ifen resistant cells after zinc treatment. These results suggest a mechanism whereby cells can continue to grow in the presence of tamoxifen and may provide a useful new therapeutic target for anti-hormone resistant breast cancer.

O-80. The introduction of better therapies lengthened survival in advanced breast cancer

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Over the last 20 years new endocrine, cytotoxic and biologically targeted agents have been introduced into breast cancer therapy, Claims for their greater efficacy over the agents used in the 1980's have been based on the result of clinical trials in the adjuvant setting and in advanced disease.

Comparison is made between the time from implementation of therapy to death, for symptomatic distant metastases, in breast cancer diagnosed in 1980-86 ($n = 428$) and in those diagnosed as previous in 1990-99 ($n = 280$),

Although the assumptions here are made that the secondary therapy will have been applied earlier in the 80-86 dataset, this is open to bias.

Therefore another analysis has to be carried out of only those women in these datasets who had distant metastases diagnosed within 5 years of the primary tumour.

Table 1. All Distant Recurrence

Dataset	Median time from DR to death
1980-86	12
1990-96	12

Table 2. Distant recurrences

Dataset	Median time from DR to death
1980-86	10
1990-96	11

Although more systemic therapies appear advantageous in the adjuvant setting there is little evidence of this greater efficacy in the treatment of distant metastases.

O-81. Fulvestrant in pretreated patients with advanced breast cancer: experience from the Institut Bergoni

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Background: Fulvestrant ('Faslodex') is a new oestrogen receptor antagonist with no agonist effects that is licensed for use in patients with advanced breast cancer (ABC) following progression on an antioestrogen.

Methods: The fulvestrant Compassionate Use Programme (CUP) permits use of the drug in patients who have progressed on prior endocrine and chemotherapies for ABC. As part of the CUP, 41 women and one man were treated with fulvestrant between August 2001 and September 2004 according to the guidelines of the French Drug Agency (AFSSAPS).

Results: Patients had a median age of 65 years (range 41–86 years) and all had ABC, including 19 patients with visceral metastases (liver and lung) and 25 patients with bone metastases. Sixteen patients received adjuvant endocrine treatment (tamoxifen) and three patients received adjuvant chemotherapy. Fulvestrant was given after a median of 3 (range: 1–5) prior endocrine treatments and a median of 1 prior (range: 0–5) chemotherapy for ABC. Twelve patients had a partial response (PR) with fulvestrant and 10 had stable disease $\geq$6 months (SD), giving an overall clinical benefit (CB) rate of 52%. Five of the six (83%) patients who received fulvestrant as 2nd-line endocrine therapy for ABC gained CB (2 PR, 3 SD). The remaining 36 patients received fulvestrant as 3rd to 9th-line endocrine ABC treatment (CB rate: 47%; 10 PR, 7 SD). In patients with visceral metastases the CB rate was 58% (6 PR, 5 SD). All patients have now ceased fulvestrant treatment; the median duration of treatment was 5 months (range: 1–38 months). Following fulvestrant, two patients received further endocrine therapy (progestins) and 21 received palliative chemotherapy. Fulvestrant was well tolerated; six patients (14%) experienced adverse events during treatment.

Conclusions: In our experience, fulvestrant is effective and well tolerated in the treatment of patients with ABC following progression on prior therapies. The CB rate appeared highest when fulvestrant was given early in the therapy sequence; however, efficacy was also retained in more heavily pre-treated patients.

O-82. Goserelin plus Anastrozole as first-line endocrine therapy for premenopausal oestrogen receptor positive (ER+) advanced breast cancer (ABC)

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We have previously reported the use of goserelin plus anastrozole as second-line endocrine therapy for premenopausal ER+ ABC. With randomised data showing superiority of third-generation aromatase inhibitors over tamoxifen as first-line therapy, we now report our clinical experience of using anastrozole alongside ovarian suppression (with goserelin) in the same setting in premenopausal women.

Twenty premenopausal patients (mean age = 42 (30–57) years) (advanced primary = 3, soft tissue = 2, bone = 8, pleura/lung = 3, stomach = 1, liver = 2, bone + liver = 1) with ER+ ABC seen over a 3-year period were treated with goserelin 3.6 mg 4-weekly plus anastrozole 1 mg daily as first-line therapy. Endocrine therapy was considered therapy of choice except in two patients with liver metastases who did not have chemotherapy due to pulmonary embolism or patient choice. All had disease assessable by UICC criteria and received therapy for $\geq$6 months (except for those who progressed prior).

Twelve patients (60%) derived clinical benefit (CB) (complete ($N = 1$) or partial ($N = 5$) response, or stable disease ($N = 6$) for $\geq$6 months) while eight progressed before 6 months. For the 12 CBs, the median duration of response is 20+ months (6–36 months). At the time of analysis, therapy is continuing in nine patients. When the two patients with liver metastases for whom chemotherapy was therapy of choice were excluded, the CB rate rose to 66%. Therapy has been well tolerated and no patients came off it because of side effects.

A combined use of goserelin and anastrozole produces CB with long duration in significant proportion of premenopausal women with ER+ ABC when used as first-line therapy. Further studies with more patients and longer follow-up are warranted.

O-83. Inhibition of haematogenous micrometastasis using Tinzaparin small oligosaccharides of heparin

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Chemokines are small proteins important in the metastasis of breast cancer cells. Binding of the chemokine CXCL12 to its receptor CXCR4 stimulates cells to migrate out of the vasculature and establish metastases. Glycosaminoglycans (GAGs – complex sugars) on the cell surface are vital for presentation of chemokine to its receptor. We aim to prevent haematogenous spread of breast cancer cells using Tinzaparin (a GAG-like drug) and short heparin molecules – oligosaccharides.

Radioligand competition binding assays were performed using a range of the oligosaccharides to compete against GAG for binding of I^{125} CXCLI2. A dp12 (degrees of polymerization) oligosaccharide was the smallest heparin derivative to compete efficiently (71% inhibition; $p < 0.001$) at low concentrations.

Mammalian cells transfected with CXCR4 (KI-CXCR4) and MDA-MB-231, a CXCR4-expressing metastatic breast cancer cell line were used in chemotaxis assays. Chemotaxis was assessed in response to CXCL12 and heparins including Tinzaparin and dp12. An *in vivo* model evaluated the effect of dp12 and a therapeutic dose of Tinzaparin upon haematological metastasis. SCID mice were injected daily from Days 0 to 28 with s/c Tinzaparin, dp12 or control salt solution, on Day 1 mice received i.v. injection of 200,000 MDA-MB-231 cells. On day 28, mice were examined microscopically to assess tumour load.

KI-CXCR4 and MDA-MB-231 migrated significantly in response to CXCLI2. Tinzaparin and dp12 inhibited CXCL12 induced migration and activation of CXCR4 ($p < 0.001$). *In vivo*, Tinzaparin decreased the number of metastases by 23% ($p < 0.004$) and decreased tumour area by 46% ($p < 0.0001$).

Heparins inhibit migration and activation of CXCR4-expressing breast cancer cells. Peri-operatively, it is known that up to 85% of patients have cancer cells within the vasculature. Low Molecular Weight Heparins prevent haematological metastasis of breast cancer *in vivo* and may have a role in cancer therapy, over and above the benefit gained from thromboprophylaxis.

O-84. Primary Taxotere versus doxorubicin for breast cancer. Five year survival analysis

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We have previously reported that taxotere primary chemotherapy has a survival advantage at 3 years compared to doxorubicin based chemotherapy for breast cancer. These findings were not reproduced in the NSABP B-27 trial. We report survival data over 5 years of follow up.

160 patients with large primary breast cancers (>4 cms) were treated with 4 cycles of doxorubicin based primary chemotherapy. Those who initially responded were randomised to receive either 4 further cycles of doxorubicin or 4 further cycles of taxotere. 96 patients were available for randomisation – 46 to doxorubicin and 50 to taxotere. All patients proceeded to surgery and standard adjuvant treatments. Survival data is now available for a median follow up time of 72 months.

Overall survival at 6 years is 82%. In patients randomised to taxotere survival is 86% and in those randomised to doxorubicin 78%. There is however no significant difference in survival between taxotere and doxorubicin (log rank $p = 0.24$).

These results have shown a non-significant improvement in survival between patients treated with taxotere and doxorubicin for breast cancer and compare to the NSABP B-27 results.

O-85. Definition of the evolutionary pathway to acquired Docetaxel resistance

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Background: Docetaxel is one of the most active agents used in the treatment of breast cancer. However, tumours may be inherently resistant or develop resistance to docetaxel during treatment. The mechanisms of resistance to docetaxel, whether inherent or acquired, are poorly understood. We have developed an *in vitro* model of docetaxel resistance in breast cancer cells to understand the genetic pathways of resistance. The aim of this study was to define the genetic changes that occur in breast cancer cells as they acquire resistance to docetaxel.

Methods: MDA-MB-231 and MCF-7 breast cancer cells were made resistant to docetaxel by exposure to increasing docetaxel concentrations (from 1 μM to 30 μM). By using cell lines with increasing levels of docetaxel resistance, we were able to identify changes associated with resistance to lower concentrations of docetaxel (early resistance) and those associated with resistance to high concentrations of docetaxel (late resistance). Microarray analysis, RT-PCR and western analysis were used to identify and validate candidate genes and proteins associated with resistance. In order to establish whether a candidate was involved in resistance we aimed to modulate expression by either gene transfection or siRNA modulation and then to re-assess chemosensitivity.

Results: Microarray analysis identified several changes in gene expression associated with early and late resistance including reduced expression of the p27 protein. Expression of exogenous p27 protein by gene transfection resulted in increased chemosensitivity to docetaxel.

Conclusions: We have used a global analysis technique to identify candidate genes involved in docetaxel resistance. We have demonstrated that p27 plays a role in resistance to lower levels of docetaxel (<1 μM). Identification of genes involved in resistance offers the possibility of targeted therapy for patients breast cancer.