ORIGINAL ARTICLE

Efficacy and safety of Everolimus and Exemestane in Hormone–Receptorr positive (HR+) human-epidermal-growth-factor negative (HER2-) advanced breast cancer patients: new insights beyond clinical trials. The EVA Study

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ABSTRACT

BACKGROUND: The BOLERO-2 trial reported that Everolimus (EVE) and Exemestane (EXE) combination is highly active and well tolerated in HR+ advanced breast cancer (ABC) patients (pts). The BALLET trial further evaluated the safety of EVE-EXE in HR+ pts, without reporting efficacy data. Aim of the EVA real-life study ~~is~~was ~~the collection of~~to collect data of efficacy and ~~safety of~~safety of EVE-EXE combination in the clinical setting, as well as ~~, exploring efficacy~~exploring efficacy ~~data per~~according to EVE Dose-Intensity (DI) ~~of EVE~~ and in previous treatment with Fulvestrant ~~pre-treated pts~~.

PATIENTS AND METHODS: This study aimed to describe the outcome of ABC pts treated with EVE-EXE combination in terms of median duration of EVE treatment and ORR in a real-life setting.

RESULTS: From July 2013 to December 2015, the EVA study enrolled 404 pts. Median follow up time was 28.8 months (27.3 – 29.7). Median age was 61 years (33 – 83). Main metastatic~~ses'~~ sites ~~of metastases~~ were: bone (69.1%), soft tissue (34.7%) and viscera (33.2%). Median number of previous treatments was 2 (1 - 7). 43.3% of the pts had received Fulvestrant and 11.1%. Median exposure to EVE was ~~28.4~~31.0 weeks (~~24.8~~15.4 – ~~33.2~~58.3) in the whole population. No difference ~~has been~~was observed in terms of EVE exposure duration according to DI (p for trend=0.27) or type of previous treatments (p=0.33). Grade 3-4 adverse events (AEs) were reported in 37.9% of the patients. Main AEs were: stomatitis (11.2%), non-infectious pneumonitis - NIP (3.8%), anaemia (3.8%) and fatigue (3.2%).

CONCLUSIONS: the EVA study provided new insights in the use of EVE-EVE combination in advanced HR+ ABC pts many years after the publication of the pivotal trial and added new data in special subgroups of pts.

Commento [MEC1]: Valter, conferma se interpretato correttamente

Commento [v2]: fatto

KEY WORDS

Everolimus

Hormone-receptor positive

Breast cancer

Fulvestrant

Dose-Intensity

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KEY MESSAGE

The combination of Everolimus and Exemestane (EVE-EXE) has been largely studied in a prospective pivotal trial (BOLERO-2), reporting better Progression-Free-Survival and Overall Response Rate (ORR) in comparison to Exemestane alone and has quickly become part of the clinical practice as a treatment for HR+ve HER2-ve advanced breast cancer patients. However, despite the wide use of the drug, some data of clinical interest are still lacking at the moment, in particular those ~~concerning the~~concerning the efficacy of EVE-EXE combination in patients pre-treated with Fulvestrant or chemotherapy, or the correlation between the real Dose Intensity and efficacy of the drug.

The EVA study is a real-life trial conducted in 38 ~~Oncologic~~Oncology Centers in Italy, which enrolled 404 HR+ve HER2-ve advanced breast cancer patients treated with EVE-EXE combination in a real life setting outside any clinical trial.

Median duration of EVE-EXE combination was higher than that reported in the pivotal trial (31.0 vs 14.6 weeks), with similar incidence of severe adverse events, namely stomatitis (11.2% vs 8%) and non-infectious pneumonitis (3% vs 3.8%). T~~;t~~hese results suggest that a better selection of patients (visceral sites: 33.2% vs 54%) and an appropriate management of adverse events can lead to a longer disease control. Previous treatment with Fulvestrant doesn't affect the efficacy of EVE-EXE combination; no difference ~~has been~~was observed in terms of EVE exposure duration according to Dose Intensity (p for trend=0.27), even if the lowest ORR was observed in those patients who received a median DI below or equal 5 mg per day.

The EVA study provides useful information for the everyday management of advanced breast cancer patients for whom EVE-EXE can ~~be~~ represent a valid ~~option of~~ treatment option.

BACKGROUND

Endocrine therapy (ET) is the treatment of choice for patients with hormone-receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) in both adjuvant and advanced settings. [1] However, despite the effectiveness of ET, many women experience disease progression, either de novo or acquired [2]. Hence, identification of valid targeted therapies, which may enhance or prolong endocrine sensitivity in these patients, is crucial.

The pivotal BOLERO-2 trial showed that dual-blockade with Everolimus (EVE), an mTOR inhibitor, plus Exemestane (EXE) more than doubled the median progression-free survival (PFS) versus EXE alone in patients with HR+, HER2−ve advanced breast cancer recurring or progressing on prior non-steroidal aromatase inhibitors (NSAIs) (Median PFS: 7.8 versus 3.2 months) [3]. The most common grade 3 or 4 adverse events (AEs) associated with EVE treatment were stomatitis (8%), anemia (6%), dyspnea (4%), hyperglycemia (4%), fatigue (4%), and pneumonitis (3%). The study enrolled postmenopausal patients whose disease was refractory to previous letrozole or anastrozole, but didn't provide any data regarding clinical outcomes according to EVE Dose-Intensity (DI), or in patients previously treated with Fulvestrant, except in a small percentage of patients (16%), despite the wide use of this drug in the metastatic setting..

The European Phase IIIb expanded-access multicenter trial BALLET [4] further evaluated the safety of EVE plus EXE in patients with HR+, HER2− advanced breast cancer recurring/progressing on prior non-steroidal aromatase inhibitors (NSAIs). In this trial, NSAIs were not necessarily the last treatment before enrollment and there was no restriction on the number of prior lines of chemotherapy. Given that BALLET was an expanded access program, the study design did not allow for PFS assessment.

At the moment, no data are available regarding the efficacy of EVE-EXE combination in unselected groups of advanced HR+ breast cancer patients,.

Aim of the EVA study is to describe the outcome of ABC pts treated with EVE-EXE combination in terms of median duration of EVE treatment and ORR in a real-life setting.~~Endocrine therapy (ET) is the treatment of choice for patients with HR+, human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) in both adjuvant and advanced settings. [Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014; 25(10): 1871–1881] However, despite the effectiveness of ET, many women experience disease progression, either de novo or acquired [Osborne KC, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med 2011; 62: 233–247]. Hence, identification of effective valid targeted therapies, which may enhance or prolong endocrine sensitivity in these patients, is crucial.~~

~~The pivotal BOLERO-2 trial showed that dual-blockade with Everolimus (EVE), an mTOR inhibitor, plus Exemestane (EXE) more than doubled the median progression-free survival (PFS) versus EXE alone in patients with Hormone Receptor-positive (HR+), HER2−ve advanced breast cancer recurring or progressing~~

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on prior non-steroidal aromatase inhibitors (NSAIs) (Median PFS: 7.8 versus 3.2 months) [Baselga J, Campone M, Piccart M, Burris III HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. N Engl JMed 2012;366:520e9.3]. The most common grade 3 or 4 adverse events (AEs) associated with EVE treatment were stomatitis (8%), anemia (6%), dyspnea (4%), hyperglycemia (4%), fatigue (4%), and pneumonitis (3%). The study enrolled postmenopausal patients whose disease was refractory to previous letrozole or anastrozole, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease.

The trial didn't provide any data regarding the effect of EVE Dose Intensity (DI) on clinical outcomes. Only 16% of the patients have received Fulvestrant before starting EVE-EXE, despite the wide use of this drug in the metastatic setting of disease.

The European Phase IIIb expanded-access multicenter trial BALLET [4xx] further evaluated the safety of EVE plus EXE in patients with HR+, HER2− ABC advanced breast cancer recurring/progressing on prior non-steroidal aromatase inhibitors (NSAIs). In this trial, NSAIs were not necessarily the last treatment before enrollment and there was no restriction on the number of prior lines of chemotherapy. Given that BALLET was an expanded access program, the methodology did not allow for PFS the assessment of PFS.

So far, at the moment no data are available regarding the efficacy of EVE-EXE combination in an unselected population of advanced HR+ breast cancer patients, or previously exposed to Fulkvestrant.

Aim of this retrospective real-life study is the collection ofto collect data regarding efficacy and safety ofsafety of EVE-EXE combination and the exploratory analysisto explore of howif Dose-Intensity of EVE, as well as some previous treatments of peculiar interest, namely Fulvestrant and chemotherapy (CHT), have an effect onaffect efficacy in the clinical setting, outside a randomized trial.

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PATIENTS AND METHODS

Study Design

This is a multicentre retrospective cohort study, which collected data of HR+ advanced breast cancer patients which received EVE-EXE combination between March July 2013 and December 2015 in 38 OncologicOncology Centres in Italy; all of them usually treat more than 150 new cases of breast cancer per year and are well representative of the Country. The study obtained the approval of all the Ethical Committees of the participating Centres sites. All patients provided written informed consent. Data were collected via electronic database. Baseline information included patient's age at metastatic diagnosis,

Commento [P5]: July

comorbidity, breast cancer history, (date of stage at initial diagnosis, any adjuvant and/or neoadjuvant therapy), hormone and HER2 status, number and sites of ~~metastasis~~metastases. Physicians were requested to provide a fully comprehensive description of previous endocrine treatments and chemotherapy including the number of previous treatment. ~~Plus S~~survival data were collected as well.

Patients

The eligible patients were female, ≥ 18 years, with documented HR+ locally advanced or metastatic breast cancer, previously treated or not with other drugs for the metastatic disease, for whom EVE-EXE was chosen by the physician, according to the clinical situation of the patient. All patients who received at least one dose of EVE-EXE combination were considered eligible. Other inclusion criteria were HER2-negative disease (IHC 0 – 1 or IHC 2, confirmed as FISH negative), measurable or evaluable lesions ~~according to RECIST 1.1 criteria~~ and ~~the~~ availability of all requested data. Data collection started when each~~the Centres~~ centre received the approval of their local Ethical Committee. Data retrieval ~~and~~ included disease characteristics, hormone receptor and HER2 status, sites of metastas~~i~~es and tumour biology, as well as previous therapies received both in the adjuvant and the metastatic setting. Patients who ~~participated~~ received EVE before July 2013 included in~~t~~to the BALLET trial or into other interventional EVE studies were excluded.

Treatment plan

Considering the inherent design of the study, no treatment plan was provided *a priori*.

The EVE starting dose was 10 mg dose, even if ~~in some instances~~ the 5 mg dose ~~was~~ could be independently cho~~o~~sen by physicians. ~~Clinicians~~ They were asked to identify all consecutive patients who fit the pre-specified criteria of the study and to collect ~~their~~ patients' data from the clinical records in an electronic case-report-form (CRF) dedicated to the study. ~~In order to calculate~~ T~~t~~he effective Dose-Intensity (DI) of EVE therapy per patient was calculated adding the ~~, we summed the~~ number of days at ~~full dose (~~10 mg~~)~~ plus those ~~,~~ at 5 mg ~~dose and~~plus the number of days without any dose (0 mg), the sum was then divided per the total administered dose for ~~by~~ the effective number of treatment days ~~in which the patient has remained on treatment~~, including the interruption periods. We subsequently identified three ~~different~~ groups of patients according to the following DIs: A) ≤ 5mg/day; B) 5.1 – 7.5 mg/day and C) > 7.5 mg/day.

Clinical outcomes

All measures of clinical outcomes were based on physician's evaluation. The primary end-point of this retrospective study was to describe the duration of EVE treatment and the toxicity~~overall response rate (ORR) and the disease control rate (DCR) of the EVE-EXE combination~~. Secondary end points were: overall response rate (ORR) and the disease control rate (DCR), the effective median ~~Dose Intensity~~DI of EVE ~~of EVE~~ and differences or similarities of patients treated in the real-life setting in comparison to those

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enrolled in the clinical trials. ~~, any grade toxicities and severe adverse events and , time of treatment duration. , progression free survival (PFS), defined as the time from the beginning of the EVE-EXE combination until the first observation of progressive disease (PD) or death from any cause.~~ Exploratory analyses with the aim of ~~exploring~~ testing a potential association between ORR ~~or DCCBR~~ and duration of treatment with ~~and~~ the median ~~effective Dose Intensity~~DI of EVE or with the type of previous treatments ~~of special interest~~ (Fulvestrant and chemotherapy) were conducted.

Patients who were not progressive or dead were censored at the data cut-off date (January, 2017).

Statistical considerations

~~VALTER da inserire~~Demographic data, baseline characteristics of patients and disease, and treatment information were summarised with standar~~ae~~d summary statistics (mean SD and range for continuous data, relative and absolute frequencies for categorical data). Relationship of these variable with response were analysed by mea~~dd~~ of a M~~m~~antel-Haenzel . Time to event analysis was described by Kaplan M~~m~~eier approach and association with ~~v~~baseline characteristic was analysed by stratified log-rank test and proportional hazard model. The number of patients was calculated in order to obtain a good fit with the cox model. 200 events were deemed sufficient for modelling up to 10 variables.

RESULTS

Patient and tumour characteristics

We retrospectively retrieved clinical data from 448 advanced breast cancer patients treated with the EVE-EXE association between ~~March~~July 2013 and December 2015. Data from 44 records did not ~~satisfied~~satisfy the pre-specified criteria and were excluded from the analysis. (Figure 1).

Median follow up time was 28.8 months (27.3 – 29.7). Median age at the moment of study enrolment was 61 years (33 – 83).

At primary diagnosis, main tumour characteristics were ductal histology (74.9%), pT2 stage (46.8%), pN1 stage (39.5%), ER+/PgR+ (85.2%), Grade 2 (57.8%).

At the time of first relapse, all patients but 38 (9.~~44.1~~%) had at least one comorbidity. Bone was the most frequent site (69.1%), followed by soft tissue (34.7%) and viscera (33.2%). Median number of treatments received for the metastatic disease was 2 (1 - 7). ~~At the EVE-EXE starting, most patients had already received chemotherapy (CHT) followed by maintenance ET (55.9%).~~ One-hundred seventy-five patients had

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received Fulvestrant (43.3%) and 45 CHT (11.1%), whereas, in 184 (45.5%) patients, aromatase inhibitors (AIs) were the last treatment before starting ~~the study combination~~EVE.

Details are summarized in Table 1.

Treatment exposure and clinical activity

At the data cut-off date (January 2017), 121 patients were still alive; 45 patients were still receiving EVE-EXE combination. The majority of the patients (276, 68.3%) started with EVE 10 mg and concluded the treatment without dose reductions; only 16 patients started with the dose of 5 mg (3.9%).

Median EVE DI was > 7.5 mg/day in ~~M~~most patients (240, 59.4%) ~~received a DI > 7.5 mg/day of EVE~~. The median duration of EVE treatment was ~~28.4~~31.0 weeks (~~24.8~~15.4 – ~~33.2~~58.3) in the whole population, ~~a~~ ~~and~~ ~~XX~~23.3, ~~YY~~ 33.8 and ~~ZZ~~ 32.5 weeks in the three DI groups. No difference has been observed in terms of EVE exposure duration according to DI (p for trend=0.27) or type of previous treatments (p=0.33).

~~Median PFS was XX months. Comparison with subgroups.~~

ORR and DCR were observed in 31.6% and 60.7% of the patients, respectively. ORR was very similar in patients who received the highest ~~(>7.5 mg/day)~~ and the intermediate DI (33.5% and 34.7%, respectively). The lowest ORRs were observed in CHT-treated patients (24.4%) and in those who received the lowest DI (18.2%). No correlation has been observed in terms of ORR (p=0.372) or DCR (p=0.078) according to the type of previous treatment ~~(p=0.372) and p=0.078 respectively)~~; borderline association was found between level of DI and ORR (p=0.068). ~~**VALTER DA VERIFICARE**~~

Safety

Treatment-related Grade 3–4 AEs occurred ~~Grade 3-4 severe adverse events (SAEs) were reported~~ in 37.9% of the patients. Main ~~SAEs~~ ones were: stomatitis (11.2%), non-infectious pneumonitis - NIP (3.8%), ~~anemia~~anaemia (3.8%~~and electrolyte alterations (10.6%)~~) and fatigue (3.2%). ~~Median duration of stomatitis was XX 15 days (XX25% 75% 8-22 days).~~ All other ~~SAEs~~ grade 3-4 AEs were observed in less than 3~~5~~% of the patients.

Median duration of stomatitis was 15 days (range ~~25%-75% 8-22 days~~). NIP ~~Pneumonitis~~ of any grade occurred in 63 patients (18.6%), but only 13 patients (3.8%) ~~experienced~~ developed Grade 3-4 event~~s~~. Median duration of NIP was 25 days (range 15-60). Steroids were used in all the patients but one; 12 out of 13 patients underwent CT scan to confirm ~~the~~ NIP~~AE~~. No deaths attributed to AEs were reported.

Details are summarized in Table 3.

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DISCUSSION

The EVE-EXE association represents one of the most recent treatments approved for HR+ metastatic breast cancer patients that progressed after an aromatase inhibitor therapy. The BOLERO-2 phase III clinical trial and the BALLET expanded access program ~~(EAP) showed~~reported, respectively, the efficacy and the feasibility of th~~is~~e treatment.

To our knowledge, ~~the EVA study~~the EVA study is the largest real-life trial reporting both efficacy and safety results and exploring the ~~effect~~ potential correlation between~~of~~ EVE Dose Intensity and~~on~~ ORR or ~~and~~ DCR, as well as describing the efficacy results in ~~different~~ special subgroups o~~f~~f patients, ~~according to previous special treatments, such as~~ namely those previously treated with Fulvestrant or~~and~~ CHT.

Our results showed that 37.9~~52.9~~% of the patients reported Grade 3~~-~~/4 ~~adverse events (AEs),~~AEs, a result~~s~~ quite similar to tha~~t~~t reported in the ~~the~~ BOLERO-2 trial (50%) and in the ~~the~~ BALLET study (42.7%).

In the ~~the~~ BOLERO-2 study, the most common~~ly~~ reported AEs affecting more than 30% of patients in the EVE-EXE arm included: stomatitis, rash, fatigue, diarrhea, nausea, decreased appetite, pneumonitis and metabolic events.

In ~~the EVA study~~the EVA study, patients mainly experienced stomatitis (11.2%)~~,~~ NIP (3.8%~~and electrolyte alterations (10.6%~~), anemia (3.8%) and fatigue (3.2%) whereas incidence of rash ~~, fatigue~~ and other AEs peculiarly associated with EVE administration was below 3%. Even if ~~This finding could be explained by the fact that s~~some special AEs could be underestimated in real life studies, especially in retrospective ones, ~~but another possible explanation~~it is possible that, with the wide use of the drug in the clinical practice, clinicians have improved their learning curve in symptoms management ~~as well~~, thus reducing the incidence of higher grade AEs in comparison to what reported in pivotal trials.

In a meta-analysis of phase 3 studies done by Rugo et Al. [~~**Rugo** HS, Hortobagyi GN, Yao J et Al. Meta-analysis of **stomatitis** in clinical studies of **everolimus**: incidence and relationship with efficacy. Ann Oncol. 2016 Mar;27(3):519-255~~]~~–~~, despite the ~~y~~ use of~~d~~ a broad definition to capture stomatitis ~~events not specifically categorized as such~~, the Authors ~~and~~ found that the overall rate (any grade) of the AE was similar across studies of four different advanced solid tumors (67%) and across the TSC trials (70%) and ~~,~~ the incidence of G~~g~~rade 3~~-~~/4 events was lower (9% in solid tumor trials and 6% in TSC trials). These results are very similar to those observed in our real-life study. Median duration of stomatitis was superimposable in the EVA study (15 days), the BALLET trial (16 days) and in metanalysis evaluation (15 days).

Grade 3-4 ~~pneumonitis~~NIP, one of the typical ~~S~~AEs related to EVE administration, was reported in 3~~0.6~~% of the patients in the ~~the~~ BOLERO-2 trial, in 1.9% of the patients enrolled in the BALLET trial and in 3.8% of our patients; the lowest incidence observed in the BALLET study could be due to the short follow up of this trial and to the cessation of collecting AEs at the moment of drug reimbursement.

Being that ~~After~~ EVE has become part of our daily practice, more attention was~~is~~ mandatory and to be shared among sites~~: this higher incidence could be explained by the emphasis given to this event by the~~

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~~medical literature, which could have led to an increase attention put by the physicians in the observation of this symptom. It is now quite usual in the daily practice to~~ ~~an accurate information about the peculiar AEs of EVE is mandatory, patients receiving EVE~~ in order to instruct patients to ~~to alert~~alert~~ing~~ their clinicians at the first appearance of symptoms like stomatitis or cough without fever: this kind of information has probably reduced the incidence of ~~SF~~AEs in the clinical practice in comparison to what observed in randomized trials.~~,~~

In our study, ~~in order to quickly perform chest X-rays, CT scan or, in selected cases, fibroscopy:~~ among the 63 patients who showed symptoms referred to pneumonitis, 51 underwent chest CT scan and received steroids, thus limiting the severity of NIP.

~~In A~~another study [6] report~~ed~~~~ing~~ safety analysis and association ~~with~~ between response and previous treatments in 181 metastatic breast cancer patients: ~~[Moscetti, 20166];~~ ~~non infectious pneumonitis~~NIP ~~was reported reported~~occurred in 1.2% of the cases: data ~~data~~ cut-off date of~~in~~ this study was ~~done at~~ March 2015, this~~at~~ means that ~~the population included~~the~~ose~~ patients observed have received ~~the~~ EVE treatment when there was less attention to peculiar symptoms such as ~~pneumonitis~~NIP; another possible explanation for this low incidence of NIP is that the widespread use of EVE in small or suburban~~peripheral oncologic~~oncology sites~~centers~~ started later in comparison to ~~the~~ academic centers, leading to the need of clinical experience to recognize uncommon~~peculiar~~ toxicities, never observed with other antineoplastic treatments.

Commento [P8]: Forse un riferimento più preciso a che studio ti riferisci sarebbe meglio…

~~Incidence of severe non infectious pneumonitis in the BALLET study was lower (1.9%) than what reported in our study, as well: the analysis of the Italian population enrolled in the BALLET trial (under publication) will help us to better analyze the potential reasons for this finding.~~

~~It is also possible that, due to the rapid publication of results coming from Phase III registration trials just after the end of the trial, the true efficacy of the drug, as well as the long-term incidence of some toxicities become evident after a wider use in the clinical practice, when the study drug is administered in unselected populations of patients.~~

Regarding clinical activity, ORR -in ~~the EVA study~~the EVA study ~~(31.6%)~~ was higher than the one reported in the BOLERO-2 trial (31.6% vs 9.5%), as well as the median duration of EVE treatment was ~~.~~ longer (31.0 vs 14.6 weeks): ~~T~~these~~is~~ findings could be due to different reasons, mainly the ~~: 1) few~~ fewest number of patients treated with multiple lines (≥ 3) (20.8% vs 54%)~~;~~ and the ~~2) longer duration of EVE exposure (31.028.4 vs 14.6 weeks); 3)~~ lowest~~r~~ presence of visceral sites (33.2% vs 56%).

~~This result was obtained despite a slight higher incidence of Grade 3-4 AEs (37.9% vs 23%), which probably didn't affect treatment continuation.~~

~~EVA study~~The EVA study provided a unique opportunity to evaluate the efficacy of EVE in patients pre-treated with Fulvestrant, a population not present ~~in~~in the BOLERO-2 trial, underrepresented in the BALLET (43.3% vs 17%), but frequently ~~observed~~present in the clinical practice.

In Fulvestrant pre-treated patients, EVE-EXE combination was ~~valid~~effective~~efficacious~~ and safe: ORR was 30.3%, median exposure to EVE very close to what observed in the other groups and incidence of AEs similar.

~~In the meantime~~~~Concurrently~~In addition to the abovementioned new insights, ~~EVA study~~the EVA study provides some suggestions for the optimization of the EVE use in the clinical practice as well: ~~reducing~~the reduction of the EVE dose below a DI of 5 mg/day is not recommended, as ~~well as~~ it is not ~~warranted~~advisable to offer EVE to patients ~~pre-treated with~~who previously received CHT in the metastatic setting, being the lowest ORRs observed in these two groups of patients.

~~EVA study~~The EVA study has obviously all the limitations ~~inherently related~~due to the observational nature of the trial, ~~and to~~ the retrospective design~~:~~ and the usefulness of collecting PFS data, which would be strongly vitiated by the type of study. ~~in addition, it wasn't possible to collect data regarding Progression-Free Survival, one of the main limits of this type of~~ese studies.

Nevertheless, the longest follow up ever reported in this type of patients (28.8 months), which has allowed us to collect long-term toxicities, the activity results in patients pre-treated with Fulvestrant, a very common clinical situation, as well as the new data on DI are all ~~strengths~~assets to be carefully considered.

~~As a final consideration regarding the efficacy results, it is quite usual to report better outcomes in the real life studies, in comparison to the paired registered trials: it depends on different timing of tumor assessment, different radiological techniques applied and less strict criteria of evaluation. For this and other reasons, results coming from the real life studies must always be considered carefully, even if they provide a unique opportunity to have information about the long-term events, very often~~almost not reported in the registered~~ration trials .~~

What does ~~EVA study~~the EVA study add to today's~~the contemporary~~ clinical scenario ~~o~~for~~f~~ HR+ advanced breast cancer treatment?

1) When selecting EVE-EXE combination for their patients, physicians are strongly encouraged to do every effort they can to manage peculiar toxicities rather than reducing DI of EVE below 5 mg/day, which can determine a lower response rate and a shorter duration of treatment

2) According to the FALCON study data [7], patients with metastatic *de novo* disease and non-visceral metastases should be considered for Fulvestrant first-line: our data indicate that EVE-EXE combination in patients pre-treated with Fulvestrant is effective and safe, thus suggesting this therapy should be considered a valid ~~s~~ second-line treatment

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In conclusion, ~~EVA study~~the EVA study provided new insights in the use of EVE-EVE combination in advanced HR+ metastatic breast cancer patients many years after the publication of the pivotal trial and represented a very positive~~magnificent~~ example of how the cooperation among ~~oncologic~~oncology centers can produce useful data for the daily clinical practice.

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DISCLOSURE

The Authors have declared no conflict of interest

~~Moreover, in 56% of patients who had interruptions or discontinuation, the reduction to the 5 mg daily dose has been adopted.~~

~~In the BALLET study, a dose change was required in 59,6% of patients, in the 16,2% of patients the onset of the adverse event represents the main reason for the discontinuation of the treatment, the adverse event arises mainly in the first three months of treatment and the median time to the first dose modification was 32 days (range 1-441).~~

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Appendix 1

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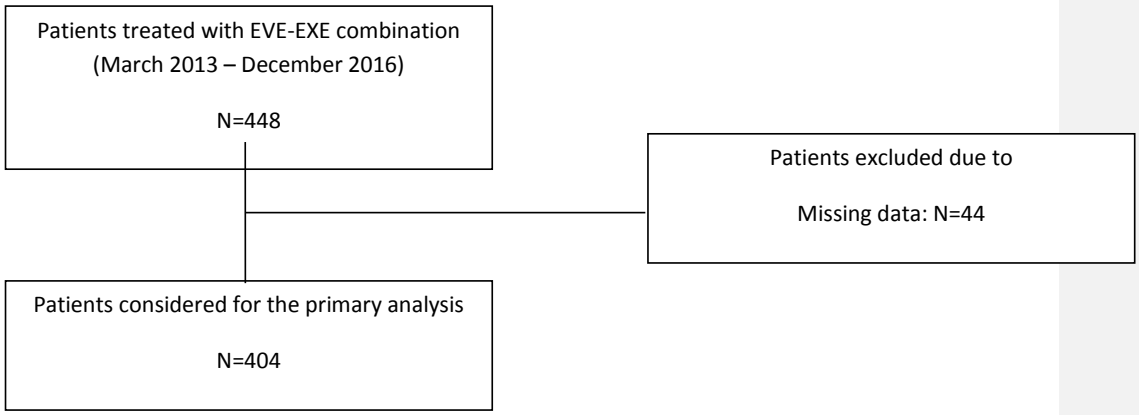
Figure 1 – CONSORT flow chart



EVE=Everolimus; EXE= Exemestane

Table 1 – Patients and tumor characteristics

Characteristic	**n=404**
Median age (range), years	61 (33-83)
- AIs last treatment	58 (35-79)
- Fulvestrant-treated	64 (36-83)
- CHT-treated	59 (33-79)
Age categories	
- < 65 years	
- ≥ 65 years	
Hormone-receptor Status, n (%)	
- ER+	377 (85.2)
- PgR+	344 (85.2)
Metastatic site, n (%)	
- Bone	279 (69.1)
- Soft tissue	140 (34.7)
- Viscera	134 (33.2)
Number of metastatic site, n (%)	
- ≥ 3	26 (6.4)
- 2	107 (26.5)
- 1	271 (67.1)
Median follow up (range), months	28.7 (27.3-29.7)
- AIs last treatment	29.1 (27.1-31.7)
Key comorbidities, n(%)	
- Vascular	111 (27.5)
- Metabolic and nutritional	42 (10.4)
- Musculoskeletal and connective tissue	18 (4.5)
- Gastrointestinal	17 (4.2)
- Other	23 (5.7)
Number of lines of prior chemotherapy in metastatic setting, n(%)	
- 1	250 (61.9)
- 2	143 (35.4)

- ≥ 3	84 (20.8)
Number of lines of prior endocrine therapy in metastatic setting, n(%)	
- 1	365 (90.3)
- 2	133 (32.9)
- ≥ 3	51 (12.6)
Key prior antineoplastic therapies, n(%)	
- Fulvestrant	175 (43.3)
- CHT	45 (11.1)
- AIs (last treatment)	184 (45.5)

CHT=chemotherapy; AIs=aromatase inhibitors; ER=estrogen-receptor; PgR=progesteron receptor;

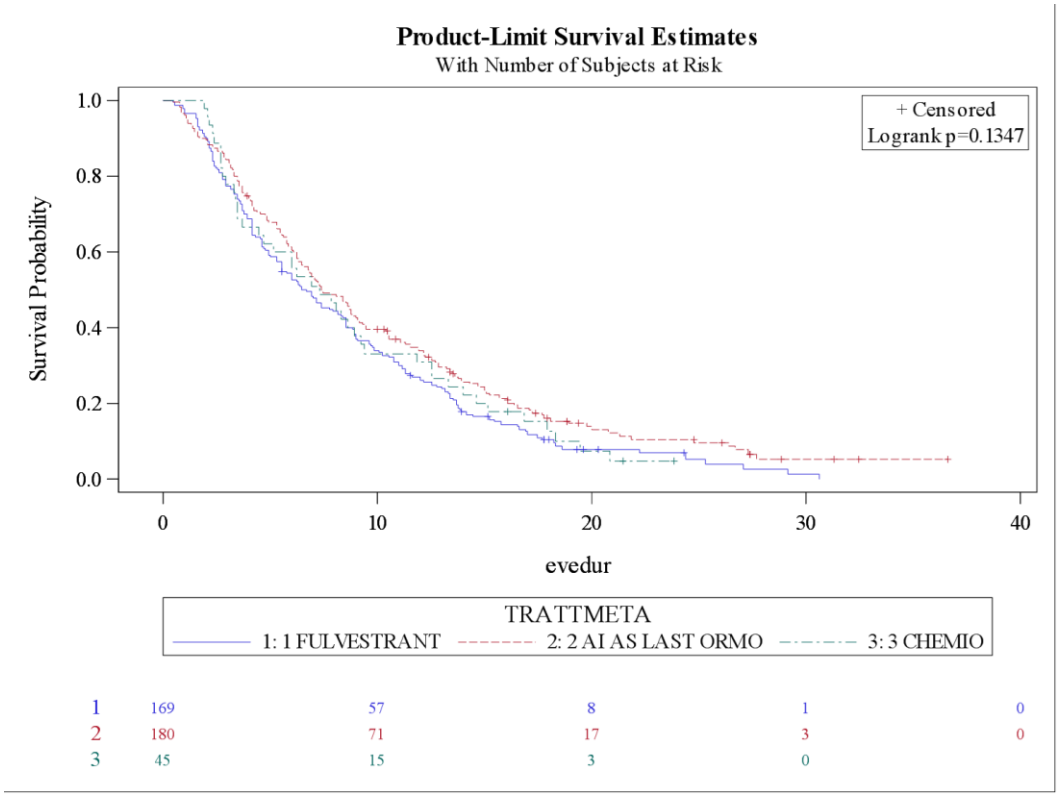
Table 2 – Efficacy analysis -

	Therapy						Dose Intensity ~~(DI)~~ (mg/day)							
	Fulvestrant		AIs		CHT		DI ≤ 5		DI 5.1-7.5		DI > 7.5		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
BEST RESPONSE														
CR	7	4.2	9	5.0	3	6.7	.	.	4	4.0	15	6.4	19	4.9
PR	43	26.1	53	29.6	8	17.8	10	18.2	31	30.7	63	27.0	104	26.7
SD	46	27.9	56	31.3	11	24.4	18	32.7	29	28.7	66	28.3	113	29.0
DCR	96	58.2	118	65.9	22	48.9	28	50.9	64	63.4	144	61.8	236	60.7
ORR	50	30.3	62	34.6	11	24.4	10	18.2	35	34.7	78	33.5	123	31.6
All	165	100	179	100	45	100	55	100	101	100	233	100	389	100

DI=Dose-Intensity; AIs= Aromatase Inhibitors; CHT=chemotherapy

Figure 2 – Median time of EVE treatment by:

a) previous therapies (months)



b) Dose-Intensity groups (months)

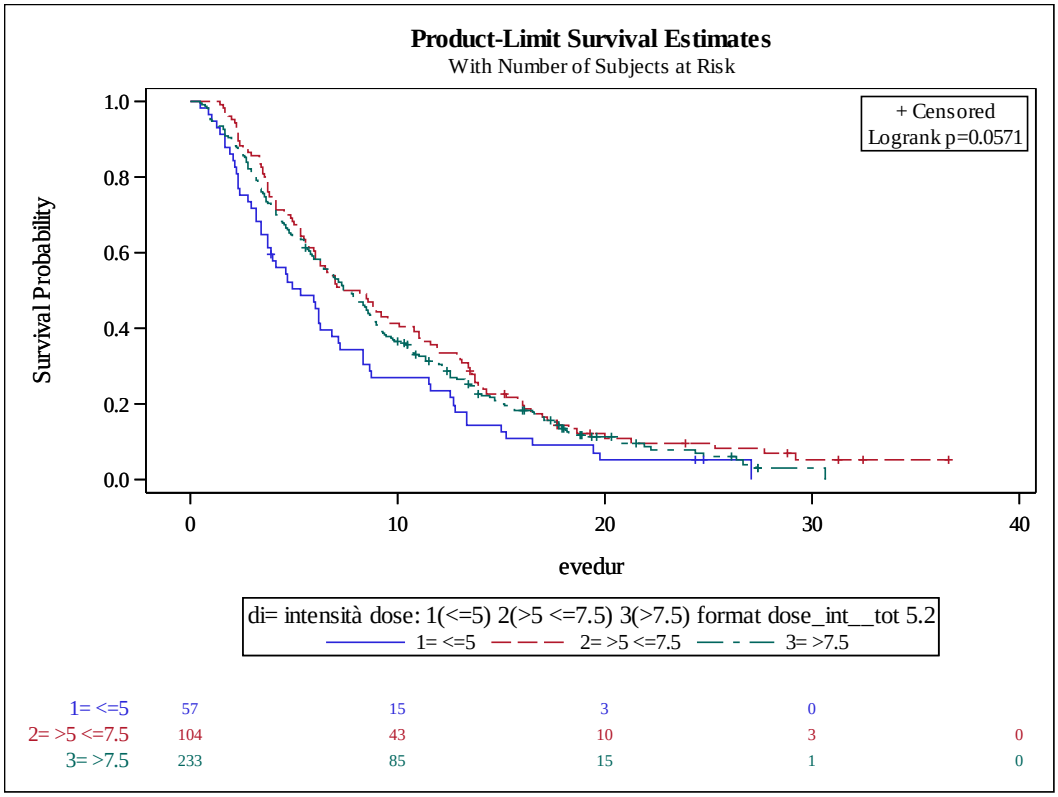


Table 3 – Adverse events (AEs) with at least 10% incidence

Adverse Events (n=404), n(%)	All grades	Grade 3-4
Stomatitis	60.8	11.2
Fatigue	39.5	3.2
Rash	25.4	2.7
NIP	18.6	3.8
Hyperglycemia	17.7	0.9
Peripheral edema	17.1	2.4
Anemia	16.8	3.8
Transaminitis	13.9	2.1
Weight loss	11.5	0.9
Hypertrygliceridemia	10.6	.
Thrombocytopenia	10.3	1.2