in several tumor types. This study was designed to compare incidence of SREs and mortality between IV-bisphosphonate therapy and assess the benefit of long-term ZOL use in a real-life setting among women with BC.

Methods: A claims-based analysis using commercial and Medicare Advantage data from over 45 US managed care plans was used to evaluate SRE rates, and mortality in patients treated with ZOL or PAM. Patients included in this study were older than 18 years with a breast cancer and a bone metastasis diagnosis between 01/01/01 and 12/31/06, and had continuous enrollment in the health plan with no evidence of bone metastasis or IV-bisphosphonate for 6 months prior to an index date of first receipt of ZOL or PAM. Patients were followed until disenrollment (including mortality) or end of study (12/31/07). In this study, persistency was defined as the absence of a >45 day gap between ZOL treatments, and SREs were defined as evidence of pathologic fracture, spinal cord compression, and radiotherapy and/or surgery to bone.

Results: The study sample included 8,757 patients with a mean age of 58.1±12.4 years; approx. 30% were treated with ZOL, 15% with PAM, and 55% with no IV BP. Longer persistency with ZOL was associated with a lower risk of fracture and all SREs (trend test p-value=0.0026 and 0.0216, respectively) [TABLE 1]. Patients treated with ZOL were found to have moderately lower incidence of SRE (incidence risk 36.2 versus 40.0 per 100 person year; p = 0.0707) and significantly lower mortality (morality rate 6.2 versus 8.9 deaths per 100 person year; p = 0.0130) compared to ADP treated patients.

Conclusions: This study showed that in BC patients with BM, longer persistence with ZOL was found to be associated with lower risk of SRE and suggests that ZOL may be more effective in preventing and delaying SREs than PAM.

Table 1. Risk of ⩾1 event per 100 person-years by ZOL persistency

Persistency category (days)	SRE	Fracture
31–90	56.2	13.3
91–180	44.9	13.3
181–365	41.2	9.8
365–546	37.5	6.2
547+	27.9	4.9
P-value: Test for trend	0.0216	0.0026

484 Poster

Impact of 4-weekly capecitabine plus paclitaxel (XP) combination therapy for metastatic breast cancer: a multicenter phase II trial (KBCSG-0609)

D. Yamamoto[1], T. Taguchi[2], N. Masuda[3], T. Nakayama[2], T. Nagata[4], M. Nomura[5], K. Yoshidome[6], H. Yoshino[7], J. Sakamoto[8], S. Noguchi[2]. *[1]Kansai Medical University, Surgery, Osaka, Japan; [2]Osaka University, Breast And Endocrine Surgery, Osaka, Japan; [3]Osaka National Hospital, Surgery, Osaka, Japan; [4]University of Toyama, Surgery II, Toyama, Japan; [5]Osaka General Medical Center, Surgery, Osaka, Japan; [6]Osaka Police Hospital, Surgery, Osaka, Japan; [7]Ishikawa Prefectural Central Hospital, Breast and Endocrine Surgery, Kanazawa, Japan; [8]Nagoya University Young Leaders Program in Health Administration, Nagoya, Japan*

Background: The combination of capecitabine and paclitaxel (XP) has demonstrated synergistic antitumor activity in preclinical models. We have previously reported a dose-finding study of the 4-weekly XP regimen in patients with inoperable or recurrent breast cancer (Masuda N, et al. Cancer Chemother Pharmacol 2008). The purpose of this phase II study was to evaluate the efficacy and safety of a 4-weekly XP regimen for MBC.

Materials and Methods: Eligible MBC pts had received ⩽1 prior chemotherapy regimen for MBC, and had received no prior P for metastatic disease and no prior X. Pts received X 825 mg/m^2 b.i.d., days 1−21, followed by a 1-week drug-free interval. P 80 mg/m^2 was administered IV weekly on days 1, 8, and 15 followed by 1-week rest period. Cycles were repeated every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR). Time to treatment failure (TTF), overall survival (OS), progression-free survival (PFS), and safety were secondary endpoints.

Results: In 44 eligible pts, median age was 57 years (range 35−73). Prior therapy included anthracycline in 34% and taxane in 16% of pts. 19% of pts had previously received chemotherapy for MBC. Lymph node and visceral metastases were present in 25% and 52% of pts, respectively. Among 41 evaluable pts, 17 achieved a partial response (PR), indicating a 41% ORR (95% CI: 27.8–56.6%). A further 6 pts had stable disease (SD) for ⩾6 months, giving a 56% clinical benefit rate. Disease control rate including any duration of SD was 85%. ORR in hormone receptor-positive MBC was 38%. ORR in hormone receptor-negative MBC was 50%. Median PFS was 8.3 months (95% CI: 5.2−9.9 months). OS is not mature. Median duration of combination therapy was 4 cycles. Six pts had switched to X mono therapy, and the median duration of X mono therapy was 5.5 cycles. Eleven pts remain on treatment. Grade 3/4 toxicities observed in ⩾5% pts were neutropenia (26%), leucopenia (10%), fatigue (7%), and hand-foot syndrome (7%). No pts discontinued treatment due to hand-foot syndrome and there was no G3/4 diarrhea. Follow-up is ongoing.

Conclusions: 4-weekly XP was an active 1st- or 2nd-line therapy at the recommended phase II dose of capecitabine (825 mg/m^2, b.i.d.) and paclitaxel (80 mg/m^2) with a manageable adverse event profile.

485 Poster

Influence of disease free interval on the efficacy of capecitabine-bevacizumab for HER2-negative metastatic breast cancer (MBC) in the RIBBON-1 trial

A. Brufsky[1], O. Ponomarova[2], S. Tjulandin[3]. *[1]University of Pittsburgh School of Medicine, Oncology, Pittsburgh PA, USA; [2]R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, Kiev, Ukraine; [3]Russian Cancer Research Center, Clinical Pharmacology and Chemotherapy, Moscow, Russian Federation*

Background: In this randomised, placebo-controlled, phase-III study, bevacizumab (A) or placebo (p) was combined with (1) capecitabine (X) or (2) taxanes/anthracyclines in two independently powered cohorts. Progression-free survival (PFS), the primary endpoint, was significantly greater with A combined with chemotherapy in both cohorts. In this analysis of the X cohort only, we examined PFS by disease-free interval (DFI), to determine the potential benefit of XA in different patient populations.

Methods: In the X cohort, previously untreated patients with HER2-negative locally recurrent or MBC were randomised in a 2:1 ratio to X (1000 mg/m^2 b.i.d. on Days 1−14 per 3-week cycle) plus A (15 mg/kg q3w) or p. For data reported at a cut-off of 24-months, DFI was defined as the interval between diagnosis of primary cancer and diagnosis of metastatic disease. For the 12-month cut-off, the definition of interval between the last dose of adjuvant chemotherapy (or surgery, if no adjuvant chemotherapy) and recurrence was used.

Results: 615 patients were enrolled into the X cohort, with a median follow-up of 15.6 months. One third of patients (205) had DFI ⩽24 months; approximately 25% of patients had a DFI ⩽12 months (XA:27%; Xp: 22%). Overall, median PFS was significantly greater with the XA combination than the Xp control (stratified analysis hazard ratio [HR] 0.69 [0.56–0.84], p = 0.0002). In the subgroups, a consistent trend for greater PFS with XA was reported in patients with either DFI ⩽24 (HR 0.76 [0.54–1.06]; XA 8.2 mo; control 6.1 mo) or >24 months (HR 0.63 [0.50–0.80]; XA 8.9 mo, control 4.7 mo). Similarly, using a DFI cut-off of 12 months, XA provided an additional benefit to both patient subgroups.

Conclusions: The XA combination as first-line therapy for HER2-negative MBC provides a significantly greater PFS than control. Irrespective of the DFI tested, whether by 12 or 24-month cut-offs, clinical benefit was greater with the XA combination than with control.

486 Poster

Intrathecal (IT) trastuzumab in leptomeningeal and central nervous system (CNS) metastases from HER2+ breast cancer (BC): What if we could bypass the blood–brain barrier (BBB)?

M. Oliveira[1], S. Braga[2], J.L. Passos-Coelho[1], J. Oliveira[1]. *[1]Instituto Português Oncologia Francisco Gentil, Department of Medical Oncology, Lisboa, Portugal; [2]Instituto Gulbenkian de Ciência, Lisboa, Portugal*

Background: Leptomeningeal carcinomatosis (LC) is a rare but quickly fatal event in the natural history of BC. HER2+ BC has an increased risk of CNS metastases but there are few data on LC frequency in this context. Trastuzumab, a monoclonal antibody against the extracellular domain of the HER2 receptor, is highly effective in systemic control of HER2+ metastatic BC (MBC). However, it is not clear if it can penetrate the intact BBB, which can cause a dissociation between systemic and CNS response to therapy. We evaluated the feasibility, safety and clinical benefit of administering trastuzumab directly into the cerebrospinal fluid (CSF) of a patient with LC and CNS metastases from HER2+ MBC.

Methods: Weekly lumbar puncture (LP) with administration of trastuzumab 25 mg and prednisolone 25 mg was performed. We prospectively assessed functional outcome, leptomeningeal gadolinium enhancement in CNS-MRI and toxicity.

Results: Upon signed informed consent, weekly trastuzumab is being administered since November 2008 to a 44 year-old patient with LC and CNS metastases from HER2+/ER+/PgR− BC. She has MBC since 2006 (lymph node, lung and liver involvement) and had already received tamoxifen, letrozole, anthracyclines, taxanes, capecitabine, iv trastuzumab and lapatinib. She had previously undergone whole brain irradiation, IT