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POSTER\*

### Magnetic resonance imaging (MRI) of pulmonary lesions with single shot fast and ultra-fast gradient echo imaging

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The purpose of our study was to evaluate the the clinical applications of subsecond MRI of thoracic lesions in direct correlation to intraoperative findings. The studies were performed on a 1.5 tesla MR-system/Magnetom SP 4000, Siemens) using a whole body resonator. We used three sequences: T1w-TurboFLASH (T1wTF), FLASH and T2w-TurboFLASH (T2wTF). Images were acquired in the coronal, transversal and sagittal plane. 20 patients with pathological findings in conventional radiography and computed tomography (CT) were studied with MRI prior resection.

For the detection of a lesion, the combination of the FLASH and the T2wTF showed the highest diagnostic gain. Due to the different, reproducible signal intensity of vascular and malignant lesions in the FLASH and T2wTF images, a clear identification was obtained without contrast media. Lesion detection as well as classification of extend was excellent in all pts. The total examination time was less than 30 minutes. A combination of single shot FLASH with a single shot T2wTurboFLASH sequence enables subsecond imaging of pulmonary lesions. All important vascular structures were reliably visualized without contrast media. While MRI does not currently have any diagnostic advantage over CT in the detection of thoracic lesions, the excellent differentiation of parenchymal lesions and vascular structures without the use of contrast media and the variability of imaging planes are significant methodological advantages.

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### Interim results of a phase II study of docetaxel (Taxotere®) in unresectable non-small cell lung cancer (NSCLC) on 204 chemotherapy naive or pretreated patients

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Taxotere® has already produced promising responses as a single agent in locally advanced and/or metastatic NSCLC. Therefore, a phase II study was started with Taxotere at a dose of 100 mg/m<sup>2</sup> every 3 weeks with a 5 day oral corticosteroid premedication. Evaluation of efficacy was performed every 2-3 cycles. Patients (pts) received 6 to 9 cycles according to response. Histologically confirmed NSCLC, KPS ≥ 60%, no brain involvement and signed informed consent were the main eligibility criteria. 29 centers in 4 countries accrued 204 pts with measurable or evaluable lesions. To date 127 pts have been assessed. The characteristics of the pts were: male: 81%; median age: 59 years (19-78); median KPS: 80% (60-100); chemotherapy pretreated pts: 31%; metastatic: 77%. Pts received a mean of 4.3 cycles (1-17). 91 pts were evaluable for response: 24 PR (26% of evaluable pts-20% of ITT pts) and 29 NC (32%) were observed and confirmed by an independent panel. Median time to progression was 2.6 months and median duration of response was 8.6 months. Median survival was 8.4 months and one year survival was 36%. Main toxicities were neutropenia: G4: 57%, G3: 14%; febrile neutropenia: 6%; infection: 30%; severe asthenia: 10%; severe fluid retention: 2%; neurosensory G-3: 2%; 2 deaths due to neutropenic infection. The results of this interim analysis confirm the published results of Taxotere® in chemotherapy naive pts as well as in pretreated pts.

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### Gemcitabine (GEM) - Cisplatin (CDDP) - Vinorelbine (VNR) combination in advanced non-small-cell lung cancer (NSCLC). A phase II randomized study

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**Purpose:** To define the activity and toxicity of the GEM-CDDP-VNR combi-

nation in advanced NSCLC.

**Methods:** Chemo-naive pts. with stage IIIB-IV, age ≤70 and PS 0-1 were randomized to receive GEM (1,000 mg/m<sup>2</sup>), CDDP (50 mg/m<sup>2</sup>) and VNR (25 mg/m<sup>2</sup>) (all drugs were given on d 1 & 8 of an every 3-week cycle) or CDDP (80 mg/m<sup>2</sup> d 1), epIDX (80 mg/m<sup>2</sup> d 1), VDS (3 mg/m<sup>2</sup> d 1) every 4 weeks, plus ionidamine (150 mg × 3 daily, orally) as standard treatment.

**Results:** On December 1996 we stopped the randomization since we had already reached the target number of 31 responses required by our study design in the experimental arm. We decided, however, to continue the accrual in this arm until the planned sample size (81). To date, 127 eligible pts. have been accrued, 73 in the experimental and 54 in the standard arm. Both treatments have been associated with a manageable toxicity. 53 and 41 pts. are evaluable for response respectively. Objective responses are 32/53 (60%; 95% CI = 46-73) and 15/41 (37%; 95% CI = 22-53). At a median follow-up of 8 months, median survival is >14 months in the experimental and 8 month in the standard group.

**Conclusion:** The GEM-CDDP-VNR combination is a highly active treatment for advanced NSCLC patients.

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### Topotecan (Hycamtin™) in small cell lung cancer (SCLC) after failure of first line therapy: Multicentre phase II study

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**Purpose:** This phase II study was conducted to confirm the documented activity of topotecan (TPT), a selective topoisomerase-I inhibitor in 2nd-line SCLC.

**Methods:** 95 males and 24 females with measurable SCLC classified as refractory (R; i.e. progressed on first-line treatment or within 3 m of stopping (n = 48)) or sensitive (S; i.e. progressed >3 m after stopping first-line treatment (n = 71)) received TPT 1.5 mg/m<sup>2</sup>/day as a 30 min infusion daily for 5 d, q 21 d. All responses were independently verified.

**Results:** 98 pts were fully evaluable for response (41 R; S 57). Responses were seen in 9 pts (8S; 1R). In S pts one patient had a CR. 11 pts had objective stable disease. For the intent-to-treat population, median survival was 21.6 wks overall (25.7 wks S, 16.3 wks R), and time to progression was 8.1 wks. In 9 pts with brain metastases, there were, within the CNS, 4 PRs and 3 SDs plus 1 CR in a patient who received concurrent RT. Toxicities were mainly haematologic, consistent with the profile of the drug.

**Conclusion:** Ardizzoni, ESMO, 1996, reported a response rate of 23% in pts demographically similar to ours, but with fewer S pts (48% v 60%), and who received twice as much TPT therapy; (median 4 cyc v 2 cyc). Of the 11 SD in our study, none had evidence of PD or intolerable side effect at withdrawal, 9 were S, and 9 are known to have received subsequent chemo; 6 were both S and received subsequent chemo. This study shows that TPT has activity in 2nd-line SCLC pts, achieving an overall median survival of 21.6 wks. TPT appears to induce, besides clinical responses, slow tumour regression or arrest of tumour growth. This, together with the activity observed in those pts with cerebral secondaries, suggests a potential role of TPT in 1st-line therapies, either as a cranial prophylaxis or as a maintenance agent. These studies are being planned.

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### High dose-density chemotherapy for small cell lung cancer (SCLC)

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**Purpose:** To explore the feasibility of administration of a high-density chemotherapy regimen in small cell lung cancer and to assess the impact in survival.

**Methods:** We treated 45 patients (pts) with SCLC with a sequential treatment consisting of 4 cycles of VEC (Vincristine 1.4 mg/m<sup>2</sup>, Etoposide 110 mg/m<sup>2</sup>, Cyclophosphamide 1 g/m<sup>2</sup> IV d 1) followed by 2 cycles of PE (Cisplatin 120 mg/m<sup>2</sup> IV d1, Etoposide 200 mg/m<sup>2</sup> IV d1-3 or 1-2). Cycles were administered every two weeks and G-CSF (filgrastim) 300 µg SC qd was administered during the interval. Complete responders with limited stage disease received prophylactic cranial irradiation and thoracic radiotherapy at the end of chemotherapy. 43 pts were male and 2 female. Median age was 59 years (36-75). 93% of pts had ECOG 0-1. 26 pts had limited stage (LS) and 19 extensive stage (ES).

## Results:

Stage	RR (%)	CR (%)	PR (%)	Median survival (months)
LS + ES	89	62	27	13 (95% CI: 10-16)
LS	100	89	11	20 (95% CI: 15-25)
ES	73	26	47	11 (95% CI: 9-13)

Main toxicity was hematological. Toxicity to VEC was mild but toxicity to PE was severe with grade 3-4 anemia in 66% of cycles, neutropenia in 48%, and thrombocytopenia in 74%. There were two toxic deaths after PE. Six patients are alive and free of disease more than 24 months after treatment. Main cause of mortality was brain metastases (46%).

**Conclusion:** This high-density dose regimen is tolerable and very effective in limited stage patients. A significant number of pts in this stage become long survivors.

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### Phase II study of paclitaxel as first line treatment for patients with extensive stage small cell lung cancer (SCLC)

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Paclitaxel has excellent antitumour activity in a variety of malignancies. Previous phase II studies in SCLC showed response rates of 34% and 41% but limited drug supplies restricted the number of cycles that could be given. We therefore performed a further phase II study in previously untreated patients with extensive stage SCLC. Paclitaxel 200 mg/m<sup>2</sup> was given as a 3-hour iv infusion at 21 day intervals with dexamethasone, chlorpheniramine and cimetidine premedication. Thirty SCLC patients (19 male, 10 female, 1 not stated) of median age 66 years (range 34-76) were treated. At entry their median ECOG performance status was 1 (range 0-2). All patients had bidimensionally measurable disease, the commonest sites being (in order) lung, lymph nodes, liver, pleural effusion, bone and skin. The median number of treatment cycles administered was 2 (range 1-10). Among 27 patients analysed, 7 (26%) achieved a partial response and 4 (15%) stable disease. Six patients died on study, 13 stopped treatment with progressive disease and 5 with toxicity. The commonest toxicities were (in order) alopecia, peripheral neuropathy, nausea, aches/pains, fatigue. One patient experienced sepsis. We conclude that paclitaxel can be safely given to SCLC outpatients with a response rate of 26%. Further studies are required to evaluate its role in combination chemotherapy regimens for SCLC.

We thank Bristol-Myers-Squibb for supporting this study.

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### Pooled analysis of topotecan (T) in the second-line treatment of patients (pts) with sensitive small cell lung cancer (SCLC)

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**Purpose:** Topotecan is a new agent for the treatment of pts with sensitive SCLC. An analysis of pooled data was performed from 3 multicenter studies of pts with bidimensionally measurable SCLC who received T after progressing 3 months after one first-line regimen.

**Methods:** Topotecan was administered as a 30-min infusion at an initial dose of 1.5 mg/m<sup>2</sup> daily times 5 q 21 days until evidence of progression or unacceptable toxicity. Responses were confirmed by independent radiological review. Data presented are for the intent-to-treat population.

**Results:** A total of 726 courses (crs) were administered, median of 4/pt (range: 1-15 crs). A total of 168 pts (120 M, 48 F) were treated; mean age was 59 y (range: 31-76 y). Median performance status was 1 (range: 0-2). Response rate was 18% (95% CI 12.1-23.6%; 10 CR, 20 PR). Median time to response was 6 wks (range: 2-15 wks). Median duration of response (calculated from the time of documented response) was 23 wks (range: 8-51 wks). Median time to progression was 12 wks (range: 0.6-79 wks); 9 pts have not progressed. Median survival was 30 wks (range: 1.3-99 wks). One year survival was 21%; 20 pts remain alive. Grade 4 neutropenia occurred in 38% of crs and was associated with infection or ≥grade 2 fever

in 4% of crs. Grade 4 thrombocytopenia and grade 3-4 anemia occurred in 11% of crs. Non-hematological toxicities were generally mild; alopecia, nausea, asthenia, and vomiting were reported most frequently.

**Conclusion:** Topotecan has activity with manageable toxicity in pts with sensitive SCLC. (Supported by SmithKline Beecham.)

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### A phase I study to investigate alternate sequencing of the combination gemcitabine followed by carboplatin in NSCLC

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**Purpose/Methods:** A phase I study evaluated the combination of gemcitabine and carboplatin in chemo-naïve patients with NSCLC. Gemcitabine at a dose of 1000 mg/m<sup>2</sup> was administered on days 1, 8 and 15 of a 28 day cycle and carboplatin (dosing based on the Calvert formula) was given immediately prior to gemcitabine on day 1.

**Results/Conclusions:** Dose limiting myelotoxicity was seen at dose level 2, AUC of carboplatin 5.2 mg/ml/min. (n = 10). In order to determine if the toxicities of the combination were sequence related, 9 patients were recruited to the reverse sequence gemcitabine/carboplatin at an AUC of carboplatin of 5.2 mg/ml/min. on day 1.

Variable	Carbo/gem (10 pts)	Gem/carbo (9 pts)
Age range (median)	41-72 (64)	39-71 (58)
PS 1, 2	9, 1	9, 0
Adenocarcinoma	3	1
Squamous	4	1
Large cell	3	2
Unspecified	-	5
Stage IIb, IV	3, 7	6, 3
Cycle range (median)	1-6 (3)	2-6 (4)
Grade III/IV Toxicities	% of cycles (n = 31)	% of cycles (n = 32)
Neutropenia	58.1	50.3
Thrombocytopenia	35.5	43.7

Evaluation of the toxicity and encouraging efficacy of this combination continues.

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### 99m-Tc-sestamibi extrusion rate correlates with resistance to cytotoxic treatment and distant metastasis in non-small cell lung cancer

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**Purpose:** Application of a test that reliably evaluates multi-drug resistance is missing. Tc-99m radiolabeled hexakis-2-methoxy-isobutyl-isonitrile (99mTc-sestamibi) is recently shown to be extruded from cells through p-glycoprotein activity. In the present study we examined the up-take and extrusion rate of the radiotracer in 25 patients with advanced non-small cell lung cancer undergoing chest radiotherapy, using a novel scintigraphic technique based on simulation guided pin-hole imaging.

**Methods:** Using a Radiotherapy simulator a 4 cm of diameter area, was marked on skin of patients, above the tumor area. Each patient received 20 mCi (740 MBq) of 99mTc-sestamibi in the antecubital vein. 10 min after the injection, a gamma camera provided with a pinhole collimator able to scan an area of 12 cm in diameter was placed on the marked skin area. Standard five minute images were taken to collect 10<sup>5</sup> to 2 × 10<sup>5</sup> counts. The same procedure was repeated at 120 min. post-injection.

**Results:** 6/25 (24%) of tumors showed 1.3-1.7 times higher extrusion rate as compared to normal lung. Increased tumor clearance of the Tc-sestamibi significantly correlated with resistance to radiotherapy (p = 0.05) as well as the existence of distant metastasis (p = 0.008). Patients with known resistance to chemotherapy had higher extrusion rate as compared to chemotherapy naïve patients (p = 0.01).

**Conclusions:** It is concluded that functional imaging of lung cancer with Tc-sestamibi may have a role in predicting response to cytotoxic treatment and in identifying tumors with aggressive behavior.