**Conclusion:** There is a rationale for use of Capecitabine in the earlier course of metastatic disease, especially after progression of first-line chemotherapy for MBC.

**481** PUBLICATION

**Multicenter study of weekly trastuzumab, paclitaxel and carboplatin followed by a week of rest every 28 days in patients with her-2+ metastatic breast cancer (MBC)**

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**Background:** Combination of Trastuzumab with Carboplatin and Paclitaxel have shown a significant activity in HER2 positive metastatic breast cancer (MBC). We have conducted a Phase II study to investigate the efficacy and safety of the combination given weekly × 3 followed by a week of rest. We present here preliminary results. Primary endpoint was objective response rate and secondary endpoints were time to progression, overall survival and toxicity of the combination.
**Methods:** Between October 2003 and April 2005, 16 patients (pats) with Her-2+ MBC (IHC 3+ or FISH+) have been included in the study. Pats received Trastuzumab (loading dose of 4 mg/kg/wk and 2 mg/kg/d following weeks), Paclitaxel (80 mg/m$^2$) and Carboplatin (AUC 2) all given weekly × 3 followed by 1 week of rest. Treatment was given until disease progression or unacceptable toxicity.
**Results:** Sixteen patients have been enrolled. Median age was 50 years (range 30–60). All pats received prior adjuvant/neoadjuvant treatment and 4 pats received one prior line for metastatic disease. All pats had PS = 0–1. Disease sites were liver 9 (56%), bone 7 (44%), lymph nodes 5(31%) and lung 3 (19%). Ten pats (63%) had ⩾ 2 lesions. 16 patients are evaluable for toxicity and have received 89 cycles with a median of 5 cycles (range 2–13). Grade 3/4 toxicities were: 4 (5%) leukopenia, 12 (13%) neutropenia, 2 (2%) thrombopenia, 3 (4%) alopecia and 1 (1%) nausea and vomiting. 14 patients have been evaluable for response; 6 CR (43%), 3 PR (21%), 3 SD lasting more than 3 mo (21%) and 2 PD (14%) resulting in an ORR of 64% (95%CI: 39.2–89.4%) and tumor growth control rate (RR+SD) in 86% of patients (95%CI: 67.4–100%). Two pats were not evaluable in this analysis for efficacy (1 too early and 1 lost to follow-up). Median duration of response is 8.4 mo. Median TTP 7.7 mo (95%CI: 2.9–12.5 mo).
**Conclusions:** This interim analisis shows a good safety profile and a promising activity. Further results would be available for presentation.

**482** PUBLICATION

**Results of Intercancer Cohort: epidemiologic Brazilian data of women with HER-2 positive metastatic breast cancer treated with trastuzumab as first-line therapy**

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The efficacy and safety of trastuzumab in HER-2 positive metastatic breast cancer have been documented in clinical trials. In particular, these trials have demonstrated that treatment with trastuzumab improves overall survival and disease-free survival in first-line therapy as monotherapy and in combination with chemotherapy. Three years after the Brazilian approval of trastuzumab it was of great interest to determine the profile of patients that are being treated with trastuzumab in first-line in clinical practice and the treatment regimens that are being used. Intercancer is a large epidemiological Brazilian data base. Eligible patients (> 18 years) were all HER-2 positive metastatic breast cancer women who started trastuzumab between October 2003 and April 2005. Patients were followed-up for at least 8 months. A total of 106 oncologists agreed to participate and to enroll all their patients data treated with trastuzumab as first-line therapy in the period.

Table 1: Patients characteristics

| | | | |
|---|---|---|---|
| Pre-menopausal | 40.6% | Post-menopausal | 40.6% |
| ER+ | 34.9% | ER− | 49.1% |
| PR+ | 41.5% | PR− | 33% |
| HER-2 IHQ 3+ | 77.4% | HER-2 FISH+ | 13.2% |
| Family History | 38% | No family history | 62% |
| Smoker | 15% | Non smoker | 85% |
| Oral contraceptives | 45% | No oral contraceptives | 55% |

Results are presented on 123 patients. Trastuzumab was used as monotherapy in 52% of the patients. The prefered dose scheduling was the 3 weekly regimen. Table 1 resumes the main patients characteristics.

# Central Nervous System

## *Oral presentations* (Mon, 31 Oct, 9.15–11.15)
## Central nervous system

**483** ORAL

**Impact of extent of resection on overall survival in newly-diagnosed glioblastoma after chemo-irradiation with temozolomide: further analysis of EORTC study 26981**

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**Background:** The impact of the extent of surgery on survival in patients with newly-diagnosed glioblastoma multiforme (GBM) remains controversial. A recent, large, multicenter, randomized controlled trial of radiotherapy (RT) versus RT with concomitant and adjuvant temozolomide chemotherapy (RT/TMZ) showed an improved median survival after combined RT/TMZ (14.6 months, 95% confidence interval (CI): 13.2–16.8); as compared to 12.1 months (95%CI: 11.2–13.0) after standard RT alone). This trial also provided an opportunity to retrospectively examine the impact of extent of resection on the outcome, and relate this to the type of adjuvant treatment.
**Methods:** 573 newly-diagnosed GBM patients were randomized to either RT or RT/TMZ. Extent of surgery was estimated by the surgeon at the time of surgery (either biopsy, partial resection, complete resection). Overall median survival (MS) and 2-year survival (2-yr S; both intent-to-treat analysis) was examined for patients receiving biopsy only (16%), partial resections (44%), or complete resections (39%) per treatment arm.
**Results:** The two treatment groups were well balanced with regard to extent of resection. Treatment with RT/TMZ was superior (in terms of overall survival) to RT alone across all groups with varying degrees of resection. This benefit was most striking in patients with complete resections, where 2-yr S was 37.1% months (95%CI: 28.0–46.3) for patients receiving RT/TMZ, compared with 14.5% (95%CI: 7.8–21.2) in those receiving RT alone. For patients with a biopsy only, 2-yr S after RT/TMZ was 10.0% (95%CI: 1.3–18.7), in contrast to 4.6% (95%CI: 0.00–10.8) for RT patients. 2-yr S in partially resected patients was 23.2% (95%CI: 15.5–30.9) after RT/TMZ, and 8.94% (95%CI: 3.9–14.0) after RT. MS in biopsied patients treated with RT/TMZ was 9.4 months (mo, 95%CI: 7.5–13.2), and 7.9 mo (95%CI: 5.4–10.6) in RT patients. For partially resected patients MS was 13.5 mo (95%CI: 11.9–16.3) after RT/TMZ and 11.7 mo (95%CI: 9.7–13.1) after RT. However, after complete resection MS was 18.3 mo (95%CI: 15.7–22.5) in RT/TMZ patients, but 14.2 mo (95%CI: 12.7–16.2) in RT patients.
**Conclusion:** The benefit of combined RT/TMZ in GBM is more pronounced in patients that have undergone more extensive resections as compared to biopsied patients. This provides a further rationale to aim for extensive resections in GBM patients.

**484** ORAL

**Functional outcome and local control after radiotherapy for metastatic spinal cord compression in breast cancer and prostate cancer patients**

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**Background:** Breast cancer and prostate cancer patients presenting with metastatic spinal cord compression (MSCC) have a better survival

prognosis than other MSCC patients and may live long enough to develop a local recurrence of MSCC. This study investigates prognostic factors and radiation schedules for functional outcome and local control of MSCC after radiotherapy (RT) in such patients.
**Materials and methods:** A total of 616 patients, 335 breast cancer and 281 prostate cancer patients, who were irradiated for MSCC between 1/1992 and 12/2003, were included in this retrospective multi-center study. Motor function was evaluated before RT and at 1 month, at 3 months and at 6 months after RT with a 5-point scale. Potential prognostic factors were investigated: age ($\leqslant$ 65 years versus > 65 years), performance status (ECOG 1–2 versus 3–4), number of involved vertebra (1–2 versus *3), pre-treatment ambulatory status (ambulatory versus non-ambulatory), time of developing motor deficits before RT (1–7 days versus 8–14 days and > 14 days), and radiation schedule (short-course RT, i.e. $1 \times 8$ Gy/1 day or $5 \times 4$ Gy/1 week, versus long-course RT, i.e. $10 \times 3$ Gy/2 weeks, $15 \times 2.5$ Gy/3 weeks or $20 \times 2$ Gy/4 weeks).
**Results:** Of the entire cohort, 197 patients (32%) showed improvement of motor function, 342 patients (55.5%) no change, and 77 patients (12.5%) deterioration. Of the 197 non-ambulatory patients prior to RT, 70 patients (36%) regained the ability to walk. Outcome was not associated with type of primary tumor, 105/335 (31%) breast cancer patients and 92/281 (33%) prostate cancer patients improved.
On multivariate analysis (ordered-logit model), functional outcome was significantly affected only by the time of developing motor deficits before RT (> 14 days better than 8–14 days and 1–7 days, $p < 0.001$). The radiation schedule did not have a significant impact ($p = 0.56$). Improvement of motor function was observed in 96/285 patients (34%) after short-course RT and 101/331 patients (31%) after long-course RT.
A recurrence of MSCC within the irradiated region of the spine (in-field recurrence) was observed in 61 patients (10%) of the entire series, 30 (9%) breast cancer patients and 31 (11%) prostate cancer patients. Median time to in-field recurrence was 9 months. According to Kaplan-Meier analysis, the 2-year-local control of MSCC was 77% after short-course RT and 92% after long-course RT ($p = 0.005$). Median survival was 19 months in the entire cohort. 167 patients (27%) died within 6 months after RT.
**Conclusions:** Functional outcome after RT was significantly influenced by the time of developing motor deficits before RT, but not by the radiation schedule (shourt-course RT as effcetive as long-course RT). Local control of MSCC was significantly better after long-course RT. Thus, patients with a poor expected survival could be treated with short-course RT, because a short treatment time means less discomfort for the patient. For patients with good survival prognosis, long-course RT should be applied to achieve better local control.

**485** ORAL

**Hypoxia-inducible Factor 1 (HIF-1) and Carbonic Anhydrase IX (CA 9) expressions in glioblastoma multiform to predict response to radiation therapy. Implication for combined treatment with carbogen and nicotinamide**

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**Background:** Tumour hypoxia is known to be associated with resistance to radiotherapy. Hypoxia induces the expression of HIF-1 and downstream genes such as CA 9.
**Materials and methods:** We examined the expression of HIF-1 and CA 9 by immunohistochemistry in GBM biopsies, and investigated their relationship with response to radiation therapy (RT). The response to RT was assessed by comparing contrast-enhanced MRI obtained before and six weeks after the completion of radiotherapy. Assessment of odds ratio were based on the logistic regression model with stepwise adjustment. The multivariate model included HIF-1 and CA 9 coded on a semi quantitative scale according to the positive tumour cell percentage (0 = no expression; + < 10%; ++ = 11%-50%; +++ = >50%), and age.
**Results:** Fifty six consecutive patients with inoperable glioblastoma treated with RT (59.4 Gy in 1.8 Gy/fraction), were included in this study (median age: 56 years, range, 30 to 67 years). Nineteen of those patients received carbogen and nicotinamide (C/N) during RT. HIF-1 was expressed in 33 of 56 (59%), and CA 9 in 38 of 52 (73%) of tumours. Tumour HIF-1 expression correlated significantly with that of CA 9 (Kappa = 0.23, $p = 0.003$). The response rate to RT for the entire population was 29%. HIF-1 and CA 9 expressions were correlated inversely with the rate of response to RT (univariate analysis: HIF-1 +: odds ratio 0.21, 95%CI: 0.06–0.71; CA 9 +: odds ratio 0.15, 95%CI: 0.04–0.59). Multivariate analysis showed that HIF-1 + (OR = 0.13, 95%CI: 0.03–0.65), CA 9 +++ (OR = 0.21, 95%CI: 0.04–0.98) and age (OR = 0.91, 95%CI: 0.82–0.99) were independent predictors of response to RT. Response rates to RT without C/N were 60% for tumours HIF-1–/CA 9–, versus 8% for those HIF-1+/CA 9+ ($p = 0.001$). In the group of patients irradiated with C/N, response rates were 50% and 38% for HIF-1–/CA 9– and HIF-1+/CA 9+, respectively. Median progression free survival was 26 weeks for patients HIF-1–/CA 9–, 16 weeks for patients HIF-1+/CA 9+ without C/N, and 26 weeks for patients HIF-1+/CA 9+ with C/N ($p = 0.007$).
**Conclusions:** Glioblastomas with expression of HIF-1 and/or CA 9 were associated with a significantly worse response to RT, independently of known prognostic factors. Carbogen and nicotinamide could reverse hypoxic profile of GBM.
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**486** ORAL

**Phase II study of erlotinib single agent therapy in recurrent glioblastoma multiforme**

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**Background:** We have evaluated the activity of erlotinib (Tarceva, OSI-774) monotherapy for the treatment of recurrent glioblastoma multiforme (GBM) in a single center Phase II trial.
**Methods:** Patients with documented recurrent or progressive GBM who have received previous radiation therapy and cytotoxic chemotherapy were eligible for enrollment. No enzyme-inducing anti-epileptic agents were allowed. Patients were treated with 150 mg of erlotinib per day until tumor progression or study withdrawal. Tumor response was determined by MRI. Analysis for EGFR amplification and/or mutation was performed.
**Results:** A total of 31 patients were enrolled and treated in this trial. We have observed no complete responses (CR) and 8 partial responses (PR) for an objective response rate of 25.8%. An additional 5 patients have had disease stabilization for greater than 3 months (SD) for a tumor control rate of 41.9% (13/31). Fifteen patients have had MRI-confirmed tumor progression (PD) within 3 months of starting erlotinib and an additional 3 patients were taken off study due to neurological deterioration but without MRI evidence of tumor progression. Although most responders subsequently developed disease progression, the median time to progression was longer for responders (355 days) than that for patients with SD (199 days) or those with PD (84 days). Three patients (9.7%), all with PR, remain progression-free on erlotinib for more than 1 year with one approaching 2 years of treatment. Five patients (16.1%) have survived for more than 1 year following the start of therapy. 6-month progression free survival was observed in 25.8% (8/31) which compares favorably to historical controls. There has been no correlation with the presence or absence of EGFR amplification, rash or diarrhea. The EGFR gene activation domain was screened for mutations in all responders; only one case of a confirmed mutation was identified.
**Conclusions:** Erlotinib appears to show activity against recurrent GBM in this small, single center Phase II study. The lack of correlation with biomarkers which have been established for anti-EGFR therapy of other cancers raises questions as to the mechanisms underlying the clinical benefit observed in this trial.

**487** ORAL

**The VEGF-R tyrosine kinase inhibitor ZD6474 enhanced the anti-tumoural effects of temozolomide in the intracerebral BT4C rat glioma model**

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**Background:** Malignant glioma is characterized by extensive pathological neovascularisation. Vascular endothelial growth factor (VEGF) is commonly believed to be the key positive regulator of glioma angiogenesis. ZD6474 is a potent, orally active, low molecular weight inhibitor of VEGF receptor tyrosine kinase activity with additional inhibitory effects on the epidermal growth factor (EGF) receptor tyrosine kinase. Temozolomide is an alkylating agent that recently has become standard treatment of glioblastoma in a concomitant schedule with radiotherapy followed by adjuvant temozolomide. We have previously shown that ZD6474 significantly inhibit tumour growth in an orthotopic intracerebral glioma model. In the present study we have investigated if ZD6474 in combination with temozolomide have any synergistic effects on the tumour growth in an intracerebral rat glioma model.
**Material and methods:** The effects of ZD6474 and temozolomide were investigated in the intracerebral BT4C rat glioma model. Animals were