of the literature (~20%). The study would expand to phase III providing that at least 3 responses were seen in the first 30 evaluable patients in the BMS-275291 arm and the one sided lower limit of the 95% CI for grade 2 or worse arthritis, arthralgia and/or myalgia was less than 50%. Eight centres (Canada [4], France [1], Germany [1], Italy [1], Spain [1]), participated in the study. Pts were randomized to BMS-275291at a dose of 1200 mg po bid or placebo, given in combination with 8 cycles of PC [paclitaxel 200mg/m2 and carboplatin AUC 6 q 3 weeks]. After completion of PC, pts continued BMS-275291/placebo until disease progression (PD) or unacceptable toxicity. The endpoints were incidence of grade 2 or worse drug related arthrotoxicity, objective response and toxicity. The planned sample size was 60 response evaluable pts (defined as pts who received 2 cycles of PC and had been reassessed for response; pts who discontinued PC early with PD were also response evaluable). 75 pts were randomized and 65 were response evaluable. Patient characteristics: performance status was ECOG 0/1/2 in 37/54/9%; median age 60 years; 92% of pts were stage IV; 74% were male. The most common sites of disease were regional and other nodes, pleural effusion, bone and adrenals. Toxicity, including hematologic, was that expected for PC, although there was a higher incidence of drug related rash (usually grade 1 or 2) in pts receiving BMS-275291 (26% vs. 11%). Arthrotoxicity was reported in 30-32% in each arm. The objective response rate was > 20% in each arm. We conclude that BMS-275291 was generally well tolerated when given in combination with PC, was not associated with dose limiting arthrotoxicity and did not appear to adversely impact on early tumour shrinkage with PC chemotherapy; as planned, the study has progressed to phase III to examine the impact of BMS-275291, in combination with PC, on overall and progression free survival.

64 POSTER DISCUSSION

## Single agent gemzar (G) and taxotere (T) given as 1st/2nd line therapy are active in advanced NSCLC: survival data from two randomized phase II studies

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G and T have been shown to be active in chemotherapy-naive and pre-treated patients (pts) with no cross resistancy. We studied G and T in various doses and schedules giving G or T up to 6 cycles first. The form of drug administration was in the first study IA q4w; G: d1,8,15; 1000mg/sqm followed by IB q4w, D: d1,8,15, 35mg/sqm and vice versa and in the second study IIA q3w; G: d1,8; 1250mg/sqm followed by IIB q3w; D: d1; 100mg/sqm and vice versa again, respectively. In case of tumor progression the opposite drug was used up to 6 additional cycles.

In total 405 pts entered the studies (IIIB/IV 15%/85%; PS<1/>1: 72/28%), and 236 have been analyzed so far. Number of pts in IA/IB/IIA/IIB were 96/48/45/47, the median survival (MS) in months were 8/5/6.5/9.5 with the corresponding confidence intervals in months [5.5;10.5]/[3.0;6.5]/[4.5;8.5]/[7.0;11.5], respectively. 1-year survival in % were 30/19/27/28 and the number of censored observations in % were 15/4/29/30, respectively.

MS differs significantly between IA and IB (Kaplan-Meier [KM]), log-rank [lr] p=.023, rank sum [rs] p=.012), but not between IIA and IIB. So far, IIA and IIB can be considered as equally efficacious, although the MS has been different. IA vs IIA and IA vs IIB showed no difference in KM. IIB is significantly superior to arm IB (lr: p=.0071 and rs: p=.0009). G and T as administered in IA, IIA, and IIB is efficacious and indicates that G and T given as 1st/2nd line treatment approach may be an alternative therapy option to conventional combination chemotherapy.

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65 POSTER DISCUSSION

## Detection of occult tumour cells in bone marrow of patients with lung cancer

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**Purpose:** To develop a reliable assay system for detection of micrometastases in BM in lung cancer patients using immunomagnetic beads coated with monoclonal anti-carcinoma antibodies

**Methods:** Consecutive patients with inoperable lung cancer admitted to hospital from Jan 2000–April 2001 were sampled. Twenty ml of BM aspirates from the posterior iliac crest were taken from each patient and mononuclear cells were isolated by Lymphoprep (Nycomed, Oslo, Norway) centrifugation and incubated with Dynabeads M-450 (Dynal, Oslo, Norway) coated with MOC 31 and 5T4 antibodies. MOC 31 recognises an epithelial-associated transmembrane glycoprotein often expressed in epithelial tumors.

5T4 is known to bind different types of carcinomas. The cells with iron containing beads bound to their surface were isolated using a strong magnet.

Tumour cells present in the enriched cell fraction were identified in a light microscope as cells with membrane rosettes of at least five beads

**Results:** At present, 131 BM samples from 111 patients have been examined, includingh 56 adenocarcinomas, 42 squamous carcinoma, and 10 SCLC. In adenocarcinoma patients, 30/56 (53%) BM samples were MOC 31 positive and 17/56 (30%) 5T4 positive. In the squamous carcinomas group, 17/42 (40%) samples were MOC 31 and 27/42 (64%) were 5T4 positive. In SCLC patients, the numbers were 5/10 MOC 31 and 2/10 5T4 positive. In the patients where repeated samples could be drawn, consistent results were obtained.

**Conclusions:** Immunomagnetic beads coated with MOC 31 and 5T4 antibody detects occult metastases in bone marrow in patients with lung cancer at a very high rate. The method is simple an fast, and the sensitivity is high obtained through the enrichment of the cells to be screened by immunomagnetic selection. The high frequency of positive cases compared to published results with other methods, seems to reflect this advantage. The MOC 31 antibody is superior to 5T4 in detecting adenocarcinoma cells, with an inverse situation in squamous carcinoma, demonstrating an advantage of using both antibodies in parallel. As for other tumour types, micrometastatic cells in BM may be an independent prognostic marker. In operable lung cancer patients, the assay may useful in selecting patients at high risk of relapse and possibly for guiding the use of postoperative chemotherapy.

The method can also be used to monitoring effect of therapy.

66 POSTER DISCUSSION

## Phase II Study of ALIMTA (pemetrexed disodium, MTA) Single Agent in Patients with Malignant Pleural Mesothelioma

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ALIMTA is a novel, multi-targeted antifolate that targets several enzymes in the folate pathway necessary for thymidine and purine synthesis. Clinical activity has been demonstrated in multiple solid tumors including lung, breast, colorectal, pancreas, and gastric cancers, and mesothelioma. From April 1999 to November 2000 62 chemonaive patients with histologically proven, advanced mesothelioma not amenable to curative therapy were enrolled in a phase II study to determine the efficacy and toxicity profile of single agent ALIMTA 500 mg/m2 given as a 10 minute i.v. infusion. Treatment was given on day 1 and repeated every 3 weeks. Tumor response was the primary outcome with secondary outcomes including time to event parameters, lung cancer symptom scale, pulmonary function tests, and lung density assessment. After 21 patients had been enrolled, daily low-dose folic acid and vitamin B12 were added to ALIMTA therapy for those patients on study at that time and for all new pts to reduce the risk of severe toxicity associated with ALIMTA.

**Results:** Patient characteristics included: 87% male, median age 67 yrs. (range 40-80); 74% epithelial type, 9% sarcomatous, 14% mixed, and Stage III = 31%, Stage IV= 54%. The median number of cycles given was 3 (range 1-16). In 62 patients evaluable for response, 9 achieved partial response (PR) (14.5%) (95% C.I. 7-26%). 34 patients had SD (55%) and 13 had PD (21%). To date, the median duration of response is +10.8 months. The median time-to-progressive disease is 5.4 months and median survival time is 10.7 months. The 1-year survival rate is 25%. Of those 45 patients who received folic acid and vitamin B12 supplementation at some point of their treatment, 8 patients responded. Five of these 8 patients received vitamins from the beginning of their treatment while another 3 patients started later. Of the 17 patients who never received vitamins, one patient had a PR. All 62 patients were evaluable for toxicity. Grade 3/4 granulocytopenia, thrombocytopenia, and anemia were observed in (percents) 14/14%, 1.7/0% and 1.6%, respectively. Non-hematological toxicities included fatigue, anorexia, nausea, and febrile neutropenia.

**Conclusion:** This study demonstrates promising activity and good tolerability of ALIMTA in mesothelioma. Randomized trials that will further define the role of ALIMTA in this disease are ongoing.

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### Gemcitabine plus Carboplatin (Gcarb) versus Cisplatin plus Vinblastine (CV) in Patients (pts) with Stage IIIB and IV Non-Small Cell Lung Cancer (NSCLC)

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**Purpose:** The combination of Gcarb has demonstrated activity in the treatment of stage III and IV NSCLC. This phase II randomized trial compared the response rate, survival rate, and toxicity of the combination of Gcarb with the combination of CV.

**Methods:** Chemonaive patients with advanced or metastatic NSCLC were enrolled in the study. Pts were randomized to receive either cisplatin 75 mg/m2 on day 1 plus vinblastine 6 mg/m2 on days 1 and 8 (arm A) or gemcitabine 1000 mg/m2 on days 1 and 8 plus carboplatin 300 mg/m2 on day 1 (arm B). Both regimens were administered on a 21-day course.

**Results:** A total of 198 patients (99 pts each in arms A and B) were enrolled in the study between July 1997 to November 1999. All pts had an ECOG performance status <2. Patients had a median age of 58.2 years (range, 30 to 78) in arm A and 59.6 years (range, 40 to 78) in arm B. In arm A, there were 15 partial responders (PR), for an overall response rate (ORR) of 15%, compared with 3 complete responders (CR) and 24 PR, for an ORR of 27% ($p < 0.05$), in arm B. Mean survival times were 239 days (95% CI, 214 - 265) in arm A and 349 days (95% CI, 299 ± 390) in arm B. One-year survival rates for arms A and B, respectively, were 9.1% and 20.2%. Percentages of pts with WHO grade (G) 3/4 hematologic and non-hematologic toxicity in arms A/B were leukopenia 0/2, thrombocytopenia 0/2, alopecia 46/33, neurotoxicity 2/1, and asthenia 35/42.

**Conclusion:** The Gcarb combination showed a good therapeutic response, a benefit in survival, and a similar toxicity profile compared with the CV combination.

## Hematological malignancies

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### An allogeneic antitumor effect after hematopoietic stem cell transplantation for colorectal and renal carcinoma

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**Purpose:** Does allogeneic hematopoietic stem cell transplantation (ASCT) have an anticancer effect in colorectal and renal carcinoma?

**Methods:** Five patients with colorectal and nine patients with renal adenocarcinoma with metastases underwent ASCT. The donors were HLA-identical siblings for nine patients and HLA-compatible unrelated donors for five patients. Conditioning included Fludarabin 30 mg/m2 for three days in patients with HLA-identical siblings and five days with unrelated donor, followed by 2 Gy total body irradiation. Antithymocyte globulin 4 mg/kg was given to patients with unrelated donors. Peripheral blood stem cells were collected after G-CSF stimulation of all donors. Immunosuppression was by mucophenolate mofetil and cyclosporine. Chimerism was determined using PCR amplification of variable number tandem repeats.

**Results:** All patients were treated as outpatients. Chimerism showed 100% donor myeloid and T-cells in 7/14 and 2/14 patients at one month after ASCT, respectively. Six patients developed grades II-IV acute GVHD. Two rejected the grafts, one died of renal toxicity, one died of an accident and two died of disease progression. One patient with colon cancer showed an 80% decrease in size of all metastases at two months. He died of pneumonia at four months and autopsy showed necrosis of all metastases with few cancer cells. Another patient with colon carcinoma have shown regression of pleura metastases, but progression of liver metastases. One patient with renal carcinoma died of grade IV acute GVHD. Pulmonary metastases had disappeared at autopsy. Among four renal carcinoma patients who are alive between 4 and 12 months after ASCT, one has shown partial response of metastases, another has shown progression as well as regression of metastases.

**Conclusion:** ASCT after minimal conditioning was well tolerated. 7/14 patients are alive after 4-12 months. Partial tumor regression (>50%) was seen in two patients with colorectal and two patients with renal carcinoma.

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### High activity rhenium-186 HEDP with peripheral blood stem cell support -a novel approach to hormone refractory prostate cancer metastatic to bone

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**Purpose:** The radioisotope Rhenium-186 HEDP has been used successfully for many years in the palliation of pain from bone metastases, with thrombocytopenia as the dose limiting toxicity. In this study we have tested the feasibility of escalating activities of Rhenium-186 HEDP by using peripheral blood stem cell support in a phase I trial. We hypothesise that by increasing the administered activity it will be possible to increase the ionising radiation dose to individual metastases allowing potential ablation of small lesions, reduction in new lesion formation, and improved disease free survival.

**Methods:** Twenty patients with hormone refractory prostate cancer metastatic to bone, minimal soft tissue metastases, and rising PSA, each received one treatment of intra-venous Rhenium-186 HEDP. Stem cells were returned 14 days post isotope treatment. A starting activity of 2500MBq was chosen following previous work by ourselves showing unacceptable toxicity without stem cell support at 3000MBq. We have now reached activities of 5000MBq, initially with increments of 250MBq and subsequently 500MBq when low toxicity rates were seen.

**Results:** All patients tolerated the treatment and stem cell transplant well. There was no incidence of grade III platelet toxicity (<50 x 109/l). Three patients (15%) had grade III leucopenia (1-2 x 109/l). A trend towards lower nadir platelet levels was seen with activities of Rhenium-186 above 3500MBq (p=0.1). Each patient had a total of 4 days spent in hospital for radioprotection purposes with all other procedures performed on an outpatient basis. As yet we have not found the maximum tolerated activity. Actuarial survival figures are encouraging compared to the literature with a median survival of 9.8 months at a median follow up of 7.5 months (range 2-36). PSA responses were seen in 60% of patients with a non statistically significant trend towards better response above 3500MBq (p=0.37).

**Conclusions:** Activities up to 5000MBq of Rhenium-186 HEDP can be administered with peripheral blood stem cell support with minimal toxicity. The potential exists for higher doses of ionising radiation to be delivered to individual metastases. We plan to continue phase I until the maximum tolerated activity is reached and then proceed to a Phase II evaluation of response.

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### Induction of differentiation of human chronic myeloid leukemia cells by synthetic 6 base phosphodiester oligonucleotides

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**Purpose:** A series of synthetic 6 base non-antisense phosphodiester oligonucleotides with either GpA, GpC, GpG or GpT dinucleotides motifs within specific sequence contexts has been identified as a potent inducer of apoptosis in a wide range of cancer cells, including acute lymphocytic leukemia cells. In this study, we have evaluated the activity of these oligonucleotides on a human chronic myeloid leukemia (CML) cell line.

**Methods:** K562 cells, derived from the leukemic cells of a CML patient in blastic crisis, were incubated for 48 h with different concentrations (2.5 to 100 μg/ml) of oligonucleotides with either GpA (BT 99-45) or GpT (BT 99-25) dinucleotides motifs within specific sequence contexts. Cellular division was monitored using a Coulter Counter. Apoptosis was evaluated