Considerable decrease of TGF-β (p<0,01), VEGF (p<0,01) and bFGF (p<0,01) in serum was observed following neoadjuvant therapy, with no significant changes in TIMP-1 and CD95L levels. In serum samples collected directly after tumor resection significant drop-down of bFGF (p<0,001) continued, while VEGF levels increased (p<0,001), TGF-β levels didn’t change and continued to be lower than before therapy (p<0,01). As previously, tumor resection didn’t affect TIMP-1 and CD95L. Serum levels of VEGF and CD95L as well as CD95L and TIMP-1 correlated well before (r=0,36, p<0,05 and r=0,48, p<0,001) and after (r=0,35; r=0,39, p<0,05) neoadjuvant therapy. Similar relation was observed for TGF-β and fibrinogen as well as fibrinogen and TIMP-1 before (r=0,499; r=0,41 p<0,01) and after (r=0,44; r=0,40, p<0,01) surgery. As expected levels of TGF-β, TIMP-1 and bFGF were significantly higher in excised tumor than in normal lung tissue (p<0,001), while no differences in VEGF and CD95L content were demonstrated. Neoadjuvant therapy considerably affected cytokines regulating tumor growth: VEGF, bFGF, TGF-β while serum markers of apoptosis CD95L or local tumor invasiveness TIMP-1 were not affected. Postoperative changes of growth factors might be due to the tumor resection and wound healing.

**Results:**

With a median follow-up of 61 months, more than 88% were uncensored (85% for CG and 90% for CaG), OOR is higher for CG (41.8% - 95%CI 34.9- 51.1) than for CaG (29.4% - 95%CI 23.2-35.6 p=0,0034). This clinical response is in line with Cyfra 21-1 median drop (-32.7% for CG and - 7.1% for CaG p=0.0028). Comparison of median survival benefits CG (overall 10.2 vs. 8.1 mo p=.00006; stage IIIB 14.2 vs. 9.9 p=.00029; stage IV 9.6 vs. 7.7 p=0.022). Differences in IFD were even more significant (overall - CG 6.2 mo vs. CaG 4.3 p<0.00001.) Survival-rates were similarly higher for CG. Haematological non-haematological side effects were detected. Seven toxic deaths (3 CG and 4 CaG were reported).

**Conclusions:** the result of our 10-year study makes clear that CG combination is more effective than CaG in which concerns response rate, IFD and survival. Haematological toxicity is similar between groups, except for thrombocytopenia, more frequent with carboplatin-based chemotherapy. Consistency of results (response, decrease of serum cyfra 21-1 and survival) obtained with the CG association in this 10-year study together with moderate toxicity, points clearly to this CT treatment as the standard for pts with advanced or metastatic NSCLC.

**P2-248 NSCLC: Cytotoxic Chemotherapy Posters, Tue, Sept 4**

**What is the standard platinium-derivative based-chemotherapy for advanced or metastatic NSCLC; a 10-years trial comparing cisplatin (C) and carboplatin (Ca) in combination with gemcitabine (G)***

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**Objectives:** to compare survival results obtained at our unit during a 10-year-time period (1997-2006) with the combinations CG and CaG in the treatment of advanced NSCLC patients (pts), and try to answer some doubts concerning the balance between efficacy (response and survival) and toxicity of these two combinations.

**Patients and Methods:** 608 pts (stage IIIB -282 IV- 324 were treated in this period (CG - 305; CaG - 303). Treatment schedules were: CG (C - 80 mg/m² d1 + G 1000mg d1 and 8 each 3 weeks); CaG (Ca - AUC 5 d1 + G - 1000mg/m² d1 and 8 each 3 weeks). Groups were well balanced in which concerns all significant prognostic factors to survival. Baseline and pos-CT characteristics were compared between groups using a 2-way-Anova analysis, OOR response rate and toxicities were compared with Fisher's exact test; in order to compare survival curves and to estimate hazard ratios and respective CI we used a Cox proportional hazards model stratified for stage and adjusted for prognostic variables.

**Results:** With a median follow-up of 61 months, more than 88% were uncensored (85% for CG and 90% for CaG), OOR is higher for CG (41.8% - 95%CI 34.9- 51.1) than for CaG (29.4% - 95%CI 23.2-35.6 p=0.0034). This clinical response is in line with Cyfra 21-1 median drop (-32.7% for CG and - 7.1% for CaG p=0.0028). Comparison of median survival benefits CG (overall 10.2 vs. 8.1 mo p=.00006; stage IIIB 14.2 vs. 9.9 p=.00029; stage IV 9.6 vs. 7.7 p=0.022). Differences in IFD were even more significant (overall - CG 6.2 mo vs. CaG 4.3 p<0.00001.) Survival-rates were similarly higher for CG. Haematological toxicity was similar for both treatments with the exception of an excess of grade 3 and 4 thrombocytopenia for CaG. Few significant non-haematological side effects were detected. Seven toxic deaths (3 CG and 4 CaG were reported).

**Conclusions:** the result of our 10-year study makes clear that CG combination is more effective than CaG in which concerns response rate, IFD and survival. Haematological toxicity is similar between groups, except for thrombocytopenia, more frequent with carboplatin-based chemotherapy. Consistency of results (response, decrease of serum cyfra 21-1 and survival) obtained with the CG association in this 10-year study together with moderate toxicity, points clearly to this CT treatment as the standard for pts with advanced or metastatic NSCLC.

**P2-249 NSCLC: Cytotoxic Chemotherapy Posters, Tue, Sept 4**

**A Phase I Trial of ABT-751 and carboplatin in patients with previously treated non-small cell lung cancer***

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality for men and women in the United States. More effective treatments are needed to prolong survival and improve quality of life. Platin-containing chemotherapy doublets are commonly used in NSCLC treatment. ABT-751 is a novel oral anti-microtubule agent targeting the colchicine binding site. As single agent, it was well-tolerated and showed a preliminary signal of activity in previously treated NSCLC. In vivo studies demonstrated additive activity between ABT-751 and cisplatin in a NSCLC xenograft model.

A phase I trial of ABT-751 and carboplatin was conducted in patients with advanced previously treated NSCLC. Primary objective was to determine the maximum tolerated dose (MTD). Secondary objectives were evaluation of toxicities, efficacy, and surrogate markers of response (cell cycle changes and cyclin D1 expression) in buccal swabs from patients at the phase II dose. Four dose levels were studied - 1: ABT-751 100 mg bid, carboplatin AUC 4.5; 2: ABT-751 125 mg bid, carboplatin AUC 4.5; 3: ABT-751 125 mg bid, carboplatin AUC 6; 4: ABT-751 150 mg bid, carboplatin AUC 6. ABT-751 was taken orally twice a day for 7 days in a 21-day cycle, carboplatin was administered intravenously on day 4 during cycle 1 to allow for pharmacokinetic analysis, and on day 1 of subsequent cycles. Rapid dose escalation was used for the first 3 dose levels followed by cohorts of at least 3 patients for the remaining dose levels.

Thirteen patients were enrolled, twelve patients completed one cycle of therapy and were evaluable for toxicities. All patients were previously treated with a carboplatin-containing regimen. All patients had stage IV NSCLC, median age was 62 years (range 46-73), 5 were women, 2 patients had Karnofsky performance score (KPS) 90, the rest had KPS 80. Seven patients had one and 5 patients had 2 prior therapies. A median of 2.5 (1-4) cycles was administered. Dose-limiting toxicities (DLTs) were assessed at the end of cycle one. Grade 3 fatigue and grade 4 thrombocytopenia and neutropenia were observed in 2/5 patients on dose level 4. Common grade 2 toxicities were constipation and peripheral sensory neuropathy (levels 2-4). MTD was dose level 3. Ten patients were evaluable for response, 2 had partial responses lasting 14 and 28 weeks (levels 2 and 4, both had one prior therapy), 4 had stable disease, 4 had disease progression. Median time to progression was 13
The recommended phase II doses are ABT-751 125 mg twice daily for 7 days and carboplatin AUC 6 on a 21-day cycle. This regimen is well tolerated and shows preliminary evidence of activity for previously treated NSCLC.

P2-250 NSCLC: Cytotoxic Chemotherapy Posters, Tue, Sept 4
A Phase II Study of Gleevec (Imatinib Mesylate) Plus Taxotere (Docetaxel) in Patients with Advanced Non-Small Cell Lung Cancer
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Background: Docetaxel has been shown to improve overall survival in patients with recurrent NSCLC. Pre-clinical data suggests synergistic activity with the combination of docetaxel and imatinib. Paul Matthew, et al demonstrated the safety of this combination in the MD Anderson trial “Targeting the platelet-derived growth factor receptor in androgen-independent prostate cancer.” Therefore this combination was administered to patients with recurrent NSCLC to determine overall response rate.

Methods: This is a phase II study of the combination of Taxotere and Gleevec in refractory NSCLC to determine tumor activity, toxicity and recommendations for further studies of this combination. Patients must have received at least one prior regimen and experienced recurrence or have been refractory to the initial treatment. Taxotere was administered at 30 mg/M2 on a weekly schedule for 3 weeks followed by one week rest. Gleevec was administered at a starting dose of 600 mg daily. Dose modifications to address toxicity were built in to the protocol.

Results: To date, a total of 10 patients have been enrolled on this study. Seven male and 3 female with a median age of 66 years (range 58-74). A total of 26 cycles were delivered to 10 patients (mean = 3). Four patients experienced fatal adverse events while on study. Two with a non-study related fatal MI (both with history of heart disease). One patient developed GI perforation not related to study (history of ischemic bowel disease). One patient suffered a fatal pulmonary embolus not related to study (history of CAD and peripheral vascular disease). Grade 4 toxicities included periordial edema (1 pt), pneumonia (2 pts), diarrhea (1 pt), dehydration (1 pt), dyspnea (1 pt), anorexia (1 pt), bilateral pleural effusion (1 pt), and neutropenia (2 pts).

Grade 3 toxicities included hypotension, renal failure, hypotension, mental status change, anorexia, azotemia, dyspnea, herpetic esophageal ulcer, pneumonia, cough, neutropenia, shortness of breath, weakness, fatigue, and anemia.

Results: Responses were minimal. Four of 10 patients received only 1 cycle. Three of those 4 suffered a fatal adverse event and tumor assessment was not performed. The fourth developed herpetic esophageal lesions and was started on 2nd line therapy prior to tumor assessment. One patient had stable disease after 2 cycles but progressed after cycle 3. One patient received 3 cycles, had stable disease after cycle 2 but refused additional therapy after cycle 3 due to grade 2 nausea. One patient had stable disease after 6 cycles then experienced a fatal pulmonary embolus. An additional patient had a partial response after cycle 4 but CT after cycle 6 demonstrated progression. Two patients progressed after cycle 2.

P2-251 NSCLC: Cytotoxic Chemotherapy Posters, Tue, Sept 4
Phase I/2 study evaluating the safety and efficacy of ABT-751 in combination with docetaxel vs docetaxel alone in subjects with advanced or metastatic non-small-cell lung cancer
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Background: ABT-751 is an orally bioavailable sulfonamide that binds to the colchicine site on β-tubulin and inhibits polymerization of microtubules. Docetaxel (Taxotere®) is an antineoplastic taxoid. Both compounds have been evaluated individually in advanced NSCLC subjects and in combination in preclinical xenograft models.

Methods: The Phase 1 open-label dose escalation portion of the study was designed to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RPTD) of ABT-751 when administered with docetaxel. For each cycle, subjects received 75 mg/m2 docetaxel IV on Day 1 and ABT-751 orally QD for 14 consecutive days followed by 7 days off drug. Dose levels of ABT-751 began at 200 mg and will escalate by 50 mg increments. Pharmacokinetic sampling was performed on Day 1 of Cycle 1. The Phase 2 portion of the study was designed to determine the effect of ABT-751 plus docetaxel on progression-free survival.

Results: The RPTD was determined to be 200 mg of ABT 751 QD for 14 days. To date, 7 subjects have been accrued into the Phase 1 portion of the study, and preliminary safety data are available for 5. One of the subjects in the 200 mg cohort experienced a dose-limiting toxicity of grade 4 thrombocytopenia. Two subjects experienced an adverse event (1 multiple sclerosis and 1 hiccups) rated grade 3 using The Terminology Criteria for Adverse Events (CTCAE) version 3.0. No grade 4 or 5 adverse events were reported. Preliminary results indicate that the pharmacokinetics of ABT-751 and its glucuronide and sulfate metabolites after concomitant administration of a single dose of ABT-751 (200 mg) with docetaxel were comparable to those after a single dose of ABT-751 (200 mg) alone in a previous study.

Pharmacokinetic parameters of ABT-751 after a 200 mg oral dose of ABT-751

| Pharmacokinetic parameters of ABT-751 after a 200 mg oral dose of ABT-751 |
|-----------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| ABT-751 With Docetaxel     | ABT-751 Alone#            | ABT-751 Glucuronide with Docetaxel | ABT-751 Glucuronide Alone# | ABT-751 Sulfate with Docetaxel## | ABT-751 Sulfate Alone# |
| N                           | 3                         | 23                          | 23                          | 3                           | 23                          |
| Tmax (h)                    | 2.3 ± 1.5                 | 2.0 ± 1.3                   | 5.0 ± 2.7                   | 4.5 ± 2.2                   | 5.0 ± 2.7                   | 4.0 ± 2.4                   |
| Cmax (μg/mL)                | 9.1 ± 5.0                 | 9.1 ± 4.5                   | 6.1 ± 4.3                   | 4.6 ± 1.7                   | 8.0 ± 3.2                   | 7.4 ± 3.2                   |
| AUC0-8 (μg*h/mL)            | 33.8 ± 15.1               | 33.0 ± 10.1                 | 30.2 ± 22.5                 | 26.6 ± 10.5                 | 43.6 ± 21.3                 | 39.5 ± 15.0                 |

#Results from Phase 1 Study M01-303 were used as a historical reference.

Conclusions: The RPTD of the combination of ABT-751 and docetaxel has been determined. Coadministration of docetaxel with ABT-751 does not appear to affect the pharmacokinetics of ABT-751.