# Safety of everolimus plus exemestane in patients with hormone-receptor–positive, HER2–negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET)

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**Background:** This European phase IIIb, expanded-access multicenter trial evaluated the safety of EVE plus EXE in a patient population similar to BOLERO-2.

**Patients and methods:** Post-menopausal women aged ≥18 years with hormone receptor-positive, human epidermal growth factor-receptor-2–negative advanced breast cancer (ABC) recurring/progressing during/after prior non-steroidal aromatase inhibitors were enrolled. The primary objective was safety of EVE plus EXE based on frequency of adverse events (AEs), and serious AEs (SAEs). The secondary objective was to evaluate AEs of grade 3/4 severity.

**Results:** The median treatment duration was 5.1 months [95% confidence interval (CI) 4.8–5.6] for EVE and 5.3 months (95% CI 4.8–5.6) for EXE. Overall, 2131 patients were included in the analysis; 81.8% of patients experienced EVE- or EXE-related or EVE/EXE-related AEs (investigator assessed); 27.2% were of grade 3/4 severity. The most frequently reported non-hematologic AEs were (overall %, % EVE-related) stomatitis (52.8%; 50.8%) and asthenia (22.8%; 14.6%). The most frequently reported hematologic AEs were (overall %, % EVE-related) anemia (14.4%; 8.1%) and thrombocytopenia (5.9%; 4.6%). AE-related treatment discontinuations were higher in elderly (≥70 years) versus non-elderly patients (23.8% versus 13.0%). The incidence of EVE-related AEs in both elderly and non-elderly patients appeared to be lower in first-line ABC versus later lines. The incidence of AEs (including stomatitis/pneumonitis) was independent of BMI status (*post hoc* analysis). Overall, 8.5% of patients experienced at least one EVE-related SAE. Of the 121 on-treatment deaths (5.7%), 66 (3.1%) deaths were due to disease progression and 46 (2.2%) due to AEs; 4 deaths were suspected to be EVE-related.

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Note: Part of these data have been presented as a poster at the 2014 San Antonio Breast Cancer Conference, 9–13 December 2014, San Antonio, TX, USA and as a poster at the 2015 European Society for Medical Oncology, 25–29 September 2015, Vienna, Austria.

**Conclusions:** This is the largest ever reported safety dataset on a general patient population presenting ABC treated with EVE plus EXE and included a sizeable elderly subset. Although the patients were more heavily pretreated, the safety profile of EVE plus EXE in BALLET was consistent with BOLERO-2.
**Clinical trial registration:** EudraCT Number: 2012-000073-23.
**Key words:** advanced breast cancer, BMI, elderly, everolimus, hormone-receptor positive, stomatitis

## introduction

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 [1–5]. However, despite the effectiveness of ET, many women experience disease progression, either *de novo* or acquired [6]. Hence, identification of effective targeted therapies, which may enhance or prolong endocrine sensitivity in these patients, continues to be of clinical importance. Two different targeted agents, everolimus [a mammalian target of rapamycin (mTOR) inhibitor] and palbociclib (a cyclin-dependent kinase 4/6 inhibitor), have each shown efficacy in this patient population [7, 8].

Extensive cross-talk between the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway and estrogen receptor signaling has been implicated as one of the key mechanisms of endocrine resistance [9–11]. Preclinical studies have shown that co-targeting both signaling pathways can synergistically inhibit tumor progression [9, 12, 13]. 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− ABC recurring/progressing on prior non-steroidal aromatase inhibitors (NSAIs) (7.8 versus 3.2 months) [14]. The present European phase IIIb, expanded-access multicenter trial, BALLET, further evaluated the safety of EVE plus EXE in patients with HR+, HER2− ABC recurring/progressing on prior NSAIs.

## methods

### patients

Post-menopausal women aged ≥18 years with histologically/cytologically confirmed HR+ ABC unamenable to curative resection or radiotherapy, recurring or progressing on prior NSAIs were enrolled. NSAIs were not necessarily the last treatment before enrollment. There was no restriction on the number of prior lines of chemotherapy. Patients were excluded if they were HER2+ by local testing, were hypersensitive to mTOR inhibitors or EXE, had received radiotherapy within 4 weeks before enrollment, had symptomatic visceral disease, brain or central nervous system metastasis or had inadequate liver, renal, cardiac or bone marrow functions. Hormone replacement therapy had to be discontinued before enrollment.

Written informed consent was obtained from all patients. The study was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by an independent ethics committee or institutional review board at each site. Dose modifications for specific treatment-emergent toxicities were advised in the protocol.

### study design and treatment

BALLET was a European, open-label, single-arm, multicenter phase IIIb, expanded access trial (EudraCT Number: 2012-000073-23). Enrolled patients self-administered EVE on day 1 and continued daily doses of EVE (either $2 \times 5$ or $1 \times 10$ mg) plus EXE (25 mg/day) in 28-day cycles. Study treatment continued until disease progression, intolerable toxicity, discontinuation from study due to other reasons, local reimbursement of EVE or death. All patients also received best supportive care for pre-existing medical conditions or adverse events (AEs), as per standard local practice. Dose adjustments were allowed for AEs that were suspected to be related to EVE (additional information in supplementary material, available at *Annals of Oncology* online). Permissible dose adjustments for EVE were 5 mg daily; 5 mg every other day. Relative dose intensity was defined as dose intensity (dosing unit/unit of time)/planned dose intensity. Permanent discontinuation involved discontinuation of either EVE or both EVE and EXE. Treatment once interrupted due to unacceptable toxicity was resumed only after recovery to grade ≤1 was achieved; reintroduction was at the initial/lower dose level according to the study protocol. Patients were withdrawn from the study if the interruption was >28 days.

### safety assessment

The primary objective was to assess the safety of EVE plus EXE based on the frequency of AEs, serious AEs (SAEs) and number of laboratory abnormalities. The secondary objective was to evaluate AEs of grade 3 and 4 severity in routine clinical practice. Exploratory analysis included safety assessments in a subset of patients aged ≥70 years. *Post hoc* exploratory analyses evaluated the impact of body mass index (BMI) on the safety profile of EVE plus EXE.

Safety assessments included recording of all AEs and SAEs with their severity and relationship to study treatments, and deaths which occurred throughout the study and up to 28 days after the last treatment. The severity of AEs was graded according to National Cancer Institute Common Terminology Criteria for AEs v4.03 or on a scale of grade 1–4. Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was assessed at baseline and at each study visit. Patients who dropped out of the study but continued on EVE through reimbursement were not followed up after their exit.

### statistical analysis

The study did not formally test any hypotheses; all analyses were descriptive. The safety analysis included all patients who received at least one dose of EVE or EXE and were evaluable at least one time point. No formal sample size calculation was carried out; the estimated sample size of 2500 patients was chosen based on the expected average accrual rate and duration of the trial based on the expected date of reimbursement in each participating country. The Kaplan–Meier method was used for the exploratory assessment of the median treatment durations in the full population and when the study treatment was administered in the first-line setting, after censoring patients who discontinued treatment due to reimbursement/switch to other EVE programs.

## results

### demographics

Between 16 May 2012 and 31 December 2013, 2133 patients were enrolled at 267 centers in 14 countries; 2131 patients were

included in the safety analysis; 2 patients were excluded due to missing baseline safety assessment.

The baseline demographic characteristics were comparable between the two treatment arms (Table 1; comparison with BOLERO-2 in supplementary Table S1, available at *Annals of Oncology* online). The majority of patients (65.1%) received EVE plus EXE as a third-line of therapy or beyond in the advanced setting. Baseline patient characteristics of elderly patients were comparable to the non-elderly except for ECOG-PS 0/1/2 and less frequent prior chemotherapy in metastatic setting (additional information in supplementary materials, available at *Annals of Oncology* online).

## treatment exposure

The median duration of follow-up was 4.6 months (range: <1–24.2 months). The median treatment duration was 3.7 months each for both EVE and EXE and appeared to be longer in patients who received EVE plus EXE as first-line therapy (4.4 months for EVE and 4.6 months for EXE). After censoring patients who discontinued treatment due to reimbursement/switch to other everolimus programs, the median treatment duration was 5.1 months for EVE and 5.3 months for EXE and as first-line therapy, 6.1 months for both EVE and EXE (Figure 1A). Most common reasons for treatment discontinuation were disease progression (36.8%), local reimbursement of EVE (33.4%) and AEs (15.8%). Those patients who dropped out of the study continued on reimbursed EVE; however, the study did not plan to follow-up on them until treatment discontinuation. The overall median RDI was 0.98 (range: 0.1–1.1) for EVE and 1.0 (range: 0.4–1.0) for EXE.

In the elderly subset, the median duration of exposure was 3.2 months for EVE and 3.5 months for EXE. After censoring elderly patients who discontinued treatment due to reimbursement or crossover to other EVE programs, the median duration of exposure was 3.8 months for EVE and 4.1 months for EXE, which was shorter compared with that in non-elderly patients, 5.0 months for EVE and 5.2 months for EXE. The median RDI for EVE was lower (0.95) in the elderly in comparison with non-elderly patients (1.0).

## dose interruptions, reductions and discontinuations

Overall, 29.6% and 1.2% of patients required dose reduction for EVE and EXE, respectively, the most common reasons being AEs (14.1% versus 0%) and medical decision (10.3% versus 0.1%). Dose interruptions for EVE and EXE were required for 55.9% and 19.3% of patients, respectively. More than half (52.3%) of the patients who needed a dose interruption were able to restart EVE at full dose. The median duration of dose interruption was 17 days. The median time to first dose modification was 32 days for EVE and 45 days for EXE. Permanent discontinuation of EVE was avoided through dose reduction in most patients; only 18.1% of these patients were unable to continue therapy thereafter for AEs. On the other hand, 15.1% of patients who never had a dose reduction stopped EVE permanently due to AEs.

Dose reductions and interruptions were higher in the elderly compared with non-elderly patients (37.7% and 60.5%, respectively, versus 26.7% and 54.2%, respectively) (supplementary

**Table 1** Baseline and treatment characteristics (including data for prior therapies by number of prior chemotherapy lines) (full analysis set)

| Characteristic | *n* = 2133 |
|---|---|
| Median age (range), years | 63.0 (28–90) |
| Age categories | |
| <70 years, *n* (%) | 1570 (73.6) |
| ≥70 years, *n* (%) | 563 (26.4) |
| Median BMI (range) | 25.7 (14.69–54.57) |
| Race, *n* (%) | |
| Caucasian | 2100 (98.5) |
| Black | 5 (0.2) |
| Asian | 1 (0.0) |
| Native American | 1 (0.0) |
| Others | 26 (1.2) |
| Ethnicity, *n* (%) | |
| Hispanic/Latino | 314 (14.7) |
| Indian | 1 (0.0) |
| Other | 1818 (85.2) |
| ECOG PS | |
| 0 | 1383 (64.8) |
| 1 | 670 (31.4) |
| 2 | 56 (2.6) |
| Missing | 24 (1.1) |
| **Characteristic** | ***n* = 2131** |
| Current disease status, *n* (%) | |
| Metastatic | 1762 (82.7) |
| Locally advanced | 369 (17.3) |
| Metastatic site, *n* (%) | |
| Bone only | 543 (25.5) |
| Visceral | 1277 (59.9) |
| Visceral only | 208 (9.8) |
| Bone and visceral | 924 (43.4) |
| Others | 775 (36.4) |
| Number of metastatic site, *n* (%) | |
| ≥5 | 469 (22.0) |
| 4 | 281 (13.2) |
| 3 | 437 (20.5) |
| 2 | 509 (23.9) |
| 1 | 435 (20.4) |
| Median time to first diagnosis (range), days | 2908 (−16 218 to −76) |
| Key comorbidities, *n* (%) | |
| Vascular | 808 (37.9) |
| Metabolic and nutritional | 676 (31.7) |
| Musculoskeletal and connective tissue | 599 (28.1) |
| Psychiatric | 410 (19.2) |
| Gastrointestinal | 259 (12.2) |
| Number of lines of prior antineoplastic therapy in metastatic setting, *n* (%) | |
| None (adjuvant therapy only) | 222 (10.4) |
| 1 | 518 (24.3) |
| 2 | 483 (22.7) |
| 3 | 345 (16.2) |
| 4 | 209 (9.8) |
| ≥5 | 350 (16.4) |
| Key prior antineoplastic therapies, *n* (%) | 2131 (100) |
| Aromatase inhibitors | 2122 (99.6) |
| Anti-estrogens | 1579 (74.1) |
| Chemotherapy in metastatic setting | 1284 (60.3) |
| Immunosuppressant | 564 (26.5) |
| Monoclonal antibodies | 272 (12.8) |

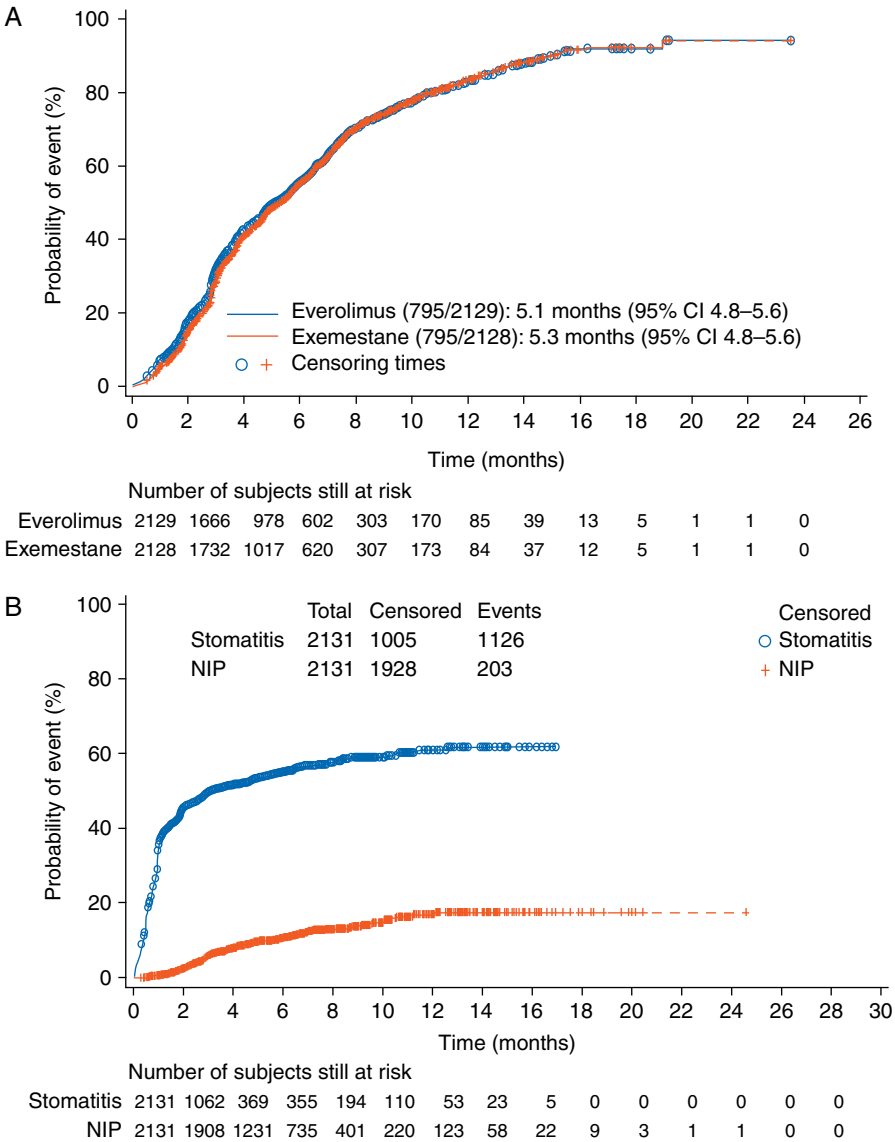


**Figure 1** (A) Kaplan–Meier curve for time to treatment discontinuation after censoring patients who discontinued treatment due to reimbursement or natural death (safety set). (B) Median time to onset for stomatitis events and non-infectious pneumonitis (NIP) events (safety set).

Table S2, available at *Annals of Oncology* online). The most common AEs requiring dose adjustment in the elderly versus non-elderly patients were stomatitis (27.9% versus 21.2%), asthenia (8.9% versus 3.6%), anemia (6.2% versus 3.1%) and non-infectious pneumonitis (NIP, 5.9% versus 4.8%), respectively. The median time to first dose modification was 30 days in the elderly and 33 days in non-elderly patients.

AEs led to permanent treatment discontinuation in 17.1% of patients (grade 3/4, 10%); the majority of these occurred within the first 3 months from treatment initiation. The most frequently reported AEs that led to permanent treatment discontinuation were (all grade; grade 3/4) NIP (2.4%; 0.8%), stomatitis (1.9%; 1.0%), asthenia (1.5%; 0.9%) and dyspnea (1.1%; 0.5%). AE-related treatment discontinuations were reported for 18.9% of the elderly versus 10.6% of non-elderly patients.

AE-related discontinuations were higher in the elderly versus non-elderly patients (23.8% versus 13.0%). In the elderly, the most frequently reported AEs leading to permanent discontinuation of EVE or EVE plus EXE in the elderly versus non-elderly patients were stomatitis (3.9% versus 1.2%) and NIP (3.4% versus 2%).

## safety

Overall, 94.7% of patients experienced at least one any grade AE and 42.7% of patients experienced at least one grade 3/4 AE irrespective of relationship to EVE. Of these, 81.8% and 15.1% of AEs were assessed by the investigators to be EVE- or EXE-related, respectively; 27.2% and 1.6%, respectively, were of grade 3/4 severity. The most frequently reported non-hematologic (all grade) AEs were stomatitis (52.8%; 50.8% were EVE-related), and asthenia (22.8%; 14.6% were EVE-related). Anemia (14.4%; 8.1% were EVE-related) and thrombocytopenia (5.9%; 4.6% were EVE-related) were the most frequently reported hematologic AEs (Table 2). The majority of EVE-related AEs were of grade 1/2 severity; the incidences of grade 3 or 4 stomatitis or

**Table 2** Adverse events of ≥10% incidence in either treatment group or grade 3, 4 adverse events of ≥0.5% incidence in either treatment group (safety set)

| Adverse event ($n = 2131$), $n$ (%) | All grades | Grade 3 | Grade 4 |
|---|---|---|---|
| Stomatitis | 1126 (52.8) | 198 (9.3) | 2 (0.1) |
| Asthenia | 485 (22.8) | 75 (3.5) | 2 (0.1) |
| Diarrhea | 359 (16.8) | 26 (1.2) | 1 (0.0) |
| Rash | 351 (16.5) | 20 (0.9) | 0 |
| Decreased appetite | 341 (16.0) | 24 (1.1) | 0 |
| Anemia | 306 (14.4) | 0 | 0 |
| Pyrexia | 299 (14.0) | 7 (0.3) | 3 (0.1) |
| Fatigue | 298 (14.0) | 26 (1.2) | 1 (0.0) |
| Hyperglycemia | 265 (12.4) | 60 (2.8) | 3 (0.1) |
| Peripheral edema | 259 (12.2) | 13 (0.6) | 0 |
| Nausea | 255 (12.0) | 13 (0.6) | 0 |
| Cough | 254 (11.9) | 8 (0.4) | 0 |
| Dyspnea | 220 (10.3) | 39 (1.8) | 4 (0.2) |
| Decreased weight | 217 (10.2) | 2 (0.1) | 0 |
| Hypercholesterolemia | 216 (10.1) | 1 (0.0) | 1 (0.0) |
| NIP | 203 (9.5) | 35 (1.6) | 6 (0.3) |

NIP, non-infectious pneumonitis.

NIP were low (Table 2; comparison with BOLERO-2 in supplementary Table S3, available at *Annals of Oncology* online).

In the elderly subset, 95.2% of patients experienced at least one AE. The most common any grade AEs in elderly versus non-elderly patients were stomatitis (55.5% versus 51.9%), asthenia (28.5% versus 20.7%) and decreased appetite (22.4% versus 13.7%); the most frequent grade 3 or 4 AEs were stomatitis (12.3% versus 8.3%), asthenia (5.7% versus 2.9%) and hyperglycemia (4.6% versus 2.3%). NIP was reported in 11.2% of elderly versus 8.9% of non-elderly patients (supplementary Table S4, available at *Annals of Oncology* online).

*Post hoc* analysis showed that the incidences of any grade AEs following EVE, including grade 3/4 AEs of special interest like stomatitis (range: 5.4%–9.8%), NIP (range: 1.3%–2.7%) and asthenia/fatigue (range: 4.1%–8.1%), were independent of the patients' BMI status (supplementary Table S5, available at *Annals of Oncology* online).

The median time to onset for stomatitis events and NIP events was 29 days (range: 1–396) and 87 days (range: 1–231), respectively (Figure 1B). The median duration of a stomatitis event was 16 days and of an NIP event was 19 days. The incidence of EVE-related AEs appeared to be lower in the first-line setting for ABC versus later lines, with a numerically lower incidence observed for stomatitis (45.6% versus 51.4%), rash (11.4% versus 15.1%), asthenia (10.9% versus 15.1%) and diarrhea (9.1% versus 10.7%). Grade 3/4 stomatitis (7.7% versus 9.4%), diarrhea (0.5% versus 0.9%), rash (0.5% versus 1.0%) and NIP (0.9% versus 1.9%) were also reported less frequently in the first-line setting versus later lines.

Overall, 21.2% of patients experienced at least one SAE regardless of the relationship to any study treatment (supplementary Table S6, available at *Annals of Oncology* online); 8.5% of patients experienced at least one EVE-related SAE. The most frequent SAEs were dyspnea (2.4%), NIP (2.2%), pyrexia (1.6%), anemia (1.3%) and pleural effusion (1.2%). Treatment-related SAEs were reported in 10.3% of the elderly versus 7.8% of non-elderly patients.

### survival and follow-up status

At the time of analysis, 121 (5.7%) on-treatment deaths were recorded in the full study population. Deaths were attributable to disease progression [66 (3.1%)], AEs [46 (2.2%)] and unknown reasons [9 (0.4%)]. On-treatment deaths were reported in 39 (6.9%) elderly patients; the deaths were attributable to progressive disease [18 (3.2%)], AEs [16 (2.8%)] (additional data in supplementary Table S7, available at *Annals of Oncology* online), and others reasons [5 (0.9%)]. AEs suspected to be EVE-related leading to death were reported in four patients: NIP (two patients), general physical health deterioration and cardiorespiratory arrest (one patient each).

Overall, 69.2% of patients received at least one anti-neoplastic medication since study treatment discontinuation (supplementary Table S8, available at *Annals of Oncology* online).

## discussion

To our knowledge, this is the largest ever reported safety dataset on a general patient population presenting HR+, HER2− ABC progressing on prior NSAIs, treated with EVE plus EXE. Further, the exploratory safety analysis in the elderly subset in BALLET is by far the largest safety dataset in this age group.

Overall, the patient population in BALLET was more heavily pretreated compared with BOLERO-2 [14]. Patients in BALLET were treated in later lines (65% versus 54% in BOLERO-2 in third-line and beyond) [14], and with more prior chemotherapy (60% versus 26% in BOLERO-2; 20.8% of patients in BALLET received ≥3 lines of chemotherapy in the metastatic setting) because the trial did not impose limitations in terms of number of prior chemotherapy [14]. This may be one of the reasons why fewer patients in BALLET received any post-treatment therapy than those in BOLERO-2 (69.2% versus 84%) [15]. The short follow-up period could be another reason for this observation.

The incidence of stomatitis (52.8% versus 59%) and NIP (9.5% versus 16%) was lower in BALLET compared with BOLERO-2 [14]; this difference may be attributed to the shorter median follow-up in BALLET compared with BOLERO-2 (4.6 versus 17.7 months). This could be because long-term safety profile of EVE could not be evaluated in those patients in BALLET who dropped out of the study but continued on EVE under reimbursement. Another plausible reason for this difference could be the variability across study sites in the reporting of low-grade stomatitis. Consistent with BOLERO-2, the most common AEs leading to treatment discontinuation in BALLET were NIP (2.4% versus 5.6% in BOLERO-2) and stomatitis (1.9% versus 2.7% in BOLERO-2) [14]. In BALLET, fewer treatment-emergent AEs were reported in the first-line setting compared with later lines.

The median duration of treatment with EVE in BALLET was lower compared with BOLERO-2 (16 versus 23.9 weeks), even though the median RDI was higher [14]. This may suggest an improvement in treatment optimization. Indeed, fewer patients in BALLET discontinued study drug due to AEs [17.1%

compared with patients in BOLERO-2 (26.3%)] [14] and clinicians preferred a temporary treatment interruption over permanently discontinuation.

The trends in the safety profile of EVE plus EXE in elderly patients in BALLET were consistent with the ≥70 years subset ($n = 121$) in the BOLERO-2 trial [16]. The median duration of exposure to EVE and EXE was shorter and the corresponding RDIs were lower in the elderly compared with non-elderly patients. Dose reductions, interruptions and AE-related study treatment discontinuations, grade 3/4 AEs, treatment-related SAEs and on-treatment deaths were higher in the elderly compared with non-elderly patients.

BALLET is also the first trial reporting the impact of BMI on safety. *Post hoc* analysis showed that the incidence of AEs was independent of BMI status. This observation bears clinical implications as it appears that patients with lower BMI do not require a lower EVE starting dose.

Given that globally relevant clinical practice guidelines for breast cancer recommend EVE plus AIs including EXE as a treatment option for patients with HR+, HER2−ABC recurring or progressing on/after prior NSAIs [1, 17], these data add safety information to the clinical relevance of the efficacy data. Given the early incidence of AE and dose interruption/modification observed in BALLET, close follow-up in the first months of therapy is indicated. We recommend a first visit 2 weeks after starting EVE (only 1 month in BALLET) in order to further reduce EVE-related discontinuation rate.

The rate of study discontinuation due to EVE reimbursement (33.4%) was high. Although these patients continued on reimbursed EVE, they could not be followed-up until definitive treatment discontinuation. This might have influenced the long-term safety profile of the study treatments and treatment duration. An exploratory analysis of treatment duration censoring patients who discontinued treatment due to reimbursement showed the median duration of treatment to be 5.1 months and 5.3 for EVE and EXE, respectively, but a similar analysis for safety was not feasible from a statistical point of view due to lack of sufficient power. Despite these limitations, the inherent strength of BALLET lies in the sizeable study population that was evaluated to provide meaningful safety data that support the utilization of the dual inhibition strategy with EVE plus EXE in this patient population.

Given that BALLET was an expanded access program, the methodology did not allow for the assessment of PFS; however, considering that the duration of exposure is a surrogate marker for PFS, this has allowed cross-trial comparisons, in particular with the BOLERO-2 trial. As is inherent to expanded access trial designs, this design of BALLET allowed for inclusion of patients unrestricted by the demographic profile of the BOLERO-2 patient population. This allowed for meaningful evaluation of the safety profile of EVE plus EXE in an a larger patient population that mimicked the real-world setting.

In conclusion, this is the largest ever reported safety dataset on a general patient population including a sizeable elderly subset, in patients with HR+, HER2− ABC progressing on prior NSAIs. The safety profile of EVE plus EXE in BALLET is consistent with previous observations from BOLERO-2. There were no new safety signals. Diligent monitoring, proactive communication, early detection and implementation of appropriate AE-management strategies can ensure better treatment optimization.

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SB: employee of Novartis. GM, EMC, PN, JGG, AM, DG, ES, IL, JM, PC: nothing to disclose.

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