The co-administration of PTX and oral VRL is unlikely to drug-drug interact on pharmacokinetics.

Conclusion: This phase I study has determined the doses of oral VRL and PTX to be used in combination. The recommended regimen of oral VRL 80 mg/m2 on days 1 and 15 and PTX 110 mg/m2 on day 1 given every 3 weeks is being tested in phase II.

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Fulvestrant ('Faslodex') demonstrates clinical benefit in heavily pre-treated patients with metastatic breast cancer

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Background: Fulvestrant (Faslodex') is an Oestrogen Receptor Downregulator that was recently shown to be at least as effective as the selective aromatase inhibitor anastrozole in the second-line, palliative treatment of advanced tamoxifen-resistant metastatic breast cancer. We evaluated Fulvestrant in postmenopausal patients with ER-positive and/or progesterone receptor-positive metastativ breast cancer after failure on at least two previous hormonal agents (adjuvant and/or advanced disease).

Materials and methods: Sixty-one patients (median 61 years of age; range 39 - 81) whose disease had progressed following prior hormonal therapy were treated with a once-monthly intramuscular injection of Fulvestrant 250 mg as part of a Named Patient' programme (AstraZeneca, Austria). Previous hormonal agents included tamoxifen (adjuvant or advanced), anastrozole (first- or second-line advanced) and exemestane (second- or third-line advanced). Twenty-two patients received Fulvestrant as second-line therapy for advanced disease, 27 patients as third-line and 12 patients as fourth-line therapy. While only 23 (38%) patients had received adjuvant chemotherapy, 38 patients (62%) had received chemotherapy for advanced disease. Thirty-three patients (54%) had bone and/or soft tissue metastases only, 9 patients (15%) had visceral metastases only and 18 patients (30%) had both.

Results: patients were evaluated every 3 months and treatment continued until disease progression. To date, 52 patients are evaluable and the median time of observation is 5.5 months (range 4 - 19+ months). We observed a partial response (PR) in 4 patients (8%), stable disease (SD) = 6 months in 25 patients (48%) and disease progression in 23 patients (44%) giving a clinical benefit rate (PR + SD) of 56%. Of the 4 patients who had a PR, 2 patients showed a reduction in the size of visceral metastases and 2 patients showed a reduction in bone/soft tissue metastases. To date, median time to progression is 5 months (range 4 - 11+ months). Fulvestrant was well tolerated and no WHO grade 3/4 toxicities were observed. Adverse events comprised WHO grade 1 nausea in 1 patient, hot flushes in 2 patients and grade 2 unspecific abdominal pains in 1 patient.

Conclusions: Fulvestrant is a promising new endocrine agent with a very favourable toxicity profile in patients with heavily pre-treated advanced breast cancer. The observed clinical benefit rate of 56% with Fulvestrant, even when used third- or fourth-line, necessitates further clinical evaluation.

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Safety and tolerability of oral ibandronate therapy in patients with metastatic bone disease

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Background: In recent years, bisphosphonates have become the therapy of choice for metastatic bone disease (MBD). However, the use of existing oral bisphosphonates is limited by their association with gastrointestinal side effects. There are also concerns over the renal safety profile of bisphosphonates as a drug class. Ibandronate is a new, highly-potent, third-generation bisphosphonate that has been developed in both intravenous (i.v.) and oral formulations for MBD management. The safety profile of oral ibandronate has been investigated in phase III clinical studies.

Patients and methods: A pooled analysis of data from two randomized, double-blind, placebo-controlled trials evaluated the safety and tolerability of oral ibandronate in women with MBD from breast cancer. Patients received oral ibandronate 50mg (n=287) or placebo (n=277) daily, in addition to their existing anti-cancer therapy for 96 weeks. Adverse events (AEs) were monitored throughout the study period. Renal toxicity was assessed via urea creatinine clearance.

Results: The percentage of patients experiencing any AE was similar between the oral ibandronate 50mg and placebo groups (94.4% vs 95.3%). The most frequently recorded AE was malignancy progression (affecting 67.5% and 70.8% of patients, respectively). There was a slightly higher incidence of drug-related AEs with ibandronate (26.6%) than placebo (17.7%), primarily due to more reports of hypocalcaemia in the ibandronate group (a common side effect of bisphosphonate therapy). Serious drug related AEs were experienced by 1.0% of patients receiving ibandronate compared with 1.4% of patients in the placebo group.

The incidence of upper gastrointestinal AEs in the pooled dataset was similar with oral ibandronate 50mg and placebo (dyspepsia 10.4% vs 8.3%, esophagitis 2.0% vs 2.2%, ulcer/hemorrhage 0.3% vs 0.7%). The incidence of renal adverse events was also comparable between the ibandronate (4.5%) and placebo (4.0%) groups. There were no reports of serious renal adverse events (renal failure) with oral ibandronate therapy, and there was a similar number of patients with decreased creatinine clearance in the ibandronate (n=4) and placebo (n=3) groups.

Conclusions: Oral ibandronate 50mg/day was well tolerated in patients with MBD from breast cancer, with a similar adverse event profile to placebo, except for hypocalcemia and dyspepsia (more frequent than placebo and >5% incidence). The results suggest that oral ibandronate has less gastrointestinal toxicity than existing oral bisphosphonate therapy (clodronate) and has no clinically significant renal toxicity, unlike existing i.v. bisphosphonates (zoledronate and pamidronate). Oral ibandronate may therefore offer a well tolerated and convenient alternative to existing bisphosphonates for MBD management.

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Predictive outcome assessment and monitoring by serum testing for HER-2/neu, EGFR, uPA and CA 27.29 in metastatic breast cancer

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Purpose: To determine the predictive and monitoring value of serum measurements of HER-2/neu, EGFR, uPA and CA 27.29 for outcome assessment of palliative chemotherapy in breast cancer by multivariate analysis.

Patients and methods: Longitudinal sera of 111 breast cancer patients with stage IV disease under cytotoxic therapy were collected and tested for the serum levels of HER-2/neu (normal: <15 ng/ml), EGFR (normal range: 52-76 ng/ml) and uPA (normal range: 857-1830 pg/ml) using enzyme-linked immunosorbent assays (Bayer/Oncogene Science,Tarrytown, USA). CA 27.29 (normal: <30 U/ml) was measured using an automated chemiluminescence immunoassay.

Results: HER-2/neu levels ranged from 5-2373 ng/ml with a median at baseline of 17.4 ng/ml. EGFR ranged from 30-136 ng/ml with a median of 57 ng/ml at baseline. uPA ranged from 411-5086 pg/ml with a baseline median of 1433 pg/ml. CA27.29 ranged from 8-12612 U/ml with a baseline median of 103 U/ml. Among all demographic, tumor specific and biochemical data in the multivariate analysis, the remission status, the number of involved organs and the serum HER-2/neu concentration were the only parameters to show a statistical significant influence on time to progression in multivariate analysis ($p=0.008$, $p=0.006$ and $p<0.001$, respectively). Patients with a serum HER-2/neu level >18 ng/ml showed a shorter progression-free survival (19 weeks) than patients with a normal serum HER-2/neu level (34 weeks). The serum concentrations of EGFR, uPA and CA 27.29 did not provide any predictive information for time to progression. We found that serum EGFR concentrations of postmenopausal patients were significantly lower than those of premenopausal patients (56.5 ng/ml versus 64.7 ng/ml, respectively). EGFR levels fell statistically significantly with age ($p=0.017$) and did not correlate with tumor mass. Decreased EGFR levels <50 ng/ml were observed in one third of stage IV breast cancer patients. HER-2/neu negative patients by FISH analysis presented decreased EGFR levels <50 ng/ml statistically significantly less often ($p=0.044$) than HER-2/neu positive patients by FISH. Serum courses of HER-2/neu, uPA and CA 27.29 reflected remission status.

Conclusions: Increased levels of serum HER-2/neu predict lack of benefit from systemic chemotherapy in metastatic breast cancer as precisely as remission status or number of involved organ systems. The biological meaning of decreased EGFR levels in metastatic breast cancer remains to be eludicated.