recurrence. For distant metastases, the presence of positive margins, the nodal involvement, the size of the tumor, the undifferentiated histological grade were factors statistically significant.

Metastatic breast cancer

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Renal safety of intravenous ibandronate with short infusion times

M. Pecherstorfer[1], I. Diel[2], D. Tripathy[3], B. Bergstrom[4]. [1] *Wilhelminenspital, Medicine and Medical Oncology, Vienna, Austria;* [2] *CGG-Klinik GmbH, Mannheim, Germany;* [3] *University of Texas Southwestern Medical Center, Dallas, USA;* [4] *F. Hoffmann-La Roche Inc, Nutley, USA*

Background: Reducing treatment toxicity is an important consideration in MBD management, not least because of the unpleasant adverse effects associated with primary cancer therapy. Existing intravenous (i.v.) bisphosphonates for metastatic bone disease (MBD) are associated with renal toxicity, such that continual monitoring of creatinine clearance levels, hydration of the patient and lengthy infusion times (up to 2 hours) may be required. There is a clinical need for an i.v. bisphosphonate that can be infused over relatively short time periods without renal adverse effects. The pharmacokinetic and renal safety profile of i.v. ibandronate, a third-generation bisphosphonate, has been investigated over infusion periods of 1560 minutes.

Patients and methods: The pharmacokinetic and renal safety parameters of i.v. ibandronate were assessed in a parallel-group study of healthy male (n=27) and female (n=30) volunteers. Subjects received a single infusion of i.v. ibandronate 6mg administered over 60 (n=19), 30 (n=20) or 15 (n=18) minutes. Pharmacokinetic parameters included maximum plasma concentrations (C max), volume of distribution(Vz), half life (t1/2), renal clearance (CLr) and fraction of dose excreted (f e). Renal function was assessed by measures of urinary creatinine clearance, serum creatinine levels, and urinary excretion of microalbumin, a1 -microglobulin or N-acetyl-b-D-glucosaminidase (b-NAG) prior to, and up to 72 hours following, infusion. In a sub-analysis of a placebo-controlled, double blind, phase III clinical trial, patients with MBD from breast cancer were randomized to receive i.v. ibandronate 6mg (n=28) or placebo (n=23) infused over a 1hour period every 34 weeks, for a 3-month period. Proteinuria, albuminuria, a1 -microglobulin or b-NAG were assessed prior to drug infusion and 1, 2, 5, 10 and 28 days following each administration, as markers of renal function.

Results: In healthy volunteers, reducing the infusion time of a single dose of i.v. ibandronate 6mg from 60 to 15 minutes was associated with an increase in C max(mean ± SD: 308 ± 44.8 ng/mL vs 397 ± 94.5 ng/mL), but had little impact on Vz (118 ± 17.7L vs 141 ± 32.1L), t (10.6 ± 1.1 hours vs 10.3 ± 2 hours), CLr (70.6 ± 14.4 mL/min vs 88.2 ±24.0 mL/min) or f (percentage dose excreted: 51.6 ± 7.30% vs 52.3 ± 10.3%). S hortening the infusion time of i.v. ibandronate 6mg from 60 to 15 minutes had no adverse effects on any of the renal function parameters assessed (creatinine clearance, serum creatinine levels, urinary microalbumin, a1 -microglobulin or b-NAG).

In patients with MBD from breast cancer, infusion of ibandronate 6mg i.v. over a 1-hour period produced no significant changes in proteinuria, albumin, a1 -microglobulin or b1-NAG levels. Transient rises in proteinuria in both the ibandronate and placebo groups were considered to be related to previously existing renal dysfunction and individual biological variability.

Conclusions: In healthy volunteers, the pharmacokinetics of i.v. ibandronate 6mg are comparable when infused over 60 or 15 minutes. Shortening the infusion time to 15 minutes had no effect on renal function parameters. In patients with MBD, 1-hour infusion of i.v. ibandronate every 3-4 weeks was well-tolerated, with no significant renal toxicity. This contrasts with renal adverse event profile of other i.v. bisphosphonates (zoledronate and pamidronate). As the pharmacokinetics of ibandronate are clinically equivalent between healthy volunteers and MBD patients, i.v. ibandronate 6mg infused over 15 minutes may also have a favourable renal safety profile in this indication. Further investigation of renal functioning following 15-minute infusion of i.v. ibandronate 6mg in patients with MBD is warranted in future clinical trials.

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A multicenter Phase II trial to evaluate gefitinib ('Iressa', ZD1839) (500 mg/day) in patients with metastatic breast cancer after previous chemotherapy treatment

G. von Minckwitz[1], W. Jonat[2], M. Beckmann[3], A. de Bois[4], U. Kleeberg[5], H. Kuhnle[6], E. Kettner[7], J. Hilfrich[8], J. Torode[9], A. Schneeweiss[10]. [1] *Klinkum der JWG-Universitaet, Zentrum fuer Frauenheilkunde und Geburtshilfe, Frankfurt, Germany;* [2] *Universitaetsklinikum Keil, Klinik fuer Gynaekologie und Geburtshilfe, Kiel, Germany;* [3] *Universitaetsklinikum Erlangen, Klinik fuer Frauenheilkunde, Erlangen, Germany;* [4] *Dr.-Horst-Schmidt Kliniken, Klinik fuer Gynaekologie und Gynaekologische Onkologie, Wiesbaden, Germany;* [5] *Haematlogisch-onkologische Praxis Altona, Hamburg, Germany;* [6] *Krankenhaus Oststadt, Frauenklinik der MHH, Abt. Gynaekologische Abteilung, Hannover, Germany;* [7] *Staedtisches Klinikum Magdeburg, Haematologische Abteilung, Magdeburg, Germany;* [8] *Henriettenstiftung Neu-Bethesda, Standort Kirchrode, Gynaekologie, Hannover, Germany;* [9] *AstraZeneca GmbH, Wedel, Germany;* [10] *Universitaetsklinikum Heidelberg, Frauenklinik, Heidelberg, Germany*

Background Epidermal growth factor receptor (EGFR) is a key modulator of tumor cell function and is considered to be a viable drug target in a variety of solid tumors. The clinical benefit and safety of gefitinib ('Iressa', ZD1839), an orally active EGFR tyrosine kinase inhibitor (EGFR-TKI), was evaluated in this non-randomized, open-label, Phase II, multicenter study of patients (pts) with heavily pre-treated, metastatic breast cancer.

Methods Eligible pts had received anthracyclines and taxanes and 1 or more chemotherapy regimen for advanced breast cancer. Pts took gefitinib (500 mg/day), the majority as 3rd- or 4th-line treatment, until disease progression. A dose delay of up to 14 days or a dose reduction to 250 mg was permitted if toxicity was observed. The primary endpoint was the clinical benefit rate (CR + PR [RECIST criteria] + SD) at 6 months.

Results Data for 46 pts, median age 54 years (range 31-70), are available as the basis for this abstract. The metastatic sites of disease were liver (51 lesions), lymph nodes (24), lung (19), skin/soft tissue (11), bone (19), and others (19). After 12 weeks, 1 pt (2.2%) had a PR, 3 pts (6.5%) had SD (2 patients >3 months) and 42 pts (91.3%) had PD. The PR was seen in a pt with 4 liver lesions at study start. After 3 months, 1 of the 4 lesions was no longer detected and pleural metastases had diminished significantly. Currently, at 168 days of therapy the pt is still receiving gefitinib. Two pts reported a significant improvement in pain at metastatic sites (1 liver, 1 bone). Adverse events (AEs) were: facial rash, 7 pts (15%); nausea, vomiting, and bowel disturbance, 26 pts (57%). CTC grade 3 AEs considered gefitinib-related were seen in 3 pts (exanthema, diarrhea, and non-infectious wound). No grade 4 drug-related AEs were reported. One pt (2.2%) withdrew due to gefitinib-related AEs (grade 2 pruritus, peripheral edema and weakness). Dose interruptions occurred in 16 pts (35%) and 6 pts (13%) had a dose reduction due to persistent grade 1/2 skin or gastrointestinal AEs. Further details of efficacy, safety, and quality of life analyses will be presented. In addition, tumor samples are being collected and will be analyzed to try to identify which patients benefit from this innovative treatment.

Conclusion These preliminary data provide evidence that gefitinib may be effective as monotherapy in recurrent breast cancer. 'Iressa' is a trademark of the AstraZeneca group of companies

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Increased pretreatment serum lactate dehydrogenase (LDH) is the most important determinant of central nervous system (CNS) metastases in patients with metastatic breast cancer.

M. Ryberg[1], D. Nielsen[2], K. Osterlind[3], P.K. Andersen[4], T. Skovsgaard[5], P. Dombernovsky[6]. [1] *Herlev Hospital Copenhagen University, Oncology, Herlev, Denmark;* [2] *Herlev Hospital Copenhagen, Oncology, Herlev, Denmark;* [3] *Herlev Hospital Copenhagen, Oncology, Herlev, Denmark;* [4] *Copenhagen University, Biostatistic, Copenhagen, Denmark;* [5] *Herlev Hospital Copenhagen, Oncology, Herlev, Denmark;* [6] *Herlev Hospital Copenhagen, Oncology, Herlev, Denmark*

Purpose: To identify predictive factors and estimate the risk of development of CNS metastases in patients with metastatic breast cancer.

Patients and methods: Data from 579 stage III-IV breast cancer pts treated between Nov. 1983- May 1995 with an epirubicin based chemotherapy were retrieved. Statistical analysis included Kaplan-Meyers survival plots, Cox proportional hazard analysis and competing risk analysis using the cumulative incidence (CI). The endpoints of interest: occurrence of CNS metastases. Meanwhile, two other event could preclude (were competitive)