The differences between 3 and 24m (p= 0.6671), the 6 and 24m (p= 0.5024) and the 12 and 24m (p = 0.1927) samples were not statistically significant. There have been no clinical relapses to date.

Comment: These data show that MRD persists in a proportion of patients despite ongoing adjuvant treatment, suggesting that disseminated tumour cells are relatively resistant to such treatments. Detection of MRD may therefore be used to identify a subgroup of patients who would not benefit from cytotoxic or hormonal therapy. Our results support those of a previous study, which found that tumour cells persisted in the bone marrow after chemotherapy (Braun et al. J. Clin. Oncol. 2000). These findings may be a reflection of the dormant nature of these cells and alternative therapeutic strategies will be required to eliminate them.

550 ORAL

ICI 182,780 (Faslodex™) versus anastrozole (Arimidex™) for the treatment of advanced breast cancer in postmenopausal women - prospective combined analysis of two multicenter trials

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ICI 182,780 (Faslodex, FAS), a novel Estrogen Receptor Downregulator, is the first in a new class of antiestrogen. We report the prospectively planned combined analysis of two phase III trials, comparing FAS 250 mg once monthly and 'Arimidex' (anastrozole, AN) 1 mg once daily in postmenopausal women progressing on prior endocrine treatment for advanced breast cancer.

The trials compared the efficacy and safety of FAS with AN. The primary endpoint was time to progression (TTP). Secondary endpoints included objective response (OR), duration of response (DOR), clinical benefit (CR+PR+SD*24 weeks) and tolerability. Patients were randomised to either FAS 250mg (n=428) by intramuscular injection once monthly or AN 1mg (n=423) taken orally daily. Patients were followed for a median of 15.1 mo. Most (98%) patients had been treated with tamoxifen. At the time of analysis, approximately 83% of patients in each treatment arm had progressed. Median TTP was 5.5 mo and 4.1 mo for FAS and AN, respectively (Hazard Ratio 0.95; CL 0.82*1.10; p = 0.48). The OR (CR+PR) rates were 19.2% and 16.5% (Odds ratio 1.21; CL 0.84*1.74; p= 0.31) and clinical benefit rates were 43.5% and 40.9% for FAS and AN respectively. Both drugs were well tolerated. Withdrawals due to adverse events (drug related) were 2.8% (0.9%) in the FAS group and 1.9% (1.2%) in the AN group. Only 0.5% (2/423) FAS-treated patients withdrew because of an injection site reaction.

At the outset of the trial 7 adverse events were pre-defined for statistical analysis. Incidences of adverse events for FAS vs. anastrozole, which in the majority of cases were mild to moderate were as follows: gastrointestinal disturbances 46.3% vs. 43.7%; hot flushes 21.0% vs. 20.6%; vaginitis 2.6% vs. 1.9%; weight gain 0.9% vs. 1.7%; thromboembolic disease 3.5% vs. 4.0%; urinary tract infection 7.3% vs. 4.3%, and joint disorders (including arthalgia, arthrosis and arthritis) 5.4% vs. 10.6% which is the only adverse event to be significantly different between the two treatments (p=0.0036). Quality of life was maintained to a similar extent with both agents

In conclusion, FAS was found to be at least as effective as the aromatase inhibitor anastrozole in second-line advanced breast cancer in patients previously treated with tamoxifen. All efficacy endpoints are9 in favour of FAS. FAS was well tolerated. Based on these data FAS will provide a valuable new treatment option for advanced breast cancer in postmenopausal women.

551 ORAL

Survival update of so14999 a large phase III trial of capecitabine/docetaxel combination therapy vs docetaxel monotherapy in patients with locally advanced (LABC) or metastatic breast cancer (MBC)

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Capecitabine (Xeloda), an oral fluoropyrimidine, has substantial antitumor activity in colorectal cancer and heavily pre-treated MBC. Capecitabine plus docetaxel (Taxotere) has demonstrated synergy in preclinical studies. Patients with LABC and MBC in whom anthracycline treatment had failed were randomised to oral capecitabine 1250mg/m2 twice daily, days 1-14 plus i.v. docetaxel 75mg/m2 day 1 q3w (n=255), or i.v. docetaxel 100mg/m2 (n=256), day 1 q3w. The baseline patient characteristics in the treatment arms were balanced. Approximately 1/3 of the patients received study treatment as 1st and 1/2 as 2nd line therapy. With a minimum follow up of 15months, overall survival was superior in the combination arm (log rank p=0.0126; HR=0.775), median of 14.5 months (95% CI 12.3-16.3) vs. 11.5 months (95% CI 9.8-12.7) for single agent docetaxel with 72% and 79% of events reached, respectively. The survival curves separate early. One year survival was 56.8% (95% CI 51-63) in the combination arm and 46.9% (95% CI 41-53) in the monotherapy arm. Survival differences were evident in the 1st, 2nd and 3rd line treatment subgroups. Approximately 2/3 of the patients received post study chemotherapy in both treatment arms. The overall tumor response rate (RR) was superior for capecitabine/docetaxel 41.6% vs. for docetaxel 29.7% (p=0.006). Time to progression (TTP) was superior with the combination (log rank p=0.0001; HR=0.652), median of 6.1 months (95% CI 5.4-6.5) vs. 4.2 months (95% CI 3.4-4.5) with docetaxel. Multivariate Cox analysis revealed performance status, ER/PR status, number of metastatic sites and liver metastases as important baseline prognostic factors. Patients receiving monotherapy experienced a higher incidence (all grades) of neutropenia, complications of neutropenia, myalgia, and arthralgia. Diarrhoea, stomatitis, nausea/vomiting and hand-foot syndrome were more common with the combination therapy. The same pattern was generally noted for grade 3/4 adverse events.

Conclusion: The addition of capecitabine to 75mg/m2 docetaxel compared to docetaxel 100mg/m2 monotherapy led to significantly superior RR, TTP and survival, with a manageable safety profile.

552 ORAL

Weekly cisplatin - epirubicin - paclitaxel (PET) with G-CSF support vs. triweekly epirubicin-paclitaxel (ET) in advanced breast cancer (ABC). A SICOG phase III trial

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Background: In a previous study the PET weekly regimen gave an ORR of about 80% in breast cancer patients with metastatic disease, while the ORR exceeded 90% in locally advanced disease. (Frasci G. et al. Breast Cancer Res and Treat 62: 87-97; 2000). The present study aimed at evaluating whether this new regimen could produce a significant prolongation of TTP in ABC patients in comparison with standard ET.

Patients and Methods: ABC pts with locally advanced (T4 or N2) or metastatic disease, who had not received prior chemotherapy (except adjuvant) were considered eligible. Women were randomized to receive PET (P 30 mg/m2/week + E 50 mg/m2/week + T 120 mg/m2/week + G-CSF) or ET (E 90 mg/m2 + T 175 mg/m2 q3wk). A minimum of 6 cycles of PET or 3 cycles of ET were delivered, and the treatment was continued up to 12 and 6 cycles, respectively in absence of disease progression. Study design: Time to treatment failure was the chosen end point. A 3-month TTF prolongation was hypothesized with PET. Thus, at least 120 patients were required in each arm. An interim analysis was planned after the accrual of half of the total planned sample size.

Results: As of April 2001, overall 125 pts have been recruited (PET=61; ET=64), and 121 are evaluable for response (PET=60; ET=61). 65 patients showed locally advanced and 60 had metastatic disease at beginning of treatment. Overall, 17 CRs and 63 PRs have been recorded for a 66% ORR. 11 CRs and 35 PRs occurred in the 63 patients with locally advanced disease (ORR=73%) as compared to 6 CRs and 28 PRs in the 58 patients with metastatic disease (ORR=59%). 12 CRs and 31 PRs (ORR=72%)

have been registered in the PET arm, as compared to 5 CRs and 32 PRs (ORR=60%) in the ET arm. The ORR with the PET arm was 82% and 59% in locally advanced and metastatic disease, respectively, as compared to 68% and 53% with the ET regimen. Anemia, peripheral neuropathy and gastrointestinal toxicity were substantially more frequent in the PET arm.

Conclusions: The results of this planned interim analysis show that the PET weekly administration produces a relevant increase of the ORR in locally advanced breast cancer patients, as compared to the ET triweekly administration. Interestingly, the CR rate is more than double with this weekly dose dense approach. The accrual continues until the planned sample size of 120 pts.

553 ORAL

Zometa® is effective and well tolerated in the prevention of skeletal related events secondary to metastatic breast cancer treated with hormonal therapy

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Zometa® (zoledronic acid), a new, highly potent bisphosphonate was compared to pamidronate (pam) in a randomized, phase III double-blind comparative trial. The primary efficacy endpoint was the proportion of patients (pts) experiencing a Skeletal Related Event (SRE), defined as pathological fracture, spinal cord compression, surgery to bone to treat or prevent a fracture and radiation therapy to bone. The trial was powered to demonstrate the non-inferiority of Zometa to the current standard of therapy, pamidronate. 408 breast cancer pts receiving first or second line hormonal therapy were randomized to receive either Zometa 4 mg/15 min/100 ml normal saline (201 pts) or pam 90 mg/2 hrs/250 ml normal saline (207 pts) every 3 to 4 weeks for 13 months. All patients were female; mean age was 59.9 (range 28-92); mean time from the initial diagnosis of cancer to randomization was 82 months for Zometa 4 mg vs 75.6 months for pam 90 mg; mean time from diagnosis of bone mets to randomization was 16 months for Zometa 4 mg vs 11.2 months for pam 90 mg. Results revealed that 42% of pts in the Zometa 4 mg group and 47% of the pts in the pam 90 mg group experienced an SRE ($p = 0.277$). Secondary endpoints including the proportion of patients with individual SREs were also assessed. Zometa 4 mg was statistically superior to pam 90 mg in preventing radiation therapy to bone (Zometa 4 mg: 16% vs pam 90 mg: 25%, $p = 0.022$). The efficacy of Zometa 4 mg was equivalent to pam 90 mg for the other SREs studied.

Lengthening the infusion time from 5 to 15 minutes (and increasing the infusion volume from 50 to 100 ml) was associated with a decrease of changes in creatinine from 11.9% to 7.7% of patients. This is comparable to the creatinine changes observed in the concurrent pam group (6%). Other common adverse events reported (> 25% of pts) were bone pain, nausea, fatigue, pyrexia, vomiting, anemia, myalgia and diarrhea.

Summary: Zometa 4 mg is superior to pamironate 90 mg in decreasing the need for radiotherapy to bone, and is equally effective in preventing other SREs, in breast cancer patients undergoing first and second line hormonal therapy. Zometa allowed a shorter infusion time and smaller dilution volume. Zometa was well tolerated with a safety profile similar to that of pamidronate.

554 ORAL

Clinical presentation and prognostic factors in breast cancer-related meningeal metastases

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Purpose: A study was conducted in order to describe the main clinical findings at the time of diagnosis of breast cancer-related meningeal metastases, and to identify prognostic factors for response to treatment.

Material and methods: The pretreatment characteristics, neurologic presentation and clinical course were retrospectively studied in 115 women treated by intrathecal chemotherapy in the Medical Oncology Department of the Curie Institute from January 1, 1992 to December 31, 1999. These parameters were tested for a potential prognostic influence on multivariate analysis. Treatment consisted in intrathecal injection of 15 mg of methotrexate during five days, plus 125 mg of hydrocortisone at day 1, with folinic acid rescue. Systemic chemotherapy was frequently associated, mainly 5-day fluorouracil continuous infusion, with eldisine and cyclophosphamide at day 1 and 5.

Results: The median age at the time of diagnosis of meningeal metastases was 55 years, with a mean interval from initial treatment of 73 months (±54 months). The clinical symptoms at the time of diagnosis were headache (49%), confusion (38%), vomiting (36%), cerebellar signs (35%), cranial nerve palsy (28%), paresis (20%) and pain (19%). Other metastatic sites were associated in 90% of patients, with no particular site distribution. Clinical symptoms led to the diagnosis in 82% of cases. Cerebrospinal fluid protein level was elevated in 91% of cases and cancer cells were detected in 78% of cases.

The response was defined as clinical and laboratory improvement and was achieved in 42% of patients (CR: 10% and PR: 32%). The median duration of survival was 100 days, 32% of patients survived beyond 6 months and 19% beyond one year. Three factors were linked with survival on multivariate analysis: infusion of systemic chemotherapy in parallel with intrathecal treatment ($p=0.0002$), performance status ($p=0.0012$) and number of previous courses of chemotherapy for metastases ($p=0.029$).

Conclusion: Three factors were found to be predictive of response to treatment: systemic chemotherapy, performance status and number of previous courses of chemotherapy.

Lung cancer 2

555 ORAL

Final results of a double-blind placebo-controlled study of adjuvant marimastat in small cell lung cancer (SCLC) patients responding to standard therapy

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Marimastat is a broad spectrum metalloproteinase inhibitor, with anti-invasive, anti-metastatic and anti-angiogenic properties in preclinical studies. This study was undertaken to determine whether marimastat could prolong survival and remission duration in patients with SCLC responding after induction therapy. SCLC patients who achieved a partial or complete response to induction therapy, with a performance status 0-2 were eligible to be randomized to receive marimastat 10 mg or placebo both po bid for up to 2 years. The study was sized to be able to detect a 33% improvement in survival with an 80% power, using a 2-sided test. The EORTC QLQ was used to assess the quality of life in both arms of the study. Between 2/97 and 4/00, 555 patients were enrolled, 135 from the EORTC and 420 from the NCIC. Major patient characteristics were well balanced between the 2 arms; 48% had extensive disease, 11% had performance status 2 at start of induction therapy, and 33% had achieved CR with 1st-line therapy. The results are summarized in the table:

Arm	Median survival (years)	P value	Median time to progression (years)	P value
Marimastat	0.78	0.9	0.36	0.81
Placebo	0.81		0.37	

Severe (grade 3-4) muscoloskeletal toxicity was significantly more frequent in the marimastat arm (18% vs 3%, $p < 0.001$). Compliance to treatment was worse in the marimastat arm. Quality of life was significantly worse for the marimastat arm at 3-month evaluation for pain in arm/shoulder, other pain, pain, and worse for emotional and social domains.

In conclusion, adjuvant therapy with marimastat failed to improve survival in patients with SCLC after induction therapy, and caused more side effects than placebo with worsening of quality of life.