Breast Cancer Res Treat (2017) 163:587–594
DOI 10.1007/s10549-017-4213-9

EPIDEMIOLOGY

Dose intensity and efficacy of the combination of everolimus and exemestane (EVE/EXE) in a real-world population of hormone receptor-positive (ER+/PgR+), HER2-negative advanced breast cancer (ABC) patients: a multicenter Italian experience

Mariangela Ciccarese[1] · Alessandra Fabi[2] · Luca Moscetti[3] · Maria Elena Cazzaniga[4] · Luciana Petrucelli[1] · Rosachiara Forcignanò[1] · Laura Isabella Lupo[1] · Elisabetta De Matteis[1] · Vincenzo Emanuele Chiuri[1] · Giuseppe Cairo[1] · Antonio Febbraro[5] · Guido Giordano[5] · Marianna Giampaglia[6] · Domenico Bilancia[6] · Nicla La Verde[7] · Evaristo Maiello[8] · Maria Morritti[8] · Francesco Giotta[9] · Vito Lorusso[9] · Agnese Latorre[9] · Claudio Scavelli[10] · Sante Romito[11] · Antonio Cusmai[12] · Gennaro Palmiotti[12] · Giammarco Surico[1]

Received: 19 March 2017 / Accepted: 20 March 2017 / Published online: 28 March 2017

Abstract
Aim This retrospective analysis focused on the effect of treatment with EVE/EXE in a real-world population outside of clinical trials. We examined the efficacy of this combination in terms of PFS and RR related to dose intensity (5 mg daily versus 10 mg daily) and tolerability.

✉ Mariangela Ciccarese
m.ciccarese@libero.it

Alessandra Fabi
alessandra.fabi@virgilio.it

Luca Moscetti
l.moscetti@icloud.com

Maria Elena Cazzaniga
marina.cazzaniga@asst-monza.it

Luciana Petrucelli
lucianapetrucelli@hotmail.com

Rosachiara Forcignanò
rosachiaraforcignano@gmail.com

Laura Isabella Lupo
lauralupo74@alice.it

Elisabetta De Matteis
dr.dematteis.elisabetta@gmail.com

Vincenzo Emanuele Chiuri
chiuriv@yahoo.it

Giuseppe Cairo
giuseppecairo15@gmail.com

Antonio Febbraro
antoniofebbraro@virgilio.it

Guido Giordano
giordano.guido81@gmail.com

Marianna Giampaglia
mariannagiampaglia@yahoo.it

Domenico Bilancia
domenico.bilancia@ospedalesancarlo.it

Nicla La Verde
nicla.laverde@fbf.milano.it

Evaristo Maiello
e.maiello@libero.it

Maria Morritti
maria.morritti@gmail.com

Francesco Giotta
francescogiotta@libero.it

Vito Lorusso
vitolorusso@inwind.it

Agnese Latorre
agnelato@libero.it

Claudio Scavelli
clascave@gmail.com

Sante Romito
santeromito@gmail.com

Antonio Cusmai
antoniocusmai@hotmail.com

Gennaro Palmiotti
gennaropalmiotti@hotmail.it

Methods 163 HER2-negative ER+/PgR+ ABC patients, treated with EVE/EXE from May 2011 to March 2016, were included in the analysis. The primary endpoints were the correlation between the daily dose and RR and PFS, as well as an evaluation of the tolerability of the combination. Secondary endpoints were RR, PFS, and OS according to the line of treatment. Patients were classified into three different groups, each with a different dose intensity of everolimus (A, B, C).
Results RR was 29.8% (A), 27.8% (B) ($p = 0.953$), and not evaluable (C). PFS was 9 months (95% CI 7–11) (A), 10 months (95% CI 9–11) (B), and 5 months (95% CI 2–8) (C), $p = 0.956$. OS was 38 months (95% CI 24–38) (A), median not reached (B), and 13 months (95% CI 10–25) (C), $p = 0.002$. Adverse events were stomatitis 57.7% (11.0% grade 3–4), asthenia 46.0% (6.1% grade 3–4), hypercholesterolemia 46.0% (0.6% grade 3–4), and hyperglycemia 35.6% (5.5% grade 3–4). The main reason for discontinuation/interruption was grade 2–3 stomatitis.
Conclusions No correlation was found between dose intensity (5 vs. 10 mg labeled dose) and efficacy in terms of RR and PFS. The tolerability of the higher dose was poor in our experience, although this had no impact on efficacy.

Keywords Everolimus · Dose intensity · Side effects · Breast cancer · Real-world population

Giammarco Surico
surico.g@alice.it

[1] Medical Oncology Unit, "Vito Fazzi" Hospital, Lecce, Italy

[2] Department of Medical Oncology, "Regina Elena" National Cancer Institute, Rome, Italy

[3] Department of Oncology/Haemathology, University Hospital, Modena, Italy

[4] Oncology Department, "AO S. Gerardo", Monza, Italy

[5] Medical Oncology Unit, "Sacro Cuore di Gesù Fatebenefratelli" Hospital, Benevento, Italy

[6] Medical Oncology Unit, "S. Carlo" Hospital, Potenza, Italy

[7] Department of Oncology, "ASST Fatebenefratelli Sacco", Milan, Italy

[8] Department of Medical Oncology, "Casa Sollievo Della Sofferenza" Hospital, San Giovanni Rotondo, FG, Italy

[9] Department of Medical Oncology, "Giovanni Paolo II" Institute, Bari, Italy

[10] Medical Oncology Unit, "S. Cuore di Gesù" Hospital, Gallipoli, LE, Italy

[11] Oncology Unit, "Ospedali Riuniti" Hospital, Foggia, Italy

[12] Oncology Unit, "Di Venere" Hospital, Bari, Italy

Introduction

The majority of advanced breast cancer (ABC) patients have an endocrine-sensitive disease at diagnosis [1, 2]. In the last decades, endocrine agents, such as aromatase inhibitors and fulvestrant, have shown efficacy in the treatment of advanced endocrine-responsive breast cancer [3–9]. Nevertheless, resistance occurs in about 40% of patients that progress after an initial response [10]. The mechanism of endocrine resistance and tumor progression involves a complex biological pathway linked to cell cycle, survival, and motility gene activation, such as phosphatidylinositol 3-phosphate kinase (PI3K), protein kinase B (akt/PKB), and mammalian target of rapamycin (m-Tor) [11]. These pathways are trigger points that promote secondary endocrine resistance in advanced breast cancer [12–14]. In preclinical models, long-term estrogen deprivation of breast cancer cells induces upregulation of the PI3K pathway, leading to independent activation of phosphorylation through the m-TOR complex 1 [13, 15].

The role of the m-TOR pathway in a clinical setting was explored in the phase 3 trial BOLERO-2 [16]. This study showed an advantage in terms of progression-free survival (PFS) and response rate (RR) in favor of the association of everolimus and exemestane (EVE/EXE), in HER2-negative advanced breast cancer patients progressing after treatment with a non-steroidal aromatase inhibitor. Two studies were conducted to evaluate the tolerability of EVE/EXE in a real-world population [17, 18]. Both the efficacy and tolerability of the association were examined, but dose interruption/reduction, dose intensity, and relation to efficacy were not investigated.

This retrospective analysis, conducted in a real-world population, aims to evaluate the correlation between dose intensity and efficacy of everolimus, in order to add new information that can be useful in daily clinical practice.

Materials and methods

The medical records of 163 HER2-negative, hormone receptor-positive ABC patients, treated in eleven Italian centers with EVE/EXE, according to the clinical practice, were reviewed. Eligible patients were required to have evaluable disease and clinical data about safety were retrieved. Primary endpoints were the tolerability of everolimus and the correlation between the daily dose intensity (5 vs. 10 mg) and response rate (RR) and progression-free survival (PFS). As secondary endpoints, the following parameters were analyzed: RR, PFS, and overall survival (OS) according to the line of treatment (from 1st to 3rd versus 4th and beyond). Adverse events were monitored monthly and classified by the National Cancer Institute

Common Toxicity Criteria (NCI CTCAE v. 4.0); response rate was evaluated according to RECIST criteria v. 1.1 every 12 weeks, from baseline until disease progression. Clinical benefit rate (CBR), defined as the sum of complete responses (CR), partial responses (PR), and stable disease (SD) equal or longer than 24 weeks, was also evaluated. Dose intensity was calculated as median daily dose in milligrams, from the first day the patient started treatment until the last day the patient received the EVE/EXE combination. Date of discontinuation was defined as the last day the patient received everolimus, regardless of exemestane. Effectiveness measures included PFS duration (from the beginning of treatment with EVE/EXE to the first recorded occurrence of disease progression or death assessed by the physician) and OS duration (from the beginning of treatment with EVE/EXE to death or censoring). Patients with an evaluable response should have received the EVE/EXE association for a minimum of 60 days. Primary endocrine resistance was defined as follows: relapse while on the first 2 years of endocrine adjuvant therapy or disease progression within the first 6 months of first-line hormonal treatment for advanced disease; secondary endocrine resistance was defined as progression after 2 years of adjuvant treatment or after 6 months from the beginning of treatment for metastatic disease [19].

Results

The data of 163 patients treated with EVE/EXE from May 2011 to March 2016 were analyzed. Data cutoff was March 2016. Patient characteristics are summarized in Table 1: the median age was 63 years (39–83), and most of the patients had visceral disease at diagnosis (55.8%). Patients treated with hormonal adjuvant therapy (HT) were 114 (69.9%), of whom 14 (12.3%) relapsed within 2 years of adjuvant treatment and 100 (87.7%) relapsed after 2 years of adjuvant HT; 133 (81.6%) patients received a median of 1 line of endocrine treatment for advanced disease (0–5). One hundred and five patients (64.4%) received chemotherapy for metastatic disease; the median number of previous lines of chemotherapy (CT) was 1 (0–6) (see Table 1).

Table 1 Patient characteristics

Patient characteristics	$N = 163$
Median age	63 years (39–83)
Median number of metastatic sites	2 (1–5)
Visceral disease	91 (55.8%)
No visceral disease	72 (44.2%)
Adjuvant HT	114 (69.9%)
Primary endocrine resistance	14 (12.3%)
Secondary endocrine resistance	100 (87.7%)
HT for advanced disease prior to EVE/EXE	133 (81.6%)
Median number of HT lines	1 (0–5)
CT for advanced disease prior to EVE/EXE	105 (64.4%)
Median number of CT lines	1 (0–6)

HT Hormonal therapy; *CT* chemotherapy

Patients were classified into three different groups, according to the everolimus dose intensity. Group A ($n = 84$, 51.6%) included patients who never stopped taking 10 mg of everolimus or temporarily interrupted and resumed treatment at a dose of 10 mg. Group B ($n = 54$, 33.1%) included patients who started with 10 mg of everolimus, temporarily interrupted it, and subsequently resumed treatment at a dose of 5 mg; we also included in this group two patients treated at a starting dose of 5 mg, because of poor performance status and comorbidities at baseline. Group C ($n = 25$, 15.3%) included patients who definitively interrupted treatment with everolimus, at 10 or 5 mg, since toxicity occurred within 60 days from the beginning of treatment (before disease evaluation).

Efficacy according to the dose intensity of everolimus

Median duration of treatment was 301 (A), 296 (B), and 36 (C) days. Median daily dose was 9.6 (A), 6.4 (B), and 7.6 mg (C). RR was 29.8% (A), 27.8% (B) ($p = 0.953$), and not evaluable (C). PFS was 9 months (95% CI 7–11) (A), 10 months (95% CI 9–11) (B), and 5 months (95% CI 2–8) (C), $p = 0.956$ (Table 2; Fig. 1). OS was 38 months (95% CI 24–38) (A), median not reached (B), and 13 months (95% CI 10–25) (C), $p = 0.002$, respectively (Table 2; Fig. 2).

Safety

Toxicity was evaluable in all population. The most frequent adverse events were stomatitis 57.7% (11.0% grade 3–4), asthenia 46.0% (6.1% grade 3–4), hypercholesterolemia 46.0% (0.6% grade 3–4), and hyperglycemia 35.6% (5.5% grade 3–4) (see Table 3). The main reason for discontinuation/interruption was grade 2–3 stomatitis.

EVE/EXE was administered as first-line treatment in 11.1% of the patients ($n = 18$), as second line in 25.8% ($n = 42$), as third line in 23.9% ($n = 39$), and in forth or beyond line in 39.2% ($n = 64$). A total of 136 out of 163 patients were evaluable for efficacy; patients included in the efficacy analysis received treatment with everolimus 10 mg and/or 5 mg for a minimum of 60 days. Complete response and partial response were observed in 6 and in 34 patients, respectively, with an overall RR of 29.4%.

Table 2 Efficacy according to the dose intensity

	Group A ($n = 84$)	Group B ($n = 54$)	Group C ($n = 25$)
Median duration of treatment (days)	301	296	36
Daily dose intensity (mg)	9.6	6.4	7.6
RR (%)	29.8	27.8*	NV
PFS (months)	9 (7–11)	10 (9–11)**	5 (2–8)
OS (months)	38 (24–38)	NV	13 (10–25)

RR Response rate; *PFS* progression-free survival; *OS* overall survival

* $p = 0.953$

** $p = 0.956$

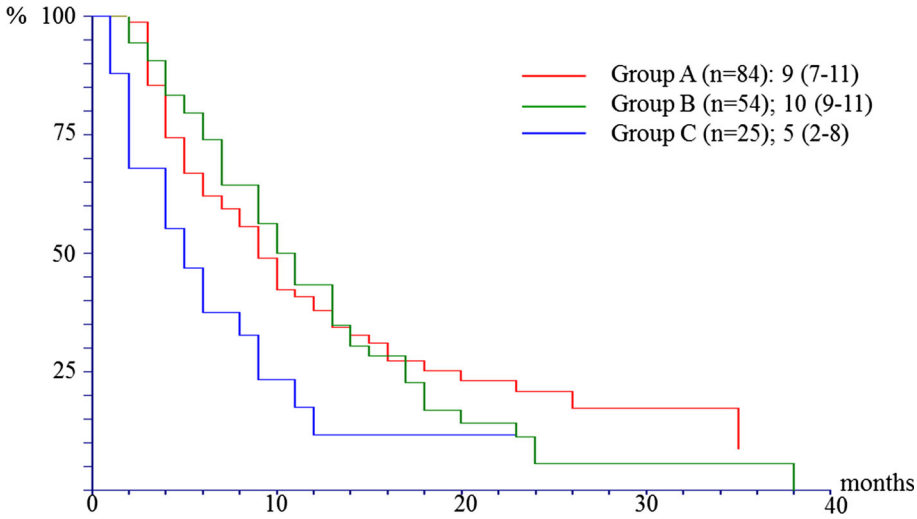

Fig. 1 Progression-free survival according to the dose intensity

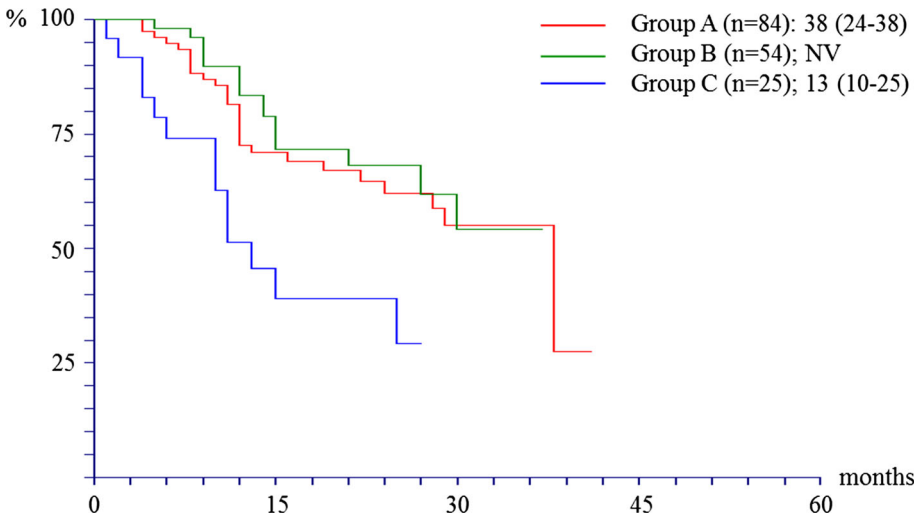

Fig. 2 Overall survival according to the dose intensity

Stable disease (SD) was observed in 59 patients and progressive disease (PD) in 37 patients. CBR was observed in 72.8% of patients. Median PFS for the overall population was 9 months (95% CI 8–9). Overall survival was 38 months (95% CI 27–38). RR according to the line of treatment (from 1st to 3rd vs. 4th and beyond) was 28.0 versus 31.5% ($p = 0.812$), respectively. PFS according to the line of treatment was 9 months (95% CI 7–9 and 7–11, respectively) in both subgroups ($p = 0.864$) (Fig. 3). OS according to the line of treatment was 38 months (95% CI 27–38) and 28 months (95% CI 16–30), respectively ($p = 0.371$) (Fig. 4).

Table 3 Incidence of adverse events

Adverse events	Overall %	Grade 3–4 %
Stomatitis	57.7	11.0
Asthenia	46.0	6.1
Hypercholesterolemia	46.0	0.6
Hyperglycemia	35.6	5.5
Anemia	31.9	4.9
Hypertriglyceridemia	27.6	0.6
Peripheral edema	25.8	1.2
Increased ALT/AST/GGT	23.9	6.1
Rash	23.3	0.6
Thrombocytopenia	22.1	4.3
Weight loss	19.0	1.2
Diarrhea	18.4	1.8
Dysgeusia	17.8	0.6
Pneumonitis	17.2	3.7
Cutaneous toxicity	16.6	1.2
Infection	16.0	3.1
Neutropenia	13.5	1.8
Anorexia (without stomatitis)	12.3	1.2
Nausea	12.3	0.0

Discussion

About 70% of patients with ABC have endocrine-responsive HER2-negative disease at diagnosis [20]. The current guidelines recommend a sequencing strategy with all the endocrine options available, to delay chemotherapy and increase the quality of life of patients with endocrine-sensitive metastatic disease [21]. Nevertheless, endocrine resistance is an event that occurs in about 30% of the population with endocrine-positive ABC [22]. New strategies have been recently investigated to overcome endocrine resistance. The efficacy of everolimus associated with exemestane was described in the BOLERO-2 trial [16] with an improvement in PFS but no impact on OS [23]. The association of EVE/EXE has a higher discontinuation rate when compared to endocrine treatment alone, because of the greater toxicity rates, as shown in the BOLERO-2 trial [16, 24, 25]. Outside of clinical trials, adherence to treatment and relative time of exposure to the drug become crucial issues in daily clinical practice. Investigation on the adherence to therapy is an unmet clinical need for oral antitumoral treatments, involving both the adjuvant and advanced settings. In a retrospective series of 8750 patients with early breast cancer [26] treated with adjuvant HT, only 47% took the prescribed therapy for the optimal duration and dose. In the BOLERO-2 trial, the median dose intensity was 8.6 mg/day [27, 28], and in the everolimus plus exemestane arm, 46% of patients had a relative everolimus dose intensity between 0.9 and 1.1; 19% of patients had a relative dose intensity between 0.7 and <0.9 and, finally, only 17% had a dose intensity between 0.5 and <0.70; no correlation was reported between dose intensity and response [24, 25]. Drug exposure in the BOLERO-2 trial was affected by age; in detail, in patients aged ≥70, the median dose intensity was lower (8.9 vs. 7.2 mg/daily) and the median exposure for both EVE/EXE was decreased [29]. No effect on response was seen in this group, despite the decreased drug dose. Dose reduction or interruption in the BOLERO-2 trial was 62%, but 44% of these patients resumed treatment at a dose of 10 mg; the difference in response between the patients that resumed treatment at a full dose and the others was not investigated. Median duration of dose reduction was 29 days in the BOLERO-2 trial [28]. In the retrospective study BRAWO, conducted in a real-world population, the compliance to EVE was between 80 and 100% of the

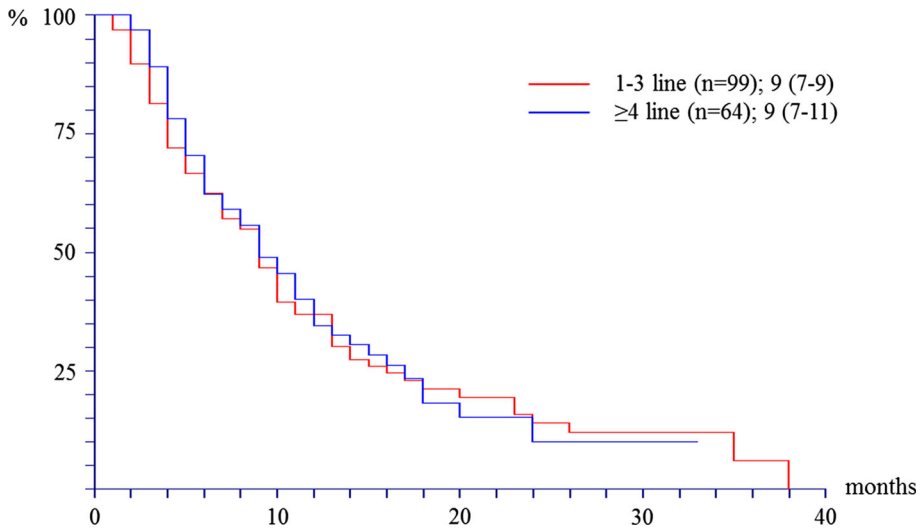

Fig. 3 Progression-free survival according to the line of treatment

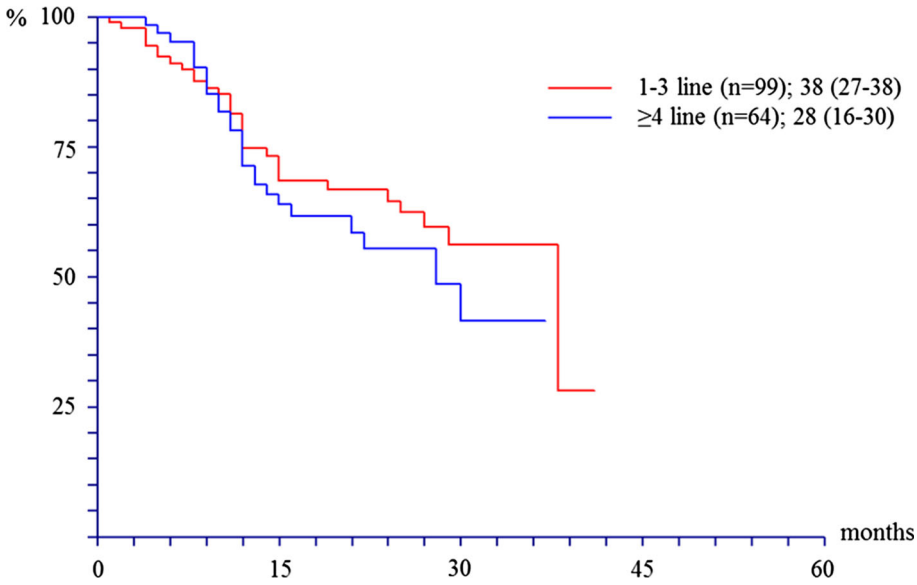

Fig. 4 Overall survival according to the line of treatment

intended dose in more than 90% of patients, as reported in patient diaries [17]. The BALLET trial reported a 56.2% of dose interruptions, a duration of treatment at 10 mg of 86 days, and a dose change of 59.6%, similar to what was reported in the BOLERO-2 trial [16, 18]. Moreover, in this study, a ≥0.90 relative dose intensity was described. No further investigation was conducted on dose intensity and response either in the BALLET or in the BRAWO study. A real-world population represents an ideal scenario to examine drug adherence and tolerability after its registration and outside of the selected population of a clinical trial. Adequate adherence to treatment with novel drugs is crucial in order to plan therapeutic strategies for endocrine-sensitive patients, in a time when new drugs are becoming available.

The percentage of interruption and/or reduction observed in our analysis was 69%, which is slightly higher than that reported in the BOLERO-2 trial [16, 25]; 15.3% of patients permanently interrupted treatment within 60 days from the start because of toxicity. The percentage of resumption at 10 mg was 20.9%, lower than that observed in the BOLERO-2 trial [16, 24], while the percentage of resumption at 5 mg was 33.1%. The median interruption of treatment lasted 27 days and the first event occurred within two months of starting treatment. The adherence to the labeled dose of everolimus appeared to be very low in our clinical experience, since only 30.7% of patients were able to continue treatment at a dose of 10 mg without interruptions. Even though the daily dose intensity differed for the 10 and 5 mg groups, 9.6 versus 6.4 mg/daily, respectively, this did not seem to influence RR and PFS.

To our knowledge, this is the first analysis conducted in a real-world population after the approval of EVE/EXE combination, to address the correlation between treatment dose and efficacy. We observed that, in an unselected population, the adherence to treatment with the full dose of 10 mg is very low, although this does not seem to decrease RR and PFS. According to the data obtained from exposure to everolimus in other solid tumors [30], we can suggest that dose intensity is not the only thing we should keep in mind when trying to achieve disease response. From a clinical point of view, we think that exposing the patient at the start to a reduced dose of everolimus (5 mg) may enable us to achieve the same results and to increase treatment adherence, with fewer side effects. The incidence and grade of adverse events are, in our study, comparable to those reported in the BOLERO trials. Furthermore, we observed some unusual toxicities, such as skin disorders that required both topical and oral corticosteroid treatment, even after the interruption of the drug, maybe linked to the drug class effect. Moreover, the lower tolerance observed in some patients could be related to a different metabolism of everolimus by cytochrome CYP3A, which has a high expression variability in the population [31].

Conclusions

We think that this study is biased by its retrospective nature, but it could suggest that continuing treatment at a full dose when we have a low adherence may not be all that matters. In conclusion, this analysis reflects the need to personalize treatment and is relevant to our everyday clinical practice. According to our findings, when a dose reduction of 5 mg is needed, physicians could increase adherence and time of exposure to the drug without compromising efficacy and PFS by keeping the reduced dose

until disease progression. At the same time, we suggest a careful evaluation of the starting dose for frail patients with comorbidities and/or taking multiple other drugs [32, 33], in order to obtain a good adherence to treatment.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Theriault LR, Carlson RW, Alfred C, Anderson BO, Burstein HJ, Edge SB, Farrar BB, Forero A, Giordano SH, Goldstein LG, Gradishar WJ, Hayes DF, Hudis CA, et al. (2013) Breast Cancer version 3.2013: featured updates to the NCNN guidelines. J Natl Compr Cancer Netw 11:753–760 (**quiz 761**)
2. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andrè F et al (2014) ESO-ESMO 2th International consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 25:1871–1888
3. Boneterre J, Buzdar A, Nabholtz JM, Robertson JF, Thurlimann B, Von Euler M, Sahmoud T, Webster A, Steinberg M (2001) Anastrozole is superior to tamoxifen as first line therapy in hormone receptor positive advanced breast carcinoma. Cancer 92(9):2247–2258
4. Nabholtz JM, Boneterre J, Buzdar A, Robertson JF, Thurlimann B (2003) Anastrozole (Arimidex) versus tamoxifen as first line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer 39(12):1684–1689
5. Mouridsen H, Gershanovich M, Sun Y, Perez Carrion R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jaenicke F, Pluzanska A, Danl M, Becquart D, Bapsy PP, Salminen E, Snyder R, Chaudri-Ross H, Lang R, Wyyld P, Bhatnagar A (2003) Phase III study of letrozole versus tamoxifen as first line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the international letrozole breast cancer group. J Clin Oncol 21(11):2101–2109
6. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, Piccart MJ, Bogaerts J, Therasse P (2007) Phase III study comparing exemestane with tamoxifen as first line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organization for research and treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 26(30):4883–4890
7. Chia S, Gradishar W, Mauriac L, Bines F, Amant F, Federico M, Fein L, Romieu G, Buzdar A, Robertson John FR, Brufsky A, Possinger K, Rennie P, Sapunar F, Lowe E, Piccart M (2008) Double blind randomized placebo controlled trial of fulvestrant compared with exemestane after prior non steroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor positive advanced breast cancer: results from EFECT. J Clin Oncol 26(10):1664–1670
8. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko N, Rustem K, Verhoeven D, Pedrini JL, Smirnova I, Lichinitser MR, Pendergrass K, Garnett S, Lindemann JPO, Sapunar F, Martin M (2010) Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor positive advanced breast cancer. J Clin Oncol 28(30):4594–4600
9. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, Verhoeven D, Pedrini JL, Smirnova I, Lichinitser MR, Pendergrass K, Malorni L, Garnett S, Rukazenkov Y, Martin M (2014) Final overall survival: Fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst 106(1):1–7
10. Buzdar AU (2014) Phase III study of letrozole versus tamoxifen as first line therapy of advanced breast cancer in postmenopausal women: analysis of survival and updated of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 22:3199–3200
11. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
12. Stephens PJ, Tarpey PS, Davies H, Van Loo P, Greenman C, Wedge DC et al (2012) The landscape of cancer genes and mutational processes in breast cancer. Nature 486:400–404
13. Miler TM, Hennessy BT, Gonzalez Angulo AM, Fax EM, Mils GB, Chen H et al (2010) Hyperactivation of phosphatydilinositol-3 kinase promotes escape from hormone receptor positive human breast cancer. J Clin Investig 120:2406–2413
14. Simoncini T, Hafezi-Moghadam A, Brazil DP, Ley K, Chin WW, Lialo JK (2000) Interaction of estrogen receptor with the regulatory submit of phospatydilinositol-3-OH kinase. Nature 407:538–541
15. De Graffenned LA, Fulcher L, Friedrichs WE, Grunwald D, Ray RB, Hidalgo M (2004) Reduced pTen expression in breast cancer cells confers susceptibility to inhibitor of PI3k kinase/akt pathway. Ann Oncol 15:1510–1516
16. Baselga J, Campone M, Piccart M, Burris H, Rugo H, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrunn F, Beck T, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwhol D, Hortobagyi G (2012) Everolimus in postmenopausal Hormone receptor positive advanced breast cancer. N Engl J Med 366:520–529
17. Jackisch C, Grischke EM, Schneeweiss A, Decker T, Uleer C, Förster F, Tomé O, WimbergerP, Kurbacher C, Mueller B, Harbeck N, Mundhenke C, SherkoK, Muth M, Kreuzeder J, Bloch W, Tesch H, Lueftner D, Schütz F, Fasching P (2015) Subgroup analysis of efficacy in routine treatment—results of the 2nd interim analysis of BRAWO, the non-interventional trial "Breast Cancer Treatment With Everolimus and exemestane for HR+ woman" Abstract ♯ P 5-19, SABCS 2014 Congress
18. Jerusalem G, Mariani G, Ciruelos EM, Martin M, Tjan-Heijnen VCG, Neven P, Gavila GJ, Michelotti A, Montemurro F, Generali D, Simoncini E, Lang I, Mardiak J, Naume J, Camozzi M, Lorizzo K, Bianchetti S, Conte P (2016) Safety of everolimus plus exemestane in patients with Hormone receptor positive Her-2 negative locally advanced or metastatic breast cancer progressing on prior non steroidal aromatase inhibitors: primary results of a phase 3b, open-label, single arm, expanded access multicenter trial BALLET. Ann Oncol 27(9):1719–1725
19. Cardoso F, Costa A, Norton L, Senkus L, Aapro M, Andrè F, Barrios CH, Bergh J, Biganzoli L, Blackwell L, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordstrom EB, Pagani O, Partridge A, Penault-Lorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B, Winer E (2014) ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol. 25(10):1871–1888
20. Jatoi I, Chen BE, Anderson WF et al (2007) Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol 25:1683–1690
21. Partridge AH, Bryan R, Carey LA, Steven EC, Davidson NE, Di Leo A, Gralow J, Hortobagyi GH, Moy B, Yee D, Brundage SB, Danso MA, Wilcox M, Smith I (2014) Chemotherapy and targeted therapy for women with Human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer:

American Society of Clinical Oncology Practice Guidelines. J Clin Oncol 32:3307–3329
22. Musgrove EA, Sutherland RL (2009) Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer 9:631–643
23. Piccart M, Hortobagyi GN, Campone M et al (2014) Everolimus plus exemestane for hormone receptor positive (HR+) human epidermal growth factor receptor-2 negative (Her-2) advanced breast cancer (BC): overall survival results from BOLERO-2. Eur J Cancer 50(Suppl 3):S1
24. Hortobagyi GN (2015) Everolimus plus exemestane for the treatment of advanced breast cancer: a review of subset analyses from Bolero-2. Neoplasia 17(3):279–288
25. Rugo HS (2016) Dosing and safety implications for oncologists when administering everolimus to patients with Hormone receptor positive breast cancer. Clin Breast Cancer 16(1):18–22
26. Hershman DL, Kushi LH, Buono D, Kershenbaum A, Tsai WY, Fehrenbacher L, Sl Gomez, Miles S, Neugut AI (2010) Early discontinuation and non adherence to adjuvant hormonal therapy in a cohort of 8769 early stage breast cancer patients. J Clin Oncol 28(27):4120–4128
27. Yardley DA, Noguchi S, Pritchard KI, Burris HA III, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, Piccart M et al (2013) Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression free survival analysis. Adv Ther 30:870–884
28. Rugo HS, Pritchard KI, Gnant M, Noguchi S, Piccart M, Hortobagyi GN, Baselga J, Perez A, Geberth M, Csoszi T et al (2014) Incidence and time course of everolimus related adverse events in postmenopausal women with hormone receptor positive advanced breast cancer insights from BOLERO-2. Ann Oncol 25:808–815
29. Pritchard KI, Burris HA III, Yto I et al (2013) Safety and efficacy of everolimus with exemestane versus exemestane alone in elderly patients with Her-2 negative hormone receptor positive breast cancer in BOLERO-2. Clin Breast Cancer 13:421–432
30. Ravaud A, ShwetaRU, Grosch K, Wing KC, Oezlem A, Sellami DB (2013) Metanalysis on the relationship between everolimus exposure and safety and efficacy: meta-analysis of clinical trials in oncology. Published online December 2013
31. Anglicheau D, Legendre C, Beaune P et al (2007) Cytochrome P450 3A polymorphisms and immunosuppressive drugs: an update. Pharmacogenomics 8:835–849
32. Johnell K, Klarin I (2007) The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600000 elderly patients from the Swedish Prescribed drug Register. Drug Saf 30(10):911–918
33. Balducci L, Goetz-Parten D, Steinman MA (2013) Polypharmacy and the management of the older cancer patient. Ann Oncol 24(Suppl 7):vii36–vii40