of type I collagen as a biochemical indicator of bone turnover might facilitate an early and valid disease surveillance. We investigated the utility of total PINP in breast cancer patients at different stages of the disease with and without bone metastases to monitor the response to therapy in relation to the serum level of PINP. The results were compared to osteocalcin and ß-carboxyterminal telopeptide (CTX) or crosslaps concentrations as historically used markers for bone metabolism, while CA15−3 was used as reference mass tumor marker.
Materials and methods: Baseline serum samples of 51 patients with metastastic breast cancer under systemic therapy were investigated. A total of 11 patients with primary breast cancer under neoadjuvant chemotherapy were used as control collective without bone spread. In total; 38 patients had been diagnosed with bone metastases while 24 had no evidence of metastastic spread to the bone. All patients with bone spread received bisphosphonates in addition to systemic treatment. Osteocalcin, CTX and PINP levels were measured on the Elecsys® 2010 analyzer (electro-chemiluminescence immunoassay – ECLIA). Cut-offs of normal were as follows: Osteocalcin: 41.3 pg/ml; CTX: 1008 pg/ml; PINP: 95 ng/ml, CA15−3: 28 U/ml. Patients were grouped based on overal treatment outcome in responders (CR/CR), stable disease (SD) and primary progression (PD).
Results: ROC analysis of osseous versus non-osseous metastatic disease revealed an area under the curve (AUC) for PINP of 0.75. The ROC result was much worse and therefore not discriminative for CTX (0.56) and osteocalcin (0.58). In our study we found no difference for the baseline levels of PINP, CTX and osteocalcin between post- and premenopausal women ($p > 0.5$ each). Patients with bone metastases showed statistically significantly higher PINP levels at baseline and at progression in comparison to patients without bone metastases at both time points ($p = 0.02$).
Conclusions: PINP concentrations can discriminate patients with bone metastases from those without osseous spread much better than osteocalcin or CTX. Further data on monitoring of patients with metastatic breast cancer and bone metastases as compared to patients without bone metastases (= bone specific monitoring) will be presented.

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Effect of intravenous and oral ibandronate on the need for analgesic interventions for metastatic bone pain: phase III trial results

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Background: Bone metastases often cause severe pain and considerable disability, which is managed most commonly with radiotherapy and/or opioid analgesics. As potent inhibitors of osteoclast-mediated bone resorption, bisphosphonates reduce skeletal-related event (SRE) rates and can also relieve metastatic bone pain. Here, we present supportive pain efficacy data from phase III trials of intravenous and oral ibandronate in breast cancer patients with bone metastases.
Materials and methods: Three 96-week, randomized, double-blind, placebo-controlled trials were conducted. In a trial of intravenous ibandronate, a 6mg dose ($n = 154$) was compared with placebo ($n = 158$) infused over 1−2 hours every 3−4 weeks. In two trials of oral ibandronate, a 50 mg daily dose ($n = 287$) was compared with placebo ($n = 277$) (prespecified pooled analysis). Bone pain was measured on a 5-point patient-rated scale from 0 (no pain) to 4 (intolerable). The requirement for radiotherapy was recorded as part of SRE monitoring. Analgesic use was measured on a 7-point scale from 0 (none) to 6 (requiring ⩾100mg morphine [or equivalent] daily).
Results: Both intravenous and oral ibandronate significantly reduced pain scores below baseline throughout 2 years of therapy (mean change at endpoint: 6mg –0.28 vs placebo +0.21, $p < 0.001$; 50 mg −0.10 vs placebo +0.20, $p = 0.001$). The incidence of events requiring radiotherapy was significantly lower in ibandronate-treated patients at endpoint (6 mg 0.91 vs placebo 1.09, $p = 0.011$; 50 mg 0.73 vs placebo 0.98, $p = 0.011$). Mean change from baseline in analgesic use score at endpoint was also lower in the ibandronate groups (6 mg 0.51 vs placebo 0.90; 50 mg 0.60 vs placebo 0.85); the between-groups difference was statistically significant for oral ibandronate ($p = 0.019$ vs placebo).
Conclusions: Both intravenous and oral ibandronate significantly reduced bone pain even with the concurrent reduction in the use of analgesics and radiotherapy. This suggests that pain relief was not due to these factors and ibandronate was responsible for pain palliation. Ibandronate offers the flexibility of effective intravenous and oral formulations to treat metastatic bone pain and other SREs.

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Phase III trial of oral ibandronate and intravenous zoledronic acid in breast cancer patients with bone metastases: comparison of bone turnover markers

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Background: There is a correlation between levels of bone turnover markers and the incidence of skeletal-related events in patients with metastatic bone disease. Ibandronate is a single-nitrogen bisphosphonate available in intravenous and oral formulations with similar efficacy. In this head-to-head, multicenter, randomized, open-label, parallel-group study, oral ibandronate was compared directly to intravenous zoledronic acid with respect to biochemical markers of bone turnover.
Materials and methods: Breast cancer patients with advanced disease and at least one confirmed osteolytic or mixed bone lesion received oral ibandronate 50 mg/day ($n = 128$) or intravenous zoledronic acid 4 mg ($n = 126$) infused over 15 minutes every 4 weeks for 12 weeks. The primary endpoint was the mean percentage change in serum levels of cross-linked C-terminal telopeptide of type I collagen (S-CTX) at the end of the study. Other assessments included urinary CTX (U-CTX), and serum levels of bone specific alkaline phosphatase (BAP), amino-terminal procollagen propeptides of type I collagen (P1NP), and osteocalcin (OC).
Results: Treatment with ibandronate or zoledronic acid was associated with comparable reductions in all bone turnover markers at study endpoint (Table 1).

Table 1: Mean (CI) percentage change from baseline in bone turnover markers

	S-CTX*	U-CTX	BAP	P1NP	OC
Ibandronate	−76 (−81 to −71)	−76 (−83 to −69)	−37 (−43 to −30)	−47 (−55 to −40)	−35 (−39 to −30)
Zoledronic acid	−73 (−81 to −65)	−82 (−87 to −77)	−26 (−43 to −8)	−39 (−52 to −26)	−26 (−43 to −8)

*Baseline S-CTX levels in the treatment groups were ibandronate 0.65 ng/ml and zoledronic acid 0.70 ng/ml

Conclusion: In this head-to-head trial, oral ibandronate was statistically non-inferior to intravenous zoledronic acid for the primary endpoint of S-CTX. Both agents also had similar effects on U-CTX and serum levels of BAP, P1NP and OC. Overall, a convenient oral ibandronate dose of 50 mg/day is as effective as intravenous zoledronic acid in suppressing tumor-induced bone resorption, suggesting comparable efficacy for the prevention of skeletal-related events (SREs). Head-to-head studies comparing SRE rates are warranted to confirm results.

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Safety and efficacy of sunitinib malate (SU11248) as second-line therapy in metastatic breast cancer (MBC) patients: preliminary results from a Phase II study

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Introduction: Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT and FLT3. Angiogenesis and proliferation of breast cancer are stimulated by autocrine and paracrine signalling involving VEGFR and PDGFR. Results are reported from a Phase II trial of sunitinib in MBC patients (pts) unresponsive to prior therapy.
Materials and methods: This open-label, multicentre, Phase II study enrolled female pts with unresectable histologically/cytologically confirmed breast adenocarcinoma and failure of prior anthracycline (A) or taxane (T) therapy (progression during or within 12 months of an A or T therapy in the adjuvant and/or MBC setting). In addition, pts were required to have measurable disease, ECOG PS of 0/1 and adequate organ function. Pts received sunitinib 50 mg q.d. orally for 4 weeks, followed by 2 weeks without treatment to comprise a 6-week cyclical regimen. Toxicity-related dose reduction was permitted. The primary endpoint was objective response rate (ORR), assessed every two cycles by RECIST. A total sample size