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Treatment Patterns, Safety, and Patient Reported Outcomes among Adult Women with Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer with or without, or with Unknown, *BRCA1/2* Mutation(s): Results of a Real-World Study from the United States, United Kingdom, and four EU Countries

Michael Patrick Lux[a, b, c] Katie Lewis[d] Alex Rider[d] Alexander Niyazov[e]

[a]Kooperatives Brustzentrum Paderborn, Paderborn, Germany; [b]Department of Gynecology and Obstetrics, Frauenklinik St. Louise, Paderborn, Germany; [c]Frauenklinik St. Josefs-Krankenhaus, Salzkotten, Germany; [d]Adelphi Real World, Oncology Franchise, Cheshire, UK; [e]Department of Patient and Health Impact, Pfizer Inc, New York, NY, USA

Keywords

Breast cancer susceptibility gene 1 or 2 status · Human epidermal growth factor receptor 2-negative breast cancer · Poly (ADP-ribose) polymerase-inhibitor · Patient-reported outcomes · Real-world evidence

Abstract

Introduction: This real-world study assessed the breast cancer susceptibility gene 1 or 2 mutation (*BRCA1/2*mut) status on treatment patterns, safety, and patient-reported outcomes (PROs) in women with human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) in the USA, the UK, and EU4 countries. ***Methods:*** Oncologists abstracted data from medical charts of adult women who presented with HER2– ABC from February to May 2015 and from March to July 2017. Data were collected using a physician-reported form and a patient-reported form, which included questions on breast cancer history/treatment and questions from PRO instruments (EuroQol 5-Dimensions 3-Levels [EQ-5D-3L], Brief Pain Inventory [BPI], European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 and its breast cancer module). ***Results:*** In total, 742 oncologists provided data for 6,161 patients; 27.5% were tested for *BRCA1/2*mut. Out of the total patient population, 3.8% had *BRCA1/2*mut, 16.6% *BRCA1/2* wild-type (*BRCA1/2*wt), and 79.5% were *BRCA1/2* unknown (*BRCA1/2*unk). Hormone receptor-positive (HR+)/HER2– ABC was more frequent within the *BRCA1/2*wt versus *BRCA1/2*mut group and triple-negative breast cancer (TNBC) within the *BRCA1/2*mut versus *BRCA1/2*wt group. More patients with HR+/HER2– ABC with *BRCA1/2*mut received chemotherapy (with or without targeted or endocrine therapy) versus *BRCA1/2*wt (66.0% vs. 50.4%; $p < 0.01$); more patients had ≥1 AE (58.0% vs. 39.1%; $p < 0.001$). Among patients with *BRCA1/2*mut versus *BRCA1/2*wt, a significantly higher proportion had some problems or worse pain discomfort ($p = 0.021$) and anxiety/depression ($p = 0.007$) as measured by the EQ-5D-3L; role functioning ($p < 0.01$) and dyspnea ($p < 0.05$) measured by EORTC were worse with *BRCA1/2*mut. Pain scores by BPI were similar between groups. ***Conclusions:*** In patients with HER2– ABC in the real-world setting, more patients with *BRCA1/2*mut had TNBC; received chemotherapy; had >1 AE; and experienced increased discomfort, anxiety, and dyspnea and diminished role functioning versus patients with *BRCA1/2*wt.

Karger@karger.com
www.karger.com/brc

Correspondence to:
Michael Patrick Lux, m.lux@vincenz.de

Introduction

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths in women [1, 2]. In 2018, there were more than 2 million new cases of breast cancer worldwide, with more than 600,000 deaths [1]. Although considerable progress in the treatment of breast cancer has been made, advanced breast cancer (ABC) is not currently curable, and the goal of treatment is to prolong survival while optimizing health-related quality of life (HRQoL) [3, 4].

Breast cancer can be classified as hormone (estrogen and progesterone) receptor-positive (HR+) or negative and human epidermal growth factor receptor 2-positive or negative (HER2–). When none of these receptors are overexpressed, patients are classified as having triple-negative breast cancer (TNBC) [5]. Of the different breast cancer classifications, HER2– breast cancer is the most common subtype, comprising 66%–78% of new cases in the USA (2013–2017), the UK, and across France, Germany, Italy, and Spain (the EU4 countries; 2012) [6, 7].

Among all female breast cancers, 5%–10% of patients have mutations in the breast cancer susceptibility gene 1 or 2 (*BRCA1/2*) [8]. In patients with metastatic breast cancer (MBC), a systematic review found that 2.7%–4.3% of patients had germline *BRCA1/2* mutations [9]. Similarly, in the German PRAEGNANT registry of 2,595 women with MBC, 5% of patients had a germline *BRCA1/2* mutation regardless of family history [10]. These mutations are known risk factors for developing certain tumors, such as breast cancer [11, 12]. Knowledge of a patient's *BRCA1/2* mutation status is important because it can influence surgical and medical treatment and is also important in estimating the risk of developing breast cancer, both in healthy individuals and those with a history of breast cancer [11, 12]. Additionally, preventive measures can be considered for healthy relatives with *BRCA1/2* mutation, such as regular mammography or magnetic resonance imaging, prescription of selective estrogen receptor modulators, or bilateral mastectomy, given the risk of contralateral breast cancer is greater in those with a family history of disease [13, 14]. Advances in DNA sequencing and improved genetic testing processes may make genetic testing more cost-effective, even in low-income countries [15, 16]. As such, *BRCA1/2* mutation testing has been proposed as a standard of care [12, 17].

In the USA and Europe, treatment recommendations and guidelines for HER2– ABC include both nontargeted (e.g., platinum-based chemotherapy) and targeted therapies for germline *BRCA1/2*-associated ABC [18–20]. Recently, in patients with ABC or MBC and germline *BRCA1/2* mutations, two poly(ADP-ribose) polymerase (PARP) inhibitors, talazoparib and olaparib, demonstrated significant improvements in progression-free survival, a manageable adverse event profile, and favorable patient-reported outcomes (PROs) compared with physician's choice of chemotherapy in two randomized, phase 3 trials [21, 22]. Despite the importance of *BRCA1/2* mutations in informing treatment and risk of recurrence in ABC, there is a dearth of real-world data on the effect of *BRCA1/2* mutation status on patient outcomes, especially PROs. This study explored the association of a *BRCA1/2* mutation status with treatment patterns, adverse events, and PROs in adult women with HER2– ABC in the USA, the UK, and the EU4 countries.

Methods

Study Design

Data for the study were obtained from the Adelphi Advanced Breast Cancer Disease Specific Progamme (DSP). DSPs are large, multinational point-in-time surveys of physicians and their consulting patients presenting in a real-world clinical setting that describe current disease management, disease-burden impact, and associated treatment effects. Oncologists were recruited to abstract data from patient medical charts and complete patient record forms for adult women with HER2– ABC treated in the USA, the UK, and the EU4 countries. Each oncologist abstracted data from medical charts for the next 8–10 consecutive adult women presenting with HER2– ABC from February to May 2015 and from March to July 2017 (two waves). The physician-reported form contained detailed questions on patient demographics, clinical assessments, clinical outcomes, medication use, and adverse events. Completion of the physician-reported questionnaire was undertaken through consultation of existing patient clinical records, as well as the judgement and diagnostic skills of the respondent physician. Physicians could only report on data they had at the time of the consultation. Therefore, this represents the evidence they had when making any clinical treatment and other management decisions at that consultation, which was entirely consistent with decisions made in routine clinical practice.

Patients identified by physicians were then voluntarily invited to complete a self-reported questionnaire, containing questions on their breast cancer history, treatment, and validated PRO instruments. Patient-reported questionnaires were completed by the patient and were independent of the physician responses. Patients provided written informed consent for use of their anonymized aggregated data for research and publication in scientific journals. The methodology and data capture processes were the same across all regions and territories, with the same questions used to ensure all data collected were comparable. See online supplementary Material (www.karger.com/doi/10.1159/000523970) for additional details on participating physicians and patients and PRO instruments used in the study.

Statistical Analysis

Patients were categorized by *BRCA1/2* mutation status into three mutually exclusive groups: *BRCA1/2* mutated (*BRCA1/2*mut), *BRCA1/2* wild-type (*BRCA1/2*wt), or unknown *BRCA1/2* status (*BRCA1/2*unk; included *BRCA* test inconclusive, not yet performed, and/or results in progress) (online suppl. Fig. S1). Mutation status did not distinguish between germline and/or somatic mutation of the *BRCA1/2* genes. See online supplementary Material for additional statistical analysis methodology.

Table 1. Patient demographics and clinical characteristics by *BRCA1/2* mutation status

	Overall (*n* = 6,161)	*BRCA1/2*mut (*n* = 235)	*BRCA1/2*wt (*n* = 1,025)	*BRCA1/2*unk (*n* = 4,901)	*p* value: *BRCA1/2*mut versus *BRCA1/2*wt, *BRCA1/2*mut versus *BRCA1/2*unk, *BRCA1/2*wt versus *BRCA1/2*unk
Data collection year, *n* (%)					
2015	3,318 (53.9)	92 (39.1)	599 (58.4)	2,627 (53.6)	<0.001/<0.001/0.005
2017	2,843 (46.1)	143 (60.9)	426 (41.6)	2,274 (46.4)	
Age, mean (SD), years	63.4 (12.1)	54.0 (11.9)	58.6 (12.1)	64.9 (11.6)	<0.001/<0.001/<0.001
Race, *n* (%)					
White	5,112 (93.0)	163 (69.4)	762 (74.3)	4,187 (85.4)	0.121/<0.001/<0.001
Black	250 (4.1)	21 (8.9)	87 (8.5)	142 (2.8)	0.797/<0.001/<0.001
Employment status, *n* (%)					
Working full- or part-time	1,238 (20.1)	86 (36.6)	298 (29.1)	854 (17.4)	0.028/<0.001/<0.001
Family history of breast/ovarian cancer, *n* %					
Yes	706 (11.5)	102 (43.4)	177 (17.3)	427 (8.7)	<0.001/<0.001/<0.001
No	4,733 (76.8)	108 (46.0)	766 (74.7)	3,859 (78.7)	<0.001/<0.001/0.005
Not known	722 (11.7)	25 (10.6)	82 (8.0)	615 (12.5)	0.195/0.420/<0.001
HR status, *n* (%)					
HR+/HER2–	4,611 (74.8)	112 (47.7)	675 (65.8)	3,824 (78.0)	<0.001/<0.001/<0.001
TNBC	1,415 (23.0)	108 (46.0)	337 (32.8)	970 (19.8)	<0.001/<0.001/<0.001
Not known	135 (2.2)	15 (6.4)	13 (1.3)	107 (2.2)	<0.001/<0.001/0.067
Diagnosis stage, *n* (%)					
IIIa	550 (8.9)	30 (12.8)	123 (12.0)	397 (8.1)	0.739/0.015/0.001
IIIb	535 (8.7)	34 (14.5)	126 (12.3)	375 (7.7)	0.329/0.001/<0.001
IIIc	498 (8.1)	46 (19.6)	140 (13.7)	312 (6.4)	0.024/<0.001/<0.001
IV	3,526 (57.2)	98 (41.7)	513 (50.0)	2,915 (59.5)	0.029/<0.001/<0.001
Current stage, *n* (%)					
IIIb	501 (8.1)	43 (18.3)	100 (9.8)	358 (7.3)	<0.001/<0.001/0.010
IIIc	546 (8.9)	47 (20.0)	176 (17.2)	323 (6.6)	0.299/<0.001/<0.001
IV	5,114 (83.0)	145 (61.7)	749 (73.1)	4,220 (86.1)	0.001/<0.001/<0.001

BRCA1/2, breast cancer susceptibility gene 1 or 2; HR+, hormone receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; mut, mutation; TNBC, triple-negative breast cancer; unk, unknown; wt, wild-type.

Ethical Approval

A complete description of the survey methodology has been previously published and validated [23–25]. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt.

The DSP methodology was noninterventional, and no identifiable protected health information was extracted during the course of the survey. Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such did not require Ethics Committee approval [26]. In addition, each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996 [27] and Health Information Technology for Economic and Clinical Health Act legislation [28].

Results

Study Population

A total of 742 oncologists provided data for 6,161 patients: 3,318 (53.9%) patients in 2015 and 2,843 (46.1%) in 2017 (Table 1). Overall, 1,696 (27.5%) patients were tested for *BRCA1/2* mutations. A substantially lower rate of *BRCA1/2* mutation testing was observed in the UK and EU4 countries (1,048/4,876; 21.5%) than the USA (648/1,285; 50.4%; $p < 0.001$). This difference was observed in both 2015 (25.0% vs. 56.9%; $p < 0.001$) and 2017 (17.2% vs. 43.6%; $p < 0.001$).

In total, 235 (3.8%) patients had *BRCA1/2*mut, 1,025 (16.6%) had *BRCA1/2*wt, and 4,901 (79.5%) were *BRCA1/2*unk. Overall, 4,611 patients (74.8%) had HR+/HER2– ABC, 1,415 (23.0%) had advanced TNBC, and 135 (2.2%) had ABC of unknown HR status (Table 1).

Patient Demographics and Clinical Characteristics

Patient age differed significantly across *BRCA1/2* mutation status groups, with patients with *BRCA1/2*mut being the youngest. Most patients were White, with the lowest percentage of White patients in the *BRCA1/2*mut group; the highest percentage of Black patients was in the *BRCA1/2*mut group. The percentage of patients currently working full- or part-time was highest in the *BRCA1/2*mut group, likely due to younger age (Table 1).

There was a significantly higher percentage of patients with a known family history of breast or ovarian cancer among patients with *BRCA1/2*mut compared with other patients. However, 46% of *BRCA1/2* mutation carriers did not have a known family history of breast or ovarian cancer. In regard to disease subtype, HR+/HER2− ABC was more frequent within the *BRCA1/2*wt group compared with the *BRCA1/2*mut group, whereas TNBC was more frequent within the *BRCA1/2*mut group compared with the *BRCA1/2*wt group (Table 1). Similar patterns were seen when patients were stratified by geographic region (online suppl. Table S1).

Current Treatments

Overall, 1,270 (66%) patients were on first-line advanced therapy, 449 (23%) on second-line advanced therapy, 156 (8%) on third-line advanced therapy, and 39 (2%) on an unknown line of advanced therapy. Among HR+/HER2− ABC patients with *BRCA1/2*mut, a larger proportion of patients received chemotherapy (with or without targeted or endocrine therapy) rather than endocrine and/or targeted therapy (66.0% vs. 29.5%). In contrast, more patients in the *BRCA1/2*unk group received endocrine and/or targeted therapy alone, rather than chemotherapy (60.5% vs. 36.9%; Table 2).

When comparing treatment across *BRCA1/2* mutation status, a significantly higher proportion of patients with HR+/HER2− ABC with *BRCA1/2*mut received chemotherapy (with or without targeted or endocrine therapy; 66.0%) compared with patients with *BRCA1/2*wt (50.4%) and *BRCA1/2*unk (36.9%; $p < 0.01$ and $p < 0.001$, respectively; Table 2). As expected, most patients with advanced TNBC received chemotherapy, irrespective of *BRCA* mutation status (Table 2).

Adverse Events

Among patients with HR+/HER2− ABC, the proportion with ≥1 adverse event was significantly higher in the *BRCA1/2*mut group (58.0%) versus the *BRCA1/2*wt and *BRCA1/2*unk groups (39.1% and 33.2%, respectively; both $p < 0.001$; online suppl. Table S2). Similarly, among patients with advanced TNBC, the proportion with ≥1 adverse event was significantly higher in the *BRCA1/2*mut group (63.9%) versus the *BRCA1/2*wt and *BRCA1/2*unk groups (38.0% and 43.2%; both $p < 0.001$; online suppl. Table S2). Fatigue, nausea, and hair loss/thinning were the most common adverse events among patients with HR+/HER2− ABC and advanced TNBC (online suppl. Table S2).

Patient-Reported Outcomes

An inverse probability-weighted regression analysis (IPWRA) was used to control for potential confounding factors for the PROs analyses. The IPWRA did not bal-

Table 2. Current treatments by *BRCA1/2* mutation status and HR status

Treatment	Overall ($n = 6,161$)	*BRCA1/2*mut ($n = 235$)	*BRCA1/2*wt ($n = 1,025$)	*BRCA1/2*unk ($n = 4,901$)	*p* value: *BRCA1/2*mut versus *BRCA1/2*wt, *BRCA1/2*mut versus *BRCA1/2*unk, *BRCA1/2*wt versus *BRCA1/2*unk
HR+/HER2−, *n* (%)					
Current treatment, *n*	4,611	112	675	3,824	
Chemotherapy with/without targeted or endocrine therapy	1,827 (39.6)	74 (66.0)	340 (50.4)	1,413 (36.9)	0.002/<0.001/<0.001
Endocrine and/or targeted therapy, no chemotherapy	2,661 (57.7)	33 (29.5)	315 (46.6)	2,313 (60.5)	<0.001/<0.001/<0.001
Other	123 (2.7)	5 (4.5)	20 (3.0)	98 (2.6)	0.384/0.217/0.515
TNBC, *n* (%)					
Current treatment, *n*	1,415	108	337	970	
Chemotherapy with/without targeted or endocrine therapy	1,273 (90.0)	91 (84.3)	286 (84.9)	896 (92.4)	0.879/0.009/<0.001
Endocrine and/or targeted therapy, no chemotherapy	51 (3.6)	11 (10.2)	14 (4.2)	26 (2.7)	0.028/0.001/0.198
Other	91 (6.4)	6 (5.6)	37 (11.0)	48 (4.9)	0.133/0.815/0.003

BRCA1/2, breast cancer susceptibility gene 1 or 2; HR, hormone receptor; HER2−, human epidermal growth factor receptor 2-negative; mut, mutation; TNBC, triple-negative breast cancer; unk, unknown; wt, wild-type.

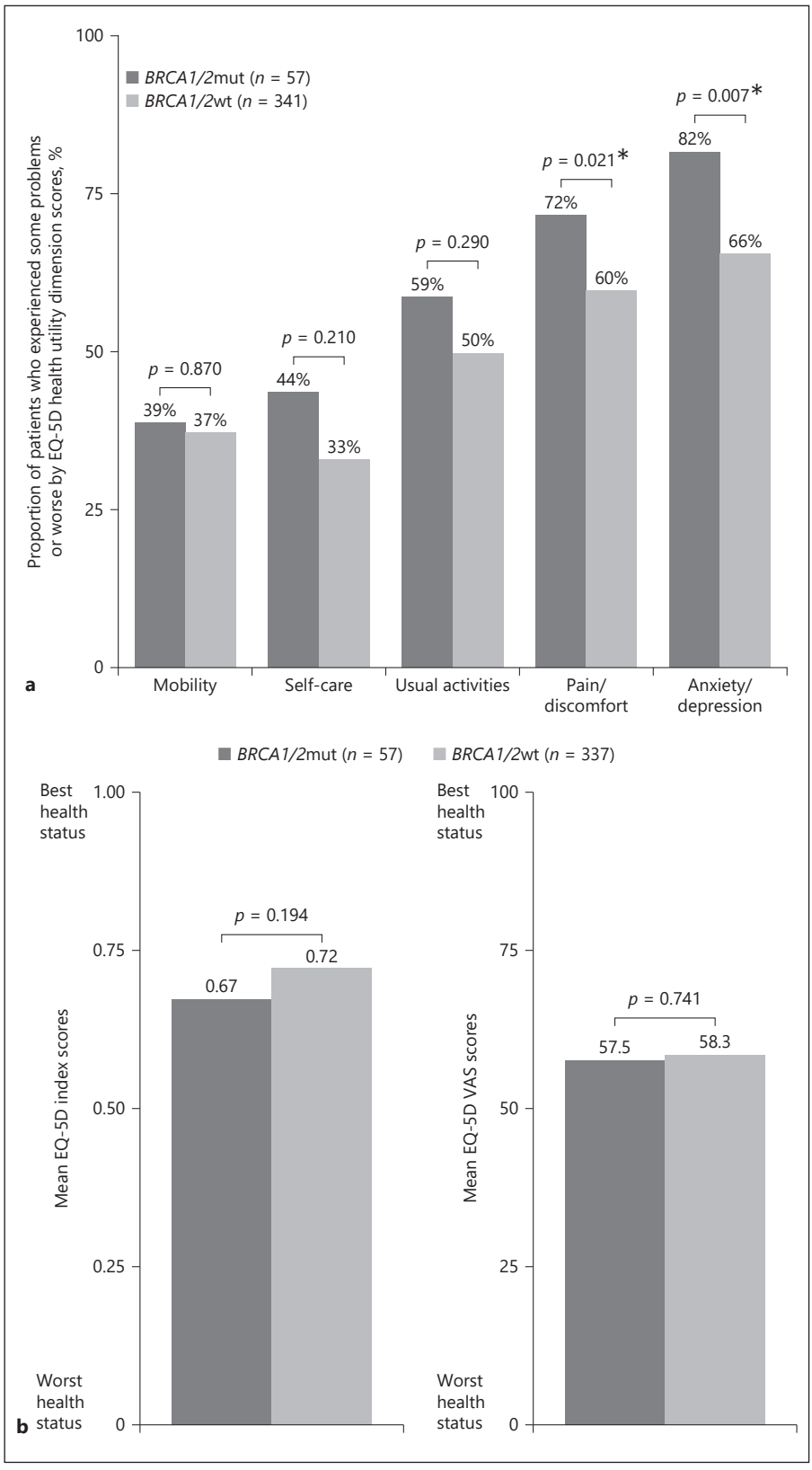

Fig. 1. EQ-5D-3L (**a**) individual dimension findings and (**b**) the health utility index and VAS score by *BRCA1/2* mutation status. The sample size varied for the EQ-5D-3L analysis (range: *BRCA1/2*mut, *n* = 56–57; *BRCA1/2*wt, *n* = 335–341). The IPWRA was balanced on age, BMI, ECOG PS, CCI, current stage, stage at diagnosis, number of previous therapy lines, and HR status. BMI, body mass index; *BRCA1/2*, breast cancer susceptibility gene 1 or 2; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels; HR, hormone receptor; IPWRA, inverse probability weighted regression analysis; mut, mutation; VAS, visual analog scale; wt, wild-type. *Significant *p* value.

ance for the *BRCA1/2*unk cohort, so the comparisons focused on patients with *BRCA1/2*mut versus *BRCA1/2*wt. Completed EQ-5D-3Ls were obtained from 394 patients, including 57 patients with *BRCA1/2*mut and 337 patients with *BRCA1/2*wt. A numerically higher percentage of patients with *BRCA1/2*mut compared with patients with *BRCA1/2*wt reported some problems or extreme problems for mobility, self-care, and usual activities. Statisti-

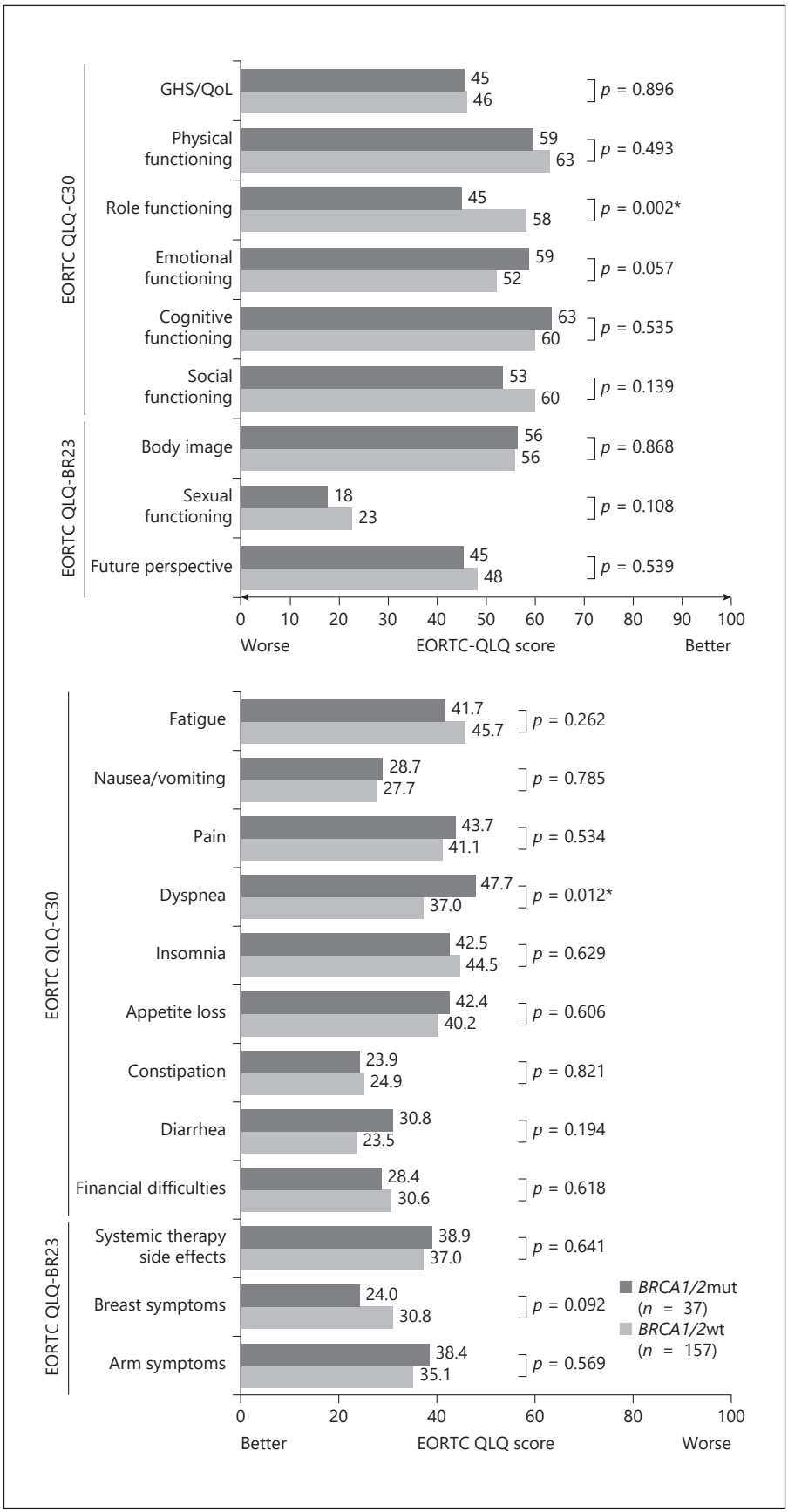

Fig. 2. IPWRA analysis for the EORTC by *BRCA1/2* mutation status: EORTC QLQ-C30 GHS/QoL, functional, and symptom scales; EORTC QLQ-BR23 functional and symptom scales. The sample size varied for the EORTC QLQ-C30 and EORTC QLQ-BR23 analysis (range: *BRCA1/2*mut, 31–37; *BRCA1/2*wt, 143–157). Hair loss and sexual enjoyment are not reported because the analysis did not balance due to low sample size. The IPWRA was balanced on age, BMI, ECOG PS, CCI, current stage, stage at diagnosis, number of previous therapy lines, and HR status. BMI, body mass index; *BRCA1/2*, breast cancer susceptibility gene 1 or 2; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-breast cancer module; GHS, Global Health Status; HR, hormone receptor; IPWRA, inverse probability weighted regression analysis; mut, mutation; QoL, quality of life; wt, wild-type. *Significant *p* value.

cally significant differences for pain/discomfort ($p < 0.05$), and anxiety/depression ($p < 0.01$) were observed in patients with *BRCA1/2*mut versus *BRCA1/2*wt (Fig. 1a). The EQ-5D-3L health utility index score and VAS score were numerically higher among patients with *BRCA1/2*wt than *BRCA1/2*mut, respectively (Fig. 1b).

Brief Pain Inventory (BPI) scores were provided by 393 patients, including 56 patients with *BRCA1/2*mut and 337 patients with *BRCA1/2*wt. Scores were similar between patients with *BRCA1/2*mut and *BRCA1/2*wt (online suppl. Fig. S2).

For the EORTC assessment, data were available from 194 patients, including 37 patients with *BRCA1/2*mut and 157 patients with *BRCA1/2*wt. Scores were comparable between patients with *BRCA1/2*mut and *BRCA1/2*wt on the GHS/QoL and most functional scales. However, the role functioning score was significantly worse for patients with *BRCA1/2*mut in comparison with patients with *BRCA1/2*wt ($p < 0.01$; Fig. 2). Across the symptom scales, a significantly worse score was reported for dyspnea by patients with *BRCA1/2*mut compared with patients with *BRCA1/2*wt ($p < 0.05$; Fig. 2), with all other scores comparable between groups.

Discussion

In this study of adult women with HER2− ABC, low rates of *BRCA1/2* mutation testing were observed in the years 2015 and 2017, with most patients having an unknown *BRCA1/2* mutation status, independent of geographic region and HR status. We found that, compared with patients with *BRCA1/2*wt, patients with *BRCA1/2*mut had differences in disease characteristics, treatment patterns, adverse events, and PROs.

In our study, TNBC was more common in patients with *BRCA1/2*mut versus those with *BRCA1/2*wt and *BRCA1/2*unk (46.0% vs. 32.8% and 19.8%, respectively). A similar pattern was observed in the PRAEGNANT registry, with 29.1% of patients with ABC and a *BRCA1/2* mutation having TNBC compared with 10.1% of patients with ABC who did not have any mutation in a cancer predisposition gene [10]. In contrast, other studies report higher rates of TNBC in patients with a *BRCA* mutation. A 2014 review article reported that approximately 80% of breast cancers arising in *BRCA1* germline mutation carriers are TNBC [29]. A systematic review and meta-analysis of patients with breast cancer also found that those with *BRCA1* mutations were almost nine times more likely to have TNBC [30] than those without *BRCA* mutations. However, in our study, fewer than half of the patients with *BRCA1/2*mut had TNBC. These findings suggest that hormone receptor status may not be a reliable predictor of *BRCA1/2* mutations and underline the possibility that patients with HR+/HER2− ABC may also have *BRCA1/2* mutations and may be appropriate candidates for certain targeted therapies instead of chemotherapy with its relevant side effects and the associated reduction in quality of life.

Patients with HR+/HER2− breast cancer and *BRCA1/2*mut were younger and more likely to be currently employed than patients with *BRCA1/2*wt or *BRCA1/2*unk. These patients were also more likely to receive chemotherapy (with or without endocrine or targeted therapy) than endocrine and/or targeted therapy alone. Patients with HR+/HER2− breast cancer and *BRCA1/2*mut also received chemotherapy at a higher rate than patients with *BRCA1/2*wt or *BRCA1/2*unk. This is possibly because of the belief that platinum-based chemotherapy is more effective in patients with ABC with *BCRA1/2* mutations [18]. Moreover, these data complement findings in the PRAEGNANT registry, in which patients with *BRCA1/2* mutations were also younger at metastasis diagnosis than patients with other mutations or patients who did not carry any mutation analyzed in the study [10].

We observed the highest incidence of adverse events in patients with *BRCA1/2*mut and TNBC disease, which is the group with the highest use of chemotherapy. The types of adverse events reported (fatigue, nausea, hair loss) were also typical of the recognized adverse effects of chemotherapy. Regarding quality of life, this finding underlines the need for better-tolerated treatments for ABC. One alternative can be chemotherapy-sparing treatments, such as the recently approved PARP inhibitors, which demonstrated superior efficacy, a manageable adverse event profile, and favorable PROs versus standard of choice chemotherapy [21, 22].

A literature search did not identify any studies assessing the effect of *BRCA1/2* mutation status on PRO endpoints in breast cancer. Analysis of the EQ-5D-3Ls demonstrated significantly worse pain/discomfort and anxiety/depression in patients with the *BRCA1/2*mut compared with those with *BRCA1/2*wt. The EORTC QLQ-C30 and QLQ-BR23 scores also demonstrated significantly worse role functioning and dyspnea in patients with the *BRCA1/2*mut. Role functioning is a measure of a patient's ability to perform daily activities, leisure time activities, and work. It is possible that the increased discomfort, anxiety, and dyspnea and diminished role functioning in the *BRCA1/2*mut group may be due to the high use of chemotherapy in these patients.

Few studies report the rate of *BRCA1/2* mutation testing in patients with breast cancer. An analysis of data from a US electronic medical record database for 8,080 patients diagnosed with HER2− ABC from 2013 to 2017 reported that *BRCA* mutation status was known for 22.9% of patients [31]. This is somewhat lower than the 50.4%

in the USA that we report here, but that analysis included only germline *BRCA1/2* mutation testing and the germline *BRCA1/2* mutation testing rate was from 2013 to 2017. In contrast, here we report both somatic and/or germline *BRCA1/2* mutation testing rates across 2015 and 2017 in the USA, the UK, and the EU4 countries. These testing rates pre-date early clinical data supporting the role of PARP inhibitors in ABC and can be used as a baseline to monitor *BRCA1/2* mutation testing. Our study also showed that a higher proportion of US patients received *BRCA1/2* testing in comparison to those in EU4. This difference could be due to the varying awareness levels of *BRCA1/2* testing as well as differing reimbursement protocols; however, further research needs to be undertaken to understand this fully.

Although patients with *BRCA1/2*mut were more likely to have a known family history of breast or ovarian cancer than patients with *BRCA1/2*wt and *BRCA1/2*unk, more than half of patients with *BRCA1/2*mut either did not have a family history or the family history was not known. This finding highlights the need for universal *BRCA1/2* mutation testing because oncologists looking to test for *BRCA1/2* mutation among patients with a known family history may miss nearly half of patients who may harbor *BRCA1/2* mutations. This finding is very similar to that in a study of 1,845 Polish women with breast cancer, in which 21/55 (39%) patients with *BRCA1* mutation had no family history of breast and/or ovarian cancer among first- and second-degree relatives [32]. These results are also similar to those reported in the PRAEGNANT registry, in which nearly 66% of patients with a *BRCA1/2* mutation did not have a family history of breast cancer among first-line relatives [10]. These findings, together with those related to disease subtype, indicate that family history and hormone receptor status are not reliable predictors of *BRCA1/2* mutations.

Our methodology is associated with limitations. Our analysis included participating patients who visited their physician and therefore may have included patients who visited their physician more frequently than or were more severely affected than the general population with ABC. Additionally, the DSP was not based on a true random sample of physicians or patients. Although minimal inclusion criteria governed participation, it was influenced by willingness to complete the survey. Physicians were asked to provide data for a consecutive series of patients, but no formal patient selection verification procedures were implemented. Patient eligibility was based on the physicians' judgement and not a formalized diagnostic checklist; this is representative of physicians' real-world patient management. The point-in-time design prevents conclusions about causal relationships, but identification of significant associations is possible. Moreover, recall bias, a common limitation of surveys, might have affected the responses of patients and physicians. However, data were collected at the time of each patient's appointment, thereby potentially minimizing recall bias. In addition, our methods ensured physicians were unaware of patient responses, but it was not possible to confirm that no information was exchanged between physicians and patients. Another limitation of the present study is that the data did not distinguish between germline and somatic *BRCA1/2* mutations. Additionally, the IPWRA was only conducted when all confounding variables included to balance the model were known. Different waves of the ABC DSP were based on questionnaires and interviews that changed over time depending on market changes, needs, and prescribing environments. Although a number of patient and clinical variables were assessed, an exhaustive list of all factors that might influence clinical outcomes in patients with ABC was not evaluated.

Despite such limitations, this study included more than 6,000 patients with ABC from real-world clinical practice across the USA, the UK, and the EU4 countries and used a well-established and validated methodology. Real-world studies play an important part in highlighting areas of concern that are not addressed in clinical trials. Patients included in clinical trials represent a small proportion of the overall population, a result of age restrictions and patients failing to meet stringent eligibility criteria [33]. Patients treated in the real-world setting may be less likely to be adherent to medication than those included in clinical trials [34]. As a result, data from real-world studies complement findings from clinical trials and provide insight into the effect of interventions in patients commonly treated in clinical practice.

Optimizing treatment for the best achievable HRQoL should be the main aim of care in ABC. This study highlighted differences in treatment, as well as worse PROs, in patients with *BRCA1/2* mutations compared with those without mutations. In addition, despite *BRCA1/2* mutation status being a key criterion in treatment selection in ABC, this study demonstrated the low level of *BRCA1/2* mutation testing in patients in the USA, the UK, and the EU4 countries. Because family history is not a reliable predictor of *BRCA1/2* mutation, *BRCA1/2* mutation status should be tested in all patients with HER2– ABC. Increased testing and identification of *BRCA1/2*mut in HR+/HER2– disease would allow for the potential use of PARP inhibitors in place of chemotherapy, with a consequent improvement in HRQoL.

Statement of Ethics

This study complies with all applicable laws of the countries in which it was performed. Data collection was undertaken in accordance with European Pharmaceutical Marketing Research Association (EphMRA) code of conduct. Research relating to market

or consumer behavior involving healthcare professionals and patients does not require clinical research Ethics Committee or independent review board approval. However, data collection in the 2017 wave received ethical approval from the Freiburger Ethik-Kommission International (017/1252) and the Western Institutional Review Board (AG-8238). Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996. Patients provided written informed consent for the use of their anonymized data for research.

Conflict of Interest Statement

Michael Patrick Lux received honoraria for lectures and performing in a consulting or advisory role for AstraZeneca, Eisai, Eli Lilly, Exact Sciences, Grünenthal, MSD, Novartis, Pfizer, PharmaMar, Pierre Fabre, Roche, and SamanTree; received reimbursed travel and accommodations expenses from Pfizer and Roche; has been an editorial board member of Medac; received fees for non-CME services from AstraZeneca, Eisai, Eli Lilly, Exact Sciences, Grünenthal, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. Katie Lewis and Alex Rider are employees of Adelphi Real World, which received financial support from Pfizer for the development of this manuscript. Alexander Niyazov is a Pfizer employee and Pfizer stockholder.

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Author Contributions

Michael Patrick Lux: contributed to the conception and design of the work and interpretation of the data; revised the manuscript critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Katie Lewis: contributed to the conception and design of the work and acquisition, analysis, and interpretation of the data; drafted and revised the manuscript critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Alex Rider: contributed to the conception and design of the work and acquisition, analysis, and interpretation of the data; drafted and revised the manuscript critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Alexander Niyazov: contributed to the conception and design of the work and acquisition, analysis, and interpretation of the data; revised the manuscript critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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