Risk Factors of QTc Prolongation in Women With Hormone Receptor–positive/Human Epidermal Growth Factor Receptor 2–negative Metastatic Breast Cancer: A Retrospective Analysis of Health Care Claims Data

Melea Ward, PhD, PharmD*; James Harnett, PharmD, MS;
Timothy J. Bell, MHA; and Jack Mardekian, PhD

Pfizer Inc, New York, NY, USA

ABSTRACT

Purpose: In addition to biomarker status, treatment selection for metastatic breast cancer (mBC) includes individual patient and clinical characteristics such as tumor burden, timing of disease recurrence, and comorbidities. Women with mBC may take medications that can increase the risk of drug-induced toxicities, including prolongation of cardiac repolarization (prolongation of QT interval). Corrected QT (QTc) prolongation, a toxicity associated with many cancer treatments, can lead to potentially life-threatening ventricular arrhythmias. As such, it is important to identify patients at risk for QTc prolongation due to comorbid conditions, concomitant medications, or electrolyte abnormalities. This real-world study estimated the proportion of women with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) mBC who may be at risk of developing QTc prolongation. Results in the elderly are also included.

Methods: This retrospective, cross-sectional cohort study used the Truven Health MarketScan and Optum Clinformatics administrative claims databases. Patients' medical and pharmacy data were evaluated to assess the risk of QTc prolongation. Prescription and medication administration claims were evaluated during the 7-day period before the index date (ie, first secondary neoplasm diagnosis). In addition, *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification*, codes were evaluated 12 months before the index date to describe congenital long QT syndrome, cardiac disease, and electrolyte abnormalities.

Findings: A cohort of 24,340 women with HR+/HER2– mBC were identified, including 5059 women aged 65−74 years and 4851 aged ≥75 years. Based on an overall analysis of risk factors (congenital long QT syndrome, cardiovascular disease, electrolyte abnormalities, or concomitant medications), 29.5% of all patients, 33.2% of patients aged 65−74 years, and 40.5% of patients aged ≥75 years had risk factors for QTc prolongation.

Implications: This analysis of real-world data indicates that almost 1 in 3 women with HR+/HER2– mBC had congenital long QT syndrome, cardiovascular disease, and/or electrolyte abnormalities or received a concomitant medication that could increase the risk of developing QTc prolongation. The risk factors for congenital long QT syndrome, cardiovascular disease, or electrolyte abnormalities were more common in older patients. This analysis emphasizes the importance of individualized benefit/risk assessment during treatment decisions, especially when considering drugs with known or possible QTc prolongation risk. (*Clin Ther*. 2019;41:494−504) © 2019 Pfizer Inc. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key Words: HR+/HER2–, metastatic breast cancer, QTc prolongation, real-world data.

* Currently employed at Humana.

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INTRODUCTION

Metastatic breast cancer (mBC) remains an incurable disease with substantial clinical and humanistic burden.[1–4] The 5-year survival rate for mBC is 27%,[5] and patients remain on treatment until therapeutic options are exhausted or until patients begin supportive care. An improved understanding of the heterogeneous nature of mBC and the corresponding emergence of new treatment options have led to a treatment paradigm that enables an individualized therapeutic approach with primary treatment goals to prolong survival, delay disease progression, and maintain or improve quality of life.[1,4]

The molecular subtype of breast cancer plays a pivotal role in the individualized treatment approach.[6] Hormone receptor–positive (HR+) breast cancer is the largest therapeutic subtype and represents the majority of all breast malignancies.[7] Endocrine-based therapy is the recommended first-line therapy for patients with HR+ disease in the absence of visceral crisis, whereas different targeted therapies are licensed and recommended based on human epidermal growth factor receptor 2 (HER2) status.[1,8] For example, cyclin-dependent kinases 4/6 (CDK4/6) inhibitors, one of the newest targeted therapy drug classes that have been rapidly adopted, were developed and subsequently approved for use in combination with endocrine therapy for HR+/HER2-negative (HER2–) mBC.[1,8] Studies have shown that the addition of CDK4/6 inhibitors to endocrine therapy significantly delays disease progression compared with endocrine therapy alone.[9–14]

An assessment of the risk/benefit profile of medications is important when making treatment decisions. The potential benefits of any cancer therapy should be carefully weighed against any potential treatment-related toxicities, the risk of which may be increased by the presence of specific comorbidities or concomitant drug administration.[4,15] The choice of therapy is also influenced by individual patient and clinical characteristics. It is well recognized that, compared with patients who have earlier stage breast cancers, women with mBC are more likely to have a higher comorbidity burden or multiple chronic conditions beyond mBC.[16] This scenario may necessitate additional medications, placing these patients at higher risk of adverse drug reactions.

Corrected QT (QTc) prolongation is a potentially life-threatening toxicity associated with some cancer therapies that increases the risk of cardiac arrhythmias (eg, torsades de pointes [TdP]) and sudden cardiac death.[17–19] Owing to the severity of the possible outcomes of QTc prolongation, regulatory requirements mandate evaluation of the risk of QT/QTc prolongation and the proarrhythmic potential of new drugs.[20] Patients with mBC may present with risk factors for QTc prolongation, such as older age, female sex, underlying cardiovascular disease, ECG abnormalities, electrolyte imbalances, and concomitant use of QTc-prolonging medications.[17,21] There are limited data on the proportion of patients at risk for QTc prolongation.

The present study used administrative claims data to characterize the real-world baseline demographic and clinical characteristics of women with HR+/HER2− mBC and to estimate the proportion at risk of developing QTc prolongation. The percentages of older patients at risk of developing QTc prolongation were also assessed.

MATERIALS AND METHODS

Study Design and Data Sources

This study was a retrospective, cross-sectional cohort analysis of women with HR+/HER2– mBC. Data were sourced from 2 large administrative claims databases covering all US census regions: the Truven Health MarketScan Research Database (King of Prussia, Pennsylvania), which includes commercial and Medicare Supplemental claims data, and the Optum Clinformatics Data Mart (Eden Prairie, Minnesota), which includes commercial and Medicare Advantage claims data. Data from January 2012 to October 2017 and May 2005 to September 2017 were obtained from the Truven MarketScan and Optum Clinformatics databases, respectively. Both databases include health care plan enrollment history and paid claims for medical (provider and institutional) services and pharmacy dispensings. Data are de-identified and were used in compliance with the requirements of the Health Insurance Portability and Accountability Act. The study was conducted with scientific purpose, value, and rigor in accordance with legal and regulatory requirements as set forth in the Good Pharmacoepidemiology Practice Guidelines, and it complied with other research standards for ethical conduct.

Patient Selection

Patients were eligible for inclusion if they were women aged ≥18 years at the index date (ie, initial date of secondary neoplasm diagnosis) who had been diagnosed with mBC, were HR+/HER2–, and were continuously enrolled in the database for a minimum of 12 months before the index date. The criteria for mBC diagnosis were as follows: (1) a diagnosis of breast cancer on 2 medical service claims, each claim ≥30 days apart, for primary breast cancer; and (2) ≥2 medical claims for a secondary neoplasm on separate days, with the first diagnosis of a secondary neoplasm ≤30 days before or any time after the first diagnosis of breast cancer.[22] The type of mBC was defined as follows: de novo mBC for those with ≥360 days of continuous enrollment before the first breast cancer diagnosis and first secondary neoplasm date diagnosed within 89 days of breast cancer diagnosis; recurrent mBC for those with a secondary neoplasm diagnosed ≥90 days after the first breast cancer diagnosis date; and unknown mBC for all remaining patients. Patients were considered HR+ if they had ≥1 prescription or medication administration claim for endocrine therapy. Patients were excluded if they received treatment indicated for HER2+ breast cancer (including trastuzumab, lapatinib, pertuzumab, and ado-trastuzumab) at any time in the data period.

Baseline Demographic and Clinical Characteristics

Demographic characteristics were analyzed at the index date. Baseline clinical characteristics, including type of mBC, type of breast cancer treatments received before the index date, and comorbidity risk, were evaluated during the baseline period (ie, the 12-month period before the index date, which is a standard time period used in claims analyses to capture comorbidities[23]). Sites of metastases were assessed during the follow-up period (see Supplemental Table I in the online version at doi: 10.1016/j.clinthera.2019.01.012). Three comorbidity indices were used to determine the underlying mortality risk and morbidity of identified patients at baseline. The Rx-Risk-V score is based on pharmacy claims covering 45 conditions and has been shown to be predictive of mortality and cost of care.[24–27] The Deyo-Charlson Comorbidity Index (D-CCI) is derived from the sum of weighted scores based on the presence of 17 medical conditions in medical claims data via *International Classification of Diseases, Ninth Revision, Clinical Modification,* codes and is used to predict long-term mortality.[28] The Quan-Charlson Comorbidity Index (Q-CCI) score estimates comorbidity burden using ICD-9 and ICD-10 coding.[29] All risk assessments excluded the malignancies category.

Concomitant Medications and Medical Conditions Associated With QTc Prolongation Risk

For assessment of concomitant medications associated with increased QTc prolongation risk, prescription and medication administration claims were evaluated in the 7-day period before the index date using a list of medications from www.crediblemeds.org with a known, possible, or conditional risk for TdP or medications to be avoided by patients with congenital long QT syndrome.[30] A 7-day period was selected because it is proximal to the index date and represents an indicator of when a patient would initiate treatment. ICD-9/10-CM codes were used in the 12-month period before the index date to describe the presence of congenital long QT syndrome, cardiovascular disease (see Supplemental Table II in the online version at doi: 10.1016/j.clinthera.2019.01.012), and electrolyte abnormalities (see Supplemental Table III in the online version at doi: 10.1016/j.clinthera.2019.01.012).

Overall QTc Prolongation Risk

An analysis of overall QTc prolongation risk was performed based on patients who had congenital long QT syndrome, cardiovascular disease, or electrolyte abnormalities or received a concomitant medication that could increase the risk of developing QTc prolongation.

Data Analysis

Descriptive statistics, including mean (SD), median, and frequency, are presented for baseline demographic and clinical characteristics when applicable. Frequencies are also presented for QTc prolongation risk factors. Data for patients at risk of QTc prolongation are described for the whole cohort and according to age strata (<65, 65–74, and ≥75 years). Data analyses were performed by using SAS software packages (SAS Institute, Inc, Cary, North Carolina).

Table I. Baseline demographic and clinical characteristics of women with hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer (mBC). Values are given as no. (%) unless otherwise indicated.

Characteristic	Overall (N = 24,340)	Aged ≥65 y (n = 9910)
Age, y		
Mean (SD)	62.1 (13.2)	75.2 (6.9)
Median (IQR)	61.0 (20.0)	74.0 (11.0)
Age by category		
18–54 y	7260 (29.8)	NA
55–64 y	7170 (29.5)	NA
65–74 y	5059 (20.8)	5059 (51.1)
≥75 y	4851 (19.9)	4851 (49.0)
Region		
South	9237 (38.0)	3246 (32.8)
Midwest	6126 (25.2)	2749 (27.7)
Northeast	3405 (14.0)	1322 (13.3)
West	4643 (19.1)	2048 (20.7)
Unknown	929 (3.8)	545 (5.5)
Insurance type		
Commercial	14,119 (58.0)	549 (5.5)
Medicare	10,221 (42.0)	9361 (94.5)
Type of mBC		
De novo	12,551 (51.6)	4251 (42.9)
Recurrent	11,384 (46.8)	5536 (55.9)
Unknown	405 (1.7)	123 (1.2)
Systemic treatments received in year before mBC diagnosis		
Endocrine therapy	6780 (27.9)	3351 (33.8)
Chemotherapy	1725 (7.1)	580 (5.9)
None*	15,835 (65.1)	5979 (60.3)
No. of metastatic sites during follow-up		
Mean (SD)	1.6 (1.0)	1.6 (1.0)
0–1	16,121 (66.2)	6123 (61.8)
>1	8219 (33.8)	3787 (38.2)
Secondary visceral neoplasm†	6480 (26.6)	3221 (32.5)
Lung	3902 (16.0)	2011 (20.3)
Liver	3813 (15.7)	1668 (16.8)
Pleura	1167 (4.8)	558 (5.6)
Secondary nonvisceral neoplasm†	22,307 (91.7)	8682 (87.6)
Lymph nodes	16,765 (68.9)	5644 (57.0)
Bone and bone marrow	8942 (36.7)	4305 (43.4)
Skin	1217 (5.0)	630 (6.4)
Ovary	303 (1.2)	91 (0.9)

(*continued on next page*)

Table I. (*Continued*)

Characteristic	Overall (N = 24,340)	Aged ≥65 y (n = 9910)
Secondary CNS neoplasm	2097 (8.6)	875 (8.8)
Comorbidity indices[‡]		
Rx-Risk-V score		
0–2	8178 (33.6)	2097 (21.2)
>2	16,162 (66.4)	7813 (78.8)
Deyo-Charlson Comorbidity Index score		
0–1	21,003 (86.3)	7491 (75.6)
>1	3337 (13.7)	2419 (24.4)
Quan-Charlson Comorbidity Index score		
0–1	18,902 (77.7)	6037 (60.9)
>1	5438 (22.3)	3873 (39.1)

CNS = central nervous system; IQR = interquartile range; NA = not applicable.
[*] Neither endocrine nor chemotherapy.
[†] Some patients had ≥1 secondary neoplasm.
[‡] Assessed during baseline period; excludes malignancies category.

RESULTS

Study Population

A total of 24,340 eligible patients were identified from the Truven MarketScan (n = 15,296) and Optum Clinformatics (n = 9044) databases for inclusion in this analysis. Baseline demographic and clinical characteristics are summarized in Table I. At the index date, the overall mean (SD) age was 62.1 (13.2) years. Approximately 40% of patients (n = 9910) were ≥65 years of age; 5059 (20.8%) were aged 65–74 years, and 4851 (19.9%) were aged ≥75 years. Slightly more than one half of the patients had a diagnosis of de novo mBC; for the remainder, mBC was recurrent or the status was unknown. In accordance with the high proportion of patients with de novo mBC, 65.1% of patients had not received previous systemic treatment. The majority of patients (66.2%) had ≤1 metastatic site during follow-up; 26.6% of patients had visceral disease (see Supplemental Table I in the online version at doi: 10.1016/j.clinthera.2019.01.012) and 91.6% had nonvisceral disease, most commonly of the lymph nodes (68.9%) and/or bone and bone marrow (36.7%). The mean duration of follow-up was 624.5 days in the overall population, 652.8 days in patients aged <65 years, and 583.2 days in patients aged ≥65 years.

Analysis indicated a relatively low comorbidity burden, with 86.3% and 77.7% of all patients and 75.6% and 60.9% of patients aged ≥65 years having a score of 0–1 for the D-CCI and Q-CCI assessments, respectively. The Rx-Risk-V score indicated a higher burden, with 66.4% of all patients and 78.8% of patients aged ≥65 years having a score >2.

Overall QTc Prolongation Risk

Analyses showed that 29.5% of the total cohort and 33.2% of patients aged 65–74 years and 40.5% of patients aged ≥75 years had congenital long QT syndrome, cardiovascular disease, and/or electrolyte abnormalities or received a concomitant medication that could increase the risk of developing QTc prolongation.

Medication Risk Factors for QTc Prolongation

Based on the www.crediblemeds.org risk categories, 4.8% of all patients had ≥1 prescription or administration claim for a medication with a known risk of TdP; the incidences were similar among patients aged 65–74 years (4.4%) and ≥75 years (4.1%) (Table II). The most common medications identified with a known risk of TdP were antibiotic, antiemetic, and selective serotonin reuptake inhibitor antidepressant drug classes. Among all patients, 8.1% received medications with a possible risk of TdP, with lower incidences in patients aged 65–74 years (7.4%) and ≥75 years (6.0%). Analgesics,

Table II. Women with hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer medication risk factors associated with increased risk of developing QTc prolongation.* Values are given as no. (%).

Risk factor	Overall (N = 24,340)	Age, y <65 (n = 14,430)	Age, y 65–74 (n = 5059)	Age, y ≥75 (n = 4851)
Medications with known risk of TdP†	1166 (4.8)	746 (5.2)	221 (4.4)	199 (4.1)
Antibiotics	488 (2.0)	317 (2.2)	91 (1.8)	80 (1.7)
Antiemetics	378 (1.6)	275 (1.9)	62 (1.2)	41 (0.9)
SSRI antidepressants	208 (0.9)	124 (0.9)	44 (0.9)	40 (0.8)
Medications with possible risk of TdP†	1980 (8.1)	1315 (9.1)	372 (7.4)	293 (6.0)
Analgesics	1341 (5.5)	861 (6.0)	269 (5.3)	211 (4.4)
Anticancer medications	211 (0.9)	167 (1.2)	24 (0.5)	20 (0.4)
Antipsychotics/antiemetics	162 (0.7)	135 (0.9)	12 (0.2)	15 (0.3)
Medications with conditional risk of TdP†	1656 (6.8)	861 (6.0)	414 (8.2)	381 (7.9)
Diuretics	678 (2.8)	302 (2.1)	185 (3.7)	191 (3.9)
Proton pump inhibitors	444 (1.8)	224 (1.6)	110 (2.2)	110 (2.3)
SSRI antidepressants	231 (0.9)	155 (1.1)	43 (0.9)	33 (0.7)
Medications to avoid in patients with congenital long QT syndrome	3 (0.01)	2 (0.01)	1 (0.02)	0
Antibiotics	2 (0.01)	1 (0.01)	1 (0.02)	0
Vasoconstrictors	1 (<0.01)	1 (0.01)	0	0
Any medication that could increase the risk of developing QTc prolongation	4154 (17.1)	2509 (17.4)	884 (17.5)	761 (15.7)
Overall QTc prolongation risk‡	7174 (29.5)	3528 (24.4)	1681 (33.2)	1965 (40.5)

SSRI = selective serotonin reuptake inhibitor; TdP = torsades de pointes.
* The medication classes listed are the most commonly filled or administered medications for each risk factor.
† Includes medications to avoid in patients with congenital long QT syndrome.
‡ Based on patients who had congenital long QT syndrome, cardiovascular disease, and/or electrolyte abnormalities or received a concomitant medication that could increase the risk of developing QTc prolongation.

anticancer medications, and antipsychotic/antiemetic agents were the most commonly prescribed medications with a possible risk of TdP. A total of 6.8% of patients in the overall cohort, 8.2% of patients aged 65–74 years, and 7.9% of patients aged ≥75 years received medications with a conditional risk of TdP; the most common medications were diuretics, proton pump inhibitors, and selective serotonin reuptake inhibitor antidepressants. Among the 30 patients with congenital long QT syndrome, 3 (10%) received medications to avoid in patients with congenital long QT syndrome, with 1 patient (20%) aged 65–74 years and none aged ≥75 years. Overall, 17.1% of all patients, 17.5% of patients aged 65–74 years, and 15.7% of patients aged ≥75 years received a concomitant medication that could increase the risk of developing QTc prolongation.

Prevalence of Congenital Long QT Syndrome, Cardiovascular Disease, and Electrolyte Abnormalities

At baseline, 15.6% of patients in the overall cohort, 20.3% of patients aged 65–74 years, and 30.3% of patients aged ≥75 years had congenital long QT syndrome, cardiovascular disease, and/or electrolyte abnormalities (Table III). Prevalence of cardiovascular disease and electrolyte abnormalities

Table III. Baseline congenital long QT syndrome, cardiovascular disease, and electrolyte abnormalities among women with hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer. Values are given as no. (%).

Risk factor	Overall (N = 24,340)	Age, y <65 (n = 14,430)	Age, y 65–74 (n = 5059)	Age, y ≥75 (n = 4851)
Congenital risk factor				
Congenital long QT syndrome	30 (0.1)	19 (0.1)	5 (0.1)	6 (0.1)
Cardiovascular disease	2667 (11.0)	810 (5.6)	716 (14.2)	1141 (23.5)
Congestive heart failure	1443 (5.9)	346 (2.4)	392 (7.8)	705 (14.5)
Bradyarrhythmias	1165 (4.8)	413 (2.9)	292 (5.8)	460 (9.5)
Myocardial infarction	469 (1.9)	114 (0.8)	144 (2.9)	211 (4.4)
Unstable angina	220 (0.9)	59 (0.4)	75 (1.5)	86 (1.8)
Electrolyte abnormalities	1587 (6.5)	603 (4.2)	445 (8.8)	539 (11.1)
Hypokalemia	838 (3.4)	337 (2.3)	229 (4.5)	272 (5.6)
Hypercalcemia	388 (1.6)	138 (1.0)	119 (2.4)	131 (2.7)
Disorders of magnesium metabolism	273 (1.1)	104 (0.7)	78 (1.5)	91 (1.9)
Hyperkalemia	266 (1.1)	68 (0.5)	86 (1.7)	112 (2.3)
Hypocalcemia	90 (0.4)	40 (0.3)	27 (0.5)	23 (0.5)
Disorders of phosphorus metabolism	60 (0.3)	28 (0.2)	14 (0.3)	18 (0.4)
Congenital long QT syndrome, cardiovascular disease or electrolyte abnormality	3808 (15.6)	1313 (9.1)	1026 (20.3)	1469 (30.3)
Overall QTc prolongation risk*	7174 (29.5)	3528 (24.4)	1681 (33.2)	1965 (40.5)

* Based on patients who had congenital long QT syndrome, cardiovascular disease, and/or electrolyte abnormalities or received a concomitant medication that could increase the risk of developing QTc prolongation.

tended to increase with age, with the exception of hypocalcemia. The most common cardiovascular disease and electrolyte abnormality risk factors overall were congestive heart failure (5.9%), bradyarrhythmias (4.8%), and hypokalemia (3.4%), which were more common among older patients.

DISCUSSION

As a risk factor for TdP and sudden cardiac death, QTc prolongation is a toxicity of significant concern. Risk of QTc prolongation is also an important part of the assessment of the risk/benefit profile of medications when making treatment decisions. The importance of identifying risk factors to minimize and manage drug-induced QTc prolongation in vulnerable patient groups is well established.[31,32] This cross-sectional, retrospective study characterized the real-world baseline characteristics and prevalence of QTc prolongation risk factors in a cohort of 24,340 women with HR+/HER2– mBC by using descriptive analyses. Comorbidity indices suggested that comorbidity burden was relatively low, especially with most patients scoring 0 or 1 on the D-CCI or Q-CCI, whereas the Rx-Risk-V score indicated a higher level of burden. These findings were expected because the Rx-Risk-V score covers more comorbidities than the D-CCI or Q-CCI,[25,26,28,29] and patients with mBC are more likely to have multiple comorbidities than patients with earlier stage breast cancer.[16] These results could also be explained by undercoding for diagnoses of comorbidities of interest.

In this real-world cohort, almost 1 in 3 women with HR+/HER2– mBC had congenital long QT syndrome, cardiovascular disease, and/or electrolyte abnormalities or received a concomitant medication that could increase the overall risk of developing QTc prolongation. This overall risk result was driven mostly by the percentage of women with medications that could increase the risk of developing QTc prolongation (17.1%) and the percentage of women with cardiovascular disease (11.0%). When only considering congenital long QT syndrome, cardiovascular disease, and electrolyte abnormalities (ie, not including concomitant medications), the proportion of patients at risk of QTc prolongation was almost 1 in 6 patients (15.6%). Older age is a known risk factor for QTc prolongation.[17] Compared with younger patients, fewer older patients had prescription or administration claims for medications with a known or possible risk of QTc prolongation that are often used to manage comorbidities of cancer and treatment-related side effects (eg, antiemetic and analgesic agents). However, older patients were more likely to receive medications with conditional risk of QTc prolongation. In addition, older patients were much more likely to have congenital long QT syndrome, cardiovascular disease, or electrolyte abnormalities, with about 1 in 5 of those 65−74 years old and almost 1 in 3 of those ≥75 years old having such risk factors. These data illustrate that risk for QTc prolongation in older patients is driven by the presence of age-related comorbidities.

Limited literature exist regarding the proportion of patients with cancer at risk for QTc prolongation. Findings from a previous small study of 363 patients with solid malignancies showed that 9.4% of patients used a concomitant medication associated with QTc prolongation and 10.2% had a history of a relevant cardiovascular disease.[33] However, that study was limited to patients who received tyrosine kinase inhibitors. In a cross-sectional retrospective study of 555 patients with cancer, 92.6% of patients received QTc-prolonging drugs, mostly commonly antiemetic agents, proton pump inhibitors, and antimicrobial agents, and 21.8% received medications involved in QTc-prolonging drug−drug interactions.[34] Furthermore, a systematic review of patients receiving conventional cancer treatment reported a QTc prolongation incidence of between 0% and 22%.[35] The present study included a large number of patients with HR+/HER2– mBC (24,340 women) and assessed several risk factors for QTc prolongation, including concomitant medication use, cardiovascular disease, electrolyte abnormalities, and congenital long QT syndrome.

Our data show the high prevalence of risk for QTc prolongation and highlight the importance of understanding this risk when considering therapeutic options in patients with mBC. Based on www.crediblemeds.org, tamoxifen, capecitabine, fluorouracil, and ribociclib are treatment options for mBC that have a possible risk for TdP.[19] It is therefore especially important to evaluate the individual patient's risk for QTc prolongation and the benefits of treatment based on comorbidities and concomitant medications when considering these treatment options. Notably, the prescribing information for ribociclib, a CDK4/6 inhibitor used in combination with endocrine therapy for treatment of women with HR+/HER2– mBC, states that the drug should be avoided with medications known to cause QTc prolongation and in patients who already have or who are at increased risk of developing QTc prolongation, including patients with long QT syndrome, uncontrolled or significant cardiac disease, or electrolyte abnormalities.[36] Although the prescribing information for tamoxifen,[37] capecitabine,[38] and fluorouracil[39] do not include a specific warning about QTc prolongation, previous studies have reported an increased risk of QTc prolongation associated with these medications in patients with cancer.[40,41]

The present analysis has several limitations. First, molecular profiling data were not available in the databases, and identification of patients with HR+/HER2– mBC was therefore based on targeted treatment history only. In addition, the source of the data is primarily from US health plans for commercial and Medicare-insured patients; thus, the results may not be generalizable to populations outside of the covered populations such as Medicaid beneficiaries. Because 2 databases were used, there is the chance that some patients may have been counted twice if they were registered in both databases. However, the benefit of a large cohort size and the increased generalizability of the data afforded by using 2 databases were considered to outweigh the potential risk of double counting. Moreover, this analysis determined the prevalence of QTc prolongation risk factors in patients with HR+/HER2– mBC based on medical and pharmacy claims. Medical claims are subject to challenges with inaccurate coding or the absence of information on comorbidities not submitted for billing purposes.

Pharmacy claims represent the prescriptions the patient has filled that are reimbursed by a health plan; thus, medications paid for solely by patients, such as over-the-counter medications (eg, some analgesics) or medical samples received, may not be captured. In addition, the periods used for capturing risk factors may underestimate risk because this analysis only assessed the 7 days before the index date for medications of interest and 12 months' preindex for diagnoses. Use of the postindex period would more comprehensively capture risk factors, especially during treatment of mBC. The use of multiple medications that cause QTc prolongation has an additive effect, further increasing the risk of QTc prolongation and TdP.[42] An area for future investigation would include an analysis stratified by number of risk factors. Finally, this analysis did not assess the incidence of QTc prolongation due to specific treatments in patients with HR+/HER2– mBC, a topic that warrants future research.

CONCLUSIONS

Safety is a major concern for women with HR+/HER2– mBC, particularly given the possible polypharmacy requirements and the potential for prolonged treatment, and it becomes an even more critical factor for currently evolving combination therapies. These real-world data show that a large proportion of patients with HR+/HER2– mBC, specifically older women, have risk factors for QTc prolongation. Knowledge of the real-world propensity for QTc prolongation and common risk factors in women with HR+/HER2– mBC are of significant interest when assessing the benefit/risk profile of treatment options. Assessing QTc prolongation risk when making treatment choices as part of individualized care for women with mBC is becoming even more critical with the increase in treatment options.

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All the authors participated in the study design and interpretation of data, wrote and/or revised the manuscript for intellectual content, and approved the final draft for submission.

CONFLICTS OF INTEREST

Dr. Harnett, Mr. Bell, and Dr. Mardekian are employees of and own stock in Pfizer Inc. Dr. Ward was a Pfizer Inc employee at the time of study design and analysis. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Pfizer Inc was involved in the study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

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Address correspondence to: Timothy J. Bell, MHA, Pfizer Inc, Health Economics and Outcomes Research, 235 E. 42nd St, New York, NY 10017, USA. E-mail: timothy.j.bell@pfizer.com

APPENDIX A. SUPPLEMENTARY DATA

Supplemental Table I. List of *ICD-9/10-CM* Codes for Sites of Metastases

Sites of Metastases	*ICD-9-CM*	*ICD-10-CM*
Visceral		
Secondary malignant neoplasm of lung	197.0	C78.00
Secondary neoplasm of pleura	197.2	C78.2
Secondary malignant neoplasm of liver	197.7	C78.72
Nonvisceral		
Secondary neoplasm of ovary	198.6	C79.60
Secondary and unspecified malignant neoplasm of lymph nodes	196.x	C70.70-C70.79
Secondary neoplasm of skin	198.2	C79.2
Secondary malignant neoplasm of the bone and bone marrow	198.5	C79.51; C79.52
Central nervous system		
Secondary malignant neoplasm of brain and spinal cord	198.3	C79.31

ICD-9/10-CM=International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification.

Supplemental Table II. List of *ICD-9/10-CM* Codes for Cardiovascular Disease

Description	*ICD-9-CM*	*ICD-10-CM*
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x	I09.81, I42.5, I42.8, I42.6, I43, I42.7, I50.x, I11.0, I13.x
Myocardial infarction	410.x (Acute myocardial infarction) 412.x (Old myocardial infarction)	I21.x, I22.x, I25.2
Unstable angina	411.1	I20.x
Bradyarrhythmias	427.81 (Sinoatrial node dysfunction) 427.89 (Sinus bradycardia NOS) 426.0-426.1x (Atrioventricular block)	I49.5, I49.8, R00.1, I44.0-I44.3

ICD-9/10-CM=International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification.

Supplemental Table III. List of *ICD-9/10-CM* Codes for Electrolyte Abnormalities

Description	*ICD-9-CM*	*ICD-10-CM*
Hypocalcemia	275.41	E83.51
Hypercalcemia	275.42	E83.52
Disorders of magnesium metabolism	275.2	E83.40, E83.41, E83.42, E83.49
Hypokalemia	276.8	E87.6
Hyperkalemia	276.7	E87.5
Disorders of phosphorus metabolism	275.3	E83.30, E83.31, E83.32, E83.39

ICD-9/10-CM=International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification.