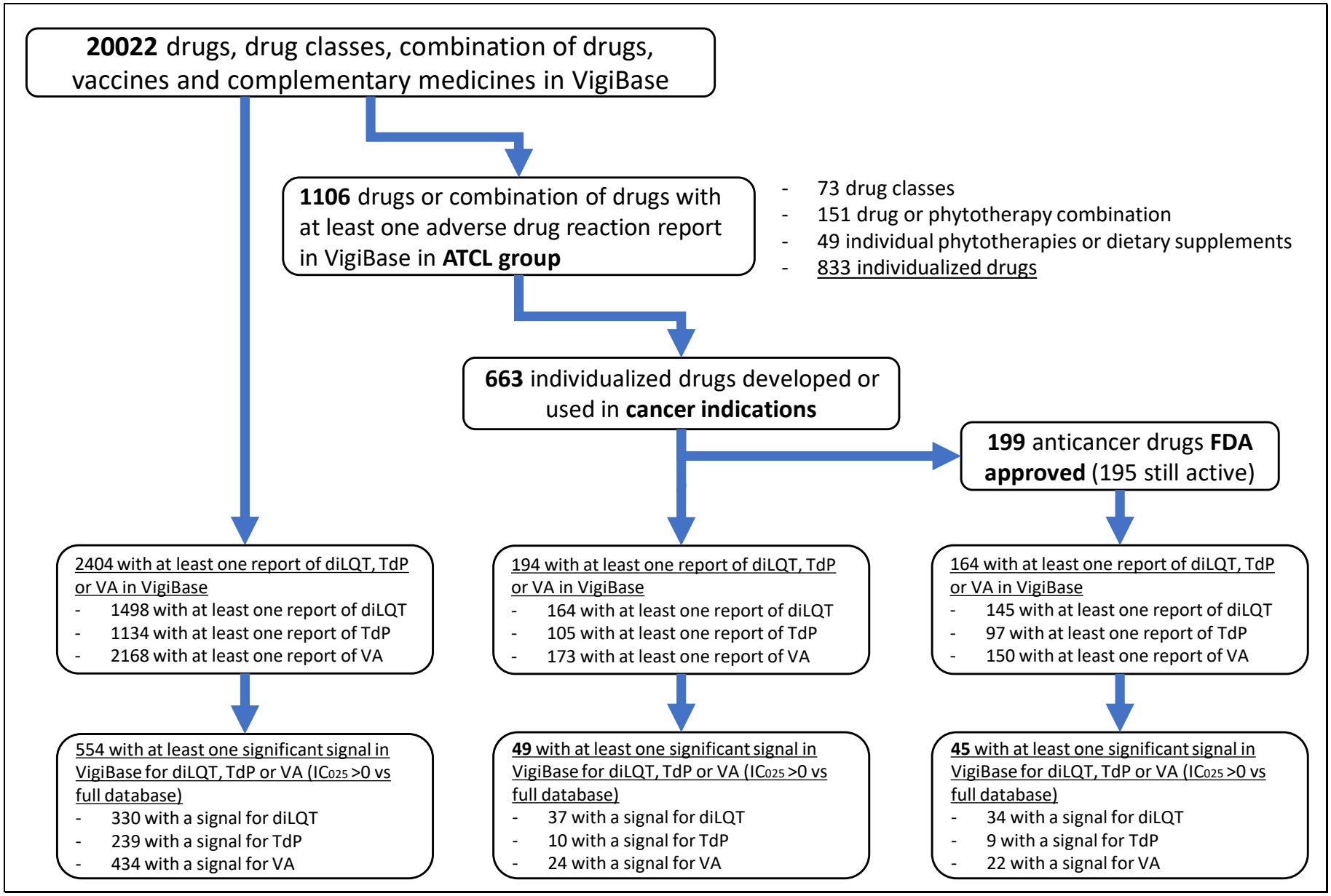
Abbreviations: N_{drug} being the number of reports for the drug, regardless of the adverse drug reaction (ADR); N_{effect} being the number of reports for the ADR, regardless of the drug.

Supplemental Table 3. Number of reports observed (N_{obs}) for a given drug and the adverse drug reaction (ADR) of interest; and disproportional association evaluated by the IC_{025} (lower-end of the 95% credibility interval, >0 is significant) for anti-cancer drugs with drug-induced Long-QT Syndrome (diLQT), ventricular arrhythmias (VA), Torsade-de-Pointes (TdP) and sudden-death (SD) in VigiBase thru Jan 1, 2019 (using full database as background). Anticancer drugs approved by US FDA (as of 1st of July 2019) are also shown even in the absence of any N_{obs} (-) for diLQT, TdP, VA and SD in VigiBase. In total, 663 anticancer drugs were referenced in VigiBase, of which 199 had an US FDA approval (195 still active as of 1st of July 2019).

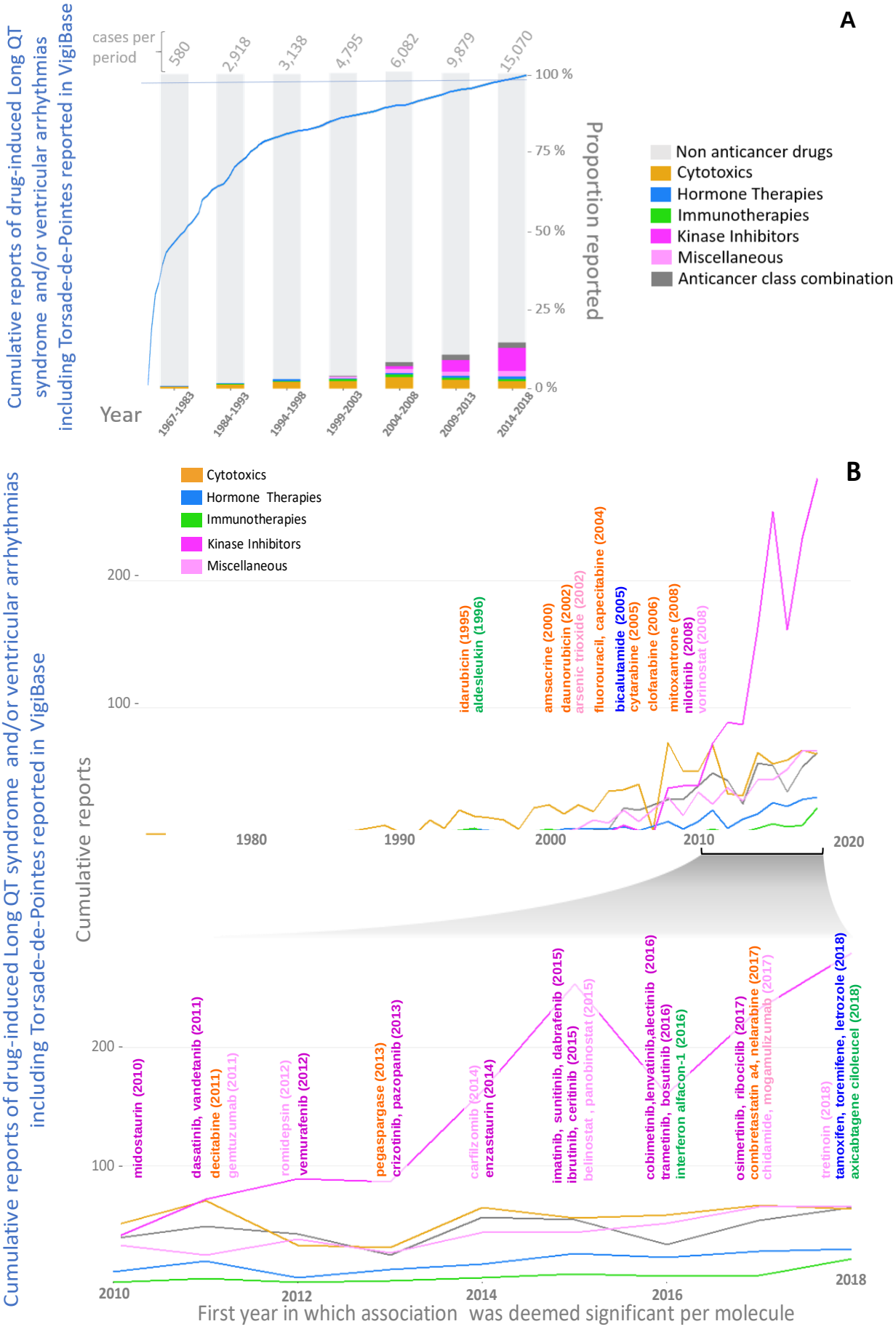
Abbreviations: N_{drug} being the number of reports for the drug, regardless of the adverse drug reaction (ADR); N_{effect} being the number of reports for the ADR, regardless of the drug.

Supplemental Table 4. Characteristics of drug-induced cardiac arrhythmia events including long-QT (diLQT), Torsade-de-Pointes (TdP), and ventricular arrhythmias (VA) associated with each of the 49 liable anticancer drugs identified as signals thru VigiBase.

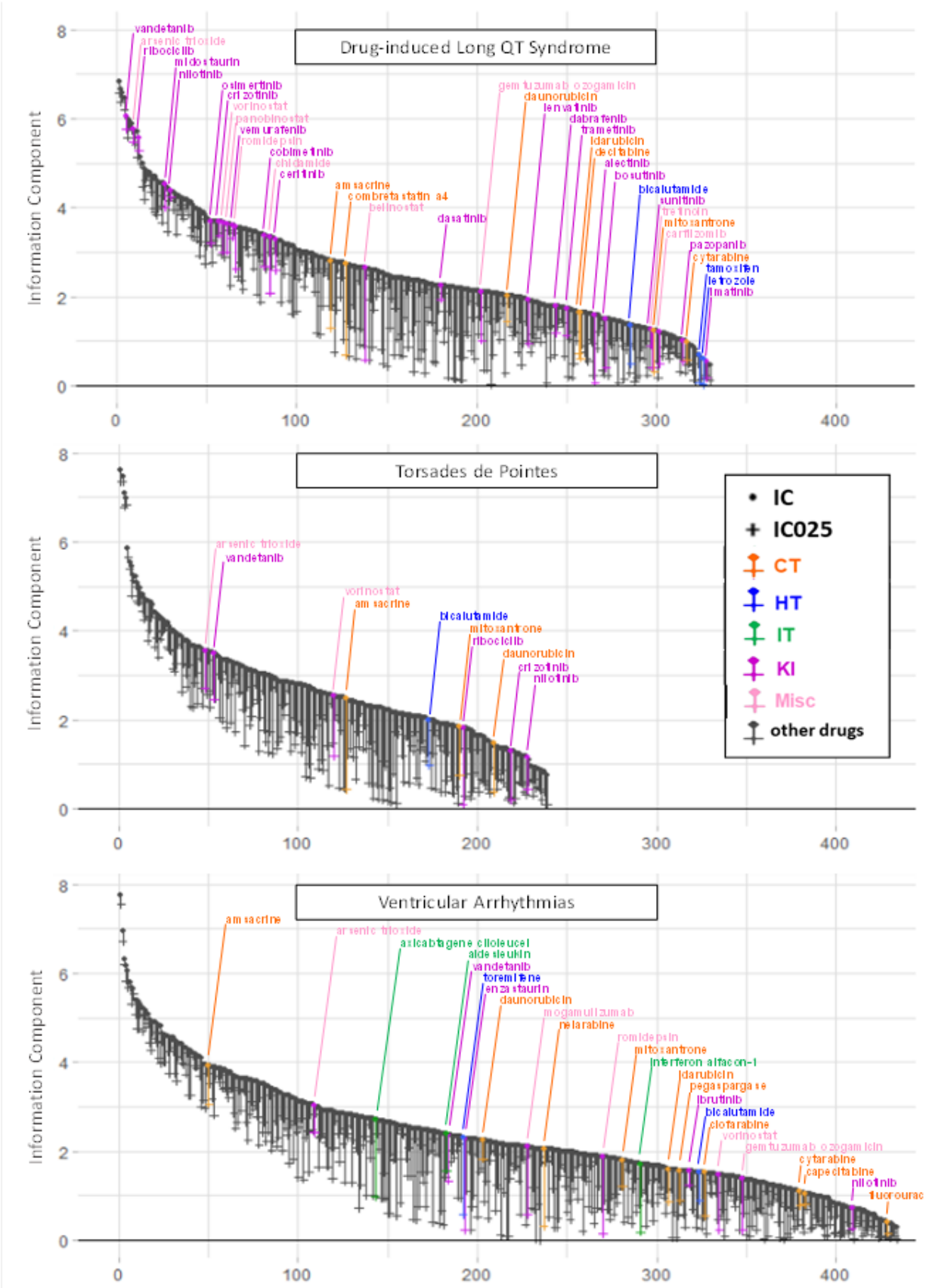
Supplementary Figure 1.



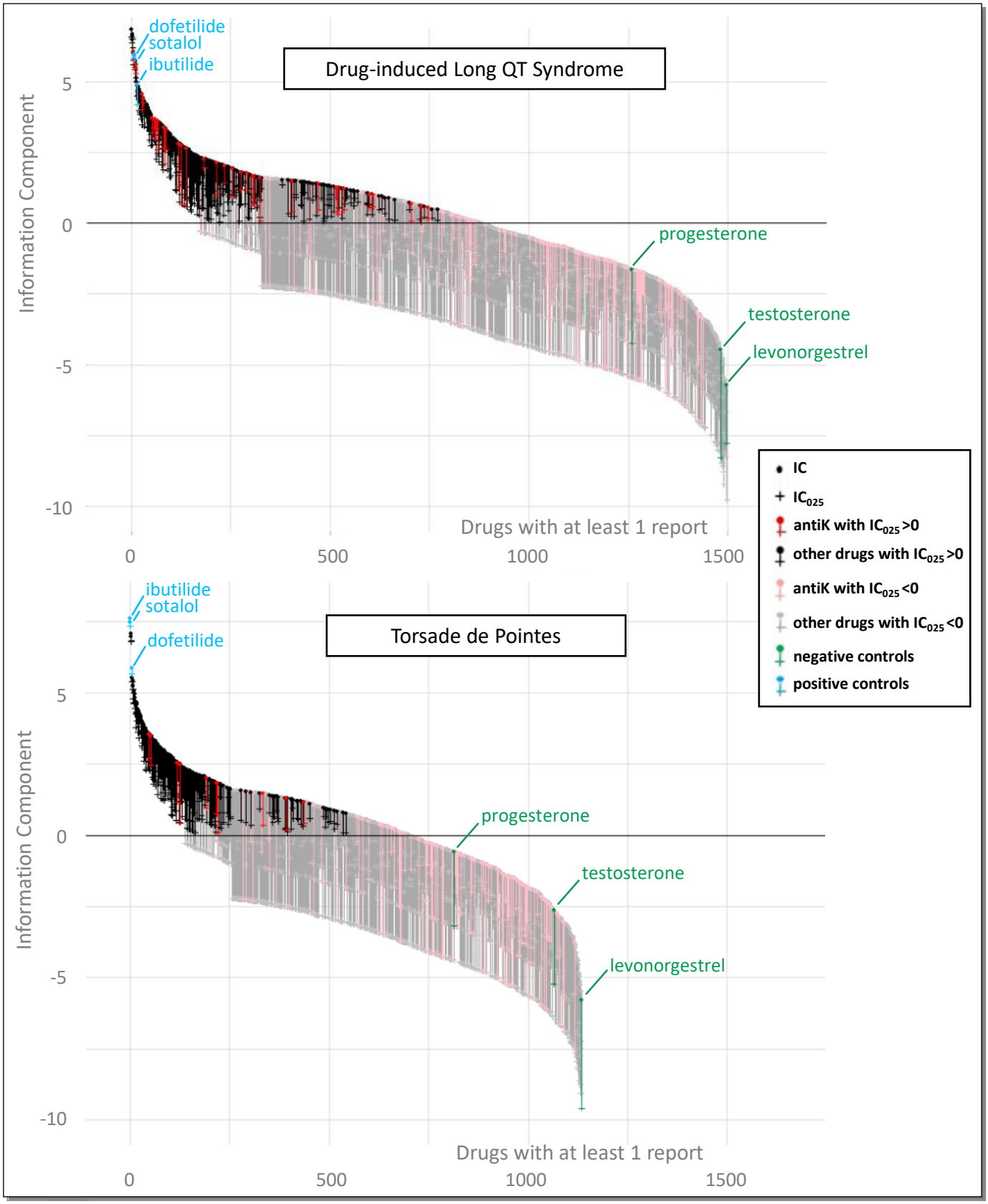
Supplementary Figure 2.



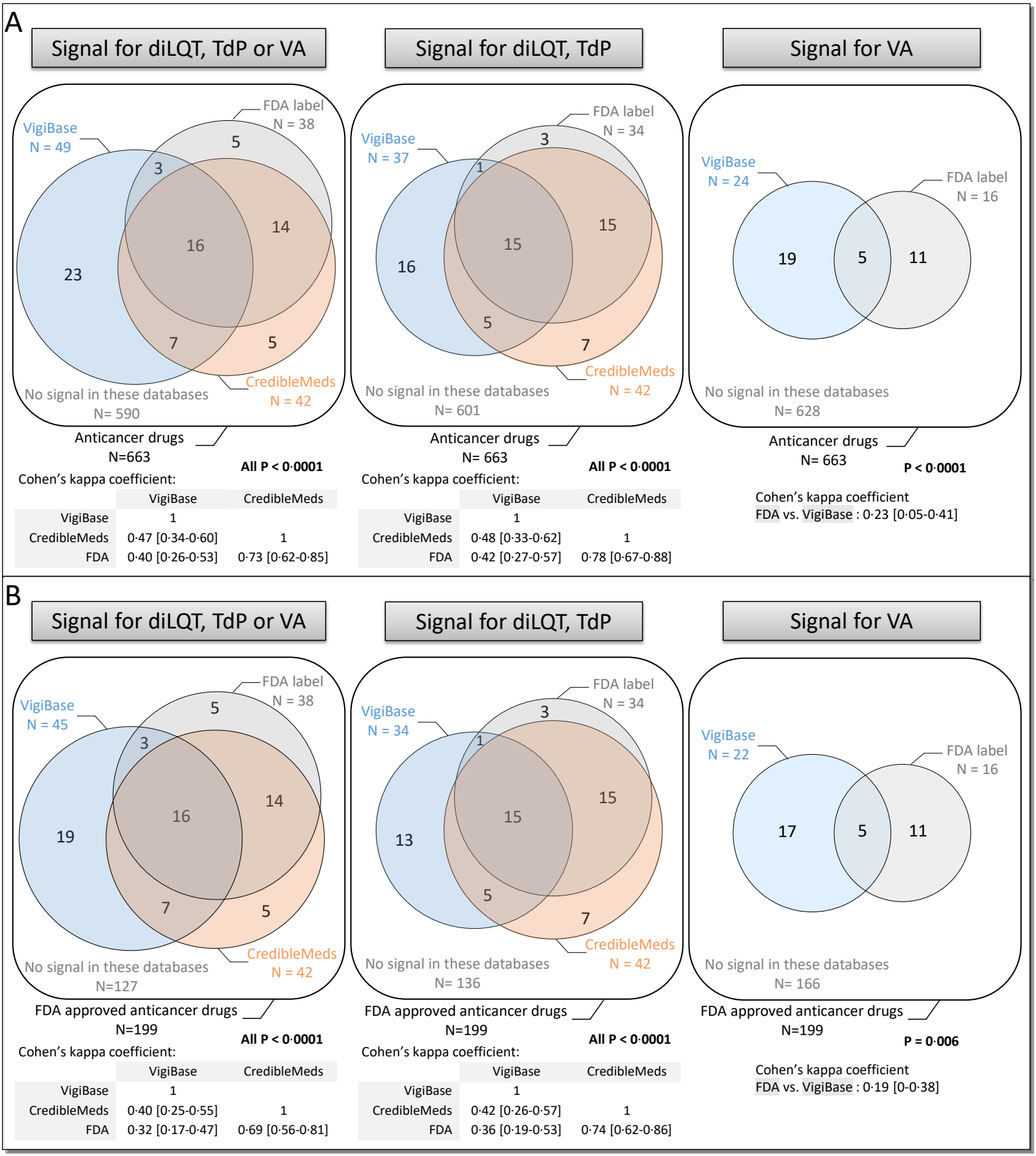
Supplementary Figure 3A.



Supplementary Figure 3B.



Supplementary Figure 4.



Supplementary Table 1.

Groups	MedDRA Terms used
Long QT Syndrome	Electrocardiogram QT prolonged **or/and** Long QT syndrome [All PTs]
Torsade de Pointes	(Cardiac arrest AND Electrocardiogram QT prolonged) **or/and** (Cardiac arrest AND Electrocardiogram QT interval abnormal) **or/and** (Cardiac arrest AND Long QT syndrome) **or/and** (Cardiac fibrillation AND Electrocardiogram QT prolonged) **or/and** (Cardiac fibrillation AND Electrocardiogram QT interval abnormal) **or/and** (Cardiac fibrillation AND Long QT syndrome) **or/and** (Cardio-respiratory arrest AND Electrocardiogram QT prolonged) **or/and** (Cardio-respiratory arrest AND Electrocardiogram QT interval abnormal) **or/and** (Cardio-respiratory arrest AND Long QT syndrome) **or/and** (Electrocardiogram QT interval abnormal AND Ventricular extrasystoles) **or/and** (Electrocardiogram QT interval abnormal AND Ventricular tachyarrhythmia) **or/and** (Electrocardiogram QT interval abnormal AND Ventricular arrhythmia) **or/and** (Electrocardiogram QT interval abnormal AND Sudden death) **or/and** (Electrocardiogram QT interval abnormal AND Ventricular tachycardia) **or/and** (Electrocardiogram QT interval abnormal AND Ventricular fibrillation) **or/and** (Electrocardiogram QT interval abnormal AND Sudden cardiac death) **or/and** (Electrocardiogram QT interval abnormal AND Syncope) **or/and** (Electrocardiogram QT interval abnormal AND Loss of consciousness) **or/and** (Electrocardiogram QT interval abnormal AND Malaise) **or/and** (Electrocardiogram QT prolonged AND Ventricular extrasystoles) **or/and** (Electrocardiogram QT prolonged AND Ventricular tachyarrhythmia) **or/and** (Electrocardiogram QT prolonged AND Ventricular arrhythmia) **or/and** (Electrocardiogram QT prolonged AND Sudden death) **or/and** (Electrocardiogram QT prolonged AND Ventricular tachycardia) **or/and** (Electrocardiogram QT prolonged AND Ventricular fibrillation) **or/and** (Electrocardiogram QT prolonged AND Sudden cardiac death) **or/and** (Electrocardiogram QT prolonged AND Syncope) **or/and** (Electrocardiogram QT prolonged AND Loss of consciousness) **or/and** (Electrocardiogram QT prolonged AND Malaise) **or/and** (Long QT syndrome AND Ventricular extrasystoles) **or/and** (Long QT syndrome AND Ventricular tachyarrhythmia) **or/and** (Long QT syndrome AND Ventricular arrhythmia) **or/and** (Long QT syndrome AND Sudden death) **or/and** (Long QT syndrome AND Ventricular tachycardia) **or/and** (Long QT syndrome AND Ventricular fibrillation) **or/and** (Long QT syndrome AND Sudden cardiac death) **or/and** (Long QT syndrome AND Syncope) **or/and** (Long QT syndrome AND Loss of consciousness) **or/and** (Long QT syndrome AND Malaise) **or/and** Torsade de pointes [All PTs]
Ventricular arrhythmias	Torsade de pointes **or/and** Ventricular arrhythmia **or/and** Ventricular fibrillation **or/and** Ventricular flutter **or/and** Ventricular tachyarrhythmia **or/and** Ventricular tachycardia **or/and** Cardiac fibrillation [All PTs] **or/and** Torsade de pointes (Complex composite query detailed above in this table)
Sudden death	Cardiac arrest **or/and** Cardio-respiratory arrest **or/and** Sudden cardiac death **or/and** Sudden death [All PTs]

Supplementary Table 2.

TOP 25 highest IC_{025} for diLQT

		diLQT (N_{effect} =18,123)		TdP (N_{effect} =8,163)		VA (N_{effect} =29,193)		SD (N_{effect} =85,350)	
drug	N_{drug}	N_{obs}	IC_{025}	N_{obs}	IC_{025}	N_{obs}	IC_{025}	N_{obs}	IC_{025}
Sertindole	618	127	6·6	16	3·6	18	2·9	32	2·7
Cisapride	8343	838	6·5	527	6·9	685	5·5	441	3·4
Bepridil	500	100	6·4	98	6·8	160	6·7	29	2·8
Bedaquiline	947	125	6·2	7	1·8	7	0·7	13	0·6
Dofetilide	6615	435	5·8	200	5·7	402	5·1	120	1·7
Vandetanib	971	97	5·8	10	2·5	10	1·3	6	-1
Sotalol	5292	339	5·7	504	7·3	711	6·2	204	2·8
Delamanid	345	53	5·6	-	-	-	-	1	-4·3
Arsenic trioxide	1642	115	5·5	14	2·7	25	2·4	20	0·6
Clofazimine	1192	89	5·4	7	1·6	9	0·9	12	0·1
Ribociclib	1738	105	5·3	4	0·1	4	-1·3	-	-
Budipine	89	30	5·1	23	4·8	26	4·8	2	-1·1
Ziprasidone	13256	473	5	121	4	151	2·6	297	2·1
Methadone	17728	507	4·7	386	5·4	415	3·7	2127	4·6
Amisulpride	5370	167	4·6	38	3·3	49	2	62	0·9
Sevoflurane	3904	119	4·5	43	3·8	121	3·9	187	3·1
Prothipendyl	594	34	4·5	3	0·2	4	-0·1	9	0·5
Pipamperone	1756	59	4·4	17	3	20	1·9	39	1·7
Cyamemazine	4020	104	4·3	19	2·4	21	1	64	1·4
Nilotinib	17471	369	4·2	18	0·4	46	0·3	92	-0·1
Amiodarone	36522	727	4·2	637	5·1	1086	4·1	501	1·4
Ibutilide	239	21	4·2	119	7·4	191	7·6	28	3·6
Flecainide	5976	134	4·1	98	4·7	558	5·7	266	3·1
Ondansetron	16767	318	4·1	190	4·4	290	3·3	269	1·6
Citalopram	33300	600	4·1	284	4·1	356	2·6	1085	2·7

TOP 25 lowest IC_{025} for diLQT

		diLQT (N_{effect} =18,123)		TdP (N_{effect} =8,163)		VA (N_{effect} =29,193)		SD (N_{effect} =85,350)	
drug	N_{drug}	N_{obs}	IC_{025}	N_{obs}	IC_{025}	N_{obs}	IC_{025}	N_{obs}	IC_{025}
Mesalazine	15080	1	-7·2	1	-6·1	11	-2·1	25	-2·1
Finasteride	15114	1	-7·2	-	-	29	-0·3	42	-1·2
Fenfluramine	15637	1	-7·2	4	-2·5	50	0·6	103	0·2
Cefoperazone; Sulbactam	16002	1	-7·2	1	-6·1	5	-3·8	34	-1·6
Ambrisentan	71150	2	-7·4	1	-8·2	43	-1·8	421	0·2
Ceftazidime	18847	1	-7·5	1	-6·4	6	-3·6	51	-1·2
Pneumococcal vaccine	165977	3	-7·6	2	-7·5	29	-3·7	560	-0·6
Ketorolac	22203	1	-7·7	2	-4·6	31	-0·7	112	-0·2
Azathioprine	22813	1	-7·7	1	-6·6	14	-2·2	34	-2·2
Levonorgestrel	185458	3	-7·8	1	-9·6	10	-5·8	21	-6
Nevirapine	23632	1	-7·8	3	-3·7	9	-3·1	30	-2·4
Macrogol 3350	24540	1	-7·8	-	-	2	-6·6	8	-4·9
Oxymorphone	27385	1	-8	-	-	1	-8·7	182	0·3
Cefaclor	27692	1	-8	-	-	6	-4·2	26	-2·9
Liraglutide	28403	1	-8	1	-6·9	19	-1·9	38	-2·3
Teriparatide	116313	2	-8·1	-	-	52	-2·2	205	-1·6
Varicella zoster vaccine	119945	2	-8·2	2	-7	16	-4·3	67	-3·4
Measles vaccine; Mumps vaccine; Rubella vaccine	128827	2	-8·3	1	-9·1	6	-6·4	109	-2·7
Testosterone	33706	1	-8·3	2	-5·2	72	0·1	292	0·7
Secukinumab	38011	1	-8·5	-	-	8	-4	17	-4·1
Botulinum toxin type a	38790	1	-8·5	1	-7·4	10	-3·6	48	-2·3
Rotavirus vaccine	41370	1	-8·6	1	-7·5	10	-3·7	191	-0·2
Iohexol	47860	1	-8·8	1	-7·7	123	0·4	351	0·5
Calcium chloride; Glucose; Magnesium chloride; Sodium chloride; Sodium lactate	64800	1	-9·2	-	-	60	-1·2	1483	2·2
Polio vaccine	94675	1	-9·8	1	-8·6	8	-5·3	334	-0·6

Supplementary Table 3.

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
abagovomab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
abarelix	Yes	54	0	-	-	0	-	-	1	1·4	-2·4	1	1	-2·8
abemaciclib	Yes	222	0	-	-	0	-	-	0	-	-	1	0	-3·8
abexinostat	no	3	0	-	-	0	-	-	0	-	-	0	-	-
abiraterone	Yes	15201	16	0·1	-0·7	7	0·1	-1·2	27	0·2	-0·4	40	-0·8	-1·3
abituzumab	no	5	0	-	-	0	-	-	0	-	-	0	-	-
abt 510	no	2	0	-	-	0	-	-	0	-	-	0	-	-
acalabrutinib	Yes	78	0	-	-	0	-	-	0	-	-	0	-	-
acalisib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
acivicin	no	6	0	-	-	0	-	-	0	-	-	0	-	-
aclarubicin	no	193	0	-	-	1	1·4	-2·4	1	0·9	-2·9	1	0·1	-3·7
afatinib	Yes	6621	1	-2·2	-6	1	-1·2	-5	2	-2·1	-4·7	10	-1·6	-2·6
aflibercept	Yes	3024	1	-3·3	-7·1	0	-	-	5	-2·1	-3·6	42	-0·7	-1·2
afuresertib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
agatolimod	no	14	0	-	-	0	-	-	0	-	-	0	-	-
aldesleukin	Yes	1553	0	-	-	0	-	-	15	2·4	1·6	29	1·9	1·4
aldoxorubicin	no	3	0	-	-	0	-	-	0	-	-	0	-	-
alectinib	Yes	1346	5	1·6	0·1	0	-	-	1	-0·8	-4·6	1	-2·2	-6
alemtuzumab	Yes	12232	7	-0·7	-2	0	-	-	7	-1·4	-2·7	64	0·2	-0·2
alisertib	no	43	0	-	-	0	-	-	0	-	-	0	-	-
alitretinoin	Yes	72	1	0·2	-3·6	0	-	-	0	-	-	0	-	-
alkycycline nos	no	2	0	-	-	0	-	-	0	-	-	0	-	-
alpelisib	no	66	1	1·4	-2·4	0	-	-	0	-	-	0	-	-
altretamine	Yes	78	0	-	-	0	-	-	0	-	-	1	0·8	-3
alvespimycin	no	9	0	-	-	0	-	-	0	-	-	0	-	-
alvocidib	no	36	0	-	-	0	-	-	0	-	-	1	1·2	-2·6
amatuximab	no	4	0	-	-	0	-	-	0	-	-	0	-	-
amg 232	no	3	0	-	-	0	-	-	0	-	-	0	-	-
amg 337	no	2	0	-	-	0	-	-	0	-	-	0	-	-
amg 820	no	3	0	-	-	0	-	-	0	-	-	0	-	-
amg 900	no	1	0	-	-	0	-	-	0	-	-	0	-	-
aminoglutethimide	Yes	557	0	-	-	0	-	-	1	0·1	-3·7	1	-1	-4·8
aminolevulinic acid	no	494	1	0·6	-3·2	1	1·1	-2·7	1	0·2	-3·6	2	-0·2	-2·7
aminopterin	no	5	0	-	-	0	-	-	0	-	-	0	-	-
amonafide	no	2	0	-	-	0	-	-	0	-	-	0	-	-
amrubicin	no	309	0	-	-	0	-	-	1	0·6	-3·2	0	-	-
amsacrine	no	287	5	2·8	1·3	3	2·5	0·4	14	3·9	3·1	10	2·5	1·5
anastrozole	Yes	13491	4	-1·6	-3·3	0	-	-	10	-1·1	-2·1	24	-1·4	-2

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
andecaliximab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
anetumab ravtansine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
apalutamide	Yes	73	1	1·4	-2·4	0	-	-	1	1·3	-2·5	0	-	-
apatinib	no	172	0	-	-	0	-	-	0	-	-	0	-	-
apatorsen	no	6	0	-	-	0	-	-	0	-	-	0	-	-
apitolisib	no	25	0	-	-	0	-	-	0	-	-	0	-	-
apr 246	no	1	0	-	-	0	-	-	0	-	-	0	-	-
aprinocarsen	no	12	0	-	-	0	-	-	0	-	-	1	1·4	-2·4
arsenic	Yes	50	2	2·2	-0·4	0	-	-	0	-	-	2	1·8	-0·8
arsenic trioxide	Yes	1642	115	5·8	5·5	14	3·6	2·7	25	3	2·4	20	1·3	0·6
arzoxifene	no	69	0	-	-	0	-	-	1	1·3	-2·5	2	1·6	-1
asciminib	no	14	0	-	-	0	-	-	0	-	-	0	-	-
asparaginase	Yes	7976	2	-1·7	-4·3	1	-1·4	-5·2	5	-1·3	-2·8	51	0·5	0
atacicept	no	4	0	-	-	0	-	-	0	-	-	0	-	-
atezolizumab	Yes	2071	1	-0·8	-4·6	0	-	-	3	-0·1	-2·2	9	-0·1	-1·2
atrasentan	no	22	0	-	-	0	-	-	0	-	-	2	2·1	-0·5
avapritinib	no	5	0	-	-	0	-	-	0	-	-	0	-	-
avelumab	Yes	324	0	-	-	0	-	-	0	-	-	2	0·3	-2·3
aviscumine	no	1	0	-	-	0	-	-	0	-	-	0	-	-
axitinib	Yes	5802	6	0·1	-1·3	2	-0·3	-2·9	7	-0·4	-1·6	15	-0·8	-1·6
azacitidine	Yes	9256	14	0·6	-0·3	2	-0·9	-3·5	16	0·1	-0·7	57	0·4	0
bafetinib	no	5	0	-	-	0	-	-	0	-	-	0	-	-
balixafortide	no	3	0	-	-	0	-	-	0	-	-	0	-	-
barasertib	no	6	0	-	-	0	-	-	0	-	-	0	-	-
bavituximab	no	3	0	-	-	0	-	-	0	-	-	0	-	-
bcg organisms-methanol extraction residue	no	40	0	-	-	0	-	-	0	-	-	0	-	-
bcg vaccine	Yes	14207	0	-	-	0	-	-	3	-3·3	-5·3	28	-1·8	-2·3
becatecarin	no	6	0	-	-	0	-	-	0	-	-	0	-	-
belinostat	Yes	61	3	2·6	0·6	0	-	-	0	-	-	1	0·9	-2·9
belotecan	no	365	0	-	-	0	-	-	0	-	-	0	-	-
bendamustine	Yes	8747	9	0·1	-1	2	-0·8	-3·4	6	-1·1	-2·5	40	0	-0·5
berbamine	no	25	0	-	-	0	-	-	0	-	-	0	-	-
bevacizumab	Yes	59059	24	-1·3	-1·9	13	-1	-1·9	88	-0·1	-0·4	375	0·5	0·3
bexarotene	Yes	638	0	-	-	0	-	-	0	-	-	4	0·4	-1·4
bgb 324	no	3	0	-	-	0	-	-	0	-	-	0	-	-
bi 2536	no	94	0	-	-	0	-	-	0	-	-	0	-	-
bi 836826	no	11	0	-	-	0	-	-	0	-	-	0	-	-
bicalutamide	Yes	4802	13	1·4	0·5	10	2	1	23	1·5	0·9	24	0·1	-0·5

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
bimiralisib	no	9	0	-	-	0	-	-	0	-	-	0	-	-
binimetinib	Yes	39	0	-	-	0	-	-	0	-	-	0	-	-
biricodar	no	2	0	-	-	0	-	-	0	-	-	0	-	-
birinapant	no	7	0	-	-	0	-	-	0	-	-	0	-	-
bis-chloroethylamino methylbenzoic acid	no	2	0	-	-	0	-	-	0	-	-	0	-	-
bisantrene	no	1	0	-	-	0	-	-	0	-	-	0	-	-
bl 8040	no	1	0	-	-	0	-	-	0	-	-	0	-	-
bleomycin	Yes	7350	2	-1·6	-4·2	1	-1·3	-5·1	6	-0·9	-2·3	30	-0·2	-0·7
bleomycin a5	no	3	0	-	-	0	-	-	0	-	-	0	-	-
blinatumomab	Yes	2341	4	0·7	-1·1	0	-	-	3	-0·3	-2·3	3	-1·7	-3·7
blp-25 liposomal vaccine	no	7	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
blu 554	no	1	0	-	-	0	-	-	0	-	-	0	-	-
bms-833923	no	1	0	-	-	0	-	-	0	-	-	0	-	-
bms 214662	no	6	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
bnc105	no	1	0	-	-	0	-	-	0	-	-	0	-	-
bortezomib	Yes	27898	36	0·4	-0·1	10	-0·3	-1·3	54	0·3	-0·1	213	0·7	0·5
bosutinib	Yes	2927	9	1·5	0·4	1	-0·3	-4·1	2	-1	-3·6	6	-1·1	-2·5
brentuximab vedotin	Yes	3025	0	-	-	0	-	-	3	-0·6	-2·6	25	0·8	0·2
brigatinib	Yes	271	0	-	-	0	-	-	0	-	-	2	0·5	-2·1
brivanib	no	18	0	-	-	0	-	-	0	-	-	0	-	-
brostallicin	no	3	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
broxuridine	no	2	0	-	-	0	-	-	0	-	-	0	-	-
bryostatin 1	no	7	0	-	-	0	-	-	0	-	-	0	-	-
buparlisib	no	33	0	-	-	0	-	-	0	-	-	0	-	-
buserelin	no	775	0	-	-	0	-	-	0	-	-	5	0·4	-1·1
busulfan	Yes	4576	1	-1·7	-5·5	0	-	-	2	-1·6	-4·2	49	1·2	0·8
buthionine sulfoximine	no	1	0	-	-	0	-	-	0	-	-	0	-	-
cabazitaxel	Yes	3309	1	-1·3	-5·1	0	-	-	0	-	-	19	0·3	-0·4
cabiralizumab	no	26	0	-	-	0	-	-	0	-	-	1	1·3	-2·5
cabozantinib	Yes	4697	2	-1	-3·6	0	-	-	3	-1·2	-3·2	10	-1·1	-2·1
cactinomycin	no	10	0	-	-	0	-	-	0	-	-	0	-	-
calaspargase pegol	Yes	1	0	-	-	0	-	-	0	-	-	0	-	-
calusterone	no	2	0	-	-	0	-	-	0	-	-	0	-	-
canertinib	no	9	0	-	-	0	-	-	0	-	-	0	-	-
canfosfamide	no	25	0	-	-	0	-	-	0	-	-	4	2·9	1·1
capecitabine	Yes	49174	27	-0·8	-1·4	18	-0·3	-1	161	1	0·8	319	0·5	0·3
capmatinib	no	10	0	-	-	0	-	-	0	-	-	0	-	-
carboplatin	Yes	55488	24	-1·2	-1·8	11	-1·1	-2·1	81	-0·1	-0·4	506	1	0·8

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Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
carboquone	no	12	0	-	-	0	-	-	0	-	-	0	-	-
carfilzomib	Yes	8109	19	1·2	0·5	1	-1·4	-5·2	18	0·5	-0·3	59	0·6	0·3
carmofur	no	62	0	-	-	0	-	-	0	-	-	0	-	-
carmustine	Yes	2941	1	-1·2	-5	0	-	-	2	-1	-3·6	20	0·5	-0·2
carotuximab	no	5	0	-	-	0	-	-	0	-	-	0	-	-
catumaxomab	no	48	0	-	-	0	-	-	0	-	-	0	-	-
cc-115	no	1	0	-	-	0	-	-	0	-	-	0	-	-
cc-122	no	5	0	-	-	0	-	-	0	-	-	0	-	-
cediranib	no	119	0	-	-	0	-	-	0	-	-	0	-	-
cenersen	no	5	0	-	-	0	-	-	0	-	-	0	-	-
cergutuzumab amunaleukin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
ceritinib	Yes	1747	21	3·3	2·6	2	1	-1·6	2	-0·4	-3	5	-0·6	-2·2
cetuximab	Yes	25913	11	-1·2	-2·2	3	-1·8	-3·8	34	-0·3	-0·8	400	1·7	1·6
cgm 097	no	6	0	-	-	0	-	-	0	-	-	0	-	-
chidamide	no	238	7	3·4	2·1	0	-	-	0	-	-	0	-	-
chlorambucil	Yes	2051	0	-	-	1	0·1	-3·7	2	-0·6	-3·2	5	-0·9	-2·4
chlormethine	Yes	1893	0	-	-	0	-	-	2	-0·5	-3·1	6	-0·5	-1·9
cilengitide	no	124	0	-	-	0	-	-	1	1·1	-2·7	1	0·5	-3·3
cisplatin	Yes	72583	21	-1·7	-2·4	12	-1·4	-2·3	82	-0·5	-0·8	384	0·2	0
cixutumumab	no	65	1	1·4	-2·4	1	1·5	-2·3	2	2·1	-0·5	0	-	-
cladribine	Yes	1803	0	-	-	0	-	-	4	0·4	-1·3	4	-1	-2·7
clofarabine	Yes	2216	5	1	-0·5	2	0·8	-1·8	11	1·5	0·5	57	2·4	2
cobimetinib	Yes	1496	20	3·4	2·7	1	0·4	-3·4	2	-0·2	-2·8	5	-0·4	-2
codrituzumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
combretastatin a4	no	25	3	2·7	0·7	1	1·6	-2·2	1	1·5	-2·3	0	-	-
conatumumab	no	5	0	-	-	0	-	-	0	-	-	0	-	-
contusugene ladenovec	no	1	0	-	-	0	-	-	0	-	-	0	-	-
copanlisib	Yes	47	0	-	-	0	-	-	0	-	-	0	-	-
corynebacterium parvum	no	18	0	-	-	0	-	-	0	-	-	0	-	-
crenigacestat	no	4	0	-	-	0	-	-	0	-	-	0	-	-
crenolanib	no	3	0	-	-	0	-	-	0	-	-	0	-	-
cridanimod	no	5	0	-	-	0	-	-	0	-	-	0	-	-
crisantaspase	no	273	0	-	-	0	-	-	0	-	-	0	-	-
crizotinib	Yes	7614	102	3·7	3·4	9	1·3	0·2	11	-0·1	-1·1	31	-0·2	-0·7
crlx 101	no	11	0	-	-	0	-	-	0	-	-	1	1·4	-2·4
crs-207	no	12	0	-	-	0	-	-	0	-	-	0	-	-
custirsen	no	23	0	-	-	0	-	-	0	-	-	0	-	-
cyclophosphamide	Yes	83277	41	-1	-1·5	7	-2·3	-3·6	95	-0·5	-0·8	417	0·1	0
cytarabine	Yes	26300	52	1	0·6	14	0·3	-0·6	89	1·1	0·8	358	1·6	1·4

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Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
dabrafenib	Yes	7612	27	1·8	1·2	2	-0·6	-3·2	6	-0·9	-2·3	20	-0·8	-1·5
dacarbazine	Yes	3856	2	-0·8	-3·4	1	-0·6	-4·4	4	-0·6	-2·3	19	0·1	-0·6
dacetuzumab	no	24	0	-	-	0	-	-	0	-	-	0	-	-
dacinostat	no	1	0	-	-	0	-	-	0	-	-	0	-	-
dacomitinib	Yes	36	0	-	-	0	-	-	0	-	-	0	-	-
dactinomycin	Yes	1837	0	-	-	0	-	-	2	-0·4	-3	8	-0·1	-1·3
dactolisib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
dalantercept	no	1	0	-	-	0	-	-	0	-	-	0	-	-
dalotuzumab	no	3	0	-	-	0	-	-	0	-	-	0	-	-
danusertib	no	24	0	-	-	0	-	-	0	-	-	0	-	-
daratumumab	Yes	3705	2	-0·7	-3·3	0	-	-	4	-0·5	-2·2	26	0·6	0
darolutamide	no	4	0	-	-	0	-	-	0	-	-	0	-	-
dasatinib	Yes	19654	94	2·3	1·9	2	-1·9	-4·5	17	-0·9	-1·6	54	-0·7	-1·2
daunorubicin	Yes	6655	28	2	1·4	9	1·5	0·4	52	2·3	1·8	149	2·3	2
decitabine	Yes	2894	10	1·7	0·6	1	-0·2	-4	1	-1·8	-5·6	22	0·7	0
defactinib	no	3	0	-	-	0	-	-	0	-	-	0	-	-
defosfamide	no	1	0	-	-	0	-	-	0	-	-	0	-	-
degarelix	Yes	2674	3	0·2	-1·9	2	0·6	-2	3	-0·4	-2·5	11	-0·2	-1·1
demcizumab	no	28	0	-	-	0	-	-	0	-	-	0	-	-
demecolcine	no	1	0	-	-	0	-	-	0	-	-	0	-	-
denenicokin	no	4	0	-	-	0	-	-	0	-	-	0	-	-
denileukin diftitox	Yes	343	0	-	-	0	-	-	3	1·7	-0·3	10	2·3	1·3
depatuxizumab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
depatuxizumab mafodotin	no	53	0	-	-	0	-	-	0	-	-	0	-	-
depsipeptide	no	1	0	-	-	0	-	-	0	-	-	0	-	-
diflomotecan	no	3	0	-	-	0	-	-	0	-	-	0	-	-
dinaciclib	no	12	0	-	-	0	-	-	0	-	-	0	-	-
dinutuximab	Yes	87	0	-	-	0	-	-	0	-	-	4	2·3	0·6
dinutuximab beta	no	27	0	-	-	0	-	-	0	-	-	0	-	-
docetaxel	Yes	87799	15	-2·5	-3·3	7	-2·4	-3·7	52	-1·4	-1·8	288	-0·5	-0·7
dovitinib	no	73	0	-	-	0	-	-	0	-	-	0	-	-
doxifluridine	no	117	0	-	-	0	-	-	0	-	-	1	0·5	-3·3
doxorubicin	Yes	67806	40	-0·7	-1·2	10	-1·5	-2·6	104	0	-0·3	380	0·3	0·1
drostanolone	no	16	0	-	-	0	-	-	0	-	-	0	-	-
dulanermin	no	10	0	-	-	0	-	-	0	-	-	0	-	-
duligotumab	no	19	0	-	-	0	-	-	0	-	-	0	-	-
durvalumab	Yes	823	1	0·2	-3·6	0	-	-	0	-	-	5	0·4	-1·2
duvelisib	Yes	26	0	-	-	0	-	-	0	-	-	1	1·3	-2·5
edotecarin	no	3	0	-	-	0	-	-	0	-	-	0	-	-

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Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
edrecolomab	no	20	0	-	-	0	-	-	0	-	-	0	-	-
efatutazone	no	1	0	-	-	0	-	-	0	-	-	0	-	-
egf816	no	6	0	-	-	0	-	-	0	-	-	0	-	-
elacytarabine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
elesclomol	no	3	0	-	-	0	-	-	0	-	-	0	-	-
elgemtumab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
elliptinium	no	6	0	-	-	0	-	-	0	-	-	0	-	-
elotuzumab	Yes	1371	2	0·4	-2·2	0	-	-	1	-0·8	-4·6	8	0·3	-0·9
emactuzumab	no	13	0	-	-	0	-	-	0	-	-	0	-	-
enadenotucirev	no	12	0	-	-	0	-	-	0	-	-	0	-	-
enasidenib	Yes	346	0	-	-	0	-	-	0	-	-	0	-	-
encorafenib	Yes	91	0	-	-	0	-	-	0	-	-	0	-	-
endostatin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
enfortumab vedotin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
eniluracil	no	8	0	-	-	0	-	-	0	-	-	0	-	-
enocitabine	no	45	0	-	-	0	-	-	0	-	-	0	-	-
entinostat	no	53	0	-	-	0	-	-	0	-	-	0	-	-
entospletinib	no	8	0	-	-	0	-	-	0	-	-	0	-	-
entrectinib	no	4	0	-	-	0	-	-	0	-	-	0	-	-
enzalutamide	Yes	33370	20	-0·7	-1·4	4	-1·8	-3·5	21	-1·3	-2	85	-0·9	-1·2
enzastaurin	no	138	1	1·2	-2·6	0	-	-	3	2·3	0·2	2	1·1	-1·5
epacadostat	no	19	0	-	-	0	-	-	0	-	-	0	-	-
epirubicin	Yes	16327	7	-1·1	-2·4	2	-1·6	-4·2	19	-0·4	-1·2	56	-0·4	-0·8
epothilone a	no	4	0	-	-	0	-	-	0	-	-	0	-	-
epothilone d	no	1	0	-	-	0	-	-	0	-	-	0	-	-
epothilone nos	no	2	0	-	-	0	-	-	0	-	-	0	-	-
epratuzumab	no	5	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
eptaplatin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
erdafitinib	Yes	2	0	-	-	0	-	-	0	-	-	0	-	-
eribulin	Yes	4582	8	0·8	-0·4	0	-	-	0	-	-	4	-2·3	-4
erlotinib	Yes	38616	9	-2	-3·1	6	-1·4	-2·8	28	-1·1	-1·7	154	-0·2	-0·5
estramustine	Yes	1143	0	-	-	0	-	-	4	1	-0·8	15	1·4	0·6
etalocib	no	22	0	-	-	0	-	-	0	-	-	1	1·3	-2·5
etaracizumab	no	3	0	-	-	0	-	-	0	-	-	0	-	-
etoglucid	no	9	0	-	-	0	-	-	0	-	-	0	-	-
etoposide	Yes	32326	22	-0·5	-1·2	5	-1·4	-3	52	0	-0·4	264	0·8	0·6
everolimus	Yes	33545	12	-1·4	-2·4	2	-2·6	-5·2	29	-0·9	-1·4	82	-0·9	-1·2
evofosfamide	no	5	0	-	-	0	-	-	0	-	-	0	-	-
exatecan	no	8	0	-	-	0	-	-	0	-	-	0	-	-

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Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
exemestane	Yes	7693	6	-0·3	-1·7	0	-	-	2	-2·3	-4·9	6	-2·5	-3·8
exisulind	no	73	0	-	-	0	-	-	0	-	-	1	0·8	-3
fadrozole	no	5	0	-	-	0	-	-	0	-	-	0	-	-
falnidamol	no	1	0	-	-	0	-	-	0	-	-	0	-	-
farletuzumab	no	51	0	-	-	0	-	-	0	-	-	0	-	-
fedratinib	no	6	0	-	-	0	-	-	0	-	-	0	-	-
fenretinide	no	14	0	-	-	0	-	-	0	-	-	0	-	-
figitumumab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
filanesib	no	6	0	-	-	0	-	-	0	-	-	0	-	-
floxuridine	Yes	284	1	0·9	-2·9	0	-	-	0	-	-	5	1·6	0·1
fludarabine	Yes	10989	6	-0·8	-2·2	1	-1·8	-5·6	14	-0·3	-1·2	74	0·5	0·2
fluorouracil	Yes	65547	20	-1·7	-2·4	19	-0·6	-1·3	138	0·4	0·2	383	0·3	0·2
flutamide	Yes	3253	1	-1·3	-5·1	1	-0·4	-4·2	4	-0·3	-2·1	9	-0·7	-1·8
formestane	no	97	0	-	-	0	-	-	0	-	-	0	-	-
forodesine	no	92	0	-	-	0	-	-	0	-	-	0	-	-
fotemustine	no	345	0	-	-	0	-	-	0	-	-	0	-	-
fp 1039	no	1	0	-	-	0	-	-	0	-	-	0	-	-
fulvestrant	Yes	4900	5	0	-1·5	0	-	-	0	-	-	13	-0·8	-1·7
galeterone	no	1	0	-	-	0	-	-	0	-	-	0	-	-
galiximab	no	3	0	-	-	0	-	-	0	-	-	0	-	-
galunisertib	no	5	0	-	-	0	-	-	0	-	-	0	-	-
ganetespib	no	20	0	-	-	0	-	-	0	-	-	2	2·1	-0·5
ganitumab	no	6	0	-	-	0	-	-	0	-	-	0	-	-
gastrin 17 vaccine	no	5	0	-	-	0	-	-	0	-	-	0	-	-
gataparsen	no	2	0	-	-	0	-	-	0	-	-	0	-	-
gedatolisib	no	14	0	-	-	0	-	-	0	-	-	0	-	-
gefitinib	Yes	6832	2	-1·5	-4·1	0	-	-	4	-1·3	-3·1	26	-0·3	-0·9
gemcitabine	Yes	45061	9	-2·2	-3·3	2	-3	-5·6	52	-0·5	-0·9	262	0·3	0·1
gemtuzumab	Yes	1729	9	2·1	1	3	1·5	-0·6	8	1·4	0·2	34	2	1·5
gestonorone	no	30	0	-	-	0	-	-	0	-	-	0	-	-
gilteritinib	Yes	7	0	-	-	0	-	-	0	-	-	0	-	-
gimatecan	no	8	0	-	-	0	-	-	0	-	-	0	-	-
gimeracil	no	5	0	-	-	0	-	-	0	-	-	0	-	-
gimeracil;oteracil;tegafur	no	14998	4	-1·8	-3·5	1	-2·3	-6	3	-2·8	-4·8	19	-1·8	-2·6
girentuximab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
glasdegib	Yes	3	1	1·6	-2·2	0	-	-	0	-	-	0	-	-
glembatumumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
glufosfamide	no	2	0	-	-	0	-	-	0	-	-	0	-	-
golnerminogene pradenovec	no	1	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
golvatinib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
goserelin	Yes	5397	2	-1·2	-3·8	1	-0·9	-4·7	5	-0·7	-2·2	28	0·2	-0·4
guadecitabine	no	10	0	-	-	0	-	-	0	-	-	0	-	-
hdm 201	no	11	0	-	-	0	-	-	0	-	-	0	-	-
histamine	no	92	0	-	-	0	-	-	0	-	-	0	-	-
histrelin	Yes	704	0	-	-	0	-	-	0	-	-	0	-	-
hydrazine	no	6	0	-	-	0	-	-	0	-	-	0	-	-
hydroxycarbamide	Yes	6128	2	-1·4	-4	0	-	-	6	-0·7	-2	28	0	-0·6
iboctadekin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
ibrutinib	Yes	21110	6	-1·7	-3·1	6	-0·6	-2	99	1·6	1·3	126	0·4	0·1
icotinib	no	61	0	-	-	0	-	-	0	-	-	0	-	-
icrucumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
idarubicin	Yes	3539	12	1·7	0·7	5	1·4	-0·1	18	1·6	0·9	42	1·3	0·9
idasanutlin	no	2	0	-	-	0	-	-	0	-	-	0	-	-
idelalisib	Yes	4888	0	-	-	0	-	-	1	-2·5	-6·3	12	-0·9	-1·8
ifosfamide	Yes	11569	4	-1·4	-3·1	3	-0·7	-2·7	9	-1	-2·1	42	-0·3	-0·8
imatinib	Yes	44671	64	0·5	0·2	1	-3·8	-7·6	37	-0·9	-1·4	146	-0·5	-0·7
imcgp 100	no	1	0	-	-	0	-	-	0	-	-	0	-	-
imetelstat	no	7	0	-	-	0	-	-	0	-	-	0	-	-
imexon	no	9	0	-	-	0	-	-	0	-	-	0	-	-
imm-101	no	9	0	-	-	0	-	-	0	-	-	0	-	-
indatuximab ravtansine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
indisulam	no	12	0	-	-	0	-	-	0	-	-	0	-	-
iniparib	no	25	0	-	-	0	-	-	0	-	-	0	-	-
inotuzumab	Yes	410	2	1·5	-1·1	0	-	-	0	-	-	0	-	-
interferon alfa-2a	no	3082	1	-1·2	-5	0	-	-	7	0·5	-0·8	17	0·2	-0·5
interferon alfa-2b	Yes	14401	4	-1·7	-3·4	2	-1·5	-4	18	-0·3	-1·1	44	-0·6	-1·1
interferon alfa-n3	no	29	0	-	-	0	-	-	0	-	-	1	1·2	-2·6
interferon alfacon-1	withdrawn	742	1	0·3	-3·5	1	0·9	-2·9	5	1·7	0·2	4	0·2	-1·5
intetumumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
ipatasertib	no	17	0	-	-	0	-	-	0	-	-	1	1·4	-2·4
ipilimumab	Yes	13997	5	-1·4	-2·9	1	-2·2	-6	11	-1	-2	60	-0·1	-0·5
iproplatin	no	4	0	-	-	0	-	-	0	-	-	0	-	-
irinotecan	Yes	28010	9	-1·6	-2·7	3	-1·9	-3·9	33	-0·4	-1	153	0·2	0
irofulven	no	17	0	-	-	0	-	-	0	-	-	2	2·1	-0·5
isatuximab	no	64	0	-	-	0	-	-	1	1·3	-2·5	0	-	-
itacitinib	no	24	0	-	-	0	-	-	0	-	-	0	-	-
ivosidenib	Yes	2	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
ixabepilone	Yes	1617	4	1·1	-0·6	1	0·3	-3·5	3	0·2	-1·9	17	1·1	0·4
ixazomib	Yes	4407	1	-1·7	-5·5	0	-	-	3	-1·1	-3·1	12	-0·7	-1·7
kte c19	Yes	117	0	-	-	0	-	-	4	2·7	1	3	1·7	-0·3
ladirubicin	no	4	0	-	-	0	-	-	0	-	-	0	-	-
lapatinib	Yes	13397	16	0·3	-0·5	2	-1·4	-4	6	-1·7	-3·1	34	-0·9	-1·4
laromustine	no	6	0	-	-	0	-	-	0	-	-	0	-	-
larotaxel	no	18	0	-	-	0	-	-	0	-	-	0	-	-
lcl 161	no	10	0	-	-	0	-	-	0	-	-	0	-	-
lenalidomide	Yes	156851	61	-1·3	-1·7	17	-2	-2·8	112	-1·1	-1·4	676	-0·1	-0·2
lenvatinib	Yes	2555	11	1·9	1	0	-	-	2	-0·9	-3·5	4	-1·5	-3·2
lestaurtinib	no	140	0	-	-	0	-	-	0	-	-	1	0·4	-3·4
letrozole	Yes	15564	25	0·7	0·1	1	-2·3	-6·1	7	-1·7	-3	27	-1·4	-2
leuprorelin	Yes	34043	10	-1·7	-2·7	7	-1·1	-2·3	35	-0·6	-1·1	102	-0·6	-0·9
linifanib	no	40	0	-	-	0	-	-	0	-	-	1	1·1	-2·7
linsitinib	no	4	0	-	-	0	-	-	0	-	-	0	-	-
lintuzumab	no	5	0	-	-	0	-	-	0	-	-	0	-	-
lipopolysaccharide	no	1	0	-	-	0	-	-	0	-	-	0	-	-
lirilumab	no	14	0	-	-	0	-	-	0	-	-	0	-	-
lobaplatin	no	702	0	-	-	0	-	-	0	-	-	0	-	-
lomeguatrib	no	3	0	-	-	0	-	-	0	-	-	0	-	-
lomustine	Yes	902	1	0·1	-3·7	0	-	-	1	-0·4	-4·2	1	-1·6	-5·4
lonafarnib	no	52	0	-	-	0	-	-	0	-	-	2	1·8	-0·8
lonidamine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
lorlatinib	Yes	275	1	1	-2·8	0	-	-	1	0·7	-3·1	0	-	-
lorvotuzumab mertansine	no	10	0	-	-	0	-	-	0	-	-	0	-	-
losoxantrone	no	7	0	-	-	0	-	-	0	-	-	0	-	-
lucitanib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
lumiliximab	no	74	0	-	-	0	-	-	0	-	-	0	-	-
lumretuzumab	no	18	0	-	-	0	-	-	0	-	-	0	-	-
lurbinectedin	no	25	0	-	-	0	-	-	0	-	-	0	-	-
lutikizumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
lxh 254	no	2	0	-	-	0	-	-	0	-	-	0	-	-
mafosfamide	no	3	0	-	-	0	-	-	0	-	-	0	-	-
mage-3a1 peptide	no	1	0	-	-	0	-	-	0	-	-	0	-	-
mapatumumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
marimastat	no	2	0	-	-	0	-	-	0	-	-	0	-	-
marizomib	no	8	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
masitinib	no	18	0	-	-	0	-	-	0	-	-	0	-	-
masoprocol	withdrawn	193	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
matrine	no	98	0	-	-	0	-	-	0	-	-	0	-	-
matuzumab	no	8	0	-	-	0	-	-	0	-	-	0	-	-
mbg 453	no	1	0	-	-	0	-	-	0	-	-	0	-	-
medroxyprogesterone	Yes	25513	4	-3·2	-4·9	5	-1·8	-3·3	18	-1·9	-2·6	25	-2·9	-3·6
megestrol	Yes	3033	1	-1·3	-5·1	0	-	-	2	-1·2	-3·8	12	-0·3	-1·2
melphalan	Yes	8333	9	0·1	-1	1	-1·5	-5·3	19	0·5	-0·2	107	1·5	1·2
mercaptopurine	Yes	6062	3	-0·9	-2·9	2	-0·3	-2·9	11	0·2	-0·8	62	1·1	0·7
merestinib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
merphalan	no	5	0	-	-	0	-	-	0	-	-	0	-	-
methotrexate	Yes	109381	18	-2·5	-3·3	8	-2·5	-3·7	85	-1	-1·3	357	-0·5	-0·7
methoxyamine	no	25	0	-	-	0	-	-	0	-	-	0	-	-
methyl aminolevulinate	no	295	0	-	-	0	-	-	0	-	-	0	-	-
methyluracil	no	1	0	-	-	0	-	-	0	-	-	0	-	-
metoprine	no	1	0	-	-	0	-	-	0	-	-	0	-	-
midostaurin	Yes	1001	34	4·5	4	2	1·4	-1·2	4	1·1	-0·6	5	0·1	-1·4
mifamurtide	no	150	0	-	-	0	-	-	0	-	-	0	-	-
miriplatin	no	158	0	-	-	0	-	-	0	-	-	0	-	-
mirvetuximab soravtansine	no	1	0	-	-	0	-	-	0	-	-	0	-	-
mitobronitol	no	4	0	-	-	0	-	-	0	-	-	0	-	-
mitoguazone	no	41	0	-	-	0	-	-	0	-	-	0	-	-
mitolactol	no	9	0	-	-	0	-	-	0	-	-	0	-	-
mitomycin	Yes	3501	0	-	-	1	-0·5	-4·2	2	-1·3	-3·9	13	-0·3	-1·2
mitopodozide	no	63	0	-	-	0	-	-	0	-	-	0	-	-
mitotane	Yes	489	3	1·8	-0·2	0	-	-	0	-	-	6	1·2	-0·1
mitoxantrone	Yes	4847	12	1·2	0·3	9	1·8	0·8	28	1·8	1·2	60	1·4	1
mk-2206	no	36	0	-	-	0	-	-	0	-	-	0	-	-
mocetinostat	no	4	0	-	-	0	-	-	0	-	-	0	-	-
mogamulizumab	Yes	497	0	-	-	0	-	-	5	2·1	0·6	0	-	-
momelotinib	no	11	0	-	-	0	-	-	0	-	-	0	-	-
mopidamol	no	6	0	-	-	0	-	-	0	-	-	0	-	-
mor208	no	7	0	-	-	0	-	-	0	-	-	0	-	-
motesanib	no	37	0	-	-	0	-	-	0	-	-	1	1·2	-2·6
motexafin	no	13	0	-	-	0	-	-	0	-	-	0	-	-
msc 2490484a	no	3	0	-	-	0	-	-	0	-	-	0	-	-
napabucasin	no	6	0	-	-	0	-	-	0	-	-	0	-	-
naptumomab estafenatox	no	2	0	-	-	0	-	-	0	-	-	0	-	-
navitoclax	no	13	0	-	-	0	-	-	0	-	-	0	-	-
nazartinib	no	5	0	-	-	0	-	-	0	-	-	0	-	-
necitumumab	Yes	135	0	-	-	0	-	-	0	-	-	3	1·6	-0·4

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
necuparanib	no	38	0	-	-	0	-	-	0	-	-	0	-	-
nedaplatin	no	3388	0	-	-	0	-	-	2	-1·2	-3·8	0	-	-
nelarabine	Yes	370	0	-	-	0	-	-	4	2·1	0·3	2	0·2	-2·4
nemorubicin	no	9	0	-	-	0	-	-	0	-	-	0	-	-
neovastat	no	1	0	-	-	0	-	-	0	-	-	0	-	-
neratinib	Yes	809	0	-	-	0	-	-	0	-	-	0	-	-
nesvacumab	no	8	0	-	-	0	-	-	0	-	-	0	-	-
ngr-htnf	no	1	0	-	-	0	-	-	0	-	-	0	-	-
nilotinib	Yes	17471	369	4·4	4·2	18	1·2	0·4	46	0·7	0·3	92	0·2	-0·1
nilutamide	Yes	444	0	-	-	0	-	-	0	-	-	1	-0·8	-4·6
nimorazole	no	17	0	-	-	0	-	-	0	-	-	0	-	-
nimotuzumab	no	58	0	-	-	0	-	-	0	-	-	0	-	-
nimustine	no	76	0	-	-	0	-	-	0	-	-	0	-	-
nintedanib	Yes	7463	1	-2·4	-6·2	0	-	-	5	-1·2	-2·7	38	0·1	-0·4
niraparib	Yes	2838	3	0·1	-2	0	-	-	0	-	-	3	-2	-4
nivolumab	Yes	27539	5	-2·3	-3·9	1	-3·1	-6·9	21	-1	-1·7	99	-0·4	-0·7
nolatrexed	no	1	0	-	-	0	-	-	0	-	-	0	-	-
nsc 601316	no	2	0	-	-	0	-	-	0	-	-	0	-	-
ny-eso-1	no	1	0	-	-	0	-	-	0	-	-	0	-	-
o6-benzylguanine	no	50	0	-	-	0	-	-	0	-	-	0	-	-
obatoclax	no	3	0	-	-	0	-	-	0	-	-	0	-	-
obinutuzumab	Yes	2599	1	-1	-4·8	1	-0·1	-3·9	3	-0·4	-2·4	16	0·4	-0·4
oblimersen	no	90	0	-	-	0	-	-	1	1·2	-2·6	2	1·4	-1·1
ofatumumab	Yes	1464	3	0·9	-1·2	0	-	-	1	-0·9	-4·7	12	0·8	-0·1
olaparib	Yes	2667	1	-1·1	-4·9	0	-	-	2	-0·9	-3·5	3	-1·9	-3·9
olaratumab	Yes	352	0	-	-	0	-	-	0	-	-	10	2·3	1·3
olivomycin	no	2	0	-	-	0	-	-	0	-	-	0	-	-
olmutinib	no	398	0	-	-	0	-	-	0	-	-	0	-	-
omacetaxine	Yes	557	0	-	-	0	-	-	0	-	-	0	-	-
omipalisib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
onartuzumab	no	51	0	-	-	0	-	-	1	1·4	-2·4	1	1	-2·8
ontuxizumab	no	4	0	-	-	0	-	-	0	-	-	0	-	-
oprozomib	no	6	0	-	-	0	-	-	0	-	-	0	-	-
oregovomab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
ortataxel	no	5	0	-	-	0	-	-	0	-	-	0	-	-
orteronel	no	14	0	-	-	0	-	-	0	-	-	0	-	-
osimertinib	Yes	2423	37	3·7	3·2	4	1·5	-0·2	4	0·1	-1·7	7	-0·6	-1·9
oteracil	no	10	0	-	-	0	-	-	0	-	-	0	-	-
otlertuzumab	no	2	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
oxaliplatin	Yes	66293	19	-1·8	-2·5	15	-0·9	-1·8	91	-0·2	-0·5	341	0·2	0
oxb 301	no	1	0	-	-	0	-	-	0	-	-	0	-	-
paclitaxel	Yes	82292	37	-1·1	-1·6	5	-2·7	-4·3	132	0	-0·2	729	0·9	0·8
pacritinib	no	7	0	-	-	0	-	-	0	-	-	0	-	-
padeliporfin	no	8	0	-	-	0	-	-	0	-	-	0	-	-
palbociclib	Yes	23300	15	-0·6	-1·4	1	-2·8	-6·6	3	-3·4	-5·5	34	-1·7	-2·2
palifosfamide	no	3	0	-	-	0	-	-	0	-	-	0	-	-
panitumumab	Yes	6155	5	-0·3	-1·8	0	-	-	1	-2·8	-6·6	23	-0·3	-1
panobinostat	Yes	1483	24	3·6	3	1	0·4	-3·4	3	0·3	-1·8	7	0	-1·2
pasotuxizumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
patritumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
patupilone	no	8	0	-	-	0	-	-	0	-	-	0	-	-
pazopanib	Yes	19816	40	1	0·5	14	0·6	-0·2	24	-0·4	-1	32	-1·5	-2
pegaspargase	Yes	4481	6	0·4	-1	3	0·5	-1·6	22	1·6	0·9	146	2·8	2·5
pegilodecakin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
pelitinib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
pembrolizumab	Yes	13275	1	-3·2	-7	0	-	-	8	-1·3	-2·5	55	-0·2	-0·6
pemetrexed	Yes	16510	3	-2·3	-4·3	2	-1·6	-4·2	18	-0·5	-1·3	92	0·3	0
pentostatin	Yes	672	0	-	-	0	-	-	0	-	-	8	1·2	0·1
peplomycin	no	44	0	-	-	0	-	-	0	-	-	0	-	-
peptichemio	no	2	0	-	-	0	-	-	0	-	-	0	-	-
perifosine	no	12	0	-	-	0	-	-	0	-	-	0	-	-
pertuzumab	Yes	6248	1	-2·1	-5·9	0	-	-	3	-1·6	-3·6	18	-0·7	-1·4
pevonedistat	no	4	0	-	-	0	-	-	0	-	-	0	-	-
pexidartinib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
pf-06664178	no	1	0	-	-	0	-	-	0	-	-	0	-	-
pf-4136309	no	11	0	-	-	0	-	-	0	-	-	0	-	-
picibanil	no	24	0	-	-	0	-	-	0	-	-	1	1·3	-2·5
pictilisib	no	18	0	-	-	0	-	-	0	-	-	0	-	-
pidilizumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
pilaralisib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
pim 447	no	15	0	-	-	0	-	-	0	-	-	0	-	-
pimasertib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
pimonidazole	no	2	0	-	-	0	-	-	0	-	-	0	-	-
pipobroman	withdrawn	136	0	-	-	0	-	-	0	-	-	0	-	-
pirarubicin	no	2193	1	-0·8	-4·6	0	-	-	0	-	-	1	-2·8	-6·6
piritrexim	no	12	0	-	-	0	-	-	0	-	-	0	-	-
pixantrone	no	140	0	-	-	0	-	-	1	1·1	-2·7	0	-	-
plevitrexed	no	3	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
plicamycin	no	69	0	-	-	0	-	-	0	-	-	1	0·9	-2·9
plitidepsin	no	16	0	-	-	0	-	-	0	-	-	0	-	-
pm00104	no	2	0	-	-	0	-	-	0	-	-	0	-	-
polatuzumab vedotin	no	33	0	-	-	0	-	-	0	-	-	0	-	-
poly iclc	no	4	0	-	-	0	-	-	0	-	-	0	-	-
polysaccharide-k	no	46	0	-	-	0	-	-	0	-	-	0	-	-
pomalidomide	Yes	25782	2	-3·4	-6	0	-	-	9	-2·1	-3·2	70	-0·8	-1·1
ponatinib	Yes	4107	8	0·9	-0·3	2	0·1	-2·5	9	0·4	-0·7	25	0·4	-0·2
porfimer	Yes	244	0	-	-	0	-	-	0	-	-	6	2	0·6
porfiromycin	no	5	0	-	-	0	-	-	0	-	-	0	-	-
pracinostat	no	15	2	2·3	-0·3	0	-	-	0	-	-	0	-	-
pralatrexate	Yes	343	0	-	-	0	-	-	1	0·5	-3·3	1	-0·5	-4·3
prednimustine	no	37	0	-	-	0	-	-	0	-	-	0	-	-
prexasertib	no	3	0	-	-	0	-	-	0	-	-	0	-	-
procarbazine	Yes	3076	1	-1·2	-5	1	-0·3	-4·1	3	-0·6	-2·7	11	-0·4	-1·3
quizartinib	no	4	2	2·3	-0·3	0	-	-	0	-	-	0	-	-
racotumomab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
radotinib	no	276	0	-	-	0	-	-	0	-	-	0	-	-
ralimetinib	no	6	0	-	-	0	-	-	0	-	-	0	-	-
raltitrexed	no	679	0	-	-	0	-	-	0	-	-	3	-0·1	-2·1
ramucirumab	Yes	3489	1	-1·4	-5·2	0	-	-	1	-2	-5·8	13	-0·3	-1·2
ranimustine	no	76	0	-	-	0	-	-	0	-	-	1	0·8	-3
ravoxertinib	no	5	0	-	-	0	-	-	0	-	-	0	-	-
razoxane	no	47	0	-	-	0	-	-	0	-	-	0	-	-
rebastinib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
rebimastat	no	18	0	-	-	0	-	-	0	-	-	3	2·6	0·5
refametinib	no	7	0	-	-	0	-	-	0	-	-	0	-	-
regn 2810	Yes	7	0	-	-	0	-	-	0	-	-	0	-	-
regorafenib	Yes	9231	1	-2·7	-6·5	0	-	-	3	-2·1	-4·2	14	-1·6	-2·4
remestemcel-l	no	1	0	-	-	0	-	-	0	-	-	0	-	-
reovirus serotype 3 dearing strain	no	10	0	-	-	0	-	-	0	-	-	0	-	-
resminostat	no	2	0	-	-	0	-	-	0	-	-	0	-	-
retaspimycin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
rg 7212	no	1	0	-	-	0	-	-	0	-	-	0	-	-
ribociclib	Yes	1738	105	5·6	5·3	4	1·8	0·1	4	0·5	-1·3	0	-	-
ricolinostat	no	2	0	-	-	0	-	-	0	-	-	0	-	-
ridaforolimus	no	45	0	-	-	0	-	-	2	2·1	-0·5	0	-	-
rigosertib	no	13	0	-	-	0	-	-	0	-	-	0	-	-
rilotumumab	no	29	1	1·5	-2·3	0	-	-	1	1·5	-2·3	5	3·1	1·6

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
rindopepimut	no	2	0	-	-	0	-	-	0	-	-	0	-	-
rituximab	Yes	65646	14	-2·2	-3	8	-1·8	-3	79	-0·4	-0·7	340	0·2	0
ro 6958688	no	8	0	-	-	0	-	-	0	-	-	0	-	-
ro 7009789	no	2	0	-	-	0	-	-	0	-	-	0	-	-
rociletinib	no	10	0	-	-	0	-	-	0	-	-	0	-	-
romidepsin	Yes	462	11	3·6	2·6	2	1·8	-0·8	4	1·9	0·1	4	0·8	-1
roniciclib	no	6	0	-	-	0	-	-	0	-	-	0	-	-
roquinimex	no	3	0	-	-	0	-	-	0	-	-	0	-	-
rovalpituzumab tesirine	no	50	0	-	-	0	-	-	0	-	-	0	-	-
rubitecan	no	25	0	-	-	0	-	-	0	-	-	0	-	-
rucaparib	Yes	2055	1	-0·7	-4·5	1	0·1	-3·7	1	-1·3	-5·1	1	-2·7	-6·5
rufocromomycin	no	3	0	-	-	0	-	-	0	-	-	0	-	-
ruxolitinib	Yes	22481	5	-2	-3·6	0	-	-	7	-2·3	-3·5	50	-1	-1·5
s 3304	no	1	0	-	-	0	-	-	0	-	-	0	-	-
sabarubicin	no	8	0	-	-	0	-	-	0	-	-	0	-	-
sagopilone	no	4	0	-	-	0	-	-	0	-	-	0	-	-
sapacitabine	no	4	0	-	-	0	-	-	0	-	-	0	-	-
sapanisertib	no	5	1	1·6	-2·2	0	-	-	0	-	-	0	-	-
saracatinib	no	8	0	-	-	0	-	-	0	-	-	0	-	-
satraplatin	no	14	0	-	-	0	-	-	0	-	-	0	-	-
scalasparagase pegol	no	1	0	-	-	0	-	-	0	-	-	0	-	-
selectikine	no	8	0	-	-	0	-	-	0	-	-	0	-	-
seliciclib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
selinexor	no	65	0	-	-	0	-	-	1	1·3	-2·5	0	-	-
selumetinib	no	101	0	-	-	0	-	-	0	-	-	1	0·6	-3·2
semaxanib	no	19	0	-	-	0	-	-	0	-	-	0	-	-
semustine	no	142	0	-	-	0	-	-	0	-	-	0	-	-
seocalcitol	no	1	0	-	-	0	-	-	0	-	-	0	-	-
sepantronium	no	1	0	-	-	0	-	-	0	-	-	0	-	-
seribantumab	no	6	0	-	-	0	-	-	0	-	-	4	3·1	1·4
siltuximab	Yes	69	0	-	-	0	-	-	0	-	-	0	-	-
sipuleucel-t	Yes	3507	2	-0·7	-3·2	1	-0·5	-4·3	11	0·9	-0·1	20	0·3	-0·4
sitimagene ceradenovec	no	3	0	-	-	0	-	-	0	-	-	0	-	-
sitosterol	no	16	0	-	-	0	-	-	0	-	-	0	-	-
sizofiran	no	17	0	-	-	0	-	-	0	-	-	0	-	-
soblidotin	no	3	0	-	-	0	-	-	0	-	-	0	-	-
sobuzoxane	no	19	0	-	-	0	-	-	0	-	-	0	-	-
sonidegib	Yes	108	0	-	-	0	-	-	0	-	-	2	1·3	-1·3
sorafenib	Yes	24936	19	-0·4	-1·1	3	-1·7	-3·8	18	-1·1	-1·9	84	-0·5	-0·8

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
sotrastaurin	no	9	0	-	-	0	-	-	0	-	-	0	-	-
spartalizumab	no	26	0	-	-	0	-	-	0	-	-	0	-	-
spebrutinib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
spisulosine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
stapuldencel-t	no	3	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
streptozocin	Yes	371	0	-	-	0	-	-	0	-	-	2	0·2	-2·4
sunitinib	Yes	29774	71	1·3	0·9	12	-0·1	-1·1	36	-0·4	-0·9	130	-0·1	-0·3
tacedinaline	no	1	0	-	-	0	-	-	0	-	-	0	-	-
talimogene laherparepvec	Yes	535	0	-	-	0	-	-	0	-	-	5	0·9	-0·6
talmapimod	no	19	0	-	-	0	-	-	0	-	-	0	-	-
tamibarotene	no	14	0	-	-	0	-	-	0	-	-	0	-	-
tamoxifen	Yes	18567	28	0·6	0	8	0	-1·2	21	-0·5	-1·2	70	-0·3	-0·7
tandutinib	no	2	0	-	-	0	-	-	0	-	-	0	-	-
tanespimycin	no	35	1	1·5	-2·3	1	1·5	-2·3	1	1·4	-2·4	3	2·4	0·4
tarextumab	no	2	0	-	-	0	-	-	0	-	-	0	-	-
tariquidar	no	15	0	-	-	0	-	-	0	-	-	0	-	-
tas 120	no	2	0	-	-	0	-	-	0	-	-	0	-	-
taselisib	no	21	0	-	-	0	-	-	0	-	-	0	-	-
tasidotin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
tasisulam	no	23	0	-	-	0	-	-	0	-	-	2	2	-0·5
tasonermin	no	176	0	-	-	0	-	-	0	-	-	0	-	-
tasquinimod	no	4	0	-	-	0	-	-	0	-	-	0	-	-
tauromustine	no	2	0	-	-	0	-	-	0	-	-	0	-	-
tazemetostat	no	6	0	-	-	0	-	-	0	-	-	0	-	-
tefinostat	no	1	0	-	-	0	-	-	0	-	-	0	-	-
tegafur	no	626	0	-	-	0	-	-	0	-	-	0	-	-
tegafur;uracil	no	1187	2	0·6	-2	0	-	-	1	-0·7	-4·5	8	0·5	-0·7
telatinib	no	4	0	-	-	0	-	-	0	-	-	0	-	-
telisotuzumab vedotin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
temoporfin	no	34	0	-	-	0	-	-	0	-	-	0	-	-
temozolomide	Yes	11985	2	-2·3	-4·9	1	-2	-5·8	14	-0·4	-1·3	55	0	-0·4
temsirolimus	Yes	3531	1	-1·4	-5·2	1	-0·5	-4·3	9	0·6	-0·5	27	0·7	0·1
teniposide	Yes	344	0	-	-	0	-	-	0	-	-	4	1·1	-0·6
teprotumumab	no	5	0	-	-	0	-	-	0	-	-	0	-	-
tertomotide	no	74	0	-	-	0	-	-	0	-	-	0	-	-
tesetaxel	no	19	0	-	-	0	-	-	0	-	-	0	-	-
tesevatinib	no	2	1	1·6	-2·2	0	-	-	0	-	-	0	-	-
testolactone	withdrawn	11	0	-	-	0	-	-	0	-	-	0	-	-
tetrathiomolybdate	no	8	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
tezacitabine	no	14	0	-	-	0	-	-	0	-	-	0	-	-
tgr 1202	no	1	0	-	-	0	-	-	0	-	-	0	-	-
thalidomide	Yes	34380	13	-1·3	-2·2	9	-0·7	-1·8	55	0	-0·4	407	1·4	1·2
thiotepa	Yes	2006	3	0·5	-1·5	0	-	-	3	-0·1	-2·1	18	0·9	0·2
thymostimulin	no	39	0	-	-	0	-	-	0	-	-	0	-	-
tiazofurine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
tigatuzumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
tioguanine	Yes	1525	1	-0·4	-4·2	1	0·4	-3·4	4	0·6	-1·1	19	1·4	0·6
tipifarnib	no	80	0	-	-	0	-	-	0	-	-	1	0·8	-3
tipiracil;trifluridine	Yes	4542	1	-1·7	-5·5	0	-	-	0	-	-	5	-2	-3·5
tirabrutinib	no	8	0	-	-	0	-	-	0	-	-	0	-	-
tirapazamine	no	61	0	-	-	0	-	-	0	-	-	5	2·8	1·3
tisagenlecleucel-t	Yes	180	0	-	-	0	-	-	1	0·9	-2·9	3	1·4	-0·7
tivantinib	no	19	0	-	-	0	-	-	0	-	-	0	-	-
tivozanib	no	88	0	-	-	0	-	-	0	-	-	1	0·7	-3·1
topotecan	Yes	5618	3	-0·8	-2·8	1	-1	-4·8	7	-0·3	-1·6	51	1	0·5
toremifene	Yes	258	2	1·7	-0·9	1	1·3	-2·5	4	2·3	0·6	8	2·3	1·2
tosedostat	no	4	0	-	-	0	-	-	0	-	-	0	-	-
tpiv 200	no	1	0	-	-	0	-	-	0	-	-	0	-	-
trabectedin	Yes	1809	2	0·1	-2·5	0	-	-	2	-0·4	-3	7	-0·2	-1·5
trametinib	Yes	7538	26	1·7	1·1	2	-0·6	-3·2	6	-0·9	-2·3	22	-0·7	-1·3
transmid	no	6	0	-	-	0	-	-	0	-	-	0	-	-
trastuzumab	Yes	27586	22	-0·3	-1	5	-1·2	-2·7	45	0	-0·4	116	-0·1	-0·4
trastuzumab duocarmazine	no	4	0	-	-	0	-	-	0	-	-	0	-	-
trastuzumab emtansine	Yes	3231	1	-1·3	-5·1	0	-	-	1	-1·9	-5·7	14	-0·1	-0·9
trebananib	no	61	0	-	-	0	-	-	0	-	-	1	0·9	-2·9
tremelimumab	no	177	0	-	-	0	-	-	0	-	-	2	0·9	-1·7
treosulfan	no	457	0	-	-	0	-	-	0	-	-	2	-0·1	-2·7
tretamine	no	3	0	-	-	0	-	-	0	-	-	0	-	-
tretinoin	Yes	5250	14	1·3	0·4	3	0·2	-1·8	8	-0·2	-1·3	19	-0·5	-1·2
triaziquone	no	1	0	-	-	0	-	-	0	-	-	0	-	-
triciribine	no	4	0	-	-	0	-	-	0	-	-	0	-	-
triptorelin	Yes	2148	5	1·1	-0·5	0	-	-	1	-1·4	-5·2	1	-2·8	-6·6
trofosfamide	no	61	0	-	-	0	-	-	0	-	-	0	-	-
troxacitabine	no	4	0	-	-	0	-	-	0	-	-	0	-	-
tucatinib	no	2	0	-	-	0	-	-	0	-	-	1	1·6	-2·2
ubenimex	no	40	0	-	-	0	-	-	0	-	-	0	-	-
ublituximab	no	14	0	-	-	0	-	-	0	-	-	0	-	-
ucn 01	no	3	0	-	-	0	-	-	0	-	-	0	-	-

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Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
ulocuplumab	no	2	0	-	-	0	-	-	0	-	-	1	1·6	-2·2
uprosertib	no	36	0	-	-	0	-	-	0	-	-	0	-	-
uramustine	no	21	0	-	-	0	-	-	0	-	-	1	1·3	-2·5
urelumab	no	13	0	-	-	0	-	-	0	-	-	1	1·4	-2·4
utomilumab	no	42	0	-	-	0	-	-	0	-	-	0	-	-
vadastuximab talirine	no	7	0	-	-	0	-	-	0	-	-	0	-	-
vadimezan	no	8	0	-	-	0	-	-	0	-	-	0	-	-
valrubicin	Yes	161	0	-	-	0	-	-	0	-	-	0	-	-
valspodar	no	10	0	-	-	0	-	-	0	-	-	0	-	-
vandetanib	Yes	971	97	6·1	5·8	10	3·5	2·5	10	2·4	1·3	6	0·4	-1
vantictumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
vanucizumab	no	4	0	-	-	0	-	-	0	-	-	0	-	-
varlilumab	no	10	0	-	-	0	-	-	0	-	-	0	-	-
varlitinib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
vatalanib	no	93	0	-	-	0	-	-	0	-	-	1	0·7	-3·1
veliparib	no	256	1	1	-2·8	0	-	-	1	0·7	-3·1	3	1·1	-1
vemurafenib	Yes	8322	106	3·6	3·3	3	-0·3	-2·3	7	-0·9	-2·1	8	-2·2	-3·4
venetoclax	Yes	3552	0	-	-	0	-	-	6	0·1	-1·3	14	-0·2	-1·1
vinblastine	Yes	4139	2	-0·9	-3·5	0	-	-	7	0·1	-1·2	33	0·8	0·2
vincristine	Yes	32745	17	-0·9	-1·7	8	-0·8	-2	65	0·3	0	341	1·2	1
vindesine	no	1086	1	-0·1	-3·9	1	0·6	-3·2	2	0·2	-2·4	2	-1·1	-3·7
vinflunine	no	477	0	-	-	0	-	-	0	-	-	0	-	-
vinorelbine	Yes	9935	4	-1·2	-2·9	0	-	-	8	-0·9	-2·1	81	0·8	0·5
vintafolide	no	13	0	-	-	0	-	-	0	-	-	0	-	-
vismodegib	Yes	4017	1	-1·6	-5·4	0	-	-	0	-	-	4	-2·1	-3·8
volasertib	no	7	0	-	-	0	-	-	0	-	-	0	-	-
volociximab	no	6	0	-	-	0	-	-	0	-	-	0	-	-
vorinostat	Yes	1378	23	3·7	3	6	2·5	1·2	7	1·5	0·2	24	1·8	1·2
vorozole	no	4	0	-	-	0	-	-	0	-	-	0	-	-
vosaroxin	no	8	0	-	-	0	-	-	0	-	-	0	-	-
voxtalisib	no	1	0	-	-	0	-	-	0	-	-	0	-	-
wnt-974	no	5	0	-	-	0	-	-	0	-	-	0	-	-
xentuzumab	no	4	0	-	-	0	-	-	0	-	-	0	-	-
zalutumumab	no	4	0	-	-	0	-	-	0	-	-	0	-	-
zanolimumab	no	1	0	-	-	0	-	-	0	-	-	0	-	-
zibotentan	no	33	0	-	-	0	-	-	0	-	-	0	-	-
zinostatin	no	1	0	-	-	0	-	-	0	-	-	0	-	-
zorubicin	no	5	0	-	-	0	-	-	0	-	-	0	-	-
zosuquidar	no	12	0	-	-	0	-	-	0	-	-	0	-	-

			diLQT (N_{effect} =18,123)			TdP (N_{effect} =8,163)			VA (N_{effect} =29,193)			SD (N_{effect} =85,350)		
Drug	FDA approved	N_{drug}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}	N_{obs}	IC	IC_{025}
10-hydroxycamptothecin	no	3	0	-	-	0	-	-	0	-	-	0	-	-
2-methoxyestradiol	no	1	0	-	-	0	-	-	0	-	-	0	-	-
3-aminopyridine-2-carboxaldehyde thiosemicarbazone	no	3	0	-	-	0	-	-	0	-	-	1	1·5	-2·3
6-methylmercaptopurine	no	1	0	-	-	0	-	-	0	-	-	0	-	-

Supplementary Table 4.

Drug	N_{obs}	single suspect culprit anticancer drug (SSCD) *	Age (years) Median [IQR]	Age (years) $N_{available}$	Male	Time to Onset (days) Median [IQR]	Time to Onset (days) $N_{available}$	Serious	Death*
aldesleukin	15	93%	53.5; [49-55]	12	62% (8/13)	4; [0-13]	7	100% (6/6)	13%
alectinib	5	100%	72; [63-76]	4	40% (2/5)	NA	0	80% (4/5)	0%
amsacrine	18	50%	63; [42-70]	16	35% (6/17)	1; [0-2]	9	89% (8/9)	17%
arsenic trioxide	132	77%	53.5; [37-70]	98	58 % (65/112)	12; [5-35]	33	89% (109/122)	6%
axicabtagene ciloleucel	4	100%	61.5; [51-64]	4	67% (2/3)	NA	0	100% (4/4)	25%
belinostat	3	67%	75	1	100% (1/1)	NA	0	100% (3/3)	33%
bicalutamide	30	93%	71; [69-76]	22	100% (29/29)	139; [3-486]	8	100 % (20/20)	10%
bosutinib	9	89%	67.5; [54-68]	6	71% (5/7)	6.5; [5-8]	2	100 % (9/9)	0%
capecitabine	161	95%	58; [48-66]	141	65% (98/151)	12; [7-64]	52	100% (134/134)	18%
carfilzomib	19	100%	67; [56-72]	18	72% (13/18)	78; [22-202]	4	79% (15/19)	26%
ceritinib	21	91%	57; [44-64]	16	32% (6/19)	13.5; [9-74]	4	62% (13/21)	10%
chidamide	7	100%	73; [64-116]	7	57 % (4/7)	0; [0-188]	6	71% (5/7)	0%
clofarabine	11	46% [a]	63.5; [38-64]	10	82% (9/11)	0; [0-0]	1	100% (11/11)	64%
cobimetinib	20	5%	58; [54-72]	13	45% (9/20)	28; [27-43]	5	90% (18/20)	5%
combretastatin a4	3	100%	73; [67-74]	3	0% (0/3)	NA	0	100% (3/3)	0%
crizotinib	102	95%	59; [48-68]	75	51% (46/90)	17; [9-78]	26	93% (93/100)	9%
cytarabine	134	22% [a]	55; [20-67]	95	60% (75/126)	11.5; [4-18]	26	98% (115/117)	40%
dabrafenib	27	11%	68.5; [60-73]	18	63% (17/27)	87; [29-162]	11	100% (26/26)	19%
dasatinib	94	85%	60; [46-67]	70	47% (37/78)	7; [4-34]	12	96% (87/91)	2%
daunorubicin	77	18% [a]	45; [18-66]	55	51% (37/73)	12; [10-22]	14	98% (62/63)	44%
decitabine	10	30%	70; [54-72]	6	50% (3/6)	NA	0	100% (10/10)	10%
enzastaurin	3	100%	NA	0	100 % (2/2)	5; [5-5]	1	100% (3/3)	100%
fluorouracil	138	95%	60; [53-69]	121	62% (85/137)	4; [2-30]	58	100% (95/95)	33%
gemtuzumab ozogamicin	16	38% [a]	67; [54-70]	9	50% (7/14)	12; [12-28]	3	93% (14/15)	50%
ibrutinib	99	96%	68; [60-74]	75	78% (72/92)	127; [67-286]	13	96% (92/96)	11%
idarubicin	27	15% [a]	47; [38-62]	23	81% (21/26)	15; [9-35]	9	95% (19/20)	44%
imatinib	64	74%	61; [46-72]	43	50% (27/54)	5; [0-14]	8	97% (57/59)	2%
interferon alfacon-1	5	100%	34	1	100% (4/4)	NA	0	100% (4/4)	20%
lenvatinib	11	100%	71.5; [64-78]	8	56% (5/9)	13; [13-13]	1	82% (9/11)	0%
letrozole	25	40% [b]	67; [57-74]	15	0% (0/22)	15; [14-52]	5	100% (17/17)	4%
midostaurin	34	56%	58.5; [49-66]	22	43% (12/28)	11; [6-24]	15	100% (33/33)	6%
mitoxantrone	36	53% [a]	58.5; [42-67]	28	48% (16/33)	92; [10-120]	9	100% (29/29)	33%
mogamulizumab	5	100%	65.5; [56-71]	4	100% (5/5)	0.5; [0-4]	4	100% (5/5)	100%
nelarabine	4	50% [a]	7.5; [6-8]	4	75% (3/4)	19	1	100% (4/4)	50%
nilotinib	397	93%	66; [54-74]	235	55% (188/342)	53; [13-214]	93	90% (343/383)	4%

osimertinib	37	100%	70; [62-75]	26	36% (12/33)	103; [72-306]	8	81% (30/37)	27%
panobinostat	24	96%	70.5; [59-73]	14	35% (6/17)	NA	0	88% (21/24)	8%
pazopanib	40	100%	65; [60-72]	32	55% (17/31)	34; [16-204]	10	100 % (39/39)	8%
pegaspargase	22	23% [a]	16 [10-20]	13	68% (15/22)	0	1	100% (22/22)	50%
ribociclib	105	80%	67; [57-73]	44	0% (0/84)	14; [13-40]	21	98% (92/94)	0%
romidepsin	13	100%	47.5; [44-51]	2	50% (2/4)	NA	0	100% (13/13)	15%
sunitinib	71	100%	66.5; [62-69]	24	70% (23/33)	31; [21-44]	6	99% (67/68)	4%
tamoxifen	28	100%	63.5; [50-78]	24	15% (4/27)	90; [16-158]	7	90% (19/21)	0%
toremifene	4	75%	73; [69-76]	4	0% (0/4)	NA	0	100% (3/3)	0%
trametinib	26	12% [c]	68; [60-73]	19	62% (16/26)	71; [28-186]	10	100% (25/25)	19%
tretinoin	14	29% [d]	51; [34-55]	12	70% (7/10)	21; [14-28]	2	92% (12/13)	7%
vandetanib	98	99%	60; [46-69]	74	58% (53/91)	29; [15-74]	22	91% (86/95)	6%
vemurafenib	106	76%	67; [60-74]	75	56% (56/100)	35; [27-154]	31	89% (93/105)	10%
vorinostat	24	83%	49.5; [49-66]	16	39% (7/18)	65	1	92 % (22/24)	12%

NA, not applicable; N_{obs}: number of reports observed for diLQT, TdP and/or VA with the drug of interest

* In this analysis, the denominator is the total number of reports (N_{obs} of diLQT, TdP and/or VA) associated significantly ($IC_{025}>0$, **Table-1**) with the drug of interest

[a] number (proportion) of reports associated with (other) antimetabolites and/or (other) anthracyclines co-suspected: clofarabine 5/11 (45%); cytarabine 84/134 (63%); daunorubicin 59/77 (77%); gemtuzumab ozogamicin 7/16 (44%); idarubicin 14/27 (52%); mitoxantrone 15/36 (42%); nelarabine 1/4 (25%); pegaspargase 17/22 (77%)

[b] number (proportion) of ribociclib coreporting in letrozole cases: 15/25 (60%)

[c] number (proportion) of dabrafenib coreporting in trametinib cases: 23/26 (88%)

[d] number (proportion) of arsenic trioxide coreporting in tretinoin cases: 9/14 (64%)