

ORIGINAL RESEARCH

Real-world clinical profile, treatment patterns and patient-reported outcomes in a subset of HR+ /HER2- advanced breast cancer patients with poor prognostic factors: data from an international study

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Background: Patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) and disease-related poor prognostic factors are not well characterized. We aimed to describe patient demographics, disease characteristics, treatment patterns and patient-reported outcomes in a subset of HR+/HER2- ABC patients with these factors [at the time when cyclin-dependent kinase (CDK) 4 and 6 inhibitors were being introduced] and understand how these factors informed treatment decisions at the time of the survey.

Methods: Real-world data were derived from a large, multinational, point-in-time survey of oncologists and their consulting patients with HR+/HER2- ABC in the EU5 and USA over March-June 2017, at the start of the changing treatment landscape. Analysis focused on four poor prognostic factors: visceral metastases, liver metastases (subset of visceral metastases), progesterone receptor-negative status and high tumor grade.

Results: In total, 2259 patients with HR+/HER2- ABC had records eligible for this analysis. At least one poor prognostic factor was present in 63% of patients (most common visceral metastases; least common progesterone receptor-negative status), with varying degrees of overlap between factors. For physician-reported outcomes, pain increased, whereas performance status and activities of daily living declined with presence of poor prognostic factors, especially liver metastases. No clear trends were observed for patient-reported outcomes. Treatment with combined endocrine therapy plus CDK4 and 6 inhibitors was infrequent, as these agents were entering the market.

Conclusions: More than 60% of the HR+/HER2- ABC Adelphi Real World Disease Specific Programme™ sample had ≥1 disease-related poor prognostic factor, and patients appeared to be heterogeneous regarding occurrence and distribution of these factors. These patients typically have increased pain and reduced performance status, highlighting the importance of implementing effective therapy with CDK4 and 6 inhibitors. Future studies could inform how the treatment landscape has evolved over time with respect to patients with poor prognostic factors.

Key words: advanced breast cancer, HR+/HER2-, health-related quality of life, prognostic factors, real-world, treatment patterns, outcomes

INTRODUCTION

Approximately two-thirds of patients with advanced breast cancer (ABC) have hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) ABC.¹ Despite advances in the management of patients with HR+/HER2- ABC, some patient characteristics are more likely to confer a poor prognosis. These include

metastases—such as visceral,^{1,2} specifically liver³⁻⁹ and cerebral;^{1,4,7} multiple metastatic sites,^{1,4,5,10} high tumor grade,^{4,9-13} negative progesterone receptor status (PgR-; i.e. loss of inhibitory crosstalk from PgR to the estrogen receptor),^{9,12,14-16} the previous use of chemotherapy,⁴ a shorter disease-free interval⁷ and black ethnic backgrounds.^{13,17,18}

As recommended in current guidelines,¹⁹⁻²¹ the foundation of first-line treatment of most HR+/HER2- ABC patients is endocrine therapy (ET), which eventually becomes ineffective.²² The development of cyclin-dependent kinase (CDK) 4 and 6 inhibitors (abemaciclib, palbociclib and ribociclib) is a key advance in HR+/HER2- ABC systemic treatment.^{19,23} Standard ET combined with CDK4

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and 6 inhibitors has significantly improved progression-free survival and overall survival (abemaciclib and ribociclib) in patients naive or previously exposed to ET,²⁴⁻³⁵ and is a preferred treatment option.¹⁹⁻²¹ The three available CDK4 and 6 inhibitors are all approved in Europe and the USA as part of an ET-based regimen for the treatment of HR+/HER2– ABC.

In general, patients with HR+/HER2– ABC and disease-related poor prognostic factors have not been well characterized, and it is unclear how the presence of these factors could guide treatment. Unlike randomized, controlled trials, studies analyzing real-world datasets can provide insights into outcomes and different approaches to care in day-to-day clinical situations.^{36,37}

METHODS

Aim

The aim of this study was to describe the patient demographics, disease characteristics, treatment patterns and patient-reported outcomes of HR+/HER2– ABC patients with a focus on disease-related poor prognostic factors.

Study design, study participants and data collection

The Adelphi Real World Disease Specific Programme™ (DSP) is a large multinational, cross-sectional survey that generates real-world data from current clinical practice.³⁸ Cross-sectional data collected via physician and patient surveys undertaken by the ABC DSP were collected over March-June 2017, at the start of the pivotal change in the treatment landscape. The full DSP methodology has been described,³⁸ and data from previous ABC DSPs have been published.³⁹⁻⁴¹

Data were collected across five European countries (France, Germany, Italy, Spain and the UK; EU5) and the USA. Oncologists from both academic and community-based practices were identified from publicly available lists of health care professionals and invited to participate in the DSP. To be eligible, participating physicians must have been medical oncologists who treated at least three ABC patients per week, were personally responsible for prescribing decisions for these patients and accepted all study rules and responsibilities. Eligible patients had an oncologist-confirmed diagnosis of ABC and were receiving treatment for ABC at the time of the study. Patients included in the DSP sample (EU5 and USA) were the next 10 suitable patients (7 irrespective of biomarker status and 3 with HR+/HER2– disease) who consulted with the physician.

Participating oncologists completed patient record forms (PRFs) that collected detailed information relating to clinical characteristics and treatment from medical records. Physicians completed PRFs for the next seven consecutive consulting patients with ABC. PRFs were then collected for the next three patients who presented with HR+/HER2– ABC, as this was the group of interest, and all analyses were

conducted in this patient population. All patients for whom a physician completed a PRF were invited to complete patient self-completion forms (PSCs), which were linked to the physician-completed PRFs. Completion of PSCs was voluntary.

Study variables

Variables extracted from the PRFs and PSCs included demographic and baseline disease characteristics, treatment received, Eastern Cooperative Oncology Group (ECOG) performance status, number and type of symptoms, number and type of concomitant conditions and the physician's opinion of patient's activities of daily living (ADL). Pain at diagnosis, current pain and analgesic use were also captured in the PRFs completed by physicians.

The PSC included patient-reported outcome instruments. General health status was evaluated using the EQ-5D-3L.^{42,43} The EQ-5D-3L comprises five single items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a 20-cm visual analogue scale (EQ-5D-VAS).^{42,43} A single health utility index score is generated using a country-specific algorithm, with 1 indicating perfect health, 0 death and <0 worse than death.⁴⁴ The EQ-5D-VAS provides a score in the range of 0-100, higher scores indicating better health-related quality of life (HRQoL).⁴⁵

HRQoL was further assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) with the breast cancer-specific module (QLQ-BR23).^{46,47} The EORTC QLQ-C30 comprises 30 items to assess functional status in five areas (physical, role, cognitive, emotional and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea), financial difficulties, overall health and HRQoL. The QLQ-BR23 includes 23 breast cancer-focused items to describe four functional scales (body image, sexual function, sexual enjoyment, future perspective) and four symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss). Higher scores indicate positive functional status and HRQoL but worse outcomes for some items (symptom severity and financial difficulty). The Work Productivity and Activity Impairment Questionnaire (WPAI)⁴⁸ was used to assess how breast cancer affected the patients' work in terms of percent activity impairment.

Poor prognostic factors

This analysis focused on four factors that were previously highlighted by Di Leo et al. (2018)⁹ as likely to confer a poor prognosis for those with HR+/HER2– ABC: (i) the presence of visceral metastases (i.e. in liver, lungs, adrenal glands, peritoneum or pleura, brain and dura), (ii) the presence of liver metastases (a subset of visceral metastases), (iii) PgR– status and (iv) high tumor grade (i.e. grade 3). Each prognostic factor of interest was reported by the consulting oncologist who abstracted information from the individual patient medical records.

Table 1. Demographic and baseline characteristic data for the total study, EU5 and US populations

Characteristics	Total (n = 2259)	EU5 (n = 1766)	USA (n = 493)
Median (25th, 75th percentiles) age, years	65.0 (56.0, 72.0)	65.0 (56.0, 73.0)	64.0 (55.0, 71.0)
Mean (SD) BMI, kg/m ²	25.0 (4.4)	24.8 (3.8)	25.9 (6.0)
Ethnic background/race, % ^a			
White/Caucasian	85	92	63
African-American	4	0	19
Hispanic/Latino	3	2	7
Other	7	6	12
Menopausal status, % ^b			
Premenopausal	12	11	14
Postmenopausal ^c	88	89	86
Number of current metastases, %			
0	15	13	22
1	42	42	45
2	30	32	23
3	10	11	8
4	3	3	2
Mean (SD) no. metastases	1.4 (1.0)	1.5 (1.0)	1.2 (1.0)
Sites of current metastases, % ^d			
Bone only	28	28	28
Liver only	6	5	9
Visceral only ^e	20	20	24
Liver (± other metastases)	23	21	23
Visceral (± other metastases)	56	56	57
Physician-reported symptoms, %			
0	34	34	36
1	27	28	23
2+	39	38	41
Type of physician-reported symptom, % ^f			
Fatigue	32	31	33
Bone pain due to bone metastases	22	24	15
Weight loss	14	12	20
Lumps (breast/under arm)	12	11	16
Hair loss	7	6	10
Other pain	5	5	5
None/do not know	34	34	36
Number of concomitant conditions, %			
0	38	41	25
1	24	23	30
2+	38	36	45
Type of concomitant condition, % ^f			
Hypertension	33	32	35
Diabetes	17	16	22
Hyperlipidemia	17	15	22
Anxiety	13	12	16
Depression	12	11	16
Osteoporosis	8	8	6

Continued

Table 1. Continued

Characteristics	Total (n = 2259)	EU5 (n = 1766)	USA (n = 493)
None of the study-listed conditions	38	41	25
Current ECOG score, % ^g			
0	30	32	24
1	50	49	57
2	15	16	14
3	4	4	4
4	1	<1	1
Unknown	<1	<1	<1

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

^a Totals may not add up to 100% due to rounding.

^b Percentages are based on n = 2209 patients with known progesterone receptor status.

^c Including natural, medically induced, ovary suppression and ablation.

^d Percentages are based on n = 1921 patients with metastases.

^e Includes liver, lungs, adrenal glands, peritoneum or pleura, brain and dura.

^f Reported frequency ≥5% of total population.

^g 0, fully active, able to carry on all pre-disease performance without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; 2, ambulatory and capable of all self-care but unable to carry out work activities; up and about >50% of waking hours; 3, capable of only limited self-care; confined to bed or chair >50% of waking hours; 4, completely disabled; cannot carry out any self-care; confined to bed or chair.

Statistical analysis

Descriptive statistics were provided for all variables of interest. For numeric variables, sample size, mean and standard deviation (SD), minimum, maximum, median and interquartile ranges were given. For categorical variables, sample size, number and percent were provided for each category. All analyses were conducted using Survey Reporter v7.0 software.

Ethical considerations

The authors obtained appropriate institutional review board approval or followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent was obtained from the participants involved. Data provided by physicians and patients were anonymized and aggregated by Adelphi Real World before receipt for analysis. The survey was reviewed and approved by the Freiburg Ethics Commission International in the EU5 and by the Western Institutional Review Board in the USA.

RESULTS

Study population: demographic and baseline characteristics

In total, 410 oncologists across the EU5 and USA completed 3999 PRFs for patients with ABC. Of the 410 oncologists, 63% spent most of their time in an academic setting, with the remainder based in community settings. Of the 3999 PRFs completed, 2259 were HR+/HER2- patients with

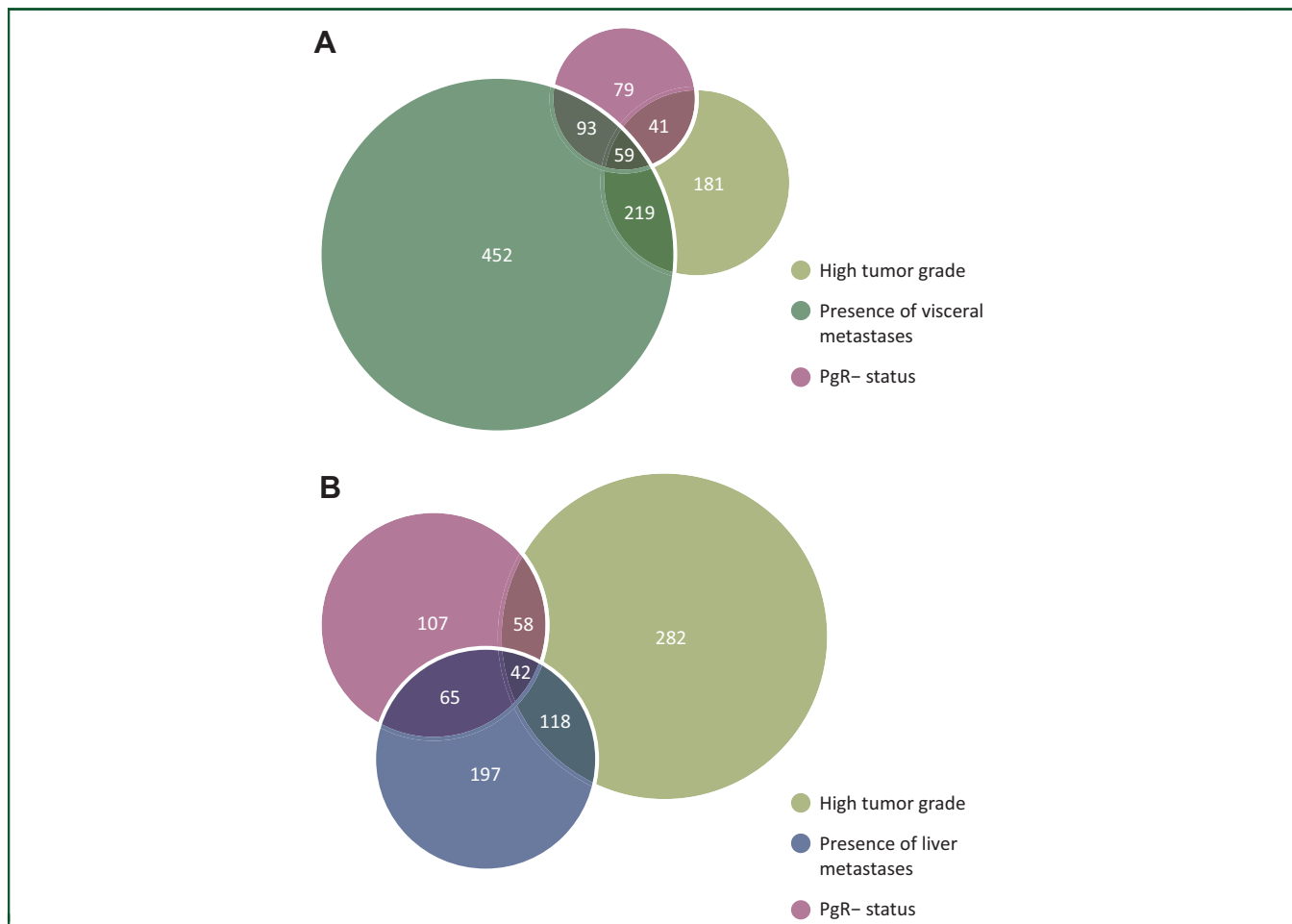


Figure 1. Overlap of presence of (A) visceral or (B) liver metastases, high tumor grade and progesterone receptor negative (PgR-) status. Of the 1711 patients with a known tumor grade and PgR- status, (A) 1124 (66%) and (B) 869 (51%) had at least one poor prognostic factor. Numbers represent *n* for each poor prognostic factor, and their intersections, where poor prognostic factor status is known for all patients (*n* = 1124 and 869, respectively). A total of 422 patients with visceral metastases had liver metastases.

records eligible for this analysis. The majority (85%) of the HR+/HER2- sample were stage IV at the time of the survey, and 58% were stage IV at initial diagnosis. A total of 676 patients (29.9% of the HR+/HER2- cohort) voluntarily provided patient-reported outcomes data. Baseline demographics and clinical characteristics stratified by voluntary completion of PSCs and according to country are provided in [Supplementary Table S1](https://doi.org/10.1016/j.esmoop.2021.100226), available at <https://doi.org/10.1016/j.esmoop.2021.100226>.

The demographic and baseline characteristics for the total, EU5 and US study populations are shown in [Table 1](#). The distributions of baseline characteristics were broadly similar between populations. They were also generally similar between individual countries ([Supplementary Table S2](#), available at <https://doi.org/10.1016/j.esmoop.2021.100226>). Only 12% of patients were premenopausal. No significant differences were observed between physician-reported demographics/clinical characteristics for patients who completed a PSC and those who did not.

Overall, 85% (1921/2259) of patients had metastases. Among the 1921 patients with metastatic (stage IV) disease, the majority had one to two metastases, with the most

frequent being visceral (56% of patients with metastases). The proportion of stage IV patients with liver metastases (also with or without any other metastases) was 23% ([Table 1](#)).

In total, 66% of patients (1485/2259) had one or more physician-reported symptoms ([Table 1](#)). Symptoms that occurred in >20% of all HR+/HER2- patients included fatigue (32%; 719/2259) and bone pain due to bone metastases (22%; 496/2259). Overall, 62% of the population (1408/2259) had one or more comorbidity; hypertension being the only condition to occur in >20% of all patients (33%; 747/2259). Certain comorbidities, including diabetes (22% versus 16%; 108/493 versus 279/1766) and hyperlipidemia (22% versus 15%; 106/493 versus 269/1766), were more common among US than EU patients. A total of 80% of patients (1813/2259) had favorable ECOG performance scores of 0 or 1.

Baseline characteristics were also examined among individual EU5 countries ([Supplementary Table S2](#), available at <https://doi.org/10.1016/j.esmoop.2021.100226>). Individual country populations were generally similar. However, the German population was, on average, younger and healthier than the other country populations in terms of symptoms and ECOG scores.

Table 2. Baseline characteristics by type of poor prognostic factor

Characteristics	Tumor grade ^a		PgR status ^b		Metastases ^c			Any poor prognostic factor ^e (n = 1124)
	High (3) (n = 524)	Low (1/2) (n = 1230)	Negative (n = 354)	Positive (n = 1855)	Presence of visceral ^d (n = 1084)	Presence of liver ^e (n = 437)	No metastases ^f (n = 338)	
Mean (SD) age, years	62.9 (11.4)	64.7 (12.0)	61.0 (12.7)	64.9 (11.7)	64.2 (11.7)	62.5 (11.8)	58.5 (12.0)	63.8 (11.6)
Menopausal status, %								
Premenopausal	16	9	16	11	12	12	21	12
Postmenopausal ^h	84	91	84	89	88	88	79	88
All tobacco smoking status, %								
Current	8	7	12	7	8	10	13	8
Former	30	28	26	28	29	29	34	29
Never	57	57	55	58	57	55	47	56
Unknown	5	7	8	7	7	6	7	7
Current pain experienced, %								
None	44	50	41	49	46	33	57	44
Mild	38	35	34	35	36	41	25	37
Moderate	14	12	15	12	14	19	12	14
Severe	3	2	6	2	3	5	3	3
Not assessed/unknown	2	1	4	1	1	1	2	1
ECOG ⁱ currently, %								
0	25	31	24	31	23	22	49	24
1	54	51	51	50	55	50	33	54
≥2	20	18	24	18	23	26	18	22
Unknown	0	<1	<1	<1	<1	<1	1	<1
ADL decrease, %								
No decrease	36	39	33	40	34	26	42	34
Mildly decreased	47	47	44	46	47	47	47	48
Moderately decreased	14	13	18	12	16	22	10	16
Extremely decreased	3	1	5	2	3	5	1	2

Data are presented as % unless otherwise indicated.

ADL, activities of daily living; ECOG, Eastern Cooperative Oncology Group; PgR, progesterone receptor; SD, standard deviation.

^a Total base size represents patients with known tumor grade; those with an unknown tumor grade are not reported.

^b Total base size represents patients with known PgR status; those with an unknown status are not reported.

^c Total base size represents patients with known metastatic status; those with an unknown status are not reported.

^d Patients with liver, lung, adrenal gland, peritoneum or pleura, brain and dura metastases, with or without other metastases.

^e Patients with liver metastases, with or without other metastases.

^f Patients with no metastases.

^g Patients with known tumor and PgR status and presence of visceral metastases, PgR– status and/or high tumor grade.

^h Including natural, medically induced, ovary suppression and ablation.

ⁱ ECOG performance status: 0, fully active, able to carry out all pre-disease performance without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; 2, ambulatory and capable of all self-care but unable to carry out work activities; up and about >50% of waking hours; 3, capable of only limited self-care, and confined to bed or chair >50% of waking hours; 4, completely disabled, cannot carry out any self-care and confined to bed or chair.

In total, 561 patients were known to be diagnosed at an early stage, with 412 (73%) receiving an adjuvant treatment. Of those who were prescribed an adjuvant treatment, 91% received adjuvant ET, 57% received adjuvant chemotherapy and 51% received radiotherapy. For patients with known treatment dates ($n = 371$), the mean (SD) treatment-free interval (TFI) between end of adjuvant ET or chemotherapy and start of first-line treatment of advanced disease was 27.0 (45.3) months (median 10.4 months). For adjuvant ET specifically, the mean (SD) TFI was 21.8 (46.3) months (median: 2.5 months; interquartile range 0.4–27.2 months). The mean (SD) duration of adjuvant ET was 45.1 (22.9) months (median 54.0 months).

Numbers of poor prognostic factors

Visceral metastases were the most frequent poor prognostic factor identified in this analysis. For patients with known metastases ($n = 1921$), 56% had visceral metastases and 23% had liver metastases. Of patients with known tumor grade ($n = 1754$), 30% had a high tumor grade of 3 at initial diagnosis of breast cancer. Of those with high tumor

grade ($n = 524$), 124 were early stage at diagnosis, 396 were advanced/metastatic and 4 were unknown. Of those with known PgR status at the time of data collection ($n = 2209$), 16% had PgR– status, the least common poor prognostic factor of those considered.

Figure 1A shows the overlap of poor prognostic factors in patients where visceral metastasis, PgR and tumor grade status were known. Although most patients had at least one poor prognostic factor, degrees of overlap varied between these factors. Most (42%) of these patients had one poor prognostic factor, 18% had two and only 3% had three poor prognostic factors. Thus, among the 2259 patients included in the analysis, 63% had at least one poor prognostic factor. The overlap of PgR– and high tumor grade with liver metastasis (Figure 1B) showed a similar profile.

Demographic and baseline characteristics by type of poor prognostic factors

Demographic and baseline characteristics for HR+/HER2– patients, given by type of poor prognostic factor, are shown in Table 2. For each poor prognostic factor category,

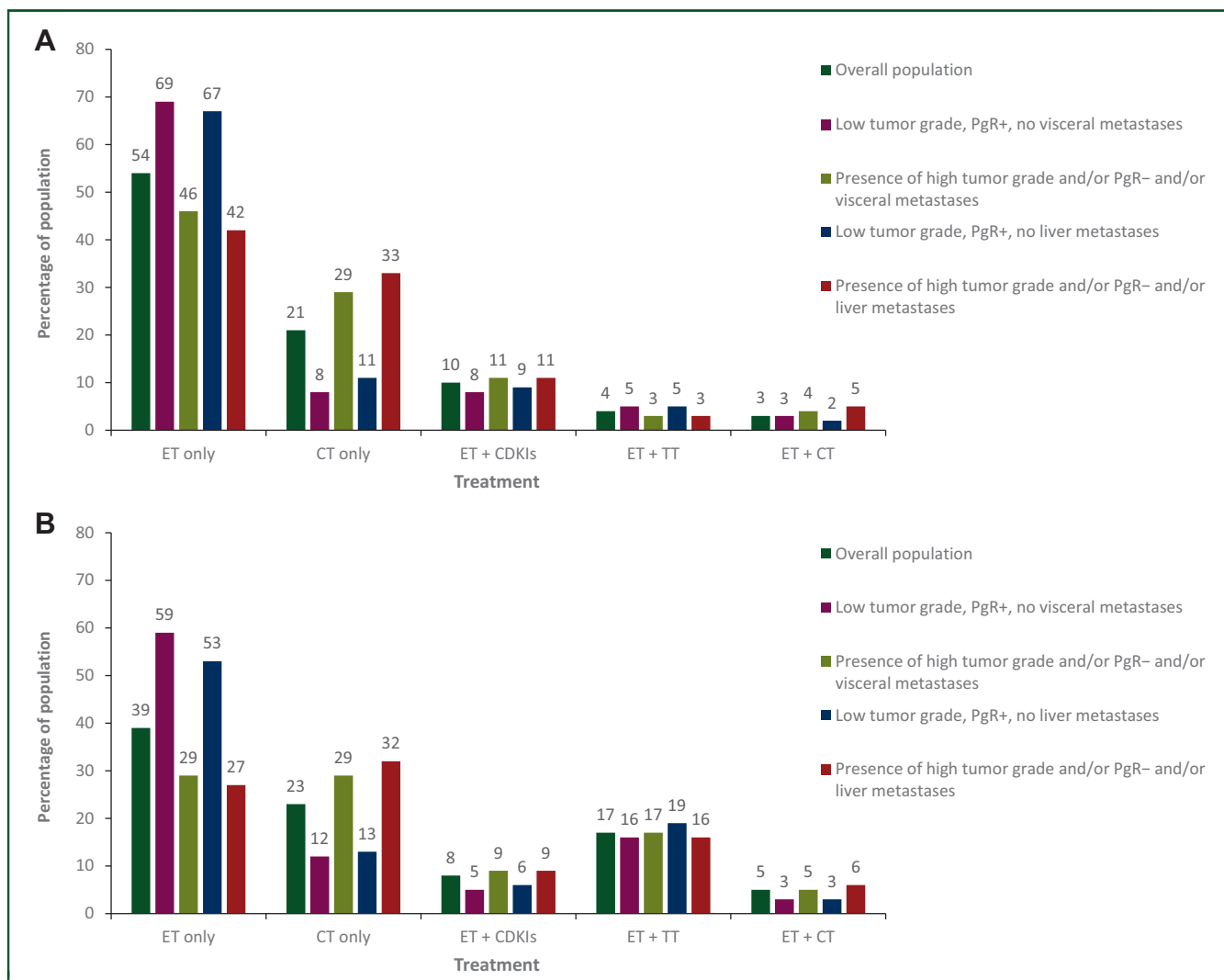


Figure 2. Major classes of (A) first-line and (B) second-line treatments for HR+/HER2- ABC (received by ≥4% of total population) by presence or absence of poor prognostic factors. Data reflect treatment of the patient at the time of the analysis. For those receiving their first-line advanced treatment, the most common single agent endocrine therapy regimen was letrozole (47%) followed by fulvestrant (13%). For chemotherapy alone these were paclitaxel (16%) and capecitabine (16%). For those receiving their second-line advanced treatment, the most common single agent endocrine therapy regimen was fulvestrant (40%) followed by letrozole (23%). For chemotherapy alone these were capecitabine (36%) and paclitaxel (25%).

ABC, advanced breast cancer; CT, chemotherapy; CDKIs, cyclin-dependent kinase 4 & 6 inhibitors; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; PgR, progesterone receptor; TT, targeted therapies.

data are given for patients with known relevant information only.

In the overall population of patients with HR+/HER2- ABC, trends for physician-assessed current performance status and patient’s ADL generally corresponded. The proportions of patients with a current performance status of 0 (i.e. fully active), or with no decrease in estimated ADL, were higher in patients without the selected poor prognostic factors than in those with these factors. Although no formal statistical analysis was conducted, the presence of liver metastases appeared to be most prominently associated with decreased performance status and ADL, and the absence of metastases (i.e. patients with stage IIIB/C disease) appeared to be associated with better performance status and ADL. For example, 22% of patients with liver metastases had a current performance status of 0 compared with 49% of patients with no metastases, and

the corresponding values for no reduction in ADL were 26% versus 42% (Table 2).

There was a general trend showing that the proportion of premenopausal patients increased with an increasing number of poor prognostic factors.

First- and second-line treatments

At the time of the analysis (March-June 2017), the most common first-line treatment regimens were endocrine monotherapy and chemotherapy (Figure 2A). Chemotherapy was prescribed more frequently in patients with poor prognostic factors than in those without poor prognostic factors (26% versus 9%). Conversely, ET was prescribed more often among those without poor prognostic factors than among those with poor prognostic factors (70% versus 48%). The prescription pattern did not appear to

Table 3. HRQoL by type of poor prognostic factor

HRQoL	Tumor grade ^a		PgR status ^b		Metastases ^c				Any poor prognostic factor ^f
	High (3)	Low (1/2)	Positive	Negative	Presence of visceral ^d	Presence of liver ^e	Presence of bone only	No metastases	
EQ-5D-3L ^g	146	406	547	125	311	166	140	124	353
Mean (SD)	0.70 (0.20)	0.70 (0.30)	0.70 (0.30)	0.70 (0.30)	0.69 (0.29)	0.70 (0.30)	0.70 (0.23)	0.81 (0.22)	0.72 (0.28)
EQ-5D-VAS	147	398	539	124	310	165	138	124	353
Mean (SD)	60.20 (23.00)	60.70 (20.90)	60.40 (20.90)	54.90 (25.50)	58.85 (23.08)	54.70 (23.30)	62.60 (20.86)	56.81 (21.38)	60.97 (22.23)
Global health status ^h	146	404	544	125	309	166	139	125	350
Mean (SD)	55.10 (24.00)	53.80 (22.90)	54.10 (23.00)	49.50 (25.30)	51.81 (23.41)	46.10 (22.40)	71.40 (23.77)	48.93 (22.82)	53.50 (23.35)
Activity impairment ⁱ	146	402	538	125	305	164	140	125	348
Mean (SD)	42.10 (26.70)	41.30 (25.10)	41.40 (25.20)	47.90 (26.60)	43.74 (25.70)	48.00 (25.40)	37.20 (24.67)	48.8 (24.91)	42.41 (26.26)

EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL, health-related quality of life; PgR, progesterone receptor; SD, standard deviation; VAS, visual analogue scale.

^a Total base size represents patients with known tumor grade; those with an unknown tumor grade are not reported.

^b Total base size represents patients with known PgR status; those with an unknown status are not reported.

^c Total base size represents patients with known metastatic status; those with an unknown status are not reported.

^d Patients with liver, lung, adrenal gland, peritoneum or pleura, brain and dura metastases, with or without other metastases.

^e Patients with liver metastases, with or without other metastases.

^f Patients with known tumor and PgR status and known visceral metastases, PgR— status and/or high tumor grade (3).

^g Patients voluntarily completed the patient self-completion forms (PSCs), which may cause variation in base size.

^h Captured by the EORTC QLQ-C30.

ⁱ Captured percent activity impairment due to breast cancer by the Work Productivity and Activity Impairment Questionnaire (WPAI).

differ whether visceral or specifically liver metastases were present. The combination of ET plus CDK4 and 6 inhibitors was prescribed as first-line therapy in 10% and 11%, respectively, of those with visceral or specifically liver metastases. Overall, the use of ET plus CDK4 and 6 inhibitors was slightly higher in patients with than in those without poor prognostic factors (Figure 2A). Of the overall population ($n = 2259$), 7% received ET plus CDK4 and 6 inhibitors at first line.

Geographically, the prescribing pattern of first-line treatments appeared to be broadly similar between the USA and EU5, with a few exceptions. Chemotherapy use was higher across the EU, particularly for patients with poor prognostic factors (EU5, 29%; USA, 19%). For those with no poor prognostic factors, European physicians prescribed aromatase inhibitors more frequently than did US physicians (EU5, 52%; USA, 39%). (Data for both comparisons were essentially the same considering the presence of visceral or specifically liver metastases.) In total, 29% of all patients in the USA versus 3% of all patients in the EU5 were prescribed CDK4 and 6 inhibitor plus ET combination treatment.

In second-line therapy following disease progression, ET monotherapy and chemotherapy were the most frequently prescribed regimens. Chemotherapy was the preferred option for those with poor prognostic factors (31% versus 13% for those without these factors), and ET was the most prescribed option for patients without these factors (64% versus 29%, respectively). Again, the presence of visceral or specifically liver metastases did not appear to markedly affect the treatment pattern (Figure 2B).

HRQoL by type of poor prognostic factor

HRQoL status (EQ-5D-3L; EQ-5D-VAS; EORTC QLQ-C30) and WPAI analyzed by number, presence and type of poor

prognostic factor are provided in Table 3. Patients with bone-only metastases were also included to provide context, since this group tends to have a better prognosis than those with the selected factors. Overall, 676 patients provided information for at least one patient-reported outcome instrument. Again, this analysis was carried out in patients with confirmed presence or absence of poor prognostic factors. Given the range of SDs for all values, there were no meaningful trends for any parameter. However, when considering EORTC QLQ-C30 global health status, scores were numerically lower (worse) for patients with liver metastases than for those with bone-only metastases (46.1 versus 71.4). Similarly, EQ-5D-VAS scores were also numerically lower (worse) when comparing these two patient subgroups (54.7 versus 62.6; Table 3). Additional findings for the EORTC QLQ-BR23 and the functional and symptom scales of the EORTC QLQ-C30 are available in Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2021.100226>.

Most patients (84%) had no or mild current pain reported by the physician at the time of survey. In general, the proportions of patients with no current pain decreased with presence of poor prognostic factors (Table 2). The highest proportion of patients with no pain was in those with no metastases.

Non-opioid analgesic use was highest in patients without poor prognostic factors (59%) versus those with poor prognostic factors (48%). Weak opioid use was higher in patients with poor prognostic factors than in those without these factors (24% versus 20%), as was the use of strong opioid analgesics (22% versus 14%).

DISCUSSION

The present analysis characterized a large European and US real-world population of patients with HR+/HER2— ABC in

terms of demographic and disease characteristics, patient-reported outcomes and treatment received, with a specific focus on poor prognostic factors. These factors were present in >60% of the HR+/HER2- ABC patient sample, with varying overlap. This confirms that HR+/HER2- ABC patients are heterogeneous regarding both the occurrence and the distribution of poor prognostic factors, which may have consequences regarding choice of treatments.

Patients with HR+/HER2- ABC in this study were predominantly postmenopausal, had one to two metastases, were symptomatic (mostly fatigue) and had one or more comorbidities (most often hypertension). Across geographies, the populations were broadly similar regarding baseline characteristics. The US population included ~20% African-American women, which may explain the higher prevalence of diabetes and hyperlipidemia in this study.⁴⁹⁻⁵¹ It was noted that the German population were younger and healthier than the populations of other EU5 countries. Although the reason for this difference is unclear, it is unlikely that it materially biased the results. Indeed, 80% of patients overall had an ECOG performance status of <2, suggesting relatively high health in this population. The mean age of this study sample was 64.3 years (SD: 11.98 years), and 88% were postmenopausal. While these characteristics align with studies that show HR+/HER2- ABC patients are more likely to be diagnosed at an older age and be postmenopausal,⁵² this study may underestimate the true impact of poor prognostic factors on the younger population. It is acknowledged that younger age may be a negative prognostic factor in HR+/HER2- breast cancer, being associated with more aggressive tumors and poorer survival.⁵³ The proportion of premenopausal patients in this study was associated with an increasing number of poor prognostic factors.

In this study, 58% of patients with HR+/HER2- ABC were diagnosed with *de novo* metastatic breast cancer. This percentage is markedly higher than that estimated by the American Association for Cancer Research (28%).⁵⁴ The reason for this difference is unclear. It may be that improved treatments in the adjuvant setting are reducing the proportion of patients progressing to metastatic breast cancer.⁵⁵ This appears to be reflected not only in our findings but also in those from another recent observational registry, which showed a rate of ~50% for *de novo* metastases, although these patients had HR+/HER2+ ABC.⁵⁶ A further curious finding was that more than one-quarter of patients diagnosed at an early stage of breast cancer received no adjuvant treatment of any type.

Among the 2259 patients included in the analysis, 676 completed PSC forms on patient-reported outcomes, and this relatively low proportion (~30%) may have introduced potential bias in terms of HRQoL. Completion of PSC forms was voluntary; possible reasons for their non-completion may be disease symptom burden, lack of time, interest or appreciation for the value of patient-reported outcomes data. In general, HRQoL and WPAl evaluations revealed no meaningful trends. It has also been previously noted, however, that patients with HR+/HER2- ABC had no or

moderate reported problems for items on the EQ-5D-3L scale.³⁹ Assessment of pain was physician reported and was therefore subjective. Most patients were deemed to have no/mild pain, and most analgesic use comprised non-opioids or weak opioids. The proportion of patients experiencing pain increased in the presence of poor prognostic factors, especially metastases. As might be expected, the presence of liver metastases was especially associated with reported pain. Also noteworthy is that our analysis showed that the proportion of patients with no pain decreased as the number of poor prognostic factors increased. In addition, EORTC QLQ-C30 global health status and EQ-5D-VAS scores were numerically lower (worse) among patients with liver metastases than among those with bone-only metastases. Taken together, these findings appear to highlight an unmet treatment need for patients with poor prognostic factors.

Despite the presence of no or mild pain in most patients, and the lack of any meaningful changes in HRQoL or WPAl data, ECOG performance status and estimated ADL declined with the presence of poor prognostic factors, especially liver metastases. These findings also underscore the impact of poor prognostic factors, particularly metastases, on physical function in this population. Overall, the data confirm our decision to highlight liver metastases (a subtype of visceral metastases) as a poor prognostic factor.

The data for our analysis were collected during the earlier part of 2017, when CDK4 and 6 inhibitors were relatively new and had not yet been fully integrated into routine clinical practice. As expected, at the start of this revolutionary change in the treatment landscape, the most common treatment options for first- and second-line HR+/HER2- ABC were ET only and chemotherapy only, broadly following treatment guidelines.¹⁹ The proportion of patients treated with chemotherapy was higher than expected, with an observed increase in use with the presence of poor prognostic factors. These findings aligned with a retrospective analysis of US patients with poor prognostic factors initiating treatment of advanced disease between 2008 and 2017.⁵⁷ The authors reported that 33% and 27% of the patient sample received an aromatase inhibitor- and chemotherapy-containing regimen, respectively. A higher proportion of those with liver metastases received chemotherapy. The presence of poor prognostic factors was associated with lower median real-world survival. Approximately half of those presenting with visceral metastases had primary endocrine resistance, illustrating the aggressive nature of the disease and limited treatment options available.

It is important to note that, although the frequency of CDK4 and 6 inhibitor use was low in the overall population, use of this class in combination with ET was slightly higher among those with poor prognostic factors. Twenty-nine percent of US patients with poor prognostic factors were prescribed first-line combination therapy with ET plus CDK4 and 6 inhibitor. The proportion of patients in the EU5 was just 3%; reflecting the limited access to this class at the time of the analysis. These early findings were indicative of the substantial impact of the class of CDK4 and 6 inhibitors on

this patient population. This highlighted the need for treatments to overcome ET resistance, delay the use of chemotherapy, and show not only clinical improvements but improvements in symptom burden and daily living in the overall population and among those with poor prognostic factors.

Findings from a recently published exploratory subgroup analysis using data from the MONARCH 2 and MONARCH 3 phase III trials, evaluating abemaciclib, demonstrated that patients with poor prognostic factors, including liver metastases, PgR– status and high tumor grade derived the largest benefit from the addition of abemaciclib to ET compared with other patient subgroups.⁹ The analysis was designed to determine independently prognostic subgroups of patients and characterize the benefit of adding abemaciclib to ET. Moreover, subgroup analysis from the MONARCH 2 trial demonstrated consistent improvements in overall survival with the addition of abemaciclib to the ET backbone.³³

The DSP approach to collecting data has limitations. First, the sample collected is not a truly random sample of patients, as the methodology states that the next ‘*n*’ consulting patients meeting the inclusion criteria are included. Patients included in the DSP sample are the next 10 suitable patients who consult with the physician and meet the eligibility criteria. Therefore, they represent a convenience sample and may not be fully representative of the overall population of ABC patients, as patients who consult frequently are more likely to be included in the sample. The DSP systematic approach to recruitment nevertheless reduces selection bias. Second, although physicians are requested to collect data on a series of consecutive patients to avoid selection bias, in the absence of randomization this is contingent on the integrity of the participating physician rather than formalized source verification procedures. Third, the quality of data depends to a large extent on the accurate reporting of information by physicians and patients, which may be subject to recall bias. A further limitation of the DSP is that, being point in time, it cannot be used to demonstrate cause and effect. However, this is not the primary purpose of the DSP, which is to provide a descriptive analysis of the population characteristics and treatment patterns rather than attempting to make statistical inferences. This may also be a limitation.

In conclusion, this large international study provides real-world data on treatment patterns, patient-reported outcomes, and demographic and clinical characteristics of patients with HR+/HER2– ABC, focusing on those with poor prognostic factors. These patients typically have increased pain and reduced performance status. There is a need to improve the efficacy of ET-based regimens and better understand the patient’s perspective as it relates to disease and treatment burden in this population. As a baseline for change, these findings could support future research into the real-world effectiveness of current treatments for HR+/HER2– ABC patients with poor prognostic factors and more aggressive disease; which would be of interest to decision-makers.

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DISCLOSURE

AD, GCC and GP have disclosed that they are employees of Eli Lilly and Company. FR and HO have disclosed they were employees of Eli Lilly and Company during the development of the analysis. AB, AR and KL have disclosed that they are employees of Adelphi Real World Ltd, who own the multi-sponsored Disease Specific Programme, and were paid by Eli Lilly and Company Ltd in the development of this analysis and manuscript. XP has disclosed an advisory role with Eli Lilly and Company, for which an honorarium was received from Eli Lilly and Company Ltd for consultancy support in the development of this analysis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ABC DSP followed European Pharmaceutical Marketing Research Association guidelines and adhered to the ICC/ESOMAR International Code on observational research. The study protocol was reviewed and approved by the FEKI institutional review board. All patients included in the DSP provided written informed consent to participate. All data were anonymized and aggregated before receipt by Adelphi Real World for analysis.

DATA SHARING

The dataset supporting the conclusions of this article is included within the article (and its additional files).

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