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

R. Coleman[1], J. Apffelstaedt[2], D. Gordon[3], P. Major[4], J. Mackey[5], A. Howell[6], R. Theriault[7], Y. Yambros[8], B. Chen[8], D. Reitsma[8]. [1] *Weston Park Hospital, Sheffield, Great Britain,* [2] *Mamma Clinic, Cape Town, South Africa,* [3] *US Oncology, San Antonio, Texas, United States,* [4] *Hamilton Regional Cancer Center, Hamilton, Ontario, Canada,* [5] *Cross Cancer Center, Edmonton, Alberta, Canada,* [6] *Christie Hospital, Manchester, Great Britain,* [7] *MD Anderson Cancer Center, Houston, Texas, United States,* [8] *Novartis Pharma, Basel, Switzerland*

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

G. des Guetz, E. Blot, M.N. Guilhaume, M. Raoul, J.Y. Pierga, V. Dieras, P. Pouillart. *Curie Institut, medical Oncology, Paris, France*

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

G. Giaccone[1], F. Shepherd[2], C. Debruyne[1], V. Hirsh[2], M. Smylie[2], S. Rubin[2], H. Martins[2], A. Lamont[1], M. Krzakowski[1], B. Zee[2]. [1] *EORTC LCG, Brussels, Belgium;* [2] *NCIC-CTG, Kingston, Canada*

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.