Patient database analysis of fulvestrant 500 mg in the treatment of metastatic breast cancer: A European perspective

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Original article

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Paolo Marchetti [a, *], Nicolai Maass [b], Joseph Gligorov [c], Karin Berger [d], Finlay MacDougall [e], Jukka Montonen [f], Jan Lewis [f]

[a] Department of Clinical and Molecular Medicine, Sapienza University of Rome and IDI-IRCCS, Rome, Italy
[b] Department of Gynecology and Obstetrics, University Medical Center Schleswig-Holstein, Kiel, Germany
[c] Department of Medical Oncology, INSERM U938, APHP Tenon, IUC-UPMC, Sorbonne University, Paris, France
[d] Real World Evidence Solutions and HEOR, IMS Health, Munich, Germany
[e] Real World Evidence Solutions and HEOR, IMS Health, London, United Kingdom
[f] AstraZeneca, London, United Kingdom

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ABSTRACT

Introduction: Clinical guidelines recommend that patients with hormone receptor (HR)-positive metastatic breast cancer (MBC) should be preferentially treated with endocrine therapy. Fulvestrant (a selective estrogen receptor degrader) is approved for use in these patients following relapse after, or relapse or progression during, antiestrogen therapy. This descriptive study analyzed European treatment patterns for HR-positive MBC in real-world clinical practice.

Methods: The IMS Oncology Analyzer (OA), a retrospective cancer treatment database reporting physician-entered patient case histories, was used to identify records for postmenopausal women with HR-positive MBC from April 1, 2004 to June 30, 2013 in France, Germany, Italy, and Spain. Treatments were allocated to mutually exclusive categories (fulvestrant-containing, aromatase inhibitor [AI]-containing, tamoxifen-containing, or chemotherapy-containing regimens) and assessed by line of therapy for MBC. Fulvestrant use was also assessed pre- and post-2010 (when fulvestrant 500 mg dosing was approved).

Results: In total, 27,214 eligible patients were included (France: 6801; Germany: 6852; Italy: 7061; Spain: 6500). Chemotherapy-based regimens were the most common first-line treatments for MBC across all countries. Across countries, the proportion of patients initiating on each treatment category ranged from: chemotherapy, 57.5–70.4%; AI, 23.5–30.1%; tamoxifen, 2.7–9.8%; fulvestrant 0.8–2.6%. When administered, fulvestrant was usually given as first- or second-line treatment. Post-2010, more patients received fulvestrant 500 mg than fulvestrant 250 mg in France, Germany, and Spain; in Italy, more patients continued to receive fulvestrant 250 mg.

Conclusion: Most patients with HR-positive MBC receive chemotherapy over endocrine therapy; fulvestrant constitutes a small proportion of treatments for such patients.

1. Introduction

Breast cancer is one of the most prevalent forms of cancer in the world and the most common cancer among women, with over 1.6 million global cases reported in 2010 [1]. Approximately 80% of all breast cancers are hormone receptor (HR)-positive [2]. Expert consensus guidelines from the European School of Oncology-European Society of Medical Oncology (ESO-ESMO), first published in 2012 [3] and updated in 2014 [4], advise that, even in the presence of asymptomatic visceral metastases, patients with HR-positive, HER2-negative advanced breast cancer should be preferentially treated with endocrine therapy. Due to tolerability issues and the efficacy of endocrine therapies, guidelines recommend that

* Corresponding author. Department of Clinical and Molecular Medicine, Sapienza University of Rome, Via di Grottarossa, 1035–1039, 00189, Rome, Italy.
E-mail addresses: paolo.marchetti@ospedalesantandrea.it (P. Marchetti), Nicolai.Maass@uksh.de (N. Maass), joseph.gligorov@aphp.fr (J. Gligorov), KBerger@de.imshealth.com (K. Berger), FMacDougall@uk.imshealth.com (F. MacDougall), jukka.montonen@astrazeneca.com (J. Montonen), Jan.Lewis@astrazeneca.com (J. Lewis).

chemotherapy agents should be reserved for patients with rapidly progressing disease or endocrine resistance.

Several endocrine agents are approved and available to treat HR-positive metastatic breast cancer (MBC). The selective estrogen receptor (ER) modulator, tamoxifen, is an antagonist of the ER on ER-positive breast-cancer cells. Aromatase inhibitors (AIs) which impede the conversion of circulating androgens to estrogen, such as the non-steroidal AIs anastrozole [5] and letrozole [6] and the steroidal AI exemestane [7], have demonstrated at least equivalent or superior efficacy compared with tamoxifen in the treatment of postmenopausal women with locally advanced breast cancer and/or MBC, with an improved tolerability profile.

Fulvestrant, an ER antagonist with no known agonist effects, suppresses estrogen signaling by binding to and degrading the ER [8,9]. Fulvestrant 250 mg was approved by the European Medicines Agency (EMA) in 2004 for the treatment of postmenopausal women with ER-positive locally advanced breast cancer or MBC for disease relapse on or after adjuvant antiestrogen therapy, or disease progression on therapy with an antiestrogen. Fulvestrant was approved as a monthly 250 mg dosing regimen based on time-to-progression data demonstrating non-inferiority versus anastrozole in postmenopausal women whose advanced breast cancer had progressed during prior antiestrogen therapy [10]. However, early clinical observations, combined with preclinical data suggesting a dose-dependent suppression of ER [11], prompted investigation of fulvestrant treatment at higher doses. The international CONFIRM trial compared fulvestrant 500 mg (fulvestrant 500 mg every month with an additional 500 mg loading dose on Day 14 of the first month) with the monthly 250 mg dose and demonstrated that fulvestrant 500 mg was associated with improved progression-free survival and overall survival (OS) in postmenopausal women with HR-positive advanced breast cancer whose disease had recurred or progressed after prior endocrine therapy [12,13]. As a result of these findings, fulvestrant 500 mg was approved by the EMA in 2010. Recently, an OS benefit for fulvestrant 500 mg compared with anastrozole has been suggested in the first-line treatment of advanced breast cancer [14]. Given the distinct mechanism of action and lack of cross-reactivity of fulvestrant compared with other endocrine therapies [15], fulvestrant would also appear to be a suitable candidate for combination therapy [16].

Real-world evidence studies provide important data on the use of therapies which can be used to compare routine clinical practice with guideline recommendations. Using data from a pan-European clinical database, the aims of this study were to identify treatment patterns by class and line of therapy in routine clinical management of patients with HR-positive MBC, and to assess patterns of fulvestrant use.

2. Methods

2.1. Data source

The data source was Oncology Analyzer (OA; IMS Health, London, UK). OA is a fully syndicated, retrospective, longitudinal cancer treatment database collecting anonymized patient-level oncology data in France, Germany, Italy, Spain, and the UK. The database reports patient case history information relating to the treatment of patients across all cancer types. Physicians in the OA panel contribute data during a 7–28-day period each quarter; for every patient they personally treat in that period (up to a specified cap ranging from 14 to 19 patients per doctor quarterly), the physician completes an OA case report form, using the patient's medical records to produce an individual case history. The OA captures approximately 2–4% of the treated prevalence across cancer types. This process is supplemented by additional data on specific indications and sub-populations such as MBC from the Enhanced Tumor Studies (ETS) database, which requests additional information from a different panel of physicians to OA, with a minimal overlap of physicians permitted. In this manner, approximately 7–10% of the treated prevalence of MBC is covered by this study.

2.2. Study design

This analysis reports treatment patterns for the relevant therapies in routine clinical care in France, Germany, Italy, and Spain. In the OA, patient records are available retrospectively from the date the physician completes the case report form detailing the diagnosis. Each patient record contains information post-diagnosis until the date the case report form is completed. Although no information is available on the patient prior to their diagnosis date, the OA questionnaire captures a range of oncology-relevant information.

2.3. Study population

Postmenopausal (status as recorded in OA) women with HR-positive MBC and a concomitant tumor stage assessment of III or IV were identified during an observation period from April 1, 2004 (immediately post-EMA approval of fulvestrant 250 mg for treatment of breast cancer) to June 30, 2013. Patients could either be diagnosed with MBC, or have been originally diagnosed with primary breast cancer with subsequent metastases, and were required to have received their diagnosis within the specified observation period; the date of diagnosis of metastatic disease was used as the index date. Patients were excluded only if they had participated in a clinical trial evaluating a drug for breast-cancer treatment at any time.

2.4. Analyses of treatment patterns

Patient records were subsequently assessed for inclusion in therapy categories using the Anatomical Therapeutic Chemical Classification System, and were allocated to one of four mutually exclusive categories in order of descending priority: fulvestrant-containing regimen; AI-containing regimen; tamoxifen-containing regimen; or chemotherapy-containing regimen (including cyclophosphamide, methotrexate and 5-fluorouracil, anthracyclines, taxanes, trastuzumab, lapatinib, bevacizumab,

Table 1
Patient attrition.

Inclusion criteria	France	Germany	Italy	Spain	Total
Breast tumor	29,467	27,602	27,518	26,899	111,486
HR-positive (HR-negative excluded)	19,380	18,715	18,661	16,795	73,551
Tumor stage III or IV (tumour stage I and II excluded)	10,174	10,503	10,919	9774	41,370
Female (males excluded)	10,165	10,489	10,904	9753	41,311
Postmenopausal (premenopausal excluded)	8350	8935	8660	7830	33,775
Diagnosis April 1, 2004 to June 30, 2013 (diagnoses outside this period excluded)	7056	7260	7432	6794	28,542
No prior participation in a clinical trial (any prior participation in clinical trial excluded)	6801	6852	7061	6500	27,214
Final population eligible for analysis	**6801**	**6852**	**7061**	**6500**	**27,214**

HR, hormone receptor.

Table 2
Distribution of first-line therapies by class-based regimen.

	N	Fulvestrant	AI	Tamoxifen	Chemotherapy
		n (%)	n (%)	n (%)	n (%)
France	6736	53 (0.8)	1841 (27.3)	182 (2.7)	4660 (69.2)
Germany	6702	172 (2.6)	2018 (30.1)	659 (9.8)	3853 (57.5)
Italy	6874	101 (1.5)	1614 (23.5)	317 (4.6)	4842 (70.4)
Spain	6368	99 (1.6)	1739 (27.3)	279 (4.4)	4251 (66.8)
All	**26,680**	**425 (1.6)**	**7212 (27.0)**	**1437 (5.4)**	**17,606 (66.0)**

AI, aromatase inhibitor.

everolimus, pertuzumab, trastuzumab emtansine, cyclophospha-mide, capecitabine, vinorelbine, gemcitabine, eribulin, cisplatin, etoposide, vinblastine, and fluorouracil). As patients receiving human epidermal growth factor receptor 2 (HER2)-targeted therapy were included in this primary analysis as having received chemotherapy, a subanalysis was performed among patients with HER2-positive disease in order to assess the proportion who received HER2-targeted therapy in the first- and second-line settings. For this analysis, HER2-positive disease was confirmed when the patient: had immunohistochemistry status of ≥3; had immunohistochemistry status of 2 with positive *in situ* hybridization results; had immunohistochemistry status of 2 with documented trastuzumab treatment; or had positive *in situ* hybridization results with no immunohistochemistry results. To identify single regimens of combination therapies and to distinguish between lines of therapy in OA, treatments were considered part of one regimen if they started within 5 days of each other, or if the duration of therapy of one treatment ran entirely within the duration of another (including treatments ending on the same day). The latest end date for the drug(s) in the regimen was considered the end of that treatment regimen; any drug that started on the end date of another regimen was considered a new treatment line. Therapies without an end date (i.e. those that were ongoing at the time of the physician questionnaire) were considered as part of one line of therapy. Chemotherapies and endocrine therapies could be considered to be part of the same combination regimen if they satisfied the above criteria. For the purposes of this analysis, lines of therapy did not consider neoadjuvant or adjuvant treatments and refer specifically to the lines of therapy for advanced disease.

The influences of multiple patient characteristics on dosing regimen were assessed; these characteristics included: age, Eastern Cooperative Oncology Group (ECOG) performance status, previous cardiovascular disease, HER2/neu status, lymph-node status, tumor stage, prior breast-cancer status (i.e. initial diagnosis), neoadjuvant treatment, date of diagnosis, type and duration of prior therapies. Reasons for treatment discontinuation, frequency of surgical procedures, costs of treatment regimens, and the number of patients treated with chemotherapy eligible for endocrine therapy were also assessed. Additionally, fulvestrant-containing regimens were also

assessed by dosage for pre- and post-2010 regimens (fulvestrant 500 mg was approved by the EMA in 2010). Specific therapy regimens in the first- and second-line settings were also recorded for each country. The proportion of patients receiving chemotherapy who were eligible for endocrine therapy (i.e. had newly diagnosed, untreated MBC; relapse during previous AI treatment; or recurrence after previous tamoxifen or AI treatment) was also recorded.

All results from this observational report are presented descriptively, with no additional statistical analyses performed. Submission to independent ethics committee was not required for OA, as data were collected on the basis of a questionnaire where the physician provided anonymized data.

3. Results

3.1. Patients

A total of 27,214 eligible patients were included in this study (France: 6801 patients; Germany: 6852 patients; Italy: 7061 patients; Spain: 6500 patients) (Table 1). The majority (over 60%) of patients at treatment initiation had no recorded treatment of breast cancer prior to their metastatic diagnosis, with the exception of patients initiating on fulvestrant, most of whom (83.5%) had initially been diagnosed with non-metastatic (i.e. early) breast cancer. Approximately half (51.5%) of all included patients were between the ages of 56 and 70 years (the median age range in all countries was 61–65 years). Most patients (82.6%) in this study had an ECOG performance status of 0 or 1. A positive-HER2/neu immunohistochemistry (IHC) status was confirmed for 21.8% of all patients.

3.2. Treatment patterns

In the first-line setting for MBC, chemotherapy-based regimens were the most common treatments across all countries assessed (Table 2). The proportion of patients with MBC who received first-line chemotherapy ranged from 57.5% in Germany to 70.4% in Italy. AIs were administered as first-line treatment in 23.5% (Italy) to 30.1% (Germany) of patients; tamoxifen in 2.7% (France) to 9.8% (Germany) of patients; and fulvestrant in 0.8% (France) to 2.6% (Germany) of patients. Patients receiving first-line chemotherapy tended to be younger than patients receiving tamoxifen or AIs in the first-line setting.

Specific treatment regimens used in the first- and second-line setting are shown in Table 3. Letrozole and anastrozole were among the five most commonly given first-line therapies in this patient group in every country assessed (first and second, respectively, in both Germany and Spain). The only country where tamoxifen was given as one of the most common therapies was Italy. Fulvestrant was not one of the 10 most commonly given first-line therapies in any country. In the subanalysis of patients with

Table 3
Specific therapy regimens administered in the first- and second-line setting for HR-positive MBC.

First-line therapies

	France (N = 6737)	n (%)	Germany (N = 6706)	n (%)	Italy (N = 6875)	n (%)	Spain (N = 6370)	n (%)
1	5-fluorouracil / cyclophosphamide / epirubicin	1024 (15.2)	Letrozole	723 (10.8)	5-fluorouracil / cyclophosphamide / epirubicin	878 (12.8)	Letrozole	701 (11.0)
2	Bevacizumab / paclitaxel	621 (9.2)	Anastrozole	648 (9.7)	Letrozole	548 (8.0)	Anastrozole	463 (7.3)
3	Anastrozole / letrozole	567 (8.4)	5-fluorouracil / cyclophosphamide / epirubicin	456 (6.8)	Anastrozole	357 (5.2)	Cyclophosphamide / doxorubicin	410 (6.4)
4	Letrozole	546 (8.1)	Tamoxifen	450 (6.7)	5-fluorouracil / cyclophosphamide / methotrexate	326 (4.7)	Docetaxel	345 (5.4)
5	Docetaxel	423 (6.3)	Cyclophosphamide / epirubicin	365 (5.4)	Docetaxel / epirubicin	299 (4.3)	Cyclophosphamide / docetaxel / doxorubicin	315 (4.9)
6	Docetaxel / trastuzumab	392 (5.8)	Cyclophosphamide / docetaxel / doxorubicin	249 (3.7)	Docetaxel	261 (3.8)	Docetaxel / epirubicin	251 (3.9)
7	Docetaxel / epirubicin	256 (3.8)	Paclitaxel	227 (3.4)	Cyclophosphamide / doxorubicin	244 (3.5)	Paclitaxel / trastuzumab	244 (3.8)
8	5-fluorouracil / cyclophosphamide / docetaxel / epirubicin	247 (3.7)	Paclitaxel / trastuzumab	196 (2.9)	Docetaxel / trastuzumab	236 (3.4)	Paclitaxel	230 (3.6)
9	Capecitabine	237 (3.5)	Exemestane	188 (2.8)	Paclitaxel / trastuzumab	211 (3.1)	Capecitabine	217 (3.4)
10	Paclitaxel	196 (2.9)	Docetaxel	178 (2.7)	Exemestane	170 (2.5)	5-fluorouracil / cyclophosphamide / epirubicin	204 (3.2)
Cumulative total for 10 most commonly used treatments		4509 (66.9)		3680 (54.9)		3530 (51.3)		3380 (52.9)
Total first-line fulvestrant		53 (0.8)		172 (2.6)		101 (1.5)		99 (1.6)
Total first-line chemotherapy		4653 (69.1)		3836 (57.2)		4828 (51.3)		4250 (66.7)
Total first-line ET		2031 (30.1)		2698 (40.2)		1946 (47.2)		2021 (31.7)

Second-line therapies

|	France (N = 3198)		Germany (N = 3400)		Italy (N = 3268)		Spain (N = 3165)	
1	Letrozole	362 (11.3)	Letrozole	383 (11.3)	Letrozole	402 (12.3)	Letrozole	405 (12.8)
2	Anastrozole	351 (11.0)	Tamoxifen	337 (9.9)	Anastrozole	271 (8.3)	Anastrozole	342 (10.8)
3	Capecitabine	334 (10.4)	Anastrozole	284 (8.4)	Tamoxifen	225 (6.9)	Tamoxifen	289 (9.1)
4	Docetaxel	239 (7.5)	Fulvestrant	203 (6.0)	Docetaxel	213 (6.5)	Capecitabine	271 (8.6)
5	Bevacizumab / paclitaxel	148 (4.6)	Docetaxel	188 (5.5)	Exemestane	181 (5.5)	Paclitaxel	209 (6.6)
6	Tamoxifen	120 (3.8)	Exemestane	187 (5.5)	Capecitabine	165 (5.0)	Exemestane	192 (6.1)
7	Paclitaxel	114 (3.6)	Paclitaxel	173 (5.1)	Vinorelbine	114 (3.5)	Fulvestrant	161 (5.1)
8	5-fluorouracil / cyclophosphamide / epirubicin	107 (3.3)	Vinorelbine	168 (4.9)	Paclitaxel	109 (3.3)	Vinorelbine	143 (4.5)
9	Exemestane	105 (3.3)	Capecitabine	149 (4.4)	Capecitabine / vinorelbine	103 (3.2)	Docetaxel	131 (4.1)
10	Trastuzumab	79 (2.5)	Trastuzumab	101 (3.0)	Trastuzumab / vinorelbine	102 (3.1)	Trastuzumab	53 (1.7)
Cumulative total for 10 most commonly used treatments		1959 (61.3)		2173 (64.0)		1885 (57.6)		2196 (69.4)
Total second-line fulvestrant		113 (3.5)		235 (6.9)		101 (3.1)		179 (5.7)
Total second-line chemotherapy		1847 (57.8)		1767 (52.0)		1782 (54.5)		1632 (51.6)
Total second-line ET		1238 (38.7)		1398 (41.1)		1385 (42.4)		1354 (42.7)

ET, endocrine therapy; HR, hormone receptor; MBC, metastatic breast cancer.

Table lists 10 most common specific regimens in each country.

Aromatase inhibitor	Chemotherapy*	Fulvestrant	Tamoxifen

*Including in combination with biologics (including trastuzumab, lapatinib, bevacizumab, everolimus, pertuzumab, and trastuzumab emtansine).
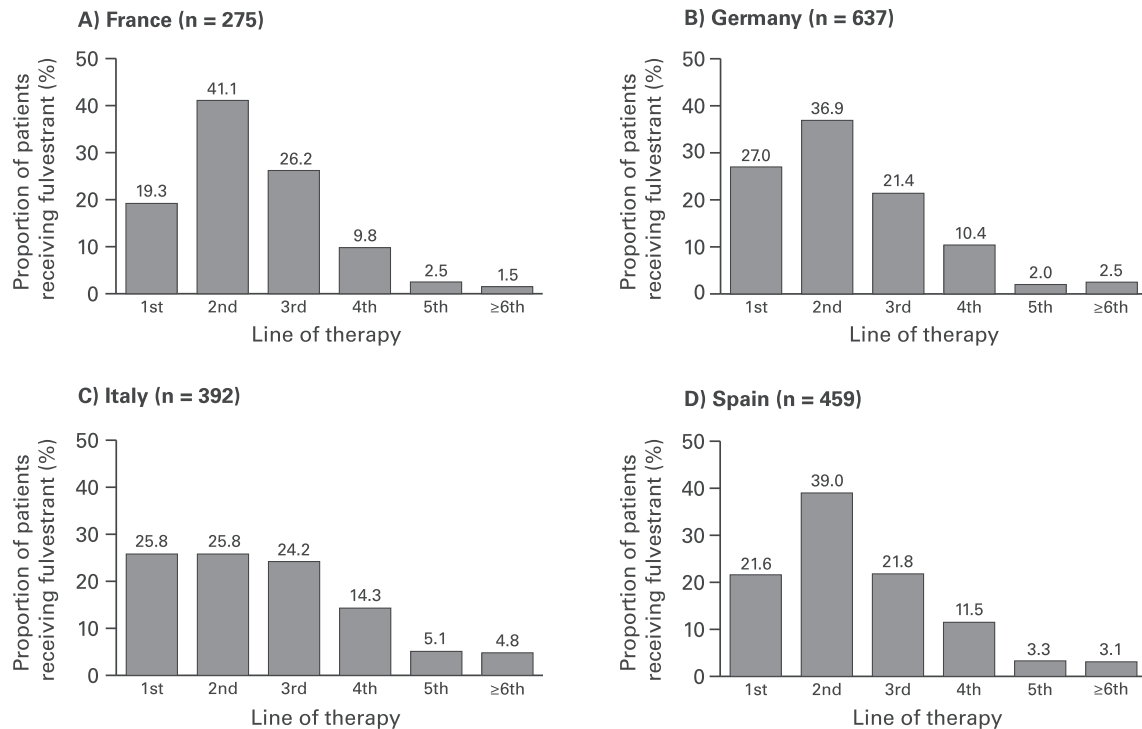
Fig. 1. Fulvestrant use by line of therapy in A) France; B) Germany; C) Italy; D) Spain. Proportion of patients calculated as number of treatments given in each line of therapy relative to total pool of patients for each country (total number of therapies given in each country could exceed total number of patients).

HR-positive, HER2-positive MBC, 59.4% of patients received HER2-targeted therapy in the first-line setting. Of these, 69.6% received HER2-targeted therapy in combination with chemotherapy and 16.5% received HER2-targeted therapy in combination with endocrine therapy; 9.9% received HER2-targeted therapy in combination with both chemotherapy and endocrine therapy, and 4.0% received HER2-targeted therapy alone.

In the second-line setting, several distinct chemotherapy regimens, anastrozole, letrozole, and exemestane, were among the most common therapies in each country. Tamoxifen was also in the five most common therapies in three of the countries assessed (and sixth most common in the other, France). Fulvestrant was only observed as the fourth most common second-line therapy in Germany, and the seventh most common in Spain. In the subanalysis of patients with HR-positive, HER2-positive MBC, 29.7% of patients received HER2-targeted therapy in the second-line setting. Of these, 48.1% received HER2-targeted therapy in combination with chemotherapy and 27.3% received HER2-targeted therapy in combination with endocrine therapy; 6.5% received HER2-targeted therapy in combination with both chemotherapy and endocrine therapy, and 18.1% received HER2-targeted therapy alone.

The majority of patients who received fulvestrant as therapy for MBC received the drug at an early stage in the treatment sequence. In Italy, fulvestrant was most commonly administered in the first-line setting (Fig. 1). In France, Germany, and Spain, fulvestrant was most commonly administered in the second-line setting. Age did not appear to influence the use of fulvestrant, with distribution of age being similar across countries (Fig. 2); in general, across all lines of therapy patients receiving chemotherapy tended to be younger and also to have a lower prevalence of cardiovascular comorbidities than patients receiving endocrine therapies. When treatment patterns were assessed over time in each country, there were no clear discernible trends; it appears that chemotherapy use in France, Italy and Spain may have been decreasing towards the

end of the analysis period (Fig. 3), but remained substantially higher than AI use. In three of the four countries assessed (France, Germany, and Spain), more patients received fulvestrant 500 mg than fulvestrant 250 mg following the approval of the 500 mg regimen in 2010 (Fig. 4); Italy was the only country in which more patients received fulvestrant 250 mg after approval of fulvestrant 500 mg. However, all countries had high proportions of patients who received fulvestrant at an unspecified dose (France, 46.2% of patients; Germany, 58.1%; Italy, 48.0%; Spain, 61.2%).

Approximately 80% of patients in all countries receiving fulvestrant as a first-line therapy for HR-positive MBC had an ECOG performance status of 0 (ranging from 20.8% in France to 30.8% in Germany) or 1 (ranging from 55.2% in Germany to 60.4% in France). These values were similar for fulvestrant given as second-line therapy (ECOG status 0: 18.1% in Germany to 19.4% in Italy; ECOG status 1: 59.3% in France to 66.9% in Spain). Across all countries, the most common reason for discontinuation of fulvestrant treatment in the first three lines of therapy was recorded as distant progression/relapse; the proportion of patients discontinuing first-line fulvestrant for this reason ranged from 29.7% in Italy to 36.0% in Germany.

The proportion of patients who received first-line treatment for MBC with non-fulvestrant endocrine therapies and who went on to receive second-line treatment with fulvestrant ranged from 7.9% in Italy to 15.4% in Spain. After receiving first-line chemotherapy, the proportion of patients receiving second-line treatment with fulvestrant ranged from 1.3% in France to 2.4% in Germany. A high proportion of patients who received chemotherapy were eligible for endocrine therapy; among those who received first-line chemotherapy, the proportion of patients who had been eligible for endocrine therapy ranged from 83.5% in Germany to 87.5% in France. Of patients who received second-line chemotherapy, the proportion of patients who had been eligible for further endocrine therapy ranged from 80.2% in Germany to 92.7% in France.
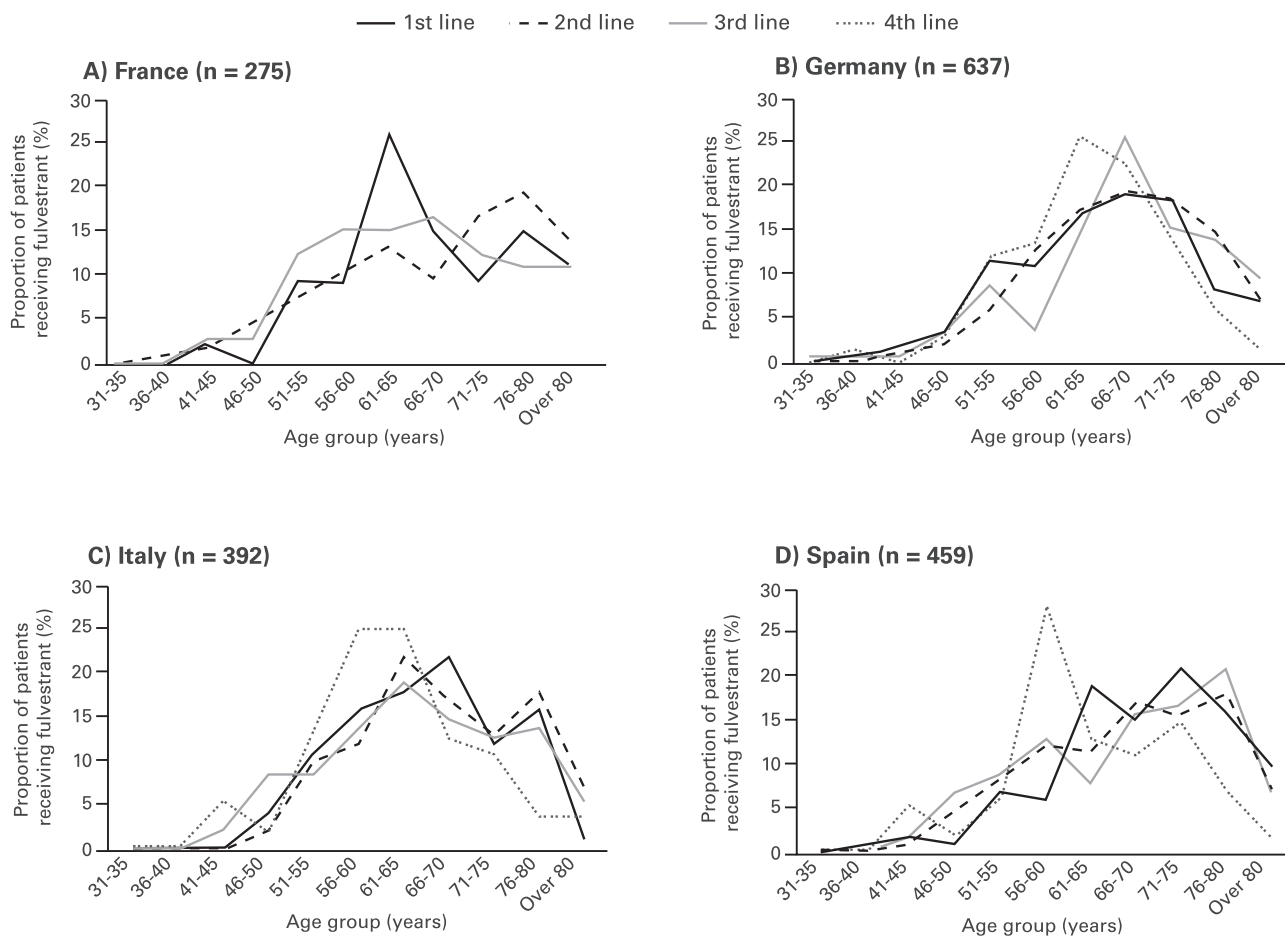
Fig. 2. Age distribution of fulvestrant use by line of therapy in A) France; B) Germany; C) Italy; D) Spain.

4. Discussion

Data from the present study suggest that, in routine clinical practice, the majority of patients received chemotherapy between 2004 and 2013 for first-line treatment of HR-positive MBC in France, Germany, Italy and Spain. These observations support those from a recent United States database analysis reporting similar values for the proportion of patients receiving chemotherapy (40%) and endocrine therapy (60%) for first-line treatment of HR-positive; patients who had received trastuzumab (i.e. were likely to have HER2-positive disease) were excluded from that analysis [17]. Any differences between the present analysis and the results of Swallow et al. after the exclusion of HER2-positive disease could be attributed to methodological differences: the Swallow study used a US claims database, whereas the present analysis assessed physician case-reporting in Europe; the Swallow study used endocrine therapy use as a proxy for HR-positive disease, whereas HR-status was confirmed by physician reporting in the present analysis, meaning HR-positive patients receiving chemotherapy with no prior or subsequent endocrine therapy are not included in the Swallow study; and lastly, the Swallow study was restricted to patients aged >50 years, which may underestimate the use of chemotherapy in younger patients (particularly if chemotherapy is preferentially given to younger patients as suggested by the present analysis). Another study assessing treatment patterns in patients with HR-positive, HER2-negative advanced breast cancer reported fewer patients receiving chemotherapy (approximately 31% of patients) than in the present analysis [18]. Again, aside from the inclusion of

patients with HER2-positive disease in the present analysis, there are several methodological differences which must be taken into account. The Andre study assessed chart records for only 355 patients across Europe, compared with over 27,000 patients in the present analysis. Furthermore, 10% of charts were excluded by the Andre study due to patients having received only one line of therapy for advanced disease. Lastly, the attrition of participating physicians in the Andre study is high (with only 3.4% of invited physicians actually contributing chart data to the final analysis), which may reflect a selection bias; it is possible that these physicians were more likely to administer chemotherapy than the physician pool assessed in our study. In support of this assertion, a subanalysis in the present study demonstrated that the majority of HER2-positive patients received first-line treatment with HER2-targeted therapies and would have been classed as having received chemotherapy in our main analysis. These observations suggests that any assessment of the treatment patterns of patients with postmenopausal HR-positive MBC should consider that the subset of patients with HER2-positive disease are more likely to receive HER2-targeted therapy than the wider clinical population.

ESO-ESMO clinical guidelines [4] suggest that endocrine therapy should be used preferentially in patients with HR-positive, HER2-negative MBC, and chemotherapy should be reserved for patients with rapidly progressing disease or for those likely to be resistant to endocrine therapy. It does appear, in France, Italy and Spain at least, that chemotherapy use may be decreasing with time, in accordance with guideline recommendations. However, chemotherapy use remains higher than AI use in France, Germany and Italy at the end
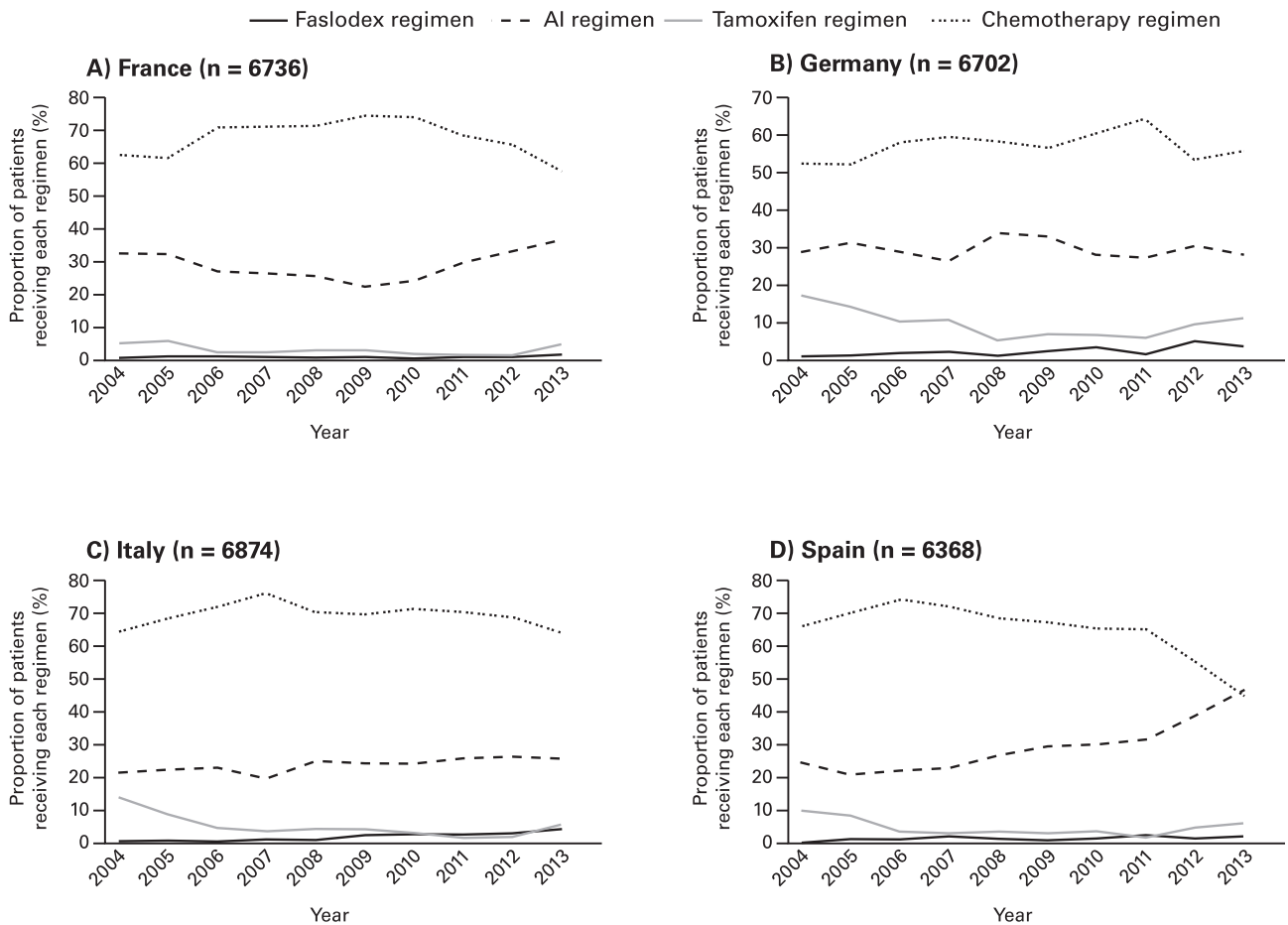
Fig. 3. Treatment regimen use over time in A) France; B) Germany; C) Italy; D) Spain.
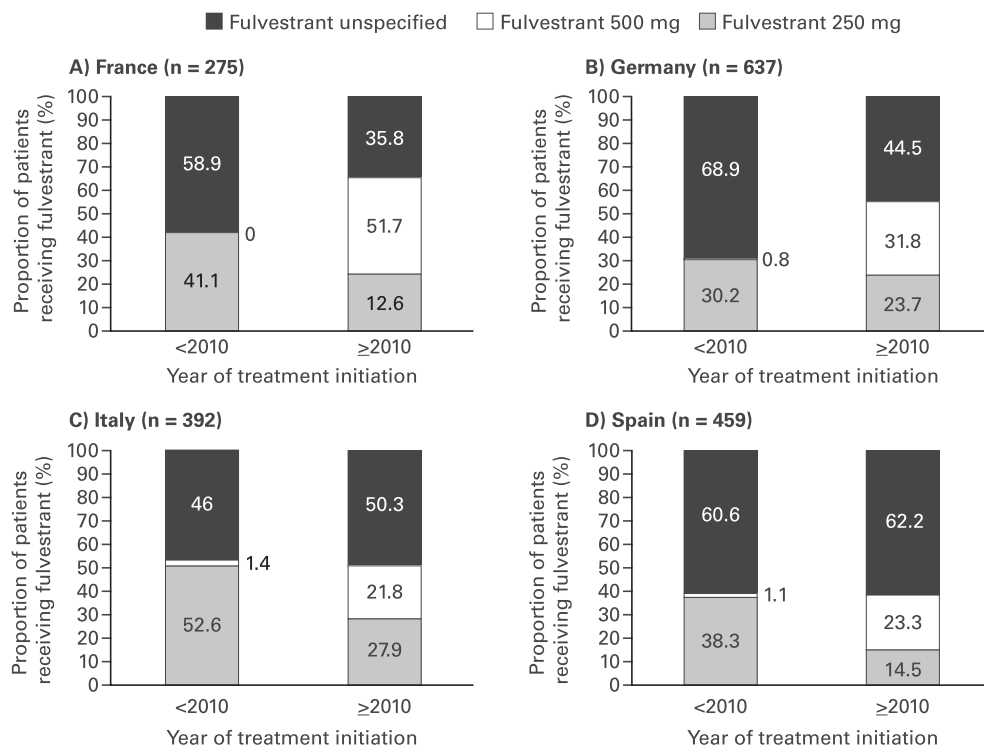

Fig. 4. Fulvestrant 500 mg versus fulvestrant 250 mg dosing pre- and post-2010 in A) France; B) Germany; C) Italy; D) Spain.

of the analysis period. It is not possible from this observational data to assess what proportion of patients were eligible for endocrine therapy by ESO-ESMO criteria, but it is plausible that some of these patients received chemotherapy.

Chemotherapy appeared to be given preferentially to younger patients with a better ECOG performance status; 86% of patients receiving chemotherapy had an ECOG status of 0 or 1. This may reflect a tendency to select chemotherapy for those best able to physically withstand its adverse effects, and for those with a longer subsequent life expectancy. Of the total population, 21.8% of patients could be confirmed as having HER2 protein overexpression as defined by American Society of Clinical Oncology guidelines [19]; approximately 90% of these patients received HER2-targeted therapy (e.g. trastuzumab, classified as chemotherapy in the present study) in the first- or second-line setting, and therefore contribute to the high levels of chemotherapy use observed when used either as monotherapy or in combination with chemotherapy.

Despite the widespread adoption of screening and consequent improvements in early detection of breast cancer, over 60% of patients receiving AIs, tamoxifen, and chemotherapy were classified in this study as having initially presented with metastatic disease without prior hormonal therapy. This proportion is higher than expected and may in part be due to misclassification (a common issue in database studies), or a selection bias among participating physicians; nevertheless it seems likely that a substantial proportion of included patients had not previously received treatment for early breast cancer.

Fulvestrant represented a relatively small proportion (1.6%) of treatment for patients with HR-positive MBC, and was not one of the 10 most common first-line therapy choices in any country assessed. When fulvestrant was administered, it was commonly given early in the treatment sequence, mainly first- or second-line. Patients were more likely to receive second-line fulvestrant following first-line treatment with another endocrine therapy than they were following first-line treatment with chemotherapy; this may indicate an awareness of fulvestrant's lack of cross-reactivity with other endocrine agents (i.e. fulvestrant retains efficacy even when patients have developed resistance to other endocrine therapies), and may also reflect that fulvestrant is currently approved for use following progression on prior endocrine therapy [20]. Following the approval of fulvestrant 500 mg in 2010, there has been a shift towards the use of this regimen; however, a high proportion of fulvestrant treatments recorded did not specify the dosage, particularly in Italy and Spain, where post-2010 dose was not specified for over 50% of patients treated with fulvestrant. It should be noted that although the fulvestrant 500 mg dosing regimen was approved in 2010, it may not have been available to all physicians directly following its regulatory approval.

Strengths of this analysis include the size of the observed population; IMS OA contains detailed oncology-relevant data collected in a consistent way across four major EU healthcare systems, and has been used in previous studies to report treatment patterns in oncology [21,22]. Supplemented by additional ETS data, approximately 7–10% of the treated prevalence of MBC is covered in this study. The patient observation period (April 1, 2004 to June 30, 2013) was chosen to represent the entire time that fulvestrant has been licensed for the treatment of MBC, also providing sufficient data for pre- and post-2010, when fulvestrant 500 mg was approved. However, it should be noted that although the fulvestrant 500 mg dosing regimen was approved in 2010, it may not have been available to all physicians directly following its regulatory approval.

Limitations of this study include that OA provides only a 'snapshot' of patients' clinical experience, and patients are not followed-up after the point of data capture; therefore, OA does not

adequately convey the subsequent progress of their disease and treatment. However, extensive requirements accompany the submission of case reports to OA, and the panel of contributing physicians for each country is carefully selected in order to ensure a representative cross-section of treating physicians.

Another potential limitation is that a very small proportion of patient data was included twice, having been obtained from both OA and ETS; however, as the physician panels are largely distinct, any such miscounting will be minimal; fewer than 5% of contributing physicians were duplicated between databases across the duration of the study period. Additionally, as OA includes only patients with HR-positive breast cancer receiving active treatment, it is likely that these results overlook a pool of patients who are not currently receiving pharmacotherapy at the time of the case report completion. Future studies may evaluate the influence of early-versus late-stage use in treatment sequence, including within the context of novel combinations as supported by emergent evidence [16,23,24]; however, during the period under evaluation, fulvestrant represented a relatively small proportion of the prescribed treatments and conducting observational studies may therefore be difficult due to the low sample size of patients receiving fulvestrant relative to longer-established therapies. Forthcoming data from phase III clinical trials assessing fulvestrant in the first- (NCT01602380) and second-line (such as the recently published PALOMA-3 trial) [16] settings over the next 12 months should further inform clinical decision-making.

In conclusion, patterns of treatment of HR-positive MBC in four European countries appears to favor chemotherapy over endocrine therapy in real-world clinical practice; fulvestrant currently constitutes a relatively small proportion of treatments given to such patients. Current clinical guidelines advocate the use of preferential endocrine therapy in these patients, unless rapidly progressing disease is observed or endocrine therapy resistance suspected.

Conflict of interest statement

Role of the funding source

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