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

of 63 was required to identify a clinical meaningful ORR ⩾15% based on Simon's Minimax 2-stage design.
Results: As of Apr 05, 64 pts (median age 51 years) were enrolled. Of these, 56% and 16% were ER+ and HER2+, respectively, and 82% had visceral disease. Fifty-two pts had prior adjuvant chemotherapy (A = 90%; T = 56%), and in the MBC setting, 62 pts were previously treated with A (26%), T (69%), capecitabine (66%), vinorelbine (23%), platinum (16%) and gemcitabine (15%). Preliminary efficacy data are available for 51 pts, seven (14%) of whom achieved partial responses and one had stable disease for 11 months. Grade 2/3 treatment-related adverse events (AEs) are listed below. No grade 4 AEs were reported.

Table 1: Most common AEs

	Percentage (N = 41)	
	Grade 2	Grade 3
Fatigue	32	5
Diarrhoea	20	7
Anorexia	17	0
Hypertension	10	5
Mouth pain	12	0
Hand–foot syndrome	5	7
Neutropenia*	15	39
Thrombocytopenia	17	15
Anaemia	12	2

*No patients with neutropenic fever

Seven (17%) of 41 pts required toxicity-related dose-reduction, and 13 (31%) required dose-interruption. Currently, 21 pts remain on treatment and only two have discontinued for toxicity.
Conclusions: This Phase II study demonstrates the clinical activity of sunitinib as a monotherapy in MBC pts unresponsive to prior chemotherapy or radiotherapy. Sunitinib has acceptable toxicity. Further studies should include pts with exposure to fewer prior regimens and sunitinib in combination therapy.

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A single institution randomized trial of taxotere (T) and xeloda (X) given in combination vs. taxotere (t) followed by xeloda (x) after progression as first line chemotherapy (CT) for metastatic breast cancer (MBC)

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Purpose: Xeloda and Taxotere have demonstrated preclinical antitumor synergy mediated by upregulation of thymidine phosphorylase. XT combination gave significantly superior overall survival, tumor response and TTP compared with T alone in patients with MBC (JCO 20: 2812, 20), but just one third of the patients receiving T continued with X after progression of the disease. We designed this study to evaluate the efficacy and toxicity of the combination of Taxotere and Xeloda compared with Taxotere followed by Xeloda after progression for Metastatic Breast Cancer (MBC).
Materials and methods: 100 patients (pts) with measurable MBC, prior adjuvant anthracyclines (100%) but no prior chemotherapy for MBC and KPS ⩾ 70 were randomized to receive: arm A = X 1,250 mg/m^2 twice daily d1–14 plus + T 75 mg/m^2 day 1; arm B = T 100 mg/m^2 day 1 followed after progression by X 1250 mg/m^2 twice daily d1–14, both given on a q3 week cycle. The two arms were well balanced for known prognostic factors: median age 58 (26–75) vs 51 (25–75) yrs, median KP 100 (70–100) both arms; hormone responsive disease 20% vs. 16%, dominant metastatic sites: viscera 70% vs. 68%, soft tissue 16% vs 13, bone 21% vs. 23%; number of involved organs: 1 = 58% vs. 52%, 2 = 30% vs. 34%, > 2 = 12% vs. 14%. We did not translate the results obtained from the use of Xeloda monotherapy into analysis of response rate and time to progression but we use them in analysis of overall survival and toxicity.
Results: See the table.
Grade 3 toxicity was more present in arm A: 70% vs. 56%; grade 4 was similarly distributed. The main toxicities were: Fatigue; 10% for both groups, Alopecia; 6% vs. 8%, Hand and foot syndrome; 24% vs. 2%, Nausea; 6% vs., 4%, Diarrhea; 16% vs. 8%, Stomatitis; 20% vs. 6%, Neutropenia; 14% for both groups, Neutropenic fever; 14% vs. 16%. We have had to reduce the dose for the 52% of the patients from the Arm A (Xeloda; 4%, Taxotere; 8%, both; 40%) and for the 30% patients from the Arm B.
Conclusion: XT provides significant TTP and OS advantage over T even after the 75% of the patient progressed on Taxotere had been cross-overed to Xeloda monotherapy.

	Group A	Group B	P value
Complete responses (%)	14	6	
Partial responses	54	34	
Overall responses	68	40	0.004
Time to progression (months)	9.3	7.66	0.0017
95%CI	(8.49–10.17)	(6.33–8.99)	
Overall survival (months)	22.00	19.00	0.006
95%CI	(20.85–23.15)	(17.85–20.15)	

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Safety comparison of oral ibandronate and intravenous zoledronic acid in metastatic breast cancer patients: Phase III data

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Background: Bisphosphonates are the standard of care for metastatic bone disease. Ibandronate is a third-generation, single-nitrogen bisphosphonate available in intravenous and oral formulations. In Phase III trials, both ibandronate formulations were well tolerated and had safety profiles comparable to placebo. In this study, oral ibandronate was compared directly with zoledronic acid in terms of safety assessments.
Materials and methods: This head-to-head, multicenter, randomized, open-label, parallel-group study recruited breast cancer patients with advanced disease and at least one confirmed osteolytic or mixed bone lesion. Patients were randomly assigned to receive oral ibandronate 50 mg/day (n = 137) or intravenous zoledronic acid 4 mg via 15-minute infusion every 4 weeks for 12 weeks (n = 137). All adverse events (AEs) were recorded throughout the study.
Results: In general, both bisphosphonates were well tolerated. However, the proportion of patients who experienced AEs was higher in the zoledronic acid group than the ibandronate group (76% versus 65%). In particular, there was a higher incidence of AEs during the first 3 days of the study for zoledronic acid than ibandronate (47% versus 8%). This was composed predominantly of acute-phase response AEs, including pyrexia, chills, flu-like illness, arthralgia, and myalgia, that were probably or possibly treatment-related. Throughout the entire study, a higher proportion of patients reported bone pain in the zoledronic acid group (21%) than the ibandronate group (12%), although the incidence of gastrointestinal (GI) AEs was slightly higher for ibandronate (23% compared with 18% for zoledronic acid). The incidence of serious AEs (ibandronate 5.8%; zoledronic acid 8.0%) and withdrawals (ibandronate 2.9%; zoledronic acid 5.1%) was lower for ibandronate.
Conclusion: In this first direct comparison of safety profiles, more patients treated with intravenous zoledronic acid experienced AEs than those treated with oral ibandronate. In particular, zoledronic acid was associated with a high incidence of an acute-phase response following initial treatment, a known side-effect with a disproportionate risk among intravenous bisphosphonates. The frequency of GI AEs was only slightly higher for oral ibandronate than intravenous zoledronic acid. Oral ibandronate represents an effective and well-tolerated treatment for metastatic bone disease with apparent AE advantages over intravenous zoledronic acid.

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Incidence and implications of HER2 and hormonal receptor overexpression in newly diagnosed metastatic breast cancer

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Background: Overexpression of the HER2 receptor protein predicts a worse prognosis and higher metastatic risk in patients (pts) with breast cancer. HER2 positivity also has a strong predictive value for the clinical benefit of trastuzumab (Herceptin®, H). The aim of this study was to assess the incidence of HER2 and ER/PR overexpression in patients with newly diagnosed metastatic breast cancer (MBC) and to compare the