Presented at the 2014 San Antonio Breast Cancer Symposium (SABCS); December 9-13, 2014; San Antonio, Texas, USA. Poster P3-06-04.

4EVER: The Impact of mTOR Inhibition on Bone Health in Postmenopausal Women With Hormone Receptor Positive (HR+) Advanced Breast Cancer Treated With Everolimus (EVE) in Combination With Exemestane (EXE)

P. Hadji,[1] H. Tesch,[2] O. Stoetzer,[3] T. Decker,[4] C. Kurbacher,[5] F. Marmé,[6] A. Schneeweiss,[7] C. Mundhenke,[8] J. Distelrath,[9] P.A. Fasching,[10] M. Lux,[10] D. Lueftner,[11] W. Janni,[12] M. Muth,[13] J. Kreuzeder,[13] E. Grischke[14]

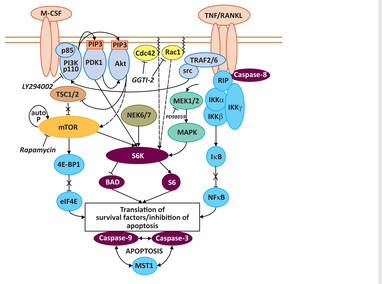
[1]Hospital North West GmbH, Frankfurt am Main, Germany; [2]Department of Oncology, Bethanien Hospital, Frankfurt am Main, Germany; [3]Department of Haemato-Oncology, Munich, Germany; [4]Oncology Ravensburg, Ravensburg, Germany; [5]Medical Centre Bonn Friedensplatz, Bonn, Germany; [6]Department of Obstetrics and Gynecology, University Hospital Heidelberg, Heidelberg, Germany; [7]National Center for Tumor Diseases, Heidelberg, Germany; [8]Department of Obstetrics and Gynecology, University Hospital Kiel, Kiel, Germany; [9]Medical Healthcare Centre East Hessen GmbH, Fulda, Germany; [10]Department of Obstetrics and Gynaecology, University Hospital Erlangen, Erlangen, Germany; [11]Med. Clinic for Haematology, Oncology, and Tumor Immunology, Charité Campus Benjamin Franklin, Berlin, Germany; [12]Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany; [13]Novartis Pharma GmbH, Nuremberg, Germany; [14]Department of Obstetrics and Gynecology, University of Tuebingen, Germany

4EVEROLIMUS
- ✓ Efficacy
- ✓ Safety
- ✓ Health Economics
- ✓ Translational Research

Introduction

- The phase III BOLERO-2 trial demonstrated that everolimus (EVE) + exemestane (EXE) more than doubled median progression-free survival (PFS) compared with placebo (PBO) + EXE in postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer progressing after nonsteroidal aromatase inhibitor (NSAI) therapy[1]
  - Final PFS by investigator review: 7.8 versus 3.2 months; hazard ratio (HR) = 0.45; 95% confidence interval (CI), 0.38-0.54; *P* < .0001
  - Final PFS by central review: 11.0 versus 4.1 months; HR = 0.38; 95% CI, 0.31-0.48; *P* < .0001
- An exploratory analysis of BOLERO-2 indicated a direct impact of EVE on bone health[2]
  - Bone markers assessed in BOLERO-2 were
    - Bone-specific alkaline phosphatase (BSAP, osteoclast metabolism)
    - C-terminal cross-linking telopeptide of type 1 collagen (CTX, bone resorption)
    - Amino-terminal propeptide of type 1 collagen (P1NP, bone formation)
  - Bone marker levels at 6 and 12 weeks decreased with EVE+EXE versus increasing with PBO+EXE
  - The cumulative incidence rate of progressive disease in bone was lower with EVE+EXE versus PBO+EXE (*P* = .04, Gray's test)
- **Figure 1** depicts a schematic overview of intracellular mammalian target of rapamycin (mTOR) signaling in the osteoclast

Figure 1. Schematic illustration of mTOR/S6K intracellular signal transduction pathways in the osteoclast.[3]



Abbreviations: Akt, protein kinase B; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P, phosphate; RANKL, receptor activator of nuclear factor-kappa B ligand; S6K, 40 S ribosomal S6 kinase; Src, steroid receptor coactivator; TNF, tumor necrosis factor; TSC, tuberous sclerosis complex.
Reprinted from Glantschnig H, et al.[4]

- The 4EVER trial further evaluated the efficacy and safety of EVE+EXE in a broader patient population than in BOLERO-2. In 4EVER there were no limitations on
  - Number of previous chemotherapy lines for advanced disease
  - Time of recurrence or progression after NSAI therapy
  - Previous EXE therapy
- The long-term influence of mTOR inhibition by EVE on bone health was investigated in the exploratory analyses of the 4EVER trial
  - Here we report changes in marker levels for bone resorption (CTX) and bone formation (P1NP and osteocalcin) in the subset of patients with bone metastases

Objective

- To further investigate the longer-term effect of mTOR inhibition on bone health as assessed by changes in marker levels of bone resorption (CTX) and bone formation (P1NP and osteocalcin) in the subset of patients with bone metastases in the 4EVER trial

Methods

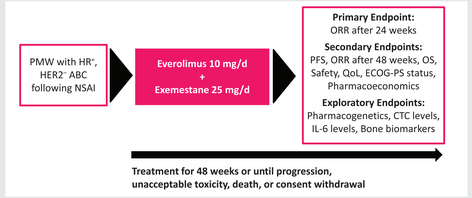
Study Design and Treatment

- Multicenter, open-label, single-arm, phase IIIB study examining everolimus (10 mg daily) and exemestane (25 mg daily; **Figure 2**)
- Postmenopausal women with HR+, HER2- metastatic or locally advanced breast cancer that recurred or progressed during or after an NSAI were enrolled
- Study treatment was for 48 weeks or until progression, unacceptable toxicity, death, or consent withdrawal
  - Further treatment after progression was at the investigator's discretion
- Tumor evaluations through computed tomography were performed for screening, at 24 weeks, and at 48 weeks or end of treatment
- Study visits were performed at baseline (day 1) and at weeks 4, 12, 24, 36, and 48 or end of treatment

Endpoints

- Primary endpoint was overall response rate (ORR; complete response + partial response) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 after week 24
- Secondary endpoints include
  - PFS
  - ORR after week 48
  - Overall survival (OS)
  - Safety assessed with the Common Terminology Criteria for Adverse Events, version 4.03
    - Incidence of adverse events (AEs), serious AEs (SAEs), changes from baseline in vital signs, Eastern Cooperative Oncology Group performance status, and laboratory results (hematology, blood chemistry—if resulting in AE) were reported
- Exploratory endpoints include
  - Correlation of response to EVE+EXE, with pharmacogenetics
  - Presence and molecular characteristics of circulating tumor cells
  - Correlation of anxiety and depression with interleukin-6 levels
  - Changes in serum biomarkers of bone metabolism

Figure 2. Study design.



Abbreviations: ABC, advanced breast cancer; CTC, circulating tumor cell; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR+, hormone receptor–positive; HER2-, human epidermal growth factor receptor 2–negative; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMW, postmenopausal women; QoL, quality-of-life.

Exploratory Bone Biomarker Analysis

- Planned exploratory analysis of changes in bone metabolism biomarker levels was conducted in the subset of patients with bone metastases at baseline
  - Analyses performed in patients with or without antiresorptive therapy
- Assessed changes of bone metabolism biomarker levels from day 1 to weeks 4, 12, and 24
  - CTX (bone resorption)
  - P1NP (bone formation)
  - Osteocalcin (bone formation)
    - Changes in other bone metabolism and endocrine biomarkers (vitamin D, testosterone, estradiol, dehydroepiandrosterone, sex hormone-binding globulin, parathyroid hormone, thyroid-stimulating hormone, follicle-stimulating hormone) will be assessed in the future

Methods (Continued)

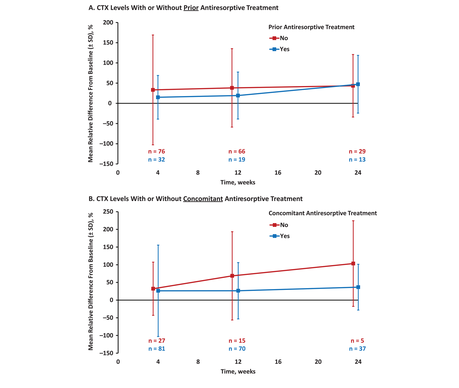
Patient Populations and Statistical Methods

- The ***Safety Set*** includes all patients who received at least 1 dose of study drug and had at least 1 postbaseline safety assessment
- The ***Full Analysis Set 1*** includes all patients who received at least 1 dose of study drug, with the exception of 18 patients from centers with issues of Good Clinical Practice noncompliance
- Descriptive statistics were used to summarize the single bone metabolism biomarkers by visit and difference from baseline; linear regression models were not used

Results

- Trial database lock occurred in June 2014
- A total of 299 patients (Safety Set) were enrolled from May 2012 to November 2012
  - The Full Analysis Set 1 included 281 patients
- Bone metastases were detected at baseline in 174 patients
  - CTX, P1NP, and osteocalcin levels were measured in patients with bone metastases
- The median relative differences from baseline in CTX (**Figure 3**), P1NP (**Figure 4**), and osteocalcin (**Figure 5**) levels were examined in patients with bone metastases at baseline with or without antiresorptive therapy
  - There were no significant differences in bone metabolism biomarker levels from baseline to week 24 regardless of the presence or absence of prior or concomitant antiresorptive treatment
  - Use of prior antiresorptive treatment was markedly different from the use of concomitant antiresorptive treatment
    - The majority of patients in this exploratory analysis did not receive prior antiresorptive treatment (**Figures 3-5**; **Panel A for each**)
    - However, most did receive concomitant antiresorptive treatment (**Figures 3-5**; **Panel B for each**)

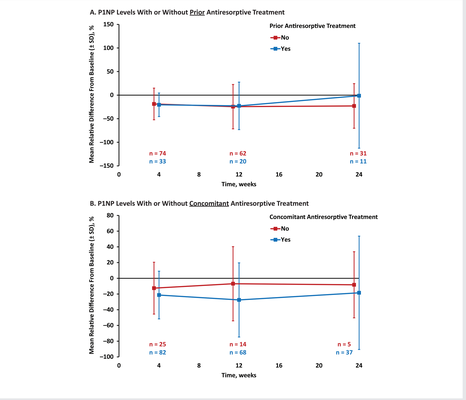
Figure 3. CTX levels in patients with bone metastases with or without antiresorptive treatment.



Abbreviations: CTX, C-terminal cross-linking telopeptide of type 1 collagen; SD, standard deviation.

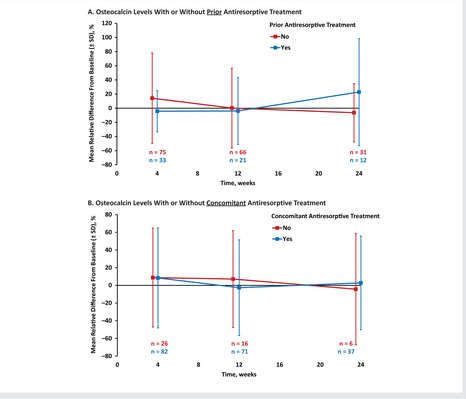
Results (Continued)

Figure 4. P1NP levels in patients with bone metastases with or without antiresorptive treatment.



Abbreviations: P1NP, amino-terminal propeptide of type 1 collagen; SD, standard deviation.

Figure 5. Osteocalcin levels in patients with bone metastases with or without antiresorptive treatment.



Abbreviation: SD, standard deviation.

Discussion

- The 4EVER trial further evaluated the efficacy and safety of EVE+EXE in a broader patient population than in BOLERO-2. In 4EVER there were no limitations on
  - Number of previous chemotherapy lines for advanced disease
  - Time of recurrence or progression after NSAI therapy
  - Previous EXE therapy
- Therefore, the patient population in the 4EVER trial was more advanced and heavily pretreated than in the BOLERO-2 study[5]
- Our results are consistent with the results of the exploratory bone analysis from the BOLERO-2 study, which had suggested a possible bone-protective effect with EVE+EXE[2]
  - Notably, these exploratory analyses include an additional timepoint (week 24) and a different bone metabolism biomarker (osteocalcin) than in BOLERO-2
- Bone metabolism biomarker levels would generally be expected to show marked differences over baseline, especially in the absence of concomitant treatment with antiresorptive agents in patients with bone metastases. However, CTX, P1NP, and osteocalcin levels remained stable regardless of the use of antiresorptive agents in the 4EVER trial
  - These data suggest that the addition of EVE to EXE may have stabilized CTX, P1NP, and osteocalcin levels
- The results from this exploratory analysis from 4EVER should be treated as hypothesis generating, and should be interpreted in the context of the study limitations:
  - Limited sample size (especially for the bone turnover marker subset)
  - Lack of a placebo arm
- Additional exploratory analyses from 4EVER (into biomarkers of bone metabolism and endocrine hormones) will be reported in the future

Acknowledgements

The results are presented on behalf of all participating sites of the 4EVER study. We thank the patients for their participation, as well as the staff at each site—all of whom significantly contributed to the success of the study. Medical editorial and graphics assistance for this poster presentation was supported by Novartis Pharmaceuticals Corporation.

References

1. Yardley DA, et al. *Adv Ther.* 2013;30(10):870-884.
2. Gnant M, et al. *J Natl Cancer Inst.* 2013;105(9):645-663.
3. Hadji P, et al. *Crit Rev Oncol Hematol.* 2013;87(2):101-111.
4. Glantschnig H, et al. *Cell Death Differ.* 2003;10(10):1165-1177.
5. Tesch H, et al. SABCS 2014. Poster P5-19-06.

Mobile Friendly e-Prints

3 ways to instantly download an electronic copy of this poster to your mobile device or e-mail a copy to your computer or tablet

Scan this QR code

Text Message (SMS)
Text: Qefbfd
to: 8NOVA (86682) *US Only*
+18324604729 *North, Central and South Americas; Caribbean; China*
+447860024038 *UK, Europe & Russia*
+46737494608 *Sweden, Europe*

Visit the web at:
http://novartis.medicalcongressposters.com/Default.aspx?doc=efbfd

NOVARTIS ONCOLOGY
AIO
Zertifiziert mit dem Gütesiegel der Kommission für translationale Forschung der AGO
AKS Arbeitskreis Klinische Studien in onkologischen und hämatologischen Praxen e.V.
Deutsche Gesellschaft für Senologie