DIRECT EFFECTS ON BONE METABOLISM INDUCED BY PERIOPERATIVE ANTHRACYCLE- AND/OR TAXANE-BASED CHEMOTHERAPY DEPEND ON THE MENOPAUSAL STATUS OF PATIENTS WITH PRIMARY BREAST CANCER

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INTRODUCTION
Loss of bone mineral density (BMD) is among the well-known sequela of pharmacological therapy of patients (pts) with primary breast cancer (PBC). Heritability, as observed in familial breast cancer (BC), strongly suggests that genetic factors play a critical role in the development of bone loss (BL). Treatment induced bone loss (TIBL) progresses more rapidly as compared to normal age-related changes of BMD and is best known to be associated with the use of aromatase inhibitors (AIs) in the adjuvant endocrine therapy of postmenopausal PBC pts (Body, 2010). Poppone et al. (2014), endocrine treatment (CT) may also lead to a deterioration of BMD but contrast to chemotherapy (CT) this phenomenon is for by far investigated so far (Hirbe et al., 2006; Bjarnason et al., 2009).

Both of these studies focused on the classical CT regimen which to no longer in common use. A few studies also investigated the effects of anthracycline-based regimens on BMD and found differences compared to CMF (Brady et al., 1998) in premenopausal PBC pts. CT-based regimens are predominantly interpreted as an indirect endocrinologic effect since the BMD decline in women experiencing secondary amenorrhea is generally less pronounced than in those retaining their ovarian function (Bjarnason et al., 2008; Body, 2010). However, CT may also have direct effects on the bone since postmenopausal PBC pts show a BMD loss which is at least as high as in premenopausal pts with secondary amenorrhea. As a matter of concern, investigations on the effects of more recent CT regimens in breast cancer patients both antracyclines and/or taxanes a already completely lacking. This retrospective study is undertaken in order to gain more insights into direct effects of modern antineoplastic and/or taxane-based CT on the bone metabolism of both pre- and postmenopausal PBC pts.

METHODS
Data of 108 PBC pts (premenopausal, n=49; postmenopausal, n=60) receiving a total of 609 PBC cycles were analyzed. All pts must have been treated with at least 2 cycles after adjuvant or neoadjuvant CT based on anthracyclines, taxanes or both. 17 pts with HER2-positive disease only were also included in the analysis. Baseline data of pts included in this study are summarized in Table 1. Pts receiving trastuzumab without CT or a CT regimen not containing anthracyclines or taxanes (such as CMF) were excluded from the analysis as were pts with severe osteoporosis as defined by a reduction of BMD of over 30% compared to their bone mineral density [BMD] at baseline or a history of osteoporosis at time of diagnosis. The following serum parameters were analyzed: C-terminal telopeptide of type I collagen (ICTP) as a marker of osteoclast function, N-terminal propeptide of type I collagen (PINP) as a marker of osteoblast function, and alkaline phosphatase (BALP) as a sum marker of bone turnover. All these parameters were measured by commercial enzyme immunoassay kits (ELIA) prior to start of CT and after each of the following cycles for a maximum of 6. Baseline bone marker levels of pre- and postmenopausal pts were compared by student’s t-tests. Absolute and relative changes of bone marker levels over time were evaluated by analyses of variance (ANOVA) for repeated measures for all statistical analyses, p<0.05 was considered significant.

RESULTS
Figure 1 shows the baseline values for ICTP, PINP, and BALP. For all three parameters, premenopausal pts had significantly higher baseline levels as compared to premenopausal pts but within the normal range except for ICTP. ICTP, p=0.027; PINP, p=0.006; BALP, p=0.007. Figure 2 shows the absolute changes from baseline for ICTP, PINP, and BALP during postmenopausal CT for PBC. With the exception of ICTP, all changes were within the normal range. The particular parameter and did not reach statistical significance for both ICTP and BALP. In premenopausal pts, however, a significant increase of BALP was observed (p=0.013). Figure 3 shows the absolute changes from baseline of all three bone markers versus baseline. Although starting from significantly different baseline levels, a trend to a large degree of variation between pre- and postmenopausal pts was distinctly improved for PINP.

Table 1: Patients’ characteristics

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<tr>
<th>Menopausal status</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
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<tr>
<td>Pts</td>
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<td>60 (55)</td>
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Table 2: Baseline values for ICTP, PINP, and BALP.

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<th>PBC cycles</th>
<th>ICTP</th>
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References

CONCLUSIONS
Our study represents one of the very few systematic evaluations of short-term effects of modern antineoplastic and/or taxane-based CT on bone metabolism in breast cancer patients. It focusses for the first time on the perioperative phase of chemotherapy and reveals the following findings:

1. Bone turnover was significantly higher in postmenopausal breast cancer patients than in premenopausal breast cancer patients.
2. Absolute and relative changes of all three bone markers over time were more largely comparable between pre- and postmenopausal pts arguing in favor of direct rather than indirect endocrine effects of CT on bone metabolism.
3. Absolute and relative changes of ICTP over time were particularly large indicating that the osteoclast function is the main target of perioperative adverse effects of postmenopausal pts on bone integrity (ICTP, PBC cycle).
4. The sustained PINP in postmenopausal pts may indicate a generally impaired ability to recover from negative pharmacological effects on bone.
5. Whether the observed short-term effects of modern perimenopausal for PBC will translate into a higher risk to further develop CTE need to be clarified in subsequent investigations which should also focus on the importance of different agents and therapeutic antibodies as such.

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