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Original article

Efficacy and safety of Everolimus and Exemestane in hormone-receptor 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 efficacy and safety of Everolimus (EVE) and Exemestane (EXE) combination in HR+ advanced breast cancer (ABC) patients. The BALLET trial further evaluated the safety of EVE-EXE in HR+ ABC patients, without reporting efficacy data. Aim of the EVA real-life study was to collect data of efficacy and safety of EVE-EXE combination in the clinical setting, as well as exploring efficacy according to EVE Dose-Intensity (DI) and to previous treatment with Fulvestrant.
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 age was 61 years (33–83). Main metastatic sites 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. Median exposure to EVE was 31.0 weeks (15.4–58.3) in the whole population. No difference was observed in terms of EVE exposure duration according to DI (p for trend = 0.27) or type of previous treatments (p = 0.33). ORR and Disease Control Rate (DCR) were observed in 31.6% and 60.7% of the patients, respectively, with the lowest ORRs confined in CHT pre-treated patients or in those who received the lowest DI of EVE. 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 HR+ ABC pts many years after the publication of the pivotal trial. The combination is safe and the best response could be obtained in patients receiving the full dose of EVE and/or after hormone-therapy as Fulvestrant in ABC.

1. 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 ABC 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− ABC patients recurring or progressing on prior 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 efficacy results.

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, as well to report safety. Efficacy results in special subgroups of patients, namely those previously treated with Fulvestrant, and according to EVE Dose Intensity have been evaluated.

2. Patients and methods

2.1. Study design

This is a multicentre retrospective cohort study, which collected data of HR+ ABC patients who received EVE-EXE combination between July 2013 and December 2015 in 38 Oncology Centres in Italy; all these sites 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 sites. All patients provided written informed consent. Data were collected via electronic database. Baseline information included patient's age at metastatic diagnosis, comorbidity, breast cancer history, (date of stage at initial diagnosis, any adjuvant and/or neoadjuvant therapy), hormone and HER2 status, number and sites of metastases. Physicians were requested to provide a fully comprehensive description of previous endocrine treatments and chemotherapy including the number of previous treatments.

2.2. 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,